



Ph.D. in Science – *curriculum* Chemical Science

***“Syntheses of silver and gold N-heterocyclic carbene complexes:
applications in sustainable catalyses and their pharmacological
activities ”***

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For those who came after:
no sacrifice is too great.
Seek truth, The rest will follow.

Abstract

Il presente progetto di dottorato è stato incentrato sulla sintesi di nuovi complessi organometallici di argento(I) e oro(I) stabilizzati da leganti carbenici N-eterociclici (NHC) alchilsolfonati. Tali leganti sono stati opportunamente funzionalizzati al fine di chiarire l'influenza dei sostituenti sulle proprietà strutturali e applicative dei sistemi metallici risultanti. Il lavoro è stato articolato in una prima fase di sintesi e caratterizzazione attraverso tecniche spettroscopiche e spettrometria di massa (NMR, FT-IR, MALDI-MS) delle nuove strutture, seguita dalla valutazione delle loro potenzialità catalitiche e citotossiche.

Per la sintesi dei leganti coordinati ai metalli centrali, sono stati impiegati imidazoli 4,5-disostituiti recanti diversi sostituenti sullo scheletro dell'anello. Gli atomi di azoto sono stati funzionalizzati in modo asimmetrico: la posizione N1 è stata derivatizzata con gruppi benzile o benzidrilici, mentre la posizione N3 è stata alchilata con catene propan- o butan-sulfonica.

I sali zwitterionici così ottenuti sono stati utilizzati come precursori di carbeni eterociclici azotati (NHC). Questi ultimi sono stati impiegati dapprima nella complessazione con argento(I) e, successivamente, convertiti nei corrispondenti complessi di oro(I) tramite una reazione di transmetallazione. I nuovi sali e complessi sono stati isolati, caratterizzati e infine testati in ambito catalitico e farmacologico.

Per i test catalitici, sono state prese in esame la sintesi di derivati di acidi propiolici da carbosilazione con anidride carbonica su alchini terminali, la sintesi di ossazolidinoni per ciclizzazione con anidride carbonica su substrati propargilamminici ed infine la reazione multicomponente A³ (Ammina-Alchino-Aldeide). Quest'ultima ha mostrato i risultati più significativi. Dopo uno screening preliminare dei solventi, sono stati valutati due substrati notoriamente difficili da impiegare, benzaldeide e paraformaldeide. In particolare, la paraformaldeide, poliacetale derivato dalla formaldeide, ha evidenziato un comportamento catalitico rilevante. Nelle condizioni adottate, il substrato polimerico partecipa alla reazione in presenza dei complessi Ag(I)/Au(I)-NHC mostrando attività già a temperatura ambiente. L'analisi dei dati ha messo in luce una tendenza superiore dei complessi di oro(I), con l'identificazione di due strutture particolarmente efficaci che raggiungono conversioni fino all'80% dopo 16 ore a temperatura ambiente.

A seguito delle valutazioni catalitiche, è stata condotta una valutazione preliminare dell'attività citotossica di una selezione dei complessi e dei sali ottenuti verso due linee tumorali mammarie, MCF-7 e MDA-MB-231, confrontando i risultati con la linea sana MCF-10A. Le analisi sono state eseguite dal gruppo di ricerca guidato dalla prof.ssa Maria Stefania Sinicropi presso l'Università della Calabria, mediante saggio MTT per la determinazione dei valori di IC₅₀ (μM) dopo 72 ore di

esposizione delle cellule alle strutture testate. Dai test emerge un'assenza di attività per i complessi Au(I)-NHC e per i sali zwitterionici, mentre i complessi Ag(I)-NHC mostrano una marcata citotossicità, risultando promettenti su entrambe le linee tumorali. Tale comportamento evidenzia una chiara metallo-selettività a favore dell'argento e sottolinea l'importanza della coordinazione del metallo centrale alle strutture N-eterocicliche per l'espressione dell'attività biologica. L'analisi comparativa delle strutture consente di delineare il contributo dei diversi elementi dei leganti NHC all'attività dei complessi. La natura dei sostituenti al ponte imidazolico, la lunghezza della catena alifatica solfonata e la presenza dei gruppi benzile/benzidrilici influenzano in modo significativo il comportamento dei sistemi studiati. Il confronto dei dati sperimentali, effettuato utilizzando le strutture più semplici come riferimenti interni, ha permesso di evidenziare correlazioni rilevanti tra modifiche strutturali e risposta dei complessi nelle attività testate. Le osservazioni ottenute suggeriscono, infine, possibili strategie di ottimizzazione per la progettazione di complessi più efficienti, sia in ambito catalitico che farmacologico.

Abstract

This doctoral project focuses on the synthesis of new organometallic silver(I) and gold(I) complexes stabilized by alkylsulfonated N-heterocyclic carbene (NHC) ligands, specifically functionalized to clarify how the nature of the substituents influences the structural and applicational properties of the resulting systems. The work comprises an initial phase dedicated to the synthesis and characterization of these new structures through spectroscopic and mass spectrometric techniques (NMR, FT-IR, MALDI-MS), followed by an evaluation of their catalytic and cytotoxic potential. For the synthesis of coordinating ligands for central metals, 4,5-disubstituted imidazoles bearing various functional groups on the ring backbone were employed. The nitrogen atoms were asymmetrically functionalized: the N1 position was derivatized with benzyl or benzhydryl groups, while the N3 position was alkylated with propane- and butane-sulfonic chains.

The resulting zwitterionic salts were used as precursors for N-heterocyclic carbenes. The latter were initially employed in complexation with silver(I) and subsequently converted into the corresponding gold(I) complexes via a transmetallation reaction. The novel salts and complexes were isolated, characterized, and further evaluated for catalytic and pharmacological applications.

Catalytic investigations focused on three transformations: the synthesis of propiolic acid derivatives via CO₂ carboxylation of terminal alkynes, the cyclization of propargylamines to form oxazolidinones, and the A³-coupling reaction (Amine–Alkyne–Aldehyde), the latter providing the most significant results. After a preliminary solvent screening, two challenging substrates, benzaldehyde and paraformaldehyde, were evaluated. Paraformaldehyde, a polyacetal derived from formaldehyde, exhibited particularly noteworthy catalytic behavior. Under the optimized conditions, the polymeric substrate participated in the reaction only in the presence of Ag(I)/Au(I)-NHC complexes, showing activity even at room temperature. Data analysis revealed a superior performance of the gold(I) complexes, with two structures achieving conversions up to 80% after 16 hours at room temperature.

Following the catalytic studies, a preliminary evaluation of the cytotoxic activity of selected complexes and salts was carried out against two breast cancer cell lines, MCF-7 and MDA-MB-231, with comparison to the healthy MCF-10A line. The analyses were performed by the research group led by Prof. Maria Stefania Sinicropi at the University of Calabria, using the MTT assay to determine IC₅₀ values (μM) after 72 hours of exposure. The tests revealed no significant activity for the Au(I)-NHC complexes or the zwitterionic salts, whereas the Ag(I)-NHC complexes displayed marked cytotoxicity and promising results on both cancer cell lines. This behavior highlights a clear metal-dependent trend favoring silver and underscores the importance of metal coordination to the N-heterocyclic framework

for biological activity. Comparative structural analysis allowed the contribution of different NHC ligand elements to be delineated. The nature of the substituents on the imidazole backbone, the length of the aliphatic sulfonated chain, and the presence of benzyl/benzhydryl groups significantly influenced the behavior of the studied systems. The experimental data, interpreted using the simplest structures as internal references, revealed meaningful correlations between structural modifications and the response of the complexes in the tested activities. Overall, the observations suggest potential optimization strategies for designing more efficient complexes for both catalytic and pharmacological applications.

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Introduction – Come forth from the cosmos

If I had to introduce someone to what gold and silver truly are, the first thing I would say is that they are star-born metals.

When our solar system was still a drifting powder keg, a fraction of this cloudy maelstrom was composed of the remnants of gargantuan clusters of merged binary neutron stars or from supernovae, which exploded in a galactic scream and spread silently toward us from the deep void. Into this portion of outer space, which was bombastic, scorching, and terrifying, quietly came gold and silver, the two noble metals that stood witness to the birth of the planet we humans would one day call Earth^[1-3]. Bestowed upon us by the heavens, these two elements have shaped human existence since the earliest stirrings of our kind. Extracted and worked with immense effort^[4], they have long shimmered upon our skin, worn as precious ornaments or displayed as symbols of power and dominion, reminding us of the stellar glow they carry within them as a mark of their birth. And we, powerless and transient beings made of carbon and breath, cling to these metals as if their stellar fire could steady our impermanence. In adorning ourselves with their light, we indulge in the quiet vanity of seeking a durability that is not ours, a shimmer forged in stars that will outlast every trace of our species. In their brilliance, we search for a reflection of what we long to be: enduring, luminous, and untouched by time. Yet we forget that the light we borrow was born in regions older and more indifferent than our minds can grasp, even as these metals remind us of the cosmic violence that brought them into being.

Still, the true depth of gold and silver lies not only in their cosmic ancestry but in the ordered arrangement of their atoms. In their very structure, the universe left a signature: a nature so permanent, so inert, and so reluctant to yield to chemical change that their endurance is not a miracle but a hidden secret of their configuration^[5, 6]. This refusal to tarnish or decay was what captivated the ancient alchemists^[7]. To them, gold and silver were not merely metals but embodiments of perfection, purity, immortality, and cosmic harmony. They believed that by understanding these substances, by imitating their incorruptibility, they might uncover the hidden laws governing both matter and spirit. They hoped to grasp the nature of change itself: how the base becomes noble, and how the mutable approaches the immutable. Their pursuit was misguided in method yet profound in intuition, for they sensed that the secrets of these metals were bound to the deepest workings of nature. Modern chemistry, having stripped away the veils that once obscured matter, has revealed what the alchemists could only imagine. Every property is a testament to the precise arrangement of protons, neutrons, and electrons that defines each element. And yet, in uncovering their nature, we have not diminished their wonder. If anything, the realization that their beauty arises from the fundamental laws of the universe only deepens our sense of awe. Gold and silver remain what they have always been: fragments of stars, born of cosmic violence, refined by human hands, and illuminated by the quiet logic of chemistry.

And so, after this necessarily solemn and lofty prelude woven through the fabric of the universe, we return our thoughts to the ground and attempt to understand a little more about the nature of these metals, beginning, in atomic order, with silver.

Chapter 1 – Silver and gold

1.1 General properties

Primarily, silver exists as a mixture of two stable isotopes, ^{107}Ag and ^{109}Ag , occurring nearly equal proportions (51.8% and 48.2%, respectively), both of which are magnetically active. The most common oxidation states of silver are 0 and +1, although other oxidation states (+2 and +3) are also known^[8]. In its metallic form, it is stable against oxygen and water, but it tarnishes in the presence of ozone, hydrogen sulfide or sulfur in the air or water due to the formation of a black silver sulfide layer. In aqueous solutions, silver readily forms soluble Ag(I)-complexes such as $\text{Ag}(\text{NH}_3)^{2+}$ ^[9], $\text{Ag}(\text{S}_2\text{O}_3)_2^{3-}$, and $\text{Ag}(\text{CN})_2^-$ in excess of their respective ions. The outer-orbital $5s^1$ electronic configuration of silver allows it to form numerous silver(I) salts and complexes with a wide variety of counterions (halide, sulfide, nitrate, oxide, acetylide compounds, cyano-derivatives, and olefin complexes). This can be explained by noting that silver has a high reduction potential in the electrochemical series ($E^0(\text{Ag}^+/\text{Ag}) = +0.799 \text{ V}$)^[10]. In fact, unlike gold and copper, silver has the lowest first ionization energy and the highest second and third ionization energies in the group, which reflects the relative destabilization of the 5s orbital and the marked stabilization of the 4d manifold. This electronic configuration renders the +1 oxidation state predominant in silver chemistry.

Sharing the same group as copper and silver, gold's ground-state configuration is $[\text{Xe}]4f^{14}5d^{10}6s^1$, and it naturally occurs as the isotope ^{197}Au , which is magnetically active. Like silver, gold's most common oxidation states are 0, +1, and +3. More than in any other transition metal, relativistic effects play a predominant role in gold's properties and provide a theoretical framework for rationalizing its observed reactivity^[11]. Two factors, spin-orbit coupling and orbital acceleration have effects on the valence electrons of the metal that are reflected in the formation of bonds with other species and are responsible for gold's unique features^[12]. Indeed, due to the high nuclear charge of gold, the core electrons interact with the nucleus while moving at a speed close to that of light, causing an increase in relativistic electron mass with consequent effects on the orbitals of the outermost electrons. There are three major consequences of these phenomena, known as relativistic effects.

Contraction of the s and p orbitals: this effect is common to all elements as their nuclear masses increase, but it is negligible for lighter elements. For gold, however, it is particularly pronounced (Figure 1), since the 4f and 5d orbitals weakly shield the highly charged-nucleus from the 6s and 6p orbitals, and the shrinking of the 6s orbital in gold is responsible for its high electronegativity relative to other transition metals, even though the p-orbitals are less contracted than the s-orbitals^[11]. This orbital contraction is so significant that, in order to observe a comparable effect, it would be necessary

to reach the nucleus of Fermium (^{100}Fm), a synthetic element obtained only artificially^[13], among the heaviest elements observed via the neutron capture process.

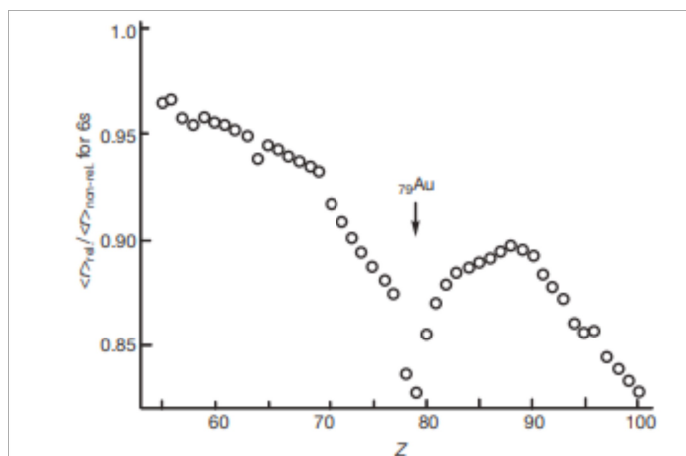


Figure 1 – Estimated 6s-orbital contraction due to relativistic effects. Smaller values correspond to a greater contraction of the orbital radius

Elimination of orbital degeneracy 5d and 6p: significant spin-orbit coupling leads to a loss of degeneracy in the 5d and 6p orbitals. In particular, this results in the hybridization of the 6s orbital with only the lowest energy 6p orbital, the $6p_{1/2}$. This is one of the factors responsible for the formation of two-coordinated linear structures in gold(I) complexes (Figure 2).

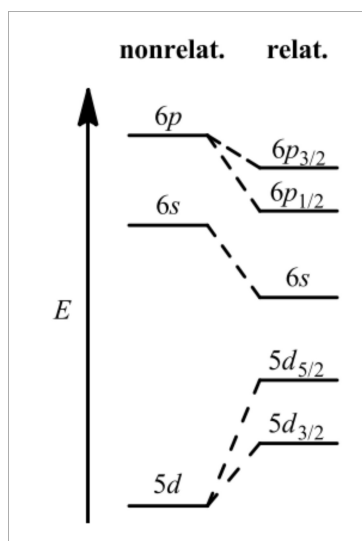


Figure 2 – Elimination of degeneracy due to increased spin-orbit coupling in gold

Diffusion of outer shells: as the s and p orbitals contract significantly, the outer 5d and 4f electrons are better shielded, consequently, they experience less nuclear attraction, leading to greater d-orbital

expansion. This effect, combined with the contraction of the 6s shell and the destabilization of the 5d shell, causes the 5d/6s gap to narrow^[14].

When present in their oxidized forms, Ag(I) and Au(I) species are extensively exploited for their ability to coordinate with and activate unsaturated substrates, thereby enhancing their reactivity in a variety of chemical transformations. It has been observed that the M(I) salts can act as a σ -Lewis acids or π -Lewis acids in homogeneous catalysis^[15-17], with a preference for σ -coordination over π -coordination due to the ready availability of empty orbitals and the relativistic contraction of the electron cloud toward σ -donor ligands such as (thio)ethers, amines, and phosphines. The d^{10} electronic configuration leads Ag(I) and Au(I) to promote interactions with most of the unsaturated systems, such as C=C, C $\equiv$ C, C=X, and C $\equiv$ X bonds (X= heteroatom). This is particularly evident with the carbon-carbon π -bond of alkynes, a property known as alkynophilicity^[18]. Besides its carbophilic character, silver(I) also displays marked oxophilicity, as it can form bonds with oxo groups. This behavior likely arises from the donation of the oxygen lone pairs into an empty orbital on silver, which may possess $d\pi$, σ^* , or π^* character^[19]. Such oxophilic character in Ag(I) has been described by analogy to gold(I)-catalyzed reactions. Moreover, the donation of the nitrogen lone pair into an empty silver orbital suppresses the nucleophilicity of nitrogen; this behavior is referred to as azaphilicity^[20]. Generally, the oxophilic and azaphilic character of silver(I) salts has been exploited in reactions such as various cycloaddition reactions, the allylation of carbonyl compounds, aldol-type reactions, Michael and Mannich reactions, and others. Another important feature of silver(I) chemistry is its affinity for halogens to form the corresponding halide salts (a property known as halogenophilicity)^[21]. In many transition-metal-catalyzed transformations, Ag(I) salts are employed to promote the precipitation of AgX (X = Cl, Br, I) from coordinatively saturated metal centers in polar protic solvents^[22].

Gold is generally less oxophilic and azaphilic than silver^[11], however, in several instances, it still shows appreciable stability when coordinating with oxygen- or nitrogen-containing groups. On the other hand, Au(I) species exhibit a higher Lewis acidity because the relativistic contraction and stabilization of the 6s and 6p orbitals lower the alkyne LUMO (Lowest Unoccupied Molecular Orbital) energy, thereby increasing gold's propensity for nucleophilic addition. Gold's higher electronegativity (2.4 compared to 1.9 for silver) also enhances its Lewis acidity when a coordination site is available. Importantly, this higher electronegativity is itself a consequence of relativistic orbital contraction; thus, relativistic effects both explain and underpin the electronegativity argument. These features explain why Au(I) catalysts excel in reactions involving alkyne and alkene activation, where strong π -polarization is required^[11]. The pronounced Lewis acidity of Au(I) species, combined with their

capacity to stabilize cationic intermediates, gives rise to a distinctive reactivity that has been widely exploited in the development of new synthetic methodologies^[23].

Generally, the bonding of transition metal complexes with π -ligands is explained on the basis of the Dewar–Chatt–Duncanson (DCD) model^[24], which describes the bond as a donor–acceptor interaction between two closed-shell fragments since the coordination character of chemical bonding is far more significant for transition metals than for main-group elements^[25]. Although this model is typically used to describe the interaction between metal centers and unsaturated ligands, this framework can also be applied to unsaturated substrates that, formally, do not act as ligands toward the metal in the complex. The bonding between these metals and an alkyne substrate is the result of a synergistic interaction of two contributions, according to the DCD model (Figure 3): one of the σ -type, resulting from the superposition of the π -orbital parallel to the main axis of the alkyne and the empty d_{z^2} -orbital of the metal, and the other of the π -type, between an occupied d_{xz} orbital of the metal which, via back-donation (retro-donation), transfers electron density to the alkyne LUMO (an antibonding π^* -orbital). During the formation of the bond between the metal center and the alkyne, there is a stretching of the C-C bond caused by the σ L→M bond, which reduces the electron density at the alkyne and redistributes it over the metal. There is also the contribution of the electron charge transferred from the metal to the π^* -orbitals of the alkyne, which causes a partial bending of the alkyne as the hybridization is slightly altered. For these reasons, alkynes can be regarded as either 2- or 4-electron donors, depending on the type of interaction they establish with the metal center.

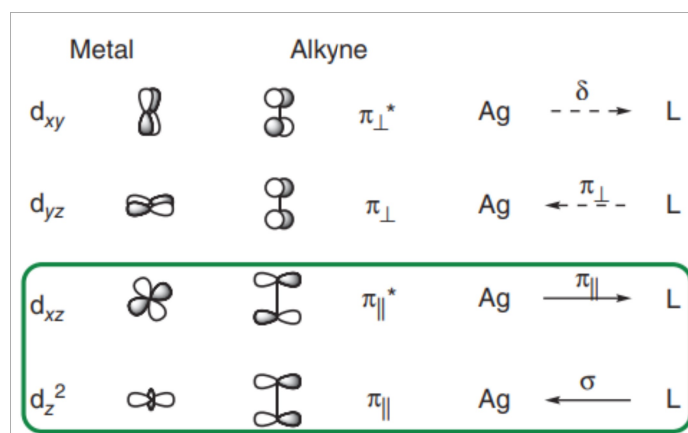
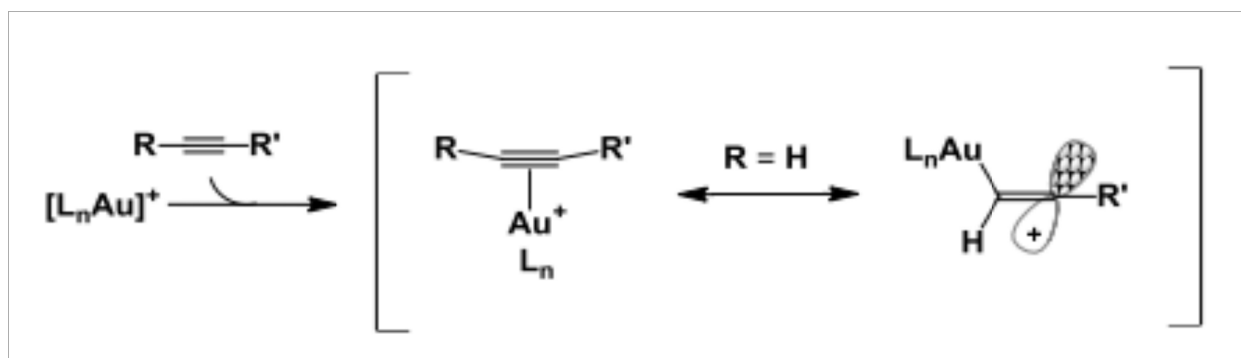


Figure 3 – Orbitals involved in the M–CC interactions according to the DCD model

As becomes clear from these considerations, in practical applications the activation of alkynes requires the presence of the cationic active species $L-M(I)^+$. The low back-donation of π electrons from the metal to the unsaturated substrate is an important factor governing the interaction between Au(I) complexes and π -systems. Barysz and Pyykkö demonstrated that Au–CO and Au–C $\equiv$ C complexes

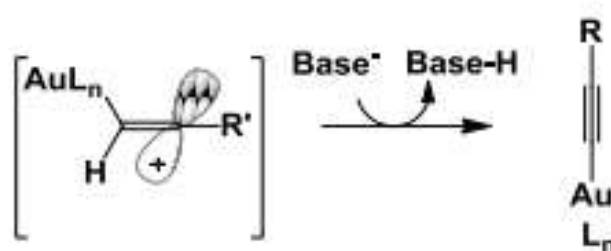
exhibit almost no π -back-donation compared to analogous coinage-metal complexes, highlighting the limited ability of gold to donate electron density into antibonding π^* orbitals^[26-28]. This behavior, however, is altered in the presence of strong σ -donor ligands such as $[\text{R}_3\text{P}-\text{M}]^+$ and $[\text{NHC}-\text{M}]^+$, which enhance electron density at the metal center and can partially increase the extent of back-donation^[29, 30]. The key step is the interaction between the metal center and the π -orbitals of the alkyne that lie perpendicular to the molecular axis. Through a dihapto (η^2) coordination, a π -interaction then results from the back-donation of electron density from filled metal d-orbitals into an antibonding π^* orbital of the alkyne. As a result, an elongation of the triple bond (trans-bending) or double bond (pyramidalization) is observed as a measure of the net shift of electron density from the bonding π orbital into the antibonding π^* orbitals. Therefore, the degree of distortion from the geometry of the unbound ligand may serve as an indication of the degree of back-bonding^[27, 28], generating a polarized M-alkyne complex in which the unsaturated bond becomes more electrophilic and thus more susceptible to nucleophilic attack (Scheme 1).



Scheme 1 – Activation of the unsaturated substrate and formation of the intermediate

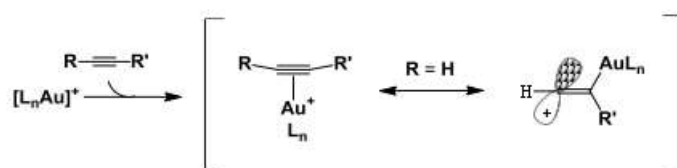
The resulting activated intermediate can undergo various pathways. One possibility is its trapping by an electrophile, in which a deargentation or deauration step occurs and the carbon–metal bond is replaced by a carbon–electrophile bond. When the electrophile is a proton, this process is referred to as protodeargentation or protodeauration^[31]. If the substrate is a terminal alkyne, the increase in the acidity of the alkynyl proton favors deprotonation in the presence of a base to form an acetylide (Scheme 2). In contrast to silver, it seems that gold is more likely to activate the unsaturated bond than to form a stable metal acetylide^[32]. Alternatively, because the nd electrons can delocalize into the non-bonding orbital of a carbocation, the metallic intermediate can undergo another type of trapping by an external nucleophile. In this case, nucleophilic attack occurs at the β -position relative to the metal, generating a new metallic intermediate through back-donation. This species can be represented by two mesomeric forms: a metal-stabilized carbocation and a metal carbene^[33].

Depending on their nature, the newly formed intermediates can then react following either carbocation-like or carbene-like pathways.

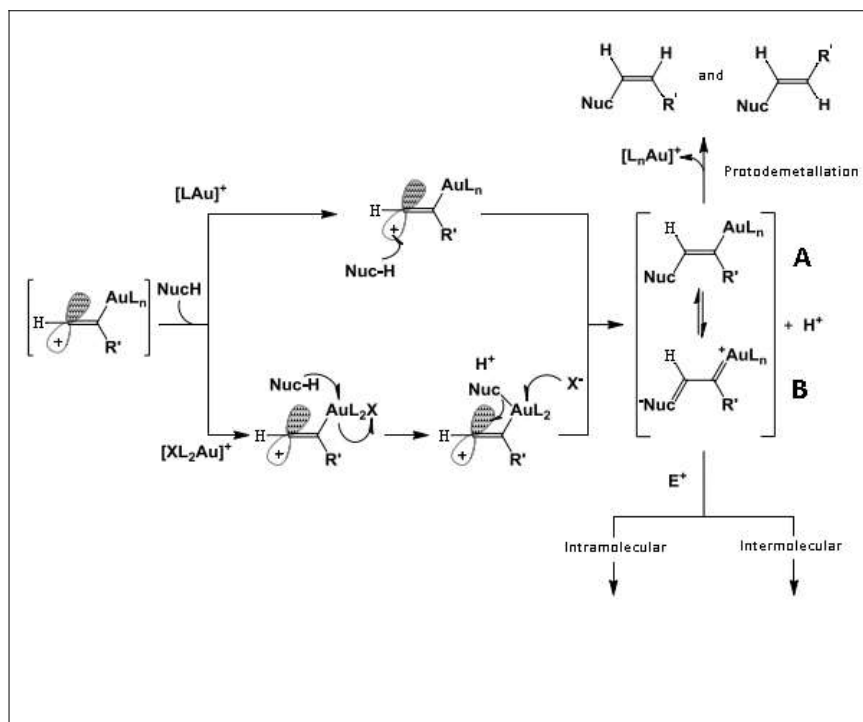


Scheme 2 – Formation of the metal acetylide

In the absence of a base or a terminal alkyne, a vinyl cation is generated (Scheme 3), which undergoes nucleophilic attack to yield a carbenoid intermediate (Scheme 4). This intermediate then evolve into intermediates A or B. Intermediate A is converted into the product following protodeauration or protodeargentation, while intermediate B may undergo further electrophilic attack.



Scheme 3 – Formation of the vinyl-cation intermediate



Scheme 4 – Evolution of the intermediates

Gold carbenoid intermediates are more common than silver ones, a behavior attributed to the relativistic expansion and shielding of the Au 5d orbitals^[34]. Although the 5d electrons lie too deep in energy to engage in strong back-bonding with antibonding orbitals, they can delocalize into lower-energy, empty nonbonding p orbitals, thereby enhancing carbenoid reactivity^[35]. The balance between the carbenoid and simple cationic character at the carbon adjacent to the metal remains structure-dependent.

The crucial advantage of these M(I) species is that the electrophilic activation of alkynes exhibiting cationic character proceeds even in the presence of strongly σ -donating ligands. This is a major benefit, as it allows the reactivity of the metal center to be finely tuned through coordination to appropriately designed ligands, enhancing not only catalytic efficiency but also improving resistance to degradative pathways. Among the various ligand classes employed with these metals, N-heterocyclic carbenes (NHCs) stand out as particularly effective. Their electronic properties and impact on the reactivity of M(I) complexes will be discussed in the next section.

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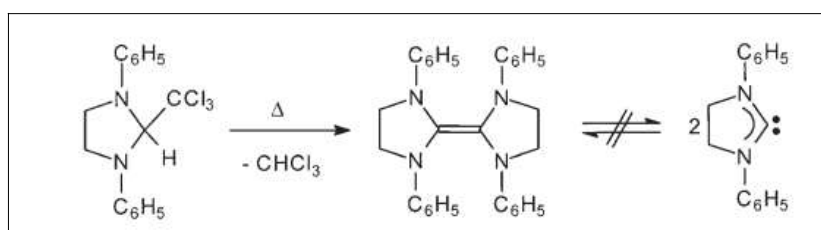
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Chapter 2 – Historical background

2.1. A brief historical perspective on NHC ligands

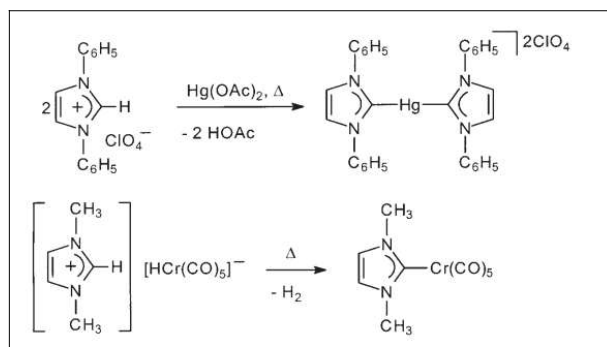
N-Heterocyclic carbenes (NHCs) are cyclic molecules that contain at least one nitrogen atom, typically positioned α to a divalent carbon center possessing six valence electrons instead of the usual eight. This broad definition encompasses several families of NHC ligands, which differ in ring size, connectivity, and the number, type and nature of the heteroatoms involved^[1, 2].

Historically, the first stable carbene to be synthesized and fully characterized was reported in 1959 by Herzberg and Shoosmith, who identified methylene^[3]. Subsequent work by Wanzlick and Öfele sought to access more structurally elaborate and isolable carbene species. They observed that coordination to transition metals enabled these species to adopt architectures that could be stabilized, bearing diverse functional groups and overcoming the limitations of simple methylene analogues. Initially, Wanzlick focused on isolating an N-heterocyclic carbene stable under ambient conditions by attempting an α -elimination from a chlorinated imidazolidin-2-ylidene precursor. Instead, the reaction afforded a dimeric product, the corresponding diaminodimer (Scheme 1)^[4]. This outcome led him to propose, and later demonstrate, that the properties of such carbenes can be modulated by the substituents on the nitrogen atoms adjacent to the carbene center^[5].



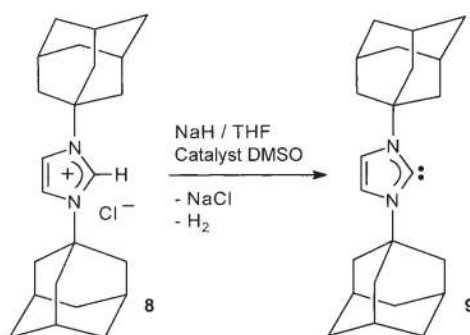
Scheme 1 – Synthetic route to entetramine through α -elimination step

Later, Wanzlick synthesized the first organometallic complex incorporating an imidazol-2-ylidene unit as an N-heterocyclic carbene ligand by reacting 1,3-diphenylimidazolium perchlorate with mercury(II) acetate^[6]. Independently, Öfele successfully obtained a chromium complex by subjecting the dimethylimidazolium hydropentacarbonylchromate(0) salt to vacuum thermolysis^[7] (Scheme 2).



Scheme 2 – M-NHC complexes obtained by Wanzlick (top) and Ofele (bottom)

Although the isolation of free carbenes initially proved elusive, it was observed that they could be generated *in situ* by deprotonating of the corresponding imidazolium salt, a process promoted by bases (such as acetate AcO^- or hydride H^-) acting on the proton at the C_2 position. Lappert and colleagues subsequently extended this line of research by investigating N-heterocyclic carbene complexes prepared from electron-rich olefins^[8, 9]. It was not until 1991 that Arduengo and co-workers succeeded in synthesizing and characterizing a stable N-heterocyclic carbene (Scheme 3). They initially attributed its stability to the steric protection provided by the adamantyl substituents on the nitrogen atoms, whose bulk prevented the carbene centers from undergoing dimerization, thereby allowing the free carbene to remain stable under ambient conditions^[10]. Until 1995, the presence of a backbone $\text{C}=\text{C}$ double bond in the imidazol-2-ylidene ring was considered a necessary structural feature for the stability of free NHCs. This paradigm was overturned by a later milestone from Arduengo: the isolation of the first NHC featuring a saturated imidazolin-2-ylidene ring^[11].



Scheme 3 – First NHC stable achieved by Arduengo

Given these premises, it is understandable why interest in this class of ligands surged as researchers sought new synthetic routes to novel NHC frameworks and their coordination to various metal centers. In many cases, NHCs proved capable of surpassing long-established donor groups, such as phosphines^[12, 13]. A notable example is the replacement of phosphine ligands with NHCs in the development of second-generation Grubbs catalysts for olefin metathesis, where NHC incorporation enhanced catalytic activity toward olefinic substrates^[14].

2.2. Structural and electronic properties of imidazolylidene N-heterocyclic carbene ligands

The adoption of N-heterocyclic carbenes as ligands has stimulated extensive interest in identifying the structural and electronic factors that govern their observed reactivity^[15, 16]. Central to this inquiry is the carbene center itself, whose electronic character is shaped by multiple factors. The carbene carbon is sp^2 -hybridized, and its valence electrons may occupy four distinct electronic arrangements (Figure 1), distributed between two localized orbitals conventionally labeled $P\sigma$ and $P\pi$, respectively, the free sp^2 hybrid orbital and the unhybridized C_{2p} orbital. Among the accessible states, the triplet 3B_1 ($\sigma^1 p\pi^1$) and the singlet 1A_1 (σ^2) lie close in energy under standard conditions, which can impart either diradical (3B_1 and 1B_1) or ambiphilic (1A_1) character to the carbene center^[16].

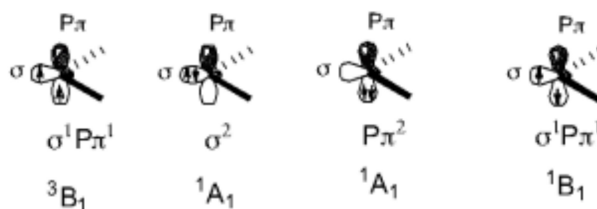


Figure 1 – Possible electronic configurations of the carbene

In the 1A_1 configuration, both electrons occupy the $P\sigma$ orbital and consequently experience intense Coulombic repulsion, an energetically unfavorable contribution that is absent in the triplet state. Conversely, the $P\sigma$ orbital is a sp^2 hybrid containing a $1/3$ s-character component, which stabilizes electrons more effectively than the pure p-type $P\pi$ orbital. The resulting energy gap between the two configurations can therefore be viewed as the promotion energy associated with elevating an electron from a highly stabilized hybrid orbital to a higher-energy $2p$ orbital, counterbalanced by the reduced electron–electron repulsion in the triplet^[17]. Because these effects compete, the resulting ground-state multiplicity is not straightforward^[18].

It is proven that the magnitude of the $P\sigma$ – $P\pi$ energy gap determines the preferred electronic configuration: the greater the stabilization of $P\sigma$ relative to $P\pi$, the stronger the tendency to adopt the singlet state 1A_1 (σ^2) and, consequently, the greater the propensity of the NHC to be a persistent carbene. This singlet configuration is particularly important because it yields a lone pair that can act as a donor toward electron-accepting centers, for example in coordination to transition metals in organometallic complexes. The energy gap between 1A_1 (σ^2) and 3B_1 ($\sigma^1 p\pi^1$), commonly denoted as ΔE_{s-t} , is therefore controlled by any factor that stabilizes or destabilizes the $P\sigma$ and $P\pi$ states. Although

it is difficult to decompose all contributions to carbene stability into distinct terms, several structural elements are recognized as key modulators of ΔE_{s-t} .

Above all, heteroatoms bonded to the carbene carbon exert a direct influence on the prevailing electronic configuration. In imidazolylidene NHCs the 2p orbitals of the two adjacent nitrogen atoms overlap favorably with the carbene's $P\pi$ orbital, whereas interaction with the $P\sigma$ orbital, which lies out of the imidazole plane, is less effective^[19]. Because the two nitrogens act as π donors toward the $P\pi$ orbital via mesomeric resonance¹, increased electron donation raises the energy of the carbon 2p orbital, making the orbital population required for a triplet rearrangement energetically less accessible^[20] (Figure 2).

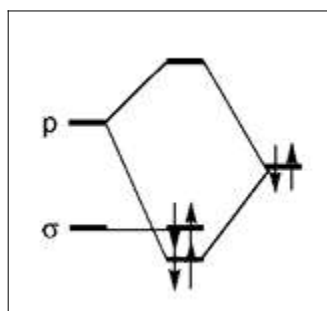


Figure 2 – Qualitative difference between the orbitals of the carbene with an N-substituted heteroatom

Additionally, the carbene carbon's electron density is altered by σ -interactions through the bonding sp^2 orbitals to the flanking nitrogen atoms, an inductive effect² that redistributes hybridization contributions and increases the s-character of the $P\sigma$ orbital. This enhanced s-character further stabilizes $P\sigma$ relative to the carbon 2p orbital, thereby enlarging ΔE_{s-t} and favoring the retention of the 1A_1 (σ^2) configuration^[35]. Structurally, these conditions are most favorable when the N–C–N angle is below approximately 100.2° ³, which facilitates formation of a three-center, four-electron π system in which the N–C bonds acquire partial multiple-bond character^[21-23]. Variations in the N–C–N angle primarily affect the HOMO energy because they alter the hybridization at the carbene carbon, thereby changing the σ - and π -bonding character of the C–N interactions. As the N–C–N angle deviates from the ideal sp^2 geometry, the hybrid orbital at carbon acquires greater p character and reduced s character.

1 IUPAC definition - <https://doi.org/10.1351/goldbook.M03844>

2 IUPAC definition- <https://doi.org/10.1351/goldbook.M03844>

3 This geometric value differs from the ideal 108° angle of a regular pentagon. Experimentally, the N–C–N angle in NHC ligands typically falls around 100.2° , which is also the reference value observed for imidazole in the case of imidazolinic ligands

This increases the p-like contribution to the HOMO, typically lowering its energy, which in turn increases ΔE_{s-t} ^[21].

Through conjugation across the N–C–N framework, substituents at the N1 and N3 positions (N–R groups) modulate the carbene's electronic nature^[24-26] primarily via their mesomeric and inductive effects on σ - and π -electron density^[27-30].

A similar rationale applies to substituents at the C4 and C5 positions of the imidazole ring. Although these positions are remote from the carbene center, their participation in the imidazole π system produces mesomeric stabilization and, simultaneously, inductive effects; in several cases these substituents have been shown to exert a measurable influence on ΔE_{s-t} . Furthermore, they can also mediate the arrangement and stability of interactions with counterions in coordinated structures^[31].

Ring aromaticity in imidazolylidene systems also requires careful qualification. Free carbene structures display only partial aromatic character: they are not perfectly planar, and their bond angles and lengths deviate from those expected for a fully aromatic ring. The key question is how charge delocalization across the ring affects carbene stability. A decisive structural element is the presence of a C4=C5 double bond. When the ring is unsaturated at C4–C5, the π system can extend from the three-center N–C–N fragment to the entire heterocycle, increasing the delocalization of the π charge. This extended conjugation does not act directly on the carbene lone pair but instead homogenizes bond character across the ring and increases orbital mixing. Consequently, the molecular geometry adapts to maximize these interactions. The net effect is an indirect stabilization of the carbene center: the optimal cyclic arrangement for N–C–N interaction is preserved and reinforced by the extended π network, which reduces the tendency to dimerize or to undergo facile protonation. This conjugation is also relevant for π -type interactions with metal centers, as a more delocalized ring can participate more effectively in back-bonding and ancillary π -acceptor/ π -donor contributions. By contrast, saturated cyclic carbenes (which lack the C4=C5 double bond) are generally less resistant to dimerization and protonation under comparable substitution patterns. Nevertheless, aromaticity itself is not the primary determinant of structural stability, since non-aromatic cyclic carbenes are known to be isolable. Instead, aromaticity contributes more significantly to the nucleophilicity of the carbene than to its intrinsic thermodynamic stability^[36].

Steric factors associated with the N-substituents are equally important. The size and spatial arrangement of N–R groups control the accessibility of the carbene center, reducing its propensity to dimerize or to react with other species, and shaping the steric environment encountered by metal centers upon coordination.

When coordination allows for metal→ligand back-donation, the carbene's carbon 2p orbital participates in π -type molecular orbitals that can interact, by symmetry, with occupied metal d orbitals.

The extent of back-donation therefore, affects ligand orientation around the metal and can induce anisotropic spatial arrangements as the coordination sphere reorganizes to accommodate bulky substituents. This steric reorganization, in turn, modulates the reactivity of the complex. For these reasons, many imidazolylidene NHCs are described as adopting “cap” or helical binding motifs (Figure 3).

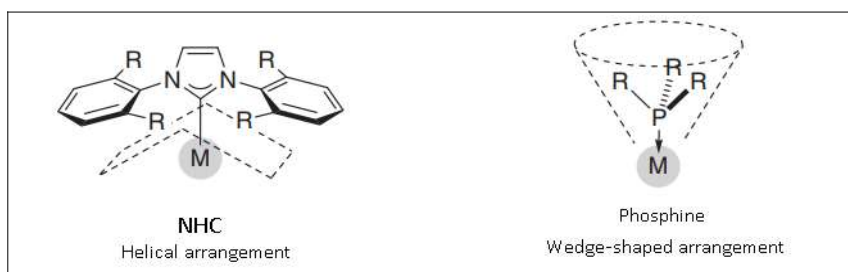


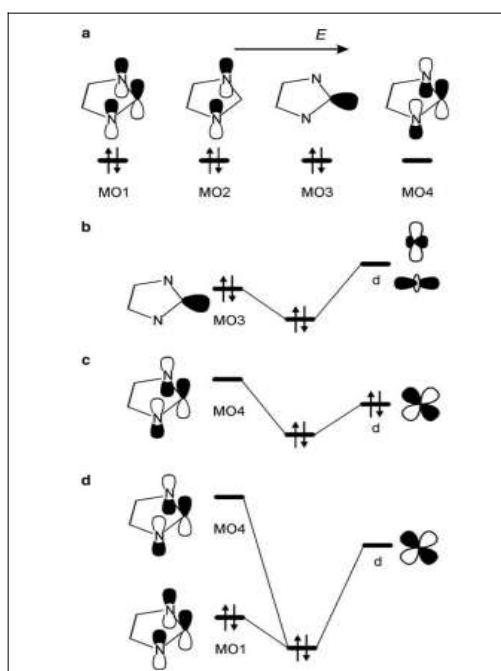
Figure 3 – Spatial arrangement of NHC ligands

Importantly, steric contributions to NHC stability and behavior are largely independent of purely electronic effects, permitting versatile functionalization: bulky groups can be introduced to impose a desired steric environment without necessarily compromising the electronic functionalities that are important for the complex’s activity and coordination properties. This distinction represents the principal difference from phosphine ligands, which possess two orthogonal lone-pair orbitals that can engage in back-donation with the coordinated metal and thus accommodate less geometrically restrictive, more isotropic binding arrangements^[32-34]. Having discussed NHC ligands and their properties, we can now examine how they coordinate to the metals introduced earlier, in the next paragraph.

2.3 Silver Ag(I)- and gold Au(I)-NHC complexes

Coordination in organometallic complexes is governed by a multifactorial energetic balance that compels ligands to adopt arrangements that minimize the total electronic and steric energy of the system. Ligand disposition, therefore reflects the optimization of electron distribution, orbital overlap, and the interplay of electrostatic and covalent interactions between the central metal and its coordinating partners. For Ag(I) and Au(I) species, the electronic structure can be described as effective d^{10} complexes following removal of an ns electron. This nearly filled valence configuration constrains the availability of low-lying acceptor orbitals and modulates the metals' Lewis acidity. As a consequence, these monovalent coinage-metal centers exhibit a limited propensity to accommodate multiple donor ligands, favoring low coordination numbers, predominantly two-giving rise to largely linear or only slightly bent geometries^[37]. The principal coordination interactions in these systems can be described as two complementary processes: σ -donation from the ligand to the metal ($L \rightarrow M$) and π -backdonation from the metal to the ligand ($M \rightarrow L$). While N-heterocyclic carbenes were long treated experimentally as strong σ -donors, similar to phosphines, but subsequent theoretical and spectroscopic investigations have established that π -type interactions are also feasible^[38].

For imidazole-based N-heterocyclic carbenes, the nature of the orbitals participating in organometallic coordination is depicted in Scheme 1.



Scheme 1 – Main interactions between the NHC molecular orbitals and the metal. Top: relative increasing order of the orbital energies

In coinage NHC-M(I) complexes, the molecular orbital picture relevant to metal–carbene bonding shows that the ligand lone pair resides in an orbital with substantial $p\sigma$ character (denoted here as MO3), which overlaps with a metal hybrid orbital formed from the filled ndz^2 and the vacant $(n+1)s$ orbital. The preference for the involvement of the metal d_{z^2} component arises from its superior directionality for axial bonding. Formally, the d^{10} configuration occupies the dz^2 orbital as occupied, which would normally prevent interaction with a singlet carbene lone pair. However, hybridization with the empty $(n+1)s$ -orbital redistributes charge and reduces Coulomb repulsion, facilitating carbene binding. This mechanism enables coordination while leaving the overall interaction largely ionic in character, with a smaller but non-negligible covalent stabilizing contribution^[39–41].

Within the coinage-metal series, computed and experimental metrics consistently indicate increasing M–NHC bond strength in the order $Ag < Cu < Au$. This trend persists across both heteroleptic NHC–M–Cl species and homoleptic $[NHC–M–NHC]^+$ complexes. For heteroleptic NHC–M(I)–Cl complexes, energy decomposition analyses attribute the dominant bonding contribution to σ donation, with π back-donation providing a smaller energetic component. Among the three metals, gold often shows a relatively larger energetic contribution from π -type back-donation due to relativistic effects that cause diffusion of d and f orbitals because of the contraction of s and p orbitals^[42]. The Ag–C_{Carbene} bond in Ag–NHC complexes, due to the much weaker π -backdonation ability of silver, is weaker than that of most other transition metal–NHC complexes. These properties of Ag–NHC complexes endow them with the potential to be used as transmetalation reagents in the synthesis of other metal–NHC complexes. In contrast, bis-carbene complexes display an almost exclusively σ -dominated coordination, a feature that rationalizes the experimentally observed facile rotation of NHC ligands about the metal–carbon bond axis^[39, 40, 35]. Even if π -interactions are weak, the σ -component in these d^{10} complexes still dominates, although the metal centers can still exhibit significant Lewis π -acidity^[43].

2.4 Historical background and synthetic approaches to Ag(I)– and Au(I)-NHC complexes

Arduengo et al. used free NHCs and AgOTf as starting materials to synthesize and isolate Ag(I)-NHC complexes for the first time^[44]. However, free NHCs are highly sensitive to air, humidity, and temperature, limiting their application. To overcome these disadvantages, researchers use alkaline-silver reagents to coordinate the imidazolium salts *in situ*. In 1998, the Lin group reported that, unexpectedly, a mixture of imidazolium salts and Ag₂O can generate stable Ag(I)–NHC complexes, with Ag₂O functioning as a mild base^[45]. Furthermore, the same group discovered that Ag–NHC complexes undergo transmetalation with gold and palladium complexes to furnish Au–NHC and Pd–NHC derivatives, demonstrating the potential of Ag–NHCs as transmetalation agents. Subsequently, Youngs's group showed that Ag–NHC complexes can act as antibacterial agents by releasing silver species slowly, thereby avoiding the reduced efficacy and skin damage associated the aggregation of simple silver salts^[46]. Finally, Fernández and co-workers reported the first application of Ag–NHC complexes as catalysts in organic synthesis^[47].

One of the most commonly employed methods involves the generation of the free carbene through deprotonation of the imidazolium precursor, which is then reacted with a suitable metal precursor to afford the corresponding complex. This methodology was historically the first to be reported, dating back to the isolation of the earliest stable N-heterocyclic carbene structures.

The main limitation of this approach lies in the need to employ carbene ligands that are isolable or sufficiently persistent under the experimental conditions to be used directly in synthesis. An alternative strategy consists of generating the organometallic complex *in situ* through deprotonation of the corresponding imidazolium salt precursor, thereby avoiding the isolation of the free carbene, either through the use of a base together with a metal precursor, by employing a metal salt whose counterion can act as a base to produce the carbene^[48] or by using silver oxide, which exhibits basic behavior while simultaneously providing the coordinating metal, as in the case of Ag₂O. This latter method is particularly suitable for the preparation of silver complexes, in which coordination is achieved using silver oxide whose oxide functions as a weak base^[45]. This method circumvents the need for inert reaction conditions, prevents the dimerization and other undesired reactions that free carbenes may undergo under the operative conditions, requires no strong base, can be performed in air at room temperature. Furthermore, it obviates solvent purification, affords selective metallation at the C2 position of the imidazolium precursor and preserves chirality^[49].

The observed efficiency of the Ag₂O method appears to correlate with the acidity and steric environment of the azolium salts, and the nucleophilicity of the NHCs^[50]. Reported data indicate that Ag₂O reacts preferentially with halide imidazolium salts compared with salts of weakly coordinating anions such as BF₄⁻ and PF₆⁻^[51], which is consistent with stronger hydrogen bonding of the C2 proton to halides and thus higher acidity^[52]. Electron-withdrawing substituents at the C4,5 positions of the imidazolium ring increase the acidity of the C2 proton and thus enhance reactivity with Ag₂O^[53, 54]. The greater the electron-withdrawing ability of the C4,5 substituents, the more acidic the C2 proton becomes^[55]. Finally, increased steric bulk around the azolium cation reduces the efficiency of the Ag₂O route, often necessitating higher temperatures, longer reaction times, or both^[48, 56, 57].

When employing these conditions for the Ag₂O-mediated metallation of NHC precursors, it is essential to consider that both substrate sensitivity and reaction parameters can strongly influence the final outcome. Extended exposure of N,N'-dialkyl imidazolium halides to more than one equivalent of Ag₂O may lead to the development of a yellow coloration in the reaction mixture. This discoloration has been attributed to the formation of Ag nanoparticles (Nps) and can typically be removed by treatment with activated carbon^[57]. In some cases, the reaction vessel can be coated with a brown powdery solid and silver mirror. This degradative process has been attributed to the formation of carbene dimers such as bisimidazolidines^[58]. Due to its super-electron-donor properties, this carbene dimer may reduce the Ag(I) ion to Ag NPs protected by imidazolium or NHCs.

Reactions of imidazolium salts with Ag₂O typically yield either neutral complexes of the type [Ag(NHC)X] or ionic [Ag(NHC)₂][AgX₂]^[59]. It has been proposed that these forms interconvert in solution through a dynamic equilibrium^[45, 59, 60]. The predominance of either the neutral or the ionic form is largely governed by the steric bulk of the NHC and the polarity of the solvent, with bulkier NHCs and less polar media generally favoring the neutral heteroleptic monomer^[61]. In many cases, the formation of Ag(I)-NHCs is accompanied by the precipitation of AgX, which leads to the isolation of non-stoichiometric [Ag(NHC)₂][(AgX₂)_n/X_{1-n}]. This complication can be mitigated by performing anion metathesis to introduce weakly coordinating anions (e.g., BF₄⁻, PF₆⁻, B(Ph)₄⁻, NO₃⁻) to generate pure [Ag(NHC)₂]⁺ salts. In some instances, however, extended reaction times lead to complete AgX precipitation and the formation of three-coordinate species of the type [(Ag(NHC)₂)X]^[62]. One limitation of silver oxides is their susceptibility to redox processes upon exposure to oxidizing or reducing agents or light. An alternative approach employs Tollens' reagent, using the [NH₃-Ag(I)-NH₃]⁺ X⁻ species as the silver precursor. This allows complexation to be carried out in polar protic solvents, including water. The principal disadvantage is that the method requires basic conditions, rendering it unsuitable for substrates that are unstable in alkaline aqueous media, containing oxidation-sensitive functional groups, and/or pH basic susceptible^[63].

NHC–Au(I) chemistry developed through a series of key discoveries that gradually established these complexes as stable, versatile, and catalytically powerful species. The first NHC–Au(I) complexes were introduced by Fehlhhammer, who obtained them through the cyclization of isocyanide ligands^[64]. Shortly afterward, Burini unexpectedly isolated a benzimidazole-based carbene coordinated to gold, marking the first structurally characterized NHC–Au(I) complex^[65]. Raubenheimer expanded the field by coordinating N-alkylated NHC ligands^[66], while Lin introduced AuSMe₂Cl as an efficient metal precursor, enabling the synthesis of NHC–Au(I) complexes via transmetalation^[45]. The catalytic potential of Au(I)–NHC complexes became evident when Herrmann’s group demonstrated their activity in the hydration of 3-hexyne^[67]. This marked the first use of NHC–Au(I) complexes as homogeneous catalysts. In 2004, Berners-Price, Baker, and co-workers reported the antimicrobial properties of Au(I)–NHCs^[68], while Çetinkaya’s group explored their antimicrobial activity^[69], highlighting the versatility of these complexes in the biological field.

NHC–Au(I) complexes are commonly obtained by transmetalation from NHC–Ag(I) species, a strategy that provides reliable access to a wide range of gold carbene complexes. Recently, however, new methods have been developed that allow direct coordination of gold to imidazolium salts under mild conditions, avoiding the need for silver intermediates^[70–72]. These approaches improve functional-group tolerance, reduce waste associated with silver salts, and simplify the overall synthetic workflow. NHC–Ag(I)–X complexes are characterized by a relatively labile coordination sphere, which facilitates ligand substitution and is often exploited in catalytic applications. In contrast, Au(I) complexes often require the deliberate abstraction of a coordinating ligand to generate the cationic species [AuL]⁺, commonly referred to as “naked gold complexes”, even if no structural proof exists that these structures are stable, isolable entities. In practice, NHC–Au–Cl complexes are widely used because of their stability and synthetic accessibility, and they are typically activated *in situ* by chloride abstraction from [LAuCl] upon treatment with a silver salt bearing a weakly coordinating anion, introducing a counterion which may show a significant impact on catalysis^[73]. Beyond halides, the literature also reports complexes featuring carboxylate, sulfonate, and triflimide anions, as well as weakly coordinating counterions such as SbF₆[−], PF₆[−], and BF₄[−], although these latter species often lack sufficient stability to yield well-defined structures. It is important to note that when the catalytically active species are generated *in situ* by chloride abstraction from [LAuCl] in the absence of an alkyne or other unsaturated substrate, significantly less reactive chloride-bridged dinuclear complexes [LAuClAuL]Y may form^[74]. The formation of these dinuclear species has been proposed to account, at least in part, for the erratic outcomes commonly referred to as “silver effects” in reactions where Ag(I)

salts are used to activate neutral gold(I) complexes $[\text{LAuY}]^{[75]}$. Practical limitations of silver salts include their costliness, inadequate solubility in some organic solvents, light and moisture sensitivity, and a propensity for reduction to metallic silver. Their hygroscopicity can introduce water that promotes alkyne hydration or hydrolysis. Water reacts with Au(I) complexes to form dinuclear oxonium species $[(\text{LAu})_2\text{OH}]\text{X}$ or triaurated oxonium salts $[(\text{LAu})_3\text{O}]\text{X}^{[76]}$, which act as catalytic reservoirs of $[\text{LAu}]^+$ fragments^[77]. When working at scale, the formation of precipitates with poor filtration properties can hamper work-up, and the presence of two coinage metals in the waste makes recycling more difficult^[78]. Instead, at least on small scale, the practice of filtering the reaction mixture through Celite to remove the precipitated AgCl is common, although controversial. Indeed, elemental analysis of the filtrate revealed that Celite filtration does not remove all traces of silver unless enough time has been allowed for AgCl precipitation, despite the fact that XPS analysis suggests the contrary^[75]. In some cases, the cationic catalyst can be poisoned by impurities with high affinity for gold (bases, halides) present in the Celite^[79] or by adventitious water resulting in the formation of complexes of the type $[\text{LAu}(\text{H}_2\text{O})]\text{X}^{[74]}$. Finally, it is worth noting that, given the metallophilic interactions between Ag and Au, complete removal of silver is not always an easy task, and the formation of heterobimetallic Ag/Au clusters has been reported^[80]. In practice, the effects of Celite filtration should always be considered, because it is often observed that different procedures for the activation of LAuCl complexes by chloride scavenging result in different catalytic performances^[81].

Up to this point, we have examined the properties of NHC ligands and the potential of Ag(I)- and Au(I)-NHC complexes. Given their versatility, they can be functionalized according to specific application needs. In this regard, the following chapter introduces one of the structural features incorporated into the NHC ligands employed in this work.

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Chapter 3 – Sulfonated NHC complexes and 4,5-substituted imidazole derivatives

3.1 Sulfonate: a chemical Velcro ball

To introduce a functional group with low coordinating ability toward the metal centers selected for organometallic complex formation, while simultaneously enhancing the compounds' solubility in aqueous media for biological assays, the incorporation of an alkylsulfonate moiety was considered appropriate.

The sulfonate group is an ionic species formed by the dissociation of a sulfonic acid ($\text{R-SO}_3\text{H}$). In water it remains in its conjugate base form R-SO_3^- down to pH 2 and can engage in hydrogen-bonding interactions in protic polar environments. Chemically similar to other anionic groups such as carboxylates^[1] and phosphonates^[2], the sulfonate group readily interacts with cationic partners. According to Pearson's HSAB model, sulfonate is an electron-rich species that binds effectively to strongly acidic Lewis centers, such as alkali cations (Na^+ , K^+) or metals with a charge-to-radius ratio near unity, conversely, it is a poor ligand for metals where the positive charge is delocalized over a larger radius^[3, 4]. By virtue of these properties, sulfonates can also perform additional roles, including the stabilization of cationic architectures^[5], the modulation of reactivity through coordination^[6, 7] and the mediation of cationic charge-transfer processes^[8, 9].

In biological systems, the sulfonate group ($-\text{SO}_3^-$) plays key roles that stem primarily from its capacity to impart a strong, permanent negative charge and high aqueous solubility to molecules. Unlike phosphate and carboxylate derivatives, whose degree of protonation can vary at physiological pH, the sulfonate moiety is derived from a very strong acid and therefore remains fully deprotonated and negatively charged in virtually all biological environments^[10, 11]. Although less ubiquitous than other groups, sulfonates occur in several biologically important molecules^[12]. Their presence markedly increases a compound's polarity and water solubility, properties that are critical for molecular transport and excretion^[13]. The fixed negative charge of the sulfonate group also serves as an anchoring point for ionic interactions with proteins and other biomolecules^[14]. Additionally, the use of sulfonated substrates is common to ensuring controlled conditions in *in vitro* assays. Biochemical studies performed *in vitro* require a stable pH, and many widely used synthetic buffering agents incorporate a sulfonate moiety. Notably, Good's buffers were specifically designed to be biologically inert and to serve as broadly applicable, universal buffers. The sulfonate substituent contributes to the high aqueous solubility of these buffers and to pKa values that are relatively insensitive to temperature fluctuations^[15, 16].

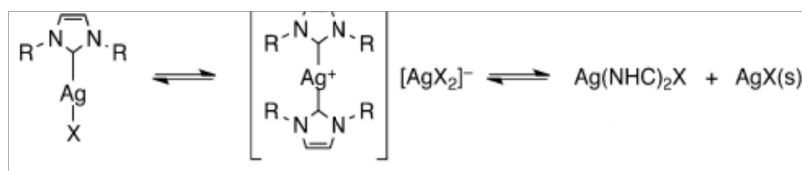
Despite the versatility of analogue sulfonate-based analogues, their use in biological applications can be controversial in some circumstances because certain derivatives have been associated with

carcinogenic activity^[17]. The documented hazard is attributed to the formation of sulfonate esters under specific conditions in the presence of water. Moreover, carcinogenic effects are thought to arise from secondary by-products of the synthetic process, which could persist at sufficiently high concentrations or be encountered with sufficient frequency to initiate carcinogenic pathways^[18]. However, such conditions have been shown to be rare and unlikely to occur under standard pharmaceutical-scale synthetic procedures; consequently, the associated risk does not appear to substantially compromise the chemical–biological performance of these compounds^[19-21].

In the context of N-heterocyclic carbene complexes, the literature describes a range of organometallic complexes bearing sulfonate functionalities introduced either by the functionalization of aromatic substrates^[22] or by N-alkylation with a substituent bearing a sulfonate group^[23-30]. Among the reagents most commonly employed for this purpose are sultones, which are cyclic sulfonate esters. The ring strain within these molecules enables ring opening via SN2 attack, since the sulfonate moiety functions as an excellent leaving group^[31, 32]. This reactivity is therefore exploited to achieve the N-alkylation of N-heterocyclic substrates. In particular, 1,3-propanesultone and 1,4-butanedisultone are widely used to incorporate alkylsulfonate substituents onto carbene precursors. In light of these considerations, the introduction of propan- and butane-sulfonate functionalities was undertaken to assess both catalytic and biological activity, with the aim of determining whether differences in alkyl-chain length constitute a meaningful determinant of these properties.

3.2 Aspects of the synthesis of sulfonated Ag(I)– and Au(I)–NHC complexes

As discussed above, the Ag₂O mediated synthesis of Ag(I) complexes from imidazolium salts and halides frequently establishes a dynamic equilibrium between homoleptic and heteroleptic species, a behaviour that is also observed for sulfonated derivatives. Because the –SO₃[–] substituent increases solubility in polar media, the polarity of the solvent becomes a primary determinant of the relative concentrations of the species present. Under typical conditions, the monomeric [NHC–Ag–X] and the ionic pair [NHC–Ag–NHC]⁺[AgX₂][–] coexist in solution. In sulfonated systems a third formulation, [NHC–Ag–NHC]⁺X[–], may additionally participate (Scheme 1). This third formulation originates from a solubility-driven perturbation of the X[–]/AgX₂[–] equilibrium in polar protic solvents. Under these conditions AgX₂[–] can partially dissociate according to $\text{AgX}_2^- \rightarrow \text{AgX} + \text{X}^-$ ^[33]. Since AgX is poorly solvated, it precipitates. The resulting shift in the X[–]/AgX₂[–] balance disfavors the ionic pair [NHC–Ag–NHC]⁺[AgX₂][–] and promotes the formation of the more stable bis-carbenic salt [NHC–Ag–NHC]⁺X[–]^[26]. By contrast, in polar aprotic or less polar media where halide solvation is stronger and AgX₂[–] is more stable, the equilibrium is biased toward greater contributions from [NHC–Ag–X] and [NHC–Ag–NHC]⁺[AgX₂][–], although concentration, temperature and specific solvent–ion interactions also modulate the speciation.



Scheme 1 – Equilibrium between mono- and bis-carbene structures of Ag(I) complexes with counterions

The [L–SO₃[–]]:[Ag⁺] ratio can be used to steer formation toward monocarbenic (1:1) or bis-carbenic (1:0.5) species, while the concentration of the halide anion [X[–]] can modulate the X[–]/AgX₂[–] equilibrium. Steric hindrance at the carbene is an additional determinant of coordination mode: bulky substituents disfavor the formation of the monocarbenic species and promote the bis-carbenic structure in low-polarity media^[34]. Conversely, monocarbenic complexes can still be isolated in polar protic solvents when the ligand bears a pronounced hydrophobic character^[35]. The simultaneous presence of mono- and bis-carbenic forms has also been reported for gold precursors obtained by transmetalation, reflecting the retention of the argentate–halide equilibria from the silver precursors^[25].

Although the sulfonate functionalities enable *in situ* complexation even in protic polar solvents, degradative processes may still occur, potentially limiting the coordination yield of the expected species. It is well established that silver complexes can undergo decomposition when exposed to air, moisture, light, acids, bases, or heat, leading to hydrolysis or changes in the oxidation state of the metal center^[36]. For sulfonate-tagged complexes, literature studies have shown that hydrolysis of the C2–Ag bond can occur in the presence of water or other proton-donor species, yielding the imidazolium salt and free silver. The latter may then undergo further degradation, such as reduction to metallic silver, detectable by the formation of a silver mirror or by the appearance of silver nanoparticles^[26]. Given the ability of the sulfonate group to coordinate to silver, the formation of structures bearing –SO₃Ag units is also possible. The presence of this species leads to a darkening of the complex, both in the solid state and in solution, most likely due to secondary redox or photophysical processes. Replacing Ag⁺ with Na⁺, by inducing the precipitation of AgCl, mitigates this darkening effect^[25].

Synthesis of sulfonated Au(I)–NHC complexes is predominantly achieved via transmetallation from the corresponding silver complexes^[22, 25]. It is noteworthy that, in some instances, the transmetallation is reported as a one-pot procedure starting from the silver-complex synthesis, without isolation of the silver intermediate. The resulting mixture can subsequently be purified by exploiting the differing solubilities of the mono- and bis-carbene species in alcohol^[34, 25, 37].

3.3 Biological properties of 4,5-imidazole derivatives

Imidazole is one of the most widespread heterocyclic structures found in nature. Since the discovery of its derivatives in the 1840s, the scaffold has attracted considerable scientific interest due to its remarkable versatility in pharmaceutical chemistry and its ability to perform a wide range of biological functions. First synthesized in 1858 by Heinrich Debus^[38], imidazole has since been incorporated into molecular frameworks designed to mimic or modulate biologically relevant structures, such as the amino acid histidine, the neurotransmitter histamine, and nucleic-acid-derived metabolites^[39, 40]. Its broad applicability arises from its distinctive electronic structure: the aromatic ring contains a rich distribution of π -electrons and two heteroatoms capable of acting as both hydrogen-bond donors and acceptors. These features enable imidazole to interact with aromatic or metal-binding sites, engage in polar and protic hydrogen-bonding interactions, and participate in acid–base equilibria near physiological pH^[41, 42]. As a consequence, imidazole-containing compounds can influence a wide variety of biological targets and exhibit diverse pharmacological activities, ranging from enzyme modulation to receptor binding^[43-45]. Given the ability of the imidazole moiety to engage in this wide range of pharmacologically relevant interactions, it is considered advantageous to combine these features with the well-documented biological activities of gold and silver. In particular, attention has focused on their use in N-heterocyclic carbene (NHC) Ag(I) and Au(I) complexes, which have been extensively investigated in recent years^[46-52]. Numerous studies have demonstrated that these organometallic systems possess significant pharmacological potential, and our research group has explored their potential applications in this context^[53-56].

The biological activity of NHC-Ag(I)/Au(I) complexes is strongly influenced by their structural properties and the interactions they undergo within the cellular environment. Literature reports show that these complexes can accumulate in mitochondria, targeting regions highly sensitive to perturbations in cellular metabolism^[57]. They are also capable of coordinating with thiol, selenol, and amine groups at specific enzymatic sites, thereby altering key biological functions^[58-60].

Moreover, several studies highlight their ability to interact with non-genomic targets, such as G-quadruplex structures, leading to the disruption of enzymatic regulatory processes^[61-63]. Interactions with genomic targets have also been documented, in which these complexes can inhibit or modify proliferative pathways in a manner reminiscent of the mechanism of action of cisplatin^[64, 65]. In addition, the long-term release of Ag⁺ ions from silver-based complexes has been reported, contributing to alterations in charge balance and interference with normal cellular activity^[66, 67]. These

combined mechanisms underline the multifaceted biological behavior of NHC-metal complexes and support their growing relevance in medicinal chemistry.

In order to further expand our research line in this field, we sought to evaluate the activity of organometallic structures with enhanced solubility in aqueous media, taking inspiration from molecular frameworks already reported in the literature^[27-30, 68].

At the same time, to broaden the investigation of the biological activity associated with different structural motifs, we selected imidazole substrates functionalized at the C4,5 positions, a substitution pattern well known for its pronounced pharmacological relevance.

For instance, the 4,5-diphenyl-imidazole scaffold is known to display significant anti-inflammatory properties, which are largely attributed to the presence of the two aryl substituents. These aromatic groups enhance hydrophobic interactions within biological targets and contribute to the stabilization of key binding conformations, thereby improving the overall affinity and selectivity of the molecule toward its biological counterparts. The pharmacological relevance of this moiety is further underscored by its role as an analgesic^[69]. Furthermore, the 4,5-diphenyl-imidazole scaffold is known to inhibit of the p38 mitogen-activated protein kinase (MAPK), a central regulator of cellular responses to inflammatory cytokines and environmental stress^[70]. The p38 MAPK pathway consists of a three-tiered phosphorylation cascade involving a MAP3K, a MAP2K, and the p38 MAP kinase itself. Activation of this pathway by extracellular stimuli leads to the phosphorylation of downstream substrates, ultimately promoting the expression of pro-inflammatory mediators^[71, 72].

Regarding the selection of 4,5-dichloro-1*H*-imidazole as a substrate, recent studies have highlighted the promising anticancer potential of its derivatives, particularly when incorporated into metal-based architectures. In this context, silver(I) N-heterocyclic carbene (NHC) complexes derived from 4,5-dichloro-1*H*-imidazole have demonstrated significant cytotoxic effects against various human cancer cell lines. Reported values for Ag(I)-NHC complexes based on 4,5-dichloro-1*H*-imidazole indicate potent cytotoxicity across multiple cancer models, including ovarian (OVCAR-3), breast (MB157), and cervical (HeLa) cell lines^[73]. Although the specific signaling pathways associated with 4,5-dichloroimidazole derivatives remain under active investigation, evidence from the broader class of imidazole-containing compounds suggests that their anticancer activity is often linked to the induction of apoptosis and cell-cycle arrest^[74]. These processes are typically triggered by interactions with key intracellular targets, including mitochondrial components, redox-sensitive proteins, and enzymes involved in proliferative signaling. Such mechanistic insights provide a valuable foundation for the continued development of 4,5-dichloroimidazole-based organometallic complexes with improved selectivity and therapeutic potential.

The benzimidazole scaffold represents a cornerstone of medicinal chemistry due to its structural resemblance to naturally occurring purines, which enables interactions with a broad spectrum of biological targets^[75]. This purine-mimetic character supports the development of numerous FDA-approved therapeutics across diverse pharmacological classes, including anthelmintics, proton-pump inhibitors, anticancer agents, and antihypertensive drugs^[76]. Its versatility is further reinforced by the wide range of pharmacological activities exhibited by benzimidazole derivatives: acting as an effective isostere of natural biomolecules, the benzimidazole core can engage with enzymes, receptors, and nucleic-acid-associated targets^[77]. This combination of structural adaptability, tunable physicochemical properties, and biological relevance underlies the enduring prominence of the benzimidazole framework in the rational design of contemporary therapeutic agents^[78]. Recently, an N-benzhydryl-benzimidazole motif has been incorporated into antitumor organometallic structures^[79], offering an intriguing direction for further investigation in this field.

The literature concerning organometallic complexes incorporating the 4,5-dicyanoimidazole scaffold and that exhibit significant biological activity is limited compared to that of the C4,5 functionalized imidazole analogues previously mentioned. Nevertheless, numerous studies demonstrate that the presence of a cyano substituent can profoundly influence biological properties, owing to the intrinsic electronic and structural features of the nitrile group. Drugs containing a cyano moiety are employed in the treatment of a wide range of diseases, from viral infections to various forms of cancer^[80]. This versatility arises from the capacity of nitriles to simultaneously enhance pharmacodynamic and pharmacokinetic properties. Their ability to engage in diverse interactions with macromolecular targets can improve binding profiles, while in some cases the cyano group also increases aqueous solubility^[81, 82].

Structurally, the nitrile group is characterized by a linear geometry, with a nitrogen atom bonded to an sp-hybridized carbon through a polarized triple bond. The electron-deficient carbon atom can act as an electrophilic center due to the strong electronegativity of the nitrogen and the high dipole moment associated with the C≡N bond, making nitriles an unusual yet highly versatile functional group. The lone pair on the nitrogen atom enables hydrogen-bonding interactions with donor groups, further expanding the range of possible noncovalent interactions^[83]. For these reasons, three main types of interactions can occur between the nitrile moiety and its targets: hydrogen bonding, hydrophobic interactions, and covalent contacts^[81]. Hydrogen bonding is particularly relevant because the nitrile group is widely recognized as a bioisostere of carbonyl, hydroxyl, and halogen substituents, all of which commonly function as hydrogen-bond acceptors. Such interactions are especially useful in peptide targeting, where the nitrile group can play a dual role. As noncovalent inhibitors, nitriles can engage in several types of interactions with the target protein, including hydrogen bonds with donor

groups from the peptide backbone or side chains. In addition, the cyano group can interact with bridging water molecules and participate in hydrophobic contacts. When directly attached to an aromatic ring, the strong electron-withdrawing nature of the cyano group can significantly modulate the electron density of the π -system, potentially promoting π - π stacking interactions between the aromatic core of a drug molecule and aromatic residues within a protein target (such as phenylalanine, tyrosine, tryptophan or histidine)^[81].

Beyond these non-covalent interactions, nitriles can also act as electrophilic warheads capable of forming covalent adducts with nucleophilic amino acid residues, most commonly cysteine or serine. In such cases, the nitrile reacts with an active-site nucleophile to form a covalent bond, whose stability can be finely tuned by substituents positioned near the cyano group. This tunability is crucial for designing inhibitors that range from reversible to irreversible^[84].

The cyano group is also considered metabolically stable and may reduce susceptibility to hepatic oxidative metabolism^[85]. Although rare cases of nitrile-related toxicity have been reported, typically associated with metabolic release of cyanide, such events are uncommon and generally negligible. Overall, nitriles are regarded as non-toxic functional groups and are typically excreted unchanged from the human body.

Regarding the role of the N-substituents, the alkylsulfonate groups will not be discussed further, as their role has been already examined in the dedicated section. Instead, we will briefly consider the potential biological relevance of the benzhydryl and benzyl groups.

The benzyl (Bn) functionality is widely employed in pharmaceutical chemistry. Commonly used as a protecting group for amines^[86], alcohols^[87], and thiols^[88], the benzyl moiety effectively shields the intrinsic chemical vulnerability of these groups across a broad range of synthetic conditions. Since these functionalities often participate in hydrogen-bonding interactions in biological environments, benzylation suppresses such interactions, thereby modulating both the structural rearrangement and the chemical activity of the molecule^[89]. When positioned near chemically susceptible functionalities or within electronically conjugated systems, the benzyl group can act as an electron donor, influencing the reactivity of adjacent sites^[90]. The methylene linker imparts additional mobility and conformational adaptability, allowing the group to orient itself with greater freedom and better accommodate potential biological targets. Furthermore, the aromatic ring can engage in non-covalent π -stacking interactions, while its hydrocarbon-rich, and weakly polarizable nature enhances the lipophilicity of the substrate^[91]. This also introduces steric bulk, which may confer spatial selectivity during molecular rearrangements or interactions with other substrates^[79].

As with the benzyl functionality, the benzhydryl group serves an analogous role when employed as a protecting group^[88, 92]. The choice of this substrate was motivated by the intention to investigate a

functional group whose literature coverage is comparatively limited relative to its trityl and benzyl analogues, thereby offering a distinct and stimulating opportunity to explore its chemical and biological behavior. The presence of two phenyl rings enhances electron-donating ability, lipophilicity, and steric bulk, while also altering the conformational landscape of the molecule due to the additional degree of freedom introduced by the second aromatic ring.

The diphenylmethane scaffold's derivatives display diverse biological activities, including antihistaminic^[93], anticholinergic^[94], and anticancer properties^[95]. Notable examples include first-generation antihistamines, in which the diphenylmethane core is a key structural element responsible for inverse agonism at the histamine H1 receptor. The scaffold is also present in several central nervous system (CNS)–active drugs; for instance, benztropine is an anticholinergic agent used in the treatment of Parkinson's disease and other movement disorders. Recent studies have identified chiral diphenylmethane derivatives as potent dual partial agonists of peroxisome proliferator-activated receptors α and γ (PPAR α/γ)^[96]. These receptors are central regulators of lipid and glucose homeostasis, making them important pharmacological targets for metabolic disorders. Furthermore, some of these diphenylmethane derivatives have been shown to inhibit the Wnt/ β -catenin signaling pathway, which is frequently dysregulated in various cancers, particularly colorectal carcinoma.

Before concluding this chapter and moving on to the next, it is important to briefly address the biological potential of imidazolium salts, even though they are not the primary focus of this dissertation. Attention to these species is warranted because they may be released into the biological environment following the hydrolytic cleavage of the coordinated metal center, and could therefore contribute to the overall biological activity of the system.

Imidazolium salts constitute a class of compounds known for their diverse biological properties^[97-99]. Beyond the structural variability introduced by different substituents, their defining feature is the presence of a positive charge delocalized within the imidazolium ring, though often centered at the C2 carbon. This cationic character enhances solubility in polar media, thereby influencing molecular bioavailability^[100], and introduces two key elements absent in neutral imidazoles: the presence of a counterion paired with the imidazolium cation, and a C2–H unit with Lewis-acidic character capable of participating in hydrogen-bonding interactions^[101]. Particularly intriguing are imidazolium structures bearing one or more charges, which often display distinctive biological activities^[97]. Among these, zwitterionic imidazolium salts are of special interest. In these systems, an internal negative charge acts as the counterion, eliminating the need for external anions that could potentially interfere with biological function^[98]. Typically, the negative charge is introduced through functional groups capable of adopting an anionic form, such as alcohols^[102], carboxylic acids^[103], thiols^[104], and phosphates^[105]. This structural design has significant implications for biological activity, as it enables pH-dependent

modulation of the zwitterion's behavior. Alternatively, sulfonate groups can be employed to introduce a permanent negative charge, which is largely insensitive to pH variations, thereby conferring a more robust zwitterionic character. Such salts have recently found applications as anticholinergic agents^[99].

The documented use of these functional groups in the literature, together with their intrinsic properties, has stimulated our interest in designing structures with potential biological relevance for the development of new organometallic complexes. These structural modifications aim to preserve the intrinsic reactivity of the metal center while enabling more efficient interactions with biological targets. The successful application of these design principles in comparable systems reported in the literature^[100] has encouraged us to pursue the development of new analogues within our research group.

3.4 References

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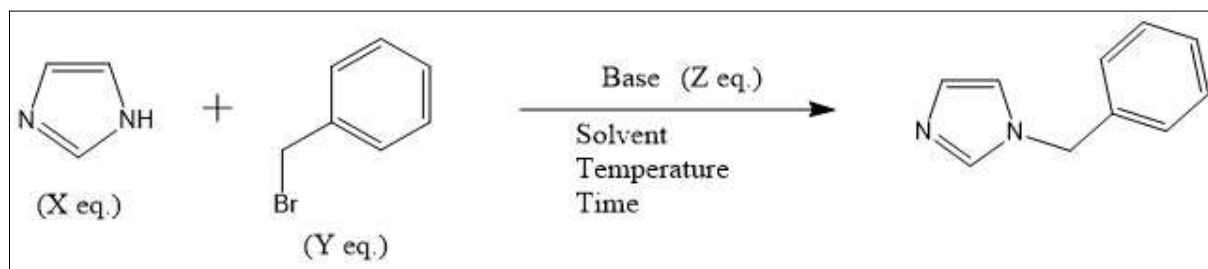
Chapter 4 – Results

4.1 Synthesis of NHC-Ag(I) and NHC-Au(I): from azolium salts to complexation

This paragraph describes the experimental trials carried out to obtain some of the structures synthesized in the course of this thesis work, illustrating the synthetic steps explored. The final procedures are reported in the paragraph dedicated in the Experimental Section.

4.1.1 Synthesis of the benzylimidazolium derivatives

The first set of structures investigated in this work consisted of benzyl-imidazole derivatives. The study began with the synthesis of 1-benzyl-1H-imidazole (FV0). Although this compound is commercially available, it was decided to synthesize it in the laboratory. Several literature procedures^[1-5] were examined to identify the most suitable synthetic route, and a series of exploratory trials under different conditions were subsequently carried out, as reported below:

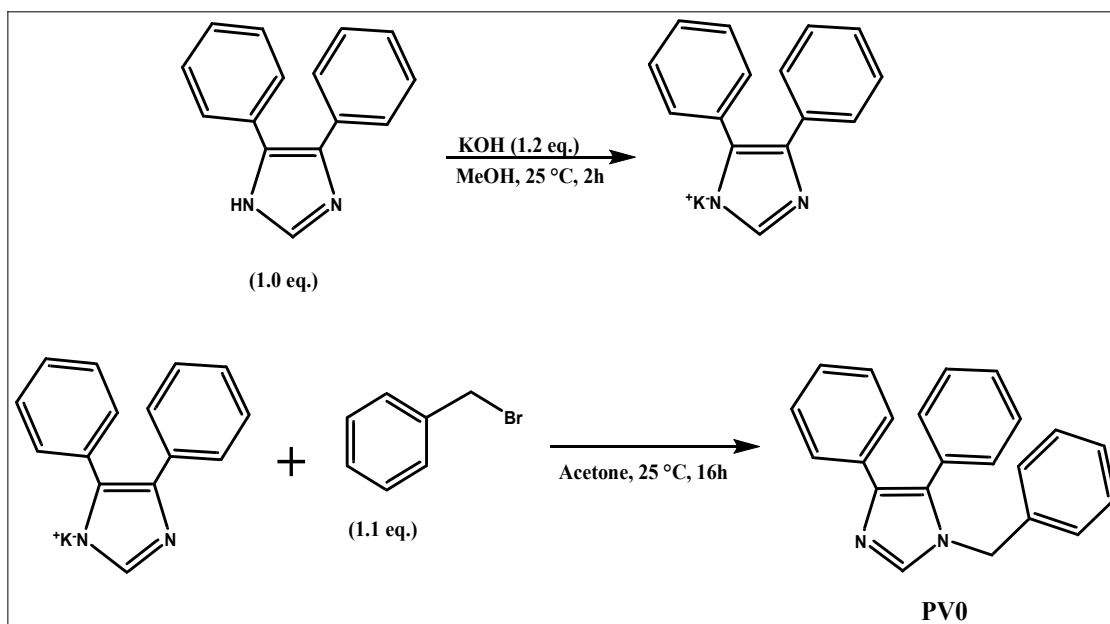


Scheme 1 – FV0 synthesis' conditions

Run	Imidazole (X eq.)	Benzylbromide (Y eq.)	Base (Z eq.)	STT	Yield recovered
1	1.0	0.5	1.0	MeCN, 90 °C, <2h	~40-50%
2	7.0	1.0	3.0	MeCN, 90 °C, <2h	~50%
3	1.0	1.0	2.0	MeCN, 25 °C, 24h	~20%
4	1.0	1.0	2.0	MeCN, 25 °C, 48h	~20%

Based on this preliminary investigation, run n°1 was selected as the most convenient route for the synthesis of the product. At an early stage, this synthetic procedure was also applied to the preparation of the other structures. However, a new protocol was subsequently developed to enable the preparation of the remaining substrates in a more straightforward manner. During these trials, a paper was identified describing the synthesis of N-substitued imidazole

derivatives under solvent-free conditions, exploiting the formation of the imidazolate species upon the melting of imidazole^[3]. Considering this approach, a procedure was tested to achieve stable and persistent formation of the imidazolate. The idea was to generate the imidazolate under basic conditions in a polar protic solvent, and then switch to a less polar medium capable of promoting the N-alkylation reaction. For this purpose, 4,5-diphenylimidazole was tested as a substrate, owing to its clear visibility under UV 254 nm, which enables the unambiguous identification of the starting material, unlike the previous imidazole substrates. The two steps are reported in the following scheme (Scheme 2):



Scheme 2 – PV0 synthetic steps

The imidazolate intermediate was first generated by dissolving the imidazole substrate in methanol at 25 °C, followed by the addition of KOH and stirring for two hours. Within minutes, the solution turned yellow, a change likely attributable to the formation of the imidazolate anion, which in conjugated heterocyclic systems can display absorption in the visible region. After stirring, the reaction mixture was concentrated under reduced pressure, and acetone was added. This solvent was selected because SN2 reactions with benzyl bromide are typically favored in polar aprotic environments (acetone, DMSO, DMF or acetonitrile). For operational convenience, DMSO and DMF were excluded, and acetone was chosen. Once a homogeneous mixture had formed, benzyl bromide was introduced, and the reaction was monitored by silica TLC (Petroleum Ether/acetone 4:1) under UV light at 254 nm. Over time,

the benzyl bromide spot diminished while the product spot emerged. Upon completion, the mixture was filtered to remove the KBr precipitate. The filtrate was evaporated, and the crude product was purified by silica gel chromatography using a PE/acetone gradient (4:1 → 3:2). Given the excellent yield obtained, the method was extended to remaining substrates, for which it proved effective.

4.1.2 Synthesis of benzhydryl-substituted imidazole derivatives

The synthesis of the benzhydrylimidazole substrates was largely carried out using the methods previously described. However, one substrate, 1-benzhydryl-4,5-dichloro-imidazole (CV00, Figure 1), required more careful optimization, leading to the evaluation of various reaction conditions.

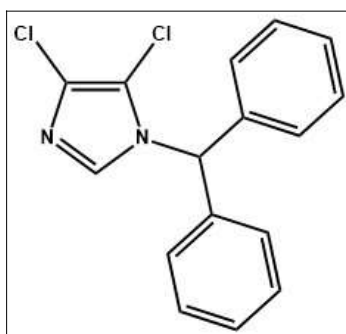
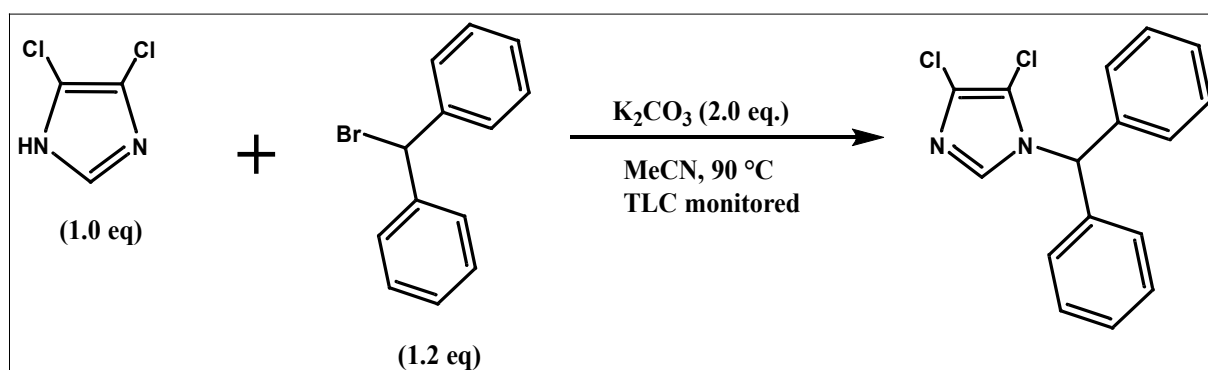


Figure 1 – CV00 structure

The synthesis of this molecule was approached through several strategies to identify a route that could be optimized for preparative purposes. Given the nature of the 4,5-dichloro-imidazole substrate, the pK_a of the N3–H proton is lower than that of the unsubstituted analogue. For this reason, the initial attempt to prepare CV00 was based on conditions previously applied to related substrates, starting with procedures employing weak bases such as K₂CO₃ and NEt₃. The first synthetic attempt was carried out under the following conditions:

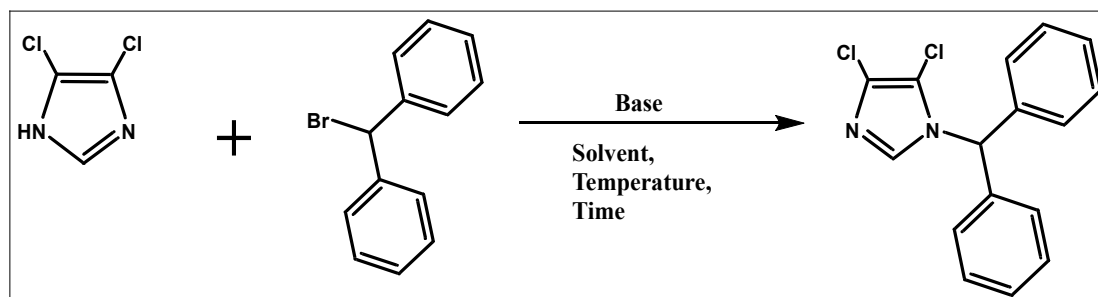


Scheme 3 – CV00 synthesis' conditions

In this case, a broader mixture of products or presumed intermediates was observed. TLC monitoring showed that the band corresponding to benzhydryl bromide gradually disappeared over time, accompanied by the formation of multiple new bands. The reaction was followed by silica TLC using a PE–EtOAc 8:2 mixture, and the plates were visualized at the end of the run under UV light at 365 nm and 254 nm.

Upon completion of the reaction, the mixture was allowed to cool to room temperature and then filtered through filter paper to remove the excess K_2CO_3 , KHCO_3 , and KBr formed during the process. The filtrate appeared as a clear and orange solution. The solvent was removed under reduced pressure to afford the crude product, which was subsequently dissolved in DCM and washed with a saturated NaHCO_3 solution and brine. The organic phase was collected and concentrated, and the crude material was purified by silica gel column chromatography using a PE–EtOAc gradient (from 4:1 to 3:2).

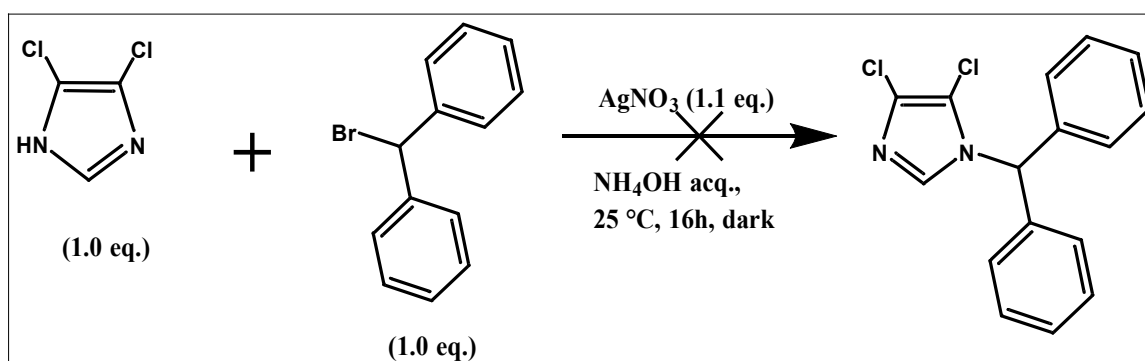
The main limitations of this synthetic procedure are the low yield (< 10%) and the challenging purification. To overcome these issues, alternative strategies were explored in an attempt to improve the overall efficiency of the substrate synthesis. To this end, different conditions and strategies were evaluated by varying both the experimental parameters and the overall synthetic workflow. Additional bases and alternative reaction conditions were tested to assess their impact on the yield:



Scheme 4 – CV00 synthesis' conditions tested

Run	4,5-dichloroimidazole eq.	Br-benzhydryl eq.	Base (eq.)	Solvent	Temperature (°C)	Time (h)	Yield %
1	1.0	1.0	K ₂ CO ₃ (2.0)	MeCN	25	48	~5-8
2	1.0	0.5	K ₂ CO ₃ (1.5)	MeCN	25	24	~5-8
3	1.0	0.33	K ₂ CO ₃ (0.66)	MeCN	25	48	~10-15
4	7.0	1.0	K ₂ CO ₃ (3.0)	MeCN	90	<1.5	~20-40
5	1.0	0.33	KOH (0.66)	MeCN	25	48	nd
6	1.0	0.9	KOH (1.1)	DMSO	25	48	nd
7	1.0	0.9	KOH (1.1)	DMSO	90	16	nd
8	1.0	1.0	NaH (1.1)	DMF	25	16	~15
9	1.0	1.0	Et ₃ N	MeCN	25	24	nd
10	1.0	1.0	Et ₃ N	DCM	25	24	~20
11	1.0	1.0	Et ₃ N	Acetone	25	24	~10

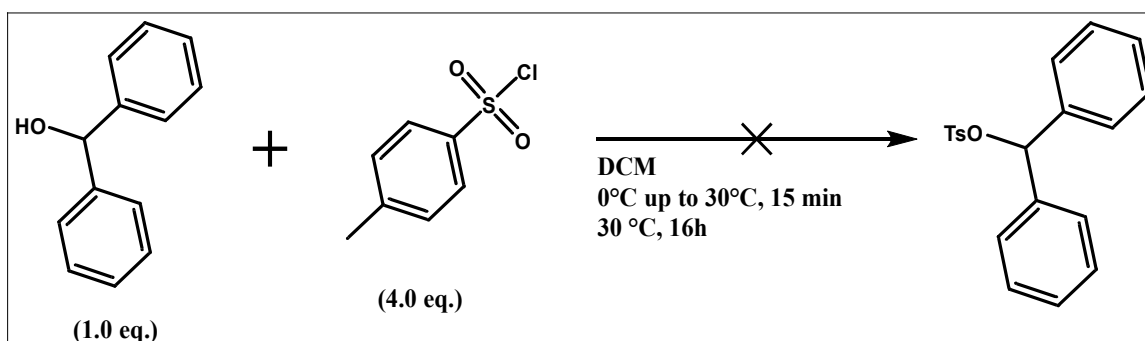
Among the experiments performed, the only condition^[1] that afforded a higher yield was run n°4. The yield, however, was not reproducible, likely due to variations in the amount of material recovered in subsequent trials. Although this procedure provided the highest yield among those tested, additional strategies were explored to further improve the outcome and reduce the equivalents of 4,5-dichloroimidazole required. One of the approaches evaluated involved the use of AgNO₃:



Scheme 5 – CV00 synthesis tested using AgNO_3

In this case, the strategy was to exploit the ability of silver to coordinate the imidazolate generated under basic conditions using Tollens' reagent^[6]. However, no encouraging outcome was obtained for the formation of the desired product, therefore, alternative approaches were considered. To promote N-alkylation on the imidazole ring, the alkylating agent was changed. The presence of multiple bands on TLC suggested that benzhydride was prone to side reactions, prompting the use of a substrate capable of providing comparable reactivity with fewer undesired pathways.

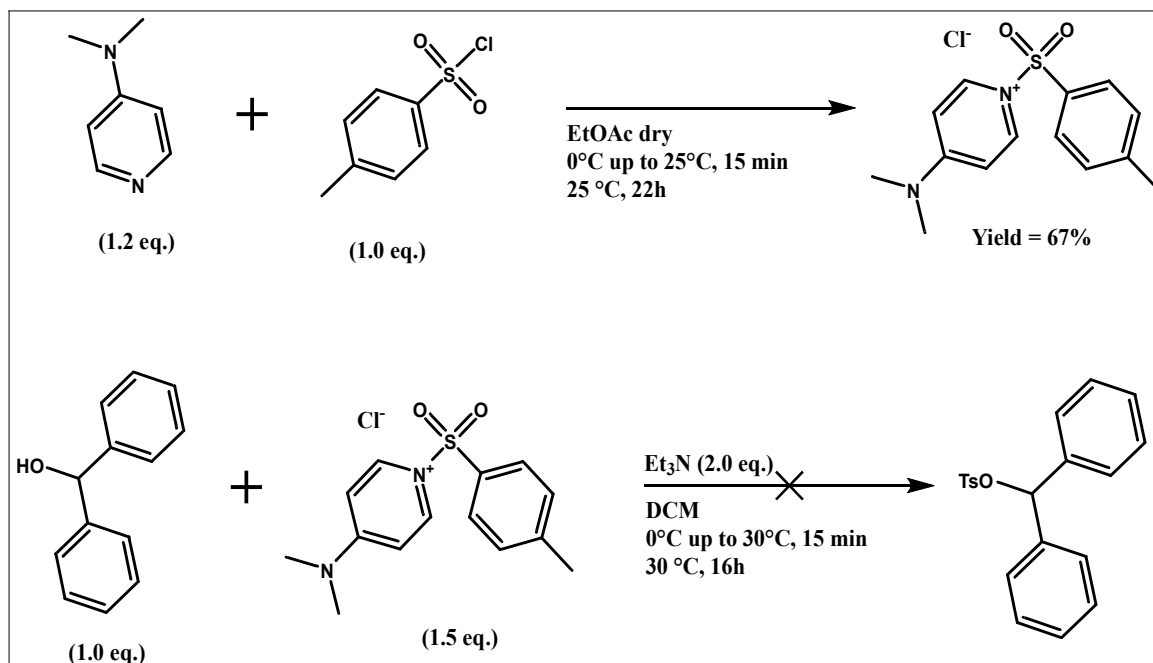
Consequently, diphenylmethanol was selected and subjected to tosylation to generate a more suitable electrophile for N-alkylation of the imidazole substrate, which exhibits poor nucleophilicity due to the two chlorine atoms. The formation of benzhydride tosylate (benzhydride-Ots) was carried out under the adopting conditions similar to literature-reported^[7]:



Scheme 6 – Benzhydride-Ots synthesis, first attempt

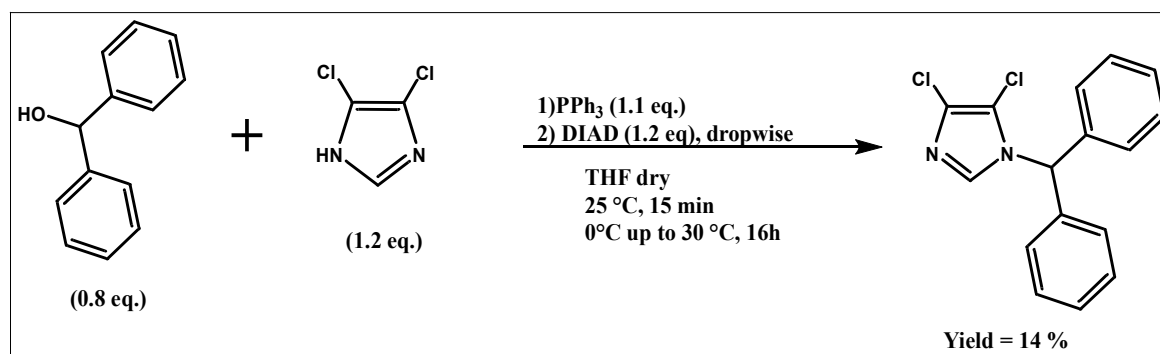
After workup, the ^1H NMR analysis did not show any evidence for the formation of the expected product. Therefore, an alternative strategy was adopted, using the p-

toluenesulfonyl-4-(dimethylaminopyridine) DMAP-Ts salt, again drawing from literature precedents^[8]:



Scheme 7 – Benzhydryl-Ots synthesis, second attempt

In this case as well, ^1H NMR monitoring did not provide any evidence for the formation of the desired product. As a final attempt, the N-alkylation of the benzhydryl moiety was carried out using diphenylmethanol through a Mitsunobu reaction^[9]:



Scheme 8 – CV00 synthesis adopting Mitsunobu conditions

The reaction was carried out by dissolving diphenylmethanol and 4,5-dichloroimidazole in anhydrous THF in a two-necked round-bottom flask at room temperature. Triphenylphosphine was added, and after 15 minutes the mixture was cooled to 0 °C in an ice–

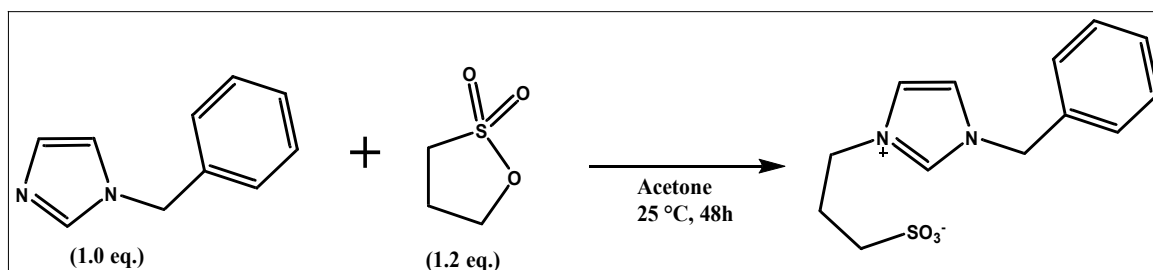
water bath. In a separate flask, a solution of Diisopropylazodicarboxylate (DIAD) in anhydrous THF was prepared and cooled to 0 °C using an ice bath. This solution was then added dropwise to the reaction mixture via syringe. Following the addition, the reaction was stirred at 0 °C for 15 minutes, then allowed to warm to room temperature and stirred for an additional 16 hours. At the end of the reaction, the solvent was removed under reduced pressure, and a 1:1 EtOAc/hexane mixture was added. The flask was stored in a refrigerator overnight. The mixture was then filtered, and the solid residue was washed with hexane^[10]. The combined filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography using a PE/EtOAc gradient (from 4:1 to 3:2). In this case, although the desired product was obtained, the reaction yield was not significantly improved compared to the previously tested procedures.

4.1.3 Synthesis of imidazolium salts

The zwitterionic salts were obtained through N-alkylation with an alkyl sulfonate chain, primarily by adapting established literature procedures. The synthetic strategy relied on the lower solubility of the resulting salts compared to the reaction solvent, a feature commonly exploited in acetone or acetonitrile to enable direct precipitation from the reaction mixture. Comparable conditions were adopted for the other derivatives, although extended reaction times were necessary due to the inherently low reactivity of the butane sultone ring. The reaction conditions employed for the first two zwitterionic salts (FV1 and FV2) are reported here as examples and were subsequently used as a reference framework for the preparation of the majority of the other zwitterionic derivatives.

Synthesis of *N*-benzyl-*N*'-(propyl-3-sulfonate)-imidazolium salt (FV1)

The first zwitterionic salt was obtained by following a procedure already reported in the literature for the synthesis of this structure ^[11]:



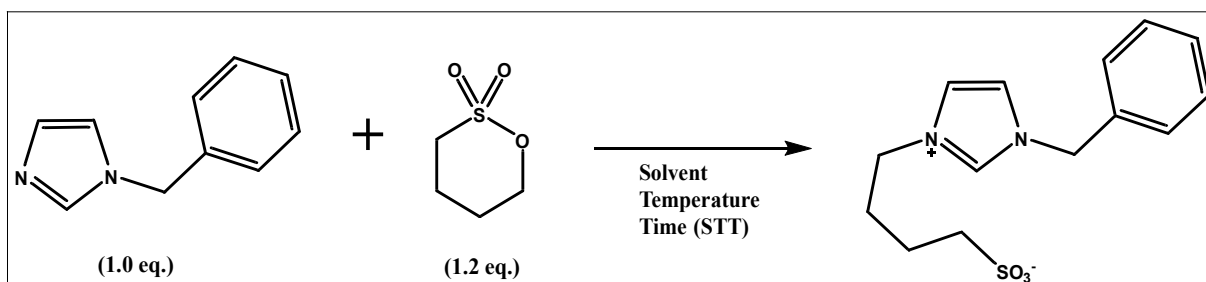
Scheme 9 – FV1 synthetic scheme

FV0 (0.3000 g, 1.92 mmol) was dissolved in acetone (10.0 mL) under magnetic stirring. 1,3-propane sultone (0.2780 g, 2.30 mmol) was added and the reaction was carried out at 25 °C for 48 hours. The white residue was collected by filtration on paper and washed three times with 7.00 mL of diethyl ether. After drying, the product was obtained as a white powder.

This procedure proved to be consistent with the literature and was also applied to the subsequent salts, although with limited success. Consequently, a different strategy was adopted, employing acetonitrile and heating the reaction mixture under reflux to facilitate the formation of the desired structures.

Synthesis of 4-(1-benzyl-1*H*-imidazol-3-ium-3-yl)butane-1-sulfonate (FV2)

This zwitterionic salt FV2 is a structural analogue of FV1, incorporating an alkyl sulfonate chain extended by a single methylene unit. Its preparation required the evaluation of several reaction conditions. The reaction conditions employed for its synthesis mirrors those used for the previously prepared analogue, and the additional synthetic trials performed for this compound are presented below:



Scheme 10 – FV2 synthetic's conditions tested

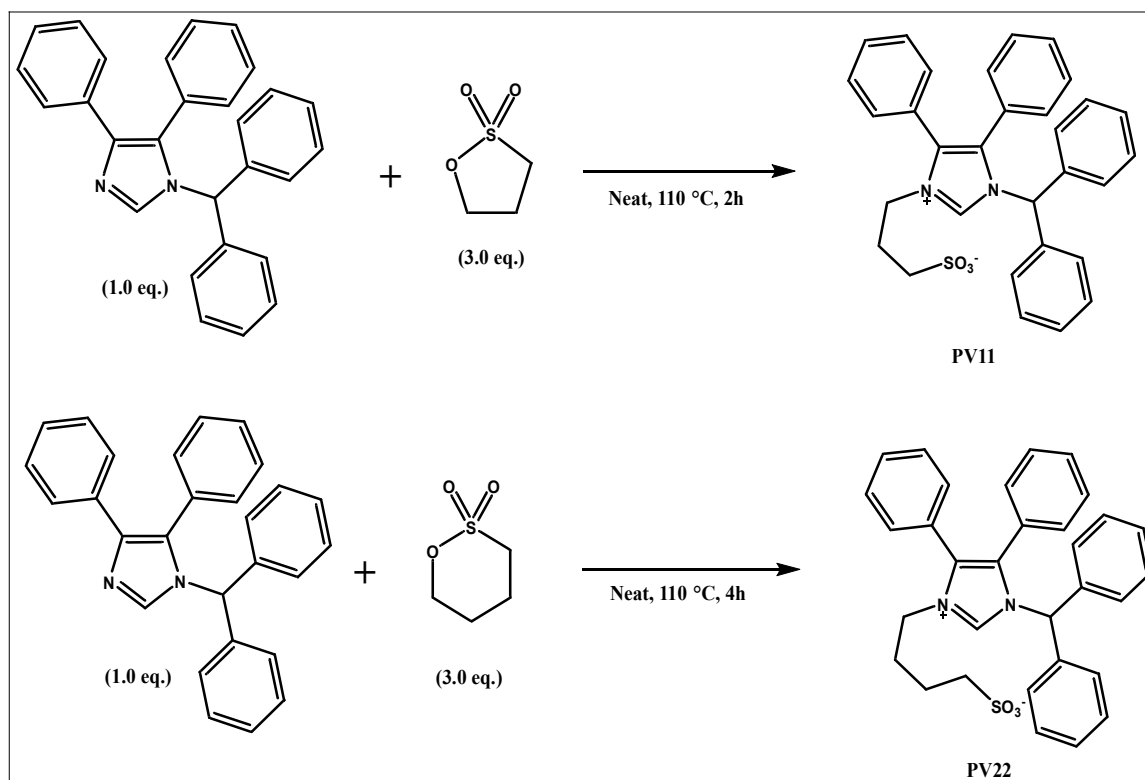
Run	STT	Yield recovered
1	Acetone, 25 °C, 48h	~55%
2	MeCN, 25 °C, 48h	~60%
3	MeCN, 90°C, 48h	~80%

Since run n° 3 proved successful, no additional experiments were carried out.

A solution of 1,4-butanedisulfone (0.3099 g, 2.28 mmol) in 2.0 mL of acetonitrile was added to a solution of FV0 (0.3000 g, 1.92 mmol) in 3.0 mL of acetonitrile. The solution was heated at 90 °C in a capped round-bottom flask (RBF) and the reaction was carried out under stirring for 48 hours. The white residue was filtered off on paper and washed three times with 7.0 mL of diethyl ether. After drying, the product was obtained as a white powder.

These two salts, FV1 and FV2, constituted the first substrates selected for evaluating the complexation methodologies applied to the silver and gold organometallic derivatives. Most of the subsequent structures were prepared using analogous synthetic strategies, although in some instances a different solvent, such as toluene, was employed or extended reaction times were required. For substrates that did not afford the desired products under these conditions, an alternative high-temperature, solvent-free protocol was adopted, exploiting the sulfonated substrate as the reaction medium^[12]. This approach was intended to drive the formation of the

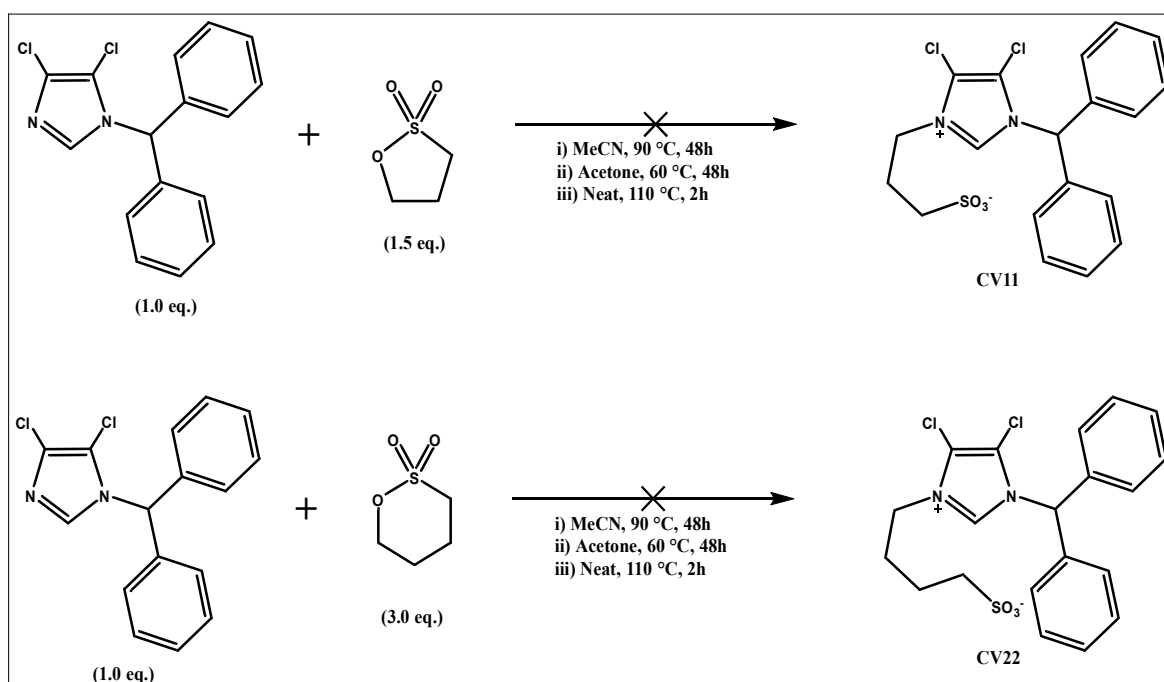
zwitterionic scaffold by operating under highly concentrated conditions. Under these circumstances, the preparation of the pair of salts (PV11 and PV22) shown below was attempted:



Scheme 11 – PV11 and PV22 solvent-free synthetic's conditions

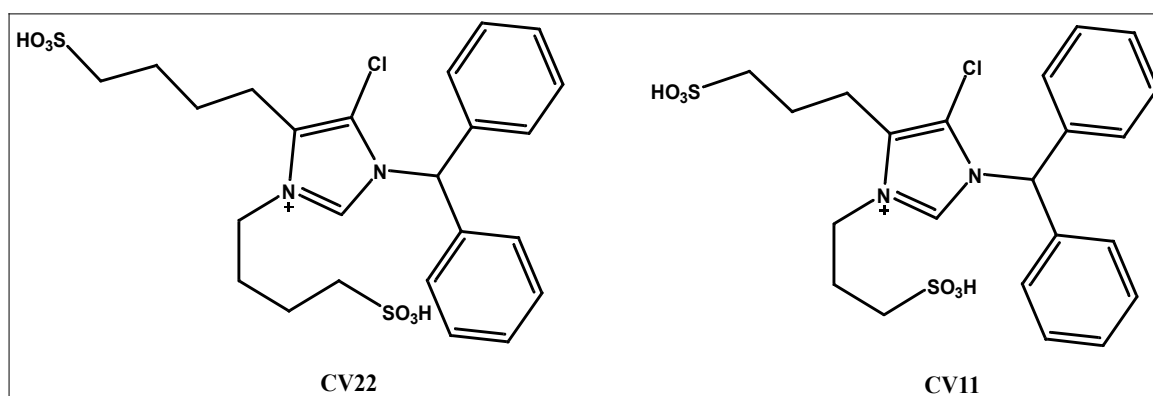
Under the conditions tested, using the sultones as the liquid reaction phase afforded the zwitterionic substrates, albeit with non-reproducible yields of approximately 10%. Optimization of the synthetic parameters proved unsuccessful, and the products were isolated by trituration with hexane. A complete NMR characterization could not be obtained, and only mass spectrometric data were recorded for PV22.

Regarding the zwitterionic structures CV11 and CV22, the attempts carried out in different solvents did not yield any isolable products. The same solvent-free conditions were also tested in these cases:



Scheme 12 – CV11 and CV22 synthetic's conditions tested

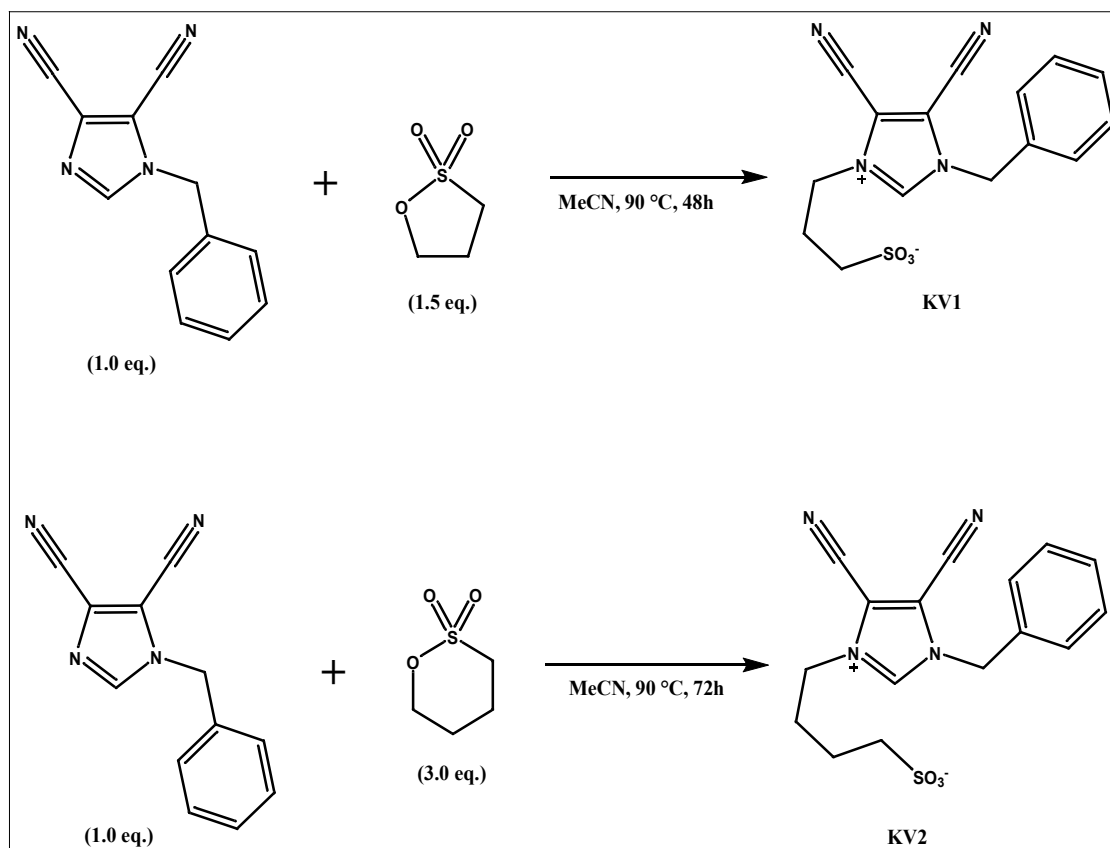
Adopting (iii) condition, although the preliminary NMR data suggested successful formation of the expected salts, mass spectrometer analysis indicated that the most consistent structural assignments correspond to species in which the alkanesulfonate chain is bound to the imidazole ring at the bridge position, replacing one of the chlorine atoms, as illustrated below:



Scheme 13 – CV11 and CV22 structures revealed from MALDI analysis

Subsequent attempts did not yield positive results; nevertheless, the aim remains to identify alternative synthetic pathways to those tested so far in order to obtain the desired structures.

Among the final structures synthesized, the salt derivatives bearing a cyano group on the imidazole bridge were successfully prepared, although only one of them could be isolated and fully characterized:

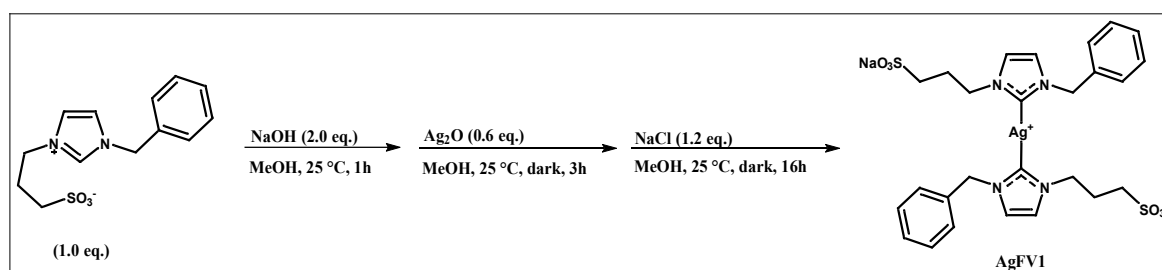


Scheme 14 – KV1 and KV2 synthetic's conditions adopted

KV1 was isolated and characterized by $^1\text{H}/^{13}\text{C}$ NMR and IR spectroscopy. KV2, on the other hand, was detectable only via ^1H NMR spectroscopy, as all isolation attempts failed to yield the pure compound. The benzhydryl-functionalized imidazolium salts, KV11 and KV22, were not obtained using the methodologies applied in this study. It is expected that further investigations will eventually allow for the isolation of these structures of interest.

4.2 Synthesis of silver Ag(I) complexes

The synthesis of the silver complexes was carried out following procedures already reported in the literature for analogous complexes bearing sulfonated NHC ligands. The initial experiments were performed by directly adapting the method reported for the synthesis of the structure named AgFV1^[11]:



Scheme 15 – AgFV1 complexation's condition adopted from literature

Although the reported synthetic procedure proved to be functional, the formation of a silver mirror and a progressive darkening of the reaction mixture were consistently observed when the procedure was tested on the other zwitterionic structures. The appearance of the silver mirror indicates the reduction of Ag(I) to metallic silver, most likely caused by the opening of the imidazolium ring, which under basic conditions becomes susceptible to side reactions involving ring cleavage and exposure of the acetamide group^[13].

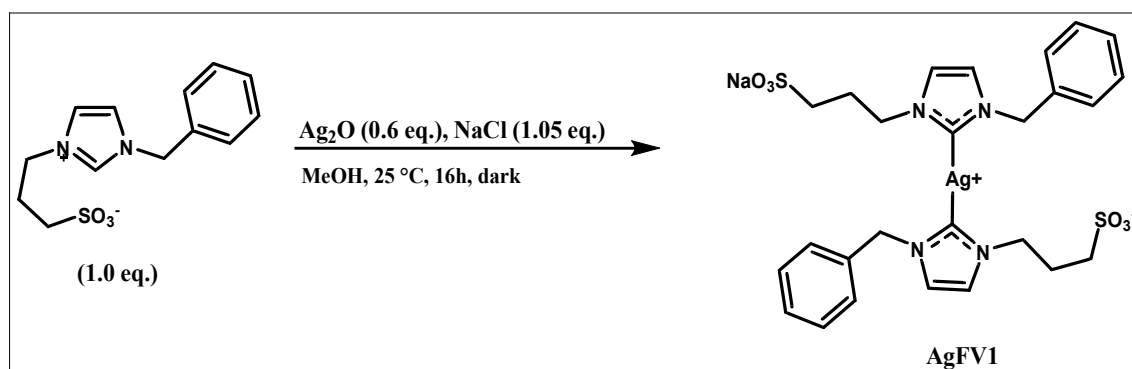
Several parameters were varied in an attempt to limit this degradation pathway, including molar ratios, reaction times, and the order of reagent addition; however, none of these modifications led to satisfactory results. A series of test complexation reactions was therefore carried out using the FV1 ligand as a reference structure, keeping the system at room temperature. These tests were summarized in a table and monitored by ¹H NMR after 24 hours. The spectra were acquired directly from the reaction mixtures in order to qualitatively identify the conditions most favorable for complex formation. Although this approach was used only as a preliminary investigation for the silver complexation of FV1 and does not necessarily define the optimal conditions for the other structures, it provided a general strategy that could be applied in the remaining cases.

Metallic precursor	Salt	Solvent	Outcome
Ag ₂ O (0,6 eq.)	\	MeOH	Negative
Ag ₂ O (1,2 eq.)	\	MeOH	Negative
Ag ₂ O (0,6 eq.)	\	CHCl ₃	Negative
Ag ₂ O (1,2 eq.)	\	CHCl ₃	Negative
Ag ₂ O (0,6 eq.)	\	CH ₂ Cl ₂	Negative
Ag ₂ O (1,2 eq.)	\	CH ₂ Cl ₂	Negative
Ag ₂ O (0,6 eq.)	\	MeCN	Negative
Ag ₂ O (1,2 eq.)	\	MeCN	Negative
Ag ₂ O (0,6 eq.)	NaCl	MeOH	Positive
Ag ₂ O (1,2 eq.)	NaCl	MeOH	Positive
Ag ₂ O (0,6 eq.)	NaCl	CHCl ₃	Negative
Ag ₂ O (1,2 eq.)	NaCl	CHCl ₃	Negative
Ag ₂ O (0,6 eq.)	NaCl	CH ₂ Cl ₂	Negative
Ag ₂ O (1,2 eq.)	NaCl	CH ₂ Cl ₂	Negative
Ag ₂ O (0,6 eq.)	NaCl	MeCN	Negative
Ag ₂ O (1,2 eq.)	NaCl	MeCN	Negative
Ag ₂ O (0,6 eq.)	\	NH ₃ (aq. conc.)	Negative
Ag ₂ O (1,2 eq.)	\	NH ₃ (aq. conc.)	Negative
Ag ₂ O (0,6 eq.)	NaCl	NH ₃ (aq. conc.)	Positive
Ag ₂ O (1,2 eq.)	NaCl	NH ₃ (aq. conc.)	Positive

The most common solvents reported in the literature for the synthesis of organometallic complexes bearing sulfonated NHC ligands were tested. Among the various attempts, the use of an ammoniacal solution proved particularly interesting, as it represents one of the most recent mild methods proposed for the preparation of NHC–Ag(I) complexes^[14]. In this preliminary screening phase, no coordinated complex was isolated; instead, the complete disappearance of the C2–H signal of the zwitterionic imidazolium salt was observed. Based on the results obtained, two procedures were identified for the synthesis of the silver complexes, referred to as method A and method B.

Synthesis of the silver complexes – one pot complexation (method A)

Method A proved to be the most versatile for the majority of the salts, allowing complexation to occur at room temperature and providing good yields of the isolated compounds. As a test synthesis, the AgFV1 complex was obtained under the following conditions:

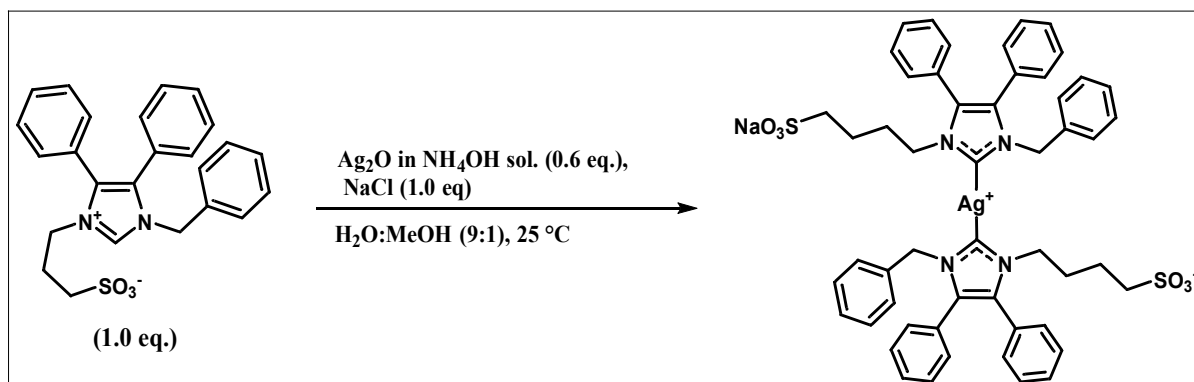


Scheme 16 – AgFV1 complexation's condition

In this way, most of the NHC–Ag(I) complexes described in this work could be obtained, facilitating of a one-pot approach. Although precipitation of the complexes can be achieved using methanol and Et_2O , it soon became evident that a more practical and reproducible isolation was obtained under the conditions reported in Method A (Experimental Section). In this procedure, the residue obtained after methanol evaporation is partially solubilized in a small volume of dichloromethane, followed by the addition of n-hexane to induce precipitation of the complex. After drying under vacuum, this method affords the coordinated structures as solid materials.

Synthesis of the silver complexes – Tollens' method (method B)

When extending the complexation tests to the other zwitterionic structures obtained, some proved to be poorly reactive under the previously established conditions. A different strategy was therefore explored, employing Tollens' reagent for the preparation of the silver complexes. The first structure tested with this approach was PV1 under the following conditions:

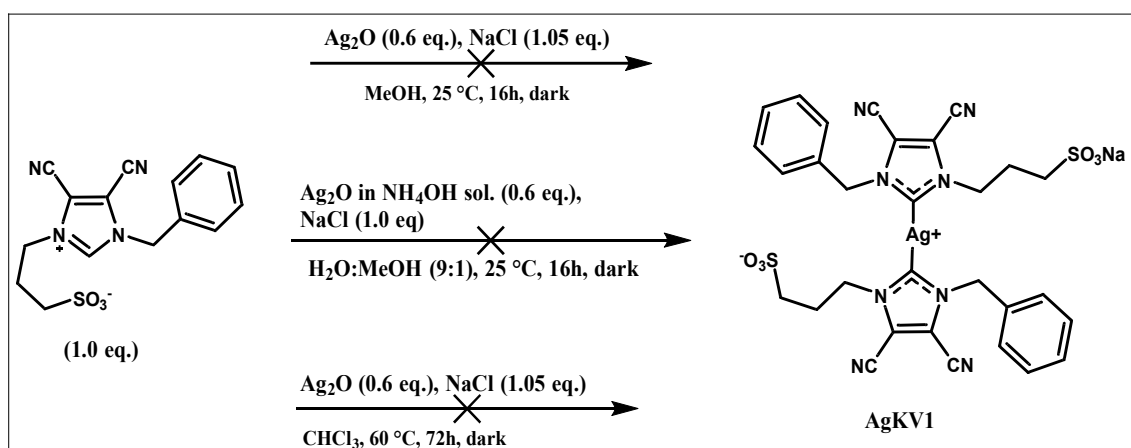


Scheme 17 – AgPV1 complexation adopting Tollens' solution

In this case, a small fraction of methanol was added to the system to improve the solubility of the salt, since it does not fully dissolve in an ammoniacal solution alone and the mixture does not homogenize properly. For the AgFV11 complex in particular, the procedure proved to be highly effective, with the complex forming within just a few minutes and being immediately isolable from the reaction mixture. Other salts were also successfully complexed using this method, as reported in the Experimental Section.

Synthesis tests for AgKV1

The only zwitterionic structure isolated from 4,5-dicyanoimidazole was KV1. All attempts to prepare and isolate KV2, KV11, and KV22 were unsuccessful. Since KV1 was the sole imidazolium salt accessible within this series, it was used for the synthesis of the corresponding silver complex by applying both methods A and B. However, neither approach proved effective. A further attempt was carried out in CHCl_3 , but this also failed to yield any isolable product:

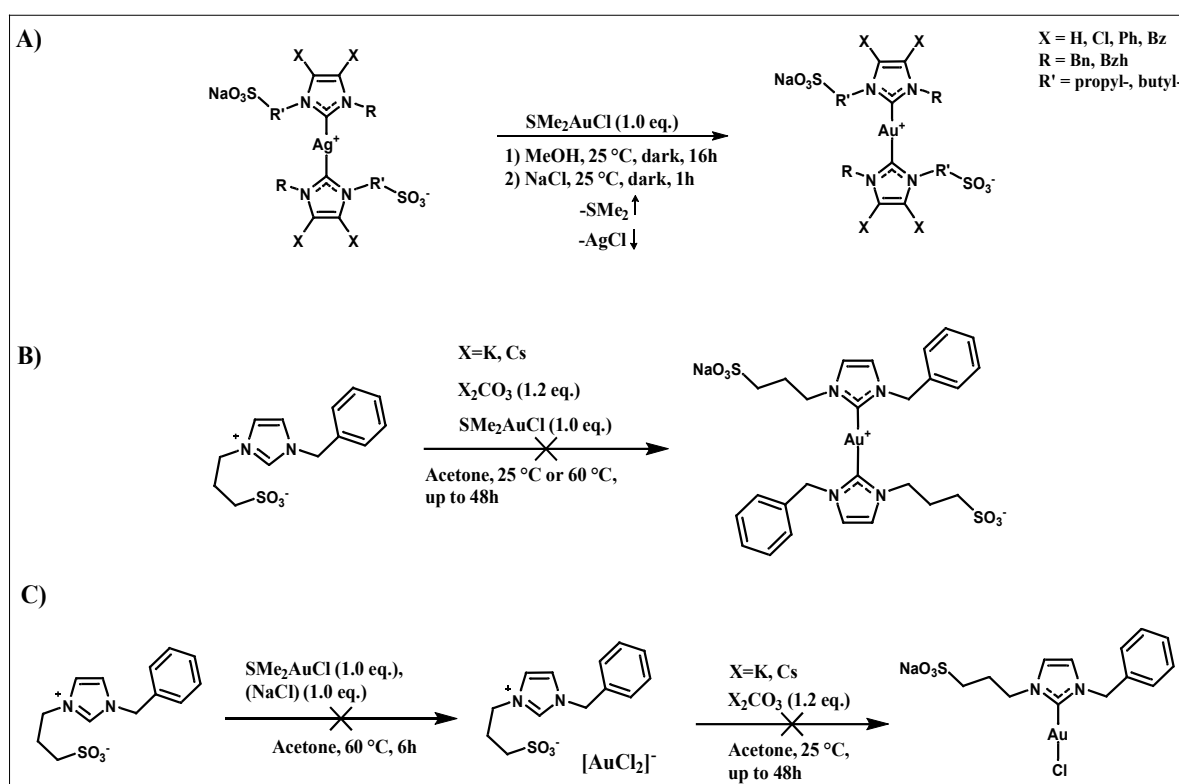


Scheme 18 – AgKV1 complexation's conditions tested

Interest in this class of structures arises from the very limited number of examples reported in the literature. Although the desired complexes could not be synthesized, additional strategies will be explored in order to extend the study to this family of organometallic systems.

4.3 Synthesis of the gold Au(I) complexes

For the synthesis of the gold complexes, a transmetallation strategy was employed starting from the corresponding silver structures. Both the direct synthesis procedure and the in situ transmetallation carried out immediately after the formation of the silver complex in solution were evaluated. To assess the effectiveness and reproducibility of the two methodologies, the zwitterionic proligand FV1 was used as a reference substrate, following the procedures reported below:



Scheme 19 – Au(I)-NHCs complexation's conditions adopted

Method A consists of the transmetallation approach. In this method, the corresponding silver complex is first prepared and, after filtration through Celite, the gold precursor chloro(dimethylsulfide)gold(I) is added to promote ligand exchange at the metal center^[15]. This step generates AgCl as a byproduct, which is subsequently removed by filtration. Methods B and C, instead, were designed to obtain the gold complex directly from the imidazolium salt, following two different strategies^[16]. In Method B, all components were combined in a single step in an attempt to form the complex directly. In Method C, the complexation was evaluated by separating the synthetic steps: first generating the aurate

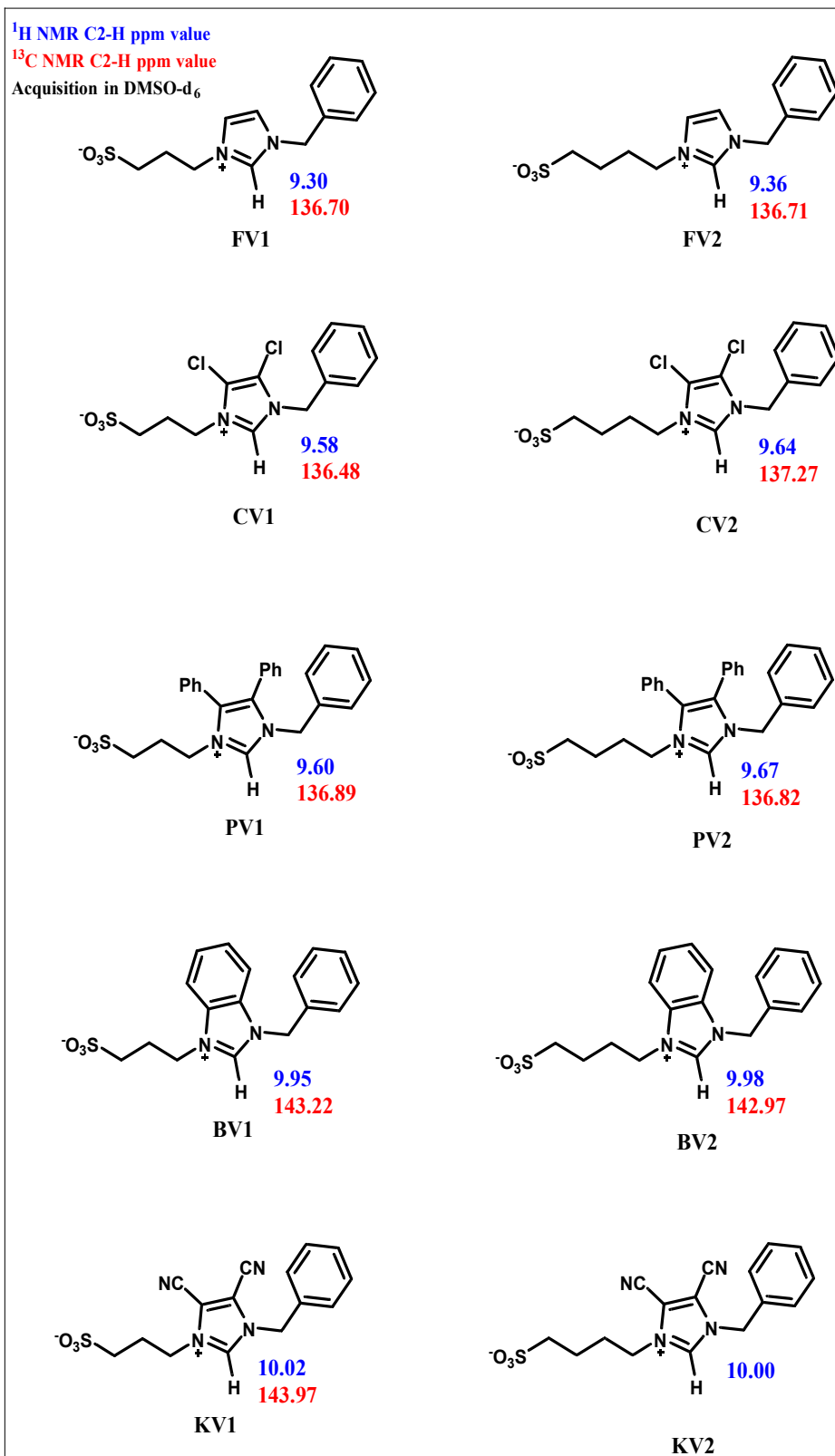
species $[\text{AuCl}_2^-]$, and then forming the carbene in situ through deprotonation of the C2–H hydrogen using a mild base. The direct-synthesis attempts did not yield the expected results for this substrate under the tested conditions. One likely reason is the poor solubility of the salt in acetone, combined with the absence of a suitable halide counterion required to promote the formation of the aurate intermediate AuX_2^- , which is usually generated in situ from halide-containing imidazolium salts. Because of time and resource constraints, further optimization of these direct routes was not pursued.

Chapter 5 – Discussion

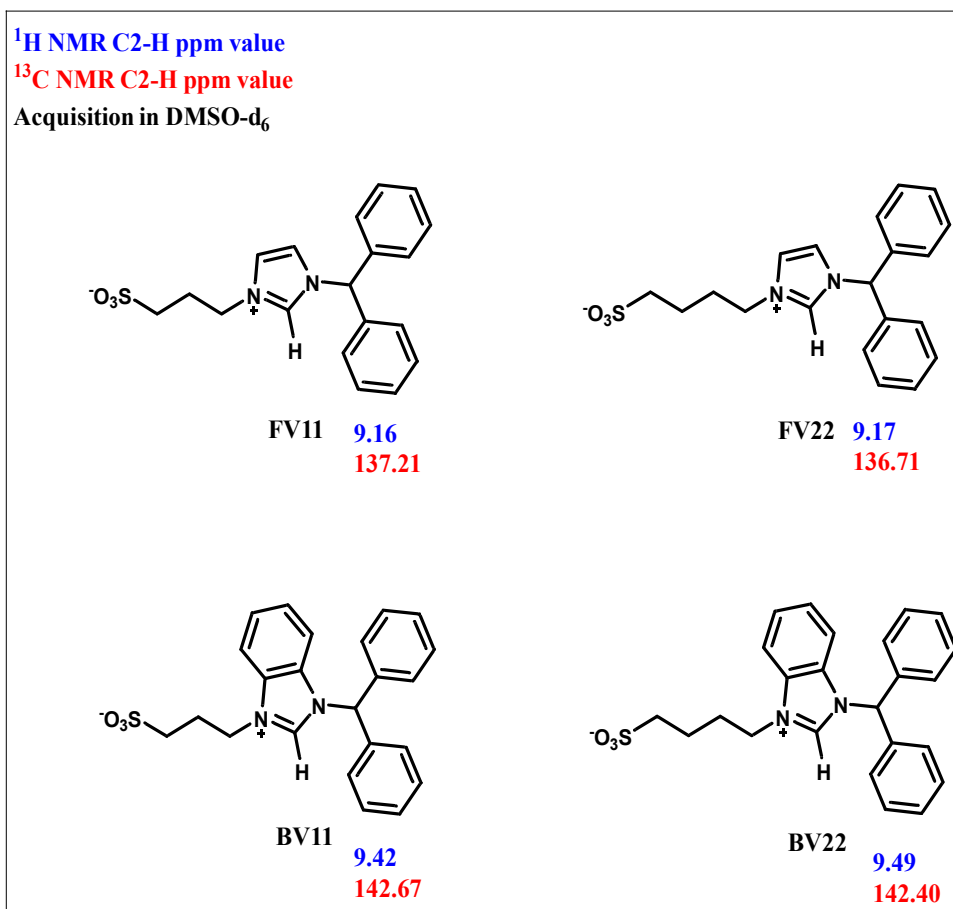
5.1 NMR Characterization of the zwitterionic salts

With the exception of a few structures, the synthesis of the N-benzyl and N-benzhydryl derivatives was confirmed by NMR analysis using the same deuterated solvents reported in the literature. Since the spectroscopic features of these compounds are already well established, no additional characterization was performed, and the acquired data were simply compared with the values previously reported. Their successful synthesis is further supported by the structural characterization of the subsequent derivatives obtained from these substrates.

The zwitterionic structures were obtained through the N-alkylation of the corresponding imidazole substrates bearing either 1-benzyl or 1-benzhydryl substituents, employing propanesultone or butanesultone to introduce the alkylsulfonate chain. According to the literature, NMR characterizations are typically performed in polar protic solvents such as D₂O or MeOD, in which these salts display higher solubility. The use of these deuterated solvents leads to H/D exchange at the C2–H position of the imidazolium ring. Experimentally, this manifests as a progressive decrease or the complete disappearance of the diagnostic C2–H signal over time^[17]. This behavior is consistent with the intrinsic acidity of the C2 carbocation and raised concerns about misinterpreting the disappearance of the signal as evidence for metal complex formation. To ensure reliable structural assignment, zwitterionic salts were analyzed in DMSO-d₆. Under these conditions, the ¹H NMR spectra clearly display the diagnostic C2–H resonance of the zwitterionic structure, observed in the 9.10–10.10 ppm region. In the ¹³C NMR spectra, the corresponding carbon signal appears near the quaternary aromatic carbon of the N-bound benzyl/benzhydryl substituent, generally between 135 and 145 ppm. This resonance shifts further downfield in the presence of electron-withdrawing substituents at positions 4 and 5 of the ring and, more broadly, tends to appear at slightly higher ppm values when the butanesulfonate chain is present, likely due to the increased charge contribution to the heterocycle. The ¹³C NMR signal of the C2 carbon is broadly consistent with the trend observed for the proton resonance, although the correlation is not always perfectly linear.



Scheme 1 – Chemical-shift values (ppm) reported for the C2–H resonance in the benzyl-substituted zwitterionic salts



Scheme 2 – Chemical-shift values (ppm) reported for the C2–H resonance in the benzhydryl-substituted zwitterionic salts

Since the C2 signal lies close to the quaternary carbon resonances of the benzyl and benzhydryl groups in the spectra, an unambiguous identification required the acquisition of a ¹³C-DEPT-135 spectrum, which allowed for a clear discrimination of the C2 resonance. Further confirmation of the assignments was obtained through 2D-NMR experiments (HSQC and HMBC), which enabled the determination of the connectivity between the resonating groups. Another element supporting the correct formation of the salt is the chemical-shift pattern observed for the sulfonate chain attached to the ring. Upon the opening of the sultone ring, the resonances of the methylene group bound to the imidazolium nitrogen (N–CH₂) and of the methylene unit adjacent to the sulfonate moiety (CH₂–SO₃[–]) undergo a marked shift. These variations are clearly detectable by comparing the ¹H and ¹³C NMR spectra, providing further confirmation of the successful formation of the zwitterionic structure. Finally, the success of the reaction is also indicated ed by the chemical-shift variations observed for the

benzylic and benzhydrylic substituents bound to the imidazolium nitrogen. Upon salt formation, the resonances of the N-CH₂ and CH groups undergo a noticeable downfield shift, a trend detectable in both the ¹H and ¹³C NMR spectra.

5.2 IR characterization of zwitterionic salts

The infrared spectroscopy characterization of the zwitterionic structures was performed using ATR-FTIR acquisition. Although the vibrational profiles of the salts are not fully resolved, the spectra clearly show the diagnostic regions corresponding to the functional groups of interest. The 1350–1500 cm⁻¹ region is associated with the C=N stretching vibrations of the imidazole ring^[18], while the 1039–1195 cm⁻¹ region corresponds to the SO₃⁻ stretching modes^[11]. The 3028–3125 cm⁻¹ region reflects the characteristic C–H stretching vibrations of the imidazolium ring^[11]. The resulting vibrational profiles support and complement the other experimental data collected.

5.3 NMR characterization of the silver-complexed structures

Once isolated, the silver complexes retain their fine powdery and generally white appearance when stored under an inert nitrogen atmosphere and at low temperatures. Exposure to temperatures exceeding ambient conditions, prolonged contact with air, or the presence of moisture induces visible changes in the solid state, typically leading to the darkening or browning of the material. Although the underlying mechanism has not been fully elucidated, this behavior is plausibly associated with partial hydrolysis of the complex followed by reduction of the silver centers, ultimately giving rise to darkened regions within the solid.

The NMR characterization of the silver complexes was carried out by dissolving the samples in DMSO-d₆, allowing a direct comparison between the spectra of the coordinated structures and those of the corresponding imidazolium precursor salts. Complex formation is confirmed by the disappearance of the C2–H signal in the ¹H NMR spectrum, this resonance, which is clearly visible in the zwitterionic salts, represents the key diagnostic marker for metal coordination at the carbene center. In the ¹³C NMR spectra, the coordinated species are expected to display the characteristic C2– 107/109Ag carbon resonance; however, in our case,

this signal is not observed. This is most likely due to extensive broadening and fast relaxation processes induced by the coordinated silver center^[19], or potentially due to the fluxional behavior of the Ag–C bond. In several complexes, additional downfield shifts are observed for protons located in proximity to the imidazole ring. These include the N–CH₂ group of the alkylsulfonate chain and the N–CH/N–CH₂ groups of the benzhydryl and benzyl substituents. Such shifts reflect the redistribution of electron density upon coordination of the carbene to Ag(I). After isolation and initial characterization, each complex was re-analyzed after twenty-four hours to assess its stability in solution at room temperature. Most of the isolated complexes showed minimal to no hydrolysis, indicating high stability under these conditions. Significant hydrolysis was observed only for the organometallic complexes AgBV11 and AgBV22. This behavior is not easily rationalized, as no evident structural features appear to predispose these particular complexes to increased lability or reduced stability. Moreover, the presence of the bulky benzhydryl substituent is expected to offer greater steric protection of the metal center against hydrolytic processes involving water or other polar protic species.

5.4 NMR characterization of the gold-complexed structures

The gold complexes were all obtained via transmetallation and, similar to the silver analogues, must be handled under an inert atmosphere and kept at low temperatures to preserve their integrity. When freshly isolated as powders, they typically appear light-coloured or slightly violet. Upon standing, the violet hue becomes more pronounced. This behavior is characteristic of certain gold complexes, where partial degradation leads to the cleavage of the metal–carbene bond and the formation of colloidal or metallic gold species, which impart the darker coloration. For this reason, the synthesis, handling, and NMR characterization were carried out expeditiously to minimize decomposition. Regarding the NMR characterization, no significant variations are observed in the ¹H NMR spectra relative to the silver intermediates, whereas the ¹³C NMR data clearly support the formation of the gold complex through the appearance of the C2–Au resonance. This signal typically appears between 160 and 170 ppm, in agreement with literature reports for sulfonate functionalized NHC–Au(I) systems^[20]. The successful transmetallation to gold offers indirect yet compelling evidence for the prior formation of the corresponding silver complexes. Even though the expected C2–^{107/109}Ag resonance is not observed in the ¹³C NMR spectra, the chemical

reactivity of the system confirms the presence of the silver-bound carbene species. In general, the signal resolution in the complexes is diminished compared to the corresponding imidazolium precursor salts. One likely explanation is the dynamic coexistence of mono- and bis-carbene species in solution, both contributing to the overall resonance pattern. In some cases, discrete sets of adjacent signals can be distinguished and attributed to the simultaneous presence of these two species; in others, this equilibrium is less evident and results in broadened or poorly resolved peaks. In a number of instances, the acquisition of the ^{13}C NMR spectrum was not feasible, as the coordinated structures underwent decomposition via hydrolysis under the measurement conditions, likely triggered by trace amounts of water in the deuterated solvent. This process generated spectra characterized by overlapping or distorted resonances, consistent with the progressive degradation of the complex.

5.5 Mass determination – MALDI characterization

The structural determination of the zwitterionic salts was supported by matrix-assisted laser desorption ionization mass spectrometry (MALDI MS). The analysis was carried out in both positive- and negative-ion modes to account for the presence of both formal charges within the zwitterionic structure, although under the operative conditions employed the response in negative-ion mode was not always detectable. The positive-ion mode consistently confirmed the presence of the expected zwitterionic species. The spectra typically display multiple peaks corresponding to more than one zwitterionic molecule, arising from gas-phase aggregates formed during the desorption and ionization process. Despite these additional signals, they do not hinder the identification of the target molecular ions, which are reliably detected in all cases. The spectra show that, once the aggregates begin to form, the dimer of the zwitterionic salt appears as the most intense signal, while subsequent peaks correspond to the trimer, tetramer, and pentamer. Not only are multiple aggregated species detected, but their relative intensities vary depending on whether a sodium cation (Na^+) is present, replacing a proton (H^+) within the cluster. The monomeric signal shows a nearby peak attributable to the presence of a sodium cation (Na^+), plausibly coordinated to the sulfonate group. The same behavior is observed for the dimer, whose relative intensity is often the highest among the detected signals. Starting from the tetramer, the relative intensities of the aggregated species and their sodium-containing analogues become inverted. This indicates that the species formed most frequently under the analytical conditions are those incorporating the Na^+ cation.

The pentameric signal shows no accompanying peak corresponding to a sodium-containing species. This may be due to the reduced stability of such a structure under the analysis conditions, since the pentamer already consists of five zwitterionic units that must remain organized and intact during flight to the detector. Alternatively, a sodium-containing pentamer may indeed form, but its mass could be too high for it to reach the detector, causing it to precipitate during the TOF flight. This possibility cannot be excluded, especially considering that the analyzer is calibrated to detect a specific mass window selected by the operator, which may have been set primarily to capture the monomer-rich region. In the literature, this type of behavior is not discussed for sulfonated structures, most likely because it has no real relevance to determining the exact mass of the molecule. Nevertheless, it is considered noteworthy to report it here, as it may be of interest for future studies involving gas-phase aggregation phenomena in such structures.

The MALDI characterization was also carried out for the Ag(I)- and Au(I)-NHC complexes, although it was not possible to obtain data for all the synthesized structures. In the MALDI(+) spectra, three main peaks can be distinguished: the peak corresponding to the precursor salt, the peak of the homoleptic complex, and the peak of the heteroleptic complex. The simultaneous presence of both complex species suggests the possibility of an equilibrium between mono- and bis-carbene forms, arising from dissociation/formation processes that may occur during the sublimation of the acidic matrix. The bis-carbene species generally shows the most intense signal, indicating that this form is predominant under the analytical conditions. The spectra also confirm the presence of the expected structures, including species bearing different counterions such as H^+ , Na^+ , and Ag^+ .

5.6 References

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Chapter 6 – Experimental section

Solvents and reagents opted for syntheses were purchased from TCI Chemicals, Fluorochem, Sigma-Aldrich and were used as received. Each reaction was carried out under nitrogen atmosphere to exclude oxygen and moisture. Yields reported are averaged on three results at least. Products obtained after each synthetic step were characterized by ^1H NMR and ^{13}C NMR spectroscopy. Spectra were recorded on different Bruker instruments at the Organisch-Chemisches Institut (Im Neuenheimer Feld 270, D-69120 Heidelberg) operating at various resonance frequencies: Bruker Avance III 300 (300 MHz for ^1H , 75 MHz for ^{13}C), Bruker Avance III 400 (400 MHz for ^1H , 100 MHz for ^{13}C), Bruker Avance III 500 (500 MHz for ^1H , 126 MHz for ^{13}C), Bruker Avance III 600 (600 MHz for ^1H , 151 MHz for ^{13}C) and Bruker Avance Neo 700 (700 MHz for ^1H , 176 MHz for ^{13}C). Additional measurements were performed using a Varian INOVA 400 MHz spectrometer at the University of Basilicata (Potenza). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), multiplet (m) and broad (br). Mass analyses were conducted using the Bruker timsTOF fleX instrument operated in MALDI mode. The samples analyzed with this instrument were processed at Organisch-Chemisches Institut, Im Neuenheimer Feld 270, D-69120, Heidelberg. MALDI FT-ICR investigations were performed using a Bruker Solarix XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) provided with a 7 T refrigerated actively shielded superconducting magnet (Bruker Biospin, Wissembourg, France). The samples were prepared in positive ion mode using a MALDI ion source (Bruker Daltonik GmbH, Bremen, Germany) and were processed at University of Salerno. The range of the mass was set to m/z 200-3000. Laser power was set to 28%, and 20 laser shots were employed for each scan. The mass spectra were calibrated externally using a mix of peptide clusters in MALDI ionization positive mode. Was applied a linear calibration. To increase the accuracy of the analysis, the samples were recalibrated internally by matrix ionization (2,5-dihydroxybenzoic acid). ATR-FTIR spectra were acquired using a diamond ATR accessory. Measurements were conducted at Organisch-Chemisches Institut, Im Neuenheimer Feld 270, D-69120, Heidelberg. Samples were analyzed as received.

General synthesis for N-benzyl-imidazol compounds

In a preheated flask was prepared a solution of KOH (3.56 mmol, 1.2 eq.) in methanol (3.0 M). The KOH pellets were left to dissolve at 25 °C under vigorous stirring, then imidazole compound was added (2.96 mmol, 1.0 eq.) and left to dissolve. The mixture was left under stirring at 25 °C for two hours, then the solvent was dried in vacuum at 40 °C. The final crude

was dissolved in acetone and left under stir for 0.5 hours at 25 °C. A solution of benzylbromide (2.37 mmol, 0.8 eq.) in acetone (2.0 M) was added dropwise in 5 minutes. The course of reaction was checked by TLC. After the disappearing of benzylbromine spot under UV light (254 nm), the mixture was filtered and the liquid phase was dried under vacuum. The crude was finally purified on silica-gel column (70-230 mesh).

General synthesis for N-benzyl-imidazolium salt compounds in acetonitrile

The N-benzylated imidazole substrate (0.644 mmol, 1.0 eq.) and sultone (0.966 mmol, 1.5 eq.) was mixed in MeCN (4.0 M). The mixture was heated at 90 °C under stirring and the reaction was carried out for 72 hours. After cooling at 25 °C, a mixture of acetone/Et₂O 1:1 was added in order to obtain a white precipitate, which was filtered on paper. The final compound was achieved after washes three times at least with Et₂O and dried under vacuum.

General synthesis for N-benzhydryl-imidazol compounds

In a preheated flask was prepared a solution of KOH (3.56 mmol, 1.2 eq.) in methanol (0.45 M). The basis pellets were left to dissolve at 25 °C under vigorous stirring, then imidazole compound was added (2.96 mmol, 1.0 eq.) and left to dissolve. The mixture was left under stirring at 25 °C for two hours, then the solvent was dried in vacuum at 40 °C. The final crude was dissolved in acetone and left under stir for 0.5 hour at 25 °C. A solution of benzhydrylbromide (2.37 mmol, 0.8 eq.) in acetone (2.0 M) was added dropwise for 15 minutes. The course of reaction was checked by TLC. After the disappearing of benzylbromine spot under UV light (254 nm), the mixture was filtered and the liquid phase was dried under vacuum. The crude was finally purified on silica-gel column (70-230 mesh).

General synthesis for N-benzhydryl-imidazolium salt compounds in acetonitrile

The N-benzhydryl imidazole substrate (0.644 mmol, 1.0 eq.) and sultone (0.966 mmol, 1.5 eq.) was mixed in MeCN (4.0 M). The mixture was heated at 90 °C under stirring in a capped flask and the reaction was carried out for 72 hours. After cooling at 25 °C, a mixture of acetone/Et₂O 1:1 was added in order to obtain a white precipitate which was filtered on paper. The final compound was achieved after washes three times at least with Et₂O and dried under vacuum.

General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy A

A solution of imidadazolium salt (0.178 mmol, 1.0 eq.) in N₂-degassed methanol (0.8 M) was prepared and was stirred for 1 hour at 25 °C. Ag₂O (0.0981 mmol, 0.6 eq.) was added, keeping the reactor in dark to prevent light. The mixture was stirred for 6 hours and then NaCl (0.178 mmol, 1.0 eq.) was added, leaving under stirring overnight. The resulting mixture was finally filtered on celite and the volume of solvent was reduced to few mL. Et₂O was added in order to make the solution opaque and the flask was left at 4 °C until a white precipitate appears. The supernatant was collected, the precipitate was dried in vacuum at 30 °C, then a mixture of DCM and hexane was added in order to facilitate the isolation of the final product. The desired product was finally recovered drying the white suspension in vacuum at room temperature.

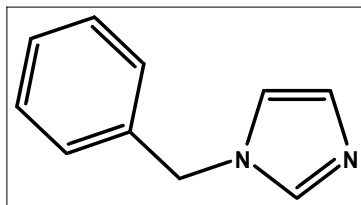
General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B

A solution of imidadazolium salt (0.178 mmol, 1.0 eq.) and NaCl (0.178 mmol, 1.0 eq.) in N₂-degassed water (0.8 M) was prepared. A second solution containing Ag₂O (0.0981 mmol, 0.6 equiv.) and aqueous NH₃ was then prepared by adding a *quantum satis* amount of NH₃(aq) until complete dissolution of Ag₂O. This mixture was subsequently added to the first solution and the reaction was stirred for four hours in the dark. The resulting white precipitate was filtered, washed with cold EtOH, and dried under vacuum at 30 °C.

General synthesis for NHC-Au(I)-Cl sulfonate complexes

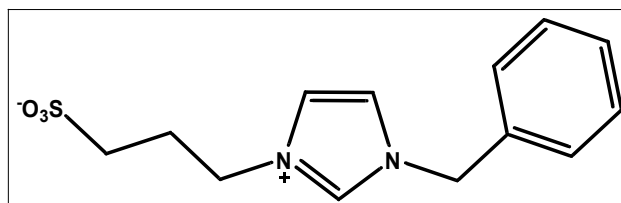
A solution of imidadazolium salt (0.178 mmol, 1.0 eq.) in N₂-degassed methanol (0.8 M) was prepared and was stirred for 1 hour at 25 °C. Ag₂O (0.0981 mmol, 0.6 eq.) was added, keeping the reactor in dark to prevent light. The mixture was stirred for 6 hours and then NaCl (0.178 mmol, 1.0 eq.) was added, leaving under stirring overnight. The resulting mixture was filtered on celite and Au(DMS)Cl (0.143 mmol, 1.0 eq.) was added to the solution, keeping under stirring in dark for 24 hours at 25 °C. NaCl (0.178 mmol, 1.0 eq.) was then added and the mixture was stirred 18 hours. The mixture was finally filtered, the solvent was removed under reduced pressure at 30 °C and the desired product was washed with cold diethyl ether.

1-Benzylimidazole (FV0)



In a double-joint reactor vessel, imidazole (1.0000 g, 14.7 mmol) was first dissolved in acetonitrile (30.0 mL) under magnetic stirring. When the solution was obtained, potassium carbonate (0.1243 g, 0.899 mmol) was added. After ten minutes, the solution was heated at 90°C. Once the solution was on reflux, a solution of benzylbromide (0.3589 g, 2.10 mmol dissolved in 10.0 mL of acetonitrile) was added by dropwise. The reaction was carried out at 85 °C until, by monitoring with TLC, the disappearing of the benzylbromide control spot was observed. Then the reaction mixture was cooled at room temperature, the liquid phase was collected by filtration and the solvent was removed under reduced pressure, leaving a whitish sticky layer. The residue was dissolved in DCM and was washed with a saturated aqueous solution of potassium carbonate (2×15.0 mL). The organic phase was collected, dried on Na₂SO₄ anhydrous and the solvent was evaporated to achieve a solid product that was finally washed with diethyl ether and n-hexane. The dry product finally obtained was powdery and whitish. Yield: 64.3%. The NMR characterization match the data reported in literature.

***N*-benzyl-*N'*-(propyl-3-sulfonate)-imidazolium salt (FV1)**

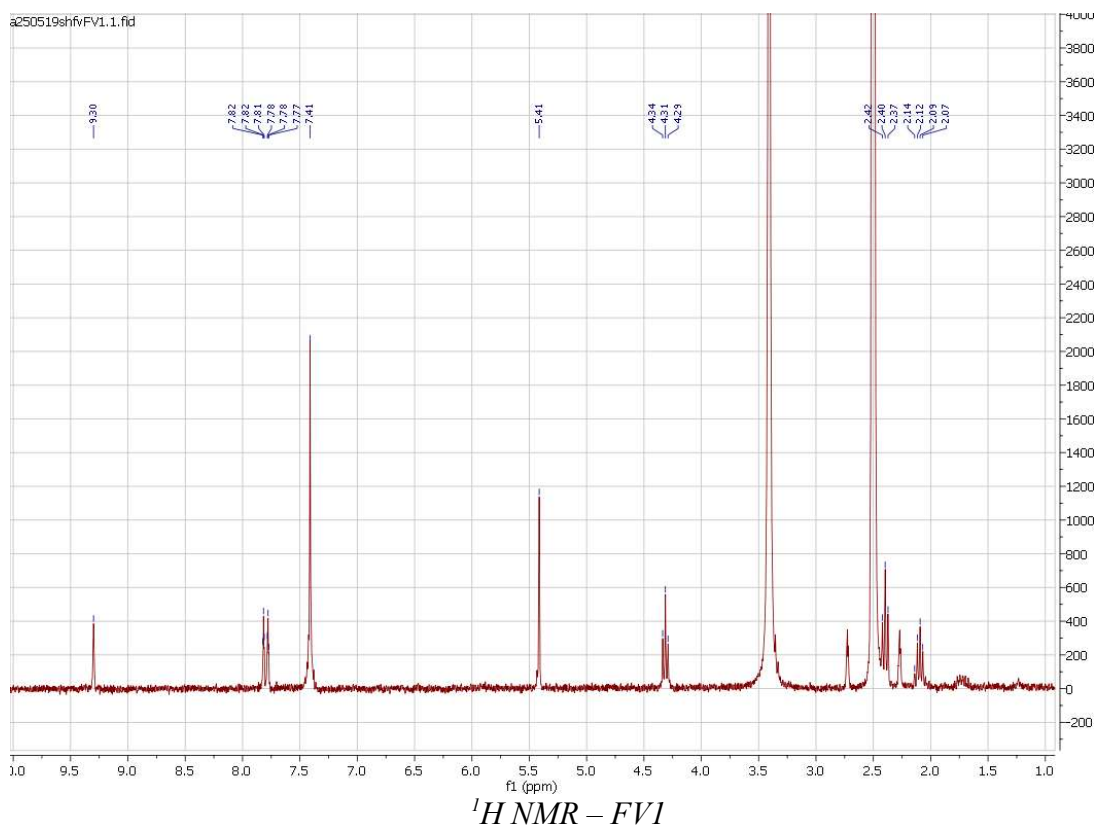


White powder. Soluble in H₂O, MeOH, slight soluble in DMSO. Yield = 62,8%.

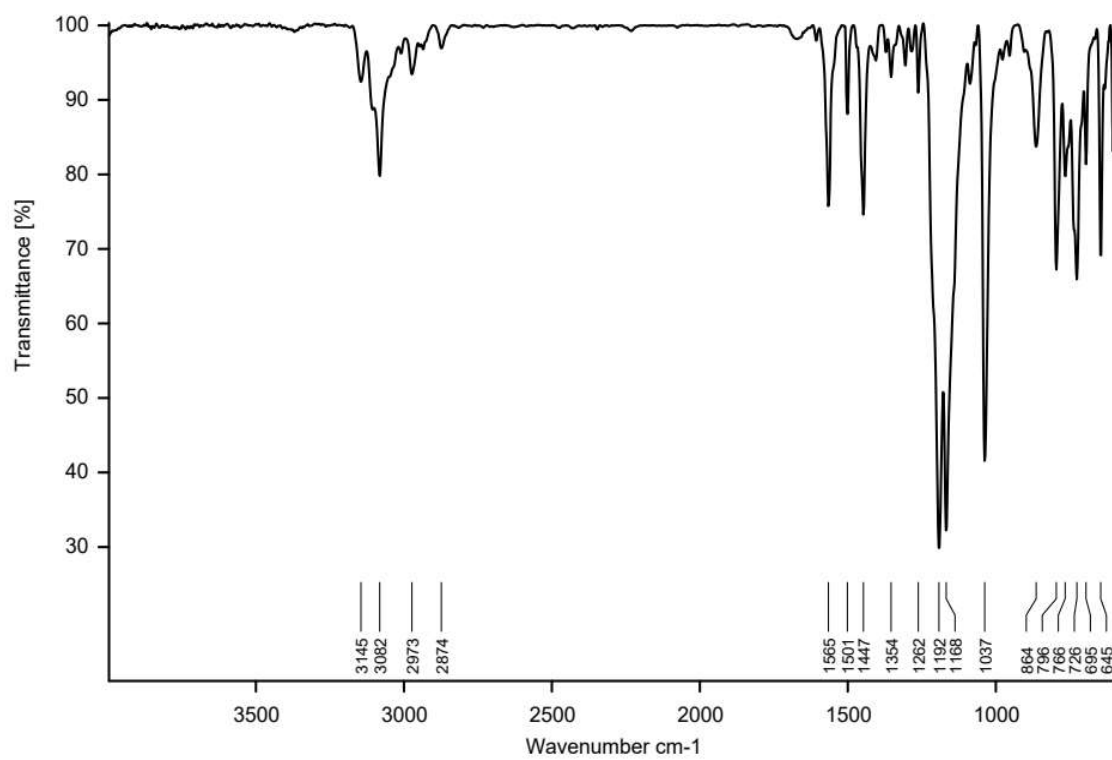
The NMR characterization match the data reported in literature^[1].

¹H NMR (400 MHz, DMSO-d₆) δ 9.30 (s, 1H, C2-H), 7.82–7.81 (t, 1H, C4-H), 7.78–7.77 (t, 1H, C5-H), 7.41 (m, 5H, Ar-H), 5.41 (s, 2H, Ph-CH₂-), 4.34–4.29 (t, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.42–2.37 (t, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.14–2.07 (q, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

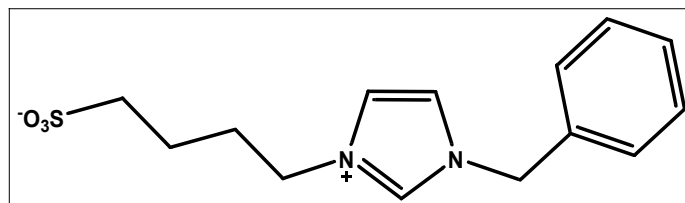
ATR-FTIR: ν 3145, 3082, 2973, 2874, 1565, 1501, 1447, 1354, 1262, 1192, 1168, 1037, 864, 796, 766, 726, 695, 645 cm⁻¹



**FV1
ATR**



***N*-benzyl-*N'*-(butyl-4-sulfonate)-imidazolium salt (FV2)**



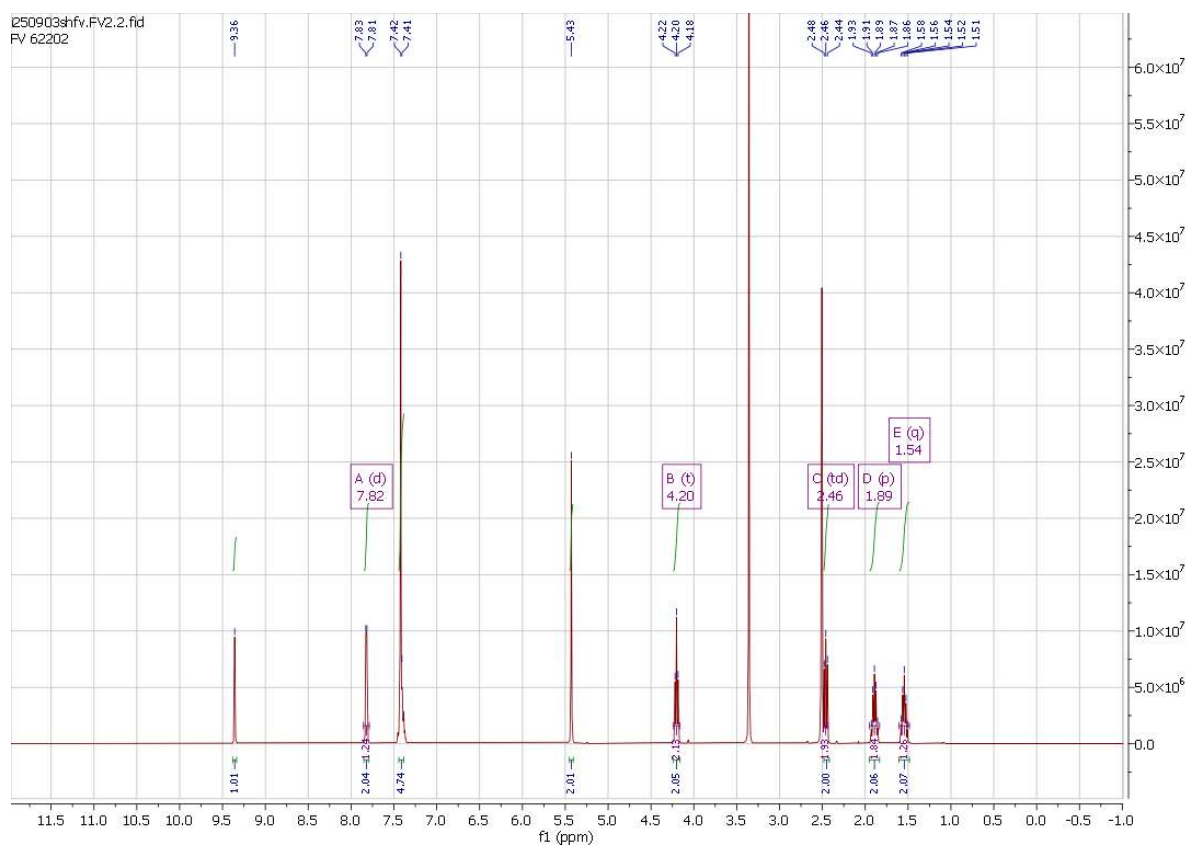
See “General synthesis for *N*-benzylated-imidazolium salt compounds in MeCN”

White powder. Soluble in H₂O, MeOH, slight soluble in DMSO. Yield = 75.0%

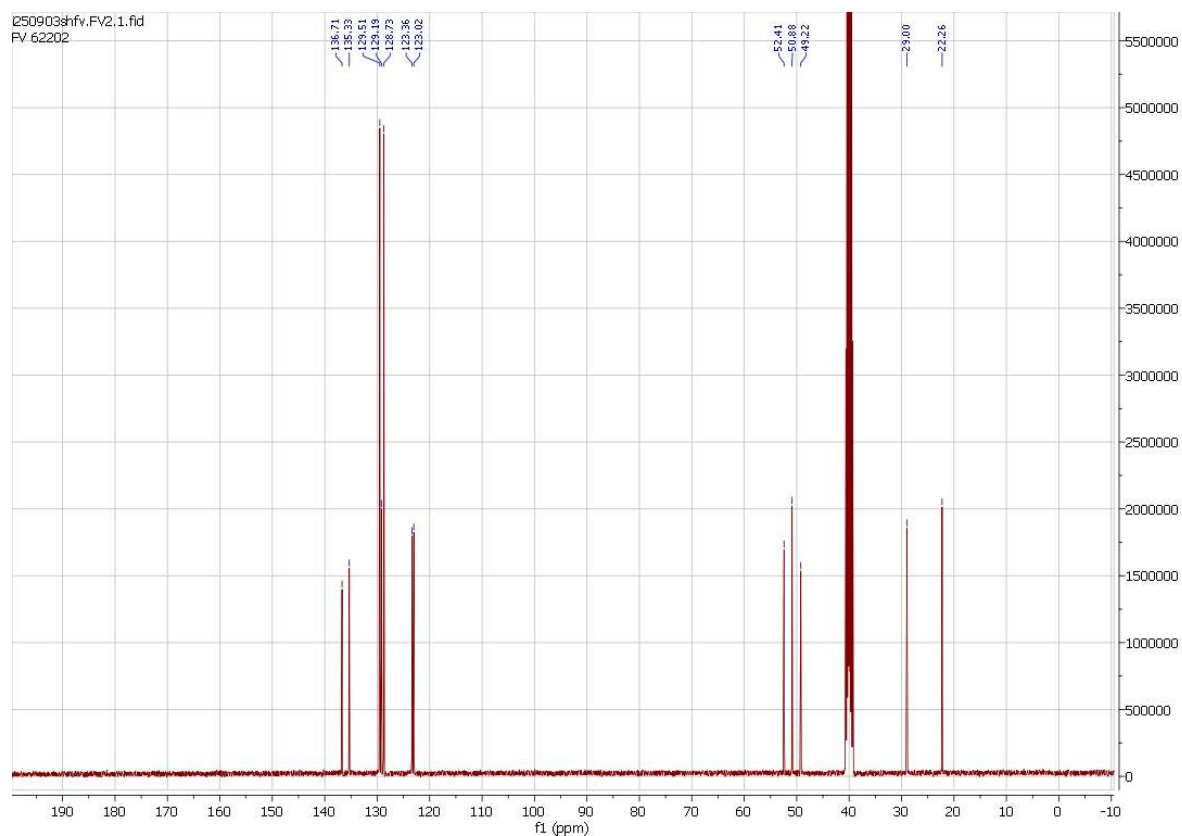
¹H NMR (400 MHz, DMSO-*d*₆) δ 9.36 (s, 1H, C2-H), 7.83–7.81 (d, *J* = 5.4 Hz, 2H, C4/5-H), 7.42 (m, 5H, Ar-H), 5.43 (s, 2H, Ph-CH₂-), 4.22–4.18 (t, *J* = 7.1 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 2.48–2.44 (t, *J* = 7.6 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.93–1.86 (q, *J* = 7.2 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.58–1.51 (q, *J* = 7.5 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻)

¹³C NMR (100 MHz, DMSO-*d*₆) δ 136.71 (C2), 135.33 (*Cipso*), 129.51, 129.19, 128.73 (Ph), 123.36, 123.02 (C4/5), 52.41 (Ph-CH₂-), 50.88 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 49.22 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 29.00 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 22.26 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻)

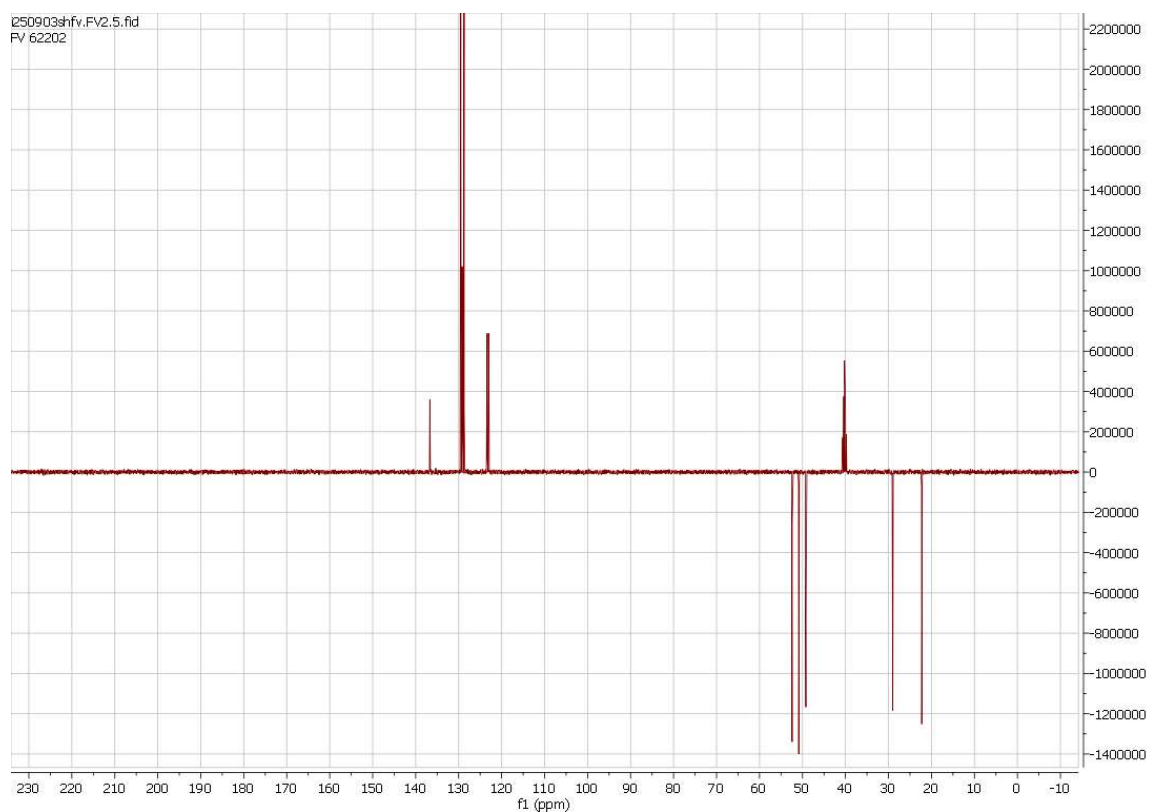
ATR-FTIR: ν 3145, 3084, 3045, 2974, 2875, 1566, 1503, 1447, 1354, 1262, 1190, 1169, 1034, 863, 795, 764, 728, 706, 645 cm⁻¹



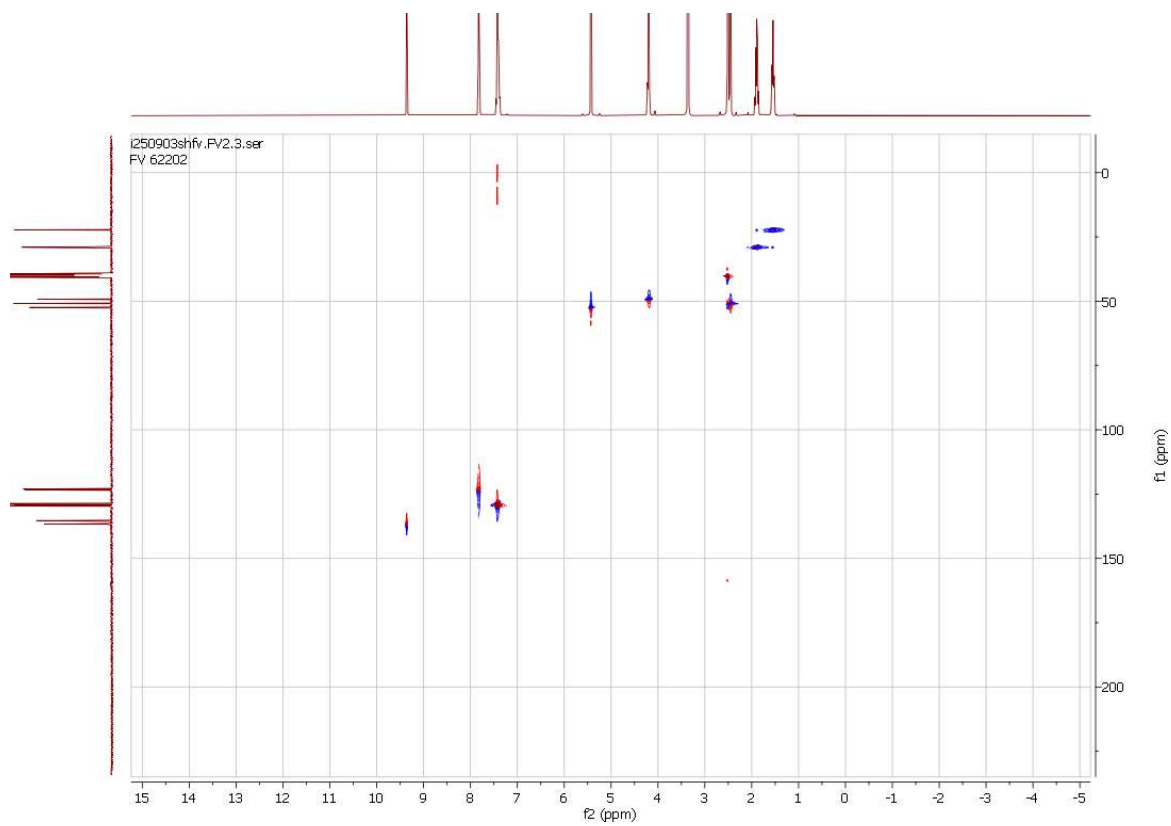
^1H NMR – FV2



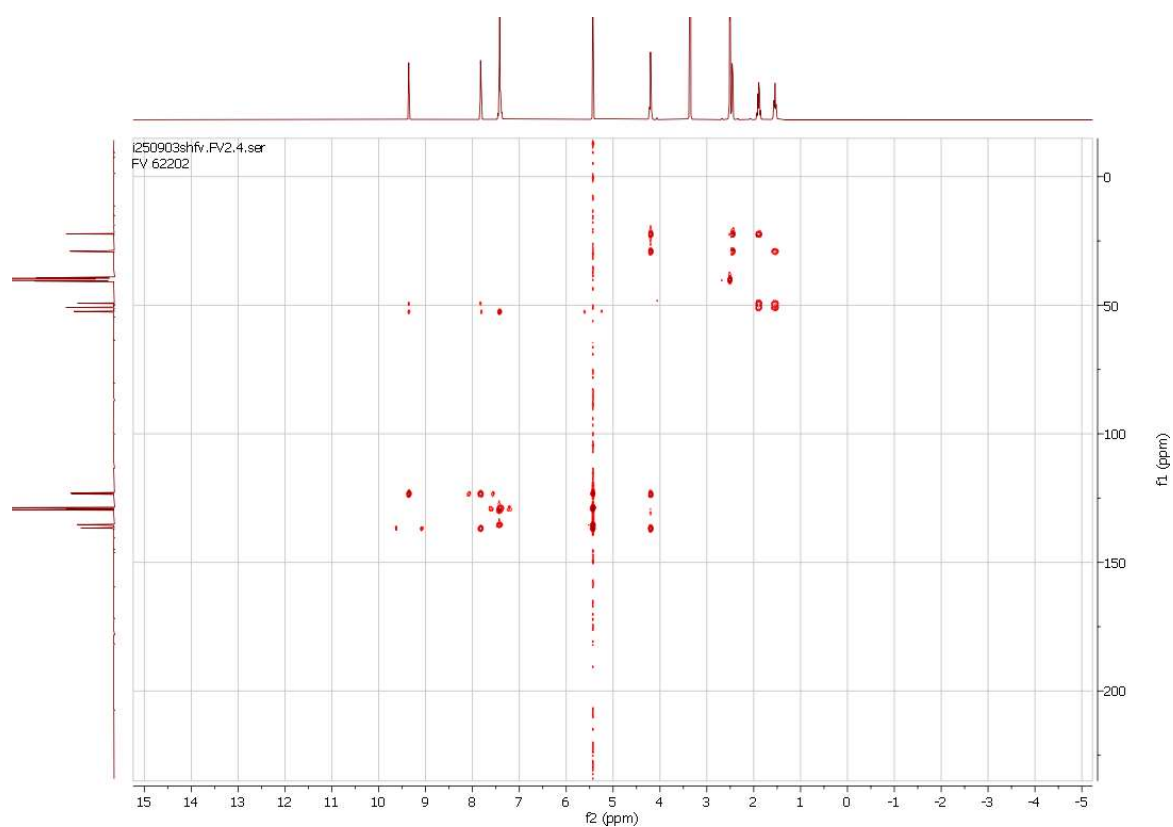
^{13}C NMR – FV2



DEPT-135 FV2

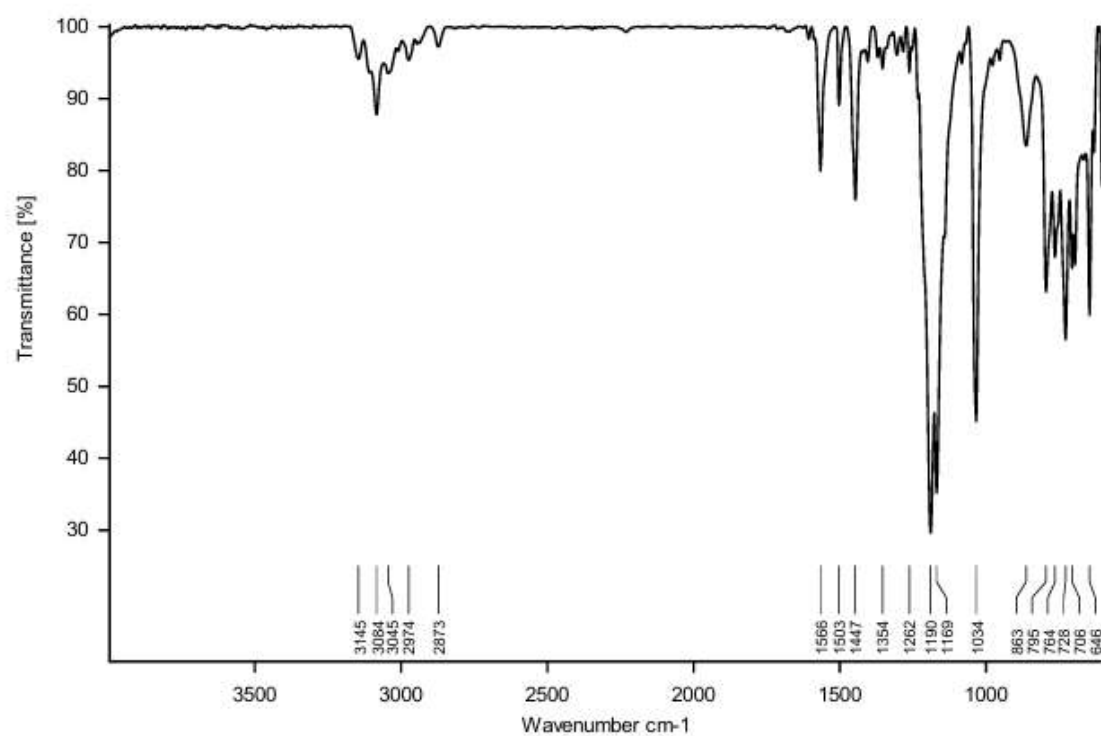


2D-HSQC FV2

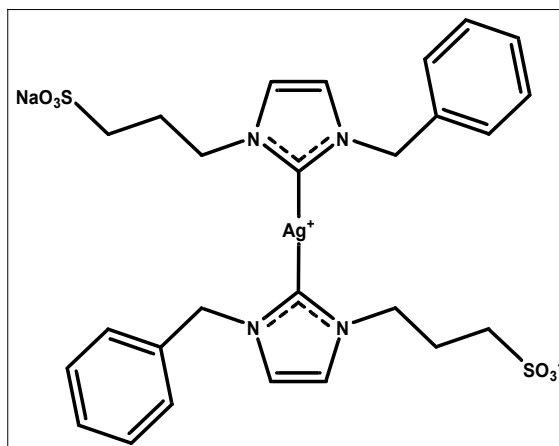


2D-HMBC FV2

FV2
ATR



Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)-2-yliden] silver chloride (AgFV1)



See “General synthesis for NHC-Ag(I)-Cl sulfonate complexes – Strategy A”

Whitish powder. Yield= 83.2%. The NMR characterization match the data reported in literature^[1].

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.56–7.55 (d, *J* = 1.95 Hz, 1H, C4/5-H), 7.54–7.54 (d, *J* = 1.9 Hz, 1H, C4/5-H), 7.40–7.31 (m, 5H, Ar-H), 5.36 (s, 2H, CH₂-Ph), 4.22–4.19 (t, *J* = 6.87 Hz, 2H, N-**CH**₂-CH₂-CH₂-SO₃[−]), 2.41–2.38 (t, *J* = 7.3 Hz, 2H, N-CH₂-CH₂-**CH**₂-SO₃[−]), 2.12–2.06 (q, *J* = 6.89 Hz, 2H, N-CH₂-**CH**₂-CH₂-SO₃[−]).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 137.58 (*Cipso*), 129.55, 128.90, 128.34 (Ar), 123.19, 122.23 (C4/5), 54.45 (Ph-CH₂-), 50.52 (N-**CH**₂-CH₂-CH₂-SO₃[−]), 49.48, 48.89 (N-CH₂-CH₂-**CH**₂-SO₃[−]), 28.15 (N-CH₂-**CH**₂-CH₂-SO₃[−]).

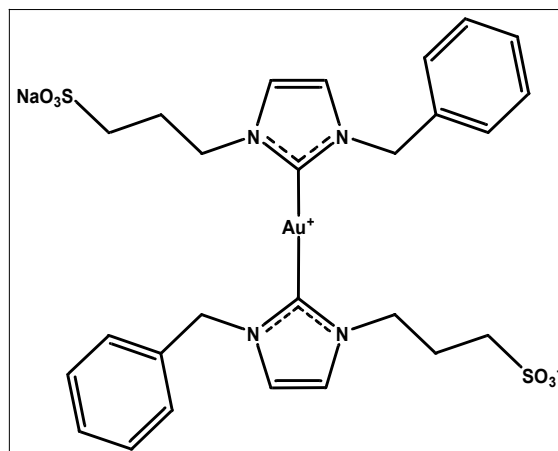
MS (MALDI-TOF, Positive mode)

m/z: 689.0634 [C₂₆H₃₁¹⁰⁷AgN₄NaO₆S₂]⁺, 691.0628 [C₂₆H₃₁¹⁰⁹AgN₄NaO₆S₂]⁺, 711.0457 [C₂₆H₃₀¹⁰⁷AgN₄Na₂O₆S₂]⁺, 713.0444 [C₂₆H₃₀¹⁰⁹AgN₄Na₂O₆S₂]⁺

MS (MALDI-TOF, Negative mode)

m/z: 422.9542 [C₁₃H₁₅AgClN₂O₃S][−], 667.0676 [C₂₆H₃₀AgN₄O₆S₂][−]

Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)-2-yliden] gold chloride (AuFV1)

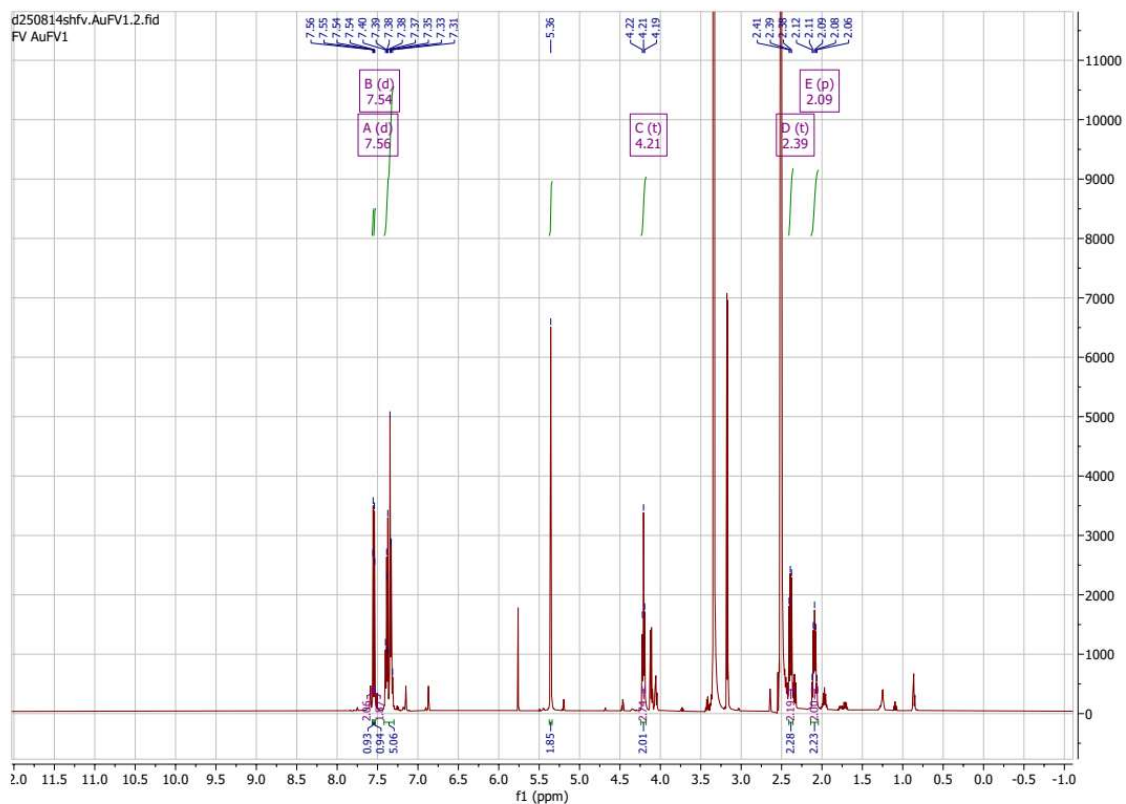
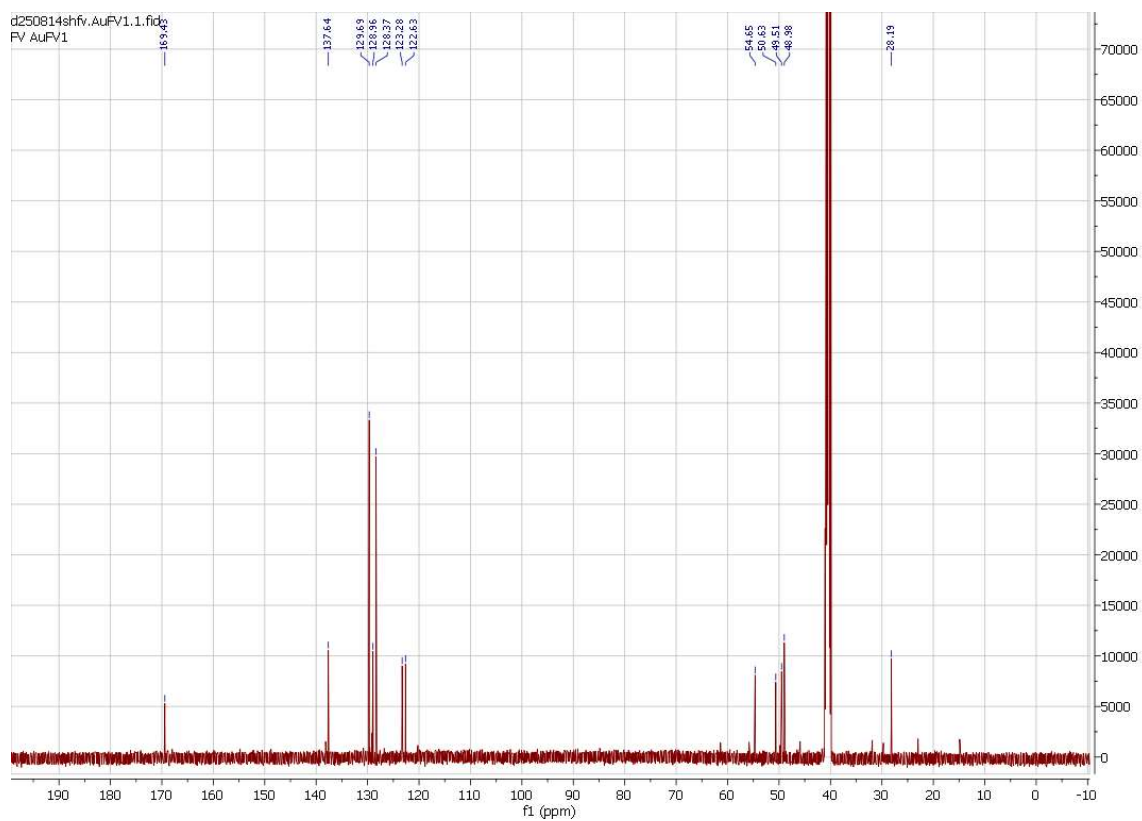


See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”

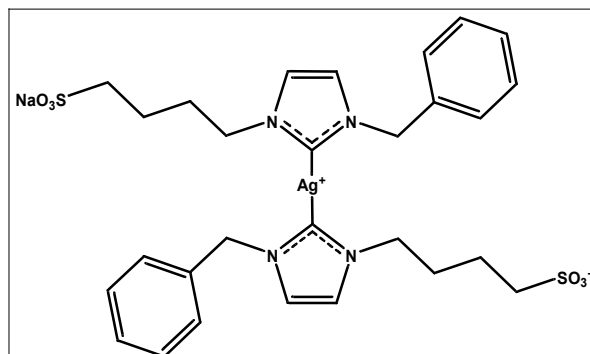
Light violet powder. Yield = 85.2 %.

^1H NMR (500 MHz, DMSO- d_6) δ 7.56–7.55 (d, J = 1.95 Hz, 1H, C4/5-H), 7.54–7.54 (d, J = 1.9 Hz, 1H, C4/5-H), 7.40–7.31 (m, 5H, Ar-H), 5.36 (s, 2H, CH₂-Ph), 4.22–4.19 (t, J = 6.87 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.41–2.38 (t, J = 7.3 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.12–2.06 (q, J = 6.89 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (126 MHz, DMSO- d_6) δ 169.43 (C-Au), 137.64 (*Cipso*), 129.69, 128.96, 128.37, 123.28, 122.63 (C4/5), 54.65 (Ph-CH₂-), 50.63 (N-CH₂-CH₂-CH₂-SO₃[−]), 49.51, 48.98 (N-CH₂-CH₂-CH₂-SO₃[−]), 28.19 (N-CH₂-CH₂-CH₂-SO₃[−]).

¹H-NMR – AuFV1 ^{13}C NMR – AuFV1

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)-2-yliden] silver chloride (AgFV2)



See “General synthesis for NHC-Ag(I)-Cl sulfonate complexes – Strategy A”

Ivory powder. Yield = 58.2%

^1H NMR (500 MHz, DMSO- d_6) δ 7.54 (dd, J = 1.37 Hz, 2H, C4/5-H), 7.40–7.33 (m, 5H, Ar-H), 5.35 (s, 1H, CH₂-Ph), 4.14–4.11 (t, J = 7.04 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.45–2.42 (t, J = 7.78 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.91–1.85 (q, J = 7.29 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.57–1.51 (q, J = 7.67 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

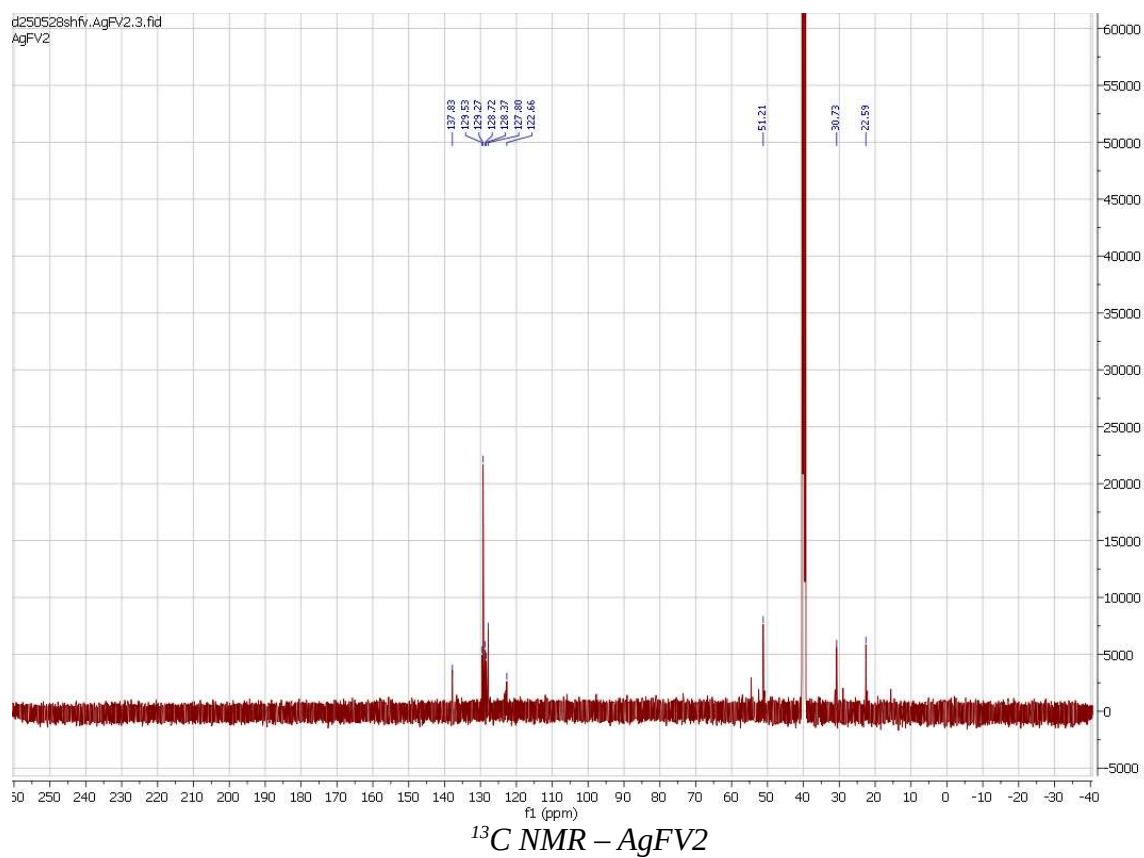
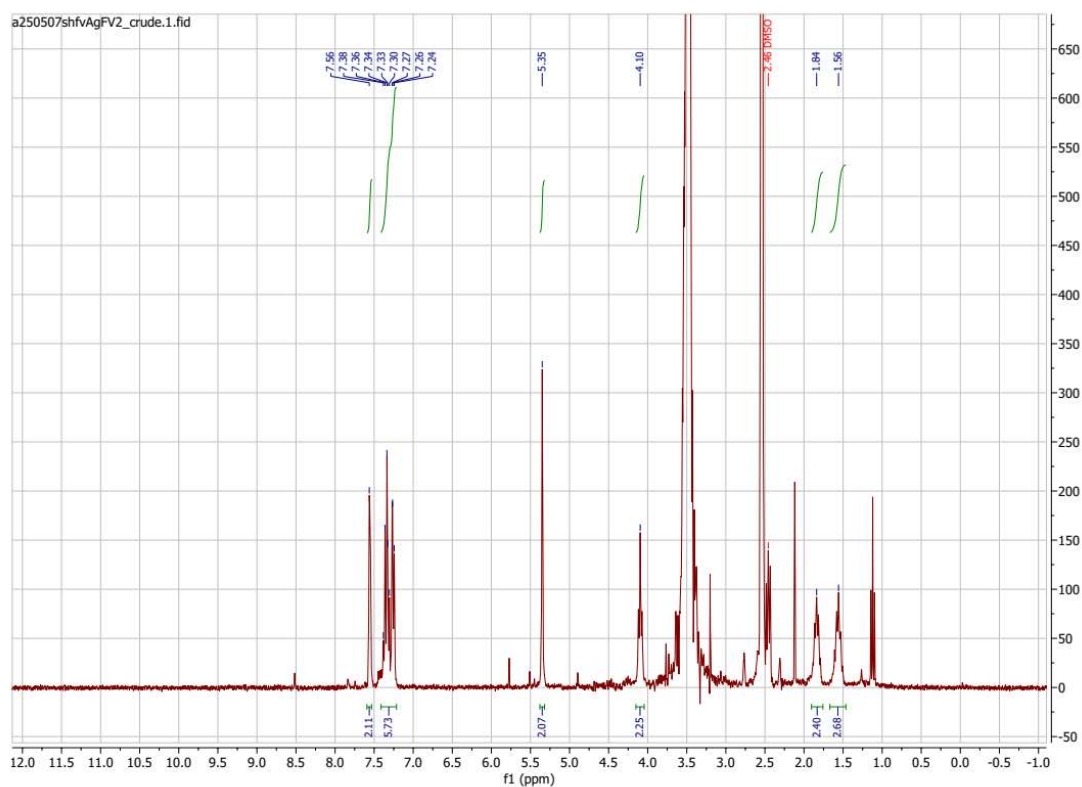
^{13}C NMR (126 MHz, DMSO- d_6) δ 137.58 (*Cipso*), 129.70, 128.94, 128.38 (Ar), 123.06, 122.67 (C4/5), 54.58 (Ph-CH₂-), 51.67 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 51.34 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 30.68 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 23.12 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

MS (MALDI FT-ICR, H₂O)

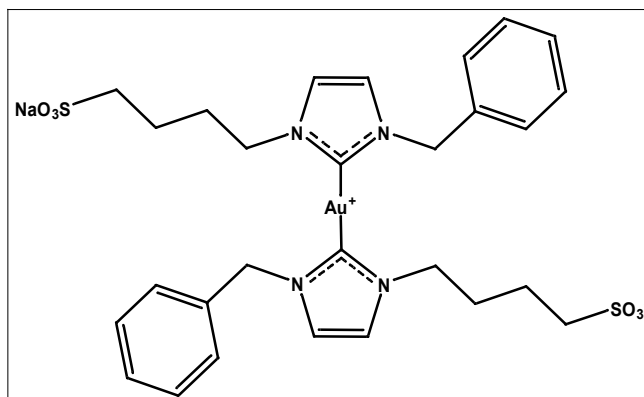
m/z : 597.18321 [C₂₅H₃₀AgNaN₄O₃S]⁺

MS (MALDI-TOF, Negative mode)

m/z : 436.9701 [C₁₄H₁₇AgClN₂O₃S][−], 695.0994 [C₂₈H₃₄AgN₄O₆S₂][−]



Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)-2-yliden] gold chloride (AuFV2)

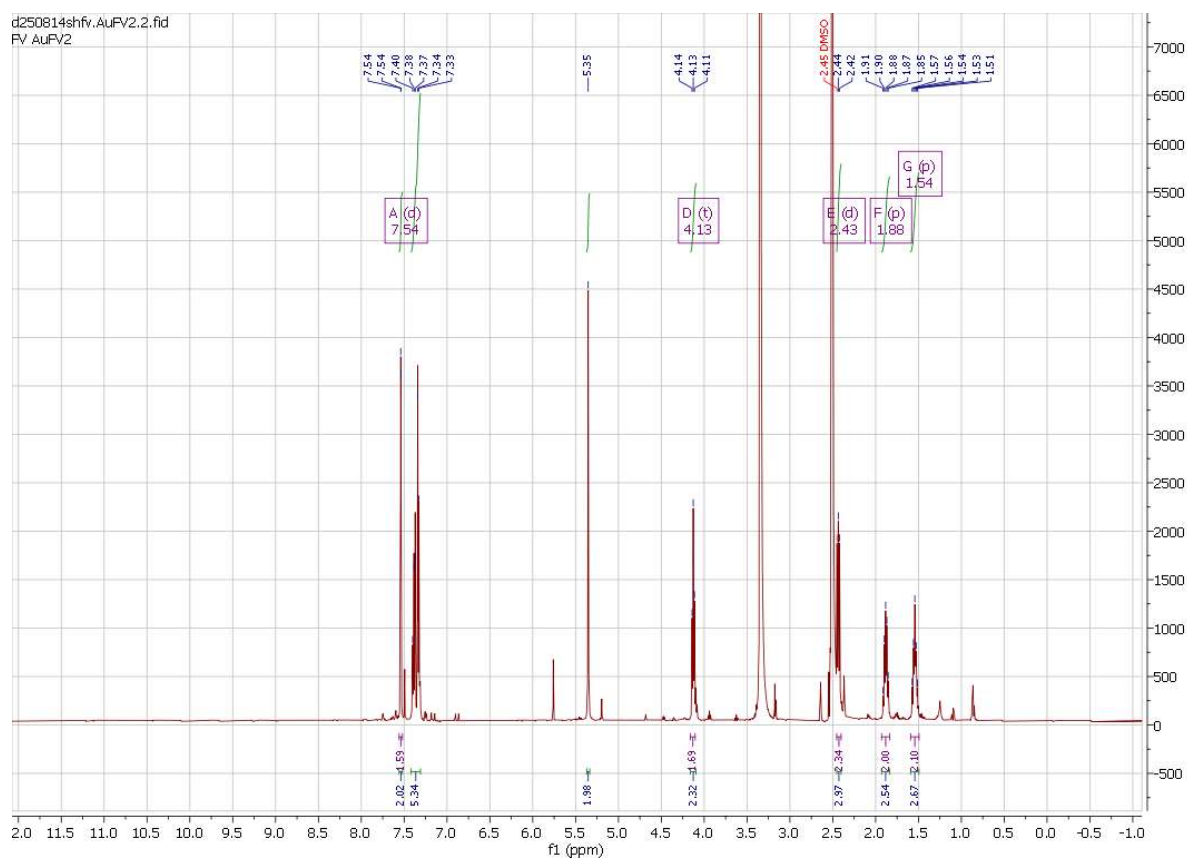


See “*General synthesis for NHC-Au(I)-Cl sulfonate complexes*”

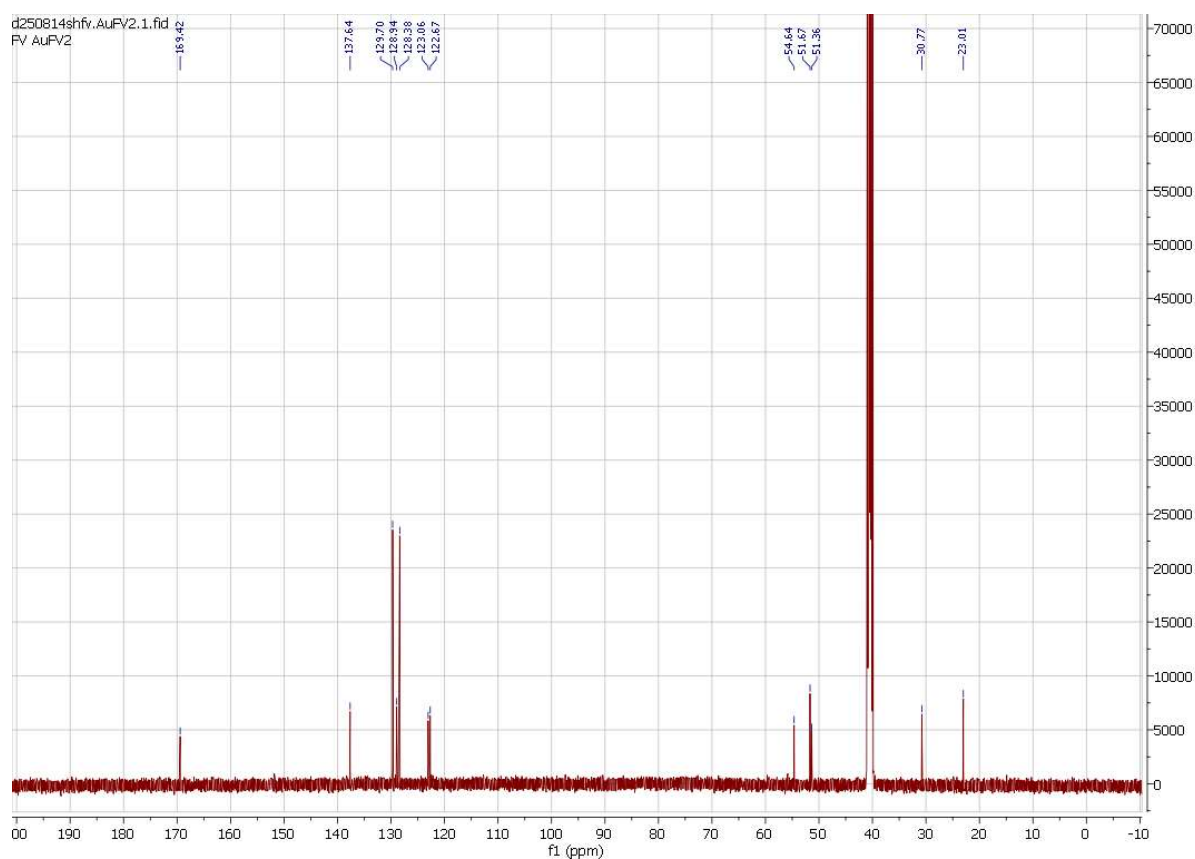
Light violet powder. Yield = 66.4 %.

^1H NMR (500 MHz, DMSO- d_6) δ 7.54 (dd, $J = 1.37$ Hz, 2H, C4/5-H), 7.40–7.33 (m, 5H, Ar-H), 5.35 (s, 1H, CH₂-Ph), 4.14–4.11 (t, $J = 7.04$ Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.45–2.42 (t, $J = 7.78$ Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.91–1.85 (q, $J = 7.29$ Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.57–1.51 (q, $J = 7.67$ Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (126 MHz, DMSO- d_6) δ 169.42 (C-Au), 137.64 (*Cipso*), 129.70, 128.94, 128.38 (Ar), 123.06, 122.67 (C4/5), 54.64 (Ph-CH₂-), 51.67 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 51.36 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 30.77 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 23.01 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

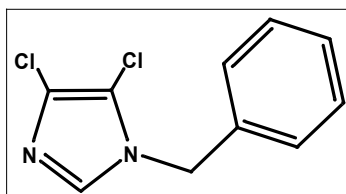


^1H NMR – AuFV2



^{13}C NMR – AuFV2

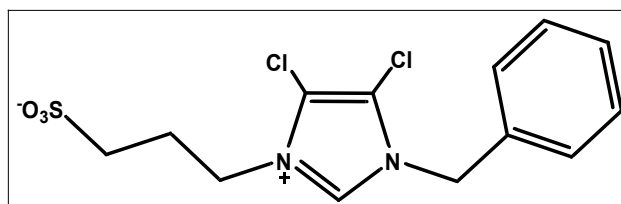
1-benzyl-4,5-dichloroimidazole (CV0)



See “General synthesis for *N*-benzylated-imidazol compounds”

Powdery and whitish. Soluble in acetone, DCM, chloroform. Yield: 64.3%. The NMR characterization match the data reported in literature^[1].

N-benzyl-*N'*-(propyl-3-sulfonate)-4,5-dichloroimidazolium salt (CV1)



See “General synthesis for *N*-benzylated-imidazolium salt compounds in MeCN”

White powder. Yield = 62,8%

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.58 (s, 1H, C2-H), 7.42 (m, 5H, Ar-H), 5.49 (s, 2H, Ph-CH₂-), 4.39–4.35 (t, *J* = 7.11 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.56–2.53 (t, *J* = 7.11 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.18–2.11 (m, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 136.73 (C2), 132.85 (*Cipso*), 129.02, 128.88, 128.21 (Ar), 119.19, 118.61 (C4/5), 51.47 (Ph-CH₂-), 47.81 (N-CH₂-CH₂-CH₂-SO₃⁻), 47.28 (N-CH₂-CH₂-CH₂-SO₃⁻), 24.67 (N-CH₂-CH₂-CH₂-SO₃⁻).

ATR-FTIR: ν 3474, 3110, 3021, 2984, 1756, 1667, 1640, 1573, 1552, 1502, 1447, 1407, 1357, 1271, 1241, 1197, 1175, 1138, 1037, 972, 884, 800, 759, 740, 698, 651 cm⁻¹

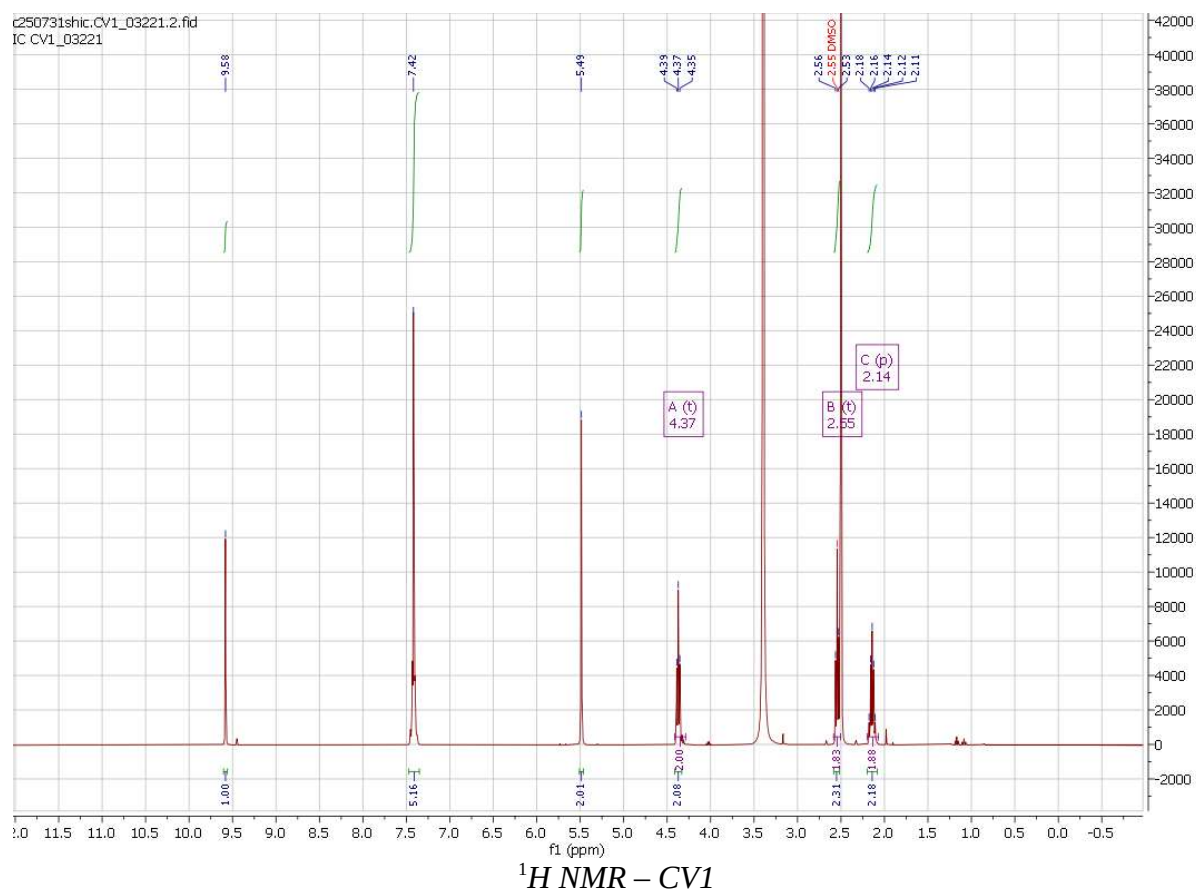
MS (MALDI-TOF, Positive mode)

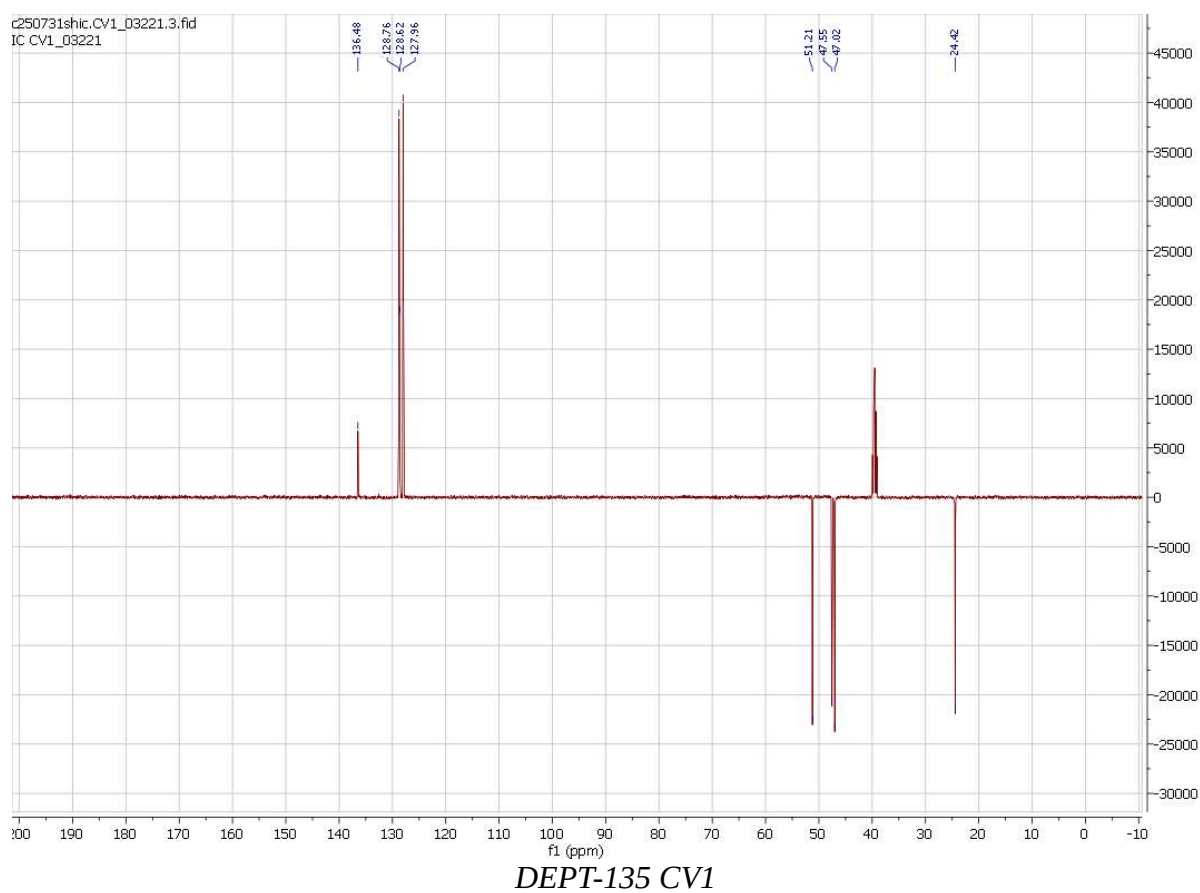
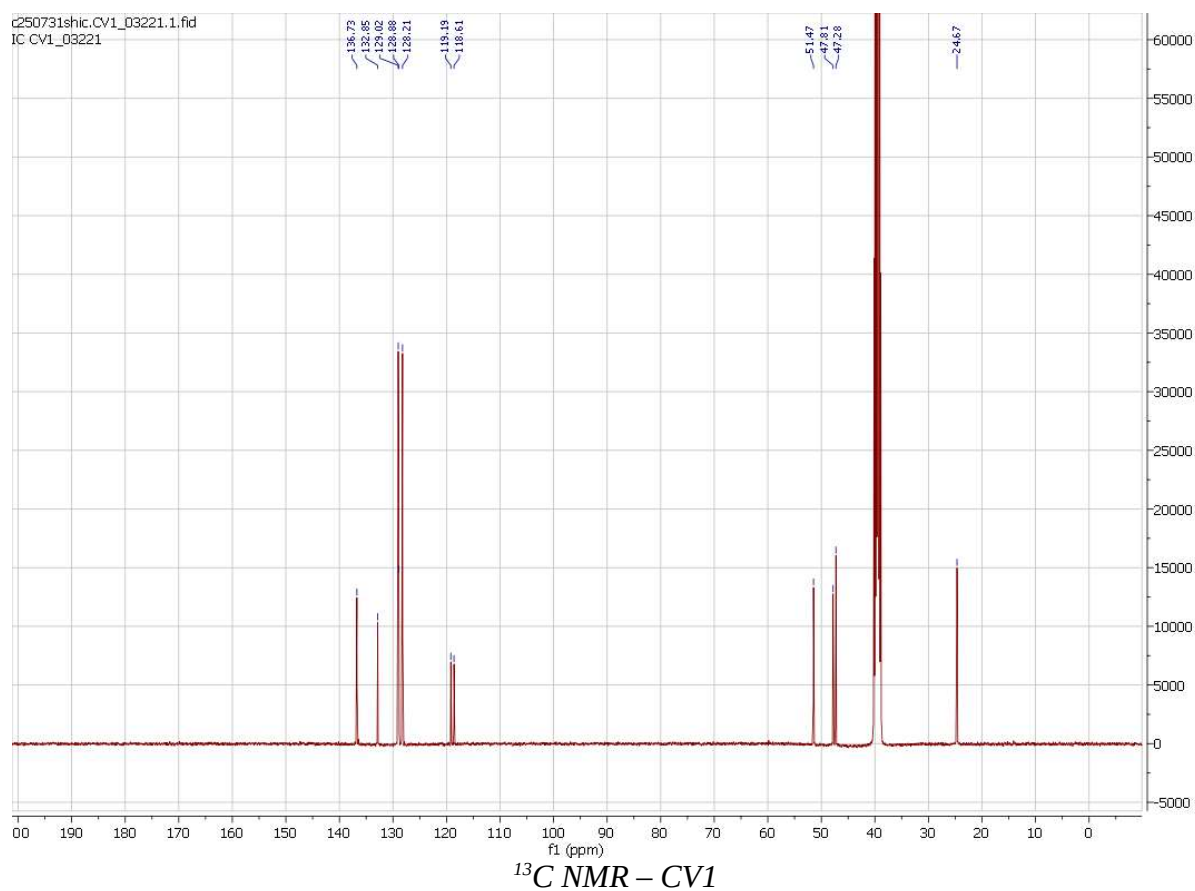
HRMS measured: 349.0181 m/z (M+H⁺); estimated: 349.0175 m/z

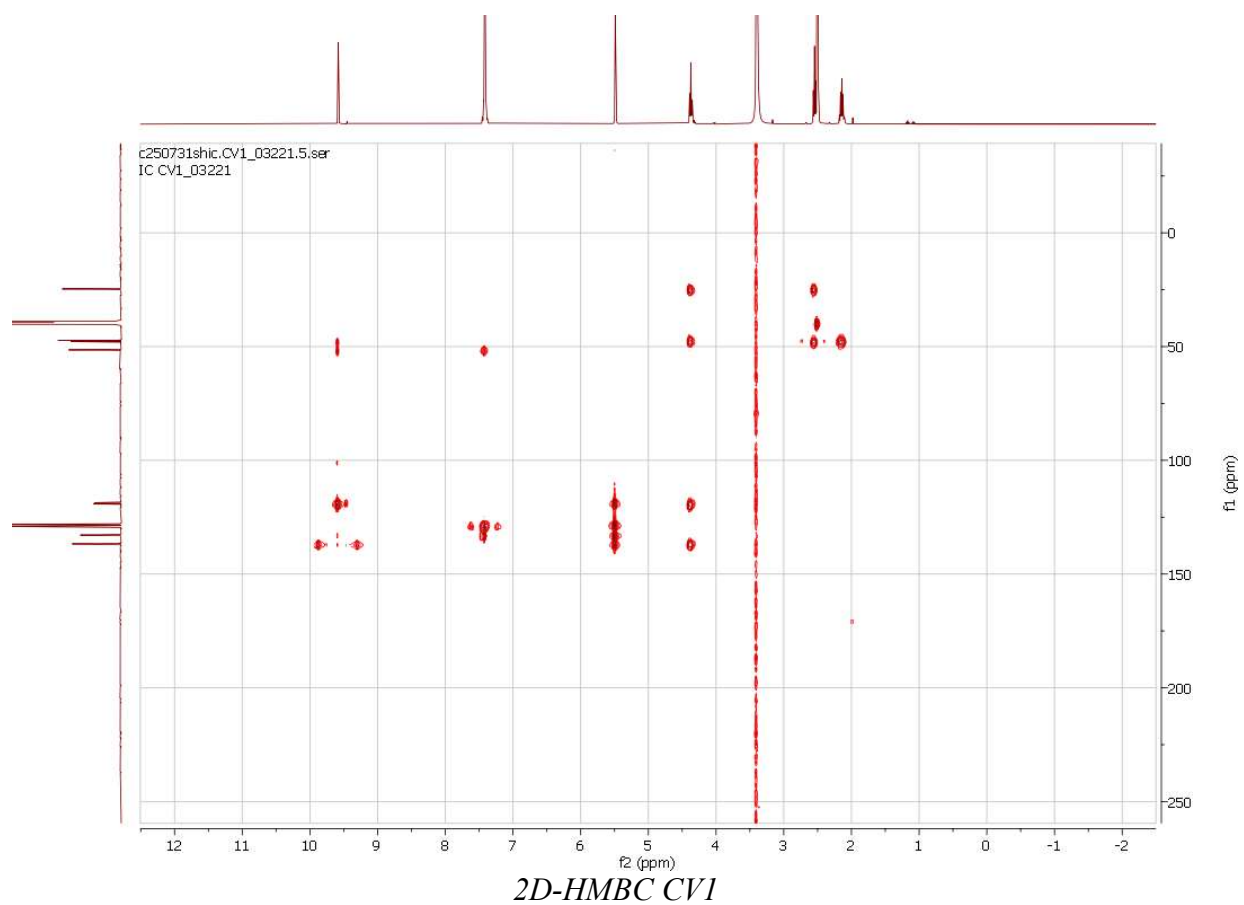
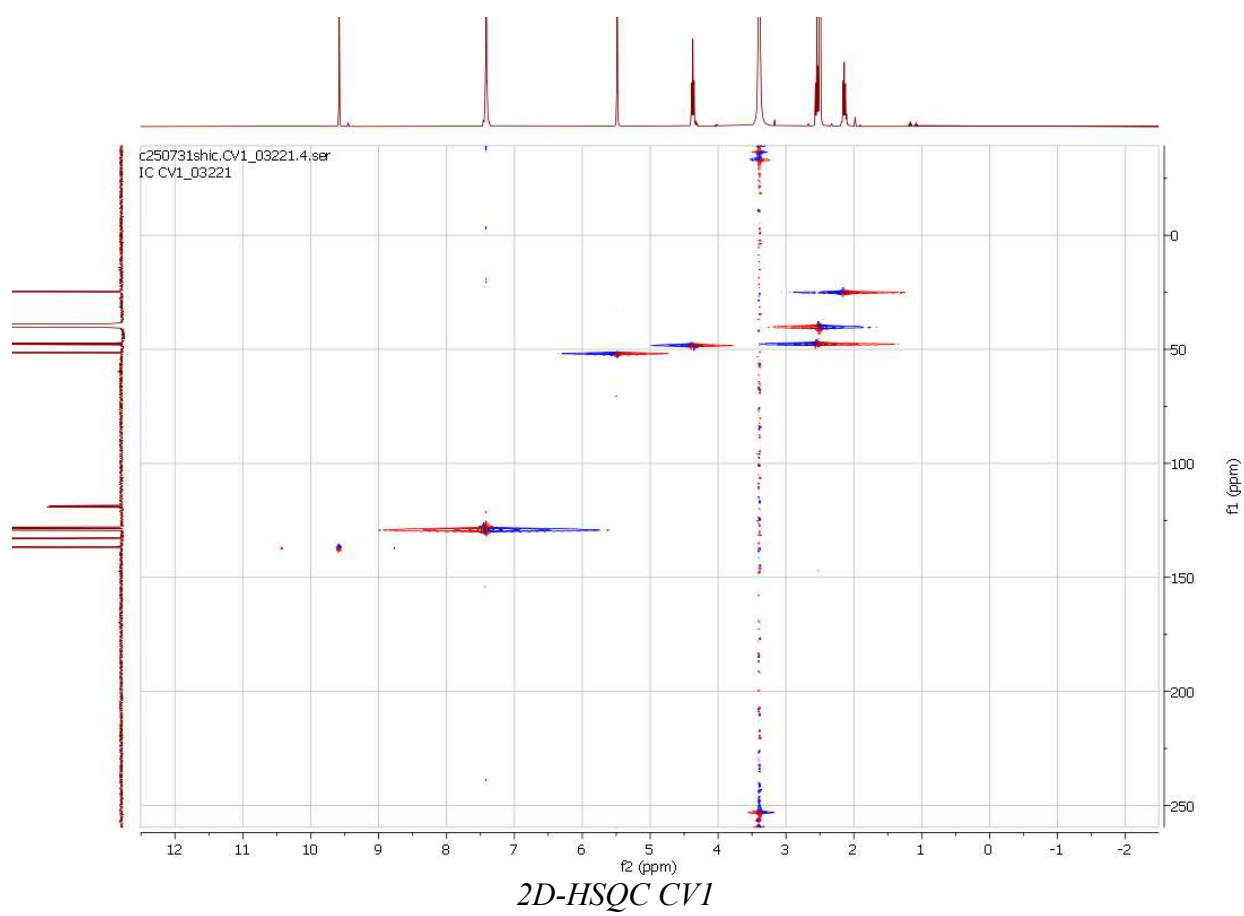
m/z: 349.0181 ($M+H^+$), 699.0261 ($2M+3H^+$), 1069.0184 ($3M+Na^++2H^+$), 1419.0265 ($4M+Na^++4H^+$), 1747.0524 ($5M+7H^+$)

MS (MALDI-TOF, Negative mode)

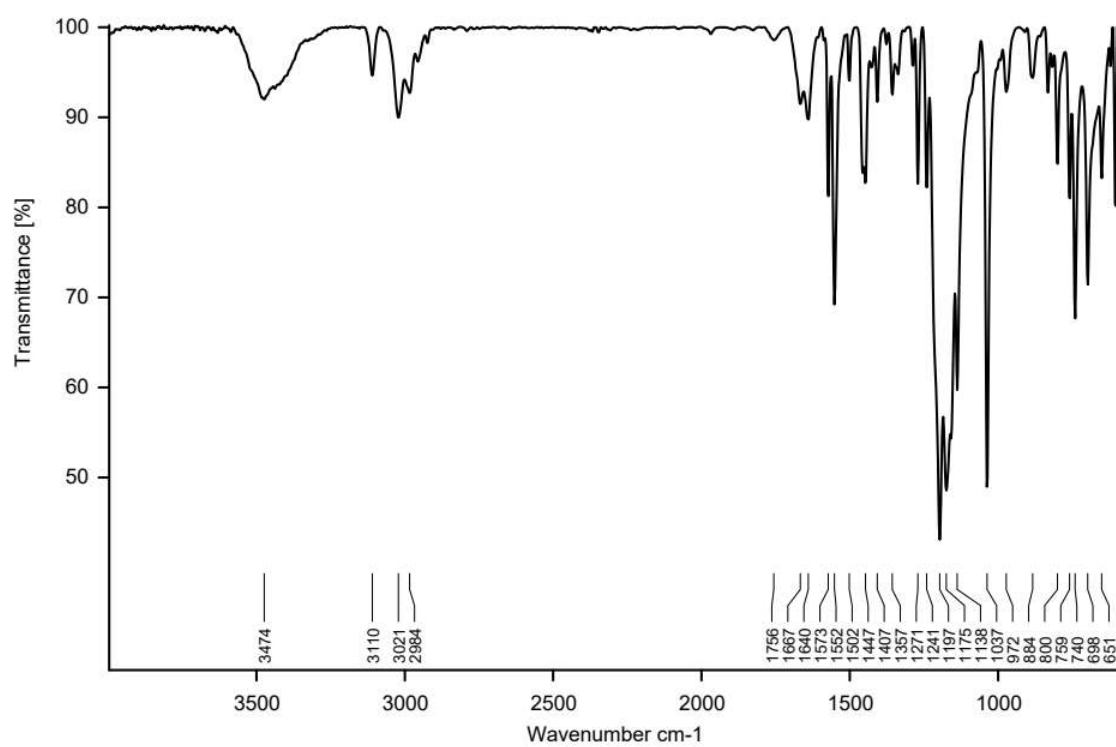
HRMS measured: 347.0032 m/z ($M-H^+$); estimated: 347.0029 m/z



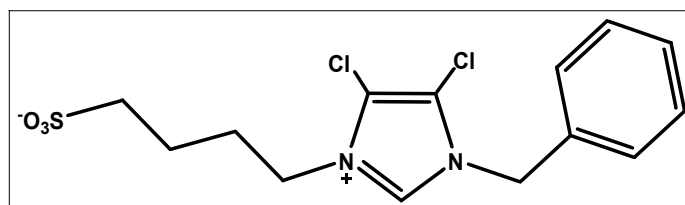




CV1
ATR



N-benzyl-N'-(butyl-4-sulfonate)-4,5-dichloroimidazolium salt (CV2)



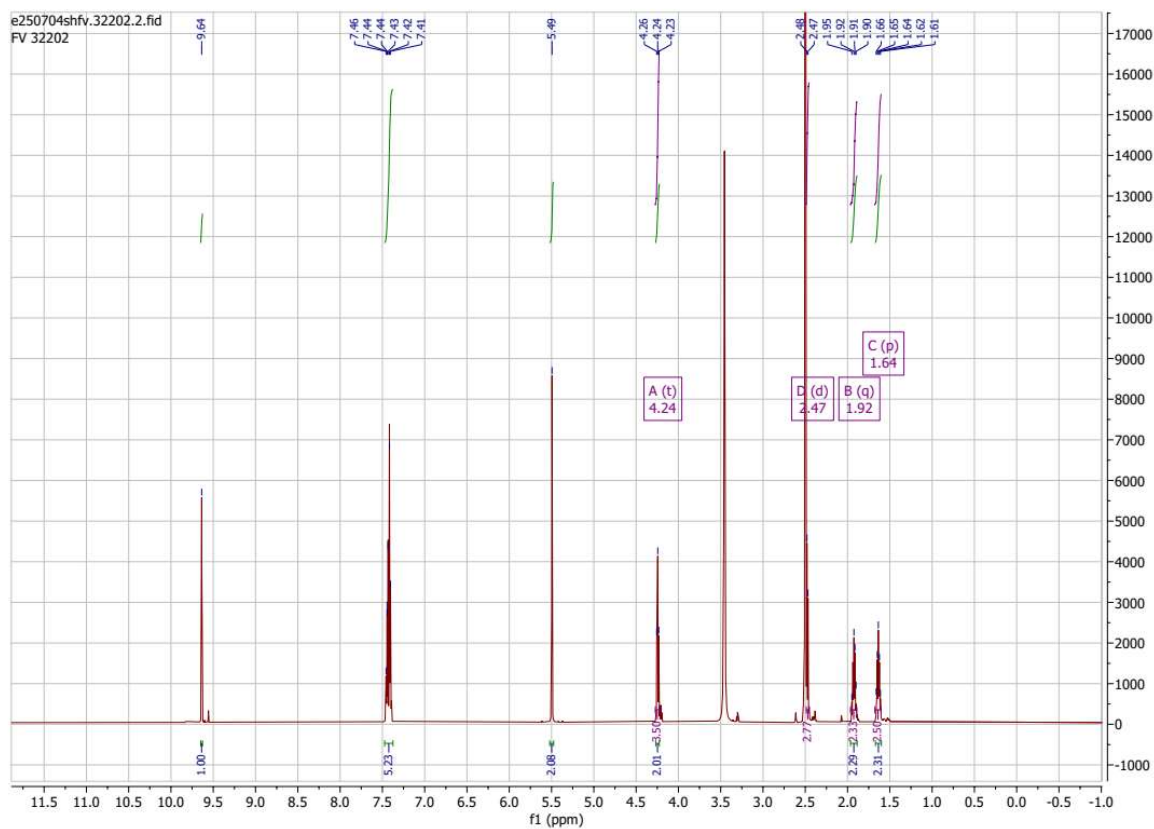
See “General synthesis for N-benzylated-imidazolium salt compounds in MeCN”

White powder. Yield = 75.0%

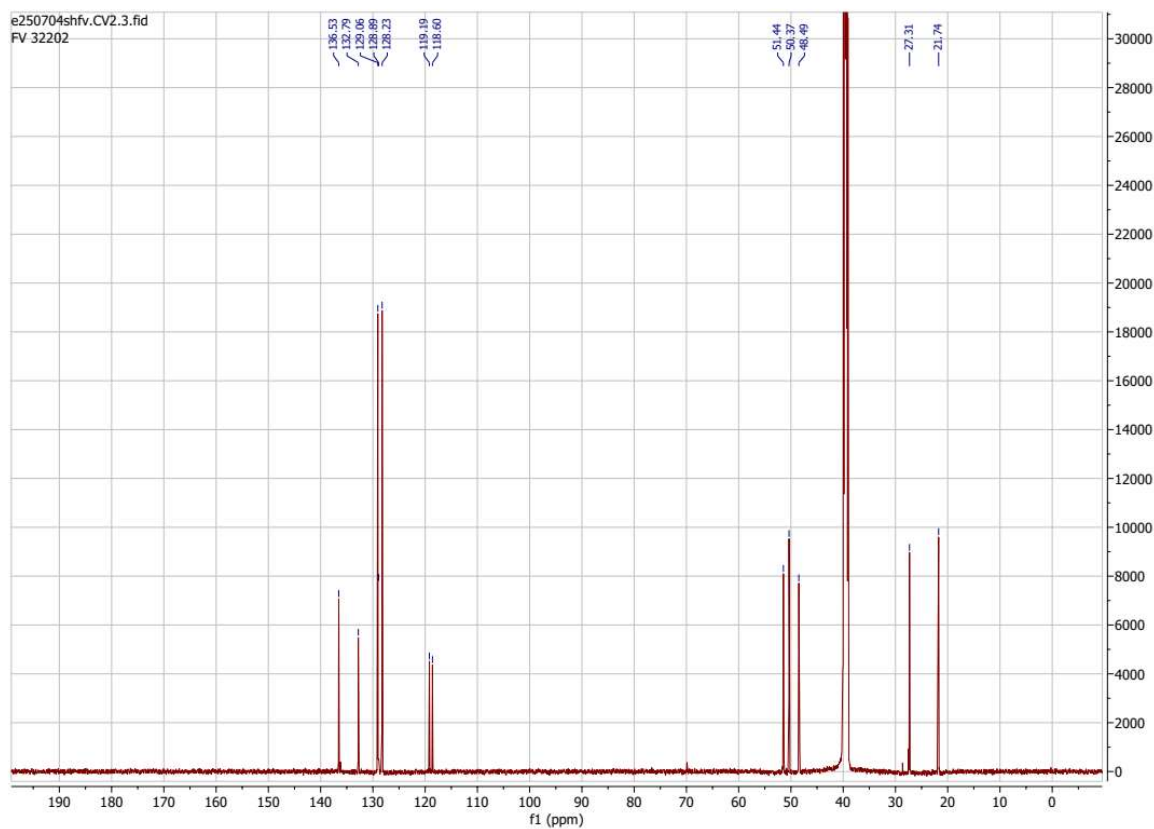
^1H NMR (600 MHz, DMSO- d_6) δ 9.64 (s, 1H, C2-H), 7.46–7.41 (m, 5H, Ar-H), 5.49 (s, 2H, Ph-CH $_2$ -), 4.26–4.23 (t, J = 7.15 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.48–2.47 (d, J = 7.43 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.95–1.90 (q, J = 7.62 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.66–1.61 (q, J = 7.57 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

^{13}C NMR (151 MHz, DMSO- d_6) δ 136.53 (C2), 132.79 (*Cipso*), 129.06, 128.89, 128.23 (Ar), 119.19, 118.60 (C4/5), 51.44 (Ph-CH $_2$ -), 50.37 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 48.49 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 27.31 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 21.74 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

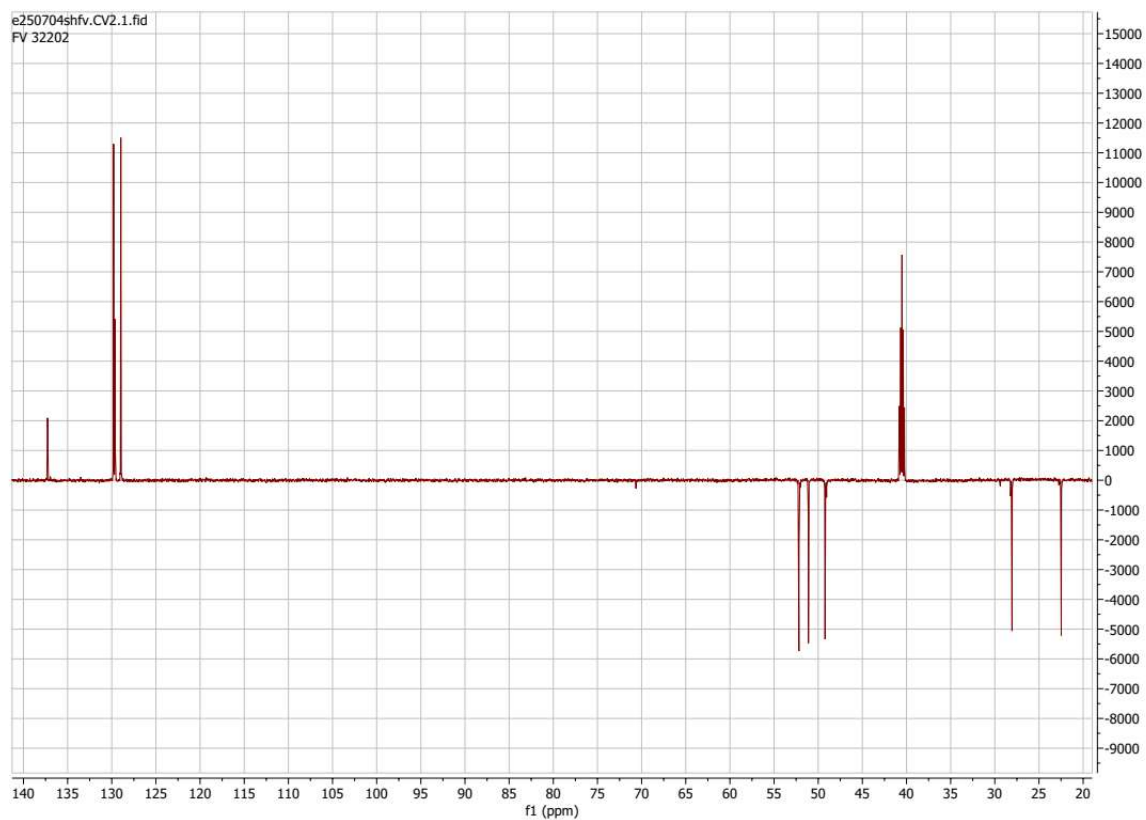
ATR-FTIR: ν 3447, 3109, 3048, 2972, 2875, 1667, 1646, 1570, 1543, 1498, 1455, 1345, 1187, 1040, 971, 781, 754, 717 cm^{-1}



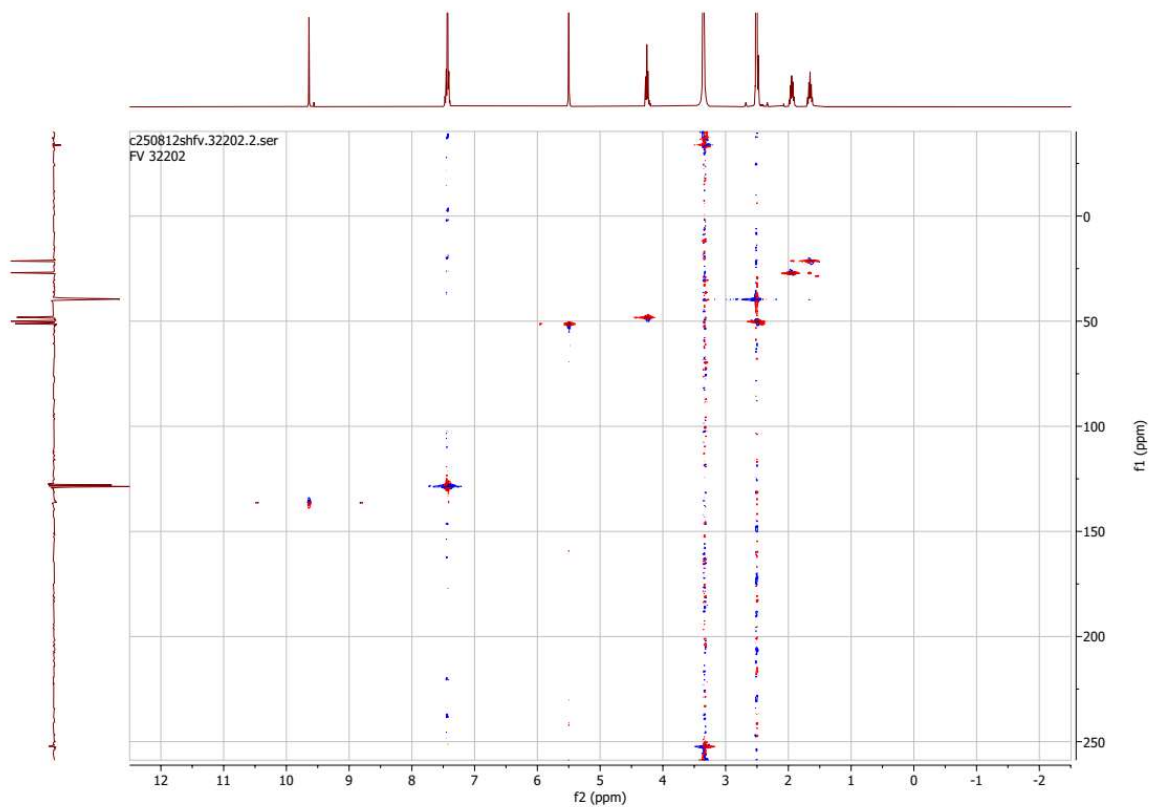
^1H NMR – CV2



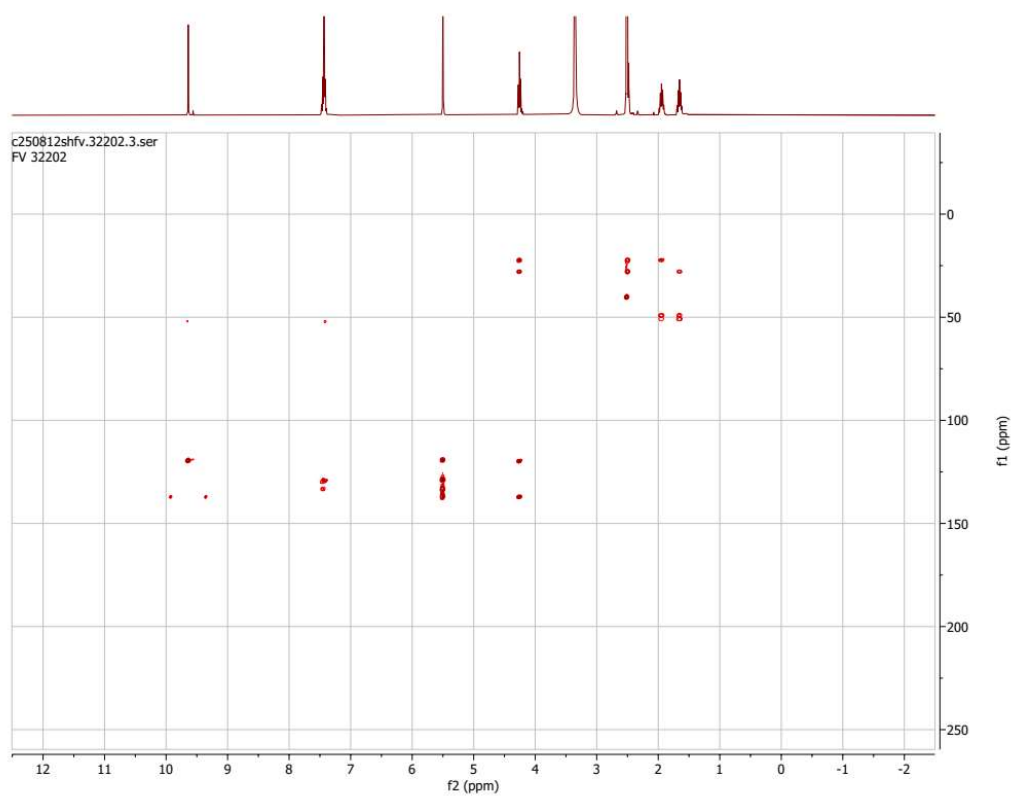
^{13}C NMR – CV2



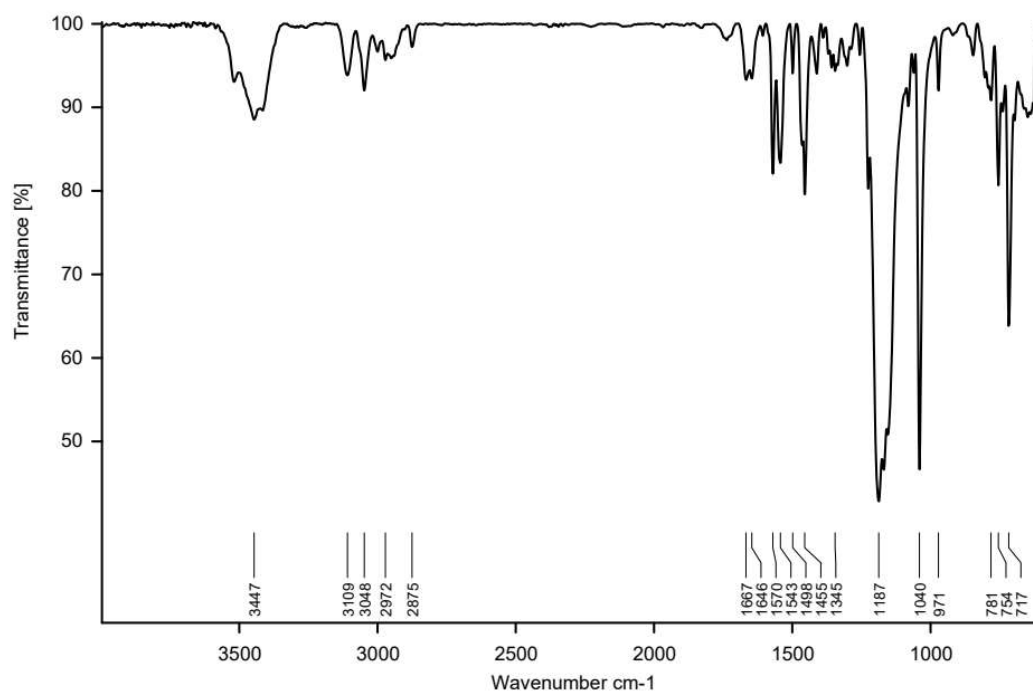
DEPT-135 CV2



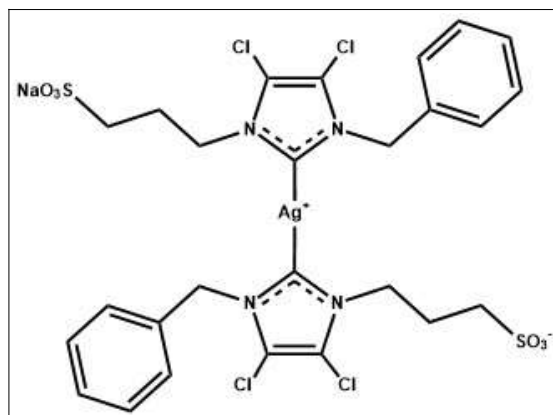
2D-HSQC CV2



**CV2
ATR**



Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)4,5-dichloro-2-yliden] silver chloride (AgCV1)



See “General synthesis for NHC-Ag(I)-Cl sulfonate complexes – Strategy A”

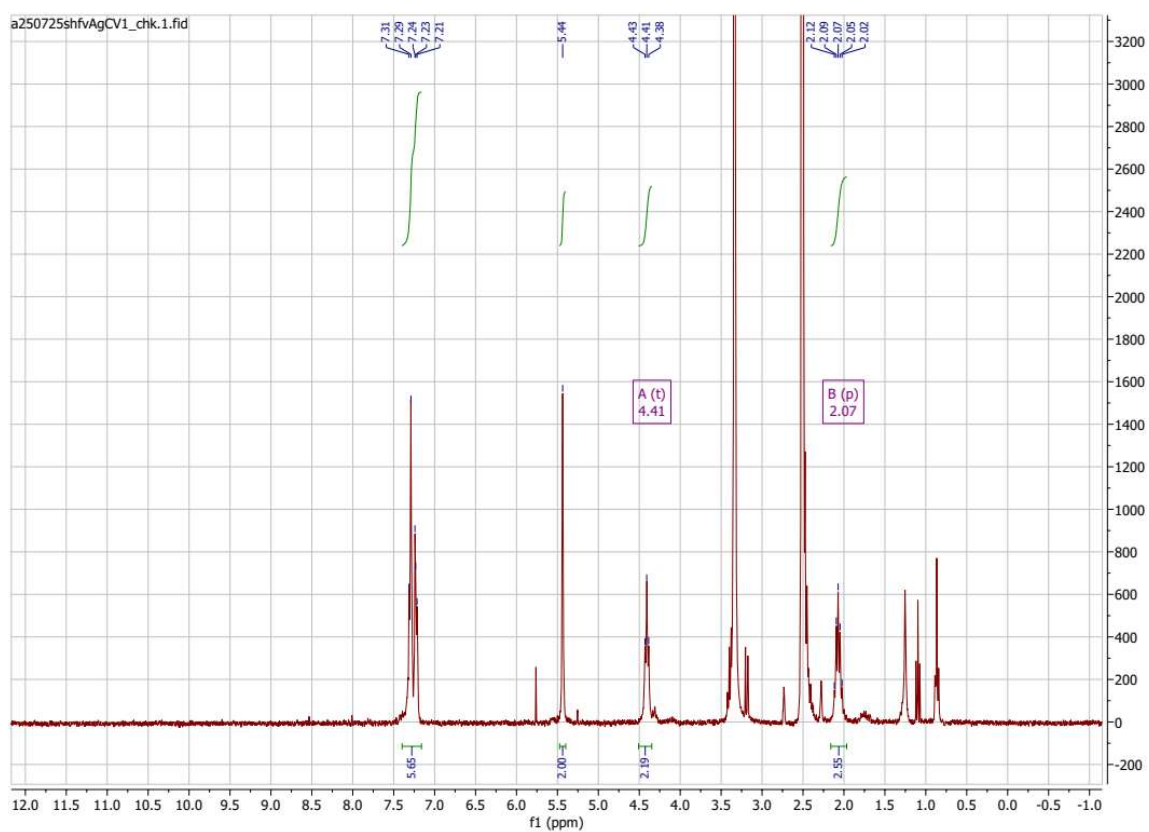
White powder. Yield = 69.3%

^1H NMR (300 MHz, DMSO- d_6) δ 7.32–7.22 (br m, 5H, Ar-H), 5.44 (s, 2H, $\text{CH}_2\text{-Ph}$), 4.43–4.38 (t, $J = 7.04$ Hz, 2H, $\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 2.12–2.02 (t, $J = 7.3$ Hz, 2H, $\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$).

^{13}C NMR (75 MHz, DMSO- d_6) δ 135.59 (C_{ipso}), 129.78 (Ar), 129.15 (Ar), 127.89 (Ar), 117.97 (Cl- $\text{C}^4\text{-C}^5\text{-Cl}$), 117.68 (Cl- $\text{C}^4\text{-C}^5\text{-Cl}$), 54.07 ($\text{CH}_2\text{-Ph}$), 50.76 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 49.27 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 27.27 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$).

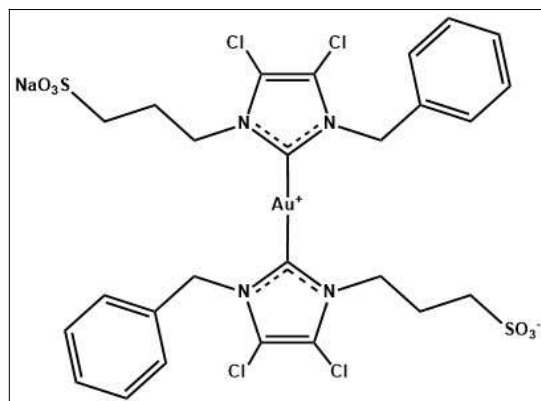
MS (MALDI FT-ICR, H_2O)

m/z : 721.00828 [$\text{C}_{24}\text{H}_{24}\text{AgCl}_4\text{NaN}_4\text{O}_3\text{S}$] $^+$, 371.00014 [$\text{C}_{13}\text{H}_{13}\text{Cl}_2\text{N}_2\text{NaO}_3\text{S}$] $^+$



^1H NMR – AgCV1

Bis-[N-benzyl-N'-(propyl-3-sulfonate)4,5-dichloro-2-yliden] gold chloride (AuCV1)

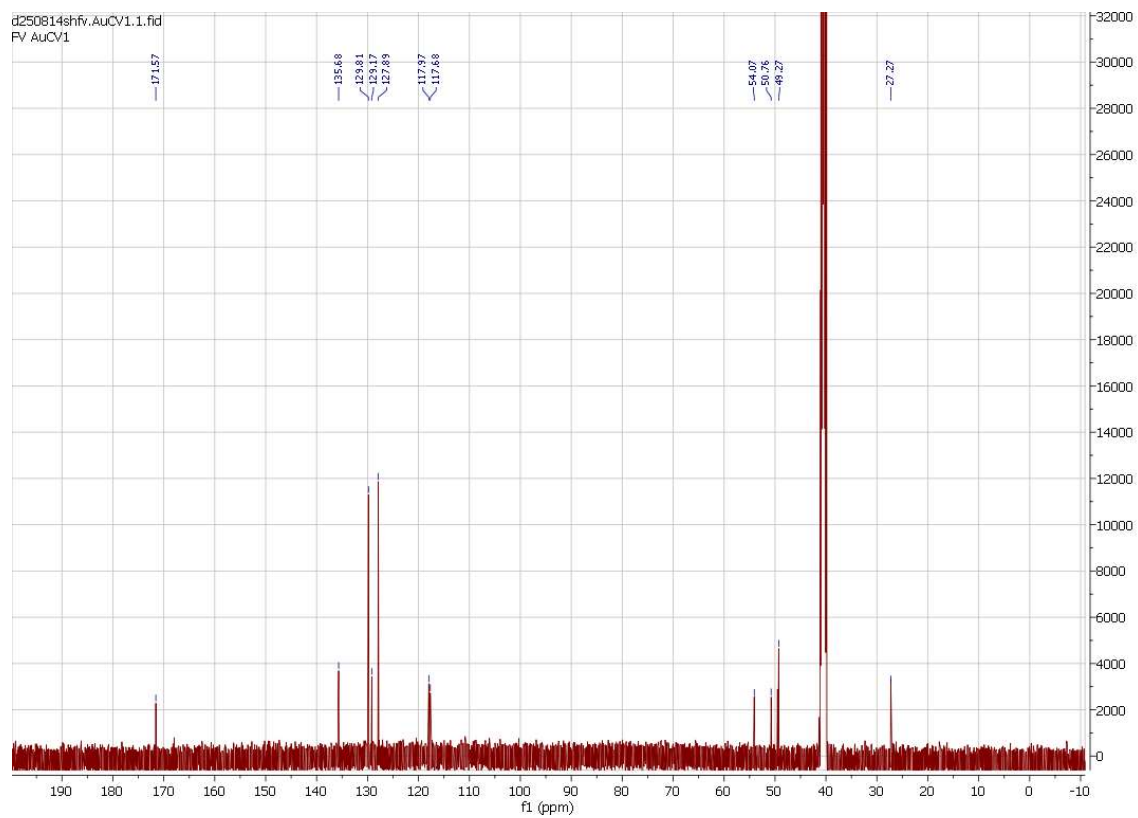
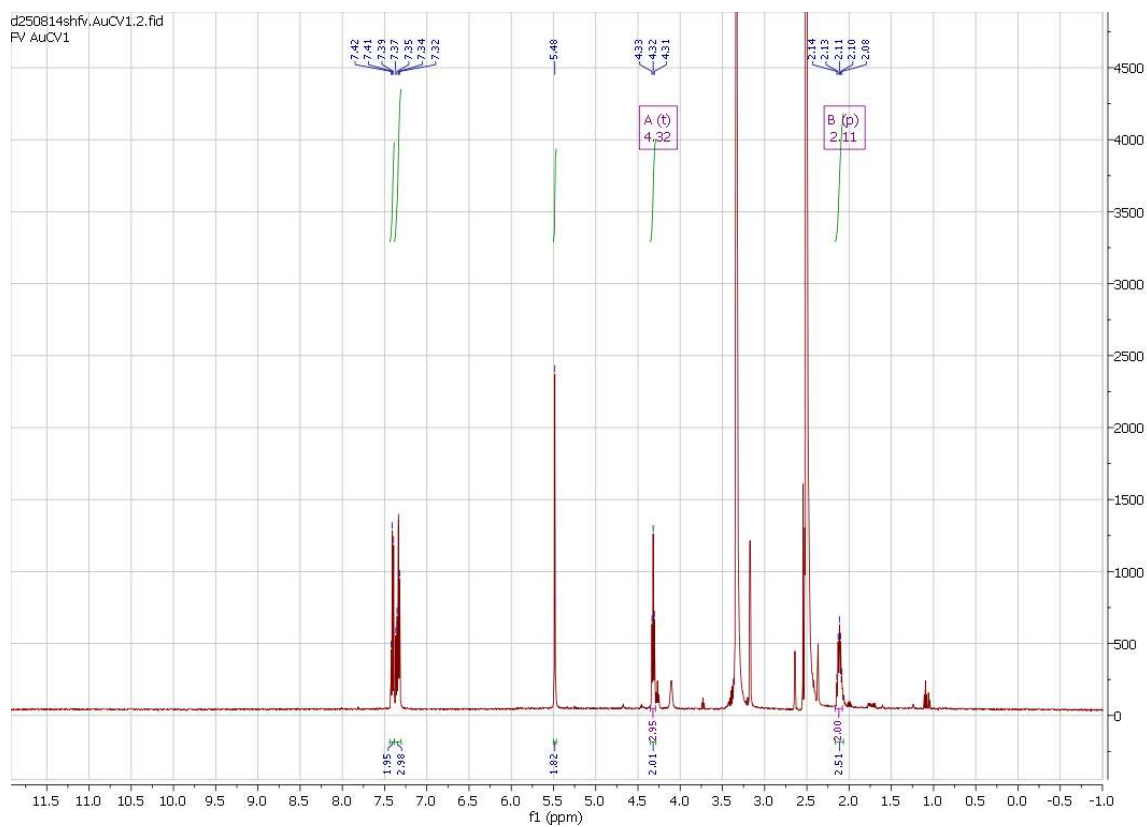


See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”

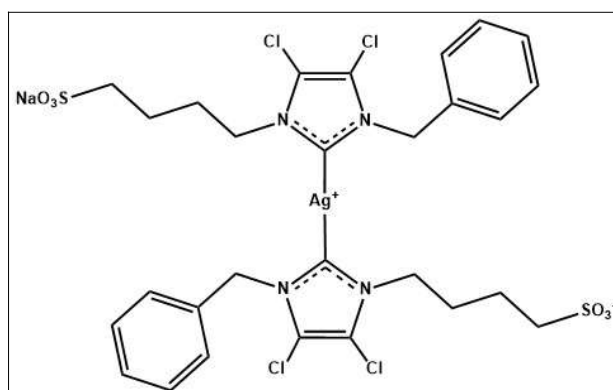
White powder. Yield = 58.0%

^1H NMR (500 MHz, DMSO- d_6) δ 7.42–7.32 (m, 5H, Ph-H), 5.48 (s, 2H, CH₂-Ph), 4.33–4.31 (t, J = 7.2 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.14–2.08 (q, J = 7.55 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (126 MHz, DMSO- d_6) δ 171.57 (C-Au), 135.68 (*Cipso*), 129.81, 129.17, 127.89 (Ar), 117.97, 117.68 (C4/5), 54.07 (Ph-CH₂-), 50.76 (N-CH₂-CH₂-CH₂-SO₃[−]), 49.27 (N-CH₂-CH₂-CH₂-SO₃[−]), 27.27 (N-CH₂-CH₂-CH₂-SO₃[−]).



Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)4,5-dichloro-2-yliden] silver chloride (AgCV2)

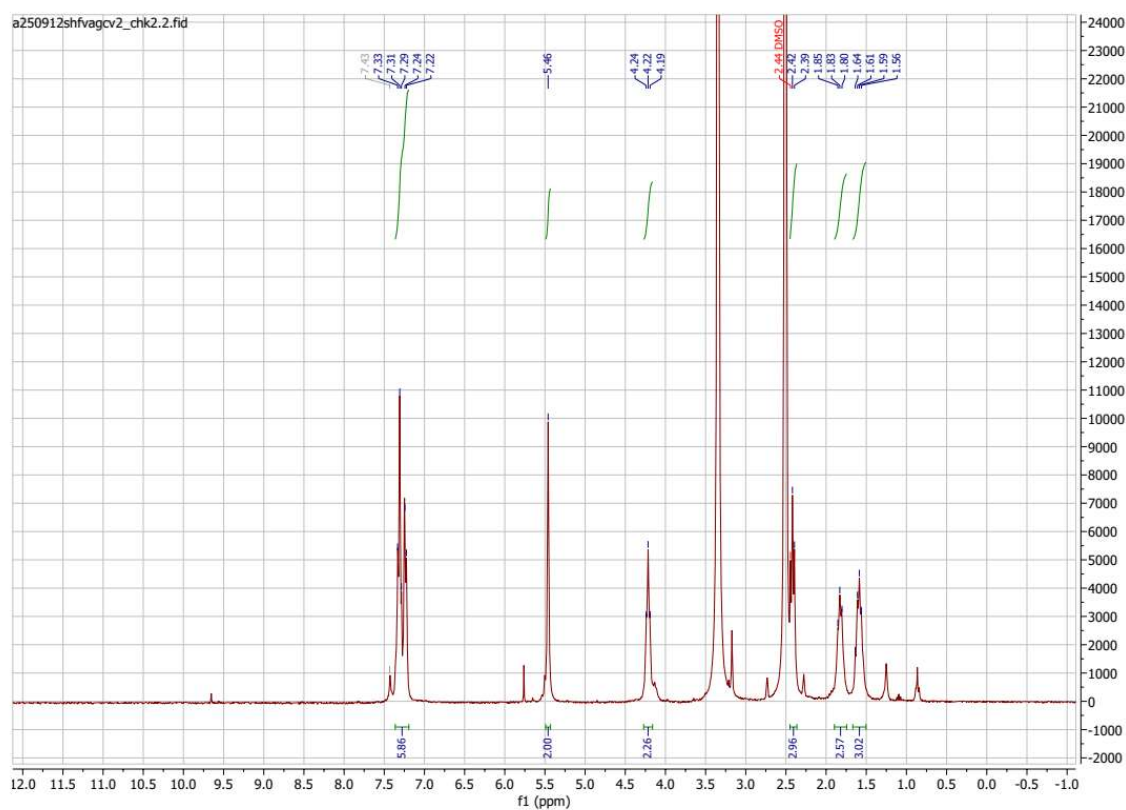


See “General synthesis for NHC-Ag(I)-Cl sulfonate complexes”

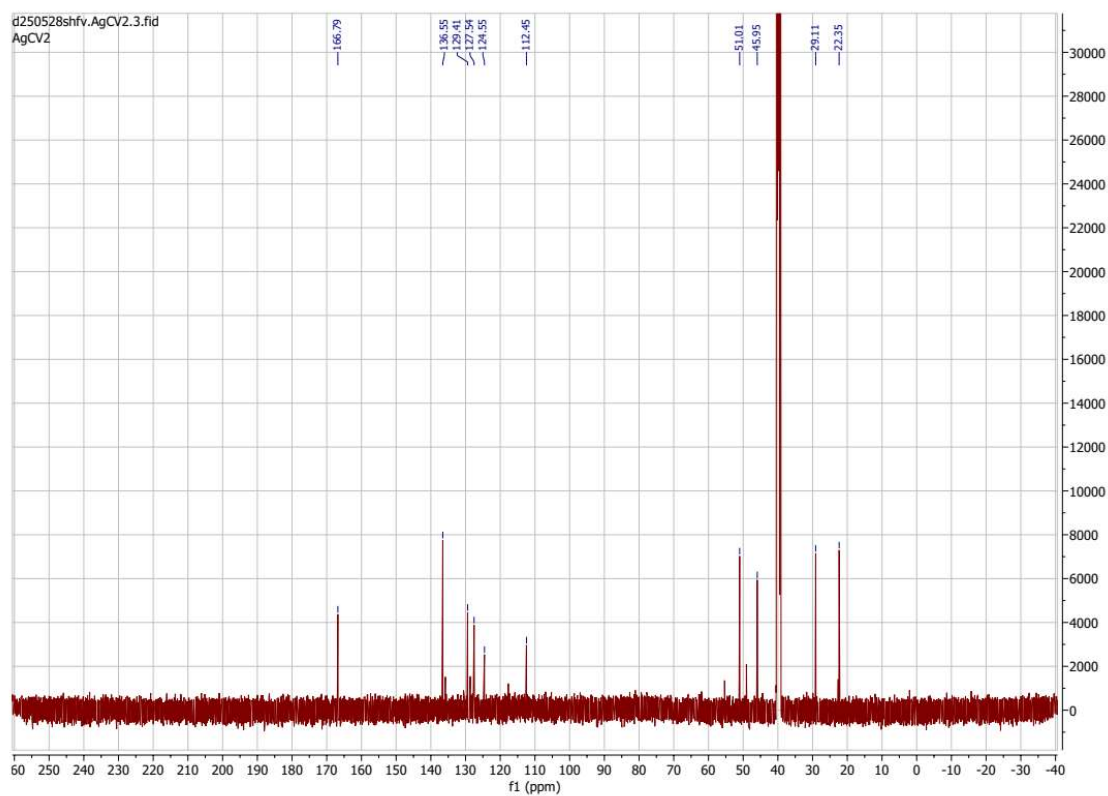
White powder. Yield = 53.3%

¹H NMR (300 MHz, DMSO-d₆) δ 7.33–7.22 (br m, 5H, Ar-H), 5.46 (s, 2H, CH₂-Ph), 4.21 (br t, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 2.44–2.39 (br t, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.83 (br m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.61–1.59 (br m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (75 MHz, DMSO-d₆) δ 134.55 (*Cipso*), 129.41, 127.54, 124.55 (Ar), 112.45 (C4/5), 51.01 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 49.06 (Ph-CH₂-), 45.95 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 29.11 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 22.35(N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).

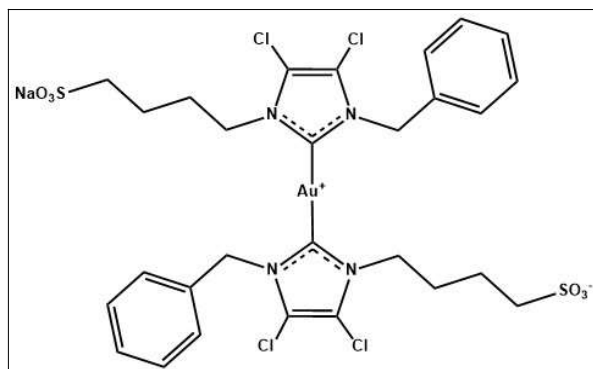


^1H NMR – AgCV2



^{13}C NMR – AgCV2

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)4,5-dichloro-2-yliden] gold chloride (AuCV2)

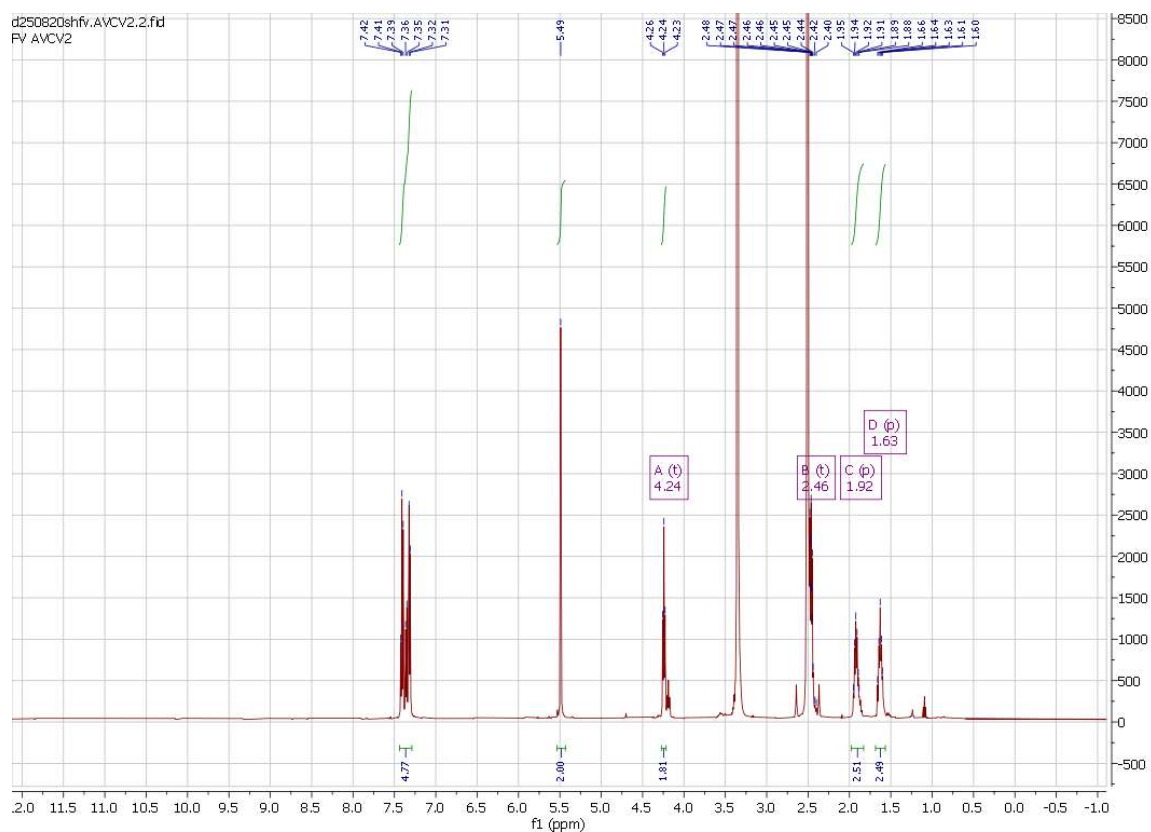


See “General synthesis for NHC-*Au*(I)-Cl sulfonate complexes”

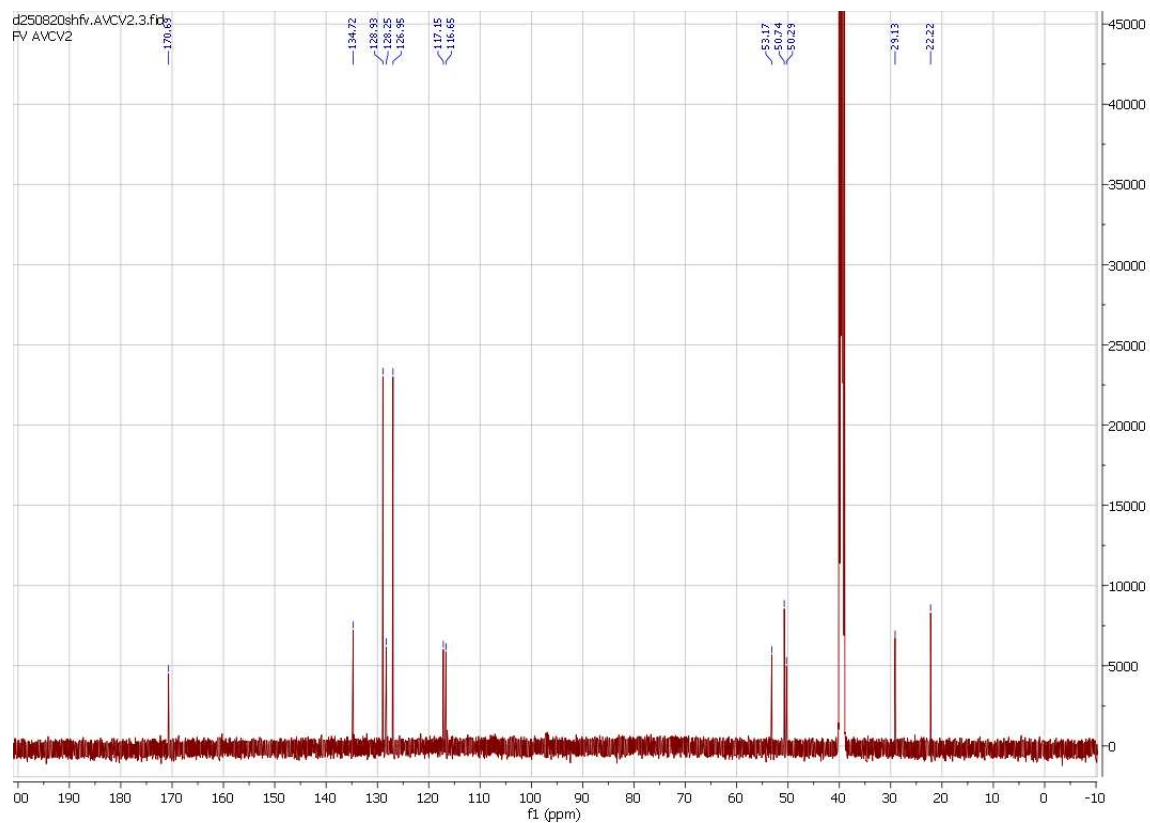
White powder. Yield = 51.2%

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.42–7.31 (br m, 5H, Ar-H), 5.49 (s, 2H, CH₂-Ph), 4.26–4.23 (t, *J* = 7.21 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 2.48–2.40 (t, *J* = 7.70 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.95–1.88 (q, *J* = 7.64 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.66–1.60 (q, *J* = 7.84 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).

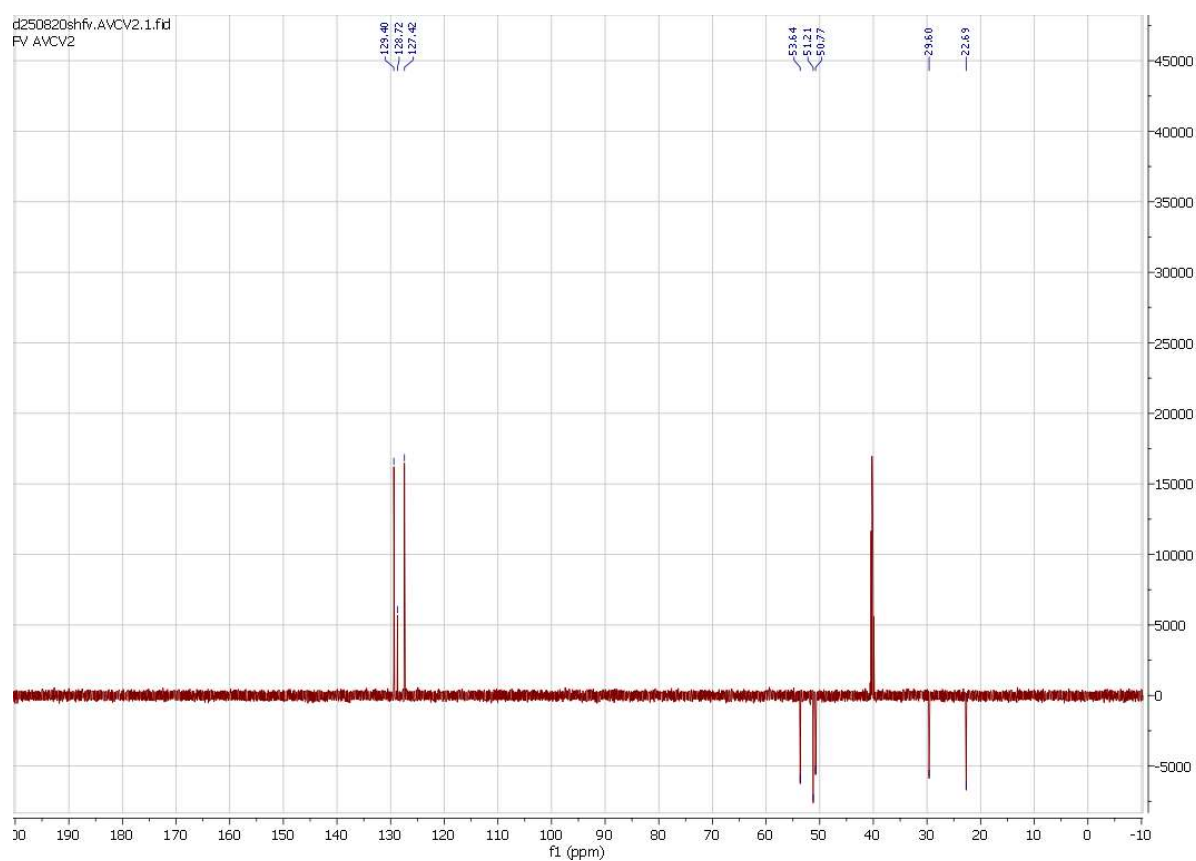
¹³C NMR (126 MHz, DMSO-*d*₆) δ 170.69 (C-Au), 134.72 (*Cipso*), 128.93, 128.25, 126.95 (Ar), 117.15, 116.65 (C4/5), 53.17 (Ph-CH₂-), 50.74 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 50.29 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 29.13 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 22.22 (N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).



^1H NMR – AuCV2

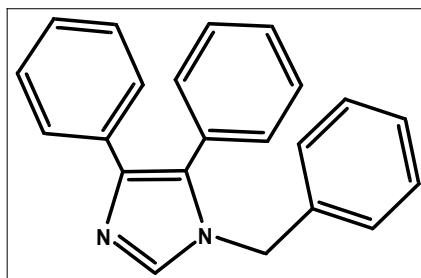


^{13}C NMR – AuCV2



DEPT-135 AuCV2

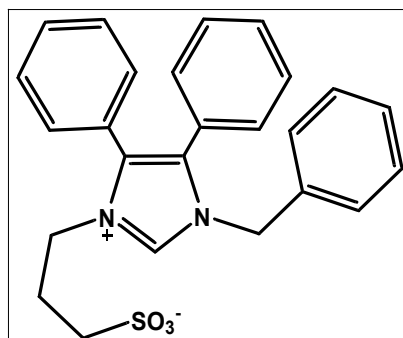
1-benzyl-4,5-diphenylimidazole (PV0)



A solution of 4,5-diphenylimidazole (0.2 g, 12 mmol) and KOH (1.1 eq.) was firstly prepared in methanol (3.0 mL) and left under magnetic stirring overnight. Then, the solvent was evaporated under vacuum and acetone was added, obtaining a mixture opaque and light orange. After ten minutes under stirring, a solution of benzylbromide (0.3589 g, 2.10 mmol) dissolved in 2.0 mL of acetone was added at once. The reaction was carried out at room temperature until, by monitoring with TLC, the disappearing of the benzylbromide control spot was observed. Then the reaction mixture was filtered on paper, the liquid phase was collected and the solvent was removed under reduced pressure, leaving a whitish sticky layer. The residue was dissolved in acetone the crude was purified on silica gel column using a mobile phase P.E:Acetone 4:1→3:2, obtaining the final product finally obtained in a crystal shape washed with small amount of cold methanol.

White powder, soluble in acetone, DMSO, slight soluble in water, MeOH. Yield > 90%. The NMR characterization match the data reported in literature^[2].

***N*-benzyl-*N'*-(propyl-3-sulfonate)-4,5-diphenylimidazolium salt (PV1)**



PV0 (0.3000 g, 1.92 mmol) was crushed in dust and dissolved in acetonitrile (10.0 mL) under magnetic stirring. Then 1,3-propane sultone (0.2780 g, 2.30 mmol) was added and the reaction was warmed up at 90 °C, keeping the solution at reflux for 72 hours, monitoring the evolution of reaction on TLC (silica gel, P.E:Acetone 1:1, spot close to starting line). The crude was dried under vacuum and the product was isolated by precipitation using DCM/Hex as solvent/non-solvent mixture. Once recovered, the product was washed with acetone. White powder. Yield = 62.8%

Alternative work-up: the crude was dried under vacuum and dissolved in a minimum quantity of MeOH. Then, Et₂O was added until opaque white color persist. The flask was left in fridge at 2 °C overnight. The solid was recovered by suction of supernatant and was dried under vacuum. In this way the purity of compound is higher than the previous work-up method.

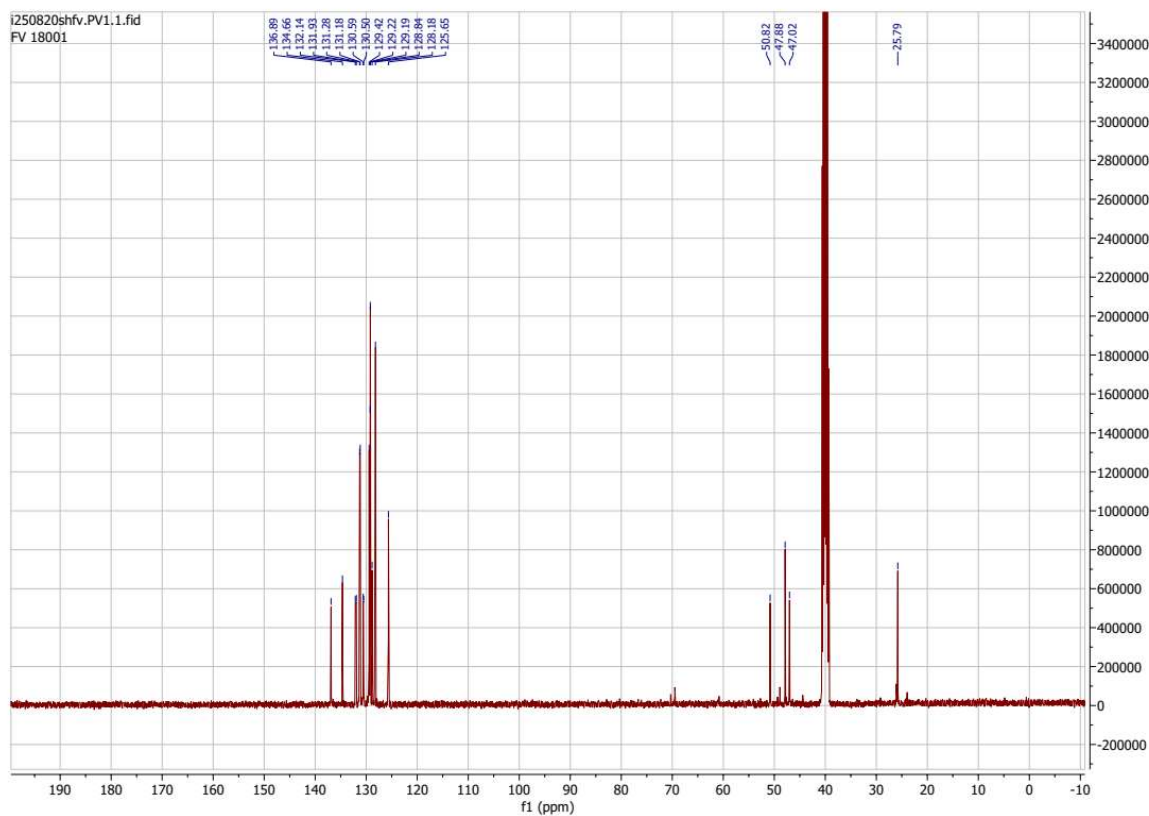
¹H NMR (500 MHz, DMSO-*d*₆) δ 9.60 (s, 1H, C2-H), 7.43–7.29 (m, 14H, Ar-H), 7.06 (br m, 2H, Ar-H), 5.39 (s, 2H, Ph-CH₂-), 4.28–4.25 (t, *J* = 7.21 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.42–2.40 (t, *J* = 7.2 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 1.95–1.92 (m, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 136.43 (C2), 134.21 (*Cipso*), 131.71 (Cq), 131.49 (*Cipso*), 130.84, 130.74, 130.15, 130.07, 128.99, 128.78, 128.76, 128.41, 127.74, 125.20 (Cq + Ar), 50.38 (Ph-CH₂-), 47.42 (N-CH₂-CH₂-CH₂-SO₃⁻), 46.58 (N-CH₂-CH₂-CH₂-SO₃⁻), 25.34 (N-CH₂-CH₂-CH₂-SO₃⁻).

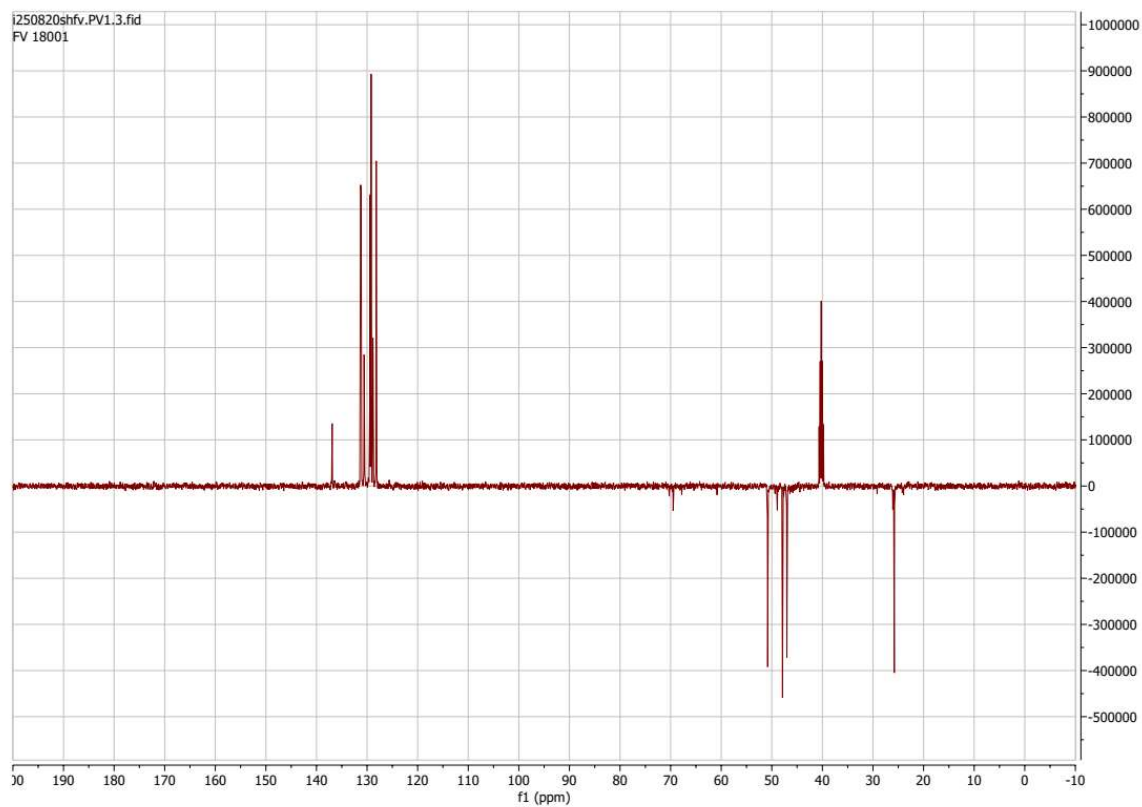
ATR-FTIR: ν 3034, 1638, 1553, 1445, 1343, 1263, 1232, 1200, 1184, 1036, 928, 851, 793, 769, 749, 730, 699, 667 cm⁻¹

m/z: 433.1584 (M+H⁺), 455.1403 (M+Na⁺-H⁺), 865.3096 (2M+H⁺), 887.2912 (2M+Na⁺-H⁺), 1297.4607 (3M+H⁺), 1319.4430 (3M+Na⁺), 1730.6145 (4M+2H⁺), 1752.5967 (4M+Na⁺+H⁺), 2162.7675 (5M+2H⁺), 2184.7479 (5M+Na⁺+H⁺)

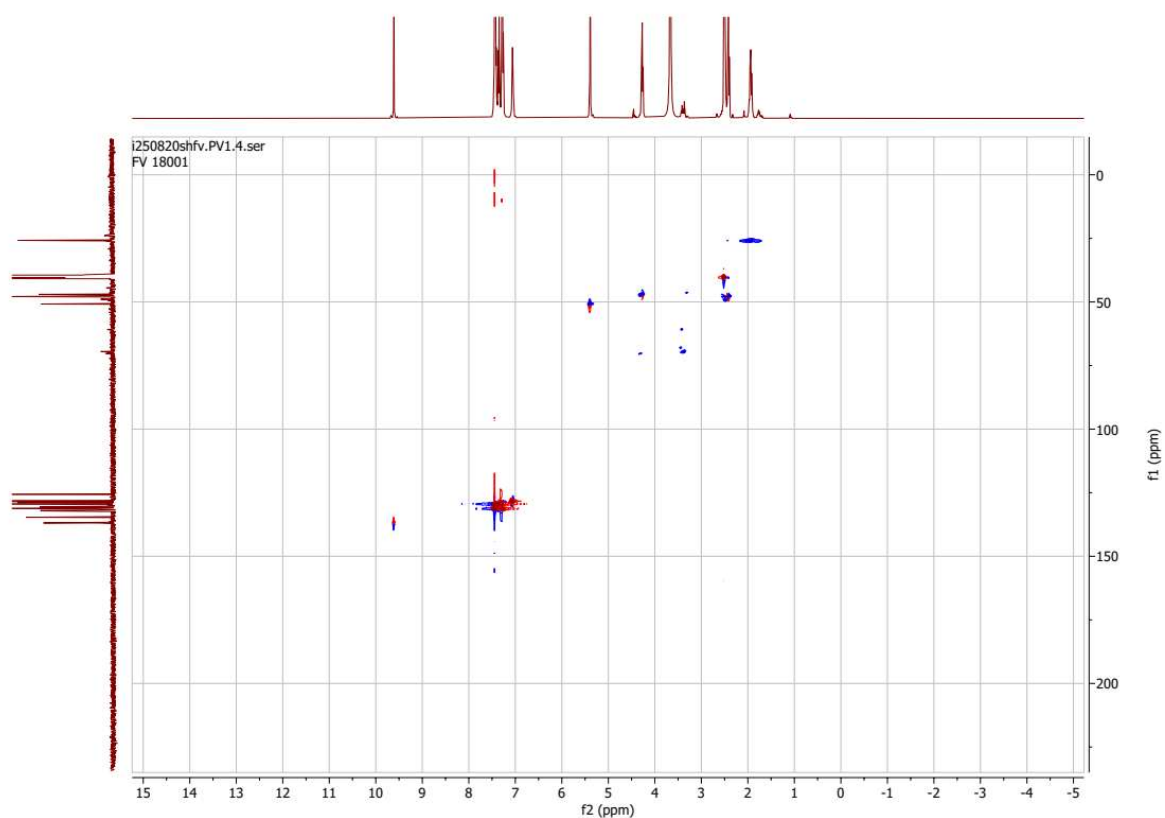




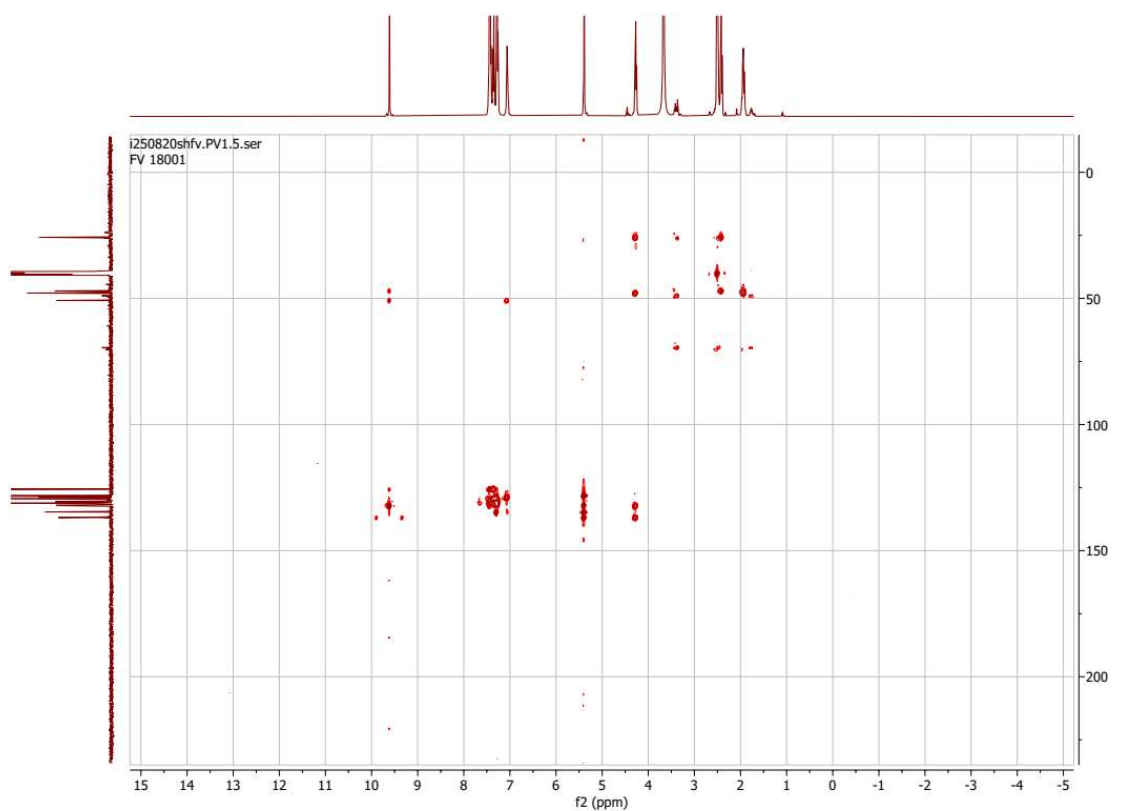
^{13}C NMR – PV1



DEPT-135 PV1

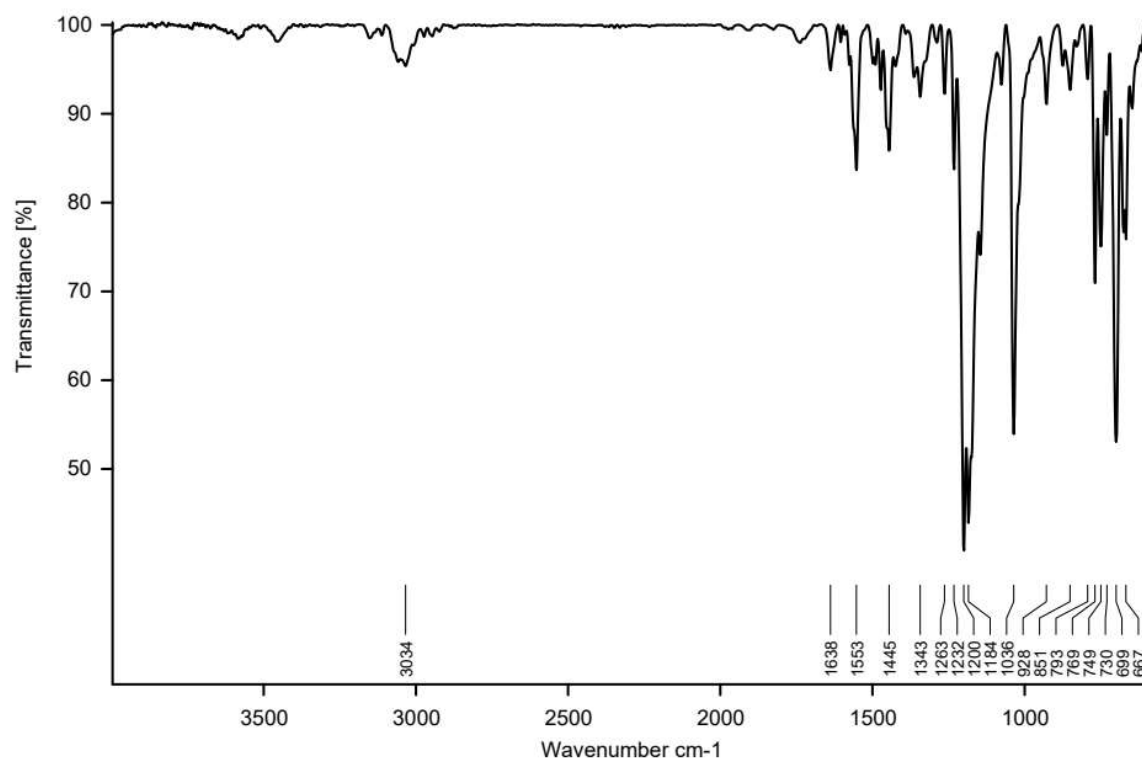


2D-HSQC PV1

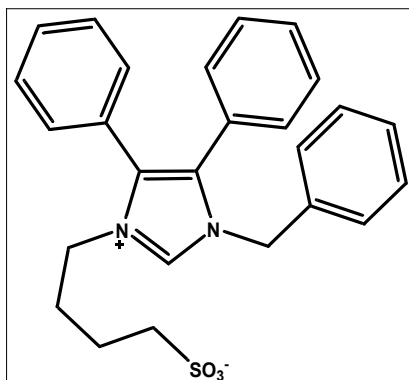


2D-HMBC PV1

PV1
ATR



***N*-benzyl-*N'*-(butyl-4-sulfonate)- 4,5-diphenylimidazolium salt (PV2)**



In a RBF PV0 was dissolved in a small amount of toluene. 1,4-butanediol (0.3099 g, 2.28 mmol) was added and the mixture has been kept at 80 °C for 10 minutes under magnetic stirring, then the temperature was raised up to 110 °C and the system was maintained at this condition for 48 hours. The mixture obtained was cooled at room temperature, acetone was added until a precipitate was obtained which was filtered off on paper washing the product with diethyl ether (6.0 mL x 3). After drying, the product appeared as a white powder. Yield = 68%

^1H NMR (500 MHz, DMSO- d_6) δ 9.64 (s, 1H, C2-H), 7.45–7.26 (m, 14H, Ar-H), 7.08–7.05 (br m, 2H, Ar-H), 5.39 (s, 2H, Ph-CH $_2$ -), 4.17–4.12 (t, J = 7.21 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.38–2.33 (t, J = 7.49 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.79–1.69 (q, J = 7.78 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.58–1.49 (q, J = 7.89 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

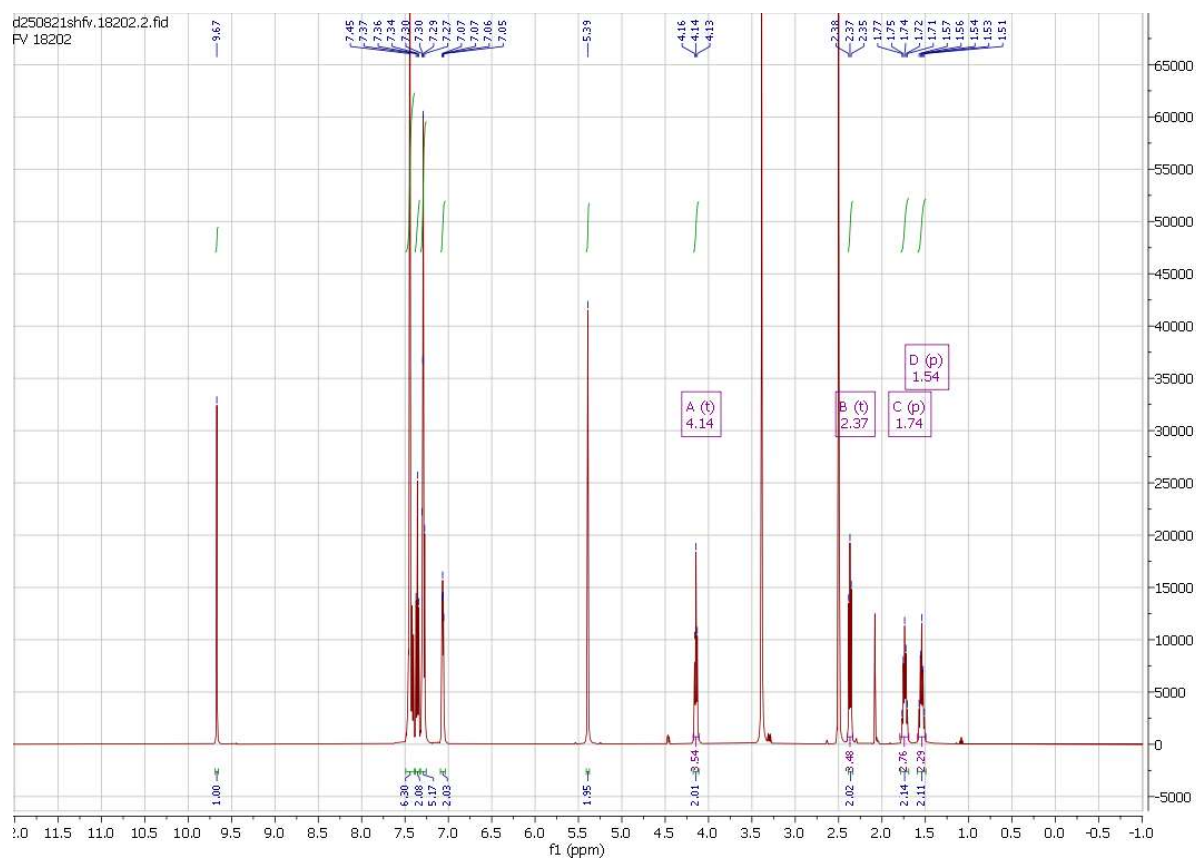
^{13}C NMR (126 MHz, DMSO- d_6) δ 136.34 (C2), 134.08 (*Cipso*), 131.75 (Cq), 131.46 (Cq), 130.81, 130.72, 130.16, 130.07, 128.96, 128.78, 128.40, 127.75, 125.13, 125.07 (Ar), 50.42 (CH $_2$ -Ph), 50.27 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 47.22 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 27.86 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 21.80 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

ATR-FTIR: ν 3483, 3114, 3027, 2965, 2869, 1626, 1555, 1491, 1452, 1417, 1352, 1300, 1209, 1172, 1073, 1034, 846, 780, 765, 732, 704, 650 cm^{-1}

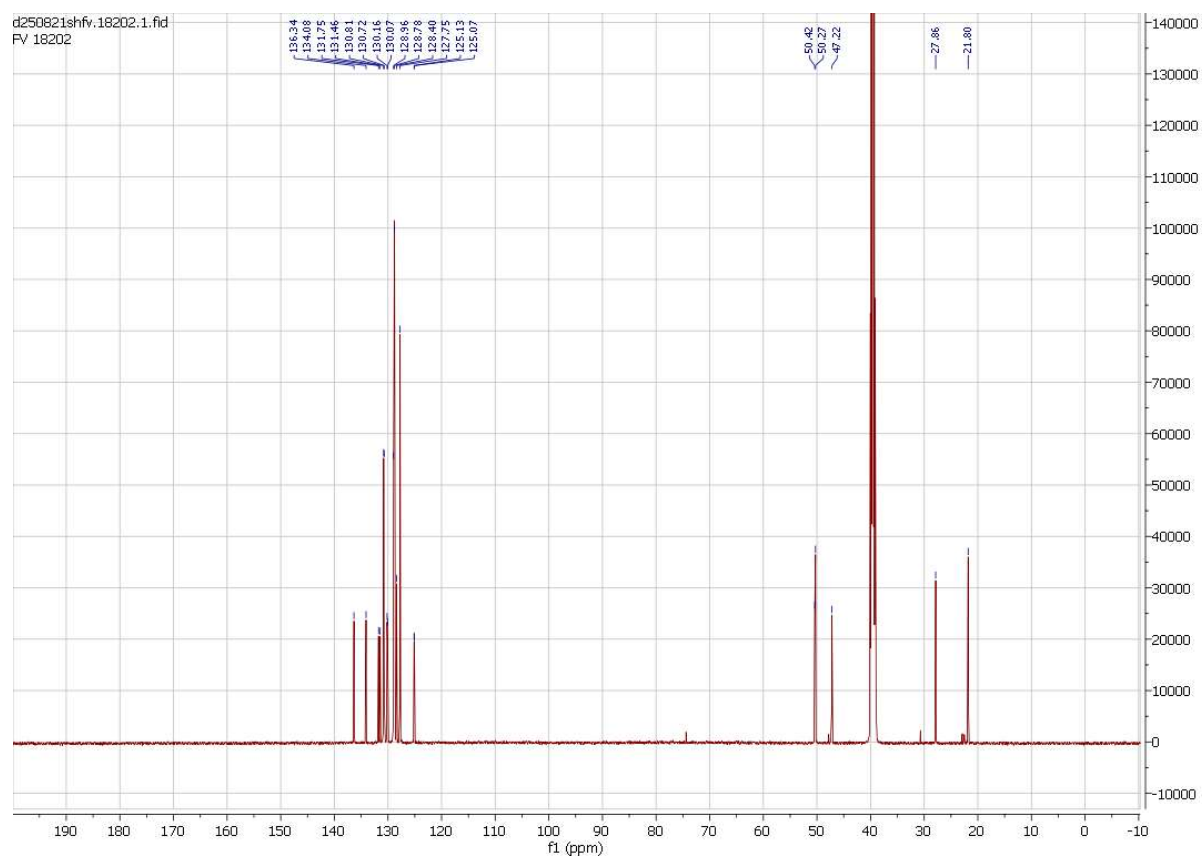
MS (MALDI-TOF, Positive mode)

HRMS measured: 447.1741 m/z ($M+H^+$); estimated: 447.1737 m/z

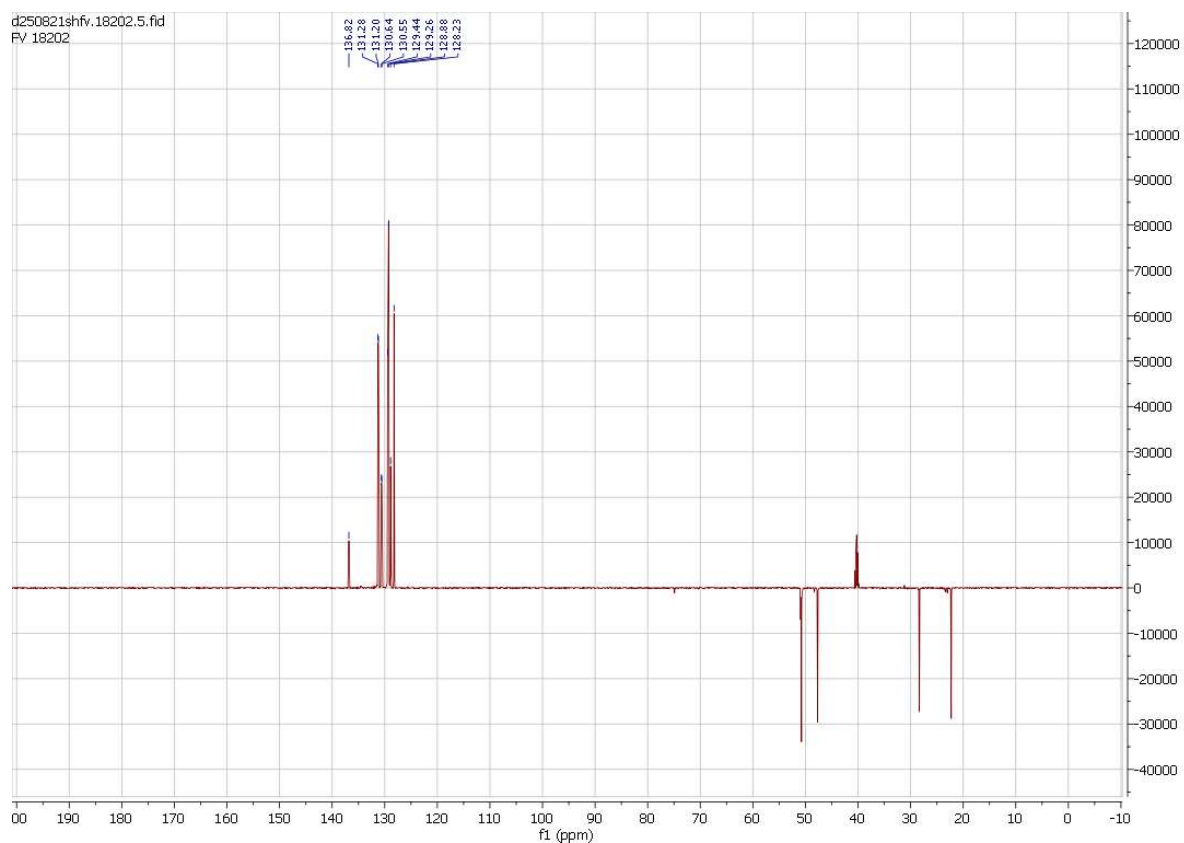
m/z: 447.1741 ($M+H^+$), 469.1559 ($M+Na^+$), 893.3407 ($2M+H^+$), 915.3222 ($2M+Na^+$), 1339.5073 ($3M+H^+$), 1361.4895 ($3M+Na^+$), 1786.6766 ($4M+2H^+$), 1808.6590 ($4M+Na^++H^+$), 2232.8439 ($5M+2H^+$)



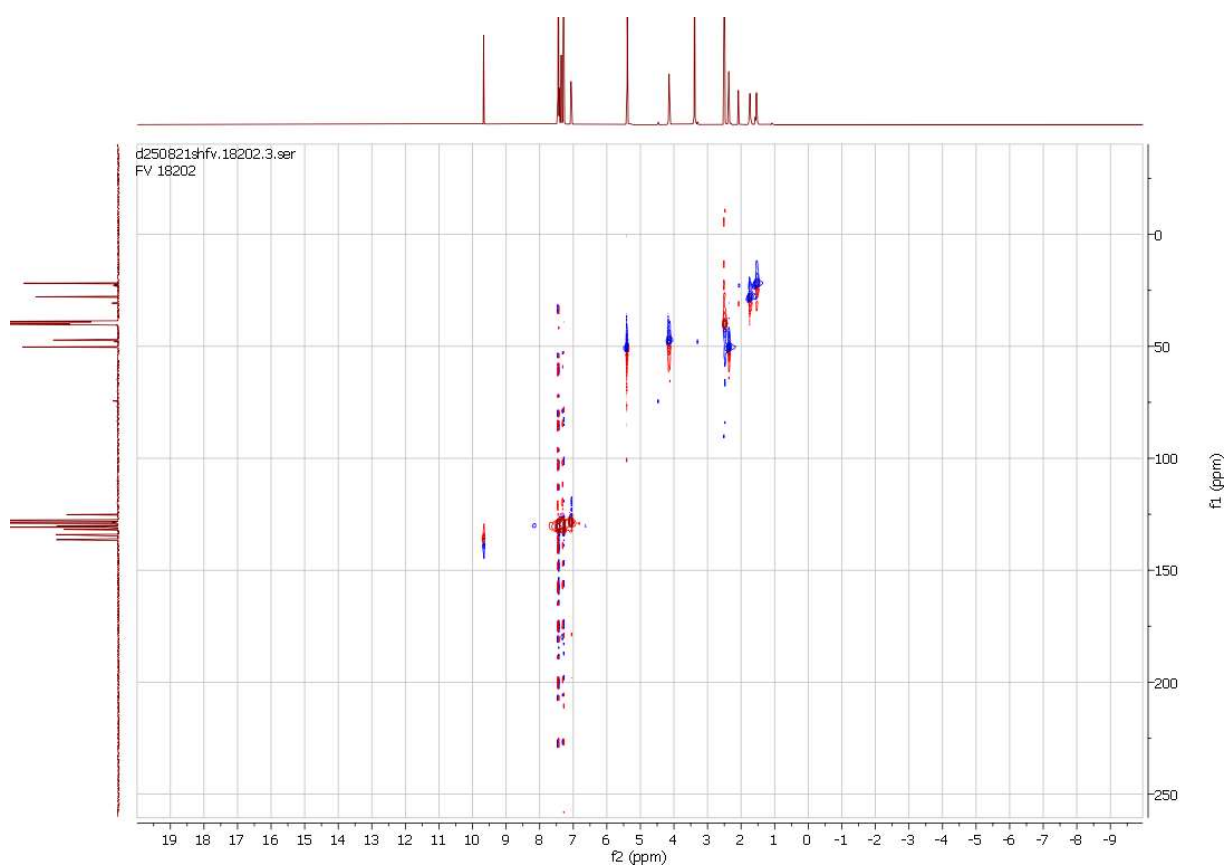
1H NMR – PV2



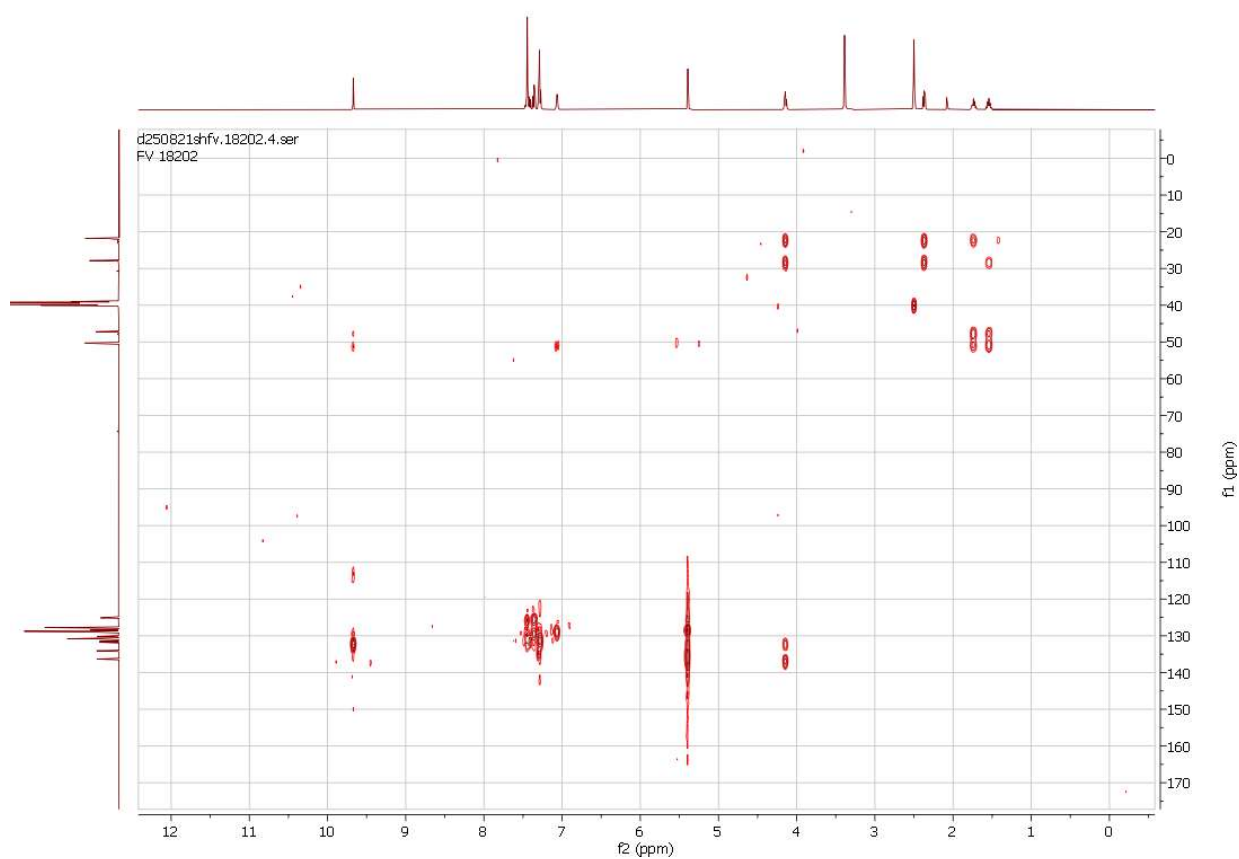
^{13}C NMR – PV2



DEPT-135 PV2

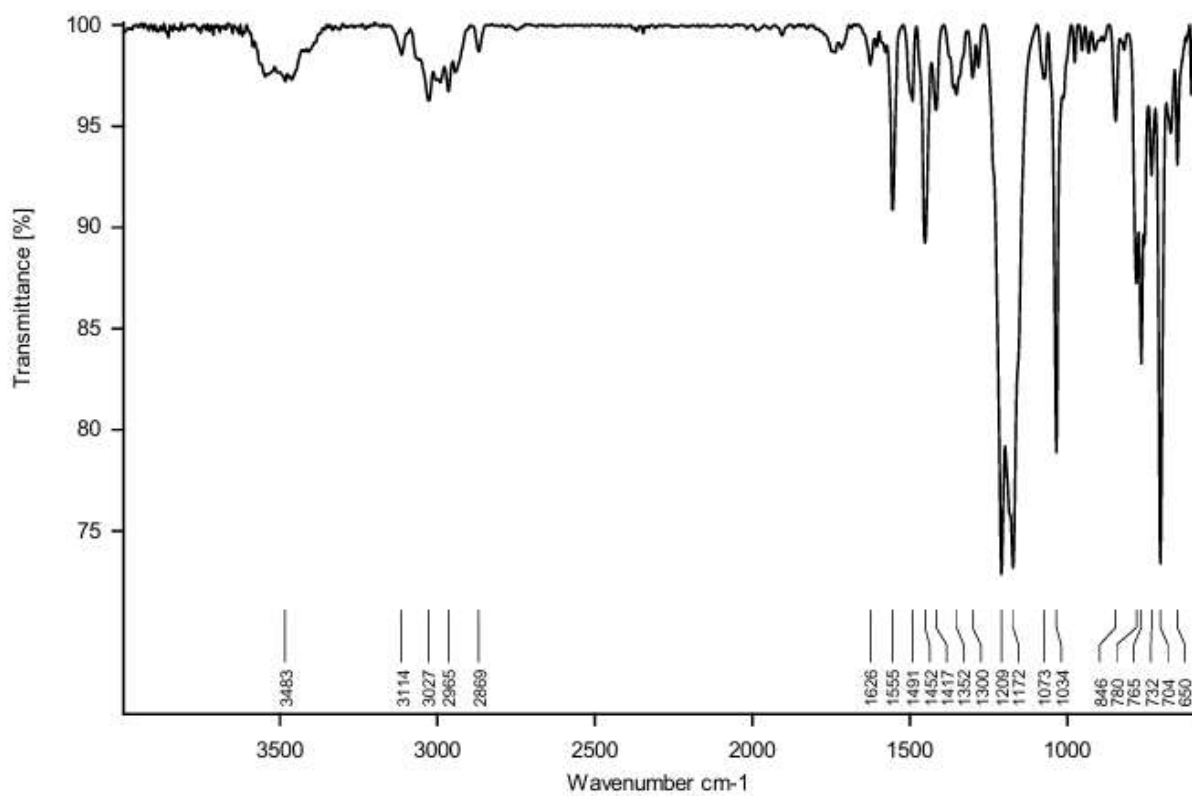


2D-HSQC PV2

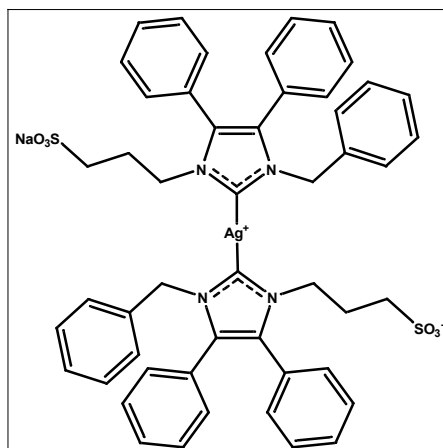


2D-HMBC PV2

PV2
ATR



Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)4,5-diphenyl-2-yliden] silver chloride (AgPV1)

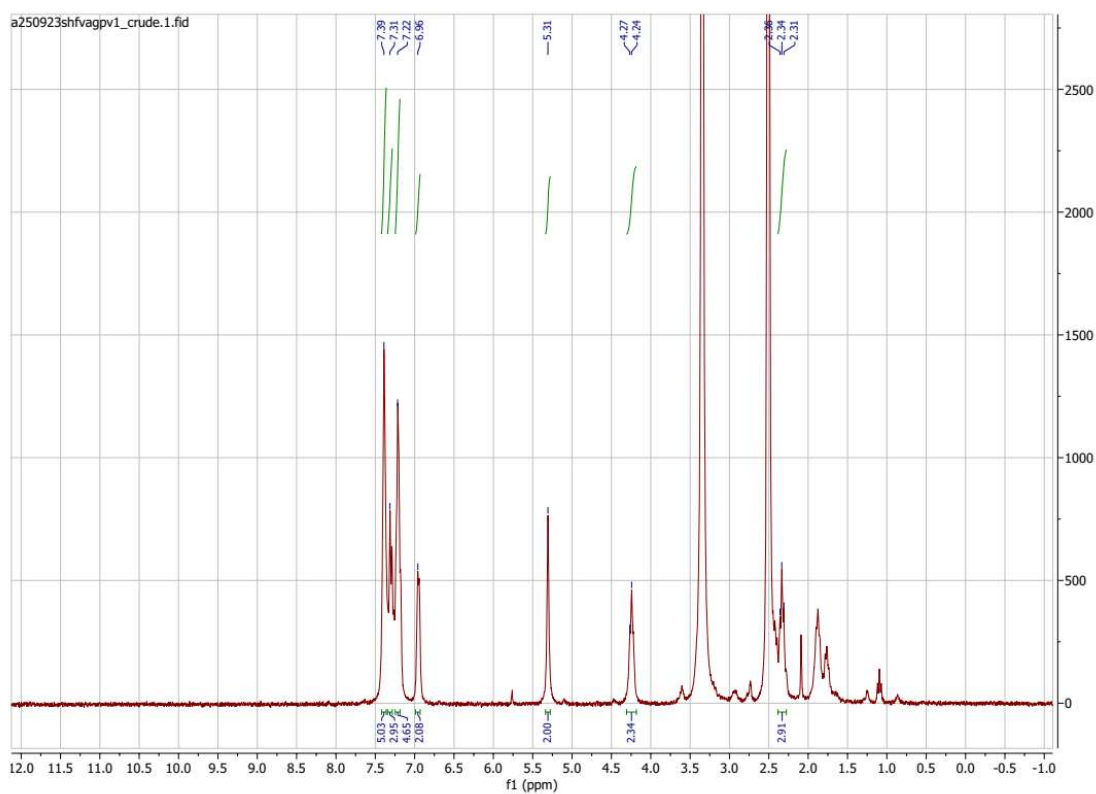


See “General synthesis for NHC-*Ag*(I)-sulfonate complexes – Strategy B”.

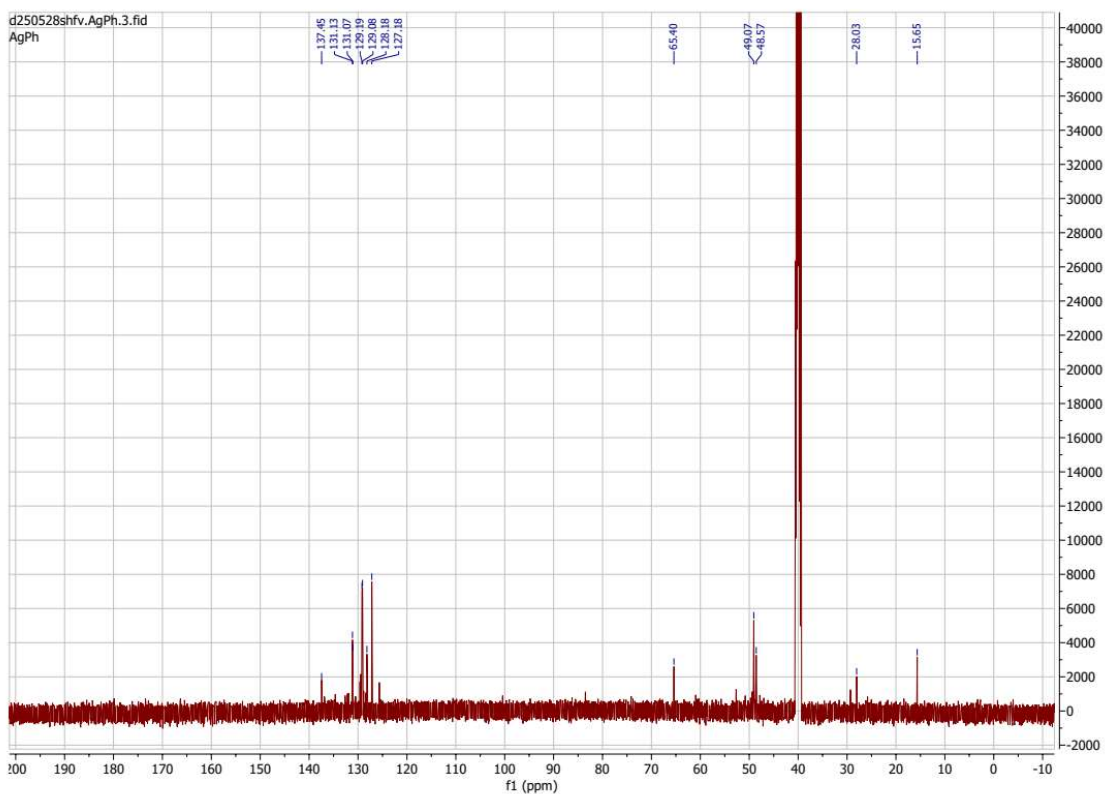
Grey-beige powder. Yield = 24.1%

^1H NMR (400 MHz, DMSO- d_6) δ 7.39–7.18 (m, 13H, Ar-H), 6.97–6.94 (m, 2H, Ar-H), 5.31 (s, 1H, CH₂-Ph), 4.25–4.20 (t, J = 7.57 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 1.89–1.87 (m, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (100 MHz, DMSO- d_6) δ 137.45 (*Cipso*), 131.13, 131.07, 129.19, 129.08, 128.18, 127.18 (Ar), 65.40 (CH₂-Ph), 49.07 (N-CH₂-CH₂-CH₂-SO₃[−]), 48.57 (N-CH₂-CH₂-CH₂-SO₃[−]), 28.03 (N-CH₂-CH₂-CH₂-SO₃[−])

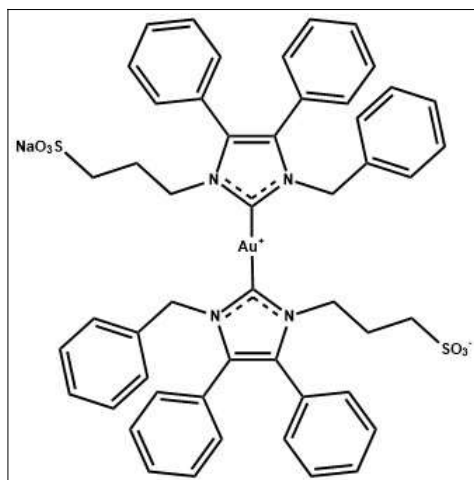


^1H NMR – AgPV1



^{13}C NMR – AgPV1

Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)4,5-diphenyl-2-yliden] gold chloride (AuPV1)



See “General synthesis for NHC-Au(I)-sulfonate complexes”. White powder. Yield = 16.0%

^1H NMR (500 MHz, DMSO- d_6) δ 7.41–7.18 (br m, 13H, Ar-H), 6.98–6.96 (m, 2H, Ar-H), 5.40 (s, 2H, CH₂-Ph), 4.25–4.22 (t, J = 7.15 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.30 (t, J = 3.20 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 1.90 (q, J = 7.58 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).

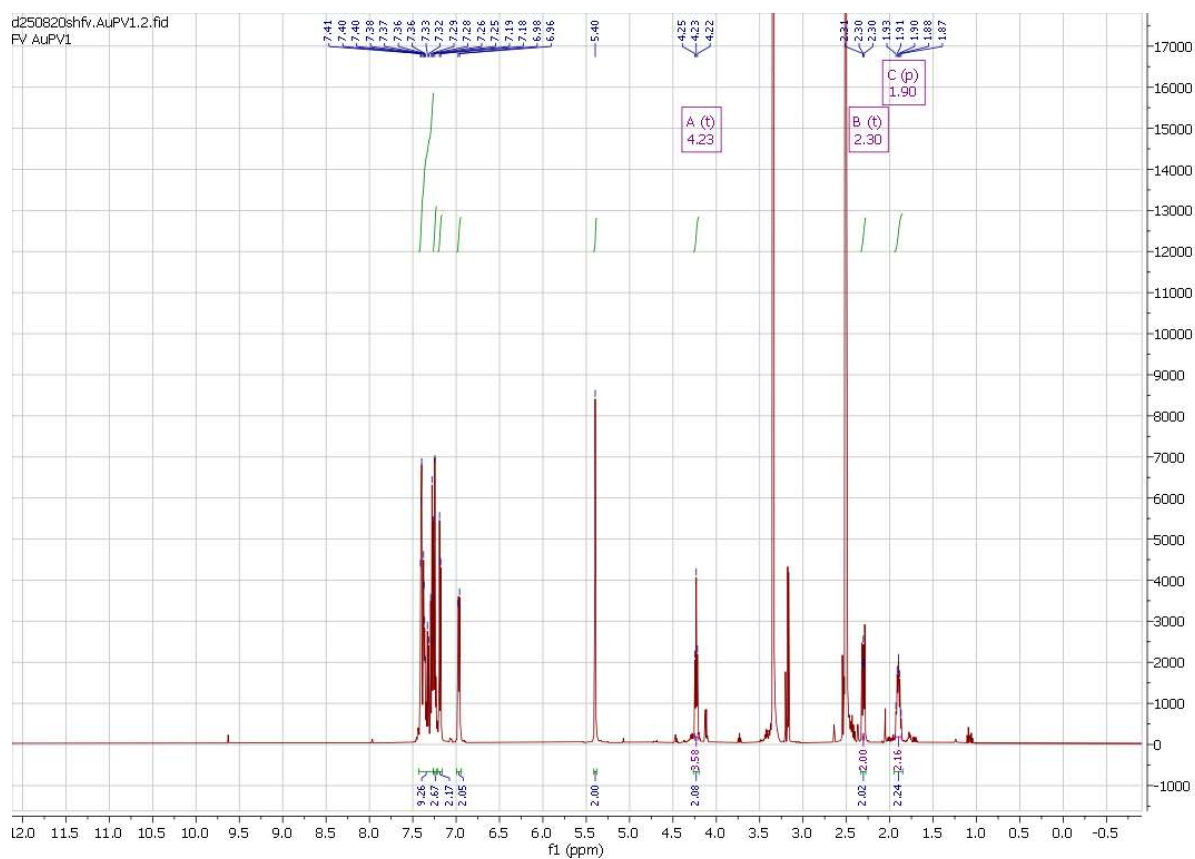
^{13}C NMR (126 MHz, DMSO- d_6) δ 169.62 (C-Au), 136.20 (*Cipso*), 131.38, 130.75, 130.67, 129.36, 129.28, 128.73, 128.54, 128.48, 127.70, 127.21, 127.18, 126.58 (Ar), 52.07 (Ph-CH₂-), 48.71 (N-CH₂-CH₂-CH₂-SO₃[−]), 48.52 (N-CH₂-CH₂-CH₂-SO₃[−]), 26.99 (N-CH₂-CH₂-CH₂-SO₃[−]).

MS (MALDI-TOF, Positive mode)

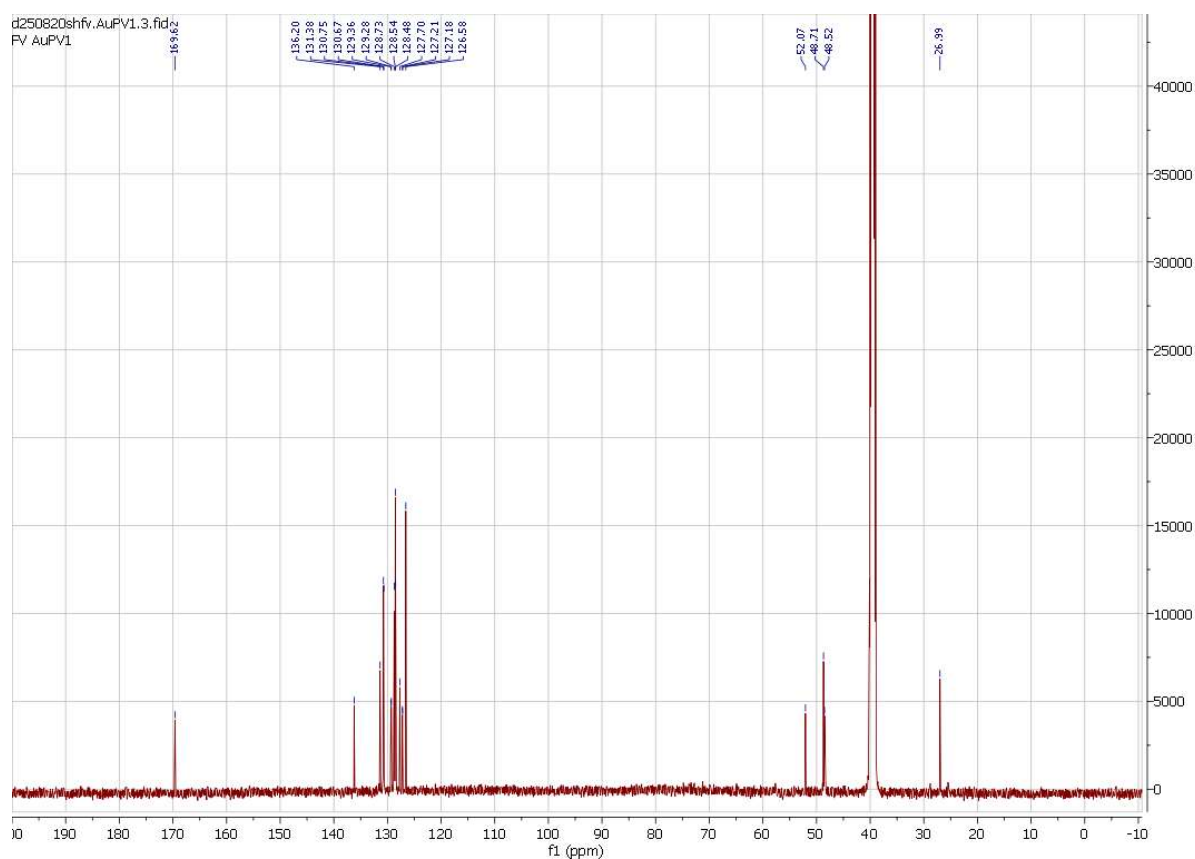
m/z : 973.2082 [C₅₀H₄₈AgN₄O₆S₂]⁺, 995.1898 [C₅₀H₄₇AgN₄NaO₆S₂]⁺, 1017.1717 [C₅₀H₄₆AgN₄Na₂O₆S₂]⁺

MS (MALDI-TOF, Negative mode)

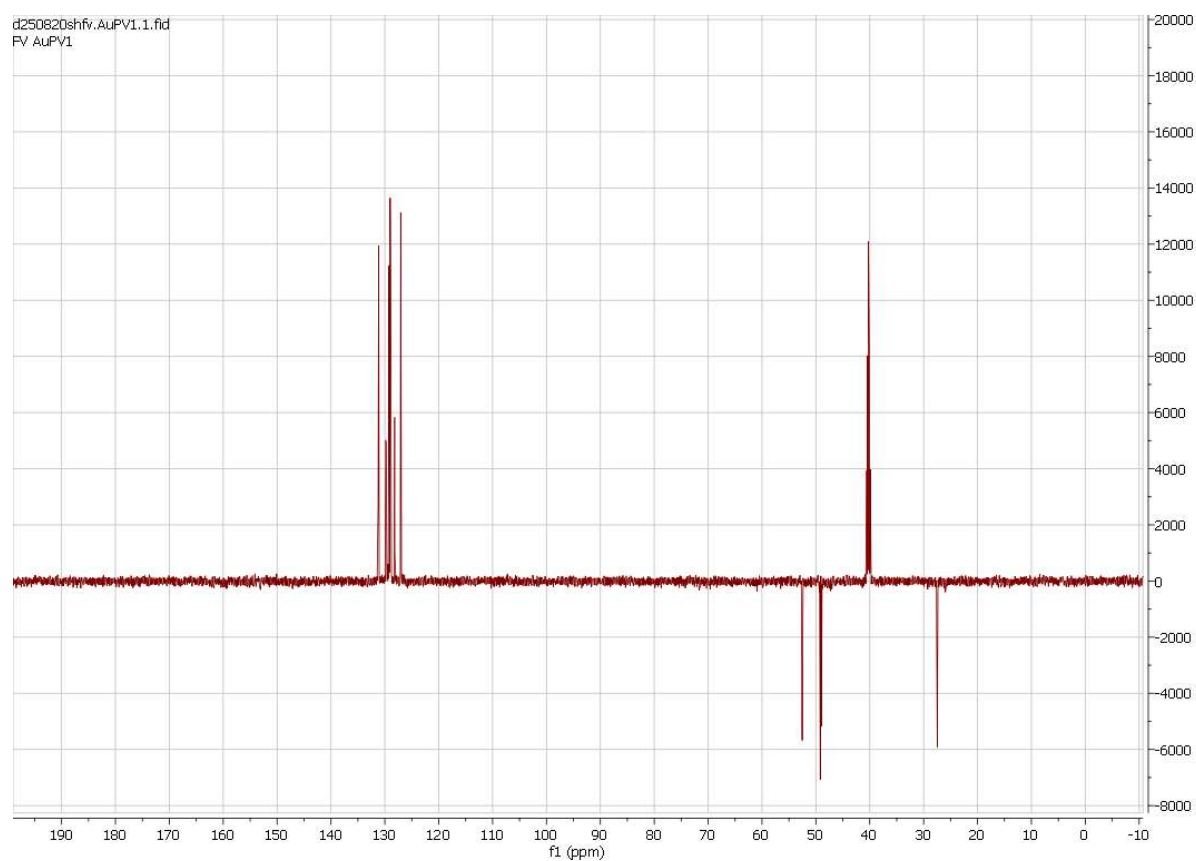
m/z : 575.0174 [C₂₅H₂₃AgClN₂O₃S][−], 971.1943 [C₅₀H₄₆AgN₄O₆S₂][−]



^1H NMR – AuPV1

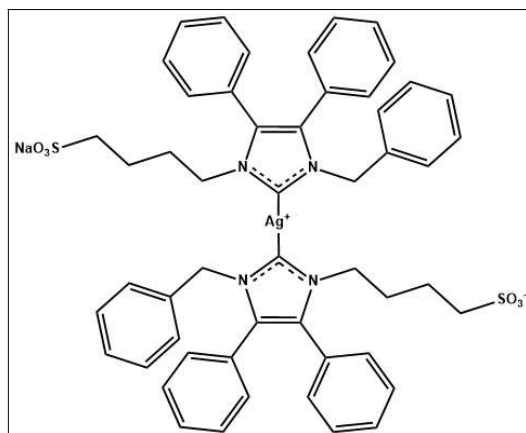


^{13}C NMR – AuPV1



DEPT-135 AuPV1

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)4,5-diphenyl-2-yliden] silver chloride (AgPV2)

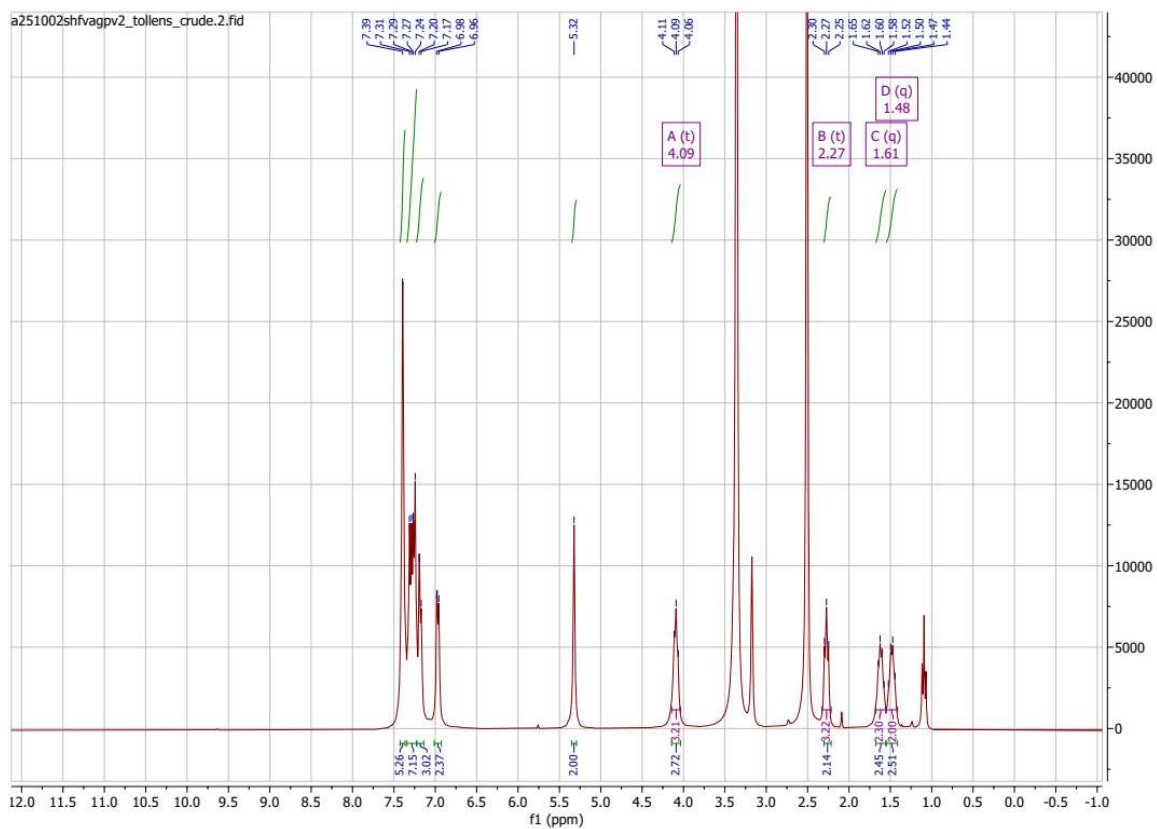


See “General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B”

Violet powder. Yield = 32.1%

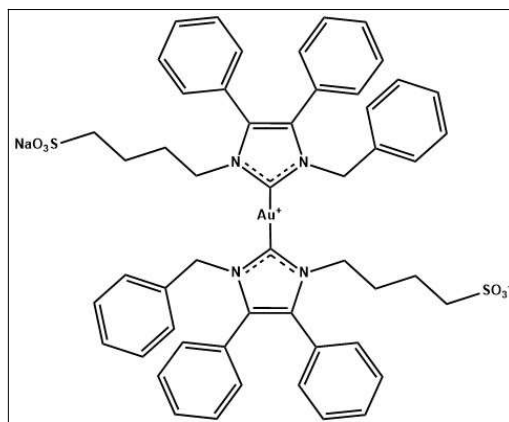
^1H NMR (300 MHz, DMSO- d_6) δ 7.39–7.17 (m, 13H, Ar-H), 6.98–6.96 (d, 2H, Ar-H), 5.32 (s, 2H, Ph-CH $_2$ -), 4.11–4.06 (t, J = 7.36 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.30–2.25 (t, J = 7.6 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.65–1.58 (m, J = 6.77 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.52–1.44 (m, J = 8.48 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

^{13}C NMR (75 MHz, DMSO- d_6) δ 136.23 (*Cipso*), 131.45, 131.25, 130.69, 128.72, 128.57, 128.49, 127.67, 127.25, 127.17, 126.58 (Ar), 52.07 (Ph-CH $_2$ -), 50.62 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 48.87 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 29.78 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 22.18 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).



^1H NMR – AgPV2

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)4,5-diphenyl-2-yliden] gold chloride (AuPV2)

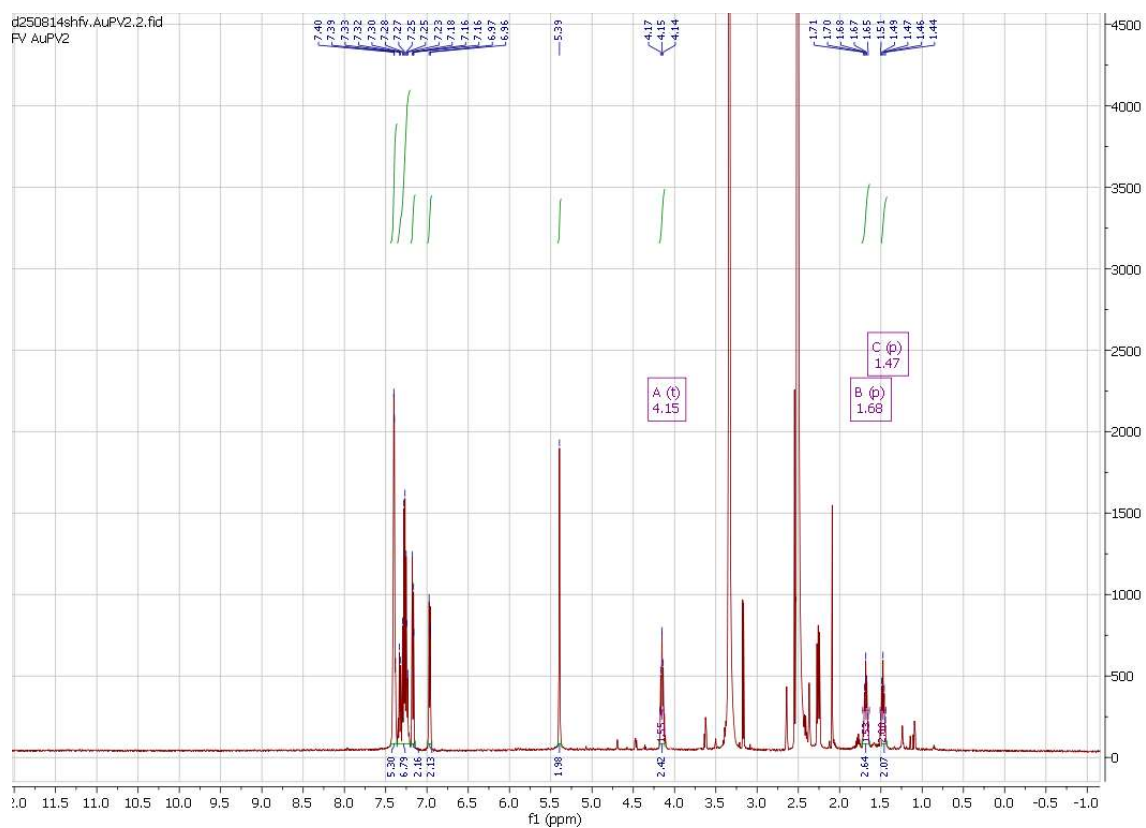


See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”

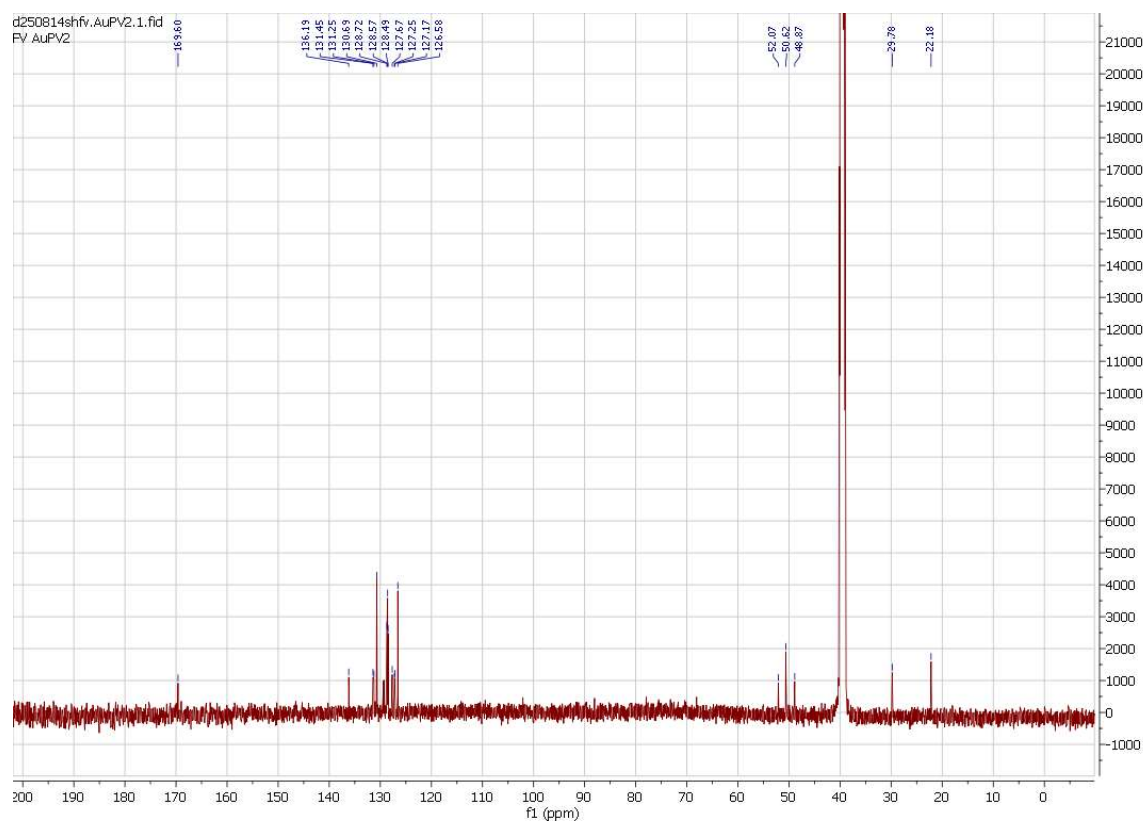
Violet powder. Yield = 20.1%

^1H NMR (500 MHz, DMSO- d_6) δ 7.40 (br m, 5H, Ph-H), 7.33–7.23 (br m, 6H, Ar-H), 7.18–7.16 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H), 5.39 (s, 2H, CH₂-Ph), 4.15 (t, J = 7.61 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.68 (q, J = 7.57 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.47 (q, J = 7.58 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (126 MHz, DMSO- d_6) δ 169.60 (C-Au), 136.19 (*Cipso*), 131.45, 131.25, 130.69, 128.72, 128.57, 128.49, 127.67, 127.25, 127.17, 126.58 (Aromatics), 52.07 (Ph-CH₂-), 50.62 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 48.87 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 29.78 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 22.18 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

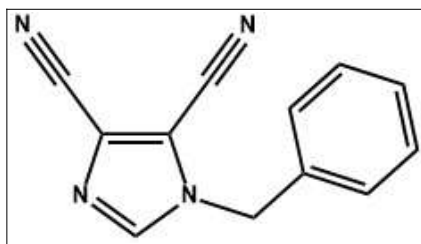


^1H NMR – AuPV2



^{13}C NMR – AuPV2

1-Benzyl-4,5-dicyanoimidazole (KV0)

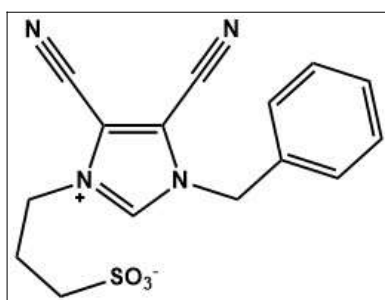


See “General synthesis for N-benzylated-imidazol compounds”.

Purified on silica gel column using a mobile phase EtOAc:P.E. 1:1, obtaining the final product finally obtained in a crystal shape.

White powder. Yield = 82.0 % The NMR characterization match the data reported in literature^[3].

N-benzyl-N'-(propyl-3-sulfonate)-4,5-dicyanoimidazolium inner salt (KV1)



See “General synthesis for N-benzylated-imidazolium salt compounds in MeCN”

White powder. Yield = 26.2 %

¹H NMR (600 MHz, DMSO-d₆) δ 10.00 (s, 1H, C2-H), 7.48 (m, 5H, Ph-H), 5.72 (s, 2H, Ph-CH₂-), 4.60–4.55 (t, J = 6.95 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.61–2.56 (t, J = 6.95 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.26–2.22 (q, J = 7.02 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (151 MHz, DMSO-d₆) δ 142.53 (C2), 132.92 (Cipso), 129.53, 129.12, 129.00 (Ph), 116.48, 114.38 (C4/5), 106.18, 105.98 (CN), 53.63 (Ph-CH₂-), 50.18 (N-CH₂-CH₂-CH₂-SO₃⁻), 47.22 (N-CH₂-CH₂-CH₂-SO₃⁻), 24.88 (N-CH₂-CH₂-CH₂-SO₃⁻).

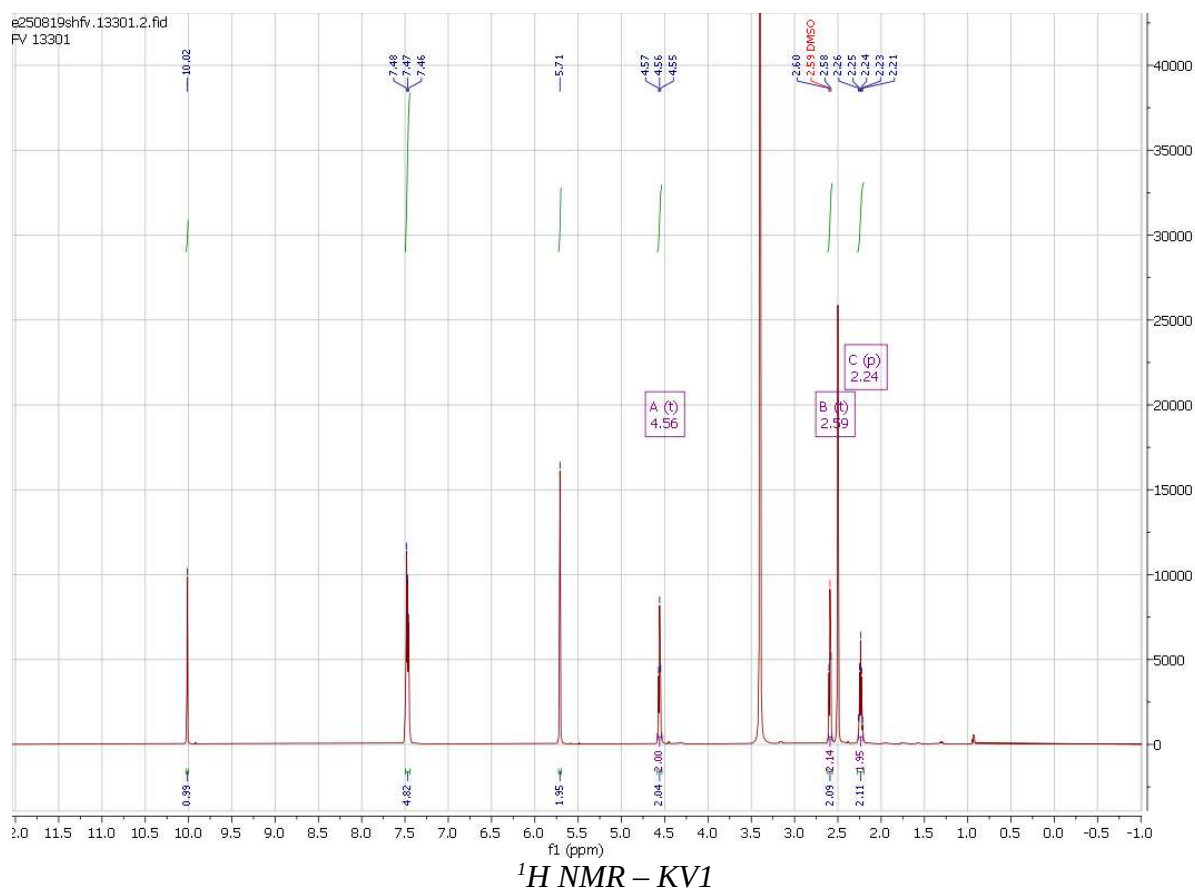
ATR-FTIR: ν 3100, 2952, 2259, 2249, 1548, 1478, 1455, 1436, 1379, 1330, 1267, 1240, 1189, 1161, 1115, 1033, 928, 887, 821, 765, 724, 710, 650, 609 cm^{-1}

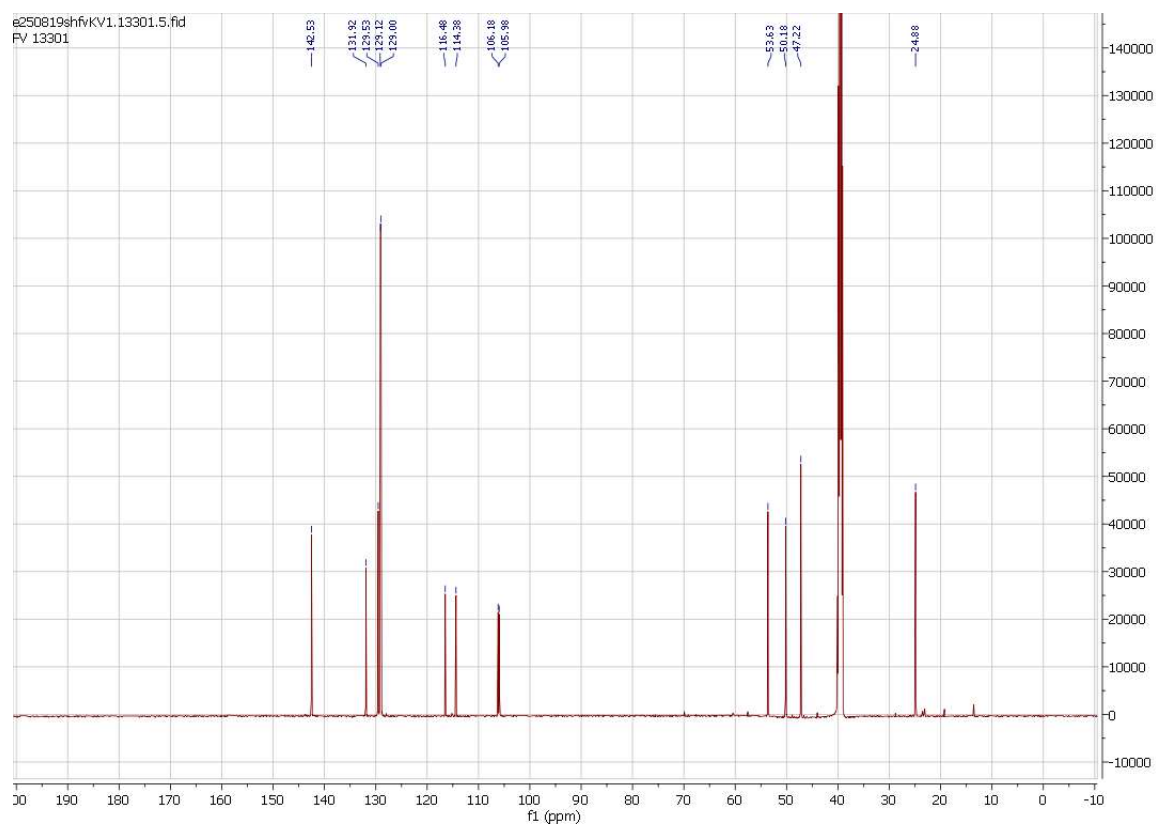
MS (MALDI-TOF, Positive mode)

HRMS measured: 331.0859 m/z [$\text{C}_{15}\text{H}_{15}\text{N}_4\text{O}_3\text{S}$] $^+$ ($\text{M}+\text{H}^+$); estimated: 331.0859 m/z

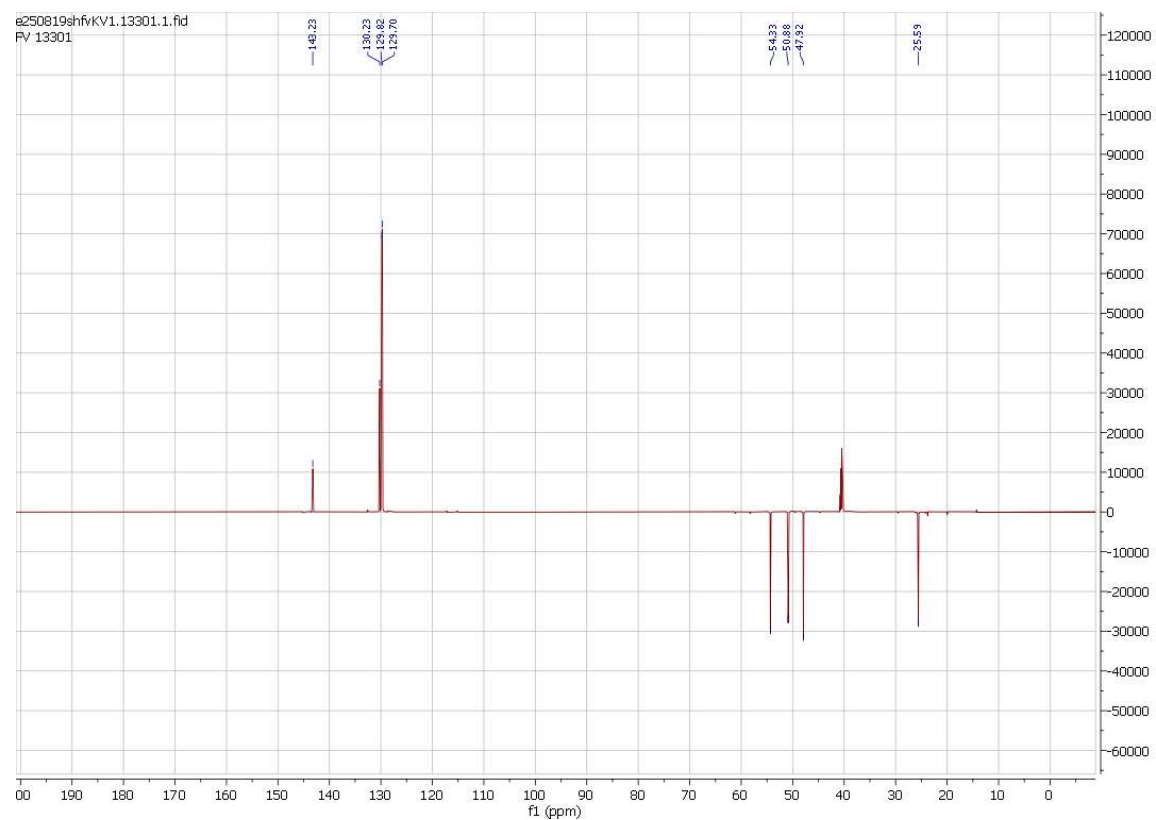
MS (MALDI-TOF, Negative mode)

HRMS measured: 329.0719 m/z [$\text{C}_{15}\text{H}_{13}\text{N}_4\text{O}_3\text{S}$] $^-$ ($\text{M}-\text{H}^+$); estimated: 329.0714 m/z

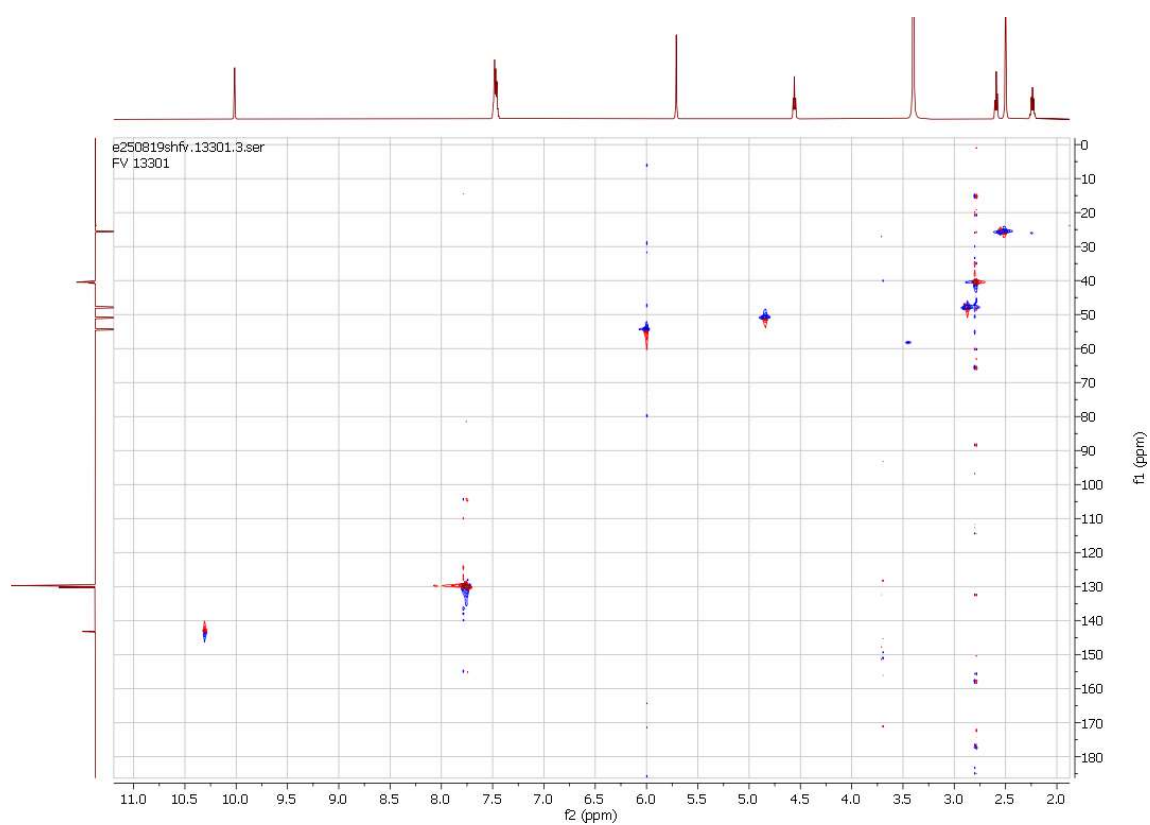




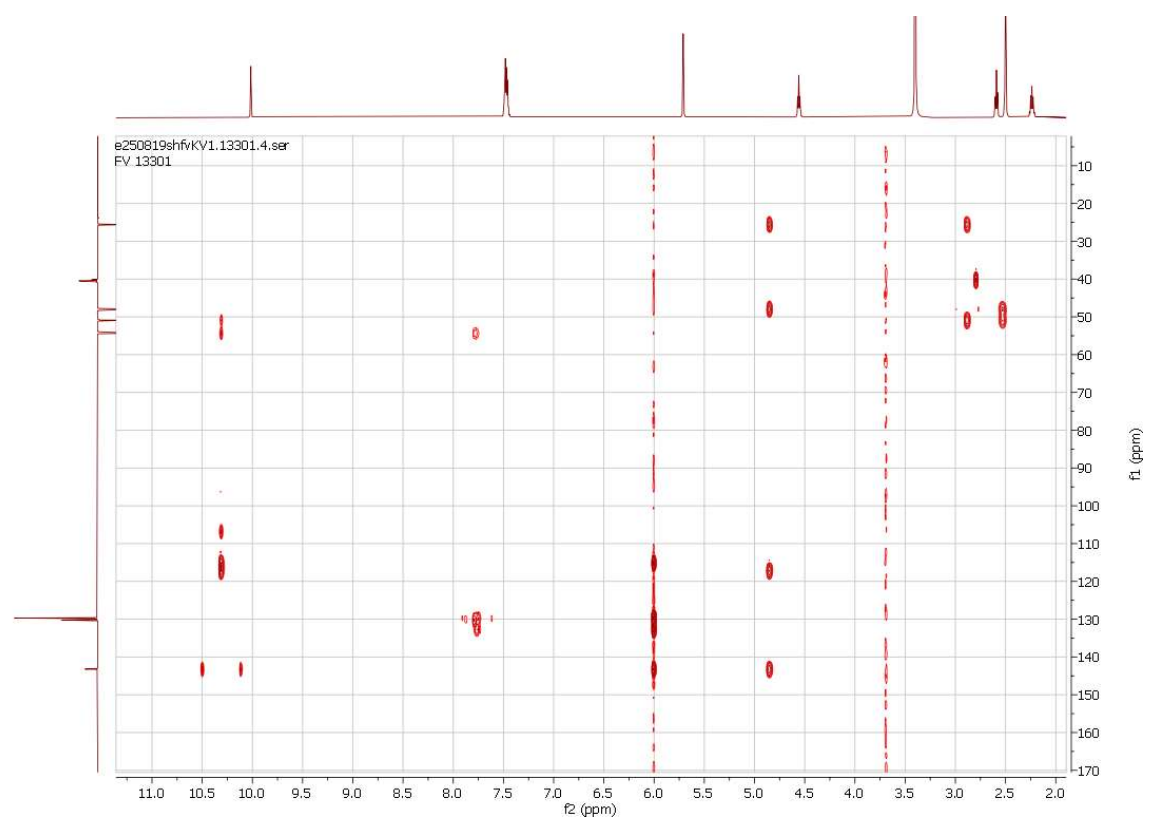
^{13}C NMR – KV1



DEPT-135 KV1

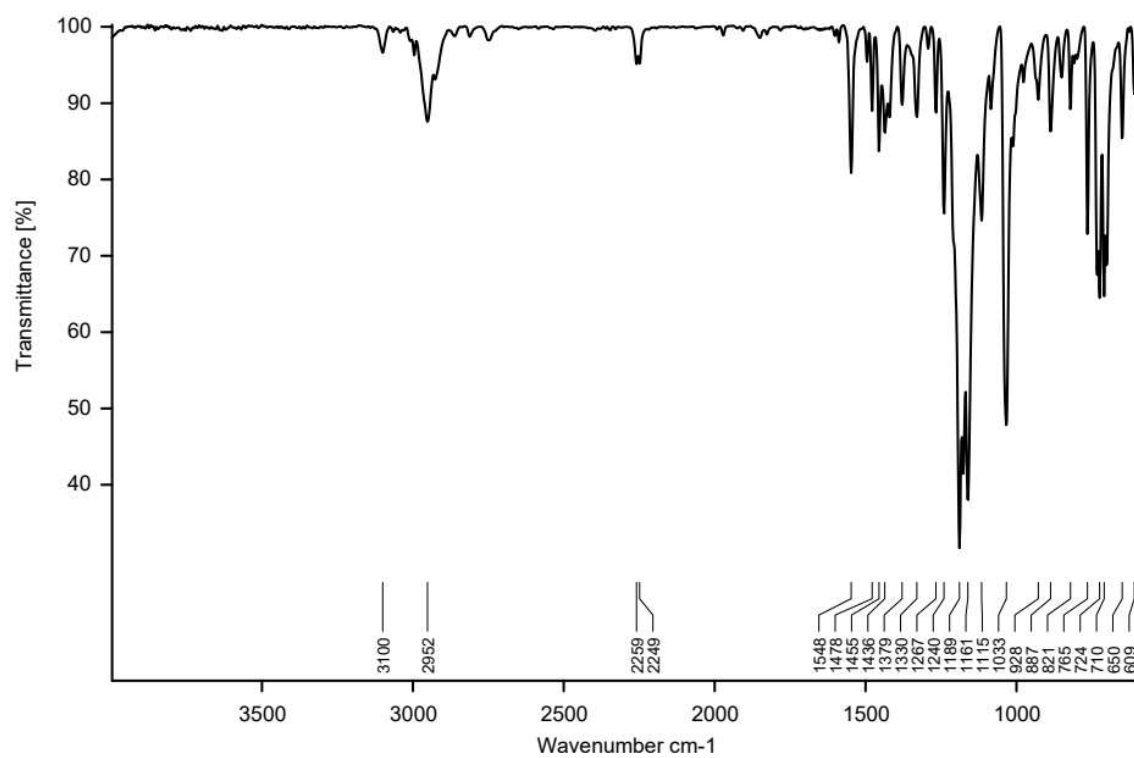


2D-HSQC KV1

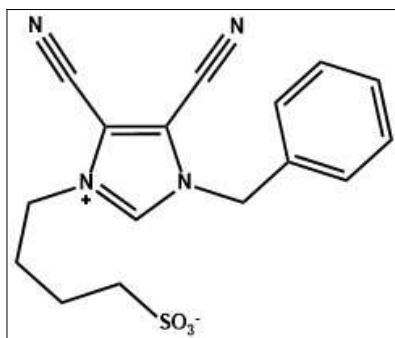


2D-HMBC KV1

KV1
ATR



***N*-benzyl-*N'*-(butyl-3-sulfonate)-4,5-dicyanoimidazolium inner salt (KV2)**



See “*General synthesis for N-benzylated-imidazolium salt compounds in MeCN*”

Not isolated.

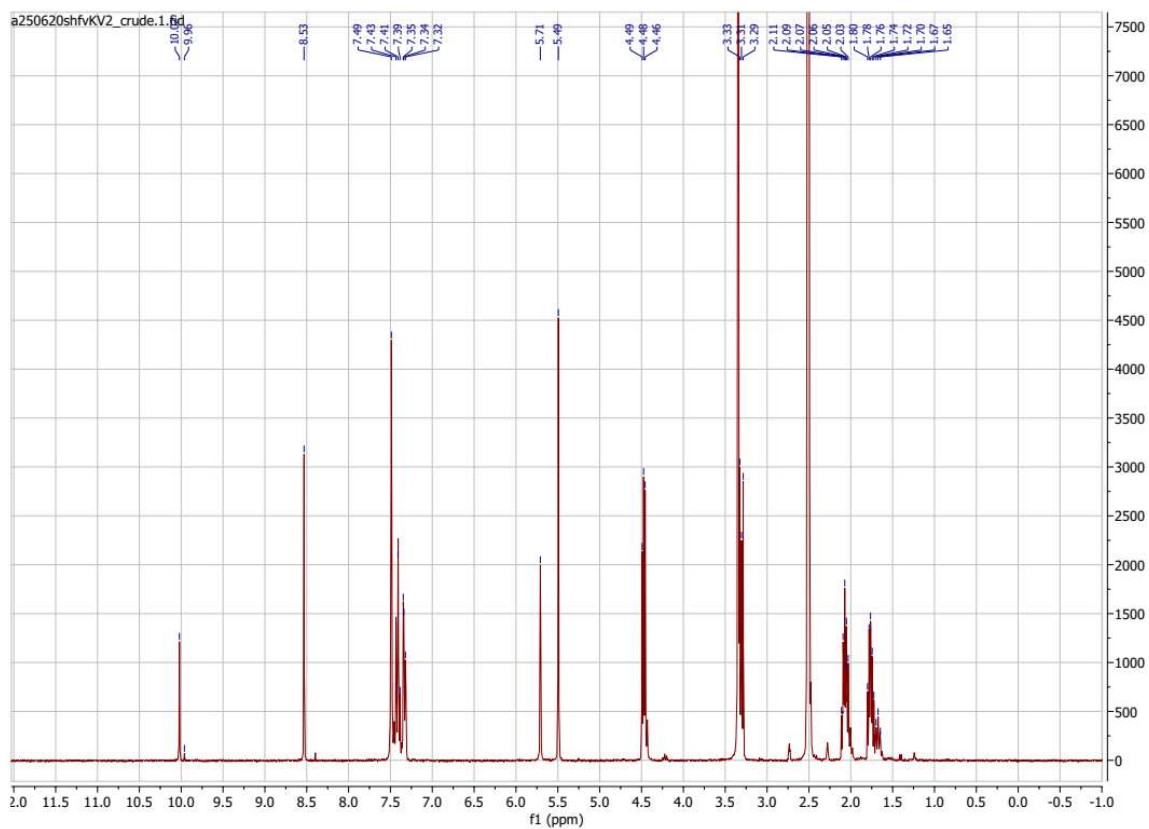
¹H NMR (400 MHz, DMSO-*d*₆) δ 10.02 (s, 1H, C2-H), 7.49–7.32 (m, 5H, Ph-H), 5.71 (s, 2H, Ph-CH₂-), 4.49–4.46 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 3.33–3.29 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 2.11–2.03 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.80–1.65 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).

MS (MALDI-TOF, Positive mode)

HRMS measured: 345.1011 m/z [C₁₆H₁₇N₄O₃S]⁺ (M+H⁺); estimated: 345.1016 m/z
m/z: 345.1011 (M+H⁺), 689.1962 (2M+H⁺)

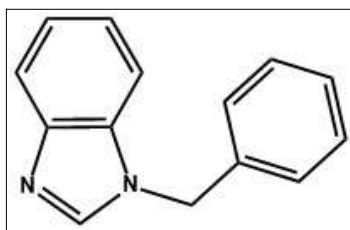
MS (MALDI-TOF, Negative mode)

HRMS measured: 343.0899 m/z [C₁₆H₁₅N₄O₃S]⁻ (M-H⁺); estimated: 343.0870 m/z



^1H NMR – KV2 (crude)

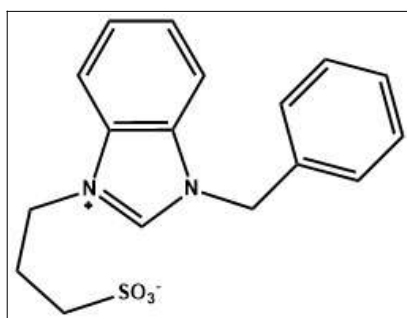
1-Benzyl-Benzimidazole (BV0)



See “General synthesis for *N*-benzylated-imidazol compounds”

Purified on silica gel column using a mobile phase P.E.:Acetone 1:1 obtaining the final product finally obtained in a crystal shape. Yield = 57%. The NMR characterization match the data reported in literature^[4].

N-benzyl-*N'*-(propyl-3-sulfonate)-benzimidazolium inner salt (BV1)



See “General synthesis for *N*-benzylated-imidazolium salt compounds in MeCN”.

White powder. Yield = 57%

¹H NMR (700 MHz, DMSO-*d*₆) δ 9.92 (s, 1H, C2-H), 8.13–8.12 (d, *J* = 8.27 Hz, 1H, benzimidazol-H), 7.92–7.91 (d, *J* = 8.27 Hz, 1H, benzimidazol-H), 7.68–7.66 (t, *J* = 7.87 Hz, 1H, benzimidazol-H), 7.64–7.62 (t, *J* = 7.47 Hz, 1H, benzimidazol-H), 7.52–7.51 (d, *J* = 7.31 Hz, 2H, Ph-H), 7.43–7.38 (t, *J* = 7.39 Hz, 2H, Ph-H), 7.37–7.34 (t, *J* = 7.31 Hz, 1H, Ph-H), 5.76 (s, 2H, Ph-CH₂-), 4.69–4.67 (t, *J* = 7.15 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.25–2.21 (q, *J* = 7.15 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (176 MHz, DMSO-*d*₆) δ 142.75 (C2), 134.08 (*Cipso*), 131.37 (C4), 130.90 (C5), 128.98 (Ph), 128.68 (Ph), 128.24 (Ph), 126.63 (Ph), 113.92 (Benzimidazole), 113.87

(Benzimidazole), 49.89 (Ph- CH_2 -), 47.52 (N- $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 45.85 (N- $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 25.29 (N- $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$).

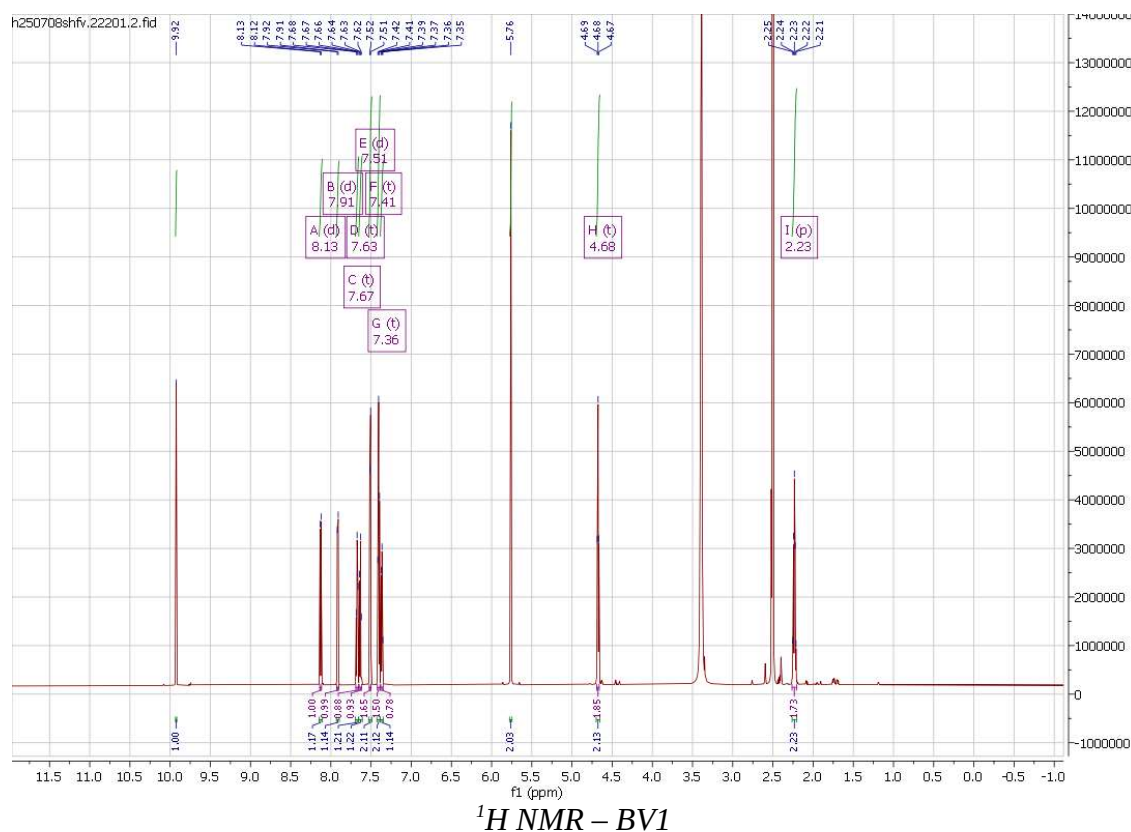
ATR-FTIR: ν 3125, 3053, 2955, 2781, 1618, 1561, 1499, 1446, 1428, 1378, 1356, 1282, 1268, 1233, 1200, 1177, 1132, 1036, 953, 865, 791, 769, 755, 741, 701, 605 cm^{-1}

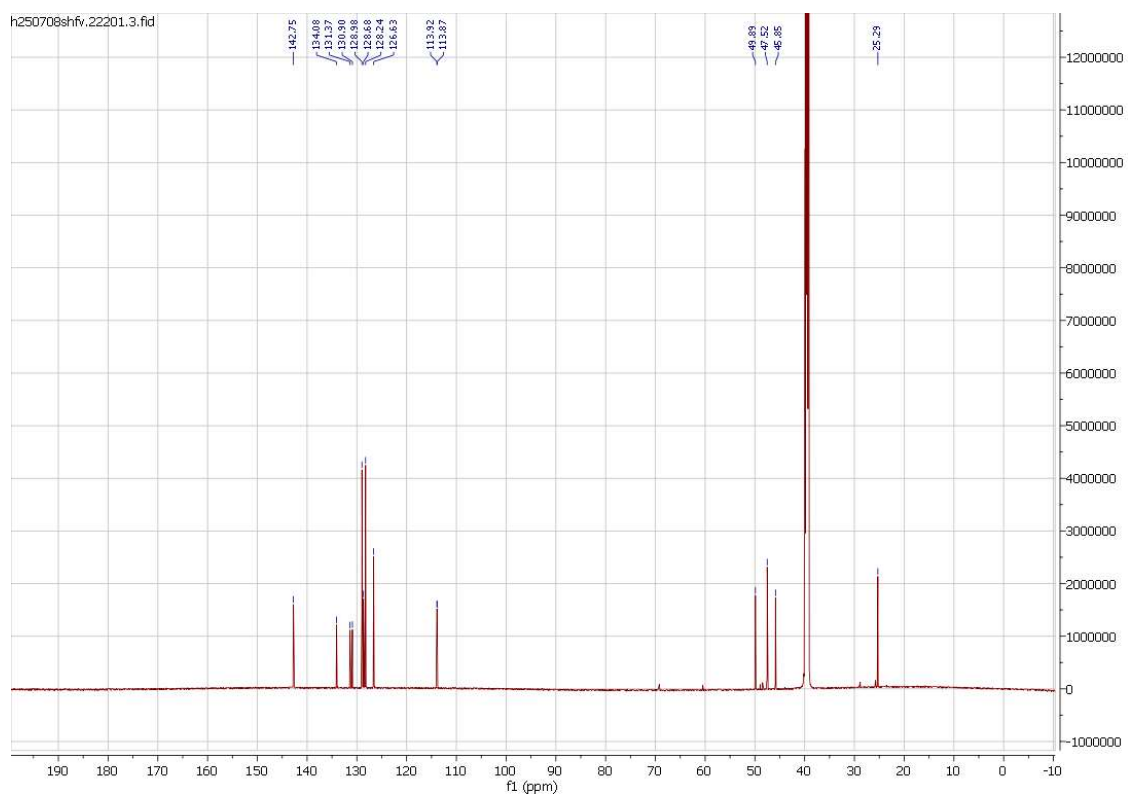
MS (MALDI-TOF, Positive mode)

HRMS measured: 331.1108 m/z [$\text{C}_{17}\text{H}_{19}\text{N}_2\text{O}_3\text{S}]^+$ ($\text{M}+\text{H}^+$); estimated: 331.1111 m/z
m/z: 331.1108 ($\text{M}+\text{H}^+$), 661.2152 ($2\text{M}+\text{H}^+$)

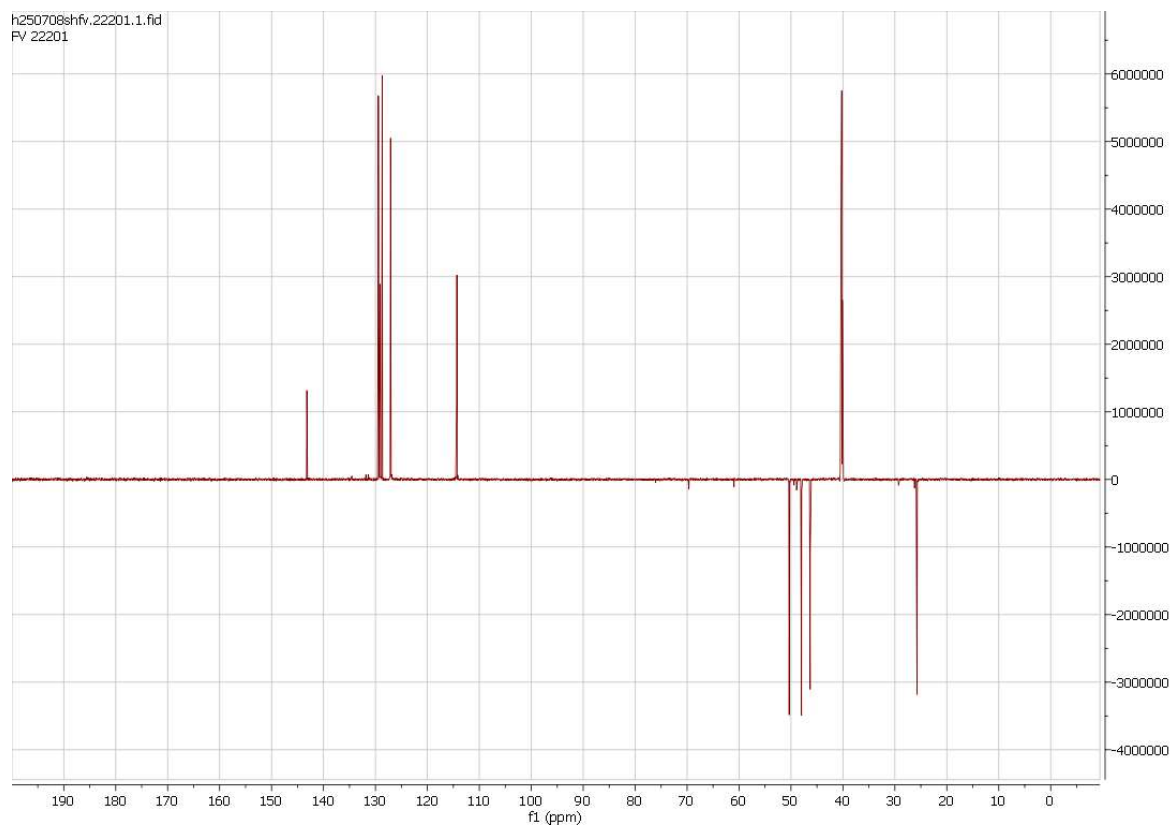
MS (MALDI-TOF, Negative mode)

HRMS measured: 329.0996 m/z [$\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_3\text{S}]^-$ ($\text{M}-\text{H}^+$); estimated: 329.0965 m/z

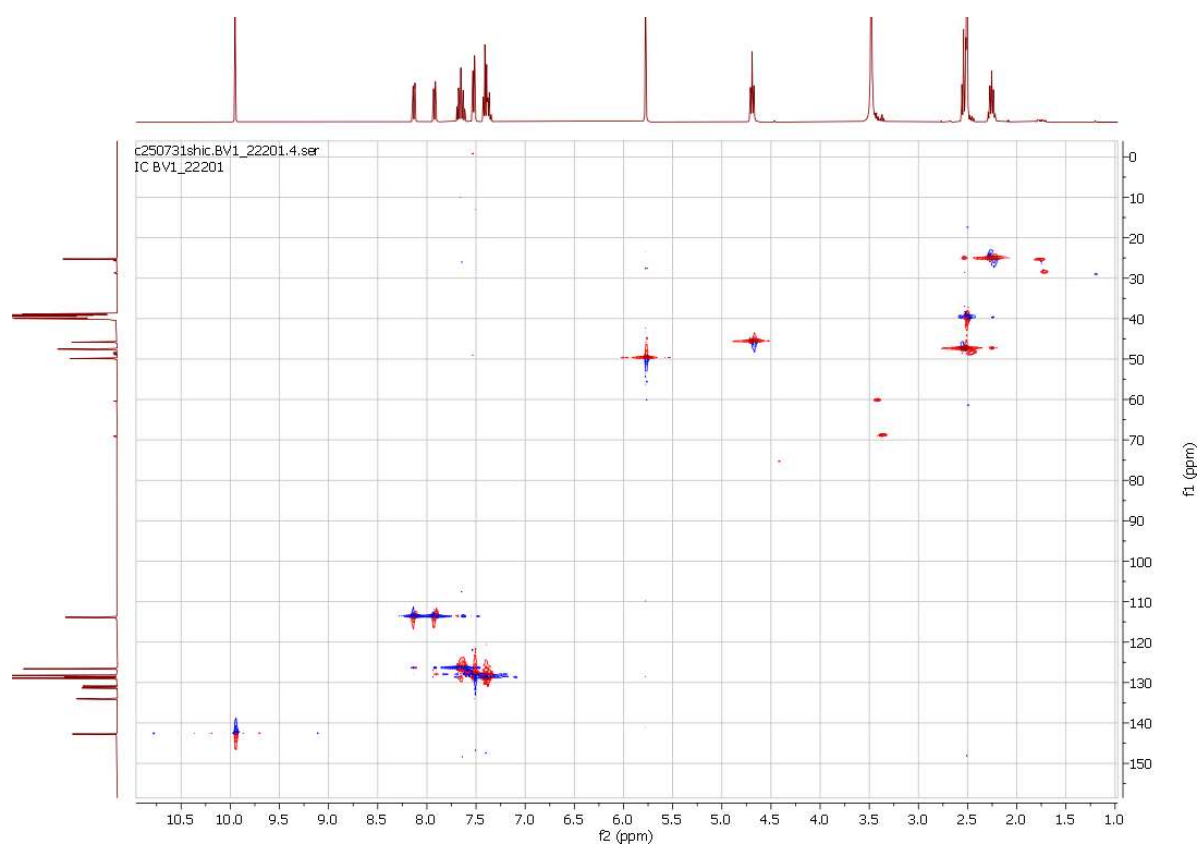




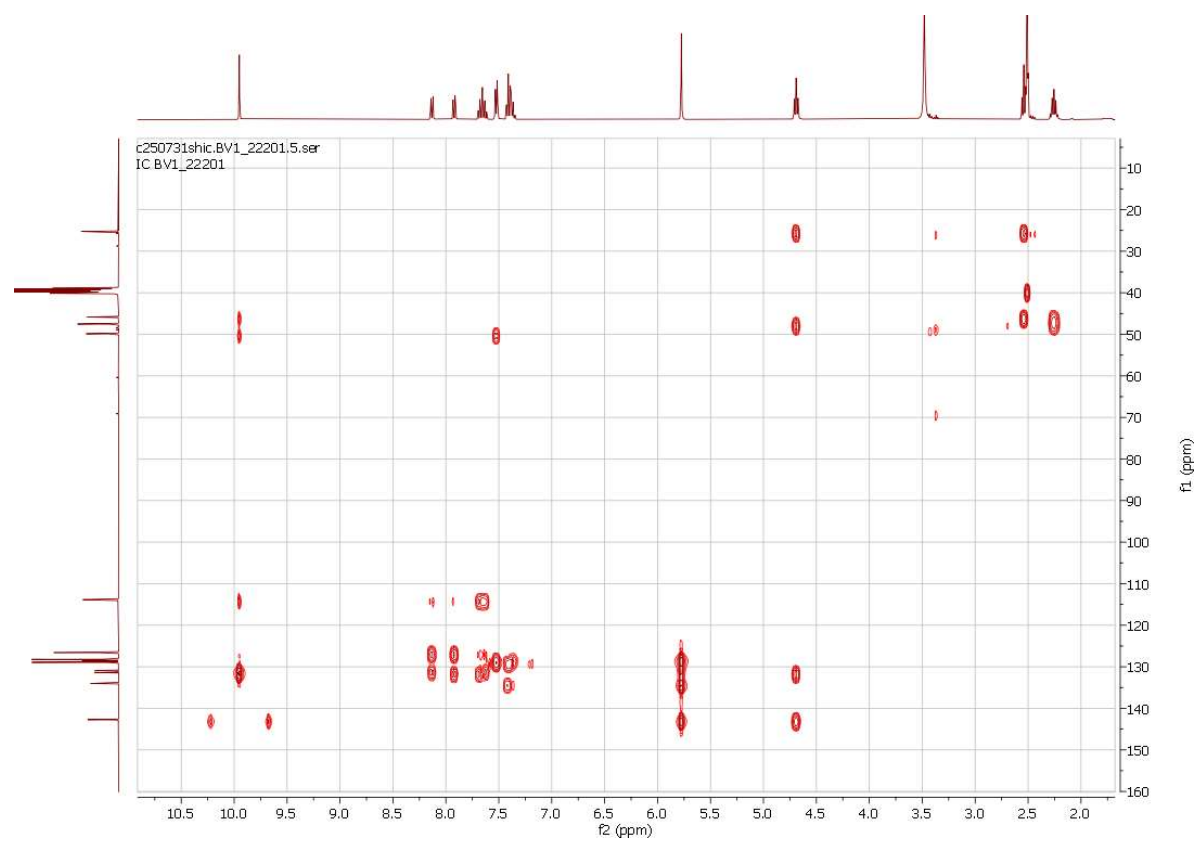
^{13}C NMR – BV1



DEPT-135 BV1

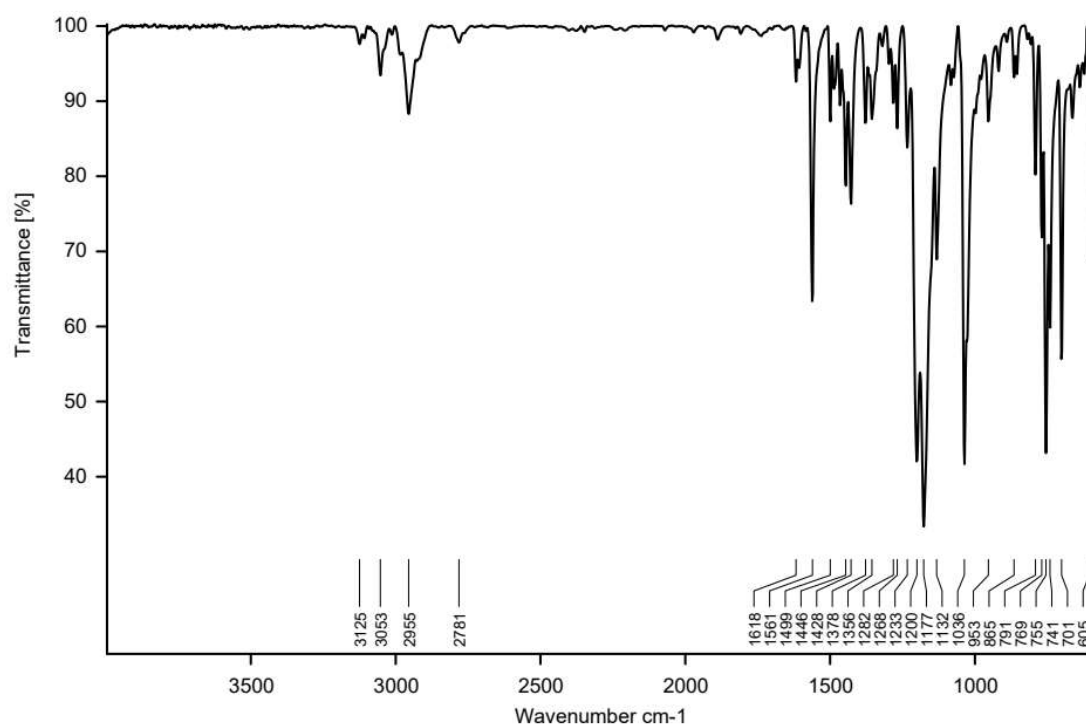


2D-HSQC BV1

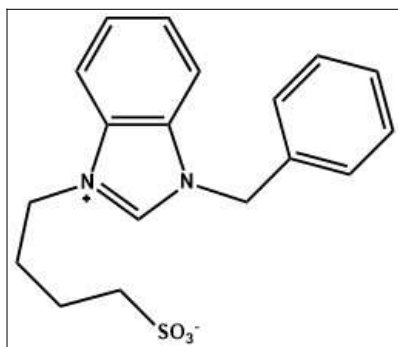


2D-HMBC BV1

BV1
ATR



***N*-benzyl-*N'*-(butyl-4-sulfonate)-benzimidazolium inner salt (BV2)**



See “General synthesis for *N*-benzylated-imidazolium salt compounds in MeCN”.

White powder. Yield = 57%

^1H NMR (400 MHz, DMSO- d_6) δ 9.92 (s, 1H, C2-H), 8.15–8.14 (dd, J = 1.28 Hz, 1H, benzimidazol-H), 7.94–7.93 (dd, J = 1.38 Hz, 1H, benzimidazol-H), 7.69–7.62 (m, 2H, benzimidazol-H), 7.53–7.50 (br m, 2H, Ph-H), 7.42–7.35 (m, 3H, Ph-H), 5.76 (s, 2H, Ph- CH_2 -), 4.56–4.53 (t, J = 7.24 Hz, 2H, N- CH_2 - CH_2 - CH_2 - SO_3^-), 2.06–2.01 (p, J = 7.84 Hz, 2H, N- CH_2 - CH_2 - CH_2 - SO_3^-), 1.67–1.62 (p, J = 7.43 Hz, 2H, N- CH_2 - CH_2 - CH_2 - SO_3^-).

^{13}C NMR (100 MHz, DMSO- d_6) δ 142.50 (C2), 134.03 (*Cipso*), 131.37, 130.86 (C4/5), 129.04, 128.70, 128.24, 126.66 (Ph), 114.06, 113.84 (Benzimidazol), 50.39 (Ph- CH_2 -), 49.90 (N- CH_2 - CH_2 - CH_2 - SO_3^-), 46.67 (N- CH_2 - CH_2 - CH_2 - CH_2 - SO_3^-), 27.63 (N- CH_2 - CH_2 - CH_2 - CH_2 - SO_3^-), 22.08 (N- CH_2 - CH_2 - CH_2 - CH_2 - SO_3^-).

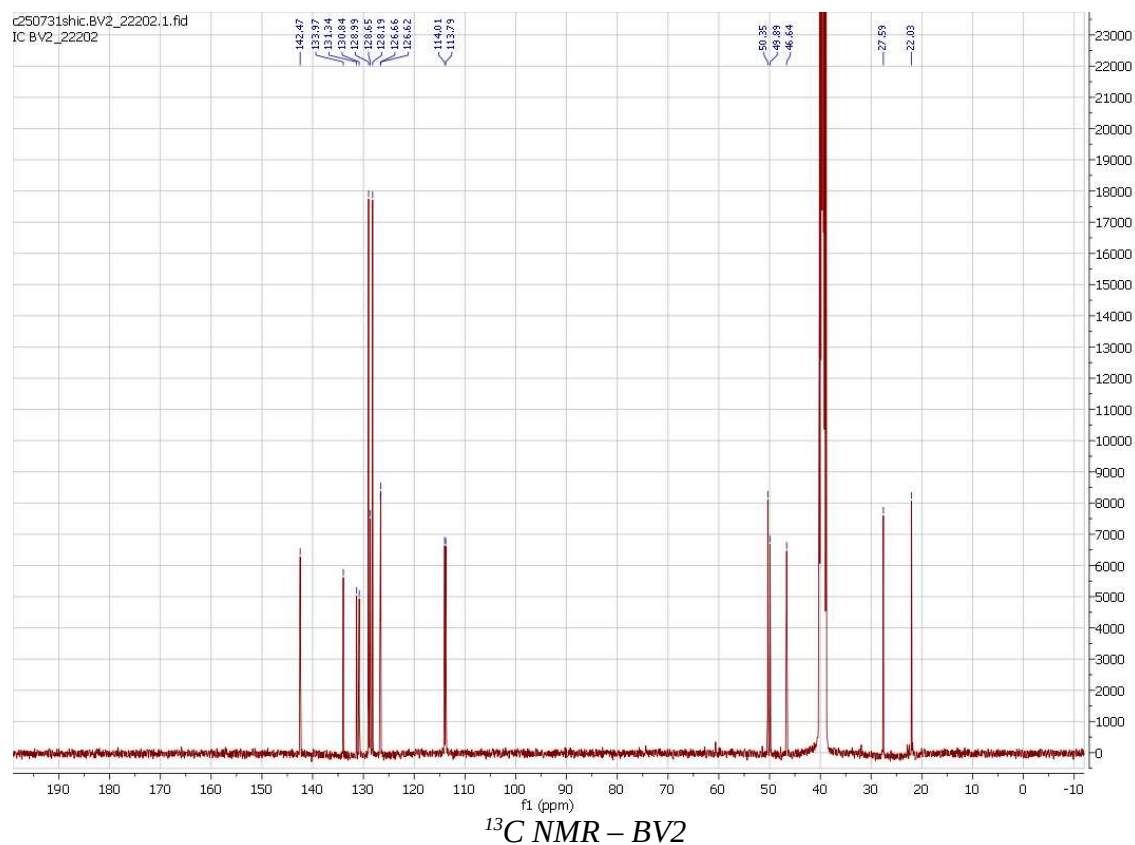
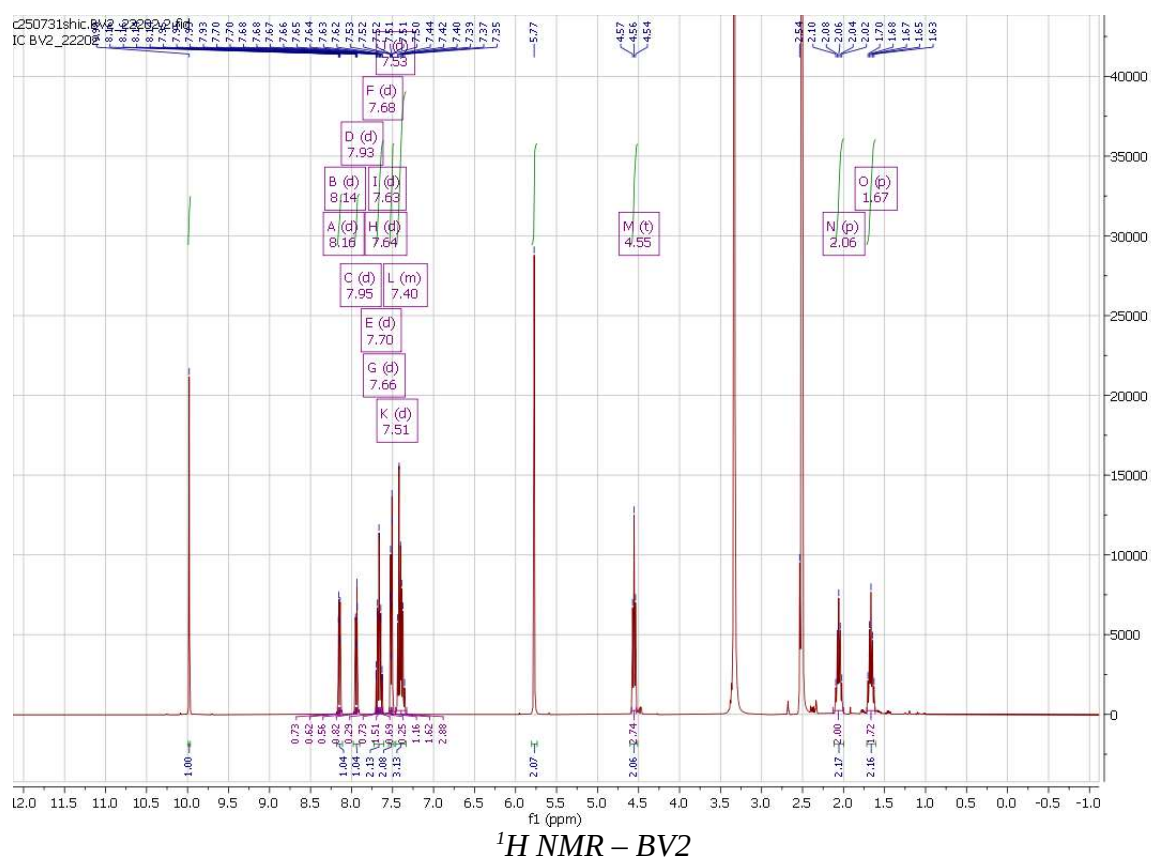
ATR-FTIR: ν 3386, 3144, 3125, 3061, 3042, 2945, 1824, 1724, 1614, 1558, 1483, 1456, 1430, 1372, 1301, 1203, 1176, 1159, 1032, 916, 784, 760, 745, 705, 626 cm^{-1}

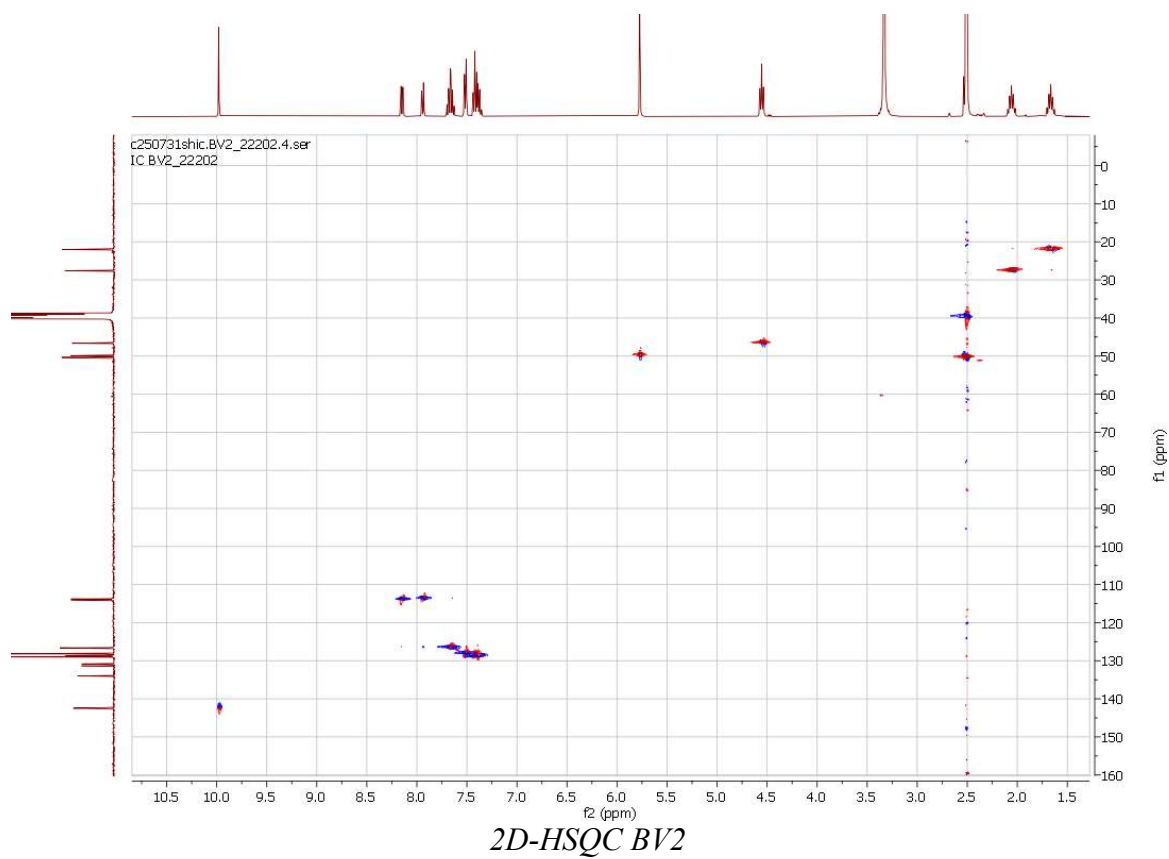
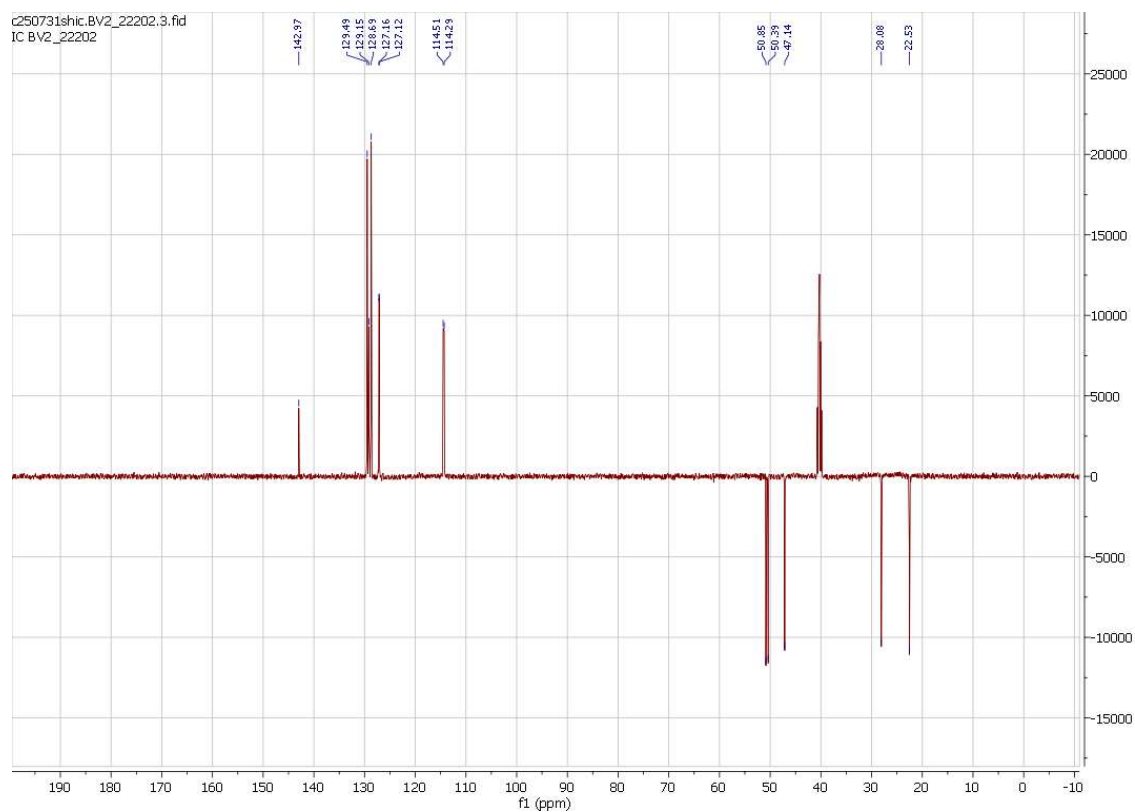
MS (MALDI-TOF, Positive mode)

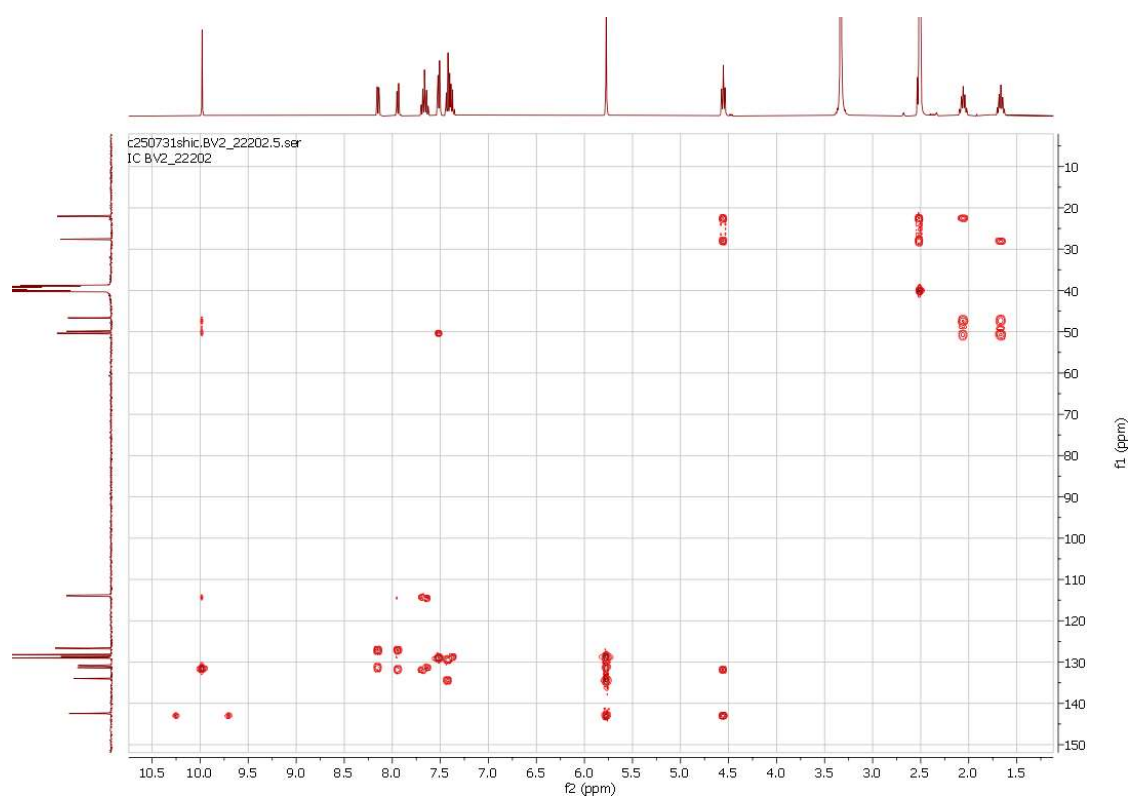
HRMS measured: 345.1264 m/z [$\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$] $^+$ ($\text{M}+\text{H}^+$); estimated: 345.1267 m/z
 m/z : 345.1264 ($\text{M}+\text{H}^+$), 689.2464 ($2\text{M}+\text{H}^+$)

MS (MALDI-TOF, Negative mode)

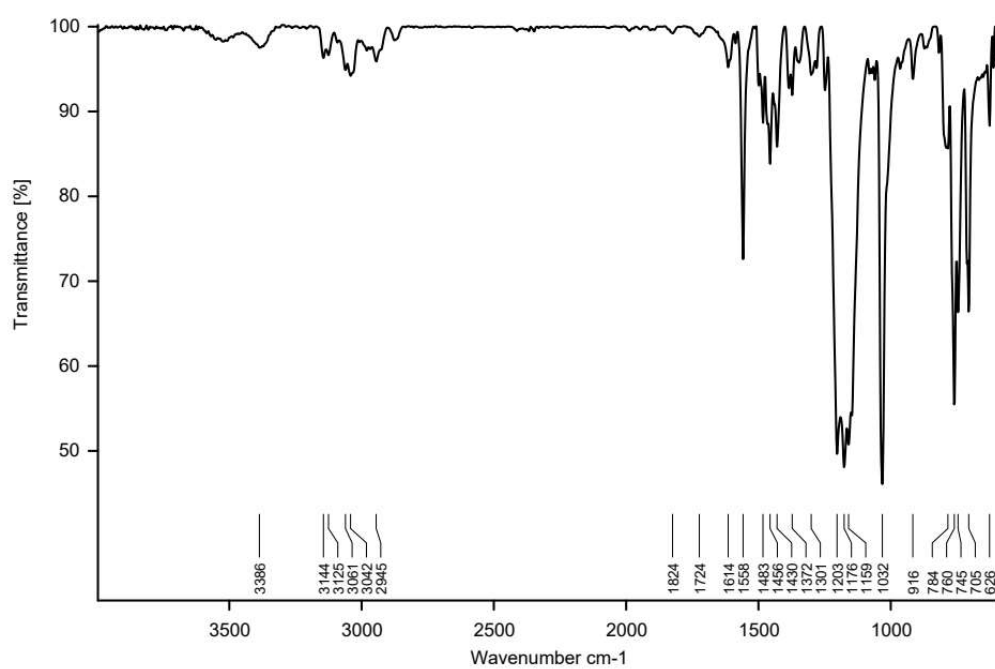
HRMS measured: 343.1152 m/z [$C_{18}H_{19}N_2O_3S$] $^-$ (M-H $^+$); estimated: 343.1122 m/z



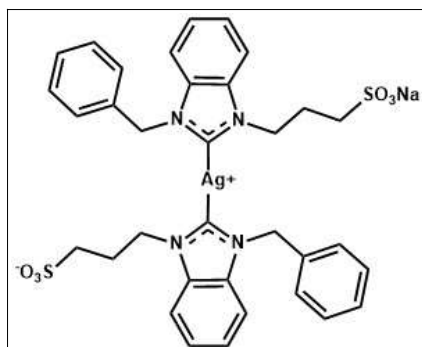




BV2
ATR



Bis-[*N*-benzyl-*N'*-(propyl-3-sulfonate)benz-2-yliden] silver (AgBV1)



See “General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B”

Ivory powder. Yield 59.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.92–7.89 (d, 1H, benzimidazol-H), 7.70–7.67 (d, 1H, benzimidazol-H), 7.47–7.29 (br m, 7H, Ar-H), 5.75 (s, 2H, CH₂-Ph), 4.72–4.67 (t, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.22–2.15 (t, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).

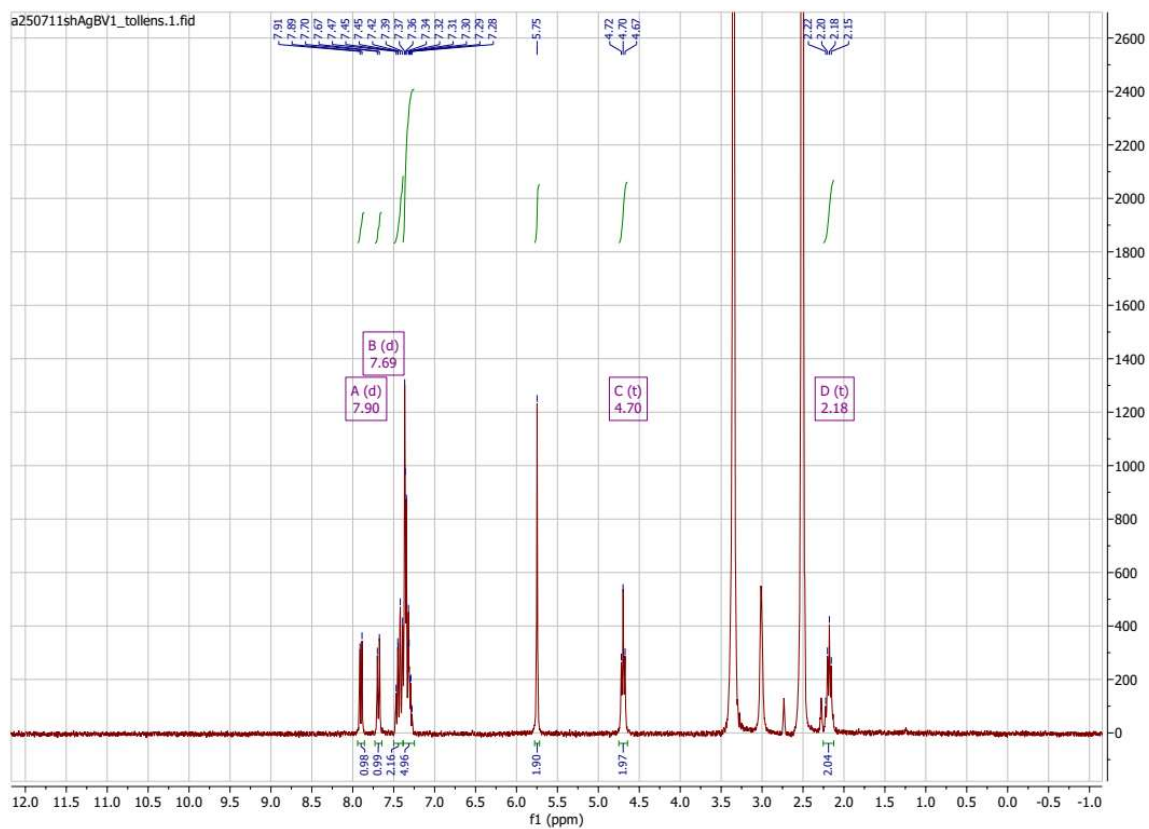
^{13}C NMR (100 MHz, DMSO- d_6) δ 136.56 (Ar), 133.88 (Ar), 133.41 (Ar), 129.67 (Ar), 128.88 (Ar), 128.13 (Ar), 125.51 (Ar), 113.40 (Ar), 61.35 (Ph-CH₂-), 52.27 (N-CH₂-CH₂-CH₂-SO₃[−]), 49.20 (N-CH₂-CH₂-CH₂-SO₃[−]), 27.19 (N-CH₂-CH₂-CH₂-SO₃[−]).

MS (MALDI-TOF, Positive mode)

m/z : 458.9905 [$\text{C}_{17}\text{H}_{17}\text{AgN}_2\text{NaO}_3\text{S}$]⁺, 544.9055 [$\text{C}_{17}\text{H}_{17}\text{Ag}_2\text{N}_2\text{O}_3\text{S}$]⁺, 769.1125 [$\text{C}_{34}\text{H}_{36}\text{AgN}_4\text{O}_6\text{S}_2$]⁺, 795.0530 [$\text{C}_{34}\text{H}_{35}\text{AgN}_4\text{NaO}_6\text{S}_2$]⁺, 875.0097 [$\text{C}_{34}\text{H}_{35}\text{Ag}_2\text{N}_4\text{O}_6\text{S}_2$]⁺, 896.9917 [$\text{C}_{34}\text{H}_{34}\text{Ag}_2\text{N}_4\text{NaO}_6\text{S}_2$]⁺, 982.9068 [$\text{C}_{34}\text{H}_{34}\text{Ag}_3\text{N}_4\text{O}_6\text{S}_2$]⁺

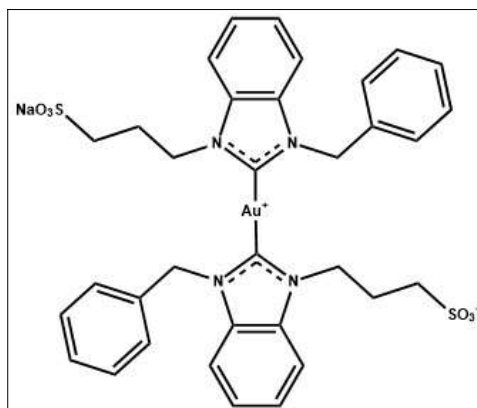
MS (MALDI FT-ICR, H₂O)

m/z : 767.11505 [$\text{C}_{34}\text{H}_{35}\text{AgN}_4\text{O}_6\text{S}_2$]⁺, 683.19921 [$\text{C}_{32}\text{H}_{31}\text{AgN}_4\text{NaO}_3\text{S}$]⁺.



^1H NMR – AgBV1

Bis-[N-benzyl-N'-(propyl-3-sulfonate)benz-2-yliden] gold chloride (AuBV1)

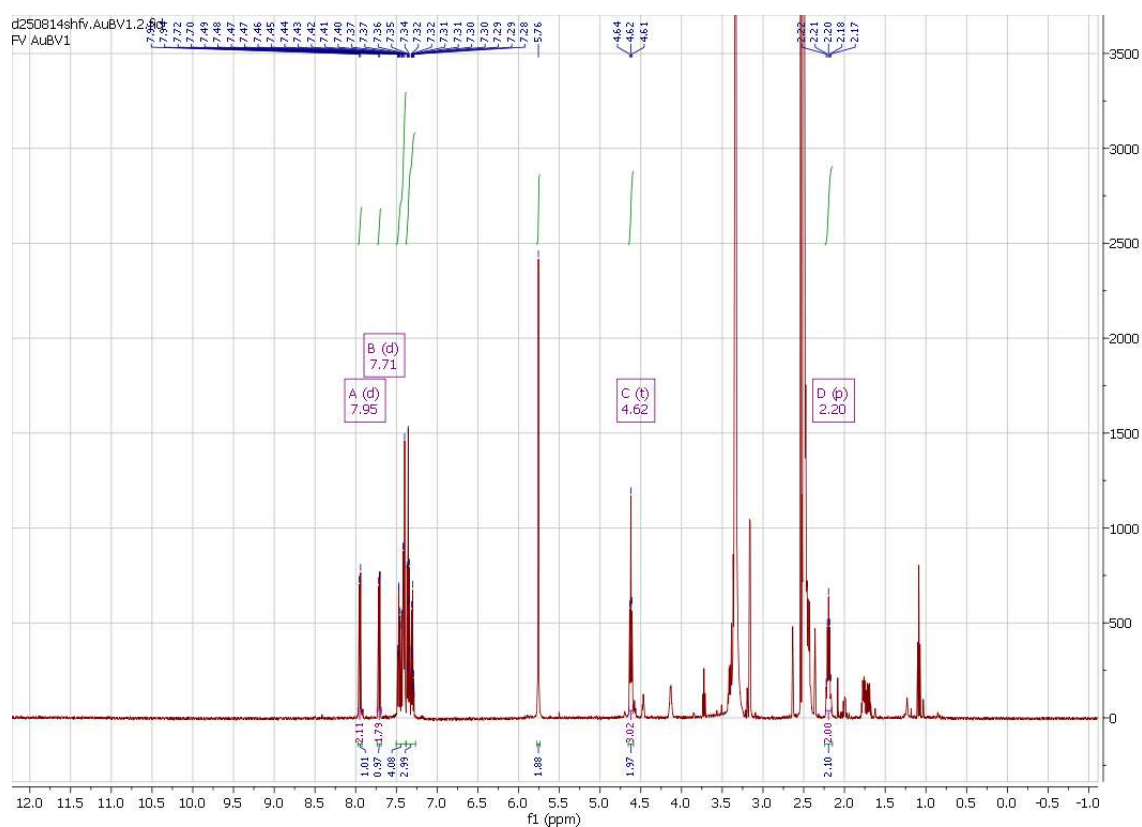


See “General synthesis for NHC-Au(I)-sulfonate complexes”.

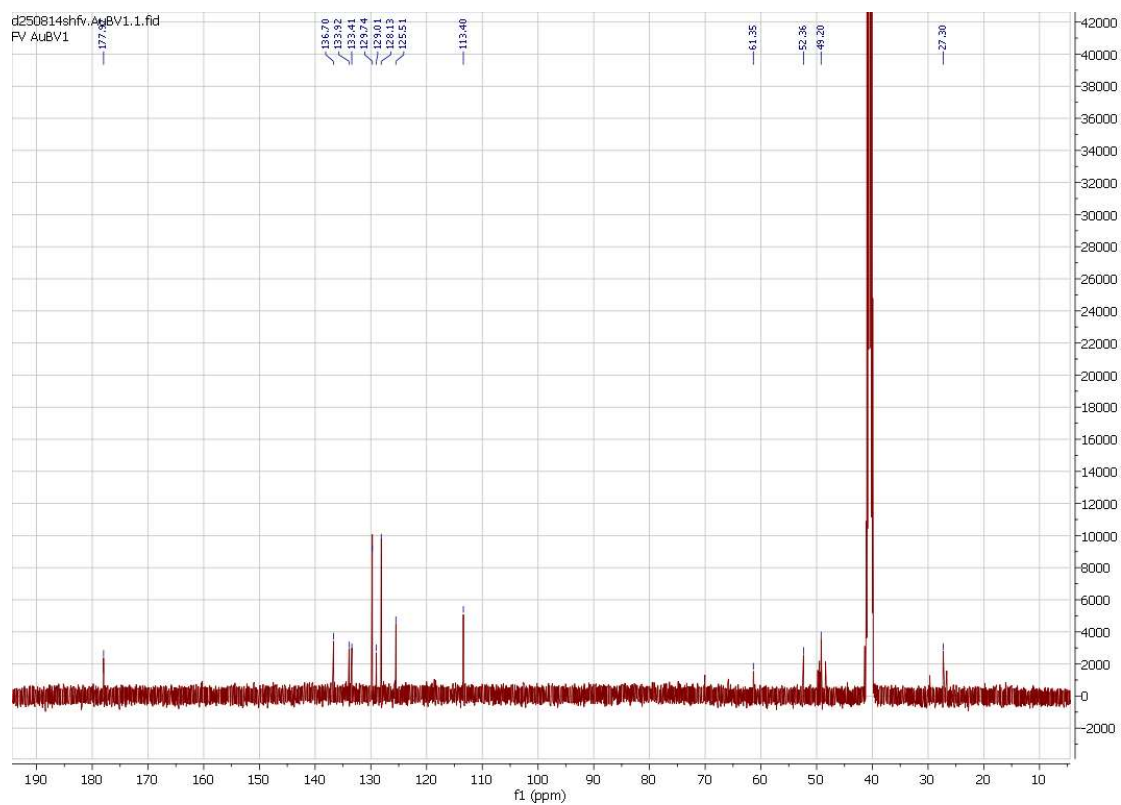
White powder. Yield = 40.2 %

^1H NMR (500 MHz, DMSO- d_6) δ 7.95 (d, J = 8.01 Hz, 1H, benzimidazol-H), 7.71 (d, J = 7.55 Hz, 1H, benzimidazol-H), 7.49–7.28 (br m, 7H, benzimidazol-H + Ar-H), 5.76 (s, 2H, Ph-CH $_2$ -), 4.62 (t, J = 7.15 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.20 (q, J = 7.21 Hz, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

^{13}C NMR (126 MHz, DMSO- d_6) δ 177.97 (C-Au), 136.70 (Ar), 133.92 (Ar), 133.41 (Ar), 129.74 (Ar), 129.01 (Ar), 128.13 (Ar), 125.51 (Ar), 113.40 (Ar), 61.35 (Ph-CH $_2$ -), 52.36 (N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 49.20 (N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 27.30 (N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

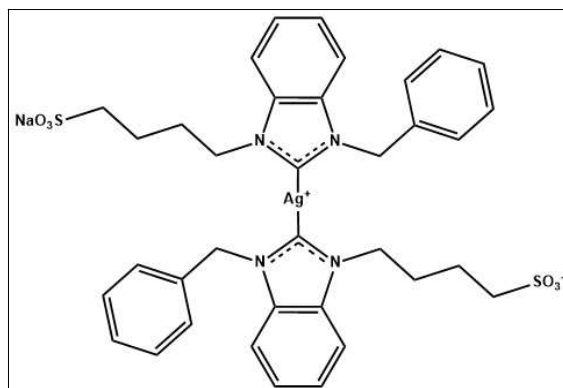


^1H NMR – AuBV1



^{13}C NMR – AuBV1

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)benz-2-yliden] silver chloride (AgBV2)



See “General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B”

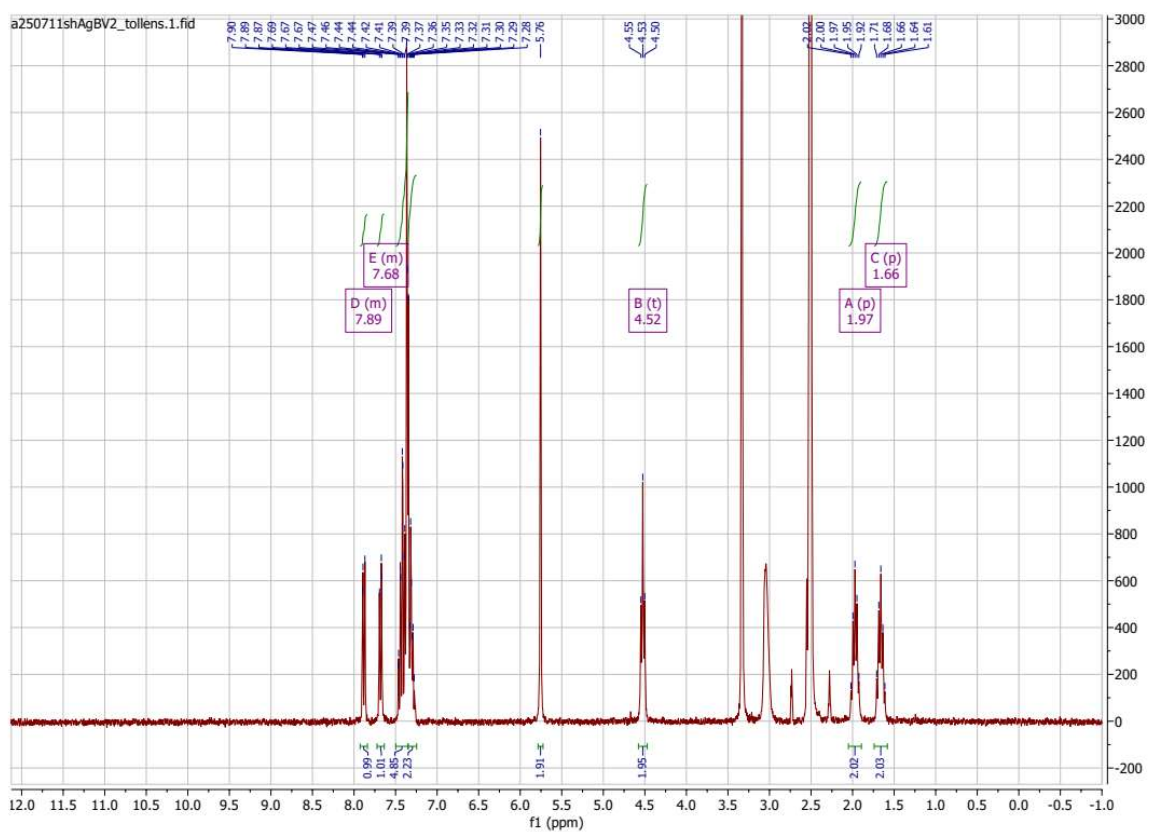
Ivory powder. Yield = 70.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.90–7.87 (dd, 1H, benzimidazol-H), 7.69–7.67 (dd, 1H, benzimidazol-H), 7.47–7.28 (br m, 7H, benzimidazol-H + Ph-H), 5.76 (s, 2H, Ph-CH $_2$ -), 4.55–4.50 (t, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.02–1.92 (q, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 1.71–1.61 (q, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

^{13}C NMR (100 MHz, DMSO- d_6) δ 136.58 (*Cipso*), 133.85 (Ar), 133.42 (Ar), 129.76 (Ar), 128.99 (Ar), 128.12 (Ar), 125.47 (Ar), 113.44 (C4/5), 113.38 (C4/5), 52.35 (CH $_2$ -Ph), 51.68 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 49.18 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 29.73 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 23.52 (N-CH $_2$ -CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

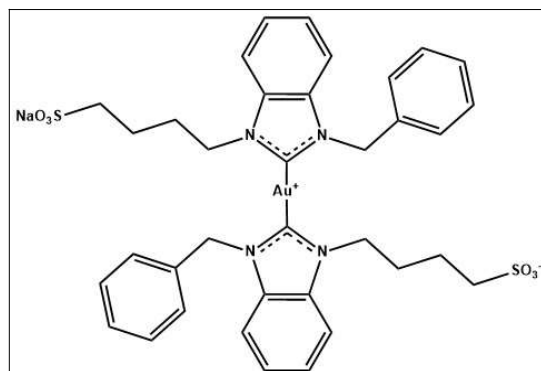
MS (MALDI FT-ICR, H $_2$ O)

m/z : 795.14548 Da [$\text{C}_{36}\text{H}_{39}\text{AgN}_4\text{O}_6\text{S}_2$] $^+$, 683.19921 [$\text{C}_{34}\text{H}_{36}\text{AgN}_4\text{NaO}_3\text{S}$] $^+$



^1H NMR – AgBV2

Bis-[*N*-benzyl-*N'*-(butyl-4-sulfonate)benz-2-yliden] gold chloride (AuBV2)

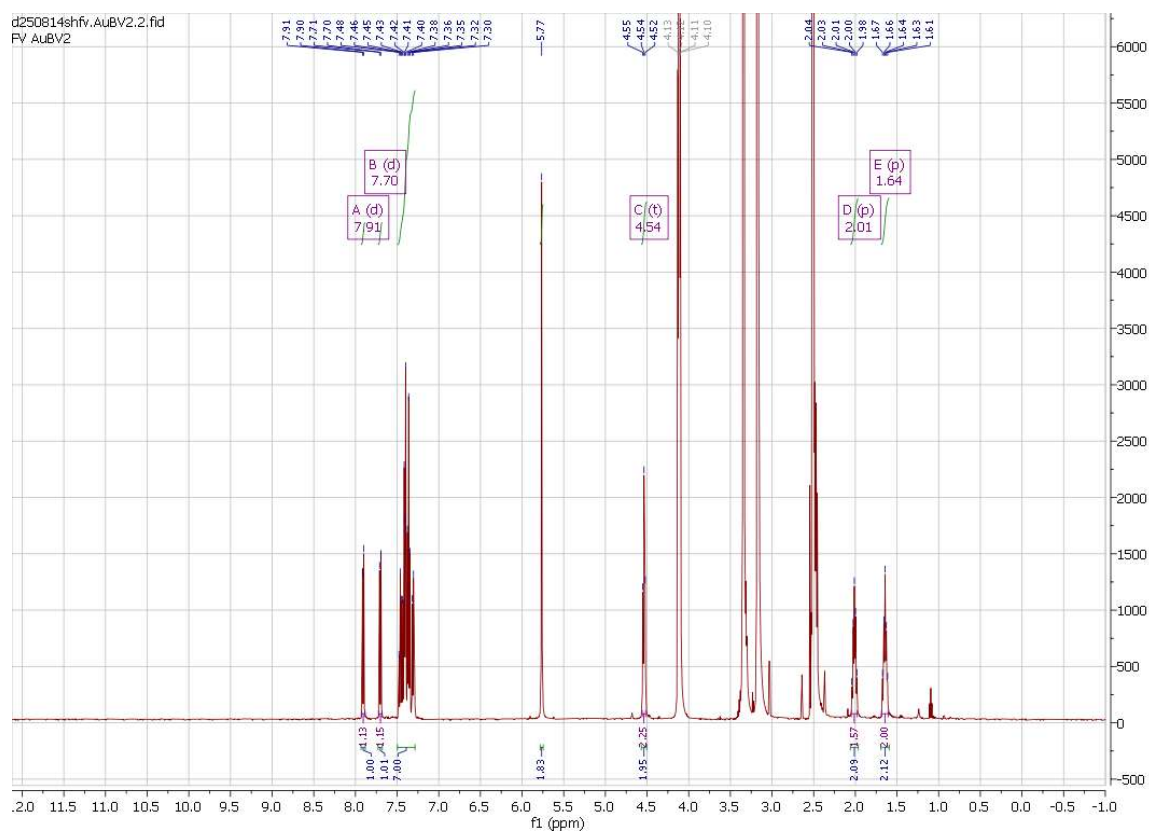


See “*General synthesis for NHC-Au(I)-sulfonate complexes*”.

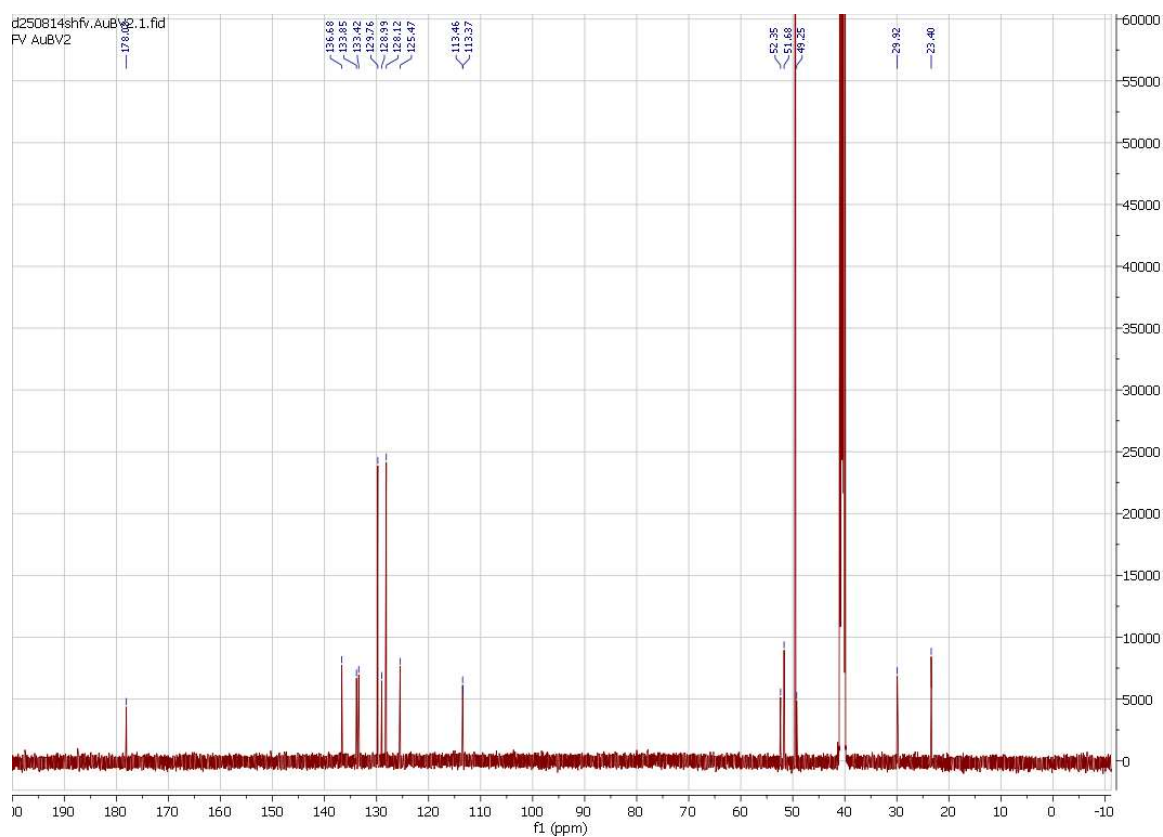
Violet powder. Yield = 34.4 %

^1H NMR (500 MHz, DMSO- d_6) δ 7.91 (d, J = 7.55 Hz, 1H, benzimidazol-H), 7.70 (d, J = 7.44 Hz, 1H, benzimidazol-H), 7.48–7.30 (br m, 7H, benzimidazol-H + Ar-H), 5.77 (s, 2H, $\text{CH}_2\text{-Ph}$), 4.54 (t, J = 7.27 Hz, 2H, N-**CH**₂-CH₂-CH₂-CH₂-SO₃[−]), 2.01 (q, J = 7.78 Hz, 2H, N-CH₂-**CH**₂-CH₂-CH₂-SO₃[−]), 1.64 (q, J = 7.69 Hz, 2H, N-CH₂-CH₂-**CH**₂-CH₂-SO₃[−]).

^{13}C NMR (126 MHz, DMSO- d_6) δ 178.08 (C-Au), 136.68 (Ar), 133.85 (Ar), 133.42 (Ar), 129.76 (Ar), 128.99 (Ar), 128.12 (Ar), 125.47 (Ar), 113.46 (C4/5), 113.37 (C4/5), 52.35 (Ph-**CH**₂-), 51.68 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 49.25 (N-CH₂-CH₂-CH₂-**CH**₂-SO₃[−]), 29.92 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 23.40 (N-CH₂-CH₂-**CH**₂-CH₂-SO₃[−]).

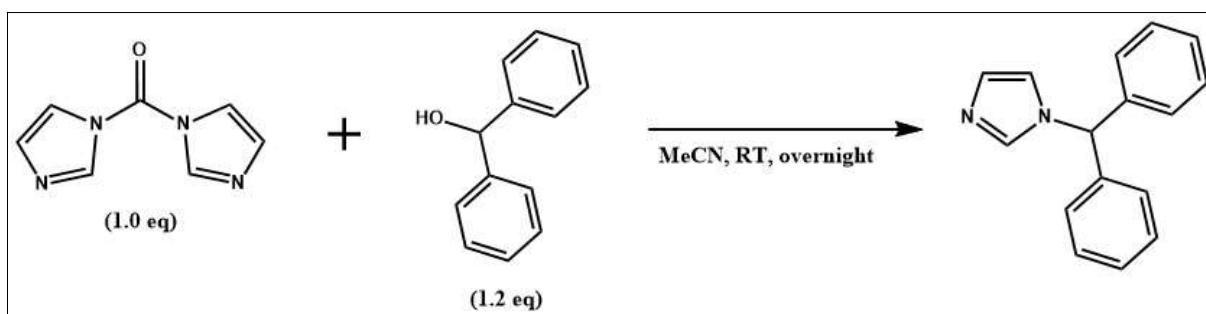


^1H NMR – AuBV2



^{13}C NMR – AuBV2

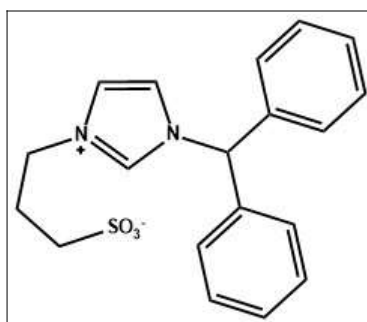
1-Benzhydrylimidazole (FV00)



Synthesis carried out following the reported method^[4]. White powder. Yield = 68%.

The NMR characterization match the data reported in literature.

N-benzhydryl-*N'*-(propyl-3-sulfonate)-imidazolium salt (FV11)



See “General synthesis for *N*-benzhydrylated-imidazolium salt compounds in MeCN”

Ivory powder. Yield = 53.0%

¹H NMR (400 MHz, DMSO-d₆) δ 9.16 (s, 1H, C2-H), 7.92 (t, 1H, C4/5-H), 7.73 (t, 1H, C4/5-H), 7.47–7.45 (br m, 6H, Ph-H), 7.31–7.24 (br m, 6H, Ph-H), 7.15 (s, 1H, Ph₂-CH-), 4.33–4.29 (t, J = 7.08 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.43–2.39 (t, J = 7.27 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.14–2.07 (q, J = 6.90 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

¹³C NMR (100 MHz, DMSO-d₆) δ 137.21 (C²-H), 136.63 (C_{ipso}-CH), 129.17 (Ph.), 128.93 (Ph.), 128.13 (Ph.), 123.26 (C^{4/5}), 122.36 (C^{4/5}), 65.81 (Ph₂-CH-N), 48.23 (N-CH₂-CH₂-CH₂-SO₃⁻), 47.47 (N-CH₂-CH₂-CH₂-SO₃⁻), 26.21 (N-CH₂-CH₂-CH₂-SO₃⁻).

ATR-FTIR: ν 3455, 3090, 2944, 1708, 1632, 1568, 1551, 1496, 1453, 1357, 1270, 1215, 1176, 1153, 1032, 851, 774, 753, 732, 694, 658 cm^{-1}

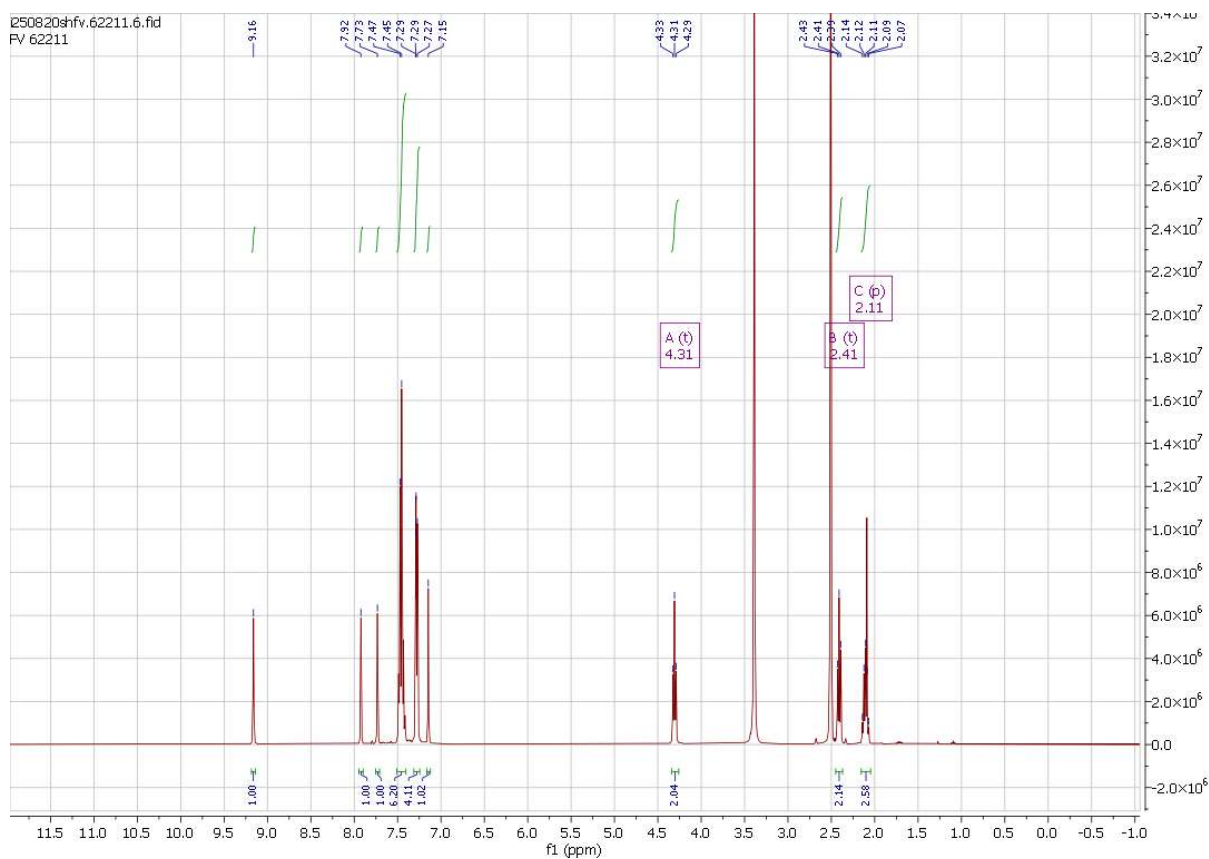
MS (MALDI-TOF, Positive mode)

HRMS measured: 357.1275 m/z [$\text{C}_{19}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$] $^+$ ($\text{M}+\text{H}^+$); estimated: 357.1278 m/z

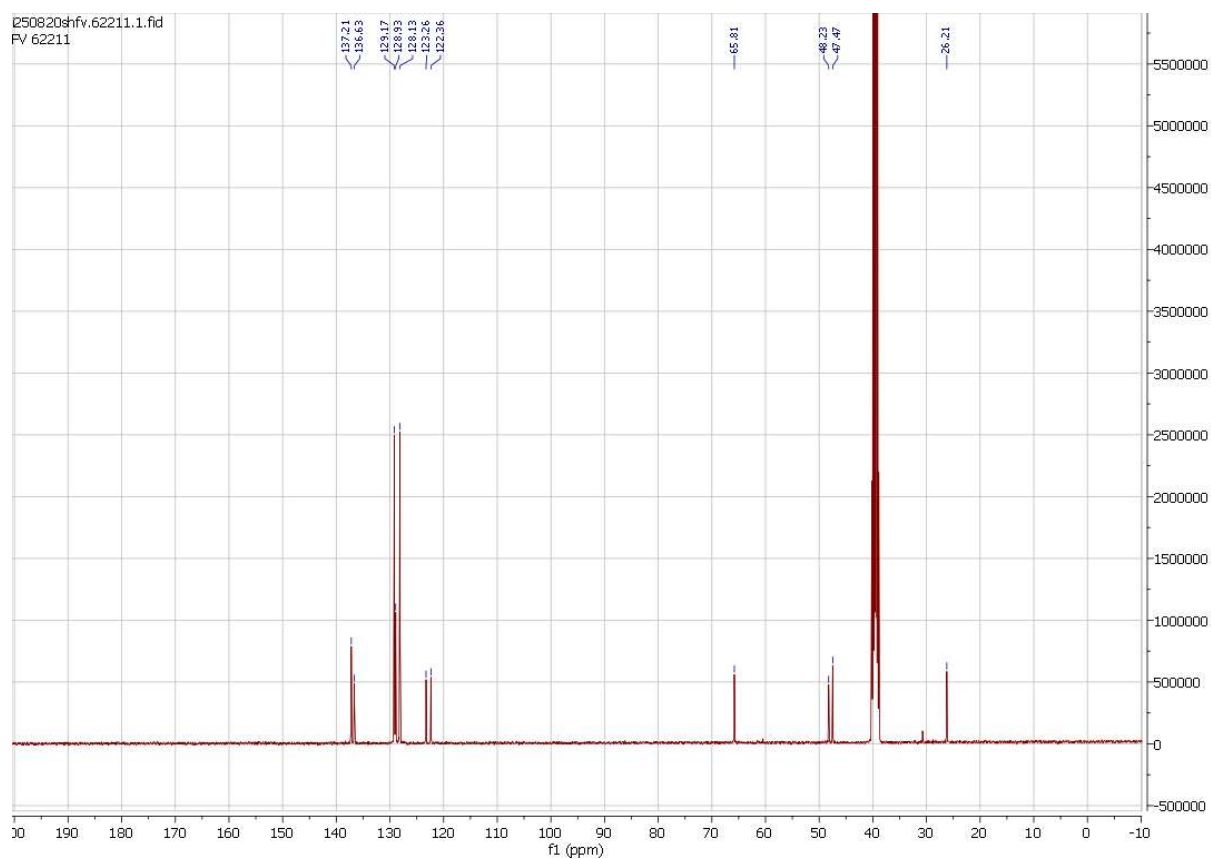
m/z: 357.1275 ($\text{M}+\text{H}^+$), 713.2472 ($2\text{M}+\text{H}^+$), 1069.3665 ($3\text{M}+\text{H}^+$), 1425.4861 ($4\text{M}+\text{H}^+$), 1782.6091 ($5\text{M}+2\text{H}^+$), 2138.7293 ($6\text{M}+2\text{H}^+$), 2494.8509 ($7\text{M}+2\text{H}^+$), 2851.9776 ($8\text{M}+3\text{H}^+$)

MS (MALDI-TOF, Negative mode)

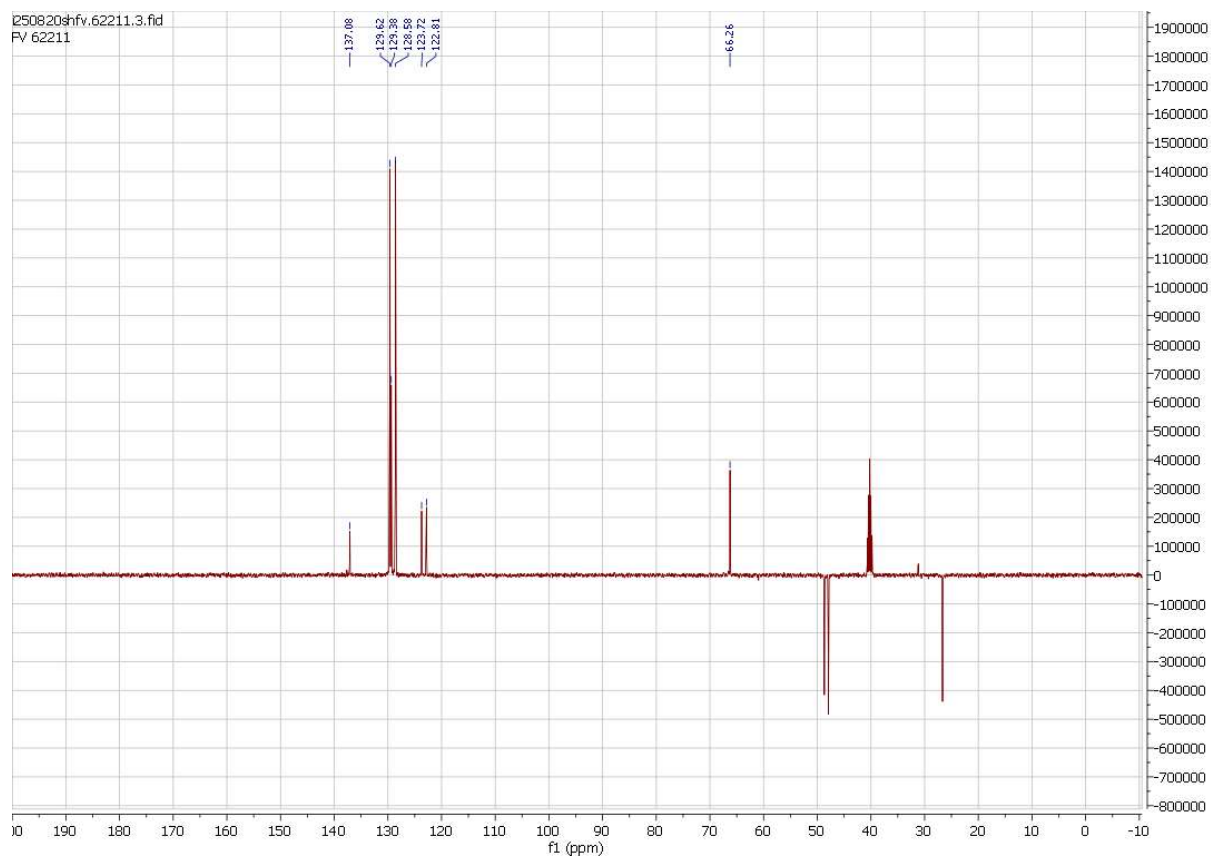
HRMS measured: 355.1120 m/z [$\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$] $^-$ ($\text{M}-\text{H}^+$); estimated: 365.1119 m/z



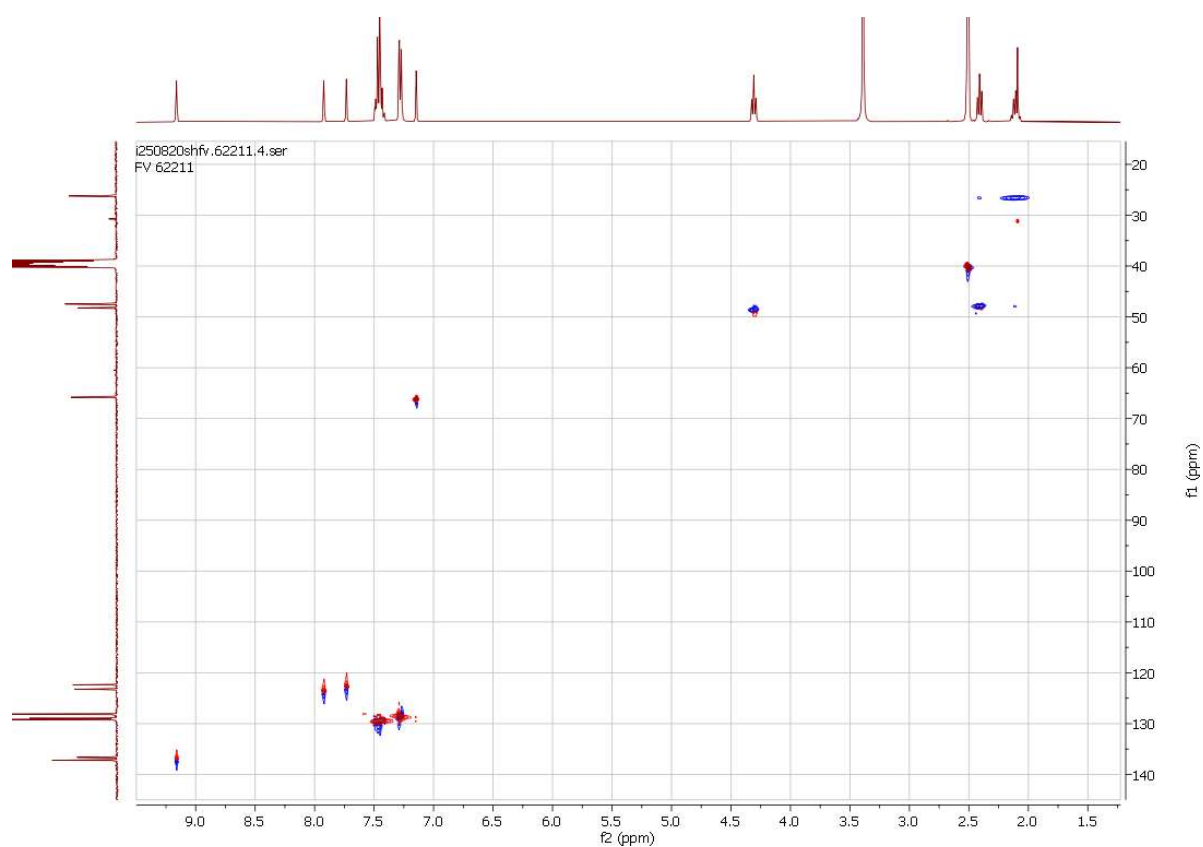
^1H NMR – FV11



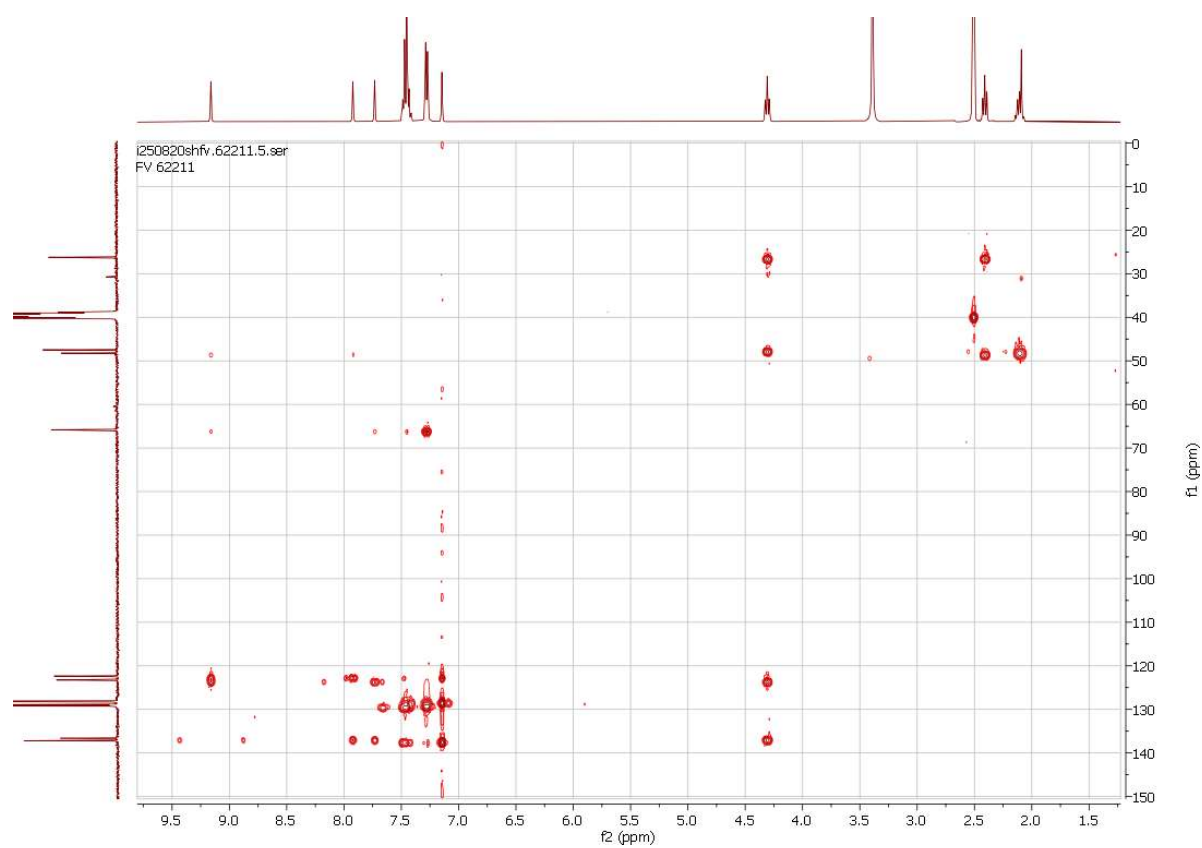
^{13}C NMR – FV11



DEPT-135 FV11

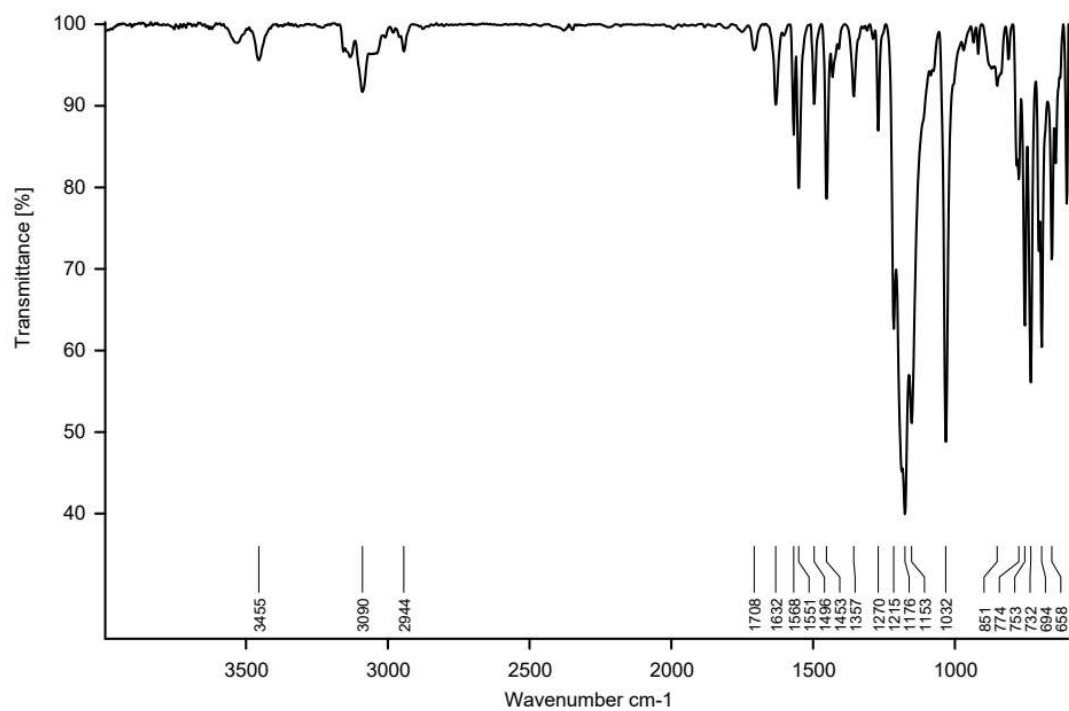


2D-HSQC FV11

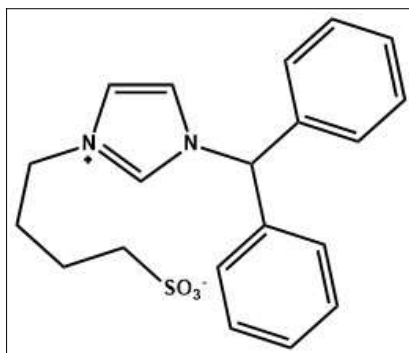


2D-HMBC FV11

FV11
ATR



***N*-benzhydryl-*N'*-(butyl-4-sulfonate)-imidazolium salt (FV22)**



See “General synthesis for *N*-benzhydrylated-imidazolium salt compounds in MeCN”

White powder. Yield = 40.0%

^1H NMR (400 MHz, DMSO- d_6) δ 9.17 (s, 1H, C2-H), 7.92–7.91 (t, 1H, C4/5-H), 7.76–7.74 (t, 1H, C4/5-H), 7.51–7.44 (br m, 6H, Ph-H), 7.29–7.26 (br m, 6H, Ph-H), 7.14 (s, 1H, Ph₂-CH-), 4.23–4.18 (t, J = 7.15 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.47–2.42 (t, J = 7.34 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.95–1.85 (q, J = 7.52 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.59–1.49 (q, J = 7.52 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (100 MHz, DMSO- d_6) δ 137.08 (C2), 136.39 (*Cipso*), 129.14 (Ar), 128.85 (Ar), 128.04 (Ar), 123.07 (C4/5), 122.45 (C4/5), 65.83 (Ph₂-CH-), 50.35 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 48.83 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 28.49 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 21.73 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

ATR-FTIR: ν 3156, 3127, 3099, 3031, 2956, 2869, 1553, 1494, 1459, 1351, 1196, 1151, 1083, 1039, 912, 752, 707, 660, 646 cm^{−1}

MS (MALDI-TOF, Positive mode)

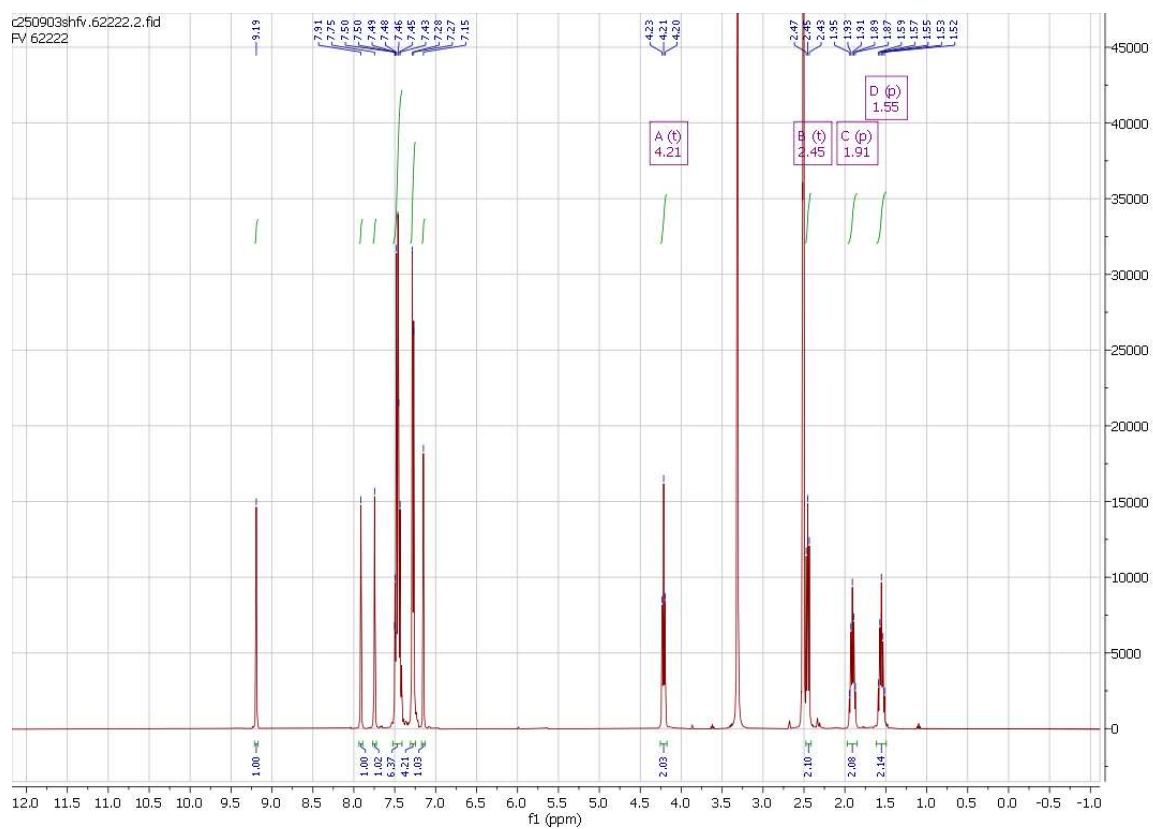
HRMS measured: 371.1427 m/z [$\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$]⁺ (M+H⁺); estimated: 571.1424 m/z

m/z: 371.1427 (M+H⁺), 393.1246 (M+Na⁺), 741.2781 (2M+H⁺), 763.2598 (2M+Na⁺), 1111.4132 (3M+H⁺), 1133.3953 (3M+Na⁺), 1481.5484 (4M+H⁺), 1503.5302 (4M+Na⁺), 1852.6867 (5M+2H⁺), 2222.8237 (6M+2H⁺)

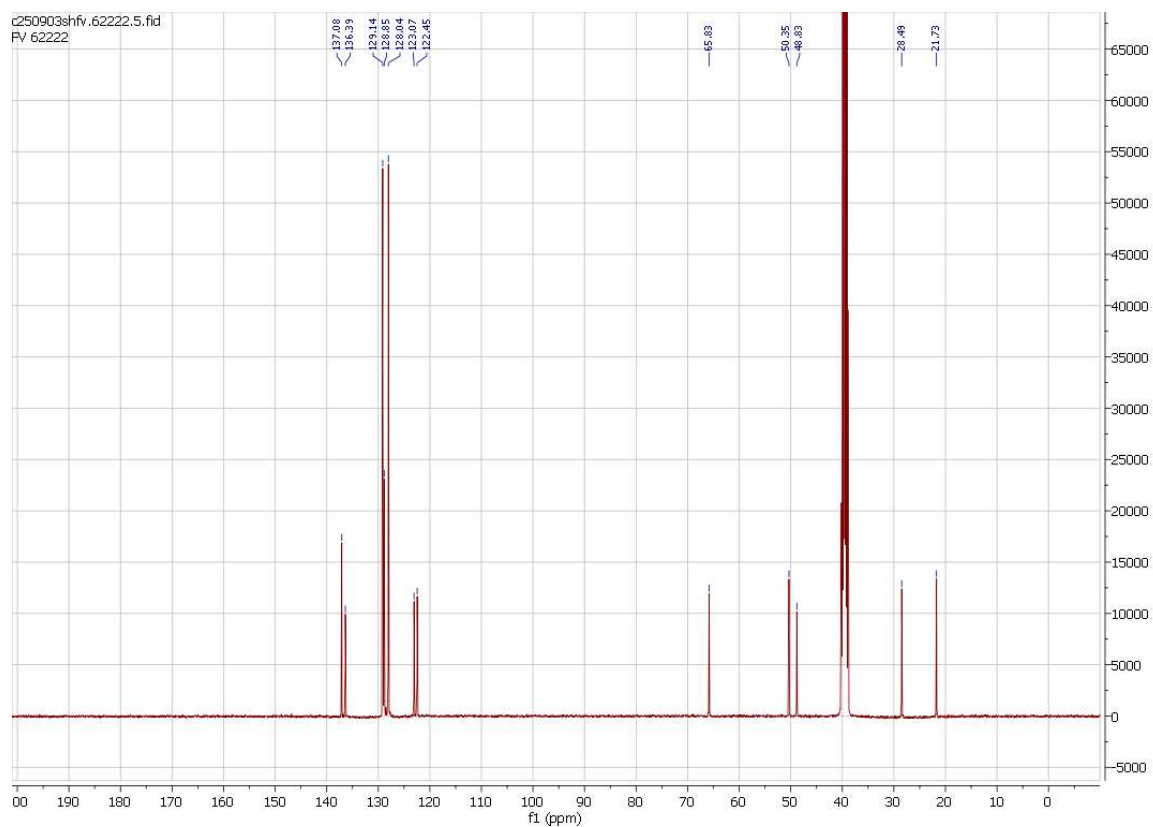
MS (MALDI-TOF, Negative mode)

HRMS measured: 369.1288 m/z [$\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$][−] (M-H⁺); estimated: 369.1278 m/z

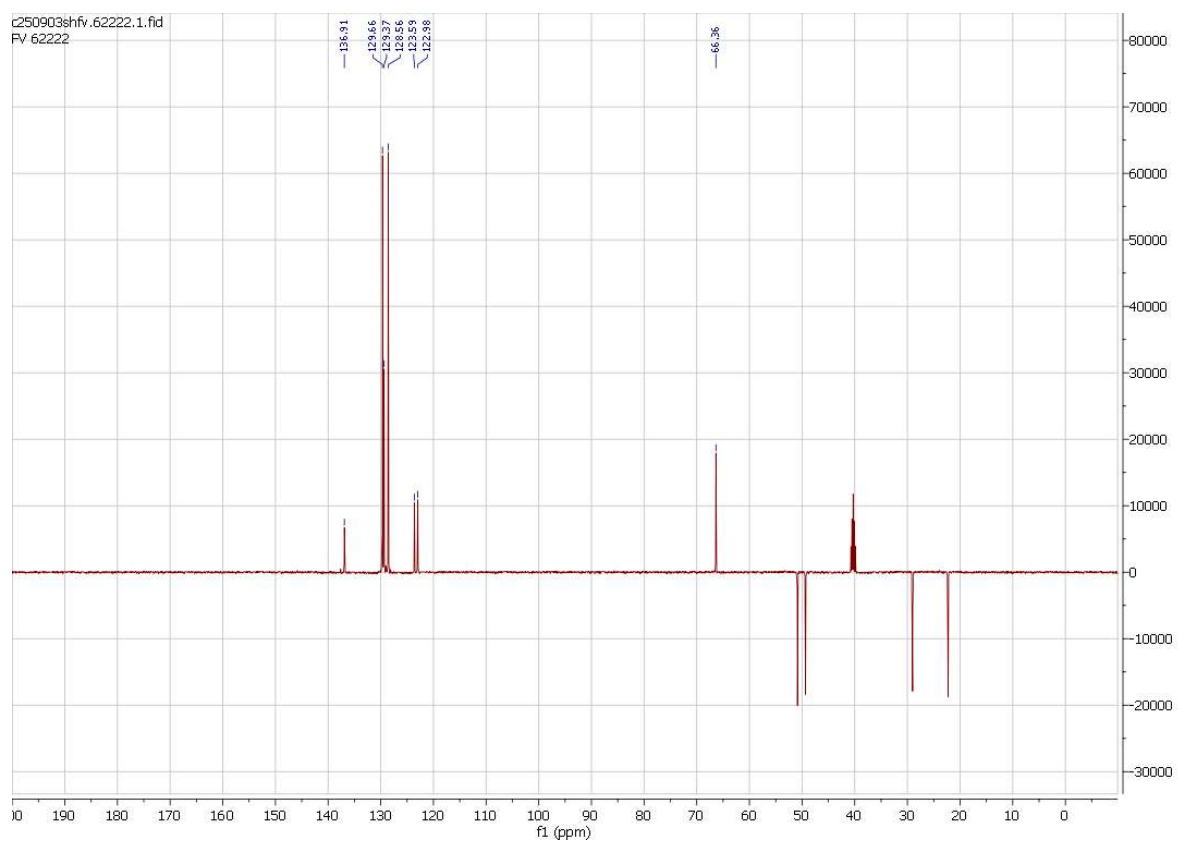
m/z: 369.1278 (M-H⁺), 739.2643 (2M-H⁺)



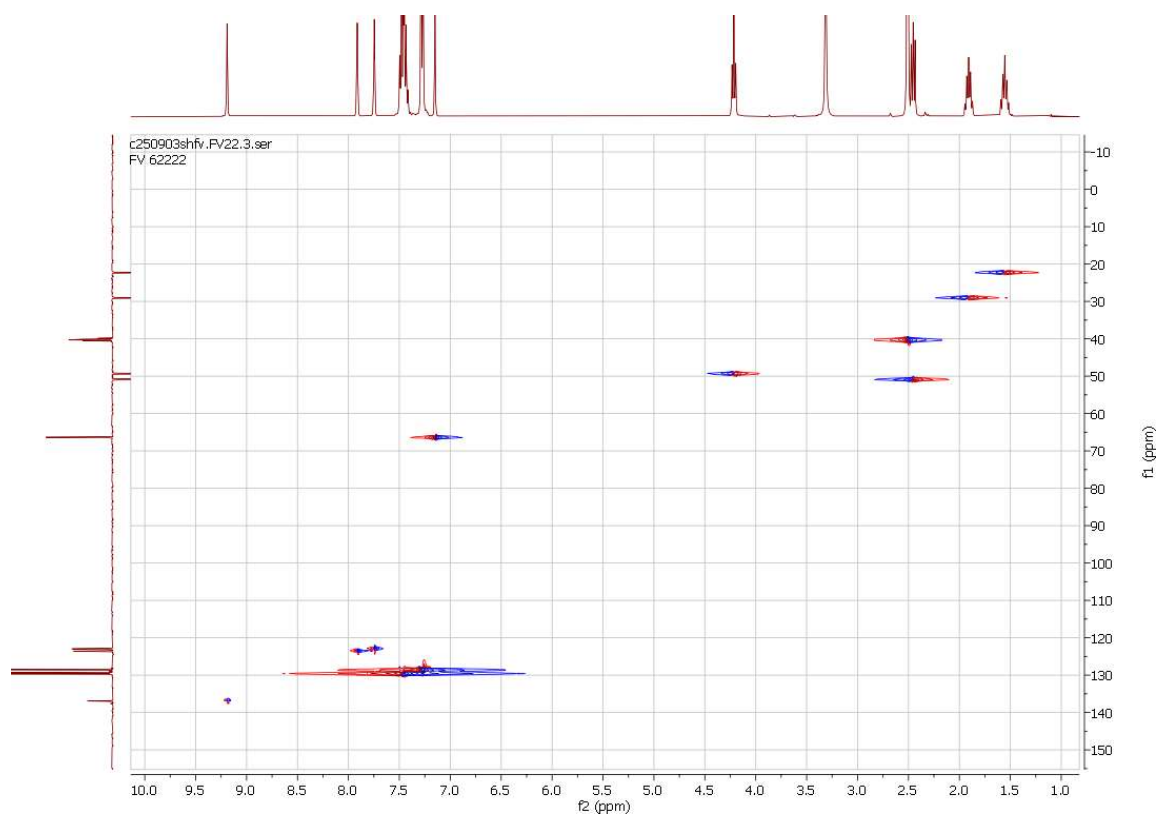
¹H NMR – FV22



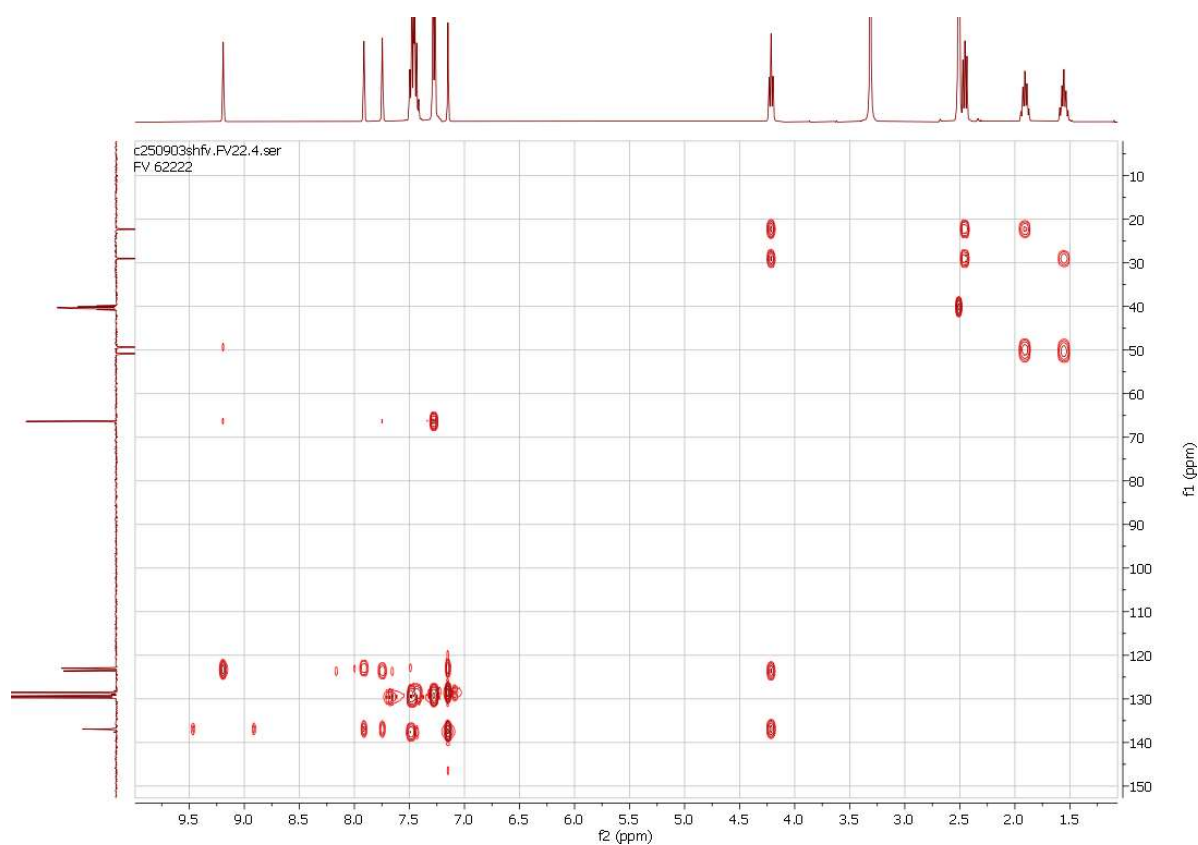
¹³C NMR – FV22



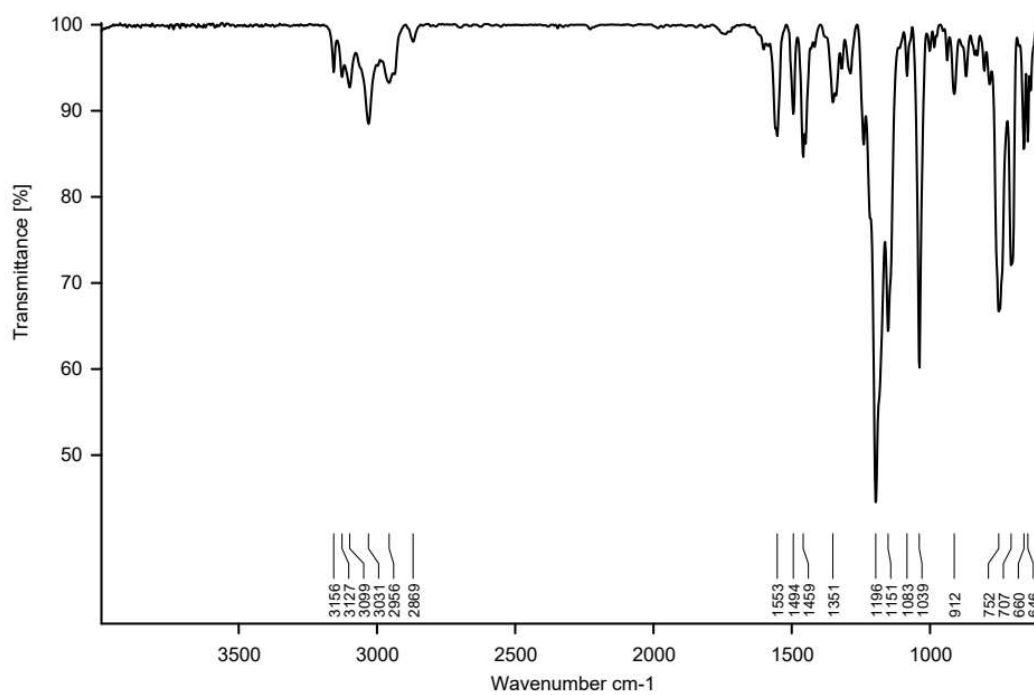
DEPT-135 FV22



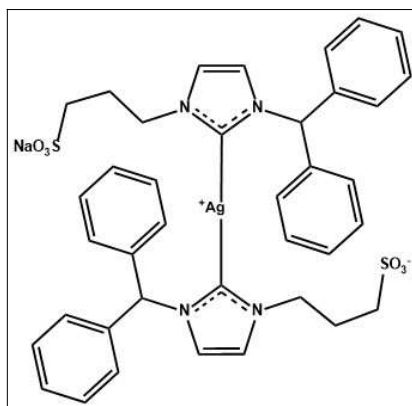
2D-HSQC FV22



**FV22
ATR**



Bis-[N-benzhydryl-N'-(propyl-3-sulfonate)-2-yliden] silver chloride (AgFV11)



See “General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B”

White powder. Yield = 82.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.59 (d, 1H, C4/5-H), 7.44–7.36 (m, 7H, Ph-H + C4/5-H), 7.19–7.17 (d, 4H, Ph-H), 7.09 (s, 1H, Ph₂-CH), 4.26–4.22 (t, J = 6.95 Hz, 2H, N-**CH₂**-CH₂-CH₂-SO₃[−]), 2.41–2.38 (t, J = 7.22 Hz, 2H, N-CH₂-CH₂-**CH₂**-SO₃[−]), 2.09–2.02 (q, J = 6.99 Hz, 2H, N-CH₂-**CH₂**-CH₂-SO₃[−]).

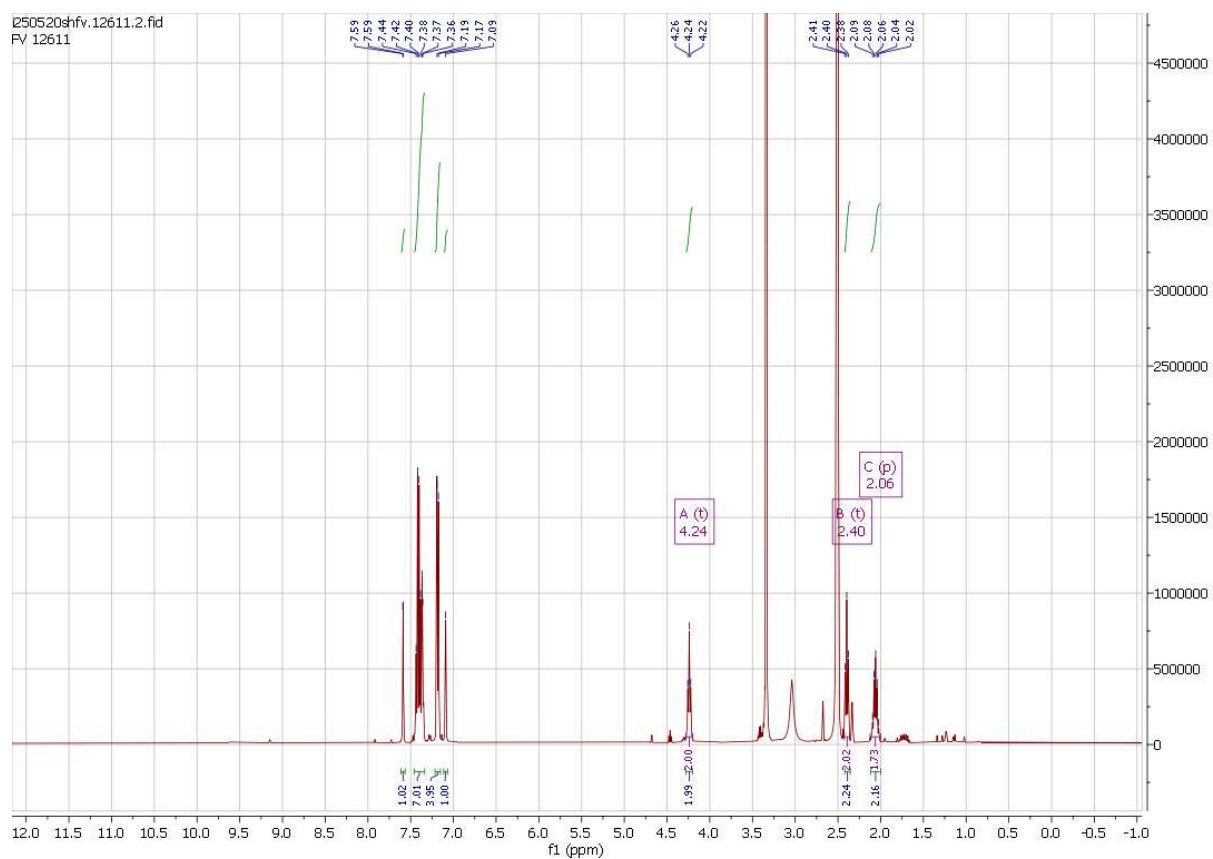
^{13}C NMR (100 MHz, DMSO- d_6) δ 140.21 (*Cipso*), 129.82 (Ar), 129.17 (Ar), 129.05 (Ar), 123.43 (C4\5), 122.36 (C4\5), 68.36 (Ph₂-CH-), 51.19 (N-**CH₂**-CH₂-CH₂-SO₃[−]), 48.62 (N-CH₂-CH₂-**CH₂**-SO₃[−]), 28.60 (N-CH₂-**CH₂**-CH₂-SO₃[−]).

MS (MALDI-TOF, Positive mode)

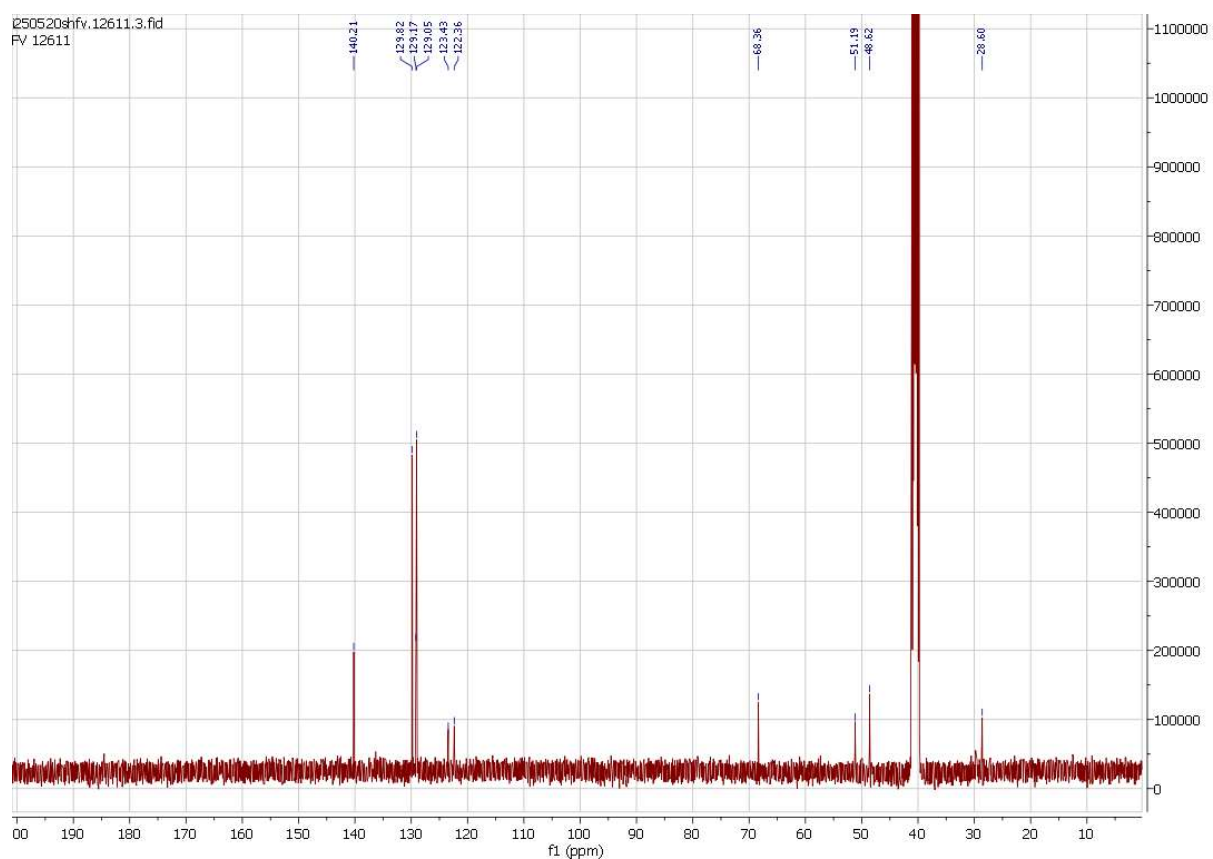
m/z : 486.880 [$\text{C}_{19}\text{H}_{19}\text{AgN}_2\text{NaO}_3\text{S}$]⁺, 681.0859, 727.0584 [$\text{C}_{37}\text{H}_{38}\text{AgN}_4\text{O}_3\text{S}$]⁺, 749.0402 [$\text{C}_{37}\text{H}_{37}\text{AgN}_4\text{NaO}_3\text{S}$]⁺, 976.1988, 1173.0056, 1401.0105

MS (MALDI-TOF, Negative mode)

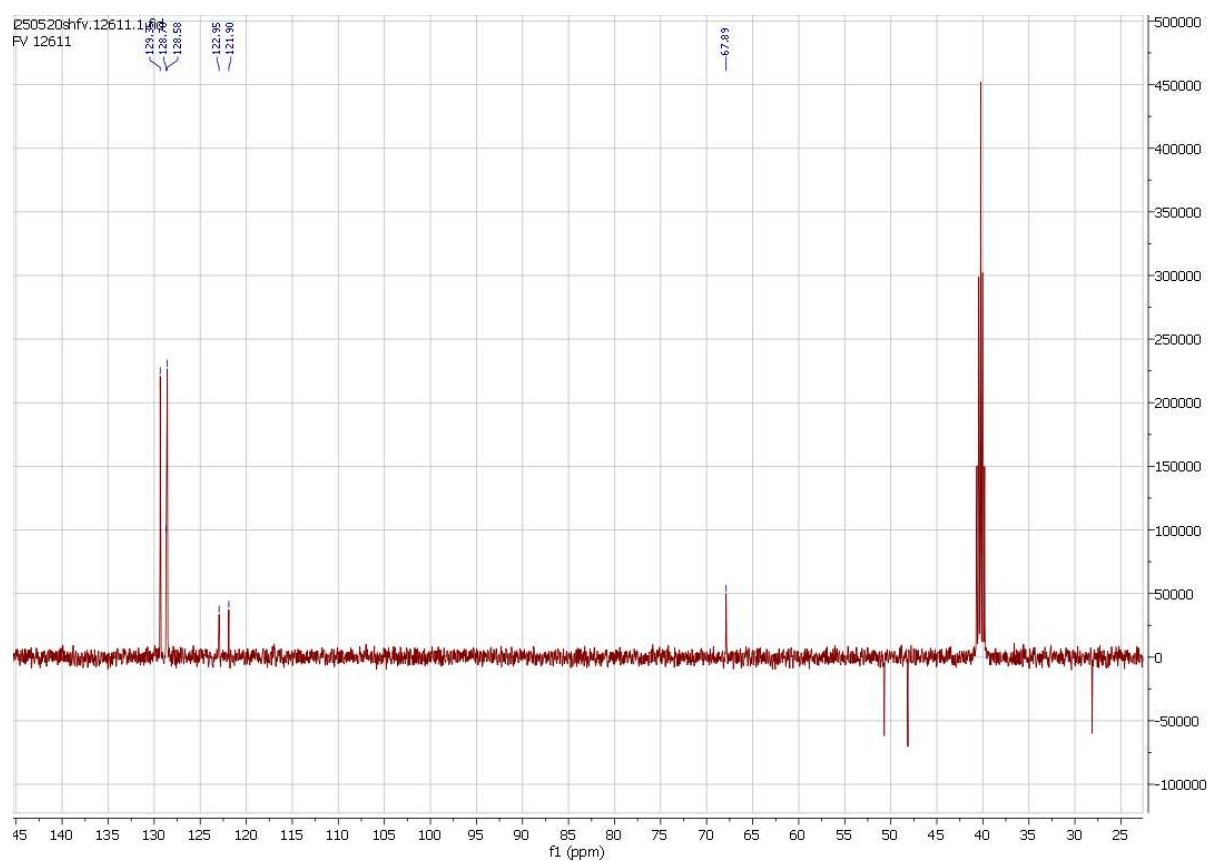
m/z : 523.2648, 667.3350, 683.3290, 705.3246, 720.0593, 743.3689, 750.4470, 765.4472, 771.2711, 783.5642, 794.3284, 799.3436, 811.4695, 829.3894, 850.3556, 861.3191



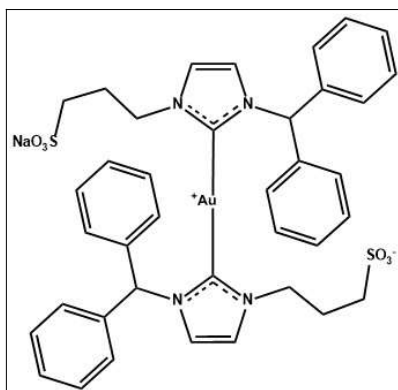
¹H NMR – AgFV11



¹³C NMR – AgFV11



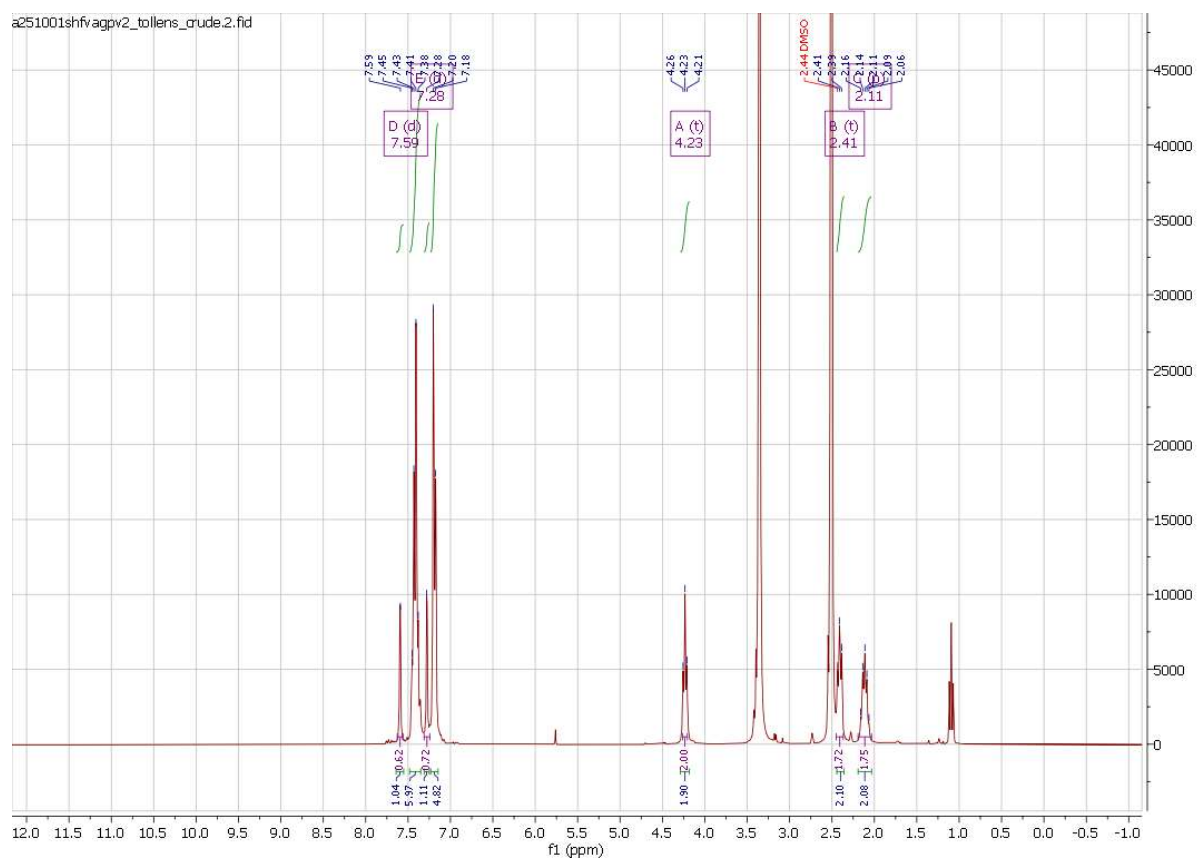
Bis-[*N*-benzhydryl-*N'*-(propyl-3-sulfonate)-2-yliden] gold chloride (AuFV11)



See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”.

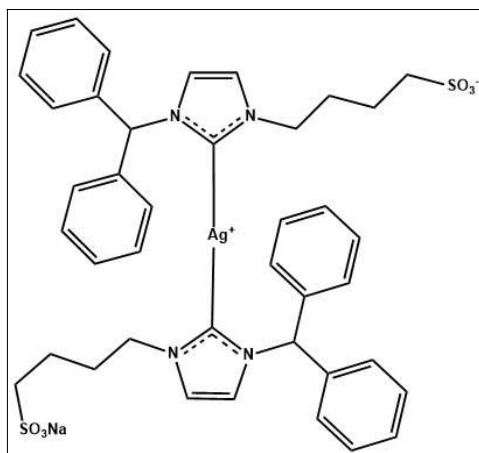
White powder. Yield = 63.4 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.59 (d, J = 1.49 Hz, 1H, C4/5-H), 7.45–7.38 (br m, 6H, Ph-H), 7.28 (d, J = 1.68 Hz, 1H, C4/5-H), 7.20–7.18 (br m, 5H, Ph-H + Ph₂-CH), 4.23 (t, J = 6.88 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.41 (t, J = 7.63 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]), 2.11 (q, J = 7.40 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃[−]).



^1H NMR – AuFV11

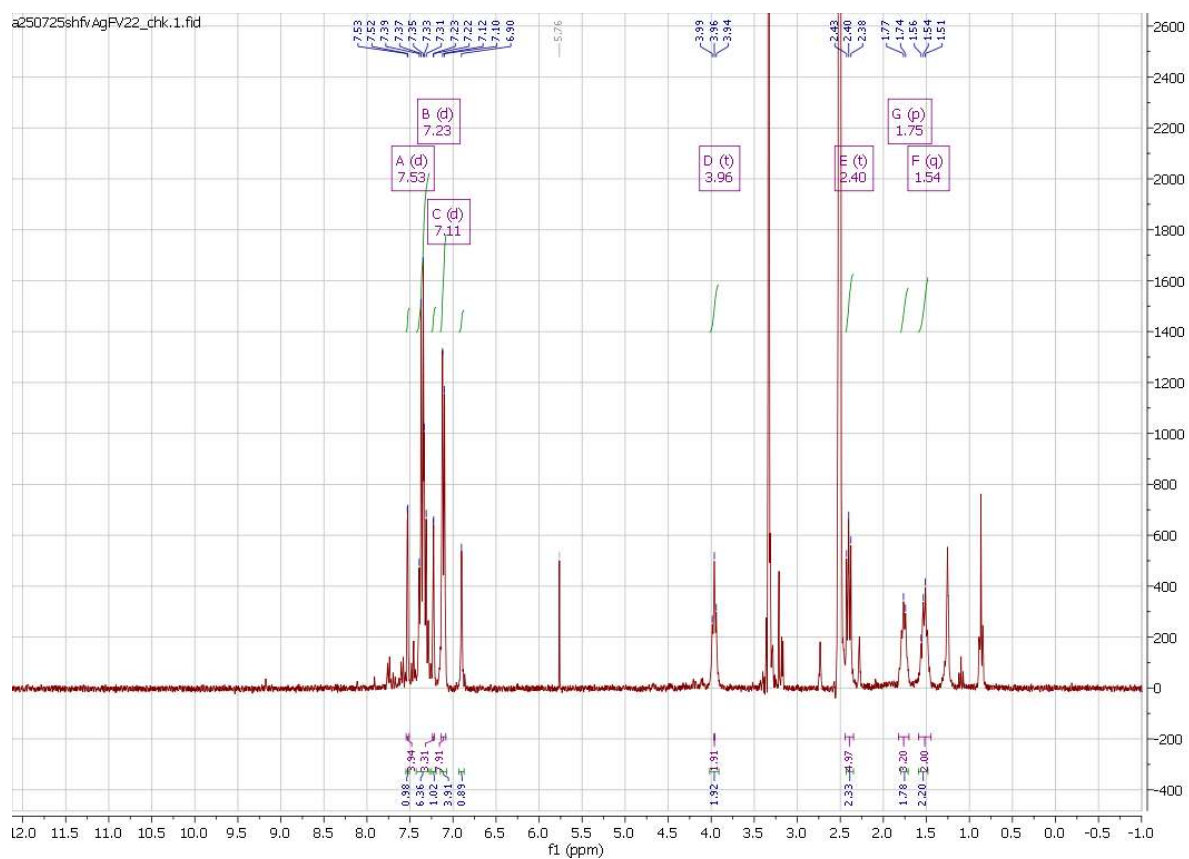
Bis-[*N*-benzhydryl-*N'*-(butyl-4-sulfonate)-2-yliden] silver chloride (AgFV22)



See “General synthesis for NHC-*Ag*(I)-sulfonate complexes – Strategy B”.

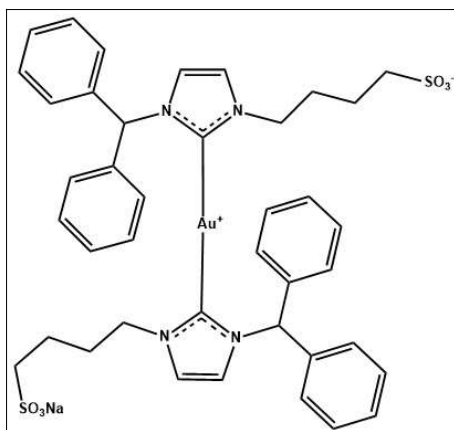
White powder. Yield = 86.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.53–7.52 (d, J = 1.79 Hz, 1H, C4/5-H), 7.39–7.31 (m, 6H, Ph-H), 7.23–7.22 (d, J = 1.65 Hz, 1H, C4/5-H), 7.12–7.10 (d, J = 6.46 Hz, 4H, Ph-H), 6.90 (s, 1H, Ph₂-CH-), 3.99–3.94 (t, J = 7.10 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.40 (t, J = 7.30 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.74 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.54 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).



^1H NMR – AgFV22

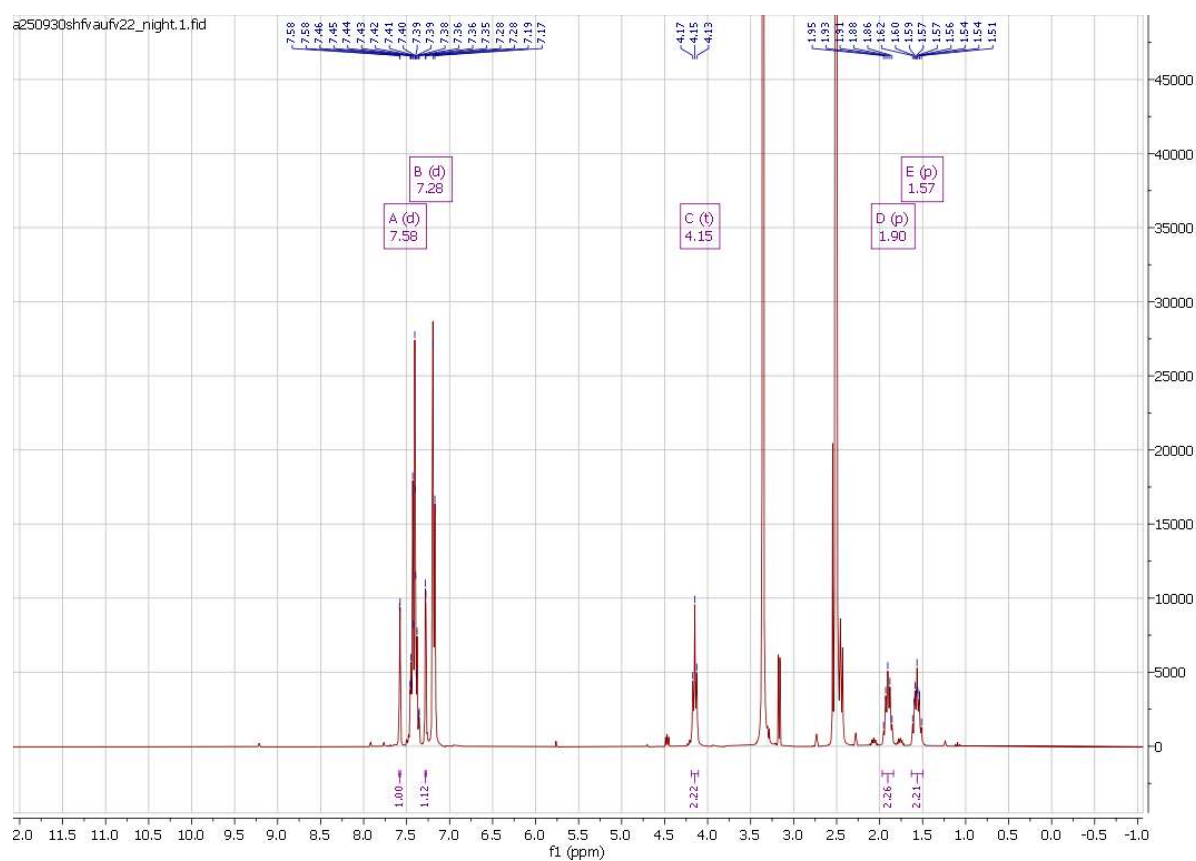
Bis-[*N*-benzhydryl-*N'*-(butyl-4-sulfonate)-2-yliden] gold chloride (AuFV22)



See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”.

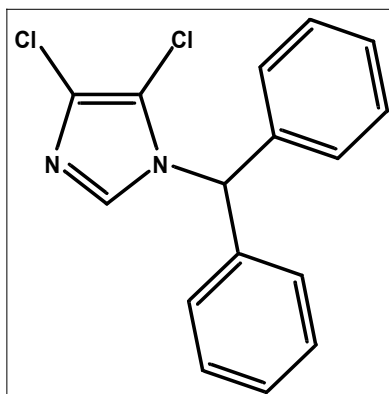
Light violet powder. Yield = 65.6 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.58 (d, J = 2.03 Hz, 1H, C4/5-H), 7.46–7.35 (br m, 6H, Ph-H), 7.28 (d, J = 2.02 Hz, 1H, C4/5-H), 7.19–7.17 (br m, 5H, Ph-H + Ph₂-CH-), 4.15 (t, J = 6.92 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.90 (q, J = 7.31 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.63 (q, J = 7.70 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).



^1H NMR – AuFV22

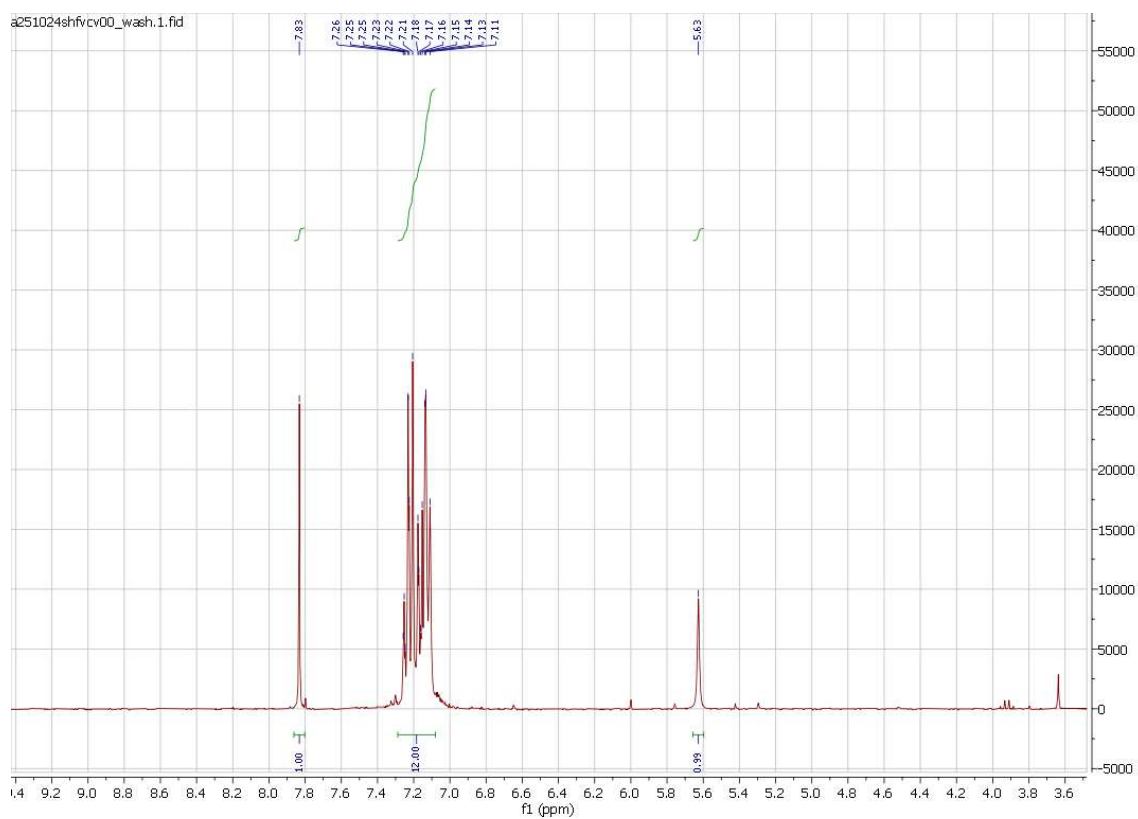
1-Benzhydryl-4,5-dichloroimidazole (CV00)



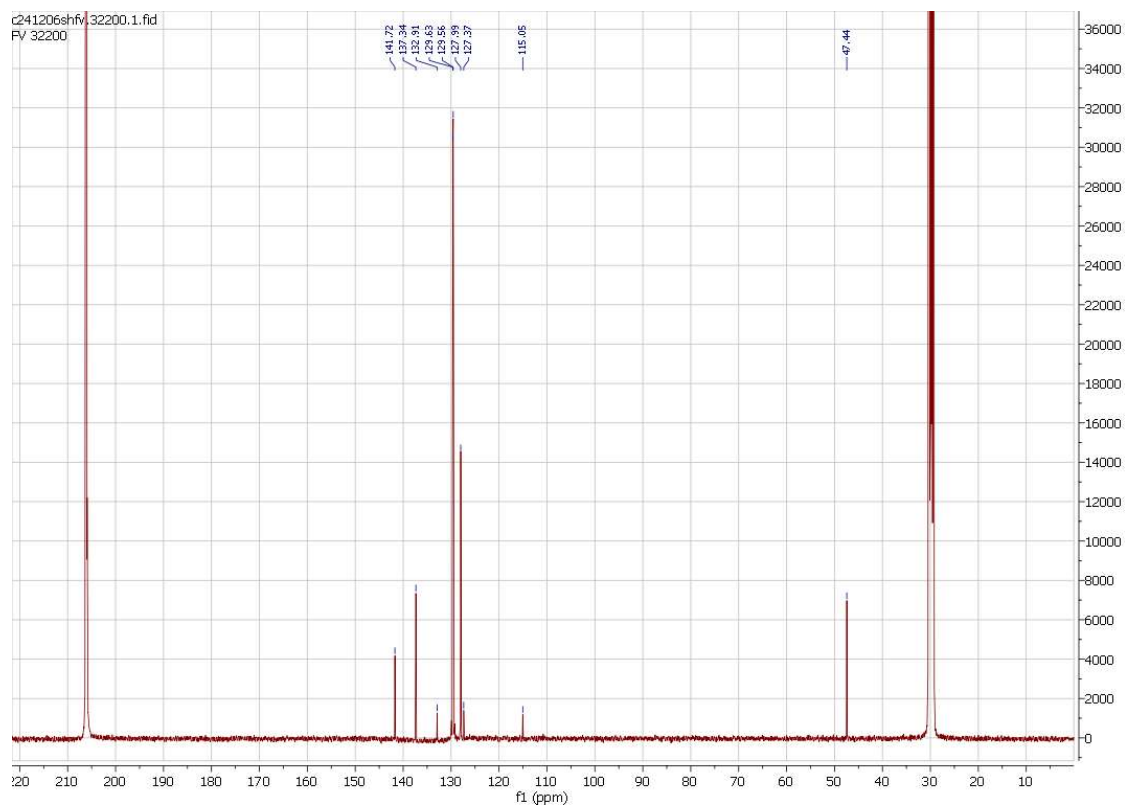
In a double joint reactor vessel, 4,5-dichloro-imidazole (0.7760 g, 5.67 mmol) was firstly solubilized in acetonitrile (30.0 mL) under magnetic stirring. When the solution was obtained, potassium carbonate (0.3355 g, 2.43 mmol) was added. After ten minutes, the solution was heated at 90 °C. Once the solution was on reflux, a solution of benzhydrylbromide (0.200 g, 8.09 mmol dissolved in 10.0 mL of acetonitrile) was added by dropwise. The reaction was carried out at 90 °C until, by monitoring with TLC, the disappearing of the benzhydrylbromide control spot was observed. Then the reaction mixture was cooled at room temperature, the liquid phase was collected by filtration and the solvent was removed under reduced pressure, leaving a whitish sticky layer. The residue was dissolved in DCM and was washed with a saturated aqueous solution of potassium carbonate (2×15.0 mL). The organic phase was collected, dried on Na₂SO₄ anhydrous and the solvent was evaporated to achieve a solid crude. The crude was dissolved in DCM and purified on silica gel column using a mobile phase P.E.:EtOAc 7:3. The final product was finally washed with EtOH, obtaining a white powder. Yield = 33.0 %

¹H NMR (400 MHz, Acetone-d₆) δ 7.83 (s, 1H, C2-H), 7.26–7.11 (m, 12H, Ar-H), 5.63 (s, 1H, Ph₂-CH-).

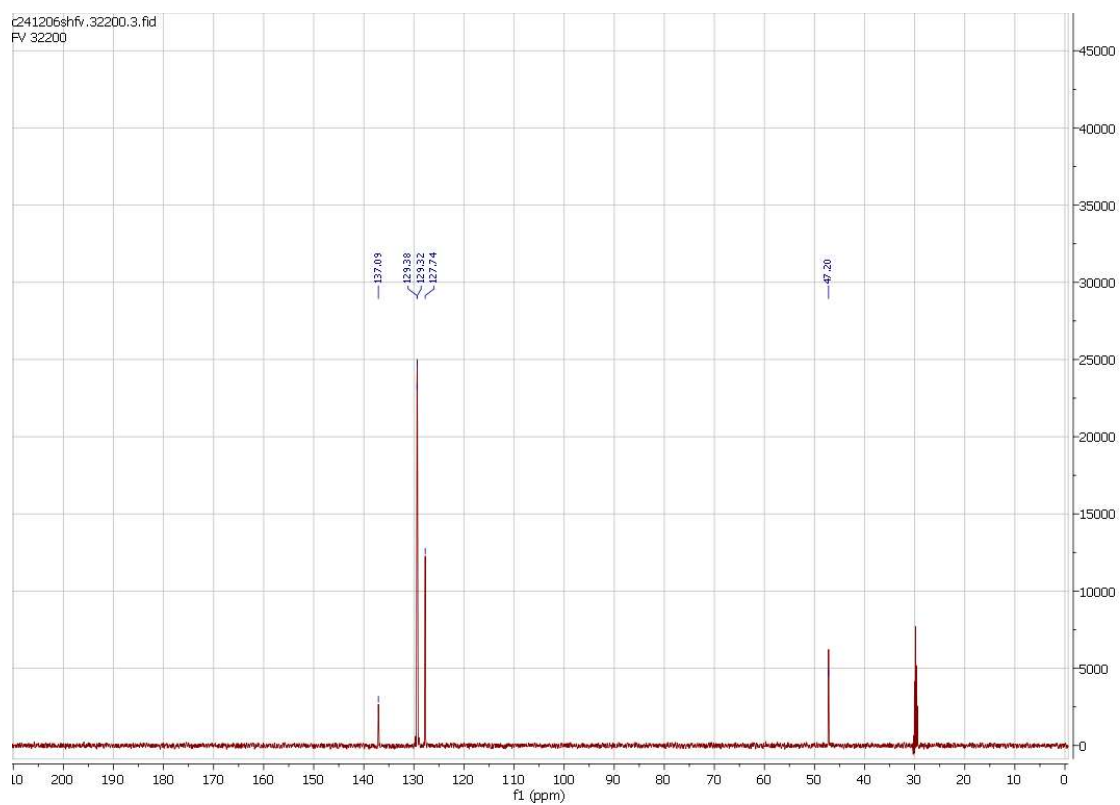
¹³C NMR (100 MHz, Acetone-d₆) δ 141.72 (*Cipso*), 137.34 (C2), 129.63, 129.56 (Ar ortho + meta), 127.99 (Ar para), 127.37 (C4/5), 115.05 (C4/5), 47.44 (Ph₂-CH-).



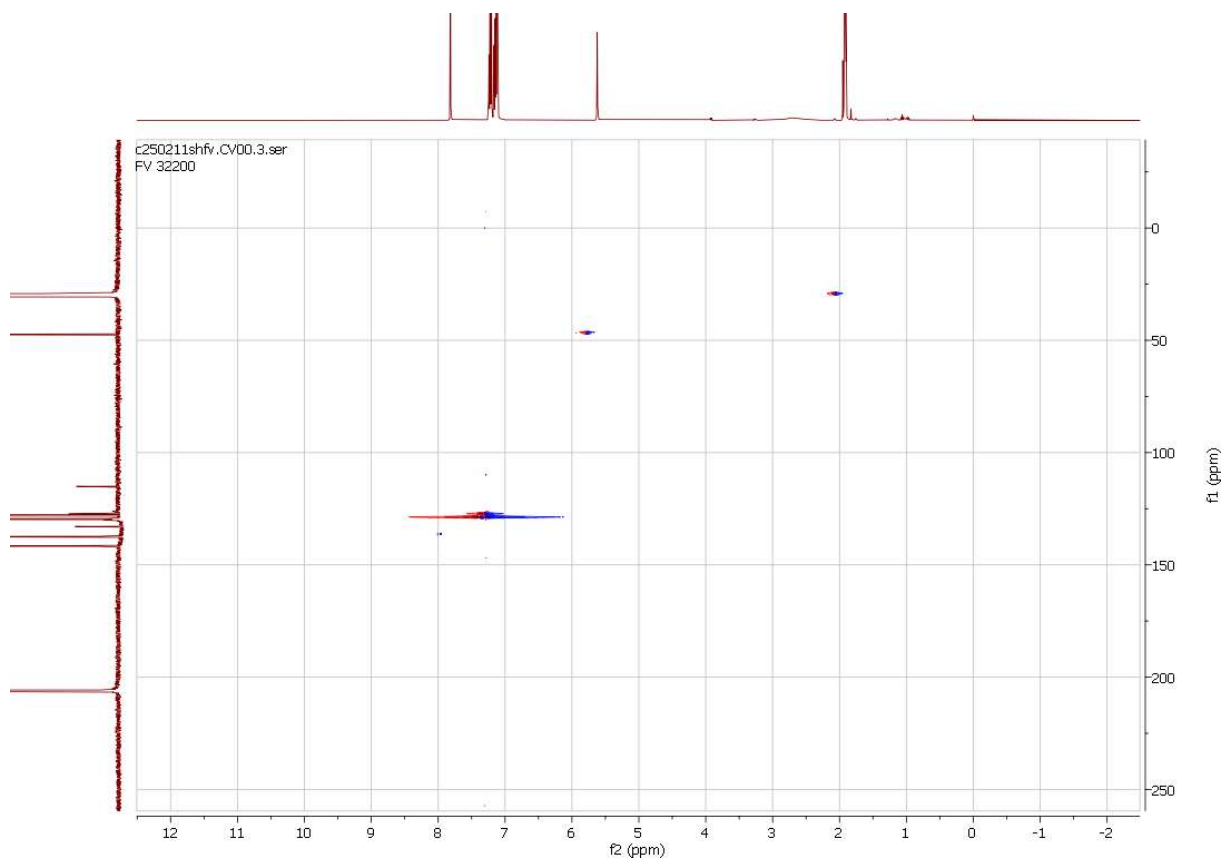
^1H NMR – CV00



^{13}C NMR – CV00

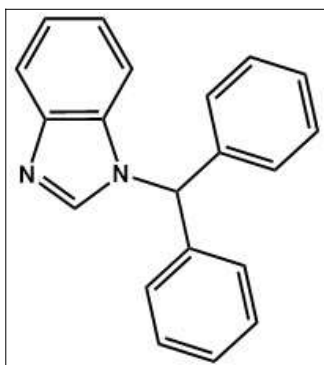


DEPT 135 – CV00



2D-HSQC CV00

1-Benzhydryl-benzimidazole (BV00)

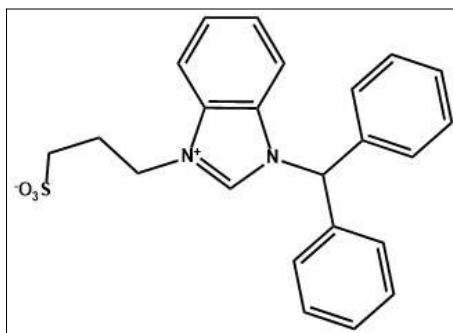


See “General synthesis for *N*-benzhydrylated-imidazolium compounds”.

Purified on silica gel column using a mobile phase P.E.:EtOAc 7:3. The final product was finally washed with EtOH, obtaining a white powder. Yield = 60.0 %

The NMR characterization match the data reported in literature^[5].

N-benzhydryl-*N'*-(propyl-3-sulfonate)-benzimidazolium salt (BV11)



See “General synthesis for *N*-benzhydrylated-imidazolium salt compounds in MeCN”.

White powder. Yield = 66.3 %

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.42 (s, 1H, C2-H), 8.18–8.16 (d, *J* = 8.35 Hz, 1H, benzimidazol-H), 7.70–7.67 (m, 1H, benzimidazol-H), 7.63–7.58 (m, 1H, benzimidazol-H), 7.51–7.40 (m, 11H, Ar-H + Ph₂-CH-), 4.66–4.63 (t, *J* = 7.27 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.48–2.47 (t, *J* = 6.98 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻), 2.22–2.16 (q, *J* = 7.21, 7.10 Hz, 2H, N-CH₂-CH₂-CH₂-SO₃⁻).

^{13}C NMR (126 MHz, DMSO- d_6) δ 142.67 (C2), 136.61 (*Cipso*), 132.15 (Ar), 131.59 (Ar), 129.73 (Ar), 129.53 (Ar), 128.89 (Ar), 127.30 (Ar), 127.12 (Ar), 114.85 (Ar), 114.52 (Ar), 64.69 ($\text{Ph}_2\text{-CH-}$), 48.16 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 46.58 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$), 25.92 ($\text{N-CH}_2\text{-CH}_2\text{-CH}_2\text{-SO}_3^-$).

ATR-FTIR: ν 3538, 3469, 3109, 3053, 1655, 1612, 1552, 1497, 1453, 1422, 1326, 1214, 1180, 1165, 1129, 1037, 1012, 797, 756, 722, 701, 624 cm^{-1}

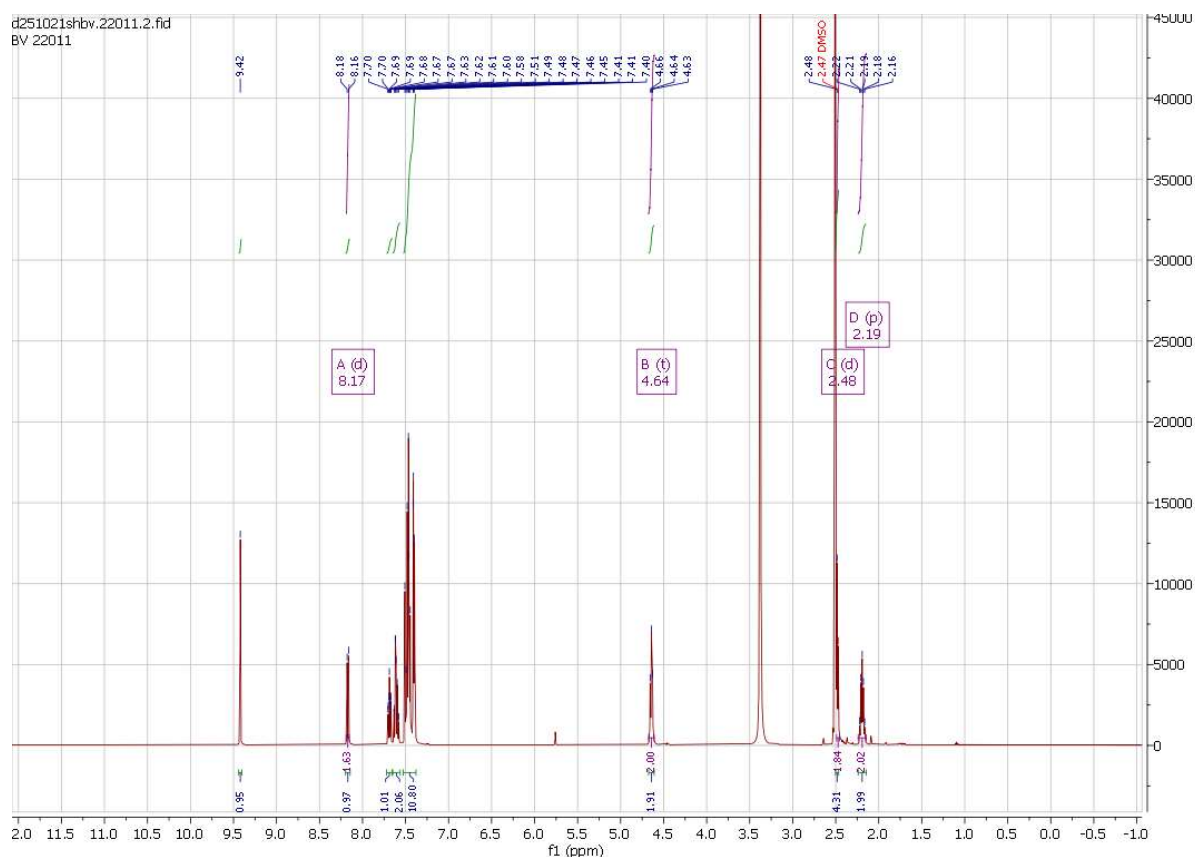
MS (MALDI-TOF, Positive mode)

HRMS measured: 407.1420 m/z [$\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$] $^+$ ($\text{M}+\text{H}^+$); estimated: 407.1424 m/z

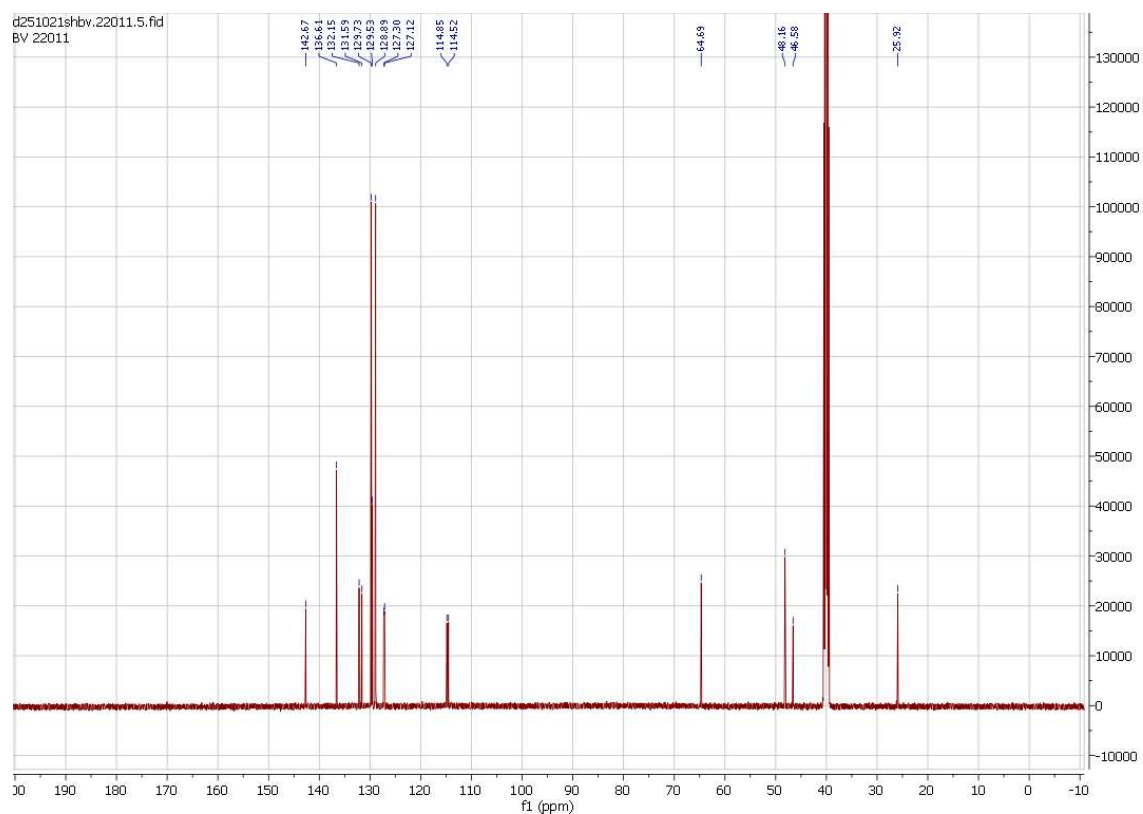
m/z : 407.1420 ($\text{M}+\text{H}^+$), 813.2784 ($2\text{M}+\text{H}^+$)

MS (MALDI-TOF, Negative mode)

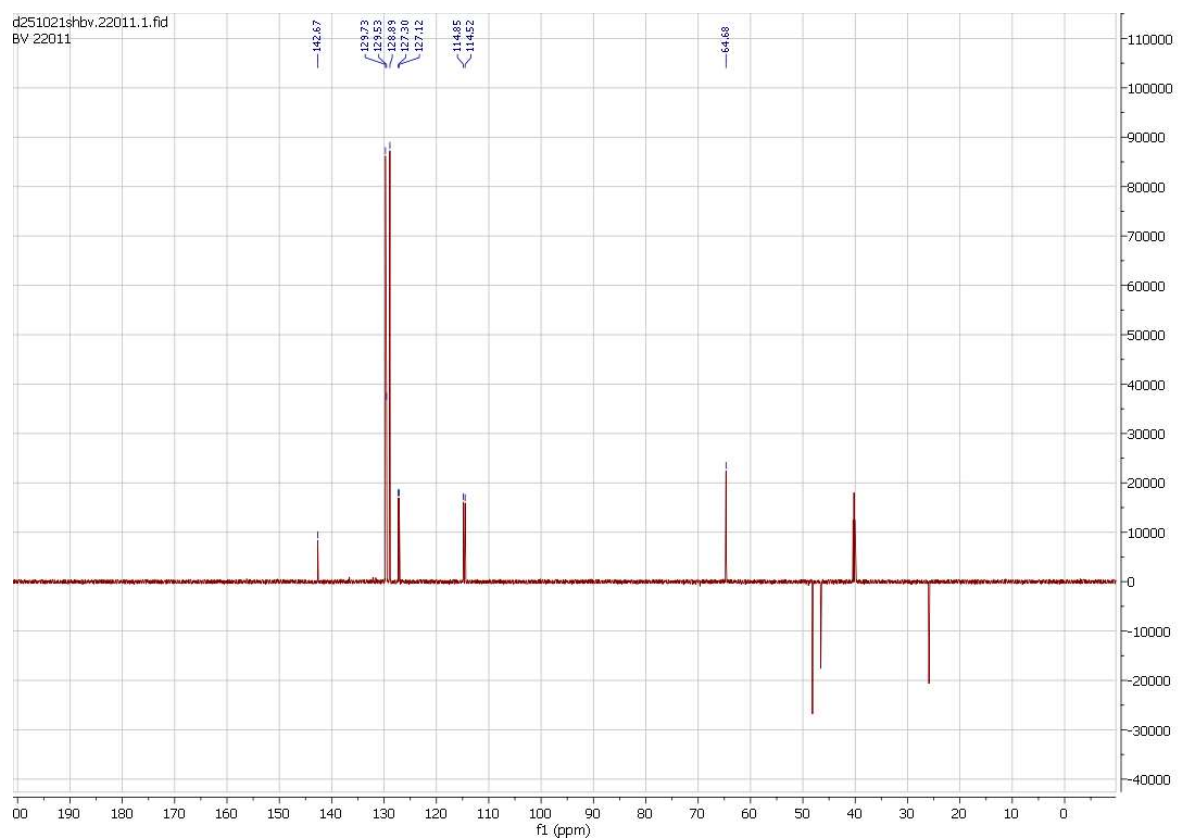
HRMS measured: 405.1312 m/z [$\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$] $^-$ ($\text{M}-\text{H}^+$); estimated: 405.1278 m/z



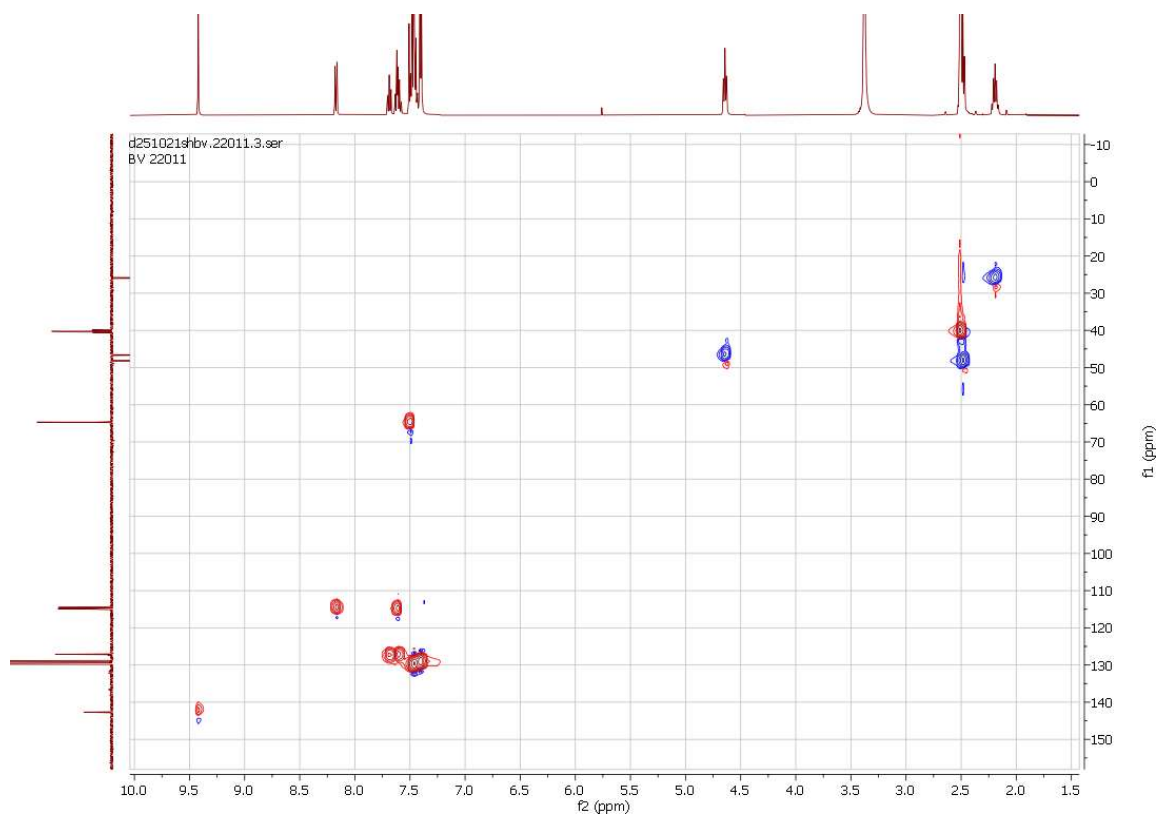
^1H NMR – BV11



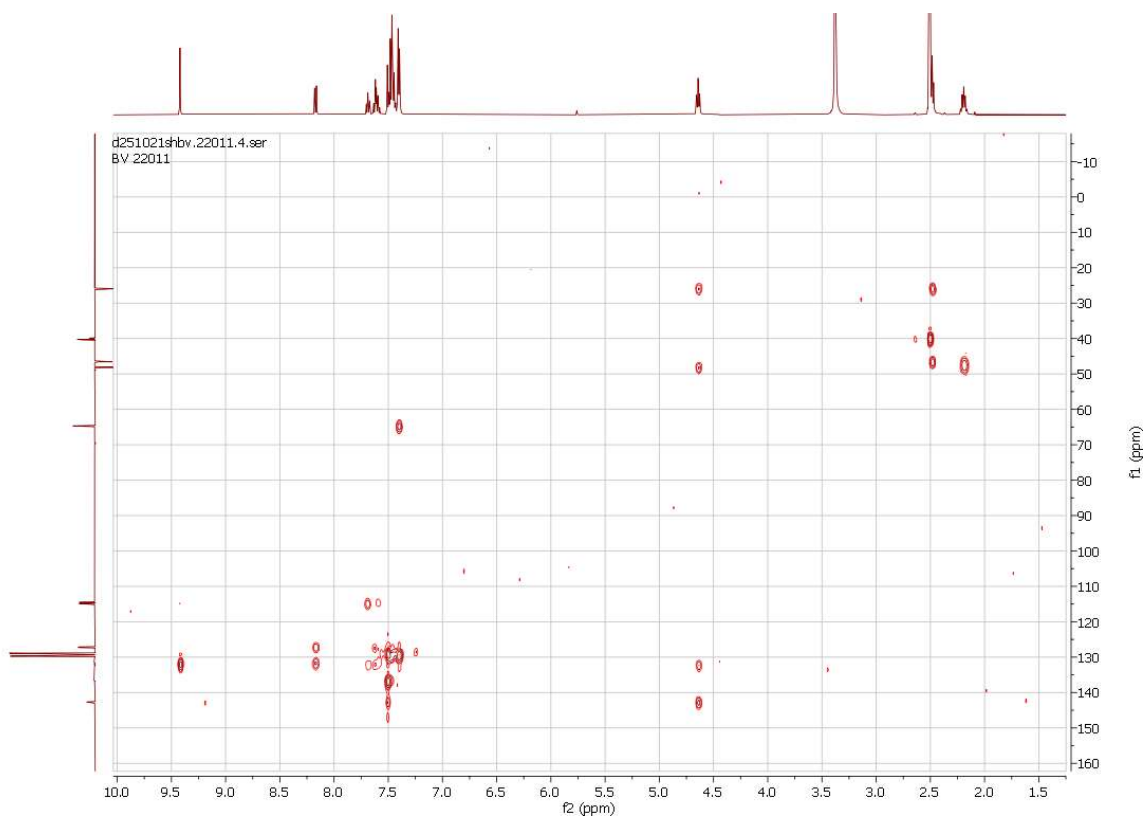
^{13}C NMR – BV11



DEPT-135 BV11

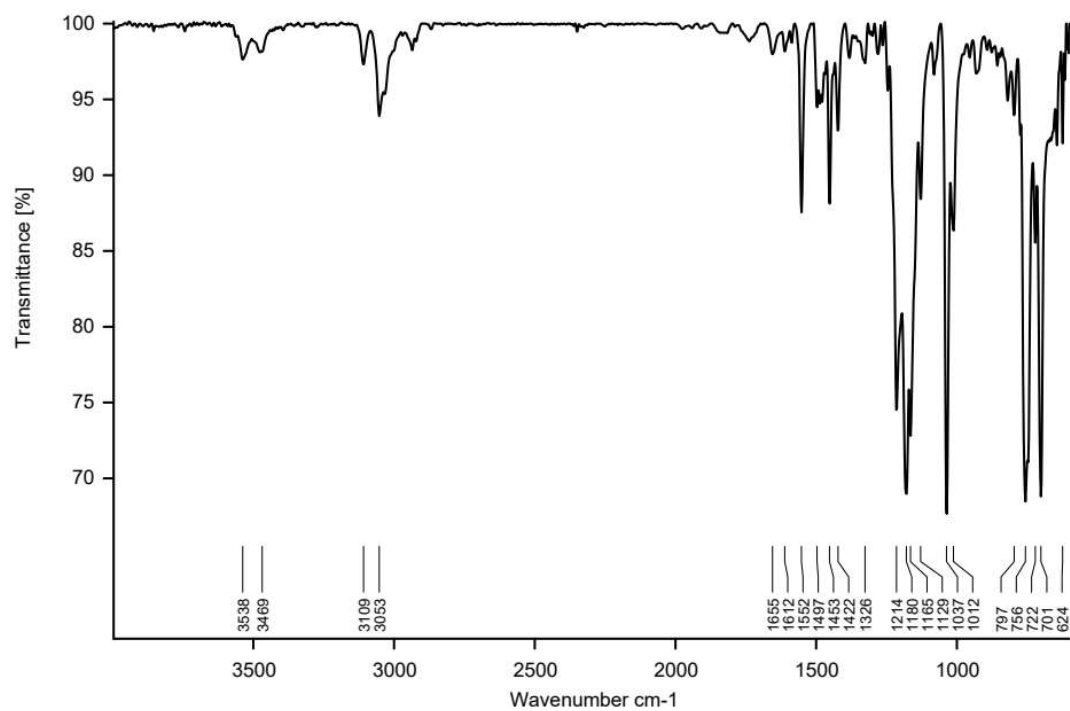


2D-HSQC BV11

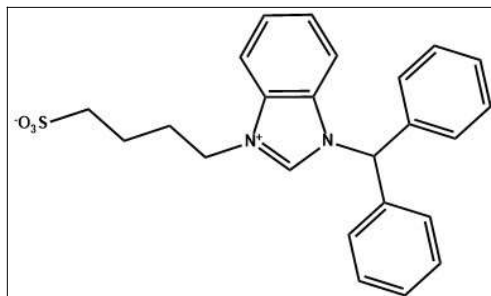


2D-HMBC BV11

BV11
ATR



***N*-benzhydryl-*N'*-(butyl-4-sulfonate)-benzimidazolium salt (BV22)**



See “General synthesis for *N*-benzhydrylated-imidazolium salt compounds in MeCN”.

White powder. Yield = 43.8 %

^1H NMR (700 MHz, DMSO- d_6) δ 9.49 (s, 1H, C2-H), 8.19–8.18 (d, J = 8.35 Hz, 1H, benzimidazol-H), 7.69–7.66 (m, 1H, benzimidazol-H), 7.62–7.60 (m, 1H, benzimidazol-H), 7.53 (s, 1H, Ph₂-CH-), 7.50–7.38 (m, 10H, Ar-H), 4.55–4.53 (t, J = 7.47 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.48–2.46 (t, J = 7.47 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 2.00–1.98 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.63–1.59 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

^{13}C NMR (176 MHz, DMSO- d_6) δ 142.40 (C2), 136.58 (*Cipso*), 132.02 (Ar), 131.63 (Ar), 129.81 (Ar), 129.53 (Ar), 128.86 (Ar), 127.34 (benzimidazol-C, inner), 127.22 (benzimidazol-C, inner), 114.80 (benzimidazol-C, outer), 114.74 (benzimidazol-C, outer), 64.59 (Ph₂-CH-), 50.84 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 47.34 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 28.30 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 22.50 (N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

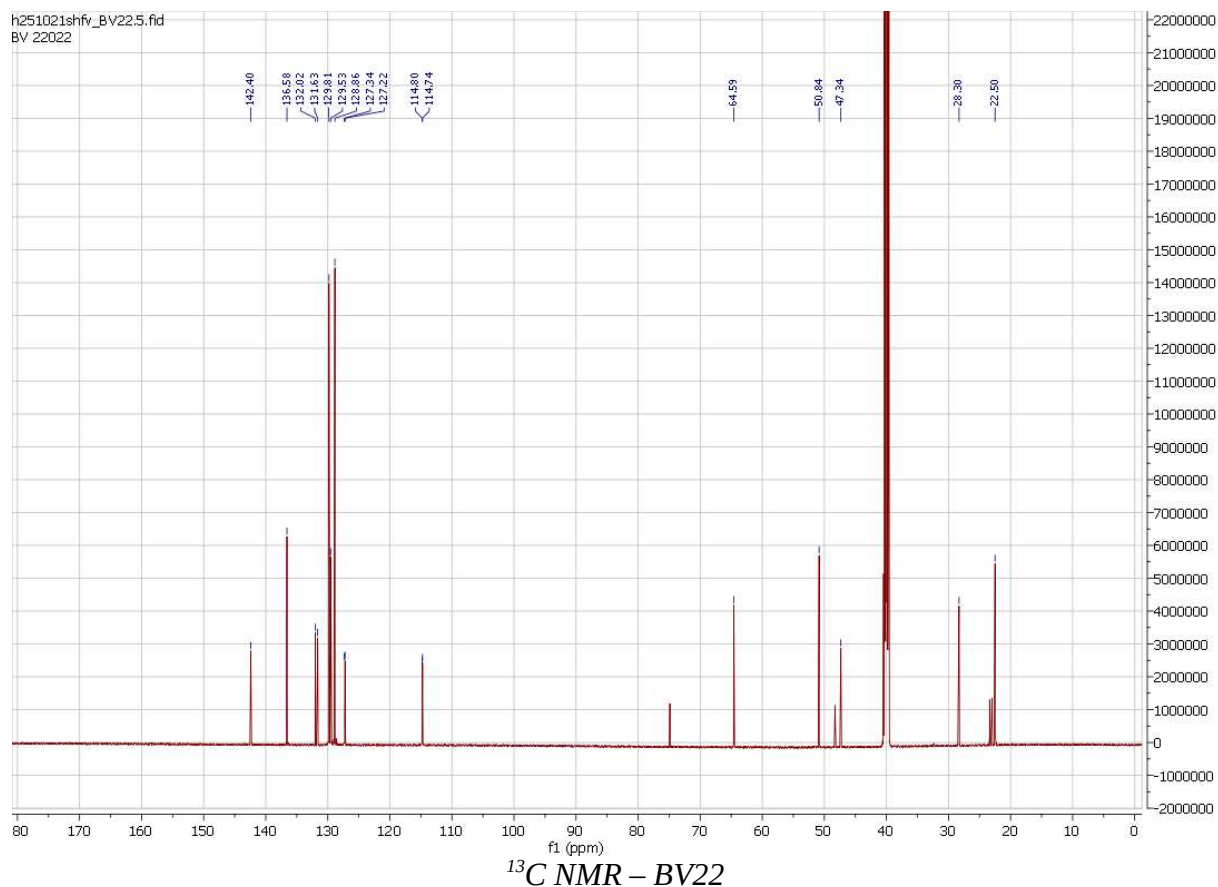
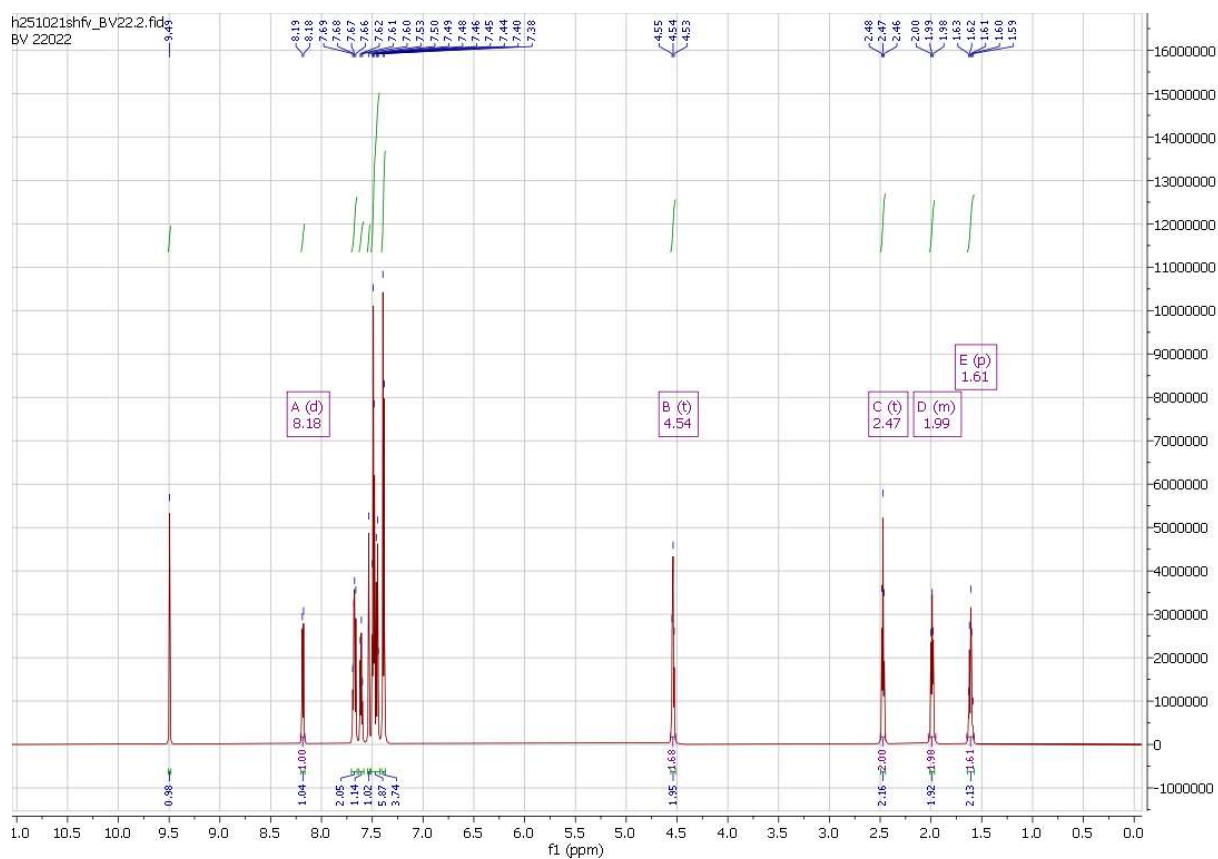
ATR-FTIR: ν 3653, 3427, 3108, 3060, 2970, 1613, 1550, 1493, 1454, 1432, 1344, 1259, 1245, 1171, 1038, 911, 825, 790, 758, 703, 628, 614

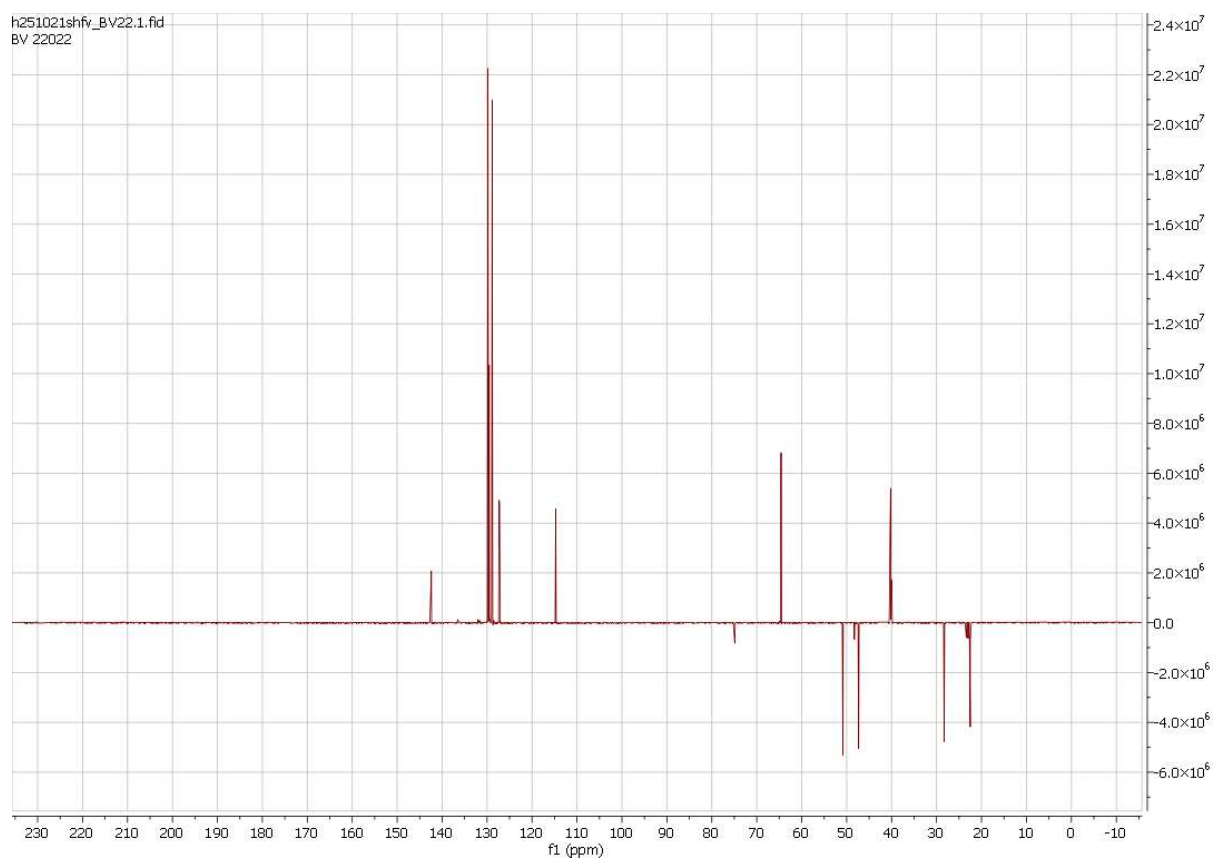
MS (MALDI-TOF, Positive mode)

HRMS measured: 421.1576 m/z [$\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$]⁺ (M+H⁺); estimated: 421.1580 m/z
m/z: 421.1576 (M+H⁺), 841.3096 (2M+H⁺)

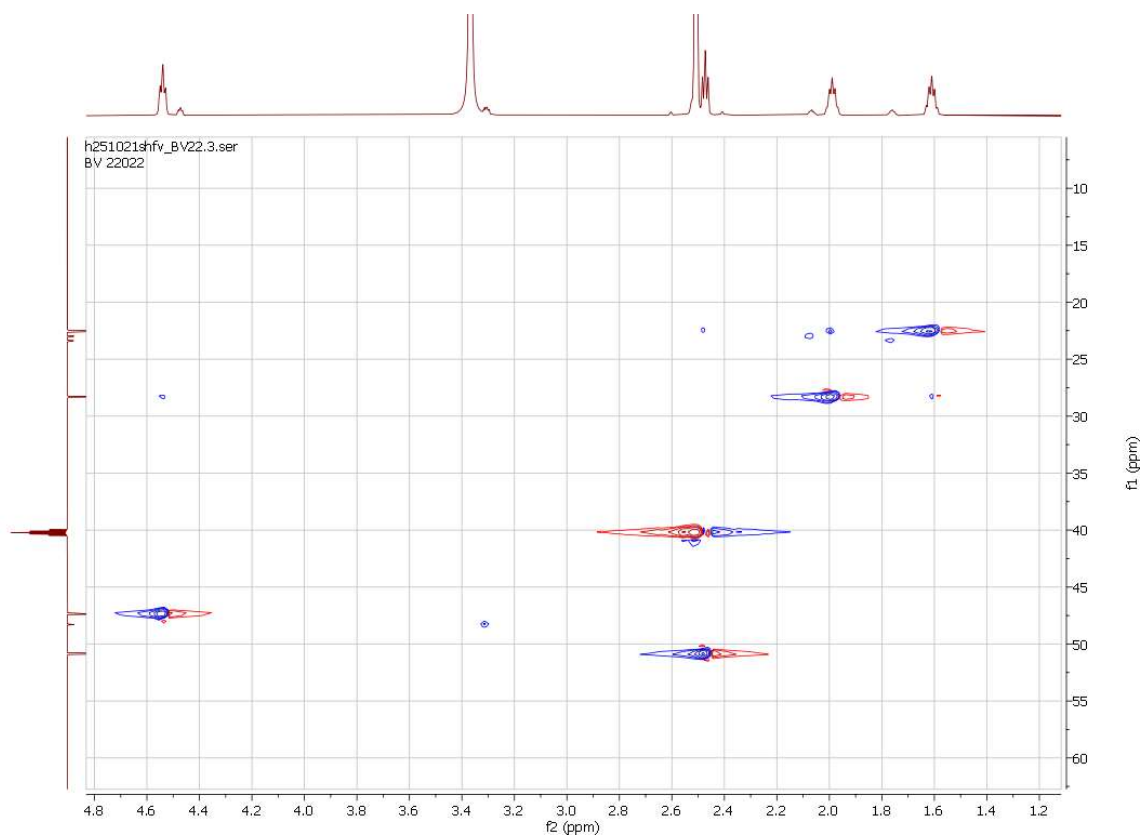
MS (MALDI-TOF, Negative mode)

HRMS measured: 419.1468 m/z [$\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$][−] (M-H⁺); estimated: 419.1435 m/z

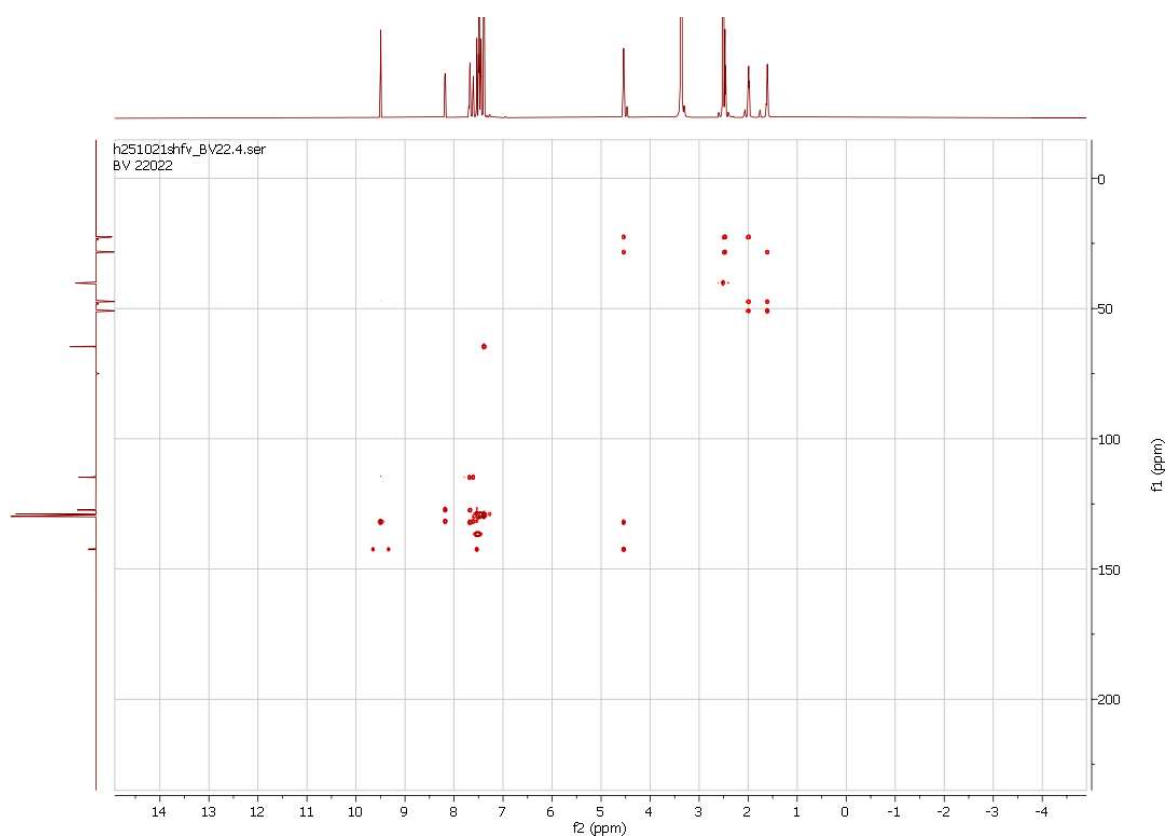




DEPT-135 BV22

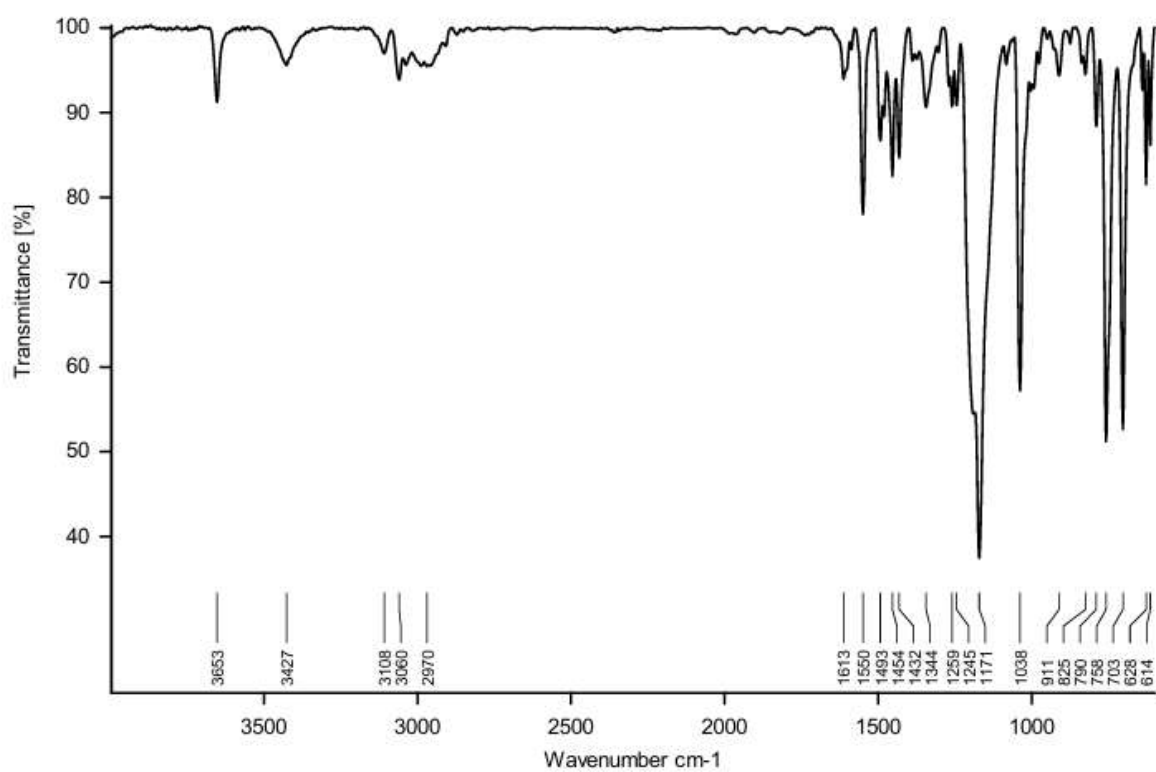


2D-HSQC BV22

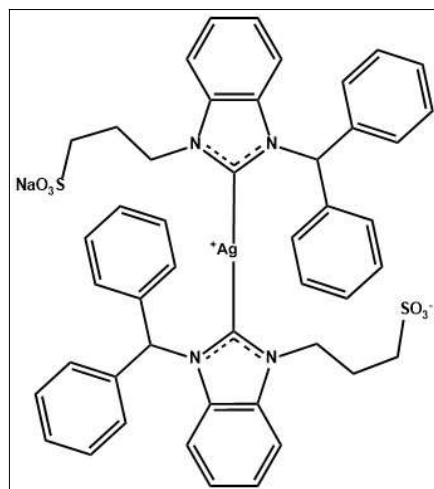


2D-HMBC BV22

BV22
ATR



Bis-[*N*-benzhydryl-*N'*-(propyl-3-sulfonate)-2-yliden] silver chloride (AgBV11)



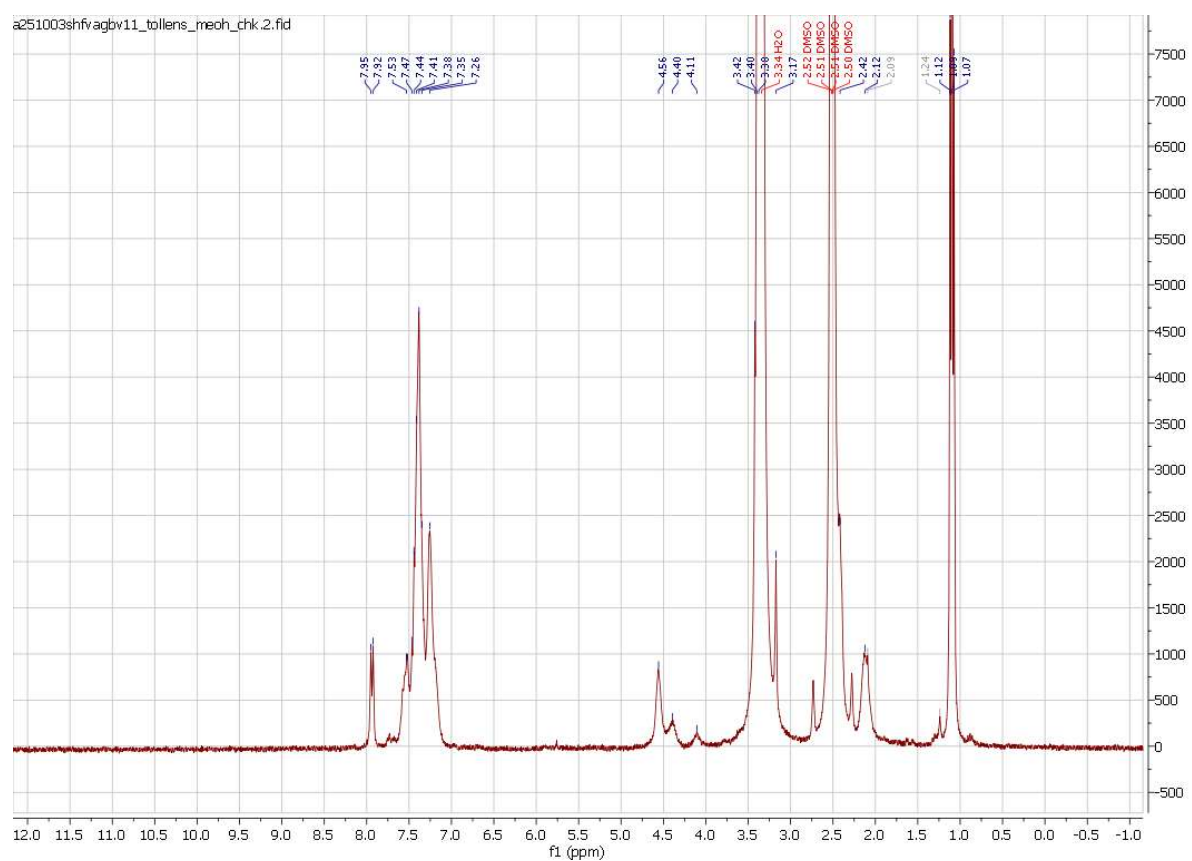
See “General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B”

Grey powder. Yield = 44.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 8.18–7.16 (br m, 7H, benzimidazol-H + Ar-H), 7.33–7.28 (br m, 6H, benzimidazol-H + Ar-H + Ph $_2$ -CH-), 4.63 (m, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$), 2.19 (m, 2H, N-CH $_2$ -CH $_2$ -CH $_2$ -SO $_3^-$).

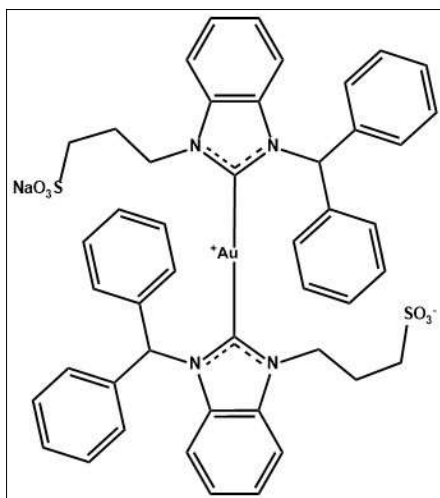
MS (MALDI FT-ICR, H $_2$ O)

m/z: 835.26131 Da [C $_{44}$ H $_{40}$ AgNaN $_4$ O $_3$ S] $^+$, 429.12517 [C $_{23}$ H $_{22}$ N $_2$ NaO $_3$ S] $^+$



^1H NMR – AgBV11

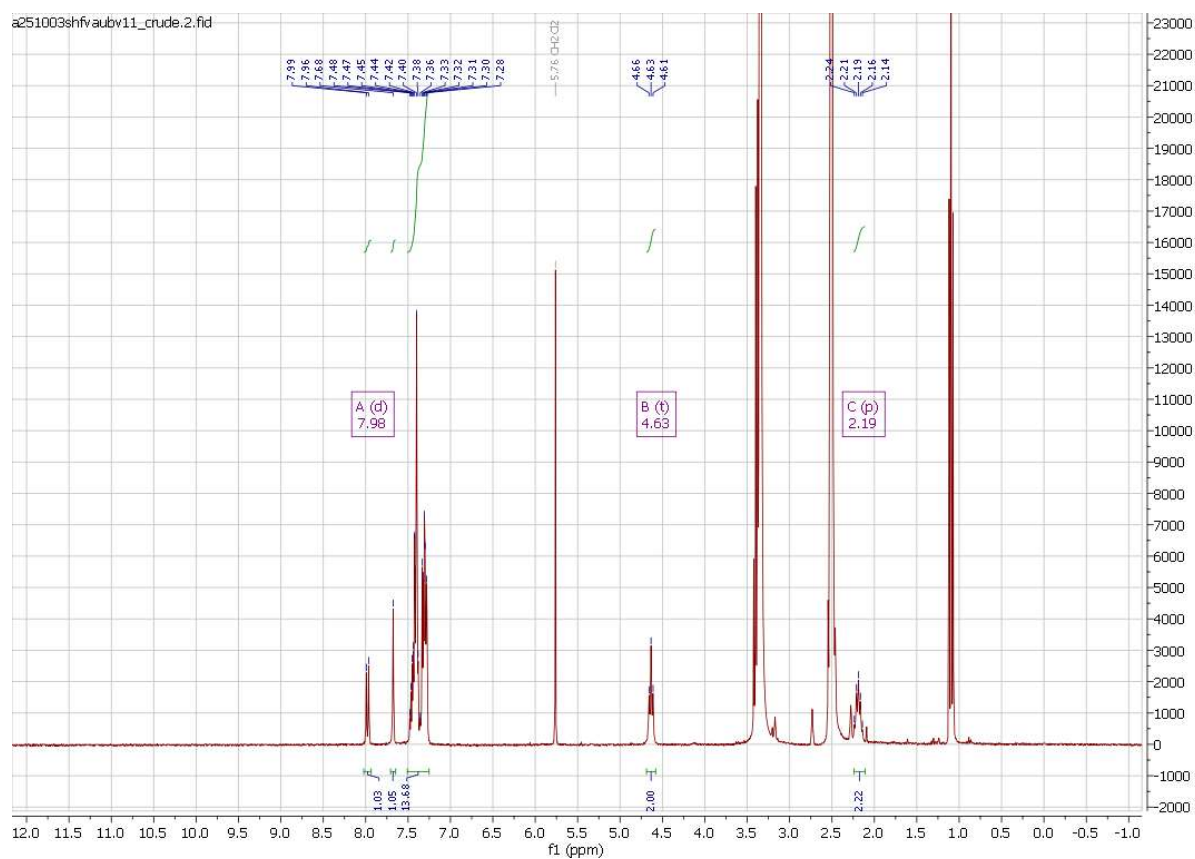
Bis-[*N*-benzhydryl-*N'*-(propyl-3-sulfonate)-2-yliden] gold chloride (AuBV11)



See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”

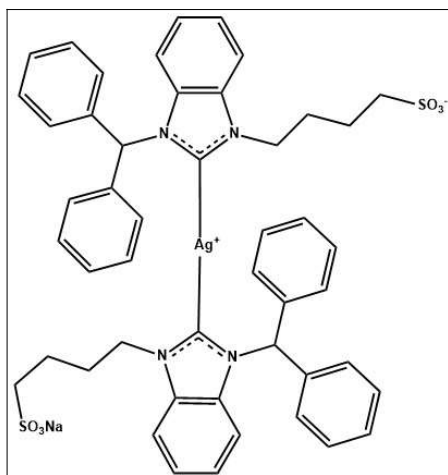
White powder. Yield = 21.0 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.98 (d, $J = 8.25$ Hz, 1H, benzimidazol-H), 7.68 (s, 1H, benzimidazol-H), 7.42 (br m, 7H, benzimidazol-H + Ar-H), 7.33–7.28 (br m, 6H, benzimidazol-H + Ar-H + $\text{Ph}_2\text{-CH-}$), 4.63 (t, $J = 6.88$ Hz, 2H, N-**CH₂**-CH₂-CH₂-SO₃⁻), 2.19 (q, $J = 7.22$ Hz, 2H, N-CH₂-**CH₂**-CH₂-SO₃⁻).



^1H NMR – AuBV11

Bis-[*N*-benzhydryl-*N'*-(butyl-4-sulfonate)-2-yliden] silver chloride (AgBV22)



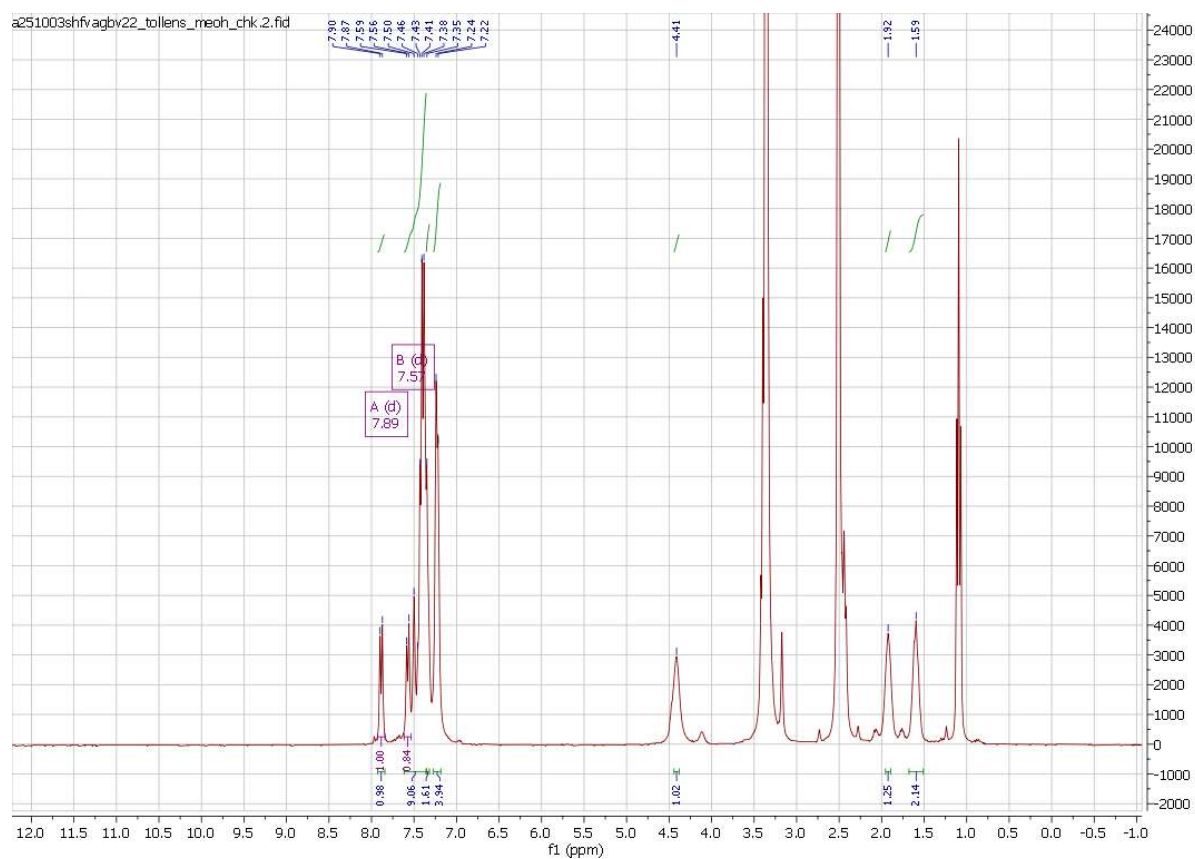
See “*General synthesis for NHC-Ag(I)-sulfonate complexes – Strategy B*”

Grey powder. Yield = 38.2 %

^1H NMR (300 MHz, DMSO- d_6) δ 7.90–7.87 (d, J = 8.1 Hz, 1H, benzimidazol-H), 7.59–7.56 (d, J = 8.25 Hz, 1H, benzimidazol-H), 7.50–7.22 (m, 12H, Ar-H + Ph₂-CH-), 4.41 (t, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.92 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]), 1.59 (m, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃[−]).

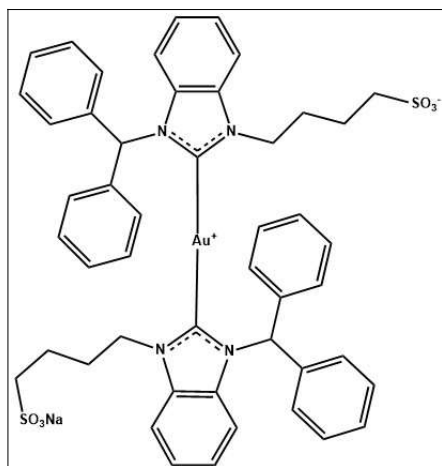
MS (MALDI FT-ICR, H₂O)

m/z : 863.29262131 [$\text{C}_{46}\text{H}_{44}\text{AgNaN}_4\text{O}_3\text{S}$]⁺, 443.14082 [$\text{C}_{24}\text{H}_{24}\text{N}_2\text{NaO}_3\text{S}$]⁺



^1H NMR – AgBV22

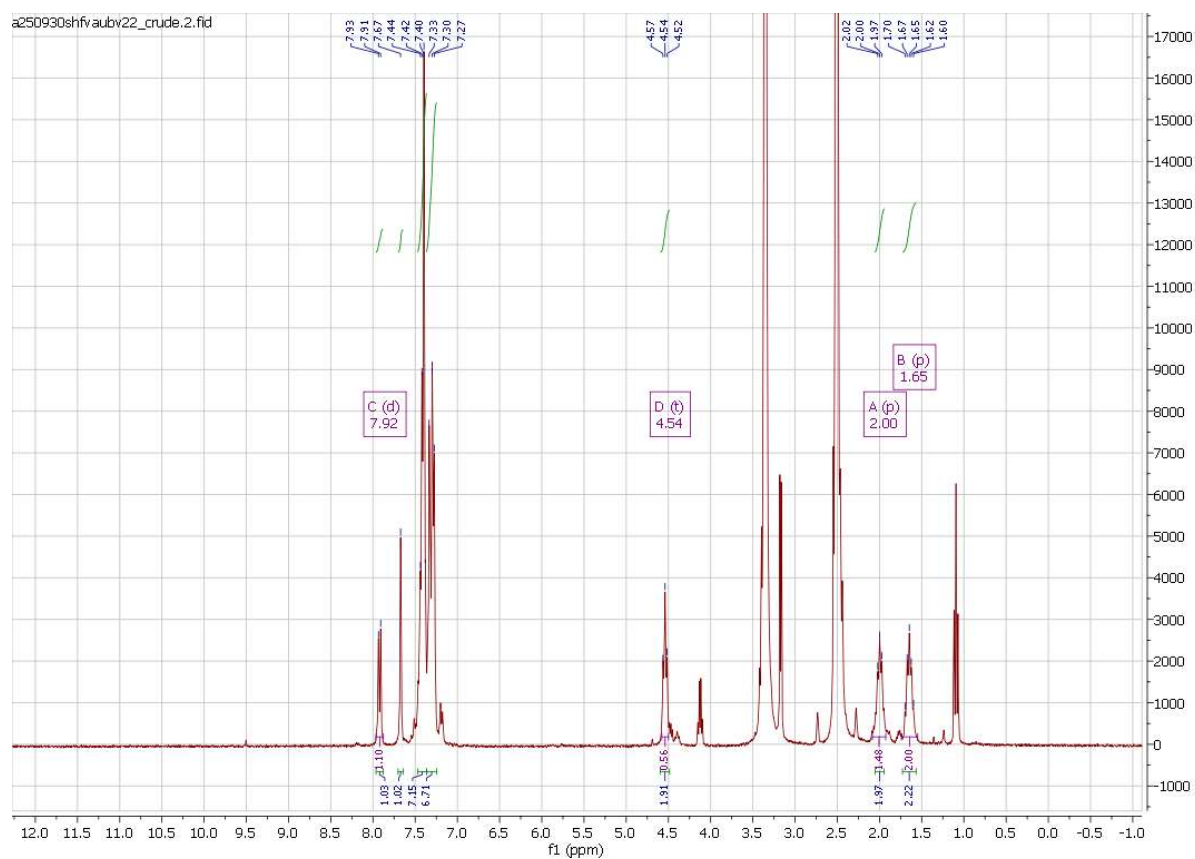
Bis-[*N*-benzhydryl-*N'*-(butyl-4-sulfonate)-2-yliden] gold chloride (AuBV22)



See “General synthesis for NHC-Au(I)-Cl sulfonate complexes”

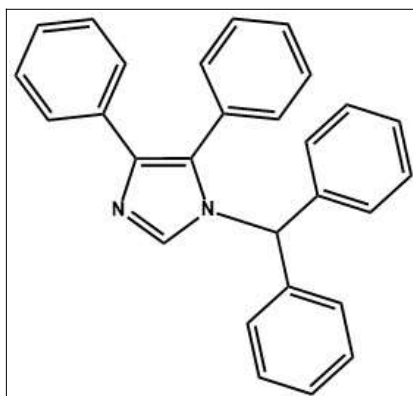
Violet powder. Yield = 17.6 %

^1H NMR (400 MHz, DMSO- d_6) δ 7.92 (d, J = 7.84 Hz, 1H, benzimidazol-H), 7.67 (s, 1H, benzimidazol-H), 7.44–7.40 (br m, 7H, benzimidazol-H + Ar-H), 7.33–7.27 (br m, 5H, benzimidazol-H + Ph₂-CH-), 4.54 (t, J = 7.11 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 2.00 (q, J = 7.34 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻), 1.65 (q, J = 8.04 Hz, 2H, N-CH₂-CH₂-CH₂-CH₂-SO₃⁻).



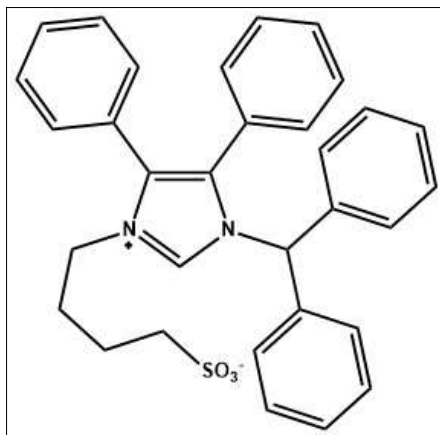
^1H NMR – AuBV22

1-Benzhydryl-4,5-diphenylimidazole (PV00)



The crude was dissolved in DCM and purified on silica gel column using a mobile phase P.E.:EtOAc 8:2. The final product was finally washed with EtOH, obtaining a clear crystal. Yield = 60.0 %. The NMR characterization matches the data already reported in literature^[5].

***N*-benzhydryl-*N'*-(butyl-4-sulfonate)-4,5-diphenylimidazolium salt (PV22)**



In a pre-heated 5 mL two-neck flask, PV00 (0.1550 g, 4.01 mmol) and 1,4-butanedisulfone (0.1640 g, 1.20 mmol) were added at 25 °C. The mixture was heated under stirring to 110 °C. After 4 hours, the reaction was allowed to cool to 25 °C, and a white solid residue was observed. The mixture was washed with hexane (2.0 mL $\times$ 3), and the resulting precipitate was filtered and air-dried. A whitish powder was obtained. Yield <10%

MS (MALDI-TOF, Positive mode)

HRMS measured: 523.2056 m/z ($M+H^+$); estimated: 523.2050 m/z

m/z: 523.2056 ($M+H^+$), 545.1877 ($M+Na^+$), 1045.4041 ($2M+2H^+$), 1065.3859 ($2M+Na^++H^+$), 1590.5871 ($3M+Na^++H^+$)

MS (MALDI-TOF, Negative mode)

HRMS measured: 521.1896 m/z ($M-H^+$); estimated: 521.1904 m/z

m/z: 521.1896 ($M-H^+$)

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Chapter 7 – Evaluation of catalytic profiles

7.1 The A³ coupling reaction and the importance of propargylamines

Propargylamines are characterized by the presence of two distinct functional groups within their molecular framework: a carbon–carbon triple bond, which can act as either an electron-donating or electron-accepting moiety, and an amino group, which can function as a nucleophilic center or as a leaving group in substitution reactions^[1]. Due to this dual reactivity, propargylamines are highly versatile intermediates and can be employed in the synthesis of a wide range of structurally diverse products^[2].

Among the most notable applications of propargylamines, their use in medicinal chemistry is particularly significant. These compounds serve as key intermediates in the synthesis of inhibitors employed in the treatment of Parkinson's and Alzheimer's diseases (Figure 1), as their structural features enable selective binding to specific protein sites that modulate or suppress the activity of certain classes of enzymatic^[3]. In particular, propargylamine-based scaffolds have shown a strong affinity toward monoamine oxidase B (MAO-B)^[4] and lysine-specific demethylase 1 (LSD1)^[5], making them valuable frameworks for the development of targeted therapeutic agents.

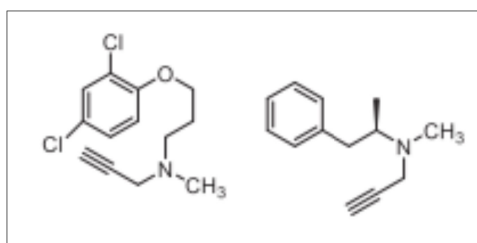
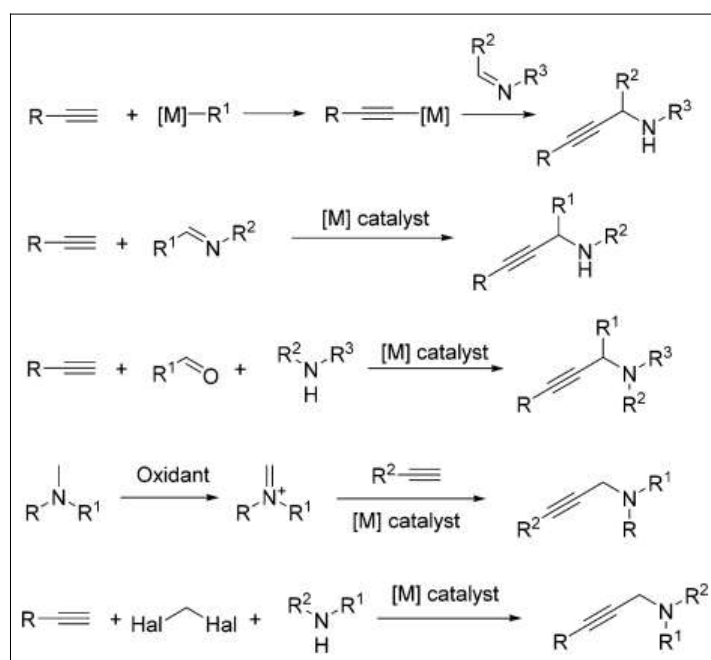


Figure 1- From left: Clorgyline and Selegiline, two substrates used for MAO inhibition

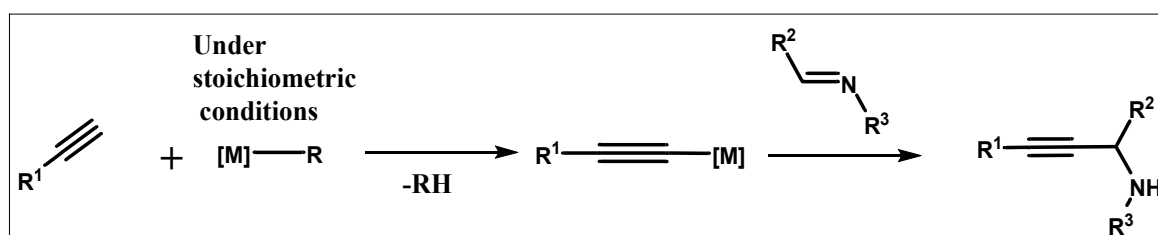
In synthetic chemistry, the preparation of propargylamines has stimulated the development of several methodologies (Scheme 1) aimed at producing these compounds most efficiently and sustainably possible, in accordance with the principles of green chemistry.



Scheme 1- Overview of common methodologies for the synthesis of propargylamine substrates

Among the various strategies reported in the literature, the direct assembly of propargylamines from simple precursors through a multicomponent transformation, known as the A³ (Aldehyde–Amine–Alkyne) coupling reaction, has attracted considerable attention. This approach not only enables the formation of the desired product in a single synthetic step but also generates water as the sole by-product. As such, it represents a valuable contribution to sustainable synthesis, an aspect of growing relevance in industrial chemistry. Moreover, the use of suitable organometallic catalysts allows the reaction to proceed efficiently under conditions that would otherwise be inaccessible, further enhancing its applicability and green credentials. The A³ reaction involves the use of three components: an aldehyde, a primary or secondary amine, and a terminal alkyne. The pivotal element of this transformation is the catalyst, which plays a crucial role in steering the reaction toward the desired product. To fully appreciate its importance, it is useful to compare the different catalytic strategies that have been proposed in the literature^[6].

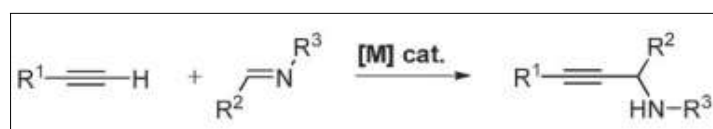
In many classical methodologies, the key step consists of the nucleophilic addition of a metal acetylide to an imine species, a transformation that efficiently yields the propargylamine framework (Scheme 2)^[7]:



Scheme 2 – Synthesis of propargylamines via formation of the metal acetylide intermediate

To generate the metal acetylide, the terminal alkyne is treated with a strong enough base to deprotonate it, forming the active nucleophile. In most cases, organometallic bases such as Lithium diisopropylamide (LDA), *t*-BuLi, or EtMgBr are employed in excessive amounts to compensate for the loss of reactivity arising from their high sensitivity to moisture^[8].

Because of the demanding operational conditions required for classical acetylide formation, including an inert atmosphere, low temperatures, and strictly anhydrous conditions, an alternative approach has been proposed. In this strategy, the terminal alkyne undergoes addition to an imine species generated in situ through the condensation of a primary amine with an aldehyde^[9], in the presence of a catalytic amount of metal salts or suitably designed transition-metal complexes (Scheme 3):



Scheme 3 – Synthesis of propargylamines assisted by a metal catalyst

In this approach, the imine is formed in a separate step, while the addition of the terminal alkyne takes place in situ. A major breakthrough was achieved in 2002, when Li and Wei introduced a one-pot, three-component protocol, that essentially represents what is now recognized as the A³ coupling reaction (Scheme 4)^[10]:

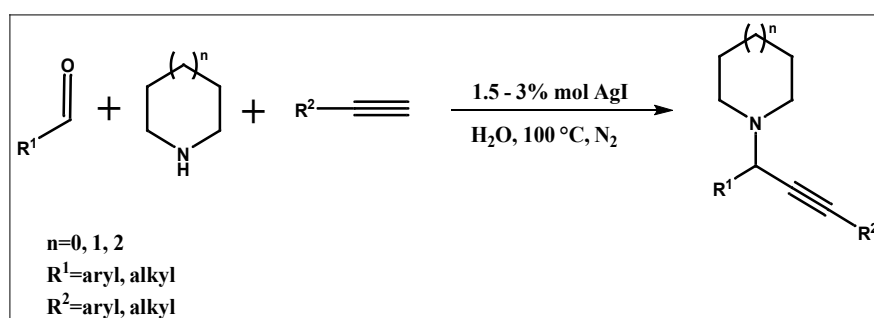


Scheme 4 – A³ coupling reaction (Aldehyde–Alkyne–Amine)

Unlike earlier methodologies, no prior treatment of the reagents is required, as they can be used directly. Despite the diversity of synthetic strategies, several mechanistic features are shared: the terminal alkyne acts as the nucleophile species that reacts with the electrophilic iminium carbon. Since neither the starting amine nor the final propargylamine product is basic enough to deprotonate the terminal alkyne, metal salts or organometallic complexes are essential for generating the acetylide in situ. These species interact with the metal center, which is believed to mediate both acetylide formation and its subsequent addition to the iminium ion. In this context, the metal center transitions from functioning as a counterion for the acetylide to serving as a coordination site during the addition step. Importantly, this catalytic pathway offers several advantages over classical approaches: it eliminates the need for strong bases, strictly anhydrous conditions, and low temperatures, thereby improving operational simplicity, functional-group tolerance, and overall sustainability^[7].

7.2 A³ coupling reactions: general

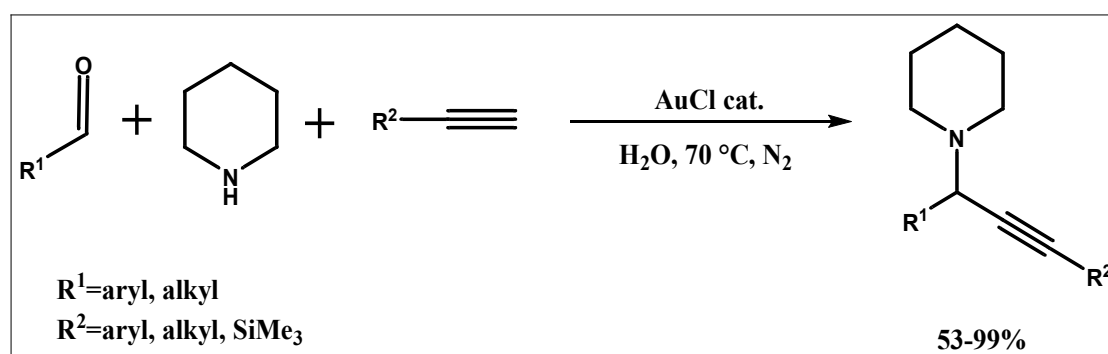
The first promising A³ coupling reactions employing gold and silver salts were reported by Li and co-workers^[8]. In these studies, Ag(I) salts were evaluated as catalysts for the coupling of aliphatic and aromatic aldehydes with both cyclic and acyclic secondary amines and arylacetylenes. These reactions were typically conducted under aqueous conditions at 100 °C under an inert nitrogen atmosphere (Scheme 5).



Scheme 5 – AgI-catalyzed A³ coupling reaction

Li's studies revealed that several Ag(I) salts, such as AgNO₃, Ag₂O, AgOAc, Ag₂SO₄, AgOTf, and AgBF₄ led to poor conversions. This result was attributed to catalyst deactivation caused by the reduction of Ag(I) to catalytically inactive metallic silver. In contrast, silver halides (AgX) displayed significantly higher efficiency, with AgI emerging as the most effective

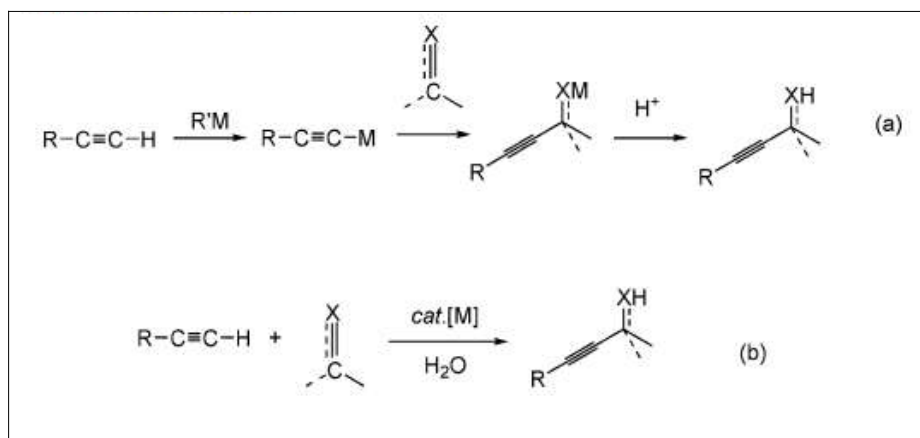
catalyst. Notably, AgI also suppressed the undesired trimerization of aliphatic aldehydes, a side reaction commonly observed with the analogous Cu(I) and Au(I) salts. Regarding substrate reactivity, aliphatic aldehydes proved to be more reactive than their aromatic counterparts, while cyclic secondary amines outperformed acyclic ones under the same conditions^[11]. The first report of an A³ coupling reaction catalyzed by gold also originated from Li and co-workers^[12]. In this study, both Au(I) and Au(III) salts were evaluated, and the best results were obtained in water using only 1 mol% of catalyst, in clear contrast to the significantly lower conversions observed in organic solvents (Scheme 6).



Scheme 6 – AuCl-catalyzed A³ coupling reaction

Both aromatic and aliphatic alkynes performed well under these conditions and, unlike what was observed with silver catalysts, aromatic aldehydes generally afforded higher yields than aliphatic ones. This is likely due to the reduced tendency of aromatic substrates to undergo undesired trimerization. Under these optimized conditions, both cyclic and acyclic secondary amines could be employed without significant differences in reactivity.

In A³ coupling reactions, the choice of reagents is guided not only by synthetic considerations but also by the intrinsic properties of the building blocks. The terminal alkyne may bear aliphatic, aromatic, or even silyl substituents (e.g., TMS)^[13]. Typically, acetylide formation is promoted by the reaction of metal salts with haloalkynes under appropriate conditions (Scheme 7a), however, it has been demonstrated that simple terminal alkynes can also be used directly in the presence of soft transition-metal complexes such as Ag(I) and Au(I)/(III), which are capable of generating the corresponding acetylide in situ without additional preactivation steps^[8] (Scheme 7b).



Scheme 7 – a): Nucleophilic addition of the traditional terminal alkyne; b): Nucleophilic addition of the terminal alkyne in the presence of a catalyst in water

The amine component may be either primary or secondary, cyclic or acyclic, and reacts with the carbonyl compound to generate the corresponding iminium intermediate. In general, secondary amines afford better results than primary ones, with the notable exception of aniline. This trend is commonly attributed to the higher reactivity of the iminium ion formed from secondary amines. A key distinction between imines and carbonyl compounds lies in the electrophilicity of the unsaturated carbon: C=O groups are intrinsically more prone to nucleophilic addition than C=N functionalities. Under the typical conditions employed for A^3 reactions, however, imines are generated in situ, and the reactive species is actually the iminium ion. The latter is significantly more electrophilic than a neutral imine, as the C=N⁺ moiety features a positively charged nitrogen that withdraws electron density from the adjacent carbon (Figure 2). Consistent with previous observations, water is once again the most effective solvent for promoting iminium formation and subsequent alkyne addition^[11].

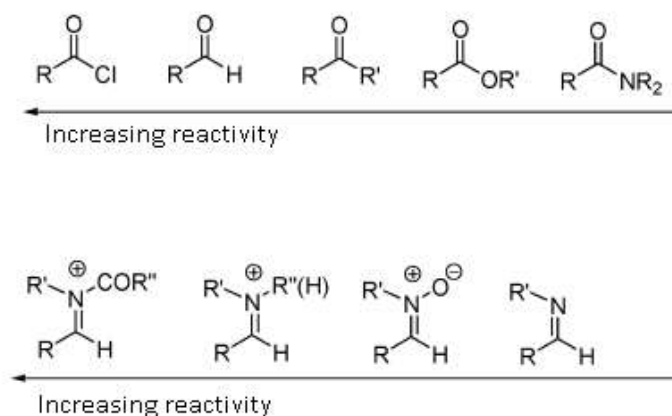


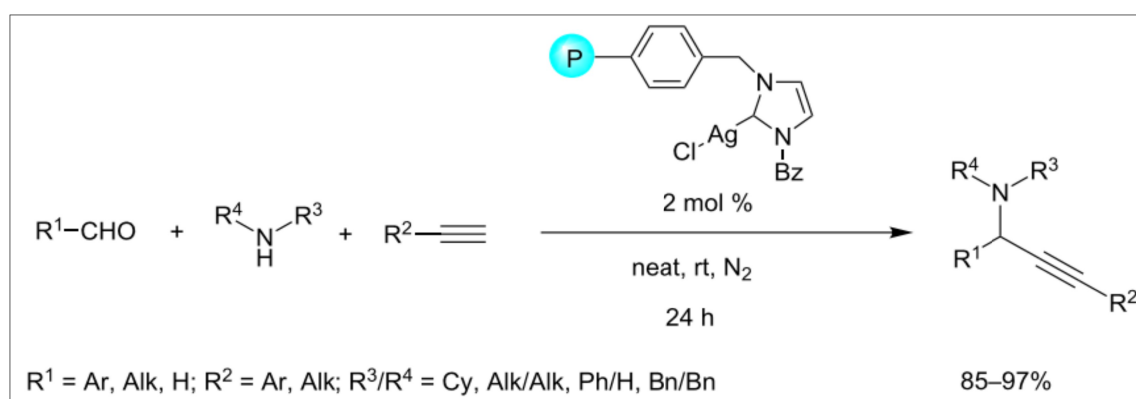
Figure 2 – Relative reactivity of carbonyl substrates (top) and imine substrates (bottom) toward nucleophilic attack by the acetylide

A recurring issue reported in the literature concerns the strong tendency of the metal center in the catalytic complex to coordinate preferentially with the nitrogen atom of the final propargylamine product rather than with the iminium intermediate. This competitive coordination leads to catalyst deactivation and, consequently, to a decrease in catalytic efficiency. For this reason, it is advantageous to employ metals that exhibit a higher affinity for the $C=N^+$ functionality. In this regard, transition metals located toward the right side of the d-block have proven to be the most effective, displaying superior reactivity in alkyne–imine addition processes^[14].

The aldehyde serves as the electrophilic partner that undergoes nucleophilic attack firstly by the amine, leading to the formation of the iminium intermediate and subsequently by the metal-acetylide. A recurrent limitation in A^3 coupling chemistry arises from the propensity of aliphatic aldehydes to undergo self-condensation via enolate formation, ultimately generating aldol-type dimers and trimers. This competitive pathway diverts the carbonyl substrate from the productive catalytic cycle and significantly compromises the overall efficiency of the transformation. For this reason, aldehydes with low enolization potential are generally preferred. Mechanistically, the extent of trimerization correlates with the degree of enolate stabilization and with the ability of the catalytic system to suppress enolization. Notably, this undesired process is markedly less pronounced in the presence of Ag(I) and Au(I/III) catalysts than with their Cu(I) counterparts. This difference is commonly attributed to the higher soft Lewis acidity of Ag(I) and Au(I), which favors coordination to the iminium or alkyne π -system rather than promoting deprotonation at the α -position of the aldehyde. As a result,

silver and gold catalysts more effectively maintain the aldehyde within the productive manifold of iminium formation and subsequent acetylide addition^[11].

The use of metal complexes has become essential to addressing two major limitations associated with simple metal salts. First, salts often fail to maintain catalytic activity over time, as they are prone to reduction to the corresponding metallic species through pathways induced by reducing agents, light, or thermal activation. Second, they do not provide access to a chiral catalytic environment^[8]. The introduction of ligands around the metal center ensures a controlled spatial arrangement of the reactive partners during the key steps of the catalytic cycle through specific interactions with the active sites. This coordination not only enhances the stability of the catalyst under reaction conditions but also improves its resistance to degradation pathways and enables its use over multiple catalytic cycles. The incorporation of N-heterocyclic carbene (NHC) ligands has proven particularly advantageous in both the catalytic and precatalytic stages^[15], most notably due to the substantial increase in thermal stability imparted by these strongly σ -donating ligands. The first application of NHC–Ag(I) complexes in A^3 coupling reactions was reported by Wang in 2008^[16] (Scheme 8) demonstrating a clear superiority over the corresponding silver halides.



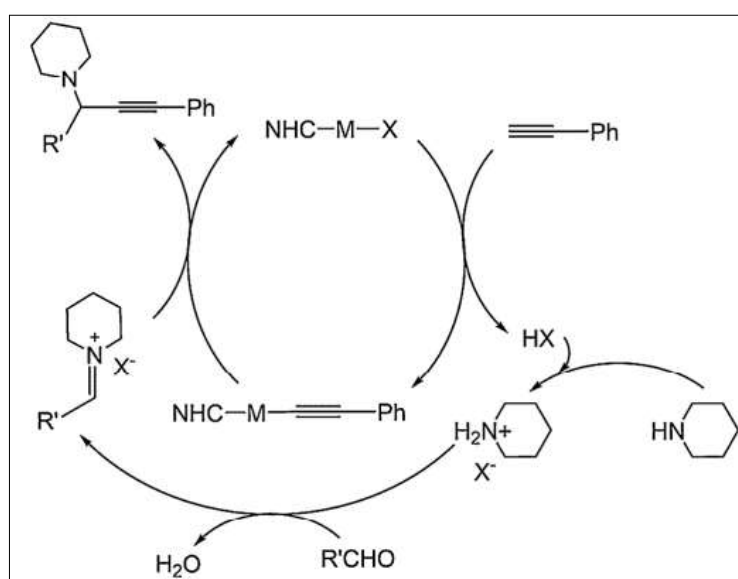
Scheme 8 – First A^3 synthesis carried out with NHC–Ag(I) complexes

In general, NHC–Au(I) and NHC–Ag(I) complexes afford superior A^3 coupling reaction outcomes in water compared to organic solvents^[17]. Several solvents are considered unsuitable for this transformation: dichloromethane, for example, can interfere with the Au(I) center by competing with the alkyne for coordination. More broadly, chlorinated solvents may release chloride ions under reaction conditions; these ions bind strongly to the metal center and significantly diminish its catalytic activity^[18, 19].

For NHC–Au(I)–X and NHC–Ag(I)–X complexes, the nature of the X[–] ligand plays a pivotal role in determining catalytic performance, particularly during the coordination of the unsaturated substrate. The electronic and steric properties of the anion influence both the formation of the active species and the ability of the metal center to engage in π -activation of the alkyne or coordination with iminium intermediate, thereby modulating the overall efficiency of the catalytic cycle^[20]. Navarro observed that when the silver complex was synthesized using acetate rather than a halide as the anionic ligand, catalytic activity increased markedly for both aliphatic and aromatic aldehydes, including otherwise unreactive ones, as well as toward linear and cyclic secondary aliphatic amines and both aliphatic and aromatic terminal alkynes^[21]. This behavior suggests that an anionic ligand with low coordinating ability facilitates the interaction between the metal center and the alkyne substrate, although the precise mechanistic rationale remains only partially understood^[22]. Silver salts are well known to form stable σ -acetylide species; however, these Ag–C $\equiv$ C bonds are often too stable to allow efficient nucleophilic addition to the aldehyde, rendering the acetylide insufficiently reactive. In contrast, silver complexes bearing strongly coordinating ligands capable of π -interactions can weaken the Ag–C bond by altering the electronic environment of the metal center. This modulation enhances the lability of the acetylide and promotes its addition to the carbonyl group. Such complexes exhibit significantly improved performance in aqueous media, whereas the use of organic solvents typically results in diminished yields, likely due to reduced acetylide lability and less favorable coordination equilibrium^[11]. In support of this mechanistic hypothesis, Li and co-workers reported in 2005^[23] that A³ coupling reactions conducted in water could also proceed efficiently using silver complexes bearing phosphine ligands. The proposed rationale is that strongly electron-donating phosphines increase the electron density at the silver center, thereby weakening the σ -acetylide Ag–C bond intermediate. This enhanced lability facilitates nucleophilic addition to the aldehyde. Silver-catalyzed A³ reactions are particularly effective even with aliphatic aldehydes and coupling partners such as anilines and ketones. Interestingly, in the absence of the phosphine ligand, the A³ coupling proceeds normally, whereas in its presence the reaction shifts predominantly toward aldehyde–alkyne coupling. This observation suggests that alternative reaction pathways may become competitive under ligand-modified conditions, and that the formation of products other than the canonical A³ adduct cannot be excluded.

Consistent with mechanistic proposals formulated for related transformations, eg. the Sonogashira coupling, the Barbier–Grignard type addition, and the Mannich reaction, it is generally accepted that the central metal engages in a π -interaction with the alkyne, thereby promoting the in situ formation of the corresponding metal acetylide. This activation step increases the nucleophilicity of the $C\equiv C$ fragment and channels it into the productive catalytic cycle. The reaction then proceeds through the nucleophilic addition of the metal–acetylide to the iminium intermediate, followed by the regeneration of the active metal complex (Figure 2)

[24].



Scheme 9 – Proposed reaction mechanism for the A^3 catalysis

The mechanistic pathway can be deconvoluted into several discrete elementary steps:

- π -activation of the terminal alkyne: the metal complex initially engages the alkyne through π -coordination, generating an activated $M\cdots(\eta^2-C\equiv C)$ adduct that primes the substrate for deprotonation.
- Base- or ligand-assisted deprotonation and formation of the σ -acetylide: the terminal proton is abstracted either by an external base or by a basic ligand within the coordination sphere, yielding the corresponding σ -acetylide. This step constitutes the formal $M-C(sp)$ bond-forming event in situ. This proton-transfer event forces the complex to reorganize its coordination environment, creating a vacant or more weakly

bound site that facilitates the interaction between the activated alkyne and the leaving ligand.

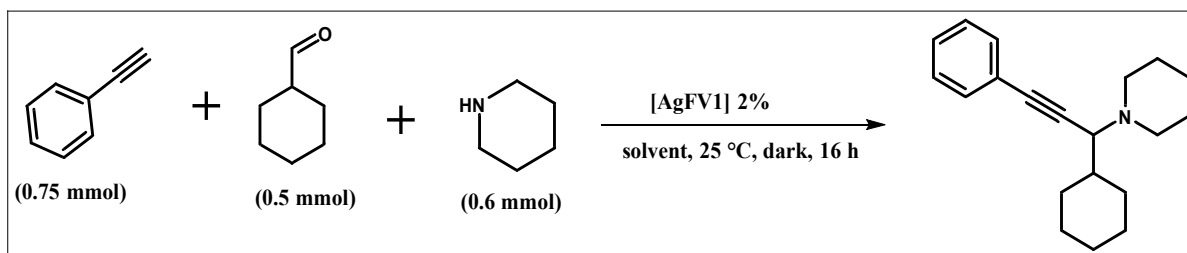
- Structural reorganization as a precatalytic feature: the metal complex adjusts its geometry and ligand distribution to promote efficient σ -acetylide formation and to enable subsequent engagement of the unsaturated substrate. In systems where the catalyst exists in its bis-ligated form, the nature of the leaving ligand becomes a critical factor. Its ability to reorganize, accept a proton, and stabilize a transient high-energy structure directly influences the efficiency of σ -acetylide formation. In this context, ligands capable of acting as internal proton acceptors are particularly advantageous: upon deprotonation of the terminal alkyne, they can transiently bind the proton and subsequently dissociate more readily, providing the necessary coordinative lability for substrate activation. The presence of such ligands eliminates the need for external bases and ensures that the complex can be fully regenerated after fulfilling its role in the proton-transfer step. Moreover, the solvent may also participate in this process; protic solvents such as water can themselves be protonated, engaging in proton-shuttling equilibrium or assisting in ligand dissociation. This additional pathway further contributes to the dynamic reorganization of the coordination sphere, facilitating the transition from the bis-ligated precatalyst to the catalytically competent acetylide-bearing species. Once the alkyne coordinates to the metal center, a partial redistribution of electron density occurs within the complex. Ligands capable of efficiently delocalizing this additional electron density contribute to the stabilization of the newly formed activated species. In the context of a potential substitution step, ligands exerting a pronounced trans-influence can facilitate the process by weakening the bond to the trans-disposed leaving group. This effect promotes a more facile structural reorganization of the complex, effectively lowering the energetic barrier associated with ligand exchange. Similarly, ligands that stabilize the transition state accelerate the reaction by enhancing σ -donation to the metal center when other ligands become less effective in the rearranged geometry, or by delocalizing the electron density transferred from the coordinated alkyne. Through these combined electronic effects—trans-influence, charge delocalization, and modulation of σ/π interactions, the complex becomes more prone to undergo substitution and to progress efficiently along the catalytic cycle.

- Proton transfer to the amine and generation of the iminium salt: the proton removed from the alkyne is transferred to the secondary amine, promoting iminium ion formation via condensation with the aldehyde, followed by the elimination of water. The resulting iminium ion serve as the electrophilic partner in the C–C bond-forming step. In the case of paraformaldehyde and benzaldehyde, the terminal alkyne adds to the corresponding iminium ion^[25], whereas with cyclohexancarboxaldehyde the addition may instead occur at the corresponding secondary imine.
- Nucleophilic addition of the metal–acetylide to the iminium intermediate and catalyst regeneration: the catalytic sequence concludes with the nucleophilic addition of the metal–acetylide to the electrophilic carbon of the iminium ion, releasing the propargylamine product. This C–C bond-forming step is typically followed by protonolysis or ligand exchange, which displaces the propargylamine and restores the catalytically active metal species. The departure of the product, often rendered more labile by the electronic reorganization accompanying the addition step, facilitates full regeneration of the complex, thereby closing the catalytic cycle.

After outlining the key factors governing this reaction, it is possible to proceed with the study carried out on a series of organometallic complexes, which were evaluated as catalysts in the A³ multicomponent reaction.

7.3 Preliminary evaluation of the catalytic activity

To identify the most suitable conditions for the newly synthesized set of complexes, a preliminary screening of reaction solvents was carried out to assess the catalytic performance of the silver and gold organometallic complexes. The AgFV1 complex was selected as a model catalyst, and cyclohexylcarboxaldehyde was initially chosen as the reference substrate for this initial optimization. The catalytic conditions adopted for the evaluation were as follows (Scheme 10):



Scheme 10 – Catalytic conditions adopted in screening of solvents

Using these substrates, a series of tests was carried out in different solvents, and the corresponding results are reported in the table below (Table 1):

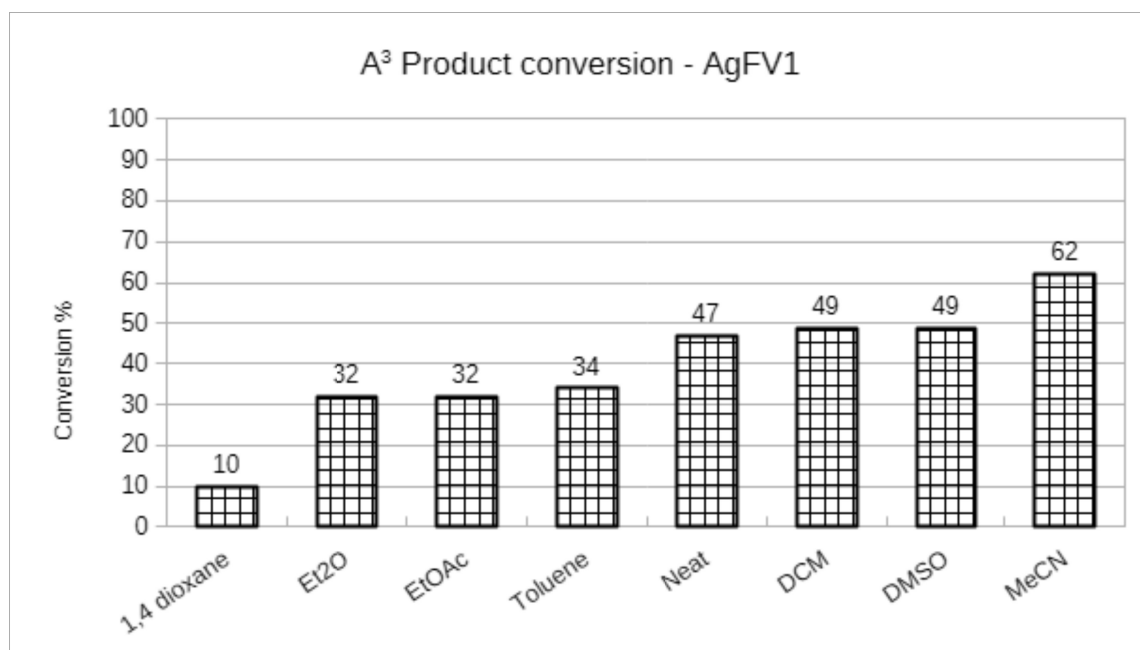


Figure 3 – Catalytic conversions achieved in different solvents

The conversion was determined using 2-bromomesitylene (1.00 equivalent relative to the aldehyde substrate) as an internal standard. From the collected data, a clear dependence of the catalytic activity on the nature of the solvent can be observed, with acetonitrile emerging as the medium in which the complex displays the highest activity among the solvents tested. Subsequently, the influence of the alkynesulfonate chain length on the catalytic performance was evaluated by comparing the AgFV1 and AgFV2 complexes (Figure 4).

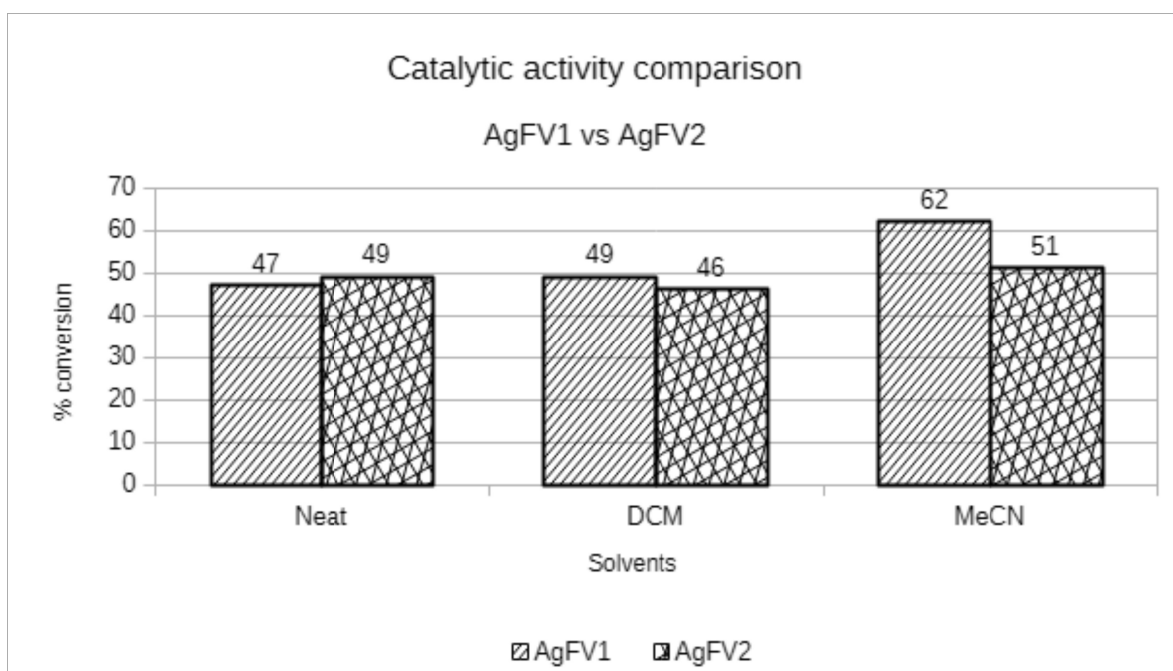


Figure 4 – Evaluation of sulfonate chain length effect on catalysis

A series of evaluations was carried out under the three most favorable conditions identified for the multicomponent reaction. From this comparison, it emerges that the catalytic activity does not differ significantly under neat conditions or in DCM, whereas, a higher activity is observed in acetonitrile for the complex bearing the propanesulfonate chain. These results suggest that, for this specific aldehyde substrate, the catalytic activity is essentially independent of the chain length, as evidenced by the tests performed under solvent-free conditions. The enhanced activity recorded in acetonitrile further underscores the strong dependence on the reaction medium, which is most likely related to the solubility of the species involved. At this stage, a comparison was made by changing the aldehyde substrate (Scheme 11). In line with previous literature reports, benzaldehyde was selected as an aromatic substrate, which is well known to be poorly reactive in this type of transformation, together with paraformaldehyde, the polymeric form of formaldehyde. The latter was chosen to assess whether catalytic activity could be maintained when the aldehyde is employed in its polymeric form. Like benzaldehyde, paraformaldehyde is generally considered challenging under these conditions, and only a few examples in the literature describe its use for the synthesis of propargylamines.

cyclohexylcarboxaldehyde as the model substrate, the study was redirected toward paraformaldehyde. The aim was to demonstrate the possibility of employing polymers analogous to polyoxymethylene, or its derivatives, in depolymerization-driven synthetic processes, with minimal or no pre-treatment required.

7.3.1 Materials and methods

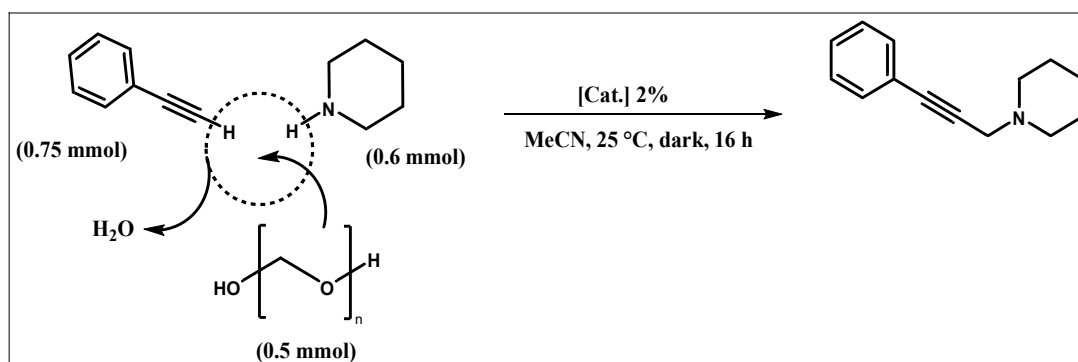
Solvents and reagents opted for syntheses were purchased from TCI Chemicals, Fluorochem, Sigma-Aldrich and were used as received. Each reaction was carried out in a preheated 4 mL glass vial to exclude moisture. Benzaldehyde was purified on silica 70-230 mesh before use (P.E.:EtOAc 9:1). Catalytic conversion yields reported are averaged on six results. Products obtained after each catalysis were detected via ^1H NMR spectroscopy and the degree of conversion was calculated by integrating the ^1H NMR signal at δ 6.89 of the two protons on aromatic carbons of 2-Bromomesitylene used as internal standard and of protons on the carbon in α to acetylenic group of propargylamine: at δ 3.43, 2H for N-(3-phenyl-2-propynyl)piperidine, at δ 3.11, 1H for 1-(1-cyclohexyl-3-phenyl-2-propynyl) piperidine, at δ 4.79, 1H for N-(1,3-diphenyl-2-propynyl)piperidine in CD_2Cl_2 , respectively. Spectra were acquired on Varian 400 (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR).

Procedure

In a 4 mL vial, the following reagents were added in sequence: phenylacetylene (0.0766 g, 0.75 mmol, 82 μL), piperidine (0.0511 g, 0.60 mmol, 59 μL), and the aldehyde (paraformaldehyde: 0.0150 g; benzaldehyde: 0.0531 g; cyclohexanecarbaldehyde: 0.0561 g) in a total volume of 2 mL of solvent. After stirring for a few minutes, the catalyst under investigation was introduced in an amount corresponding to 2 mol% relative to the aldehyde substrate. The vials were covered with aluminum foil and stirred at 25 $^\circ\text{C}$ for 16 hours. Upon completion, 2-bromomesitylene (0.0995 g, 76.5 μL) was added as an internal standard, and the catalytic conversion was estimated by comparing the intensity of the internal standard with the signals corresponding to the reaction products.

7.3.2 Results

To broaden the evaluation of the catalytic activity, the remaining synthesized complexes were tested (Scheme 12), focusing on the gold and silver complexes bearing the propylsulfonate functionality.



Scheme 12 – Catalytic conditions with paraformaldehyde

The conversion values obtained for the various synthesized complexes are reported (Figure 6).

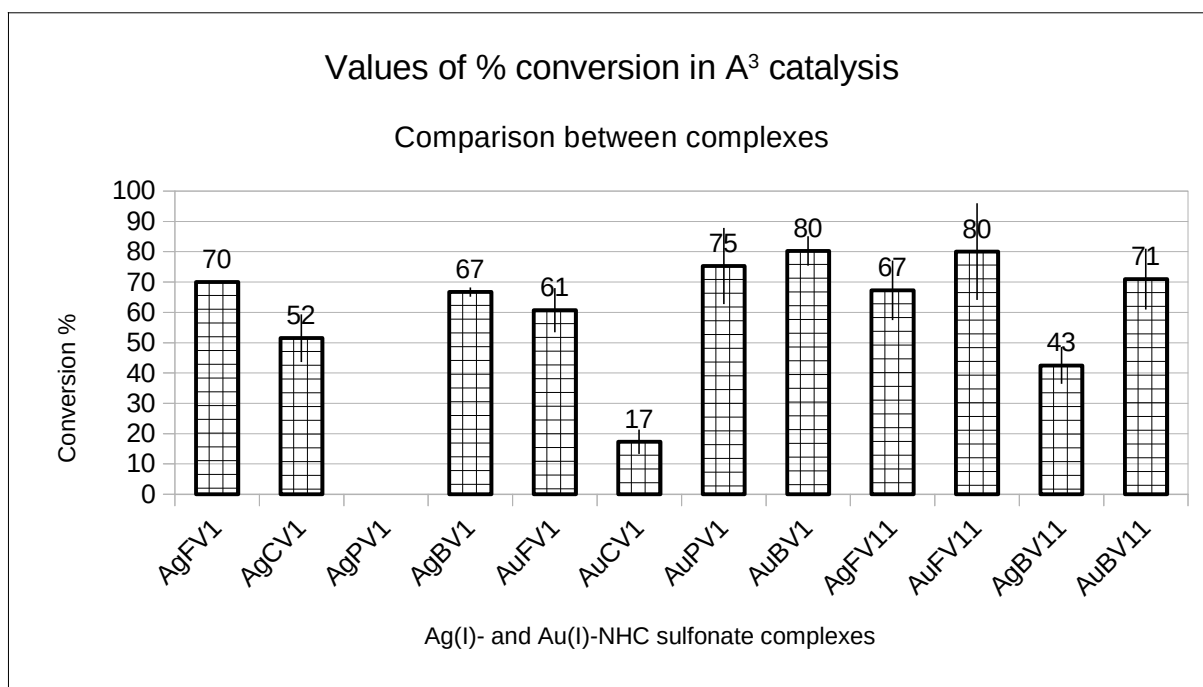


Figure 6 – Catalytic conversions of tested Ag(I)- and Au(I)-NHC complexes

Analysis of the collected data is that the measurements display an inconsistent level of precision. This indicates that the procedure is affected by statistical fluctuations, likely arising from two main factors: the intrinsic instability of the complexes over time due to hydrolysis, which regenerates the zwitterionic salt form and consequently reduces both the purity and reactivity of the catalyst. Nevertheless, the collected results still reveal a discernible trend in catalytic activity between the Ag(I)- and Au(I)-based compounds. Following the observed trend, the increase in metal acidity from Ag(I) to Au(I) leads to a decrease in the recorded conversion to the product (Figure 7):

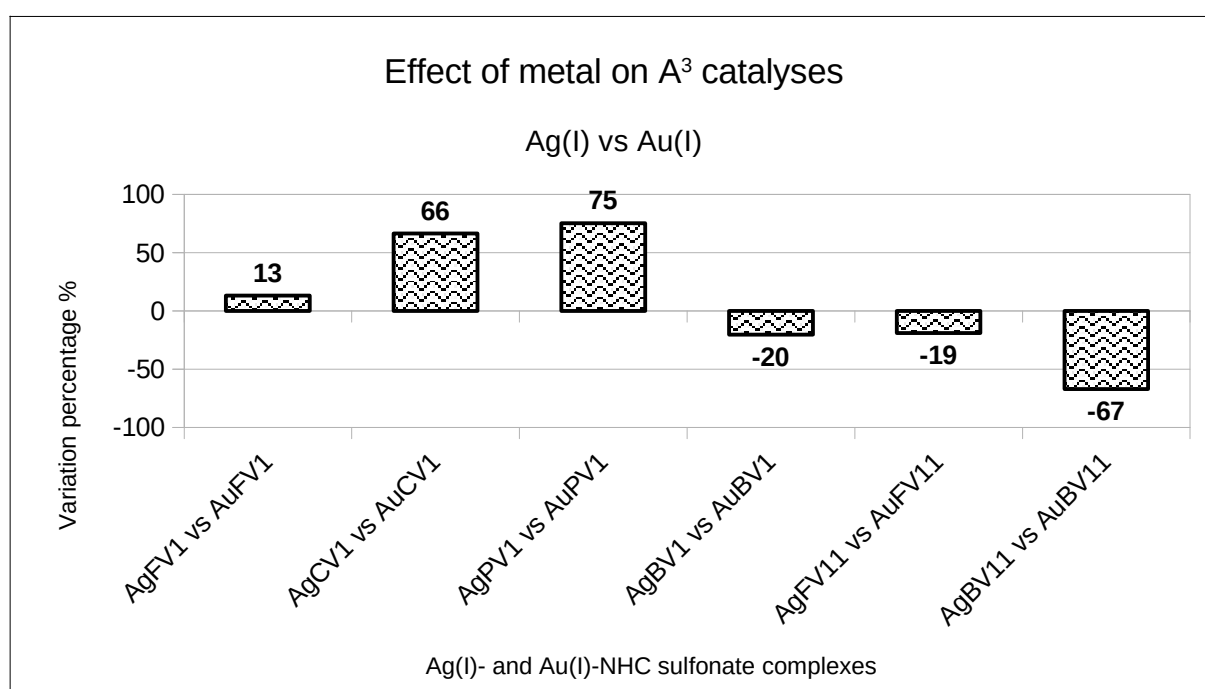


Figure 7 – Comparison between Ag(I)- and Au(I)-NHC tested complexes

In principle, higher acidity should be beneficial, as it facilitates the formation of the acetylide from the alkynyl substrate. However, this also results in a reduced nucleophilicity of the acetylide itself, which may in turn diminish the ability of the complex to mediate the catalytic process between the substrates. This hypothesis is further supported by the comparison of the catalytic activity observed for the Ag/AuFV1 and Ag/AuCV1 pairs. In the first case, no substituents are present at the C4,5 positions of the ring; therefore, the variation of the metal center is the only differing parameter. In contrast, in the Ag/AuCV1 pair, the presence of chlorine substituents imparts a significant electron-withdrawing effect on the structure, increasing the Lewis acidity and consequently reducing the catalytic activity of the complex.

For the subsequent structures, however, the trend reverses: changing the metal center results in an increase in the observed catalytic activity. This behavior is clearly illustrated by the Ag/AuPV1 and Ag/AuBV1 pairs. In both cases, an enhancement in catalytic performance is observed, which may be rationalized by a more favorable electronic match between the metal acidity and the electronic properties provided by the carbene ligand. However, the catalytic activity observed is not significantly different from that of the other structures, suggesting that a compensation likely occurs between the effects imparted by the acidity of the metal center and those arising from the ligand. The value obtained for AgPV1 is anomalous within the series: although a higher catalytic activity was expected compared to the other complexes, its actual activity could not be reliably determined. It is possible that, under the reaction conditions, the complex undergoes a degradation or inhibitory process; however, this aspect has not yet been investigated further, and additional studies would be required to clarify the origin of this lack of activity. In contrast, AuPV1 exhibits a higher catalytic activity than its silver analogue, and the recorded value provides further insight into the decisive role of the electronic match between the metal and the ligand. Its activity exceeds that of AuFV1 due to the stronger mesomeric effect exerted by the phenyl groups, yet remains comparable to that of AgFV1, the metal center of which is less acidic. The Ag/AuFV11 and Ag/AuBV11 complexes provide a clearer insight into the role of the benzhydryl group (Figure 8):

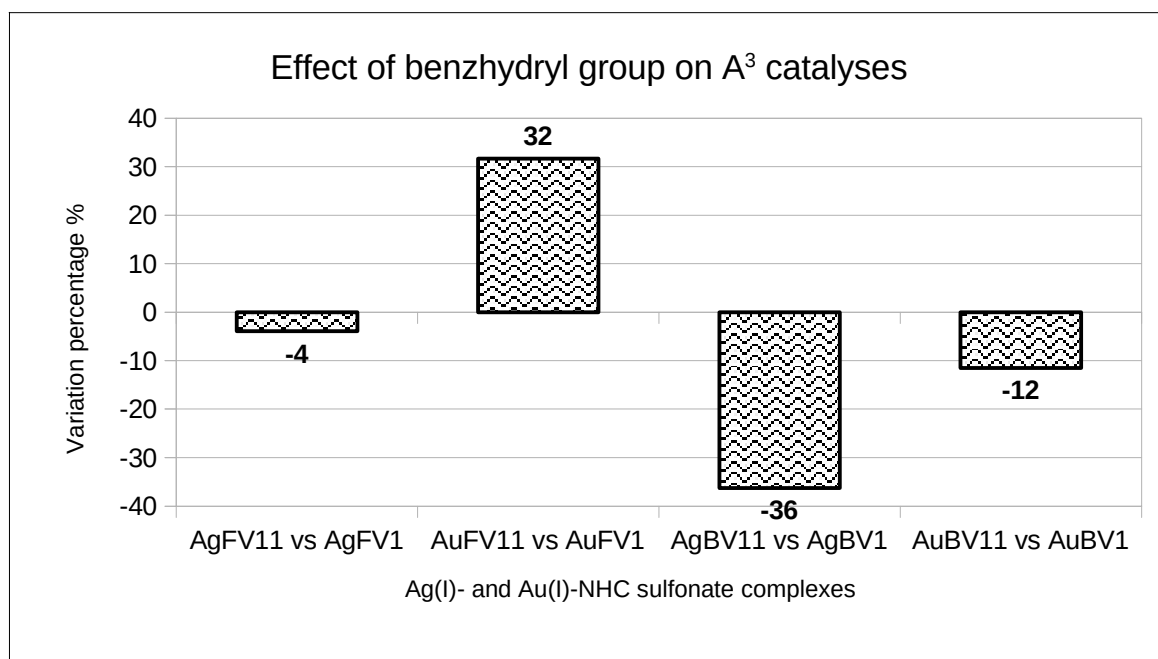


Figure 8 – Comparison between benzhydryl and benzyl bearer Ag(I)- and Au(I)-NHC tested complexes

As previously discussed, the properties of the metal-carbene bond in an imidazolylidene NHC complex are strongly influenced by the nature of the N-substituents. The benzhydryl group contains one additional phenyl ring compared to the benzyl group, imparting a stronger inductive and mesomeric donating effect through the methine ($-\text{CH}-$) group. Despite this, only AuFV11 appears to benefit from the presence of this group, whereas the overall trend indicates a decline in catalytic activity. A pronounced effect is again observed in the presence of the benzimidazole scaffold. No further investigation was carried out on this point, but it is plausible that divergent effects arise between the benzhydryl system and the fused aromatic framework of the benzimidazole core, both electronically and sterically.

Regarding the influence exerted by the substituents on the imidazole backbone, a general decrease in activity can be observed across most complexes (Figure 9), with the exception of the gold derivatives AuPV1 and AuBV1. In the case of the silver-based complexes, the presence of the benzhydryl group and other electron-withdrawing substituents leads to a reduction in catalytic activity, with a particularly marked decrease observed for AgCV1.

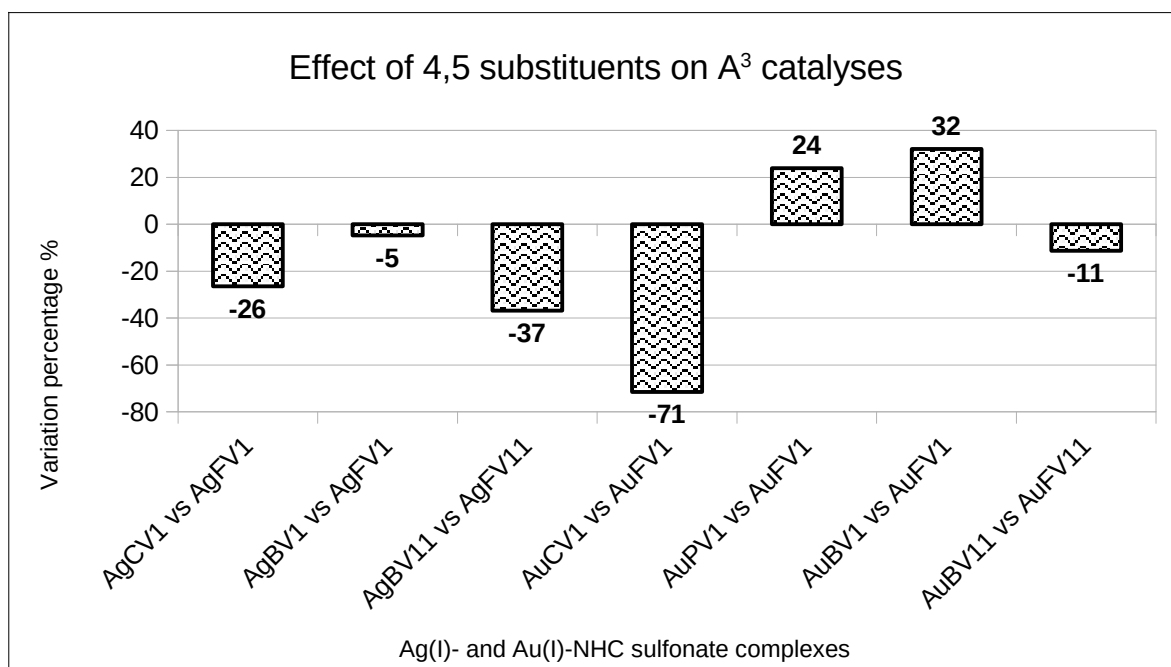
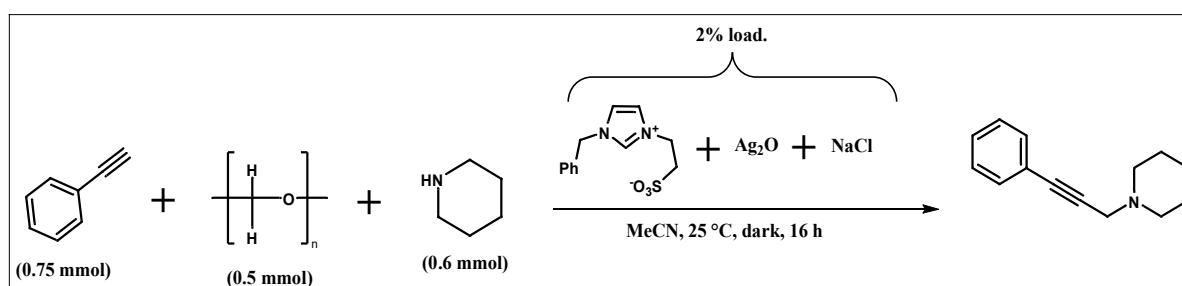


Figure 9 – Comparison between butan- and propansulfonate chain bearer Ag(I)- and Au(I)-NHC tested complexes

7.4 A³-coupling tests using AgFV1's synthetic reactants – results and discussions

During the catalytic investigations, a control experiment was designed to determine whether the use of the pre-formed complex was essential for the observed catalytic activity. To this end, a reaction system was prepared containing all the reagents required for the synthesis of the propargylamine, but instead of adding the isolated complex, the individual components necessary for its in situ formation were introduced in the corresponding proportions (Scheme 13).



Scheme 13 – Catalytic conditions adopted to validate the activity of the complex structure

The results showed a significantly higher conversion compared to the reaction mediated by the pre-formed complex. Additional control tests were then carried out, excluding the imidazolium salt and, separately, excluding the halide salt; in both cases, identical catalytic values were recorded. This revealed that, regardless of the presence of the ligand or the complexed structure, silver oxide (Ag_2O) is capable of catalyzing the A³ reaction under the conditions described above (Figure 10).

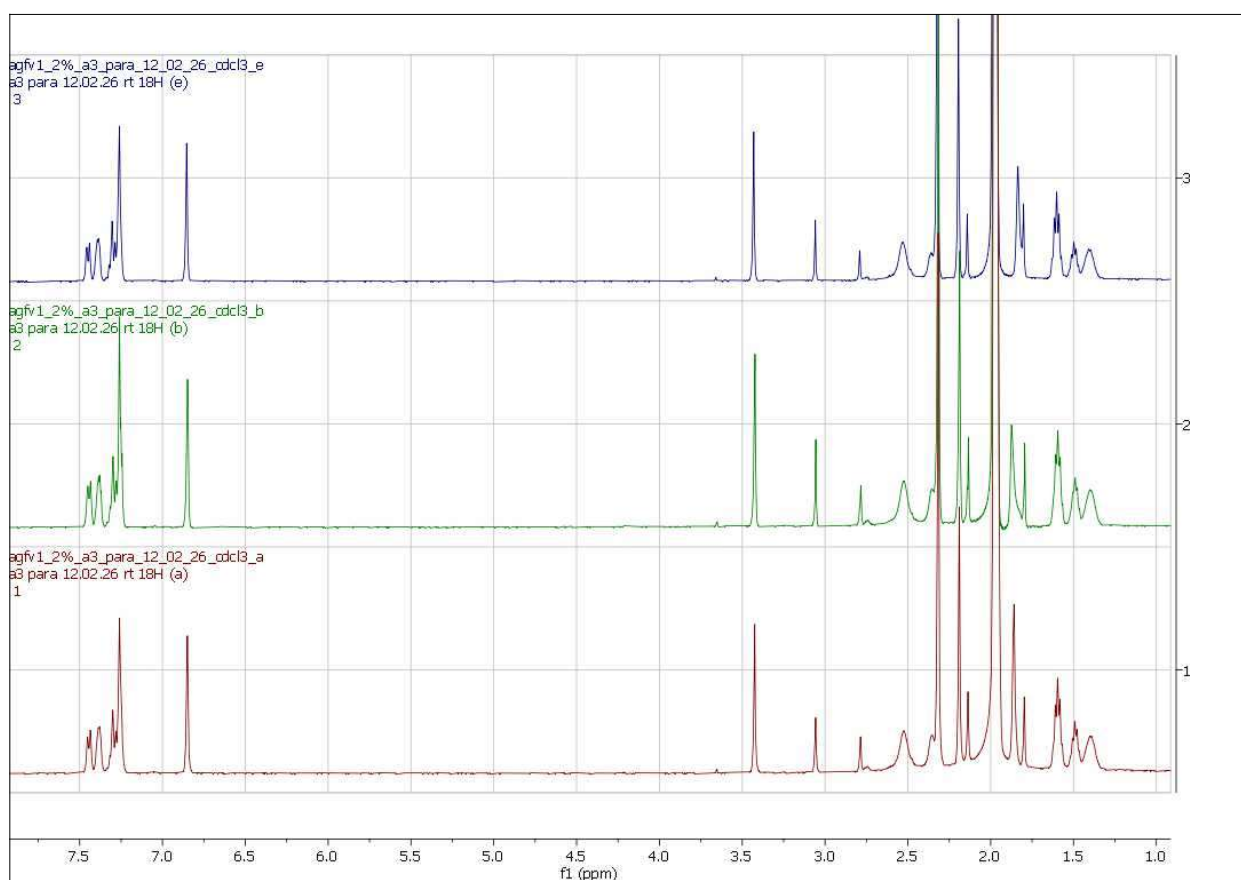


Figure 10 – ^1H NMR recorded on different conditions: 1) $\text{Ag}_2\text{O} + \text{FVI} + \text{NaCl}$; 2) $\text{Ag}_2\text{O} + \text{NaCl}$; 3) Ag_2O

A survey of the scientific literature on catalyzed A^3 couplings shows that reports involving paraformaldehyde as the aldehyde component are limited. Several studies describe unsuccessful attempts using this reagent, however, the catalytic activity of silver oxide in A^3 reactions employing paraformaldehyde has been highlighted. Notably, Ag_2O is typically reported in nanoparticulate form rather than as a standard commercially available reagent^[26].

7.4.1 Materials and methods

Solvents and reagents opted for syntheses were purchased from TCI Chemicals, Fluorochem, Sigma-Aldrich and were used as received. Each reaction was carried out in a preheated 4 mL glass vial to exclude moisture. Catalytic conversion yields reported are averaged on two results. Products obtained after each catalysis were detected via ^1H NMR spectroscopy and the degree of conversion was calculated by integrating the ^1H NMR signal at δ 6.89 of the two protons on aromatic carbons of 2-Bromomesitylene used as internal standard and of protons on the carbon at δ 3.43, 2H for N-(3-phenyl-2-propynyl)piperidine) in CD_2Cl_2 . Spectra were acquired on Varian 400 (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR).

Procedure

In a 4 mL vial, the following reagents were added in sequence: phenylacetylene (0.1532 g, 1.5 mmol, 164 μL), piperidine (0.1022 g, 1.2 mmol, 118 μL), and paraformaldehyde (0.0300 g; 1.0 mmol) in a total volume of 2 mL of MeCN. After stirring for a few minutes, FV1 (0.0056 g, 0.02 mmol), Ag_2O (0.0023 g, 0.01 mmol) and NaCl (0.0012 g, 0.02 mmol) were added in order to introduced an amount corresponding to 2 mol% of in situ formed complex, relative to the aldehyde substrate. The vials were covered with aluminum foil and stirred at 25 $^\circ\text{C}$ for 16 hours. Upon completion, 2-bromomesitylene (0.1991 g, 152 μL) was added as an internal standard, and the catalytic conversion was estimated by comparing the intensity of the internal standard with the signals corresponding to the reaction products. A total of six run was done:

Run	FV1 (mmol)	Ag_2O (mmol)	NaCl (mmol)	Yield %
1	0.02	0.01	0.02	86
2	0.02	0.01	0.02	85
3	null	0.01	0.02	87
4	null	0.01	0.02	91
5	null	0.01	null	88
6	null	0.01	null	87

During our investigation, tests were performed to verify the catalytic activity previously attributed to silver oxide, and results consistent with the literature were observed when the reaction system was subjected to conditions analogous to those used for the complexes. The catalytic performance of Ag₂O proved to be superior, yielding approximately 90% conversion in the cases examined, compared to the synthesized complexes.

Other silver salts, such as AgOAc and AgNO₃, as well as Tollens' reagent, were also tested, but none exhibited catalytic activity comparable to that of Ag₂O.

Procedure

In a 4 mL vial, the following reagents were added in sequence: phenylacetylene (0.1532 g, 1.5 mmol, 164 μ L), piperidine (0.1022 g, 1.2 mmol, 118 μ L), and paraformaldehyde (0.0300 g; 1.0 mmol) in a total volume of 2 mL of MeCN. After stirring for a few minutes, AgNO₃ (0.0034 g, 0.02 mmol), AgOAc (0.0034 g, 0.02 mmol) and Ag₂O dissolved in NH₄OH (0.0023 g, 0.01 mmol) were added in order to introduced an amount corresponding to 2 mol% of silver(I) compound relative to the aldehyde substrate. The vials were covered with aluminum foil and stirred at 25 °C for 16 hours. Upon completion, 2-bromomesitylene (0.1991 g, 152 μ L) was added as an internal standard, and the catalytic conversion was estimated by comparing the intensity of the internal standard with the signals corresponding to the reaction products. A total of three run was done:

Run	AgNO ₃ (mmol)	Ag ₂ O in NH ₄ OH (mmol)	AgOAc (mmol)	Yield %
7	0.02	null	null	nd
8	null	0.01	null	nd
9	null	null	0.02	nd

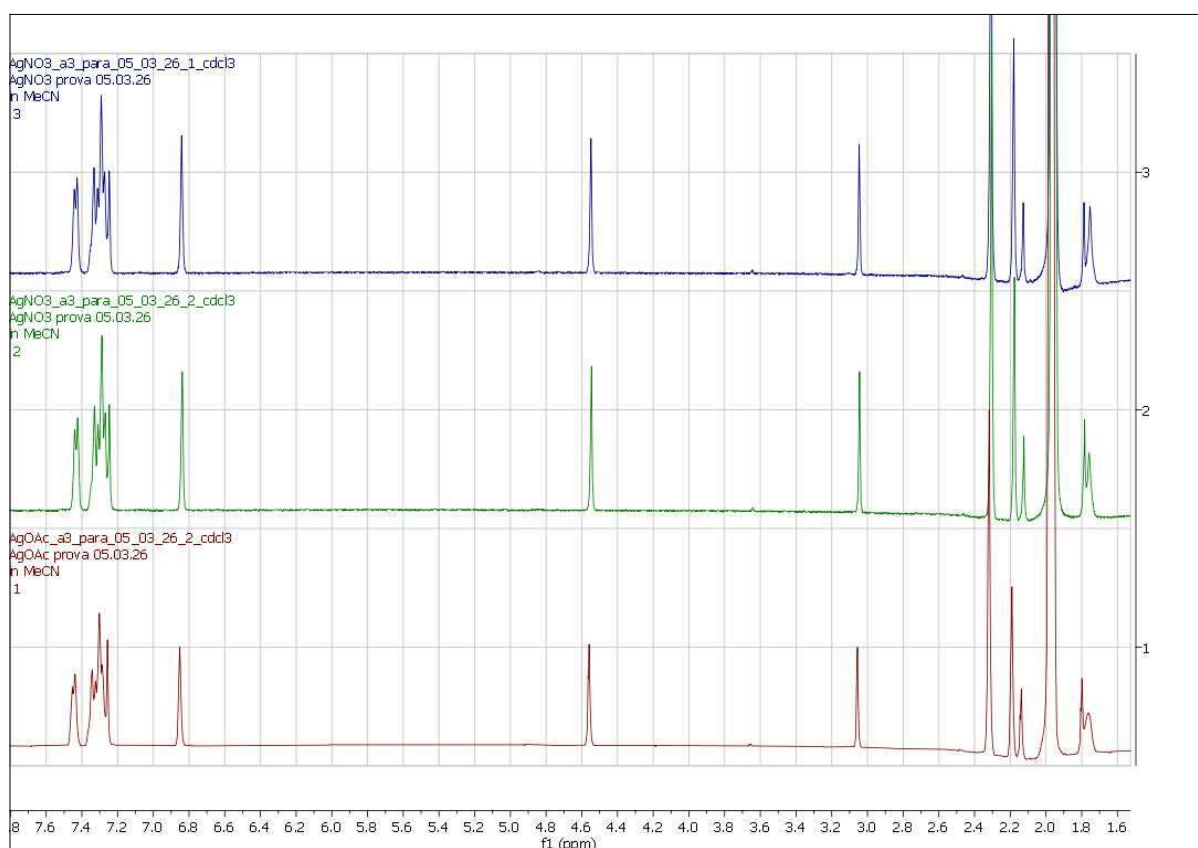


Figure 11 – ^1H NMR recorded on different conditions: 1) AgNO_3 ; 2) Ag_2O (Tollens); 3) AgOAc

Although this outcome appears unfavorable when compared to the catalytic performance of the tested complexes, it is nonetheless noteworthy that the use of Ag_2O as a catalyst, excluding the formation of nanostructured species, combined with paraformaldehyde may offer valuable insights for future investigations into the depolymerization of polymeric chains analogous to polyoxymethylene-like chains. Further studies will be conducted to assess the applicability of silver oxide in other contexts. In light of these considerations, it is worth highlighting that, despite their lower activity, the synthesized complexes still exhibited a promising catalytic response toward a substrate that remains poorly explored, such as paraformaldehyde.

Looking ahead, future work will extend the catalytic evaluation by examining the reactivity of different terminal alkynes and amines, thereby broadening the substrate scope of investigation for this class of complexes.

7.5 Carboxylation of terminal alkynes: mechanistic and synthetic considerations

Coupling reactions represent a widely employed and highly refined class of transformations in synthetic chemistry due to their ability to forge bonds that are notoriously difficult to obtain through conventional methods or protracted multistep sequences. Among these, couplings involving Csp centers are particularly prominent, as they require preserving the integrity of unsaturated functionalities while simultaneously forming a new bond to an sp-hybridized carbon. Such reagents are frequently generated as metal acetylides, utilizing transition metals (TM-acetylides such as organocopper species), p-block metals (Al, Zn), or alkali metals (e.g., Grignard-type RCCMgX). More recent approaches rely on functionalizing the acetylenic moiety with suitable functional groups, such as TMS or boronic acid derivatives B(OR)_3 . Within this context, propiolic acid derivatives offer significant advantages: the leaving group is $-\text{COOH}$, which is eliminated via decarboxylation upon heating, producing CO_2 that escapes the reaction environment as a gas, leaving no additional species that may interfere with the process or require tedious purification. The release of CO_2 provides a powerful thermodynamic driving force, thereby promoting product formation. In some cases, no metals or additional reagents are required, and the reaction progress can be conveniently monitored by GC-MS or LC-MS owing to the carboxylic functionality, which imparts a distinct retention behavior useful for tracking consumption of the starting material^[27].

In recent years, the synthesis of these species has attracted considerable interest within the framework of environmentally sustainable methodologies, particularly those employing carbon dioxide as a C1 synthon for the preparation of this class of compounds. These strategies can be categorized as short- to medium-term CO_2 fixation, depending on substrate stability. Owing to their versatility and relevance in fine-chemical synthesis, modern approaches increasingly aim to incorporate CO_2 through protocols that are both efficient and atom-economical^[28].

One of the main challenges associated with the use of gases as reagents is the volume-to-surface ratio between the substrate and the gaseous molecules with which it must interact. More precisely, it is the effective reaction volume, the spatial domain within which the reagents must collide in order to react, that becomes difficult to control. Gases inherently resist confinement within a defined volume, which is why pressure and temperature are often

manipulated to increase their solubility and effective concentration in the reaction environment. Ensuring that the reaction kinetics are maintained, it requires keeping the concentration of the gaseous reagent as close as possible to the stoichiometric or saturation requirements, typically by exploiting the pressure–temperature dependence to compress the gas. This often necessitates the use of autoclaves or pressurized vessels specifically designed to withstand such rigorous conditions. An alternative strategy to enhance the availability of a gaseous reagent is to dissolve it in a suitable solvent. According to Henry’s law, the solubility of a gas in a solvent is temperature-dependent, allowing estimation of the saturation level and enabling a homogeneous distribution of the gas without the need for high pressures^[29]. Another approach involves generating the gaseous reagent in situ. In this case, solid surrogates are utilized. These are typically more stable, easier to handle, and often more economical than the pure gas. Under specific conditions, the gaseous species is released either through a chemical reaction among components that do not interfere with the main transformation or through a thermally controlled physical process^[30].

In the case of carbon dioxide, the most common surrogates are carbonate derivatives which, upon reaching their decomposition temperature, release CO₂ locally within the reaction medium. The gas, once generated and contained within the reaction volume, can then react with the substrates present in the system. One drawback of this approach is the requirement for relatively large amounts of surrogate, since the amount of CO₂ released must still reach a threshold partial pressure to ensure sufficient reactivity.

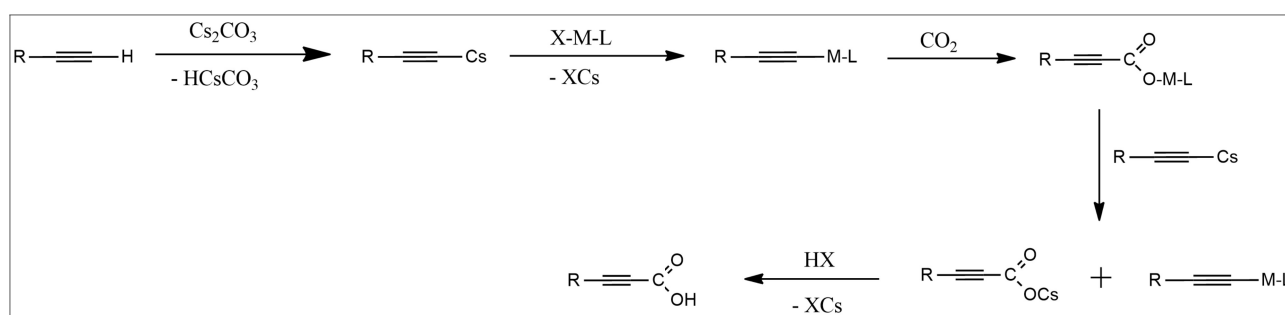
To overcome this limitation, recent research has focused on maximizing the exposure of carbon dioxide to potential active sites by incorporating the gas into high-surface-area materials inspired by zeolitic architectures, such as Metal-Organic Frameworks (MOFs), Zeolitic Imidazolate Frameworks (ZIFs), and related structures, and by employing heterogeneous catalytic systems that provide more robust and sustained activity. The goal is to achieve a balance between CO₂ availability and the physical parameters of the system, enabling the utilization of carbon dioxide under conditions approaching ambient pressure and temperature^[31].

Regarding the use of coniage-metal catalysts, the literature reports several key examples that have marked important milestones in the application of transition metals in this field^[32, 33]. Recently, our research group has developed a promising organometallic complex for carbon dioxide fixation aimed at the synthesis of propiolic acid derivatives^[34]. To expand this study to additional NHC–Ag(I) complexes, and further experiments were conducted using sulfonate-

based NHC derivatives. The proposed catalytic cycle, as reported in the literature, is outlined below.

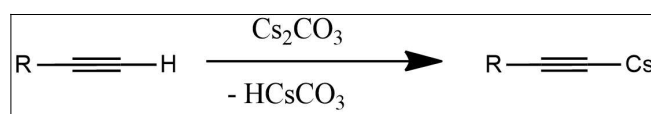
Catalytic cycle

Through a nucleophilic insertion process, a molecule of CO₂ is added to a terminal alkyne to afford the corresponding alkynoic acid (Scheme 14). The transformation is promoted by Ag(I) and Au(I) organometallic complexes, which serve as the active catalysts for the synthetic process. The steps outlined below are broadly consistent with the mechanistic pathways reported in the literature.



Scheme 14 – Teoretical catalytic steps proposed in literature explaining carboxylation at terminal alkynes

Step 1: Formation of the Cs–acetylide intermediate

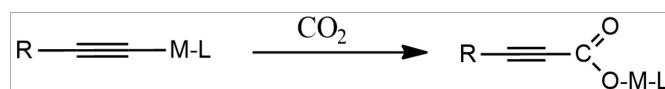


In this step, the terminal alkyne undergoes deprotonation of the acetylenic proton by a basic species to generate the corresponding acetylide, a nucleophile capable of attacking the electrophilic carbon atom of carbon dioxide. This initial stage requires three components: a species able to activate the unsaturated substrate to facilitate deprotonation, a base capable of abstracting the terminal proton, and a counterion that stabilizes the resulting acetylide, keeping it available in the reaction medium for the subsequent steps of the synthetic sequence. Ag(I) and Au(I) centers serve as Lewis acids to active the unsaturated substrate. Regarding the choice of base, the literature consistently reports cesium carbonate (Cs₂CO₃) as the most effective option for this class of reactions^[31, 35].

Step 2: Generation of the active catalytic species

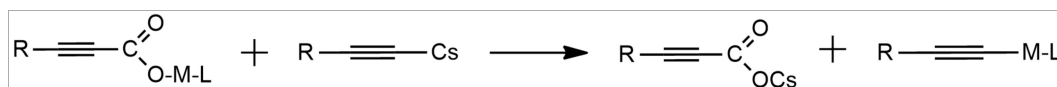
Once the putative active species has been generated, it reacts with the terminal alkyne to form the corresponding metal acetylide. In this phase, the catalyst must possess an available coordination site to accommodate the unsaturated substrate. This requirement is presumably fulfilled through the metathesis-driven formation of the cesium salt (CsX), which liberates the metal center and enables coordination of the alkyne. Although no experimental data are currently available to confirm this hypothesis, computational studies support this step as the most plausible scenario to rationalize the structure of the catalytic cycle and the nature of the species involved. Once the metal acetylide has been formed, the subsequent stage is the nucleophilic insertion of carbon dioxide.

Step 3: Insertion of carbon dioxide



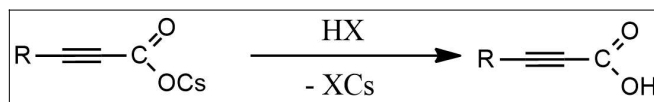
In this stage, carbon dioxide inserts into the C–M bond of the metal acetylide. Two parameters are central to this step: the electronic match between the nucleophilic character of the acetylide and the electrophilic carbon of CO₂, and the oxophilicity of the metal center, which is modulated by the ancillary ligand. Any factor that attenuates the nucleophilicity of the acetylide correspondingly reduces its reactivity. This effect is observed, for example, when electron-withdrawing substituents are present on the substrate, as they delocalize the electron density away from the acetylide center, thereby diminishing its ability to undergo nucleophilic attack at the CO₂ carbon.

Step 4: Generation of the cesium carboxylate and turnover of the catalyst



In this final stage of the catalytic sequence, following CO₂ insertion, the conjugate base of the propiolic acid is released through regeneration of the active species by reaction with a new carbonate equivalent, thereby closing the catalytic cycle. The resulting carboxylate anion can be stabilized by a cesium cation (Cs⁺), as proposed in most mechanistic models. This stabilization is crucial because it allows the cesium carboxylate to be formed as a discrete intermediate, which can subsequently be protonated to furnish the final propiolic acid derivative. The importance of employing cesium as the counterion becomes evident here: its strong affinity for the carboxylate oxygen, which exceeds that of the catalytic metal center, ensures efficient product capture and prevents inhibitory recoordination to the metal, thus facilitating catalyst turnover and product release.

Final Step: Protonation of the cesium carboxylate



In this final transformation, the cesium carboxylate undergoes acidic work-up to yield the protonated carboxylic acid, while cesium cation is displaced and converted into an easily isolable inorganic salt. This typically occurs upon treatment with a strong hydrohalic acid in aqueous medium, leading to the formation of a poorly soluble CsX salt that precipitates from the reaction mixture. The protonation step thus releases the final carboxylic product in its neutral form and simultaneously removes cesium from the organic phase, completing the overall synthetic sequence.

7.5.1 Results and Discussions

The carboxylation of the terminal alkyne was initially carried out under the conditions reported in the article previously published by our research group^[34]. As a first step, the AgFV1 complex was selected as a model structure to determine the optimal conditions for subsequent tests on the other synthesized complexes. Preliminary experiments were conducted in three aprotic polar solvents: DMSO, DMF, and MeCN. Although these are not the solvents with the highest CO₂ solubility, they are frequently reported in the literature as suitable media for the carboxylation of terminal alkynes. The experimental conditions employed were as follows.

7.5.2 Materials and methods

Solvents and reagents opted for syntheses were purchased from TCI Chemicals, Fluorochem, Sigma-Aldrich and were used as received. Each reaction was carried out in a 20 mL glass vial fitted with a rubber septum. Before use, the vial were kept in an oven at 120 °C overnight, allowing any trace of moisture to be expelled. K₂CO₃ and Cs₂CO₃ were crushed and kept in an oven at 120 °C for 4 hours before their use. Spectra were acquired on Varian 400 (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR) in CDCl₃. The acquisition on crude of reaction was done and compared with signals of reactant (phenylacetylene).

Procedure

In a pre-heated 20 mL vial, phenylacetylene (1 mmol, 0.1021 g), the base (1.2 equiv. relative to phenylacetylene), and AgFV1 (0.0138 g, 2 mol%) were added in 8 mL of solvent. The vial was sealed with a rubber septum, a needle was inserted down to the bottom of the vial, and carbon dioxide was bubbled through the mixture, maintaining a constant gurgling flow. The vial was then covered with aluminum foil and stirred at 25 °C. The various experiments performed are reported in the table below.

Run	Base (g)	Solvent	Time (hours)
1	K ₂ CO ₃ (0.2073)	DMF	6
2	K ₂ CO ₃ (0.2073)	DMF	24
3	Cs ₂ CO ₃ (0.4887)	DMF	24
4	K ₂ CO ₃ (0.2073)	DMSO	24
5	Cs ₂ CO ₃ (0.4887)	DMSO	24
6	K ₂ CO ₃ (0.2073)	MeCN	24
7	Cs ₂ CO ₃ (0.4887)	MeCN	24
8	K ₂ CO ₃ (0.2073)	Acetone	24
9	Cs ₂ CO ₃ (0.4887)	Acetone	24

At the end of the reaction, the mixture was diluted with water and the aqueous phase was acidified with 37% HCl until pH 2 was reached. The mixture was then transferred to a separatory funnel, and EtOAc was added to extract the organic phase. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Before purification of the crude residue, ¹H NMR analysis was performed to assess the presence of the desired product; however, under all tested conditions, no signals attributable to the expected acid (3-Phenylpropionic acid) were detected.

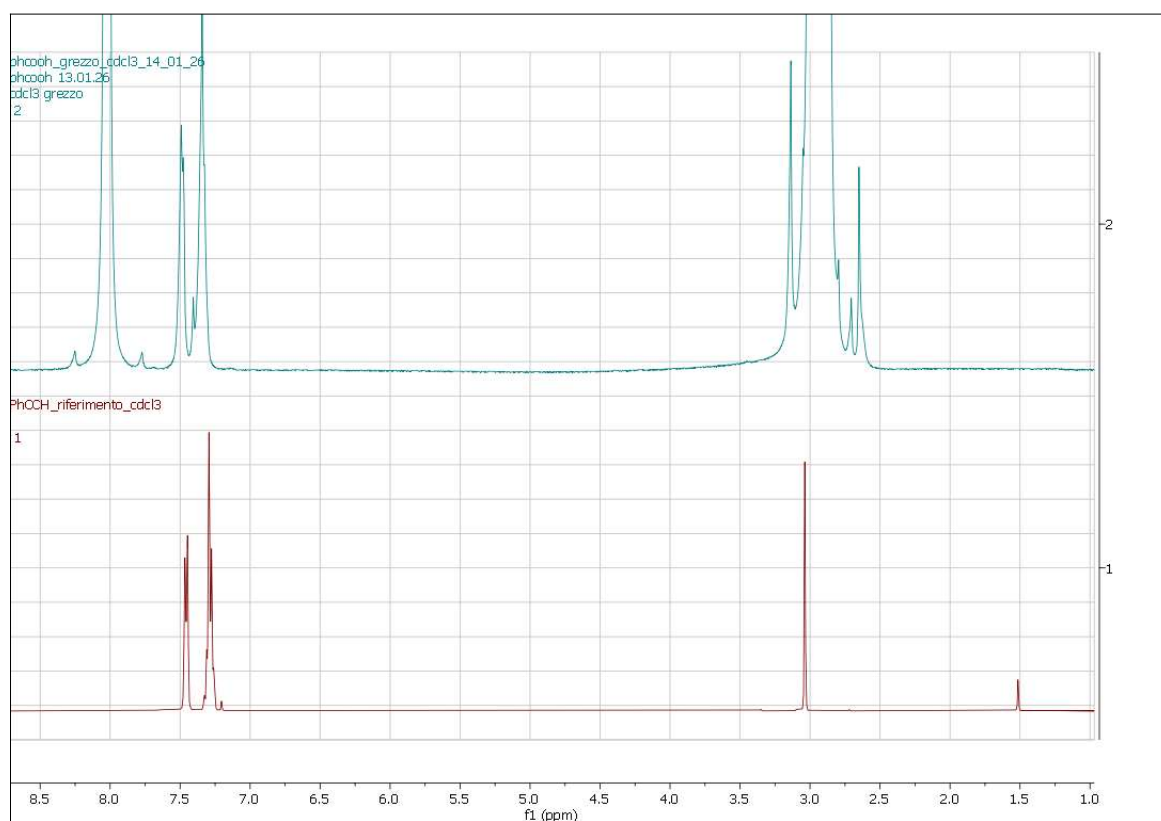


Figure 12- Comparison between NMR spectra (CDCl_3 , 400 MHz): the crude reaction mixture is shown at the top, and the reference substrate (phenylethyne) at the bottom.

In addition to the three solvents most frequently reported in the literature, a further test was carried out in acetone, which is generally considered a better solvent for CO_2 solubility, however, no positive outcome was observed in this case either.

Initially, it was hypothesized that the lack of reactivity might stem from poor solubility of the complex in the selected solvents. A solubility test of the AgFV1 complex was therefore performed under using the same concentrations employed in the reaction conditions. No solubility issues were observed in DMSO or DMF, whereas MeCN and acetone showed a marked decrease in solute dissolution. As an additional verification, the stability of the complex in DMSO and DMF was evaluated. A 24-hour stability study was conducted on a solution of AgFV1 in both solvents.

Procedure

In a pre-heated 4 mL vial, FV1 (0.040 g), Ag₂O (0.0087 g), and NaCl (0.0083 g) were added in 2 mL of solvent. The vial was then covered with aluminum foil and stirred at 25 °C. The experiments performed are reported in the table below.

Run	Solvent	Time (hours)
10	DMF	6
11	DMF	24
12	DMSO	6
13	DMSO	24

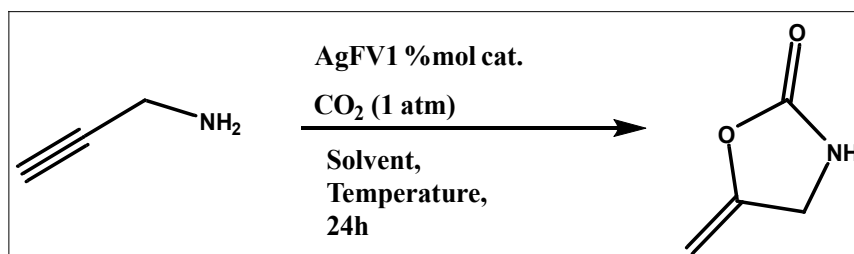
From the reaction monitoring, the disappearance of the diagnostic ¹H NMR signal of the zwitterionic salt confirmed its successful coordination to the metal center. Coordination was complete after 6 hours in DMF, whereas in DMSO, the salt signal was still present. After 24 hours, the signal did not reappear in DMF, however, the experiment in DMSO resulted in the formation of metallic silver (silver mirror), indicating thermal decomposition of the complex.

Initially, by monitoring the in situ formation of the complex, we hypothesized that the limited reactivity could be attributed to a longer catalyst induction period. However, even when the reaction time was extended beyond 24 hours, the reaction did not yield any encouraging results, and no further attempts were made using different catalytic structures or increased catalyst loading. The potential activity of the complexes was therefore evaluated in a different catalytic transformation: the synthesis of oxazolidinones.

7.6 Cyclization catalysis tests for the synthesis of oxazolidinones

The use of carbon dioxide as a C1-building block for introducing carboxylate groups can be exploited by nucleophilic sites capable of reacting with the gaseous molecule to generate carboxylated-functionalized intermediates. Among the substrates that display this reactivity are propargylamines bearing a primary amino group. Under appropriate conditions, it has been shown that these substrates can form carbamic intermediates which, in the presence of an alkyne moiety activated toward nucleophilic attack, undergo intramolecular cyclization. In this process, the activated alkyne is subject to a nucleophilic attack by the carboxylate oxygen, leading to the formation of a five-membered ring and yielding oxazolidine-2-one structures^[36].

In our case, several conditions were tested to determine whether any catalytic activity could be observed, using AgFV1 as the model catalyst and a propargylamine as the model substrate (Scheme 15). We choose 2-propyn-1-amine (CAS. 2450-71-7) as substrate to test this reaction:



Scheme 15 – Catalytic conditions tested for synthesis of 5-Methylene-1,3-oxazolidin-2-one

7.6.1 Materials and methods

In a pre-heated 20 mL vial, 2-Propyn-1-amine (1 mmol, 0.0551 g) and AgFV1 were added in 4 mL of solvent. The vial was sealed with a rubber septum, a needle was inserted down to the bottom of the vial, and carbon dioxide was bubbled through the mixture, maintaining a constant gurgling flow. The vial was then covered with aluminum foil and stirred for 24 hours. The various experiments performed are reported in the table below.

Run	NHC-M(I) % loading (g)	Solvent	Temperature (°C)
14	AgFV1 2% (0.0138 g)	DMF	25
15	AgFV1 2% (0.0138 g)	DMF	60
16	AgFV1 2% (0.0138 g)	MeOH	25
17	AgFV1 10% (0.0690 g)	MeOH	25
18	AgFV1 10% (0.0690 g)	MeOH	40

7.6.2 Results

Preliminary tests indicated the formation of a species that was likely carboxylated; however, comparison with literature data did not allow any correspondence to be assigned to the expected product. Even when the catalyst loading of the AgFV1 complex was substantially increased to 10 mol%, no significant effect on the formation of the cyclic product was observed. When compared with the data reported in the literature^[37], no significant correspondence was found (Figures 13&14). In light of these results, the investigation was not pursued further.

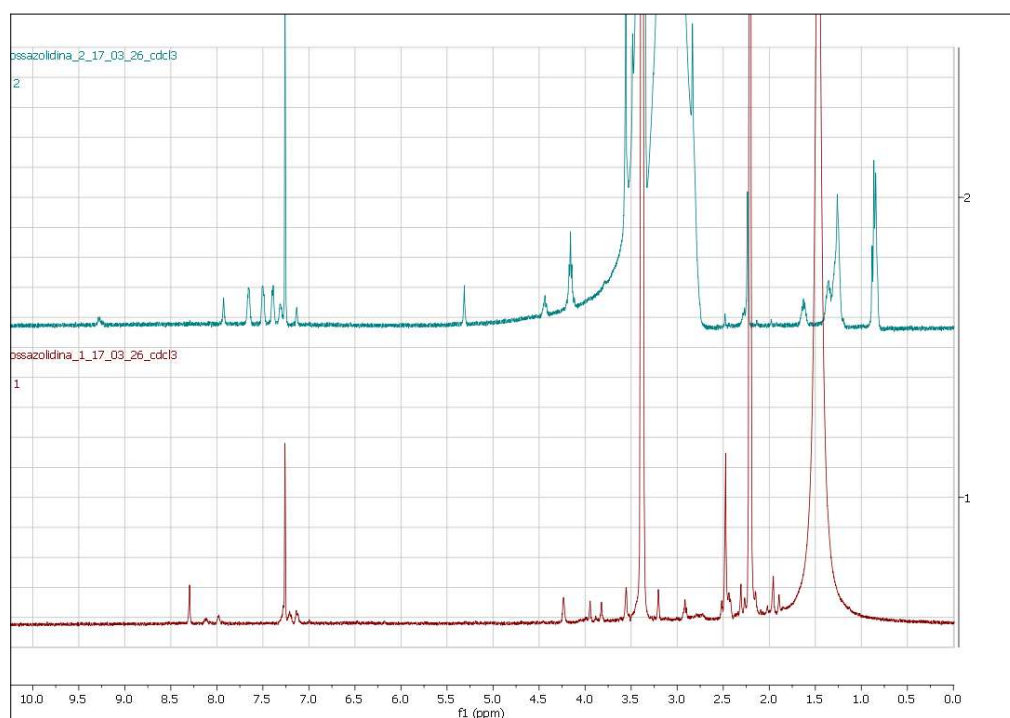


Figure 13 – Comparison between ^1H NMR spectra (CDCl_3 , 400 MHz): the crude reaction mixture at the top, and the reference substrate at the bottom (2-Propyn-1-amine).

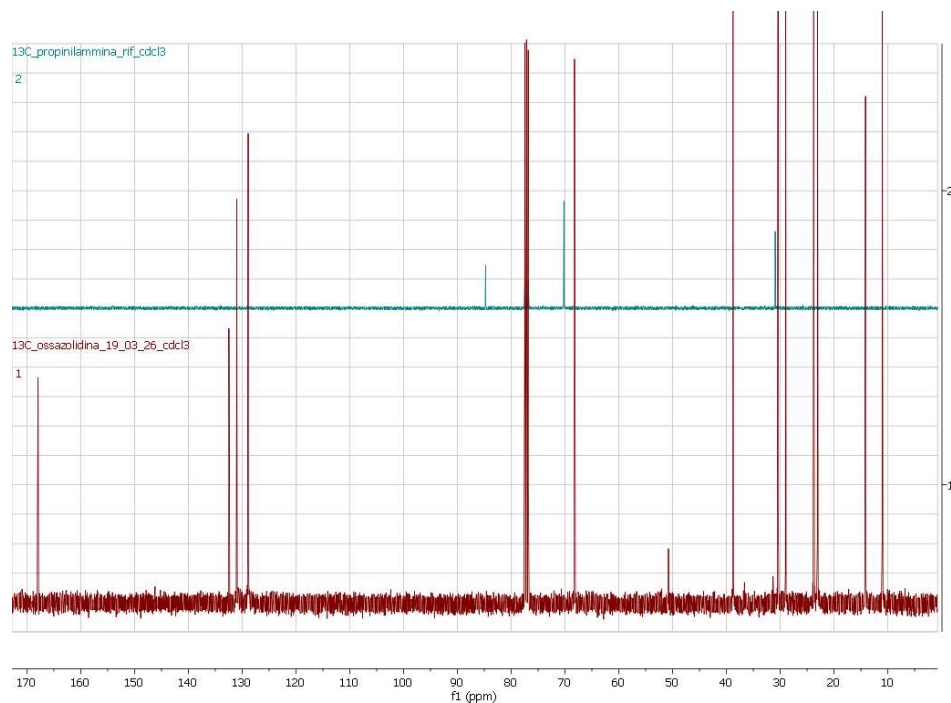


Figure 14 – Comparison between ^{13}C NMR spectra (CDCl_3 , 100 MHz): the crude reaction mixture at the bottom, and the reference substrate at the top (2-Propyn-1-amine).

7.7 References

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Chapter 8 – Evaluation pharmacological profiles

8.1 Evaluation of the antitumor activity of sulfonated NHC–Ag(I) and NHC–Au(I) complexes

The anticancer activity of the complexes was evaluated using the MTT cell viability assay on two breast cancer cell lines: MCF-7, an estrogen receptor-positive strain, and MDA-MB-231, a triple-negative line. The antiproliferative effect was assessed after 72 h of treatment, after which MTT was added. After cell lysis, absorbance values were measured at 570 nm and normalized against a negative control consisting of cells treated with the vehicle alone (DMSO). All compounds were tested at different concentrations (1, 10, and 25 μ M). Selectivity was further assessed using the non-tumorigenic epithelial cell line MCF-10A.

Although this preliminary 72-hour IC₅₀ evaluation does not fully define the biological profile of a compound, it provides rapid and essential insights into the behaviour of the tested complexes. First, it allows for the assessment of antitumor activity over an extended exposure period: a compound that still displays a high IC₅₀ after 72 h is unlikely to be of interest for further studies, as this suggests limited cytotoxic efficacy. At the same time, the parallel analysis on healthy MCF-10A cells reveals potential non-selective or late-onset cytotoxic effects, including degradation-related or inhibitory phenomena that may emerge over time. Finally, comparing IC₅₀ values between tumor and healthy cells enables an initial estimation of selectivity: a high ratio indicates preferential activity toward cancer cells, while acknowledging that this remains a relative rather than absolute measure of selectivity. The comparison between MDA-MB-231 and MCF-7 is particularly informative because these lines represent two biologically distinct models of breast carcinoma. MCF-7 cells belong to the luminal A subtype and depend on hormone-mediated signaling due to the presence of ER and PR receptors and, to some extent, HER2 responsiveness. In contrast, MDA-MB-231 cells are triple-negative, lacking the major membrane receptors and displaying a far more aggressive, invasive, and treatment-resistant phenotype. Comparing these two models therefore allows one to evaluate whether a compound's activity depends on the presence of hormone receptors or whether it acts through more general, receptor-independent mechanisms. Moreover, the ability of a compound to retain efficacy against MDA-MB-231 cells is particularly relevant, as this subtype represents one of the most clinically challenging forms of breast cancer. Assessing the response of both lines thus provides a more comprehensive picture of the compound's therapeutic potential and its possible selectivity toward tumors with markedly different biological features.

8.2 Materials and methods

Cell culture

The cell lines used were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA).

- Human breast cancer cells MCF-7 (estrogen receptor (ER)-positive) and MDA-MB 231 (known as triple-negative cells, *i.e.*, not overexpressing human epidermal growth factor receptor 2-HER2), were maintained in Dulbecco's Modified Eagle Medium/Nutrient Mixture F12 Ham (DMEM/F12) supplemented with 5% fetal bovine serum (FBS), 1% L-glutamine and 100 units/mL of penicillin/streptomycin.
- MCF-10A human mammary epithelial cells, were cultured in DMEM/F12 medium, supplemented with 5% horse serum (HS), 100 units/mL penicillin/streptomycin, 0.5 mg/mL hydrocortisone, 0.02 µg/mL human epidermal growth factor (hEGF), 10 µg/mL insulin and 0.1 mg/mL cholera enterotoxin^[1].

Cells were maintained at 37°C in a humidified atmosphere of 95% air and 5% CO₂ and periodically screened for contamination. Each experiment was carried out in multi-well plates in which cells were plated in quantities determined following the cell counting process. All compounds were dissolved in dimethyl sulfoxide (DMSO; Sigma, St. Louis, MO, USA) and opportunely diluted in cultured medium to obtain working concentrations.

Trypsinization

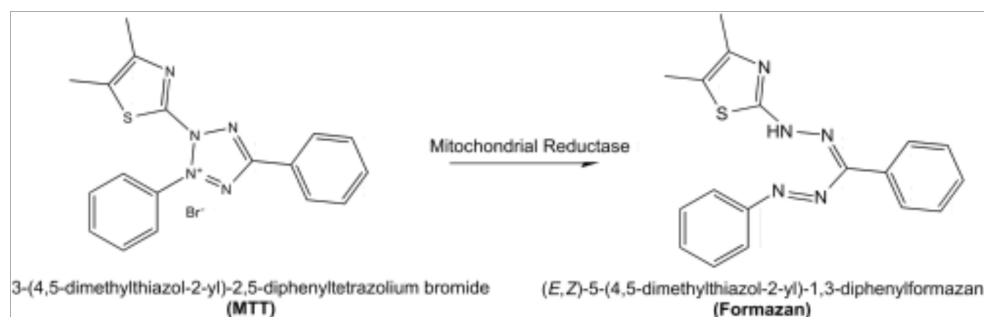
Trypsinization is the technique used to detach adherent cells from the surface of the culture plate, allowing their subsequent seeding into multi-well plates for treatment with the compounds under investigation. The culture medium is first aspirated, and the cells are washed three times with phosphate-buffered saline (PBS) in order to remove residual serum, which inhibits trypsin activity. Trypsin, a proteolytic enzyme, is then added to facilitate cell detachment from the substrate. The plate is incubated for a few minutes until the cells begin to detach. The cells are subsequently resuspended in serum-containing medium to neutralize trypsin activity, counted, and used as required.

Cell counting

Cell counting is based on the exclusion of the Trypan Blue dye by viable cells. Unlike dead cells, viable cells possess an intact cytoplasmic membrane that prevents the dye from entering the cytoplasm. An aliquot of the cell suspension obtained after trypsinization is diluted with the dye and loaded into a Bürker counting chamber for microscopic analysis. The number of cells per milliliter is calculated using the following equation: average number of cells counted / number of chamber squares $\times$ dilution factor $\times$ chamber conversion factor.

MTT Assay

The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay (Sigma-Aldrich, St. Louis, MO, USA) (Figure 1) was employed to evaluate the in vitro anticancer activity of the complexes, following a previously reported protocol. This colorimetric assay is based on the ability of metabolically active cells to reduce MTT into an insoluble purple formazan product through the action of mitochondrial reductase enzymes, thereby providing an indirect measure of cell viability and proliferation^[2].



Scheme 1- Reduction in MTT in the corresponding formazan

Cells have been seeded on forty-eight well plates and grown in complete medium. Before being treated, cells have been starved in serum free medium for 24h for allowing cell cycle synchronization. 72h after treatments, fresh MTT resuspended in PBS, was added to each well final concentration (0.5mg/mL). After 2h incubation at 37°C, cells have been lysed with DMSO, and then optical density was measured at 570 nm using a microplate reader. The absorbance values have been used to determine the IC₅₀ for each cell line using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). Data are representative of three independent experiments; standard deviations (SD) have been shown.

8.3 Results and discussions

The results, expressed as IC_{50} values (μM), and reported in Table 1, generally indicated that the silver-based complexes exhibited significant cytotoxic activity, whereas their gold-based analogues and the corresponding zwitterionic salts were inactive against the tested cell lines.

	IC_{50} (μM)		
	MCF-7	MDA-MB-231	MCF-10A
AgFV1	14.51 $\pm$ 0.45	11.53 $\pm$ 0.12	>25
AgFV2	12.36 $\pm$ 0.60	12.11 $\pm$ 0.21	>25
AgCV1	11.86 $\pm$ 0.69	12.06 $\pm$ 0.45	>25
AgCV2	14.55 $\pm$ 0.27	10.24 $\pm$ 0.12	>25
AgPV1	3.00 $\pm$ 0.19	1.99 $\pm$ 0.54	>25
AgPV2	4.82 $\pm$ 0.47	4.16 $\pm$ 1.23	>25
AgBV1	3.60 $\pm$ 0.42	3.05 $\pm$ 0.53	>25
AgBV2	4.16 $\pm$ 0.39	3.20 $\pm$ 0.53	>25
AgFV11	2.74 $\pm$ 0.12	1.93 $\pm$ 0.22	>25
AgFV22	10.21 $\pm$ 0.53	12.79 $\pm$ 0.22	>25
AgBV11	17.83 $\pm$ 0.41	13.21 $\pm$ 0.14	>25
AgBV22	18.37 $\pm$ 0.30	13.51 $\pm$ 0.24	>25
AuFV1	>25	>25	>25
AuFV2	>25	>25	>25
AuCV1	>25	>25	>25
AuFV11	>25	>25	>25
FV1	>25	>25	>25
FV2	>25	>25	>25
CV1	>25	>25	>25
CV2	>25	>25	>25
PV1	>25	>25	>25
PV2	>25	>25	>25
BV1	>25	>25	>25
BV2	>25	>25	>25
FV11	>25	>25	>25
FV22	>25	>25	>25
BV11	>25	>25	>25
BV22	>25	>25	>25

Table 1- IC_{50} values, expressed as μM on three different cell lines (MCF-7, MDA-MB-231, and MCF-10A). The values represent the mean $\pm$ standard deviation of three different experiments performed in triplicate.

The results of this preliminary investigation highlight several key points. After 72 hours of exposure, the IC₅₀ values recorded for all active complexes are comparable. This suggests that their cytotoxic activity is governed by mechanisms that are not strictly dependent on receptor-mediated signaling, as both MCF-7 and MDA-MB-231 cells responded similarly, implying the involvement of alternative cellular processes. Interestingly, these trends may reflect structural features inherent to the organometallic scaffolds. The overall trend indicates in most cases better activity against MDA-MB-231 cells, with values comparable to those obtained for MCF-7. In the following sections, the activities observed will be examined to identify potential correlations between structural features and biological effects.

Evaluation of cytotoxicity and selectivity in cell lines

For the MCF-7 cell line, the activity of the complexes spans from a maximum IC₅₀ value of 18.37 μ M to a minimum of 3.0 μ M (Figure 1), whereas for the MDA-MB-231 line the IC₅₀ values range from 13.51 μ M to 1.93 μ M.

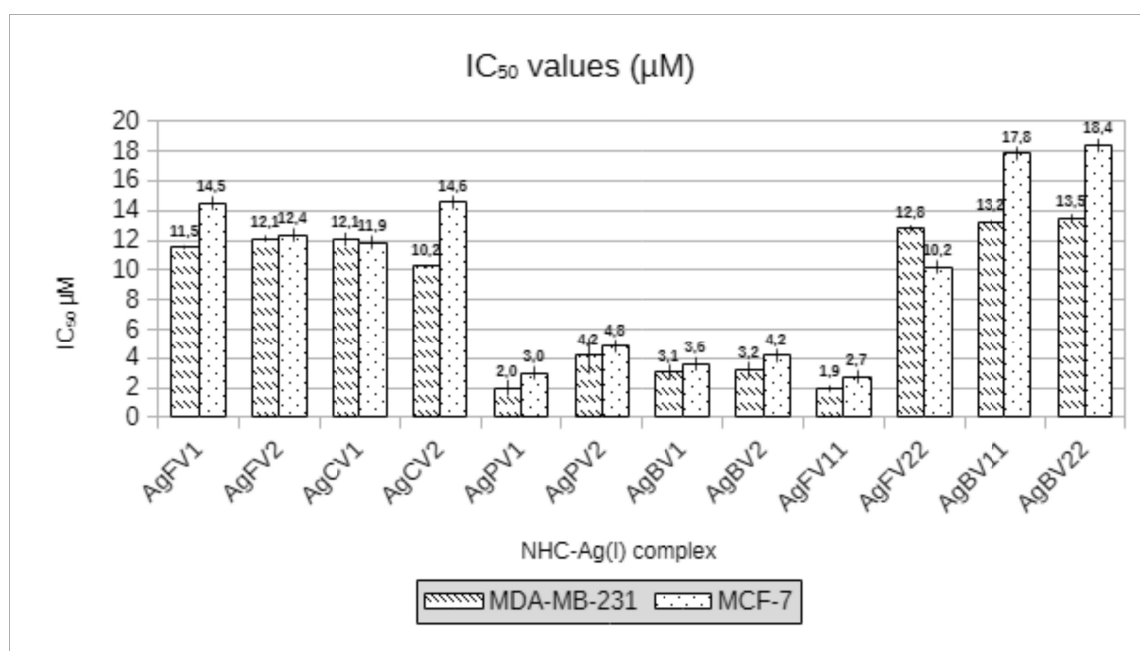


Figure 1 – Histogram representing the IC₅₀ cytotoxicity values of the silver complexes tested on the MCF-7 and MDA-MB-231 cancer cell lines

Based on the collected data, it is possible to estimate a minimum value for the selectivity index (SI_{50}), calculated according to the following ratio:

$$SI_{50} = \frac{IC_{50} \text{ MCF-10A}}{IC_{50} \text{ tumor cell line}}$$

As the IC_{50} value for the reference healthy cell line MCF-10A exceeds 25 μM , this value was adopted as the minimum reference value for estimating the selectivity index. Three threshold reference values can be considered:

$SI_{50} > 1 \rightarrow$ lower toxicity towards healthy cell line then tumor line

$SI_{50} = 1 \rightarrow$ same toxicity towards healthy cell line and tumor line

$SI_{50} < 1 \rightarrow$ higher toxicity towards healthy cell line then tumor line

Examining the estimated values, it becomes evident that the complexes exhibiting lower cytotoxic activity against cancer cell lines are also those with reduced selectivity toward healthy cells.

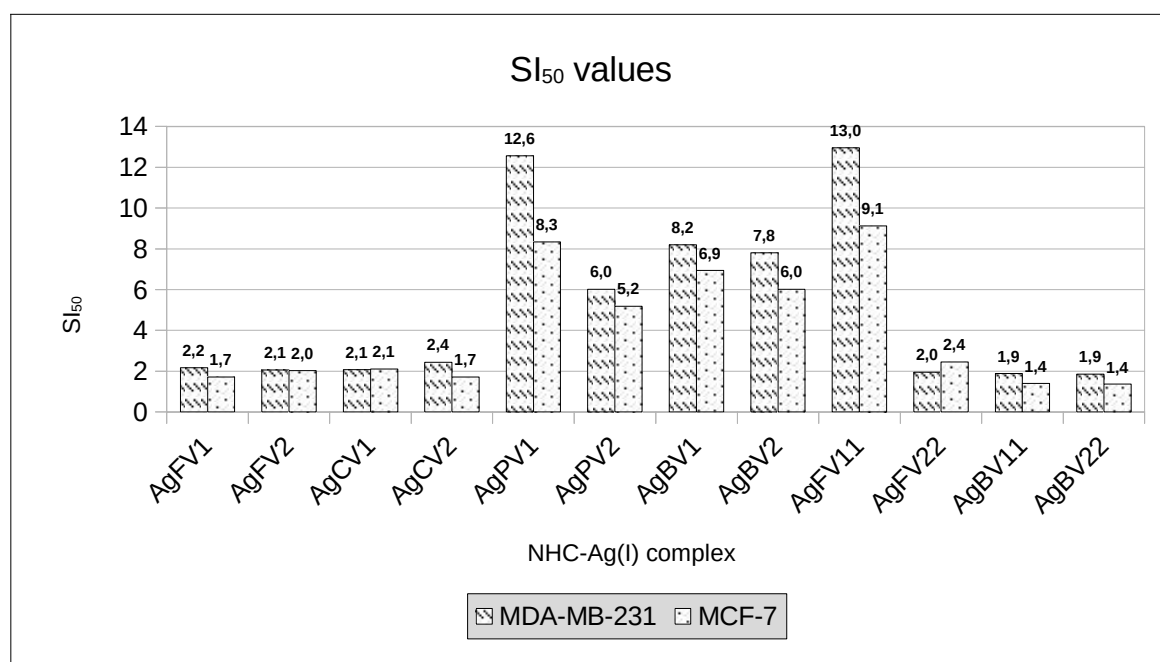


Figure 2 – Histogram representing the SI_{50} selectivity values of the silver complexes tested on the MCF-7 and MDA-MB-231 cancer cell lines

Although these values are not fully accurate due to the approximate IC_{50} estimation for the healthy cell line, they still provide a meaningful comparative index that allows the activities of the complexes to be evaluated relative to one another and helps clarify the structural factors influencing cellular selectivity.

To gain insight into the structural determinants underlying the cytotoxic effects of the active organometallic complexes, their IC_{50} values were compared. The parameters considered included the length of the alkynesulfonate chain, the presence of either an N-benzyl or an N-benzhydryl substituent and the substituents at positions 4 and 5 of the imidazole ring.

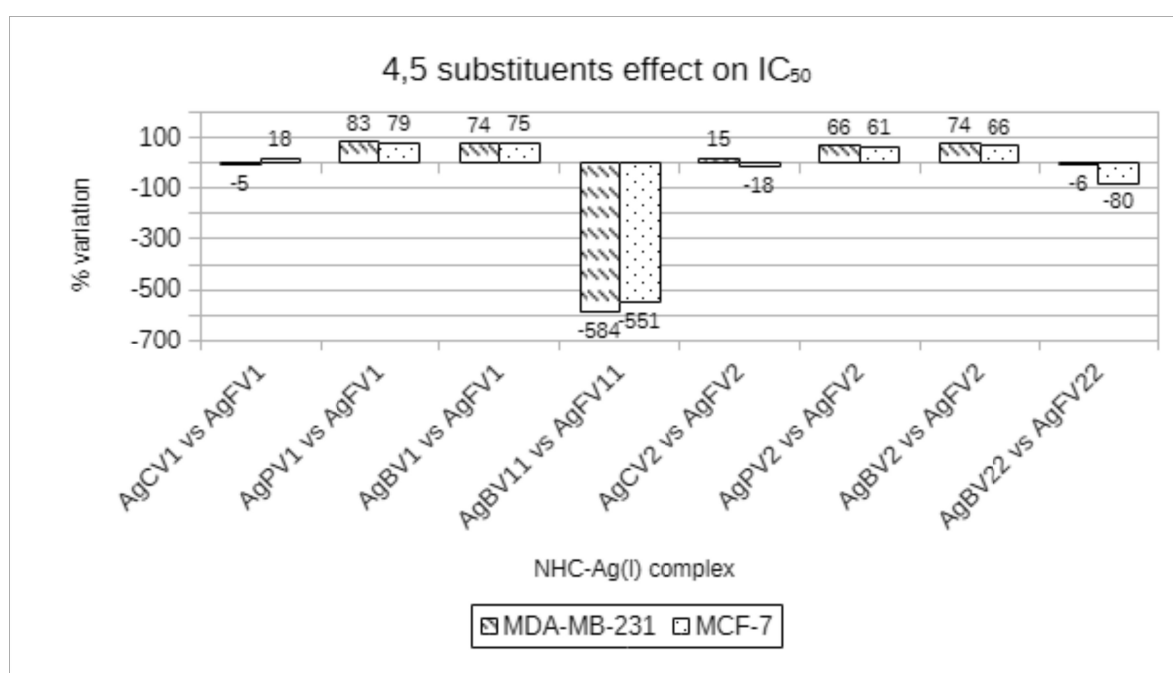


Figure 3 – Comparison between IC_{50} values of the Ag(I) complexes for evaluating the effects of the 4,5-substituents

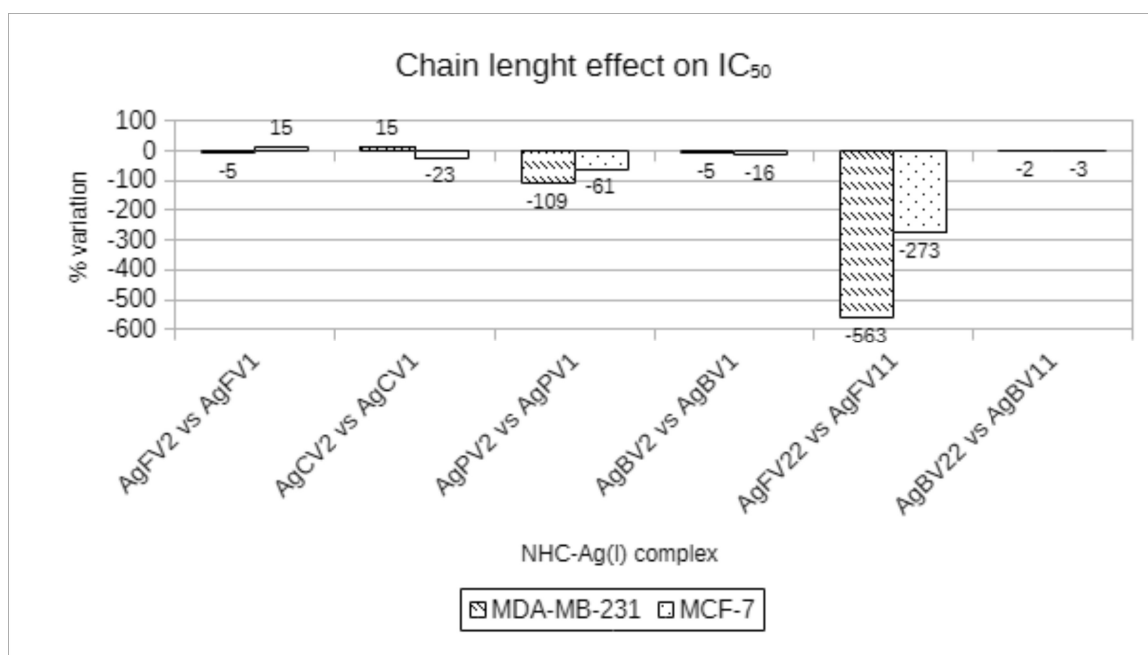


Figure 4 – Comparison between IC_{50} values of the Ag(I) complexes for evaluating the effects of sulfonate chain lenght

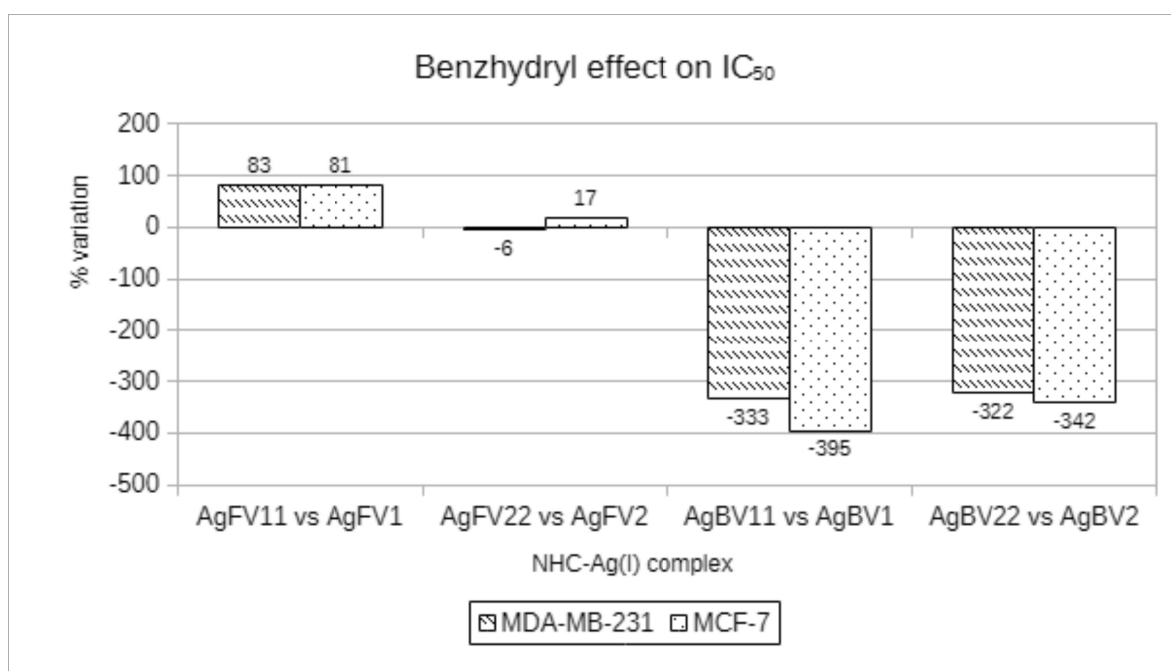


Figure 5 – Comparison between IC_{50} values of the Ag(I) complexes for evaluating the effects of benzhydryl group

When examining Figure 3, the observed trend shows an improvement in cytotoxic activity for both phenyl-substituted and benzimidazole-based complexes, which follow a comparable pattern, indicating only a negligible distinction between these substituents. The presence of

chloro atoms does not alter the activity relative to hydrogen and, for benzyl-containing structures, the cytotoxic response remains almost comparable regardless of the alkynesulfonate chain length. An exceptionally divergent behavior can be observed for the AgBV11 structure, which combines a benzimidazole scaffold with a benzhydryl substituent. To better understand this deviation, it is useful to examine the trends reported in Figures 4 and 5.

In Figure 5, analogous structures differing only in the length of the aliphatic chain are compared. For most complexes, no significant effect is observed; the only exception is the AgFV11/AgFV22 pair, which lacks additional substituents but contains a benzhydryl group. One might incorrectly assume that, in this case, the drastic reduction in cytotoxic activity arises from the different length of the sulfonate chain. However, a closer examination reveals that the AgFV1/AgFV2 pair, bearing a benzyl rather than a benzhydryl substituent, shows a negligible effect upon chain elongation. This suggests that the disruptive element is likely the benzhydryl group itself, a hypothesis further supported by the trends reported in Figure 5.

When comparing structures bearing an N-alkylated benzhydryl substituent instead of a benzyl group, the effects differ markedly. Enhanced activity is observed for AgFV11, which lacks substituents at the 4,5-positions and contains the propanesulfonate chain. In contrast, an incompatibility emerges between the extended chain and the N-benzhydryl-imidazole scaffold, as the improvement in activity recorded for AgFV22 is significantly lower than that observed for AgFV11. The most significant divergence arises from the combination of the benzhydryl group with the benzimidazole scaffold. This comparison further confirms that benzimidazole-based structures exhibit reduced activity when the benzhydryl substituent is present, relative to their benzyl analogues. Notably, the magnitude of this reduction is independent of the alkynesulfonate chain length, indicating that in this case the dominant contribution to the activity arises from the presence of the benzhydryl moiety. The trend observed for the selectivity indexes closely mirrors that of the cytotoxic activity.

Finally, since the selectivity values are derived directly from the cytotoxicity data, the trend observed for the selectivity indexes closely mirrors that of the cytotoxic activity.

Comparative analysis between the two cell lines

By plotting the IC_{50} and SI_{50} values, the overall distribution of the complexes can be more clearly visualized in terms of their combined cytotoxic and selectivity against tumor cells. Complexes located in the upper-left region of the graph correspond to those with higher cytotoxic potency and greater selectivity. From these graphical distributions, AgFV11 and AgPV1 stand out as the lead structures, showing the most favorable activity–selectivity profile across both cell lines.

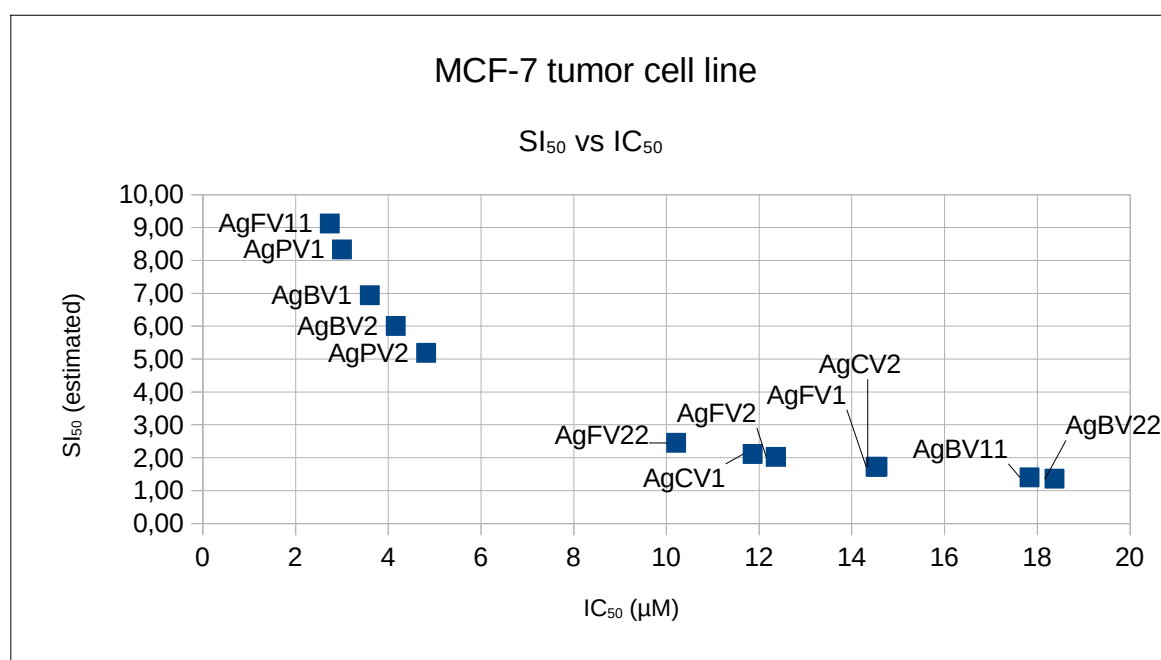


Figure 6 – Data distribution of the cytotoxic activity of Ag(I) complexes in MCF-7 tumor cell line according to IC_{50} and SI_{50}

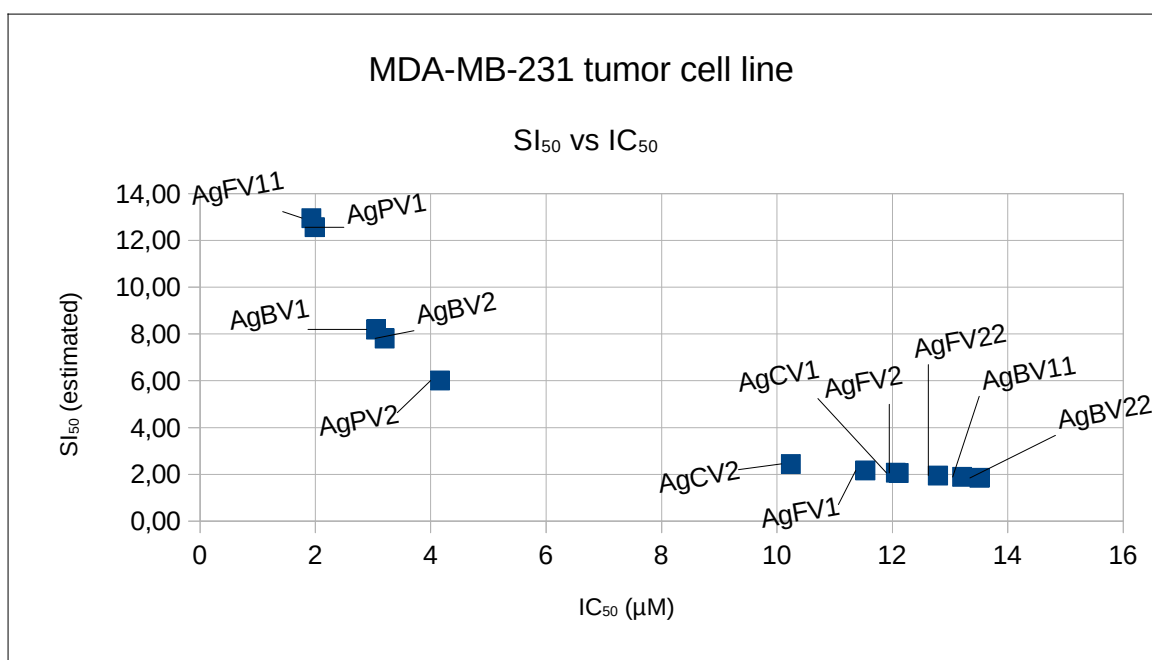


Figure 7 – Data distribution of the cytotoxic activity of Ag(I) complexes in MDA-MB-231 tumor cell line according to IC₅₀ and SI₅₀

By comparing the two cell lines, it was possible to quantify the extent of the variation in both antitumor activity and selectivity. To achieve this, the following parameters were evaluated:

$$IC_{50ratio}\% = - \left(1 - \frac{IC_{50}MDA-MB-231}{IC_{50}MCF-7} \right) \times 100$$

$$SI_{50ratio}\% = - \left(1 - \frac{SI_{50}MDA-MB-231}{SI_{50}MCF-7} \right) \times 100$$

The parameter IC_{50ratio}% expresses, in percentage terms, the extent to which the IC₅₀ improves or worsens in the more aggressive MDA-MB-231 cell line compared to the less aggressive MCF-7 line. A negative value indicates the percentage reduction in IC₅₀ for a given complex against MDA-MB-231 relative to MCF-7.

The parameter SI_{50ratio}% expresses, again in percentage terms, the degree to which selectivity improves or decreases in MDA-MB-231 compared to MCF-7. A positive value indicates the percentage increase in SI₅₀ for a given complex toward MDA-MB-231 relative to MCF-7 (Figure 8).

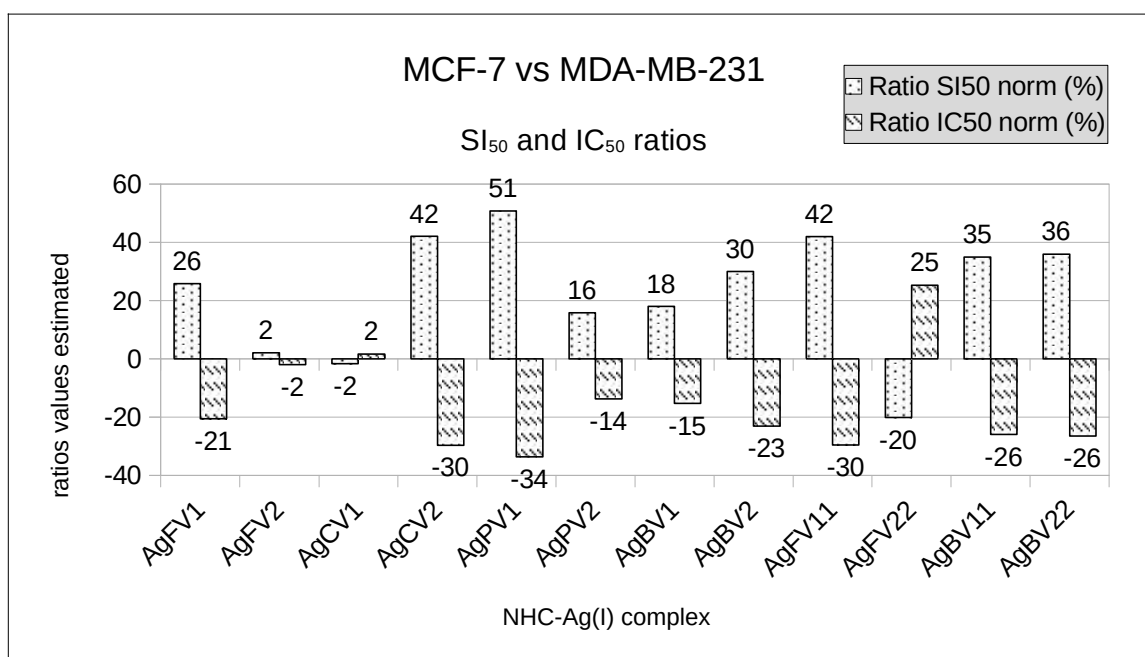


Figure 8 – Normalized percentage ratios of IC₅₀ and SI₅₀ to assess percentage changes in MDA-MB-231 compared with MCF-7

This comparative analysis confirms AgPV1 as the most effective complex against the more aggressive MDA-MB-231 cell line, showing an improvement of approximate 34% improvement in IC₅₀ and a 50% increase in selectivity relative to MCF-7. Although AgFV11 appears comparable to AgCV2 in terms of relative variation, previous observations clearly indicate that AgCV2 is among the least active complexes. Its apparent improvement is therefore merely a consequence of the relative relationship between the two cell lines, demonstrating only that its activity, despite being low, remains slightly more favourable toward MDA-MB-231. Departing from the general trend, AgFV22 displays greater potency against the MCF-7 line, even though it also belongs to the group of less active complexes.

In conclusion, among the tested compounds, AgFV11 exhibited the highest activity, with IC₅₀ values of 1.93 μ M in MDA-MB-231 cells and 2.74 μ M in MCF-7 cells. AgPV1 also displayed notable activity, with IC₅₀ values of 1.99 and 3.00 μ M in MDA-MB-231 and MCF-7 cells, respectively. Overall, the highest cytotoxic activity against tested tumor cell lines was observed for NHC-Ag complexes containing a non-fused imidazole ring with either unsubstituted or phenyl-substituted positions at C4-C5, whereas chlorine substitution at the same positions markedly reduces activity. The elongation of the alkylsulfonate chain (from three to four carbon units) does not improve the activity and, in some cases, leads to a decrease (e.g., AgFV11 vs AgFV22). The introduction of the benzhydryl substituent typically results in reduced activity, particularly in the benzimidazole-based structures, although the fused-ring system itself confers an improvement in the antitumor properties of the complexes in which it is present.

Notably, none of the tested silver complexes exhibited cytotoxicity toward the healthy MCF-10A cell line. The zwitterionic structures tested do not exhibit cytotoxicity, nor do the gold complexes employed. This can be attributed to the role played by the organic frameworks when coordinated to silver, as well as to a metal-selective behaviour of the cellular targets involved in the cytotoxic response. The fact that the cytotoxic activity of the silver complexes is comparable in both tumour cell lines likely implies that the targeted processes or substrates are not involved in estrogen-regulated pathways, as the cytotoxicity observed in the MDA-MB-231 line is essentially equivalent to that of MCF-7.

This work contributes to our group's ongoing evaluation of the antitumor activity of new gold- and silver-based N-heterocyclic organometallic complexes. The most recent active structures on the same tumor cell lines are shown in the scheme below, together with the IC₅₀ values obtained under the same conditions.

8.4 References

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Conclusions

In this doctoral project, new silver and gold organometallic complexes bearing N-heterocyclic carbene ligands with a sulfonated group were successfully synthesized and characterized. All the obtained complexes exhibit water solubility owing to their sulfonate functional group. The reaction products were characterized by ^1H - and ^{13}C -NMR, MALDI-MS, and FT-IR. The newly implemented procedures for the preparation of N-substituted intermediates enabled access to known products in good yields and under mild conditions, proving comparable to, and in some cases superior to, the methods reported in the literature. Most of the targeted zwitterionic salts were obtained, and the adopted strategies for the synthesis of the metal complexes consistently proved effective.

The catalytic tests revealed an interesting activity profile in the A^3 multicomponent reaction, employing paraformaldehyde as the polymeric source of formaldehyde. Although only a few successful applications using paraformaldehyde have been reported in the literature, the series of complexes evaluated under the selected conditions displayed promising conversion to the expected product, with gold complexes generally outperforming their silver analogues. This observation is encouraging for potential applications to other polyacetal substrates, to combine depolymerizing conditions with the catalytic capabilities of these or related sulfonated organometallic structures.

Preliminary evaluation of the antitumor activity of the tested compounds demonstrated notable cytotoxicity toward the MCF-7 and MDA-MB-231 cancer cell lines, with good selectivity over healthy cells. The metal-selective behavior observed for the silver complexes, together with the similar pharmacological response across both cell lines, suggests mechanisms that transcend cell-line-specific features and may involve processes common to both, potentially linked to redox pathways or thiol-containing sites inhibited by silver. Further studies will be conducted to elucidate the mechanisms involved.

Papers published and conferences

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Conference poster presentation: F. Viceconte,* A. Mariconda, P. Longo “Sulfonated N-Heterocyclic carbene silver(I) and gold(I) complexes in Π -functionalization of alkynes”, XLIX Italian Conference of Inorganic Chemistry – INORG2023 - Perugia, 12th-15th September 2023

Conference oral presentation: F. Viceconte,* A. Mariconda, P. Longo “Novel sulfonated N-heterocyclic carbene silver(I) and gold(I) complexes in A³-coupling catalysis”, "Il contributo dei giovani chimici in Campania" II edizione – Caserta, 19th July 2024

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