

Títol del treball:

Synthesis, characterization and reactivity of a Au(III)-NHC complex

Estudiant: Souhaila El Ghaddar
Chkadri

Correu electrònic: u1946228@campus.udg.edu

Tutor: Xavi Ribas Salamaña

Cotutor*: Hugo Christian Valdés Rivas

Empresa / institució: Química Bioinspirada, Supramolecular i Catàlisi (QBIS-CAT)

Vistiplau tutor (i cotutor*):

Nom del tutor: Xavi Ribas Salamaña

Nom del cotutor*: Hugo Christian Valdés Rivas

Empresa / institució: Bioinspired, Supramolecular and Catalysis
Chemistry group (QBIS-CAT)

Correu(s) electrònic(s): xavi.ribas@udg.edu hugo.valdes@udg.edu

*si hi ha un cotutor assignat

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ABSTRACT

The research on N-heterocyclic carbene (NHC) ligands has been tremendously expanded in organometallic and catalysis fields during the last two decades. In fact, they have been widely used for the design of highly catalytic active species for several processes, including cross-coupling, metathesis, dehydrogenation, hydrogenation, among other reactions. This wide applicability is mainly due to the fact they can be easily prepared and are highly tunable, as well as they form very σ -strong bonds with practically any transition metal.

Currently, gold NHC complexes are taking an important role in medicine and catalysis. In the realm of catalysis there are several topologies described with a wide range of applications, for example: halogenation of aryls, cycloisomerization of propargylic amides, the Meyer-Schuster reaction (*rearrangement of secondary and tertiary propargylic alcohol to α , β -unsaturated ketones*), [3+3] rearrangement and double hydroarylation of diyne diether. On the one hand, in medicine, the use of gold (III) species for the treatment of cancer covers more importance, due to gold can be eliminated easily from our body.

In our goal of synthesizing a pincer Au(III) complex bearing a NHC-aryl-NHC, we have achieved the synthesis and characterization of the desired a NHC-aryl-NHC bis-azolium salt and the corresponding a new bimetallic Au(I)-NHC complex **3**, where each gold center is bonded two NHC moieties, and the arene moiety is not affected. We noticed that the ligand structure with n-butyls is more soluble. In order to get the proximal arene moiety into play, the oxidation of the bimetallic Au(I) complex with Br₂ was performed and a bimetallic Au(III)-NHC complex (**4**), where each gold(III) center is bonded to two Br⁻ and two NHC moieties. Also we tried the substitution of the coordinated bromide anions with pyridine or benzoic acid to activate the reactivity of the Au(III) centers, but with no success, probably due to the high stability conferred by the Br anions.

We finally tested complex **4** as catalyst for the arylation of aldehydes and the cycloisomerization of 4-pentanoic acid, but the catalysis were not successful in either case. We can conclude that the reactivity of complex **4** can only be activated for catalysis if a reliable methodology for removing the coordinated halides is developed in the future.

RESUM

La investigació sobre els lligands N-heterocíclics (NHC) s'ha estès àmpliament en els camps de l'organometàl·lica i de catàlisi durant les dues últimes dècades. De fet, s'han utilitzat per a disseny d'espècies actives altament catalítiques per a diversos processos, incloent-hi acoblament creuat, metàtesi, deshidrogenació o hidrogenació, entre altres reaccions. Aquestes aplicacions es deuen principalment al fet que es poden preparar fàcilment, a més que formen enllaços σ forts amb pràcticament qualsevol metall de transició.

Actualment, els complexos NHC d'or han adquirit un paper important en medicina i catàlisi. En l'àmbit de catalític s'han descrit diverses estructures amb una àmplia gamma d'aplicacions, per exemple: l'halogenació d'arils, la cicloisomerització d'amides propargíliques, la reacció de Meyer-Schuster (*reordenament d'alcohols propargílics secundaris i terciaris a cetones α , β -insaturats*), el reordenament [3+3] i la doble hidroarilació de diéters. En medicina, l'ús d'espècies d'or (III) pel tractament de càncer cobra major importància, ja que l'or pot ser eliminat fàcilment del nostre cos.

El nostre objectiu és sintetitzar un complex d'Au(III) amb un lligant NHC-aril-NHC, i hem aconseguit la síntesi i caracterització de la desitjada sal de bis (azoli) NHC-aril-NHC i el corresponent nou complex bimetàl·lic Au(I)-NHC **3**, on cada centre d'or està unit a dos NHC, i la resta de l'arè no es veu afectat. Observem que l'estructura del lligant amb n-butils és més soluble. Per posar en joc la fracció de arè proximal, es va realitzar l'oxidació del complex bimetàl·lic Au(I) amb Br_2 , obtenint un complex bimetàl·lic Au(III)-NHC (**4**), on cada centre d'or (III) està unit a dues molècules de Br^- i dues de NHC. També vam provar la substitució dels anions bromur coordinats amb piridina o àcid benzoic per activar la reactivitat dels centres d'Au(III), però sense èxit, probablement a causa de l'alta estabilitat que confereixen els anions Br^- .

Finalment, vam provar el complex **4** com a catalitzador per a l'arilació d'aldehids i la cicloisomerització de l'àcid 4-pentanoic, però la catàlisi no va tenir èxit en cap dels dos casos. Podem concloure que la reactivitat el complex **4** només pot activar-se per la catàlisi si es desenvolupa en el futur una metodologia fiable per eliminar els halurs coordinats.

RESUMEN

La investigación sobre los ligandos N-heterocíclicos (NHC) se ha extendido enormemente en los campos de la organometálica y de catálisis durante las dos últimas décadas. De hecho, se han utilizado para el diseño de especies activas altamente catalíticas para varios procesos, incluyendo acoplamiento cruzado, metátesis, deshidrogenación o hidrogenación, entre otras reacciones. Estas aplicaciones se deben principalmente al hecho de que se pueden preparar fácilmente, además de que forman enlaces σ fuertes con prácticamente cualquier metal de transición.

Actualmente, los complejos NHC de oro están adquiriendo un papel importante en medicina y catálisis. En el ámbito de la catálisis se han descrito varias estructuras con una amplia gama de aplicaciones, por ejemplo: la halogenación de arilos, la cicloisomerización de amidas propargílicas, la reacción de Meyer-Schuster (*reordenamiento de alcoholes propargílicos secundarios y terciarios a cetonas α , β -insaturadas*), el reordenamiento [3+3] y la doble hidroarilación de diéteres. En medicina, el uso de especies de oro (III) para el tratamiento del cáncer cobra mayor importancia, ya que el oro puede ser eliminado fácilmente de nuestro cuerpo.

Nuestro objetivo es sintetizar un complejo de Au(III) con un ligando NHC-arilo-NHC, y hemos logrado la síntesis y caracterización de la deseada sal de bis(azolio) NHC-arilo-NHC y el correspondiente nuevo complejo bimetalico Au(I)-NHC **3**, donde cada centro de oro está unido a dos NHC, y el resto del areno no se ve afectado. Observamos que la estructura del ligando con n-butilos es más soluble. Para poner en juego la fracción de areno proximal, se realizó la oxidación del complejo bimetalico Au(I) con Br₂, obteniéndose un complejo bimetalico Au(III)-NHC (**4**), donde cada centro de oro (III) está unido a dos moléculas de Br⁻ y dos de NHC. También probamos la sustitución de los aniones bromuro coordinados con piridina o ácido benzoico para activar la reactividad de los centros de Au(III), pero sin éxito, probablemente debido a la alta estabilidad que confieren los aniones Br⁻.

Finalmente, probamos el complejo **4** como catalizador para la arilación de aldehídos y la cicloisomerización del ácido 4-pentanoico, pero la catálisis no tuvo éxito en ninguno de los dos casos. Podemos concluir que la reactividad del complejo **4** sólo puede activarse para la catálisis si se desarrolla en el futuro una metodología fiable para eliminar los haluros coordinados.

LIST OF ABBREVIATIONS

| | |
|------|----------------------------|
| Å | Angstrom |
| °C | Degree Celsius |
| ESI | Electrospray ionization |
| M | Metal |
| mg | milligram |
| mmol | millimol |
| mL | millilitre |
| MS | Mass Spectrometry |
| NHC | N-Heterocyclic carbene |
| NMR | Nuclear Magnetic Resonance |
| ppm | Part per million |
| py | Pyridine |
| XRD | X-ray diffraction |

1. INTRODUCTION

1.1. Carbenes

The International Union of Pure and Applied Chemistry (IUPAC) defines a carbene as *the electronically neutral species CH₂; and its derivatives. The carbon is covalently bonded to two univalent groups of any kind or a divalent group, and bears two nonbonding electrons, which may be singlet or triplet state (Figure 1)*. These electron states depend on the energy splitting between the sp²-hybridized σ orbital and the unhybridized p orbital (generally referred to as p_{π}). The geometry of a carbene also depends on the degree of the hybridization of the carbene-carbon atom itself. Two geometries can be distinguished: i) linear and ii) bent. The first one is rarely observed, and the most common is the bent one.⁷ Furthermore, most of the carbenes are unstable in the free state; this instability (both thermodynamic and kinetic) contributes to the very strong binding of carbenes to metal atoms by disfavoring dissociation.

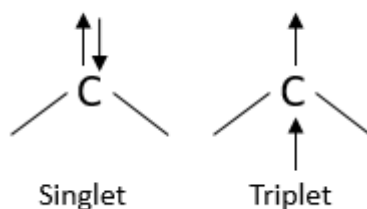


Figure 1. Carbene electron states: singlet (left) and triplet (right).

Two extreme types of coordinated carbenes can be distinguished, the Schrock and the Fischer type. Schrock carbenes form two covalent bonds *via* interaction of the triplet CR₂ fragment with a metal ion having two unpaired electrons thus R substituent attached to the carbon carbene are hydrogen atoms or alkyl groups (Figure 2A). The metals attached to Schrock carbenes are mid transition metal such as Ti(IV), Ta(V) or Mo(VI). Because each M-C bond is polarized toward the carbon, the carbon atom is more electronegative than metal, consequently this kind of carbenes is considered as nucleophiles.

On the other hand, Fischer carbenes are predominantly σ -donor ligands *via* the hybridized-sp² orbital, but the empty p_{π} orbital on the carbon atom is also π -acceptor *via* backdonation from the M(d_{π}) orbitals. In this case, the groups attached next to the carbene-carbon are heteroatoms, such as nitrogen or oxygen. Typically, Fischer carbenes form stable complexes with Fe(0), Mo(0) and Cr(0). Interestingly, Fischer carbenes act as electrophile due to the direct C→M donation is only partly compensated by M→C backdonation.

Between these two extremes, there are the N-heterocyclic carbenes (NHC) (Figure 2C). They consist in a cycle that contains at least one nitrogen atom, which is bonded directly to the carbon carbenes. The presence of this nitrogen confers very interesting features to the carbene. For instance, the σ -electron-withdrawing nitrogen atom inductively stabilizes the carbene σ orbital. Furthermore, the sp^2 -hybridized nitrogen atom possesses filled unhybridized p orbitals which by a symmetric combination forms a bonding interaction with the vacant carbene p_π orbital. All these contribute to the high stability of the NHC complexes. In fact, NHC ligands form stronger bonds with metal centers than most classical ligands, such as phosphines. This renders NHCs complexes especially resistant to dissociation, allowing the generation of highly electron-rich transition metal centers, which is beneficial for the development of stable and highly active catalysts.⁵

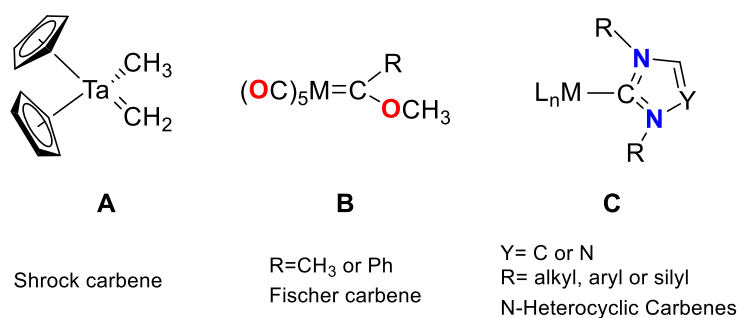


Figure 2. Examples of the different types of carbenes.

1.2. Gold Chemistry

Gold has been present around us since ancient times. Traditionally, it has been used in jewelry, but more recently it has been used for medicinal purposes, and for the development of advanced materials and catalysis.⁶ Gold is element 79 and its symbol is Au. Its electron configuration is $[\text{Xe}] 4f^{14}5d^{10}6s^1$.

The common oxidation states of gold are (0), (I) and (III). In this sense, the geometry of gold is strongly dependent of its oxidation state; Au(I) usually forms linear complexes with a coordination number of 2, while Au(III) forms square planar complexes with a coordination number of 4. Furthermore, Au chemistry stands out from other transition metals due to its electrochemical potential which is the lowest one. Thus, Au(III) and Au(I) can be easily reduced to Au(0) with a weak reducing agent. Furthermore, Au has the highest electronegativity among the transition metals, consequently it possess a “noble” character, showing a low reactivity.⁶

The uses of gold complexes are strongly related with the oxidation state of Au. For example, Au(III) species has attracted much attention for medical purposes since it is able to form square planar complexes, similar to *cis*-platin. In fact, some Au(III) complexes have been tested *in-vitro* for the treatment of cancer, finding potential candidates to substitute the toxic *cis*-platin. However, one drawback is the tendency of Au(III) to be reduced to Au(I) in physiological conditions due to its high reduction potential and fast hydrolysis rate.

In order to circumvent this situation, and improve the activity of Au(III) complexes, a common strategy consists in using multidentate ligands which can stabilize the high oxidation state of gold (*Figure 3*).⁹ On the other hand, Au(I) species are widely used as catalysts, for examples in cyclization reactions.

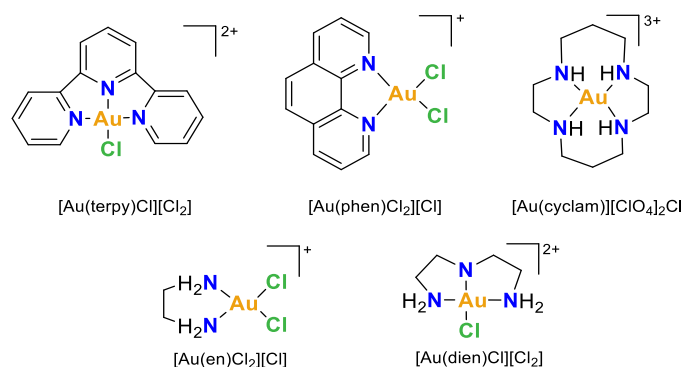


Figure 3. Multidentate N-based ligands based on gold(III).

The discovery of novel Au complex has contributed to widen the gold chemistry and their applications. Some organogold species that have been recently used as catalytic intermediates include vinyl, gem-diaurated, π -complexes or carbene species, as well as hydride and fluoride derivatives. Moreover, the synthesis of the new ligands, such as C, P mixed C^NC (VI, *Figure 4*) or C^P (IV, *Figure 4*) donor ligands of different hapticity (*an affix giving a topological indication of the bonding between a π -electron ligand and the central atom in a coordination entity according to the IUPAC*) is one of the main factor that allows the growing gold chemistry. It is worth to note that some of these ligands are stable single carbenes, for example, NHC's (I, *Figure 4*), N-acyclic (diamino)-carbenes (ADC) (II, *Figure 4*) or cyclic (amino) (alkyl) carbenes (CAAC) (III, *Figure 4*). Such ligands have been important to the study their fundamental structure, the bonding modes of gold, and their applications. In fact, NHC and phosphine ligands (IV, *Figure 4*) provide a suitable environment to the metal to produce both biological and catalytic active species.⁶

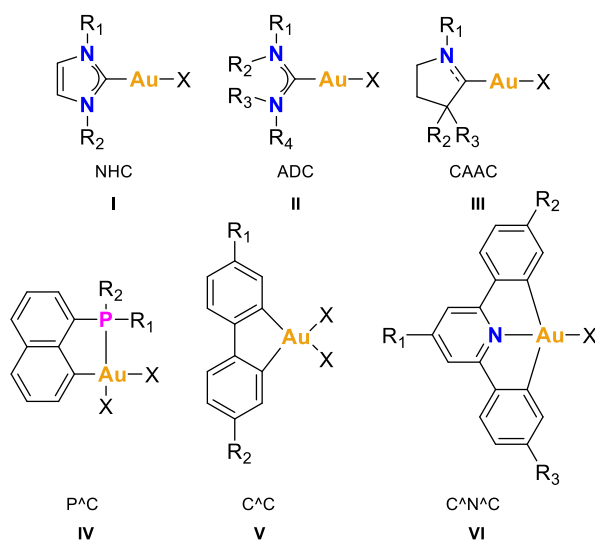


Figure 4. Representative examples of gold complexes.

1.3. Reactivity of Au-NHC complexes

The chemistry of Au(I) NHC complexes is predominant. An interesting report was described by Nolan and co-workers, reporting an hydroxide complex of the type $[\text{Au}(\text{OH})(\text{IPr})]$ ($\text{IPr} = N,N'$ -bis(2,6-diisopropylphenyl)imidazol-2-ylidene) synthesized from the commercially available $[\text{Au}(\text{Cl})(\text{IPr})]$. Its reactivity was evaluated, towards different organic compounds with acidic protons (Figure 5). Using this strategy, they easily prepared a series of complexes with phenyl, cyano, hydride, among other ligands in high yields (> 90%). Furthermore, the reaction were carried out in air, and some of the complexes were fully characterized by X-ray diffraction studies. This methodology was very convenient for obtaining more sophisticated structures in an easy way, and in high yields. Probably, the most interesting one was the Gasgosz-type complex $[\text{Au}(\text{NTf}_2)(\text{IPr})]$ ($\text{NTf}_2 =$ bis-(trifluoromethane-sulfonyl)imide), which was previously synthesized by laborious methodologies involving silver-based complexes.⁴

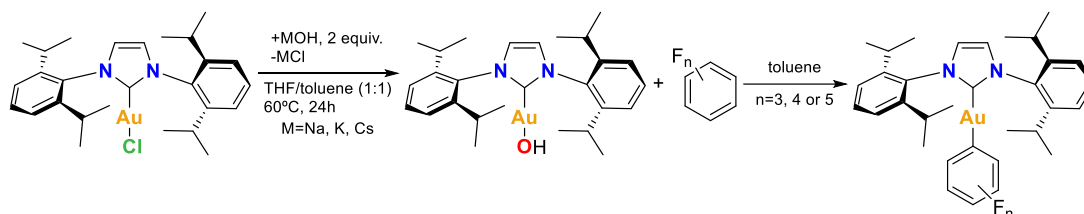


Figure 5. Synthesis of $[\text{Au}(\text{OH})(\text{IPr})]$ complex.

In 2013, Frémont and co-workers described the catalytic activity of a series of cationic NHC gold(I) and gold(III) complexes of the type $[(\text{NHC})\text{Au}(\text{Py})](\text{PF}_6)$ $[(\text{NHC})\text{AuCl}_2(\text{Pyr})](\text{PF}_6)$ respectively (VII, Figure 6).¹⁰ Gold(I) complexes were obtained by reacting $[(\text{NHC})\text{AuCl}(\text{Py})]$ with $[\text{Ag}(\text{PF}_6)]$ and pyridine (Py) in dichloromethane. The high affinity of Ag(I) to halogens, besides the high insolubility of the halogenated silver salt, promotes the reaction. Crystal X-ray analysis showed a practically lineal geometry around gold(I), with an angle between NHC-Au-Py of 179.1° . In order to prepare the Au(III) derivatives, they reacted $[(\text{NHC})\text{Au}(\text{Py})](\text{PF}_6)$ with iodobenzene dichloride at room temperature for 3 hours (Figure 6). The $[(\text{NHC})\text{AuCl}_2(\text{Pyr})](\text{PF}_6)$ complexes were obtained in 84% yield. As expected, the geometry of the metal was slightly distorted square planar, where the Py ligand remains *trans* to NHC ligand. Furthermore, the complexes were catalytically active in the halogenation of aryls, cycloisomerization of propargylic amides, the Meyer-Schuster (*rearrangement of secondary and tertiary propargylic alcohol to α , β -unsaturated ketones*), [3+3] rearrangement and double hydroarylation of diyne diether. In all cases the yield ranges between 56 and 81%.¹⁰

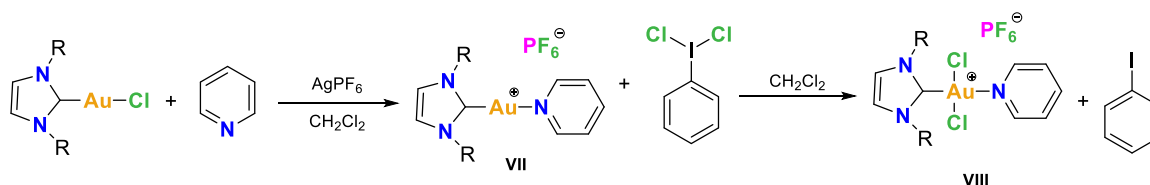


Figure 6. Synthesis of $[(\text{NHC})\text{Au}(\text{I})(\text{Pyr})](\text{PF}_6)$ complex (VII) and the oxidized $[(\text{NHC})\text{Au}(\text{III})(\text{Pyr})(\text{Cl})_2](\text{PF}_6)$ (VIII).

In 2012, Nolan and co-workers described different transmetalation reaction with gold(I) complex. In this case they work with arylboronic acids since organoborons are stable in air. They performed the reaction in different solvents, in Cs_2CO_3 or KOH has a base, and at different temperatures (room temperature, 50°C or 70°C) (Figure 7).³

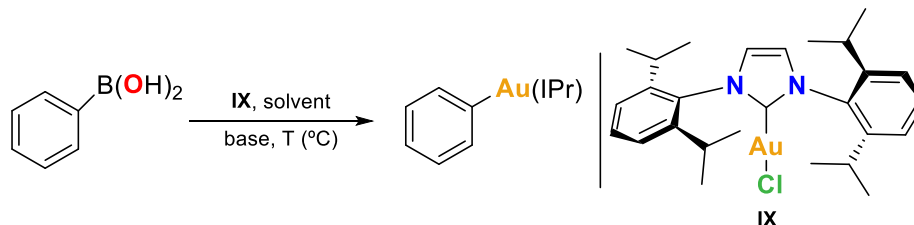


Figure 7. Transmetalation of boronic acid to NHC-Au(I) complexes.

1.4. Gold NHC complexes in catalysis

A catalyzed process involves a reaction rate increase by using an external substance. A catalyzed reaction follows another pathway that decreases the activation energy. According to the nature of the catalytic species, there are two kinds of catalysis: homogeneous and heterogeneous catalysis. In the first one, the reagents and catalyst are in the same phase, while in a heterogeneous catalysis, the catalyst is found in another phase, thus the catalyst can be easily recovered once the reaction finished. However, both types of catalysis are commonly used.²

Recently, gold complexes have exhibited an outstanding catalytic performance. In particular, when a NHC ligand is coordinated to gold generate highly active catalysts. As stated above, NHC ligands may forms a strong bond with a metal through a σ -donation, and in a less extent by a π -backdonation, generating electron-rich metals, which results beneficial to promote some catalytic processes. Moreover, steric and electronic factors contributed to the stability of the NHC complexes.¹¹

The catalytic applications of Au-NHC complexes are very wide, ranging from redox to cross-coupling reaction. They also may act as soft Lewis acids. In the next paragraphs some relevant catalytic applications of Au-NHC complexes are described.

In 2013, Cadierno and his group described the cycloisomerization reaction of γ -alkynoic (Figure 8). In order to carried out this reaction, they used a water soluble NHC-Au(III) complex as catalyst in aqueous media. This procedure allows to obtain enol lactones in an easy and economical way.¹³

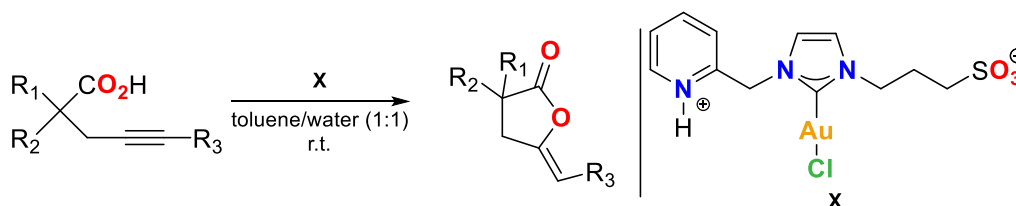


Figure 8. Cycloisomerization of γ -alkynoic acid using a gold(III) catalyst.

Other interesting example was reported by Peris and co-workers. They described the hydroamination of phenylacetylene by Au(I) complexes with polyaromatic-NHC ligands (Figure 9). Interestingly, the addition of pyrene promotes the catalytic reaction by the formation of π - π interactions. The catalytic reaction was tested with a wide range of anilines.⁸

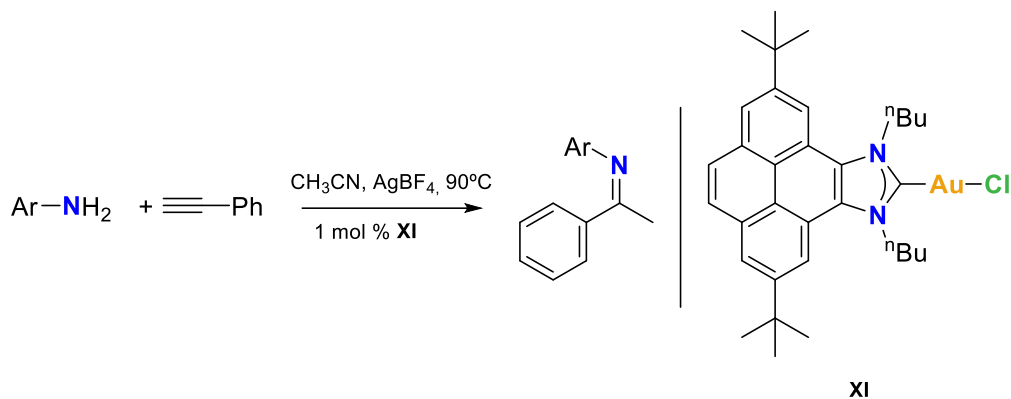


Figure 9. Hydroamination of Phenylacetylene with gold(I).

In 2015, QBIS-CAT research group described the C-N bond formation catalyzed by a Au(I)-NHC catalyst (Figure 10). The reaction of 2-(2-iodophenyl)pyridine with anilines in the presence of the cationic Au(I)-NHC complex afforded the respective *N*-phenyl-2-(pyridin-2-yl)aniline compound in good yields. It is worth to note that, this transformation is typically catalyzed by Cu or Pd¹², and this is one of the few examples of C-N bond formation catalyzed by Au(I) species.

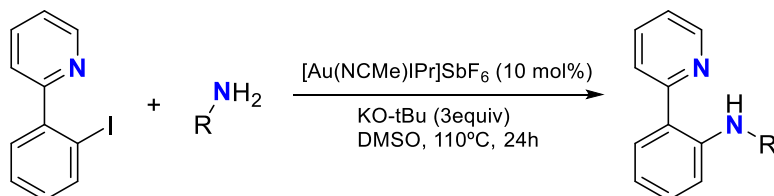


Figure 10. C-N bond catalyzed by a Au(I)-NHC complex.

2. OBJECTIVES

The aim of this project consist in *studying the reactivity of Au(III) bis-NHC complex*. This general objective can be divided in the following more specific objectives:

- Synthesis and characterization of a bis-azolium salt through a reported synthetical methodology. For this purpose we followed the protocol described by Joon Cho and co-workers (*Figure 11*).¹

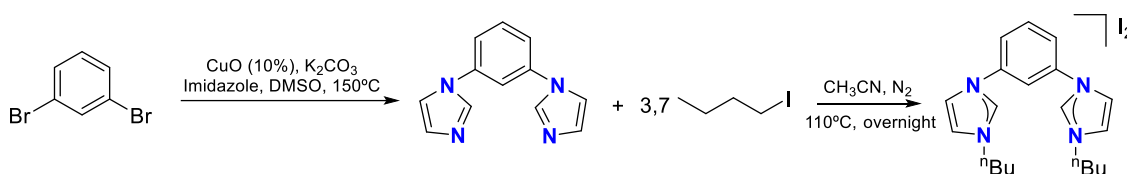


Figure 11. Reaction of the synthesis of 1,3-di-(imidazolium)benzene.

- Preparation of Au(III)-pincer complex (*Figure 12*) where the Y are going to be PF_6^- and R, ⁿbutyl.

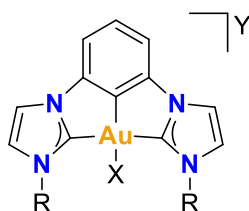


Figure 12. Au(III)-pincer complex.

- Characterize the obtained compounds by NMR spectroscopy and mass spectrometry. When possible, the molecular structure of the isolated compound will be confirmed by X-ray diffraction.
- Reactivity evaluation of the obtained gold(III)-NHC complex. Once the complex is obtained, its reactivity and catalytic activity in cross coupling reactions will be evaluated.

3. RESULTS AND DISCUSSION

3.1. Synthesis and characterization of bis-azolium salt

The desired bis-azolium salt was synthesized in three steps from 1,3-dibromobenzene. The first step consisted in the reaction between 1,3-dibromobenzene with imidazole in the presence of a catalytic amount of Cu(II) (Figure 13). This reaction was previously described and allows the synthesis of 1,3-di(imidazole)benzene in high yield (75%).¹

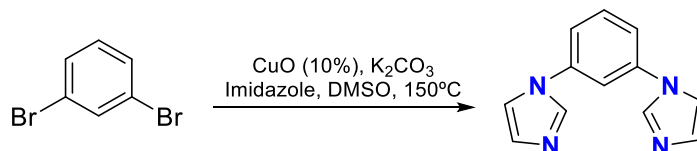


Figure 13. Synthesis of 1,3-di(imidazole)benzene.

The second step consist in the quaternization of the nitrogen atoms to afford the bis(azolium) salt **1** (Figure 14). This reaction was carried out with an excess of 1-iodobutane at 110°C under nitrogen atmosphere. The reaction was left overnight, following by the precipitation of the product by the addition of diethyl ether. The incorporation of the butyl fragments provides a suitable solubility in organic solvents of the desired azolium and to the related complexes, which is very important to evaluate their reactivity.

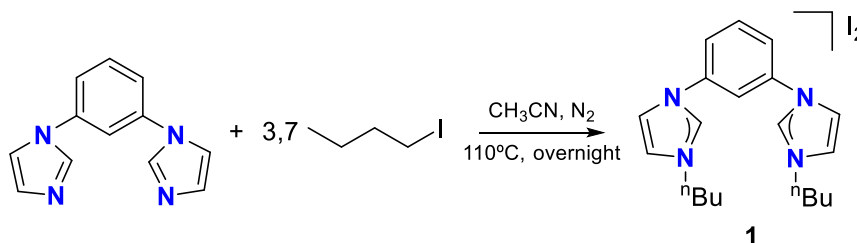


Figure 14. Synthesis of the bis-azolium salt **1**.

Finally, we decided to exchange the iodide counteranion by PF₆⁻. For this purpose, we react **1** with an excess of NH₄PF₆ in methanol at room temperature overnight to obtain compound **2** (Figure 15) (43%). We corroborated the molecular structure of **2** by ¹H-NMR. In the typical region of aliphatic protons, we observed the corresponding signal of the butyl fragment. Whereas, in the aromatic proton region, we observed the signals of the aryl and imidazole fragments. The characteristic signal of the acidic protons (NCHN) was observed as a singlet at 9.7 ppm. This last signal is very typical for azolium salts, and the chemical shift is typical for this kind of compounds.¹

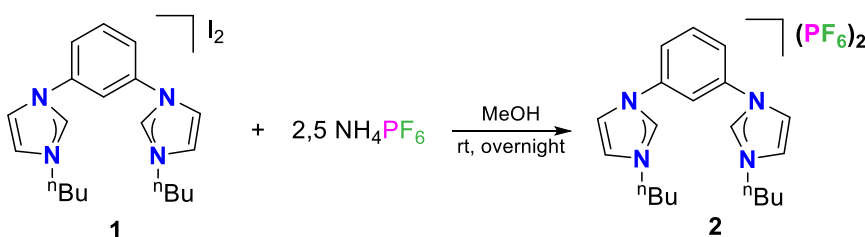


Figure 15. Exchange of the iodide counteranion by PF₆⁻ to obtain compound **2**.

With the azolium salt in hand, we decided to prepare the corresponding gold(I) complex. Thus, the reaction of chloro(triphenylphosphine)gold(I) with **2** in the presence of cesium carbonate in acetone at 50 °C afforded the bimetallic complex **3** (Figure 16). The same product was observed when we used chloro(Diethylsulfide)gold(I) and triphenylphosphine instead of chloro(triphenylphosphine)gold(I). In both cases, after the reaction time we observed a purple precipitate in the reaction, which presumably corresponds to a gold(0) species, but it was not identified or isolated. In order to purify the desired complex, we filtered the solution through a short pad of Celite®. Then, the acetone was removed, and the solid residue was washed several times with diethyl ether to remove the remaining triphenylphosphine.

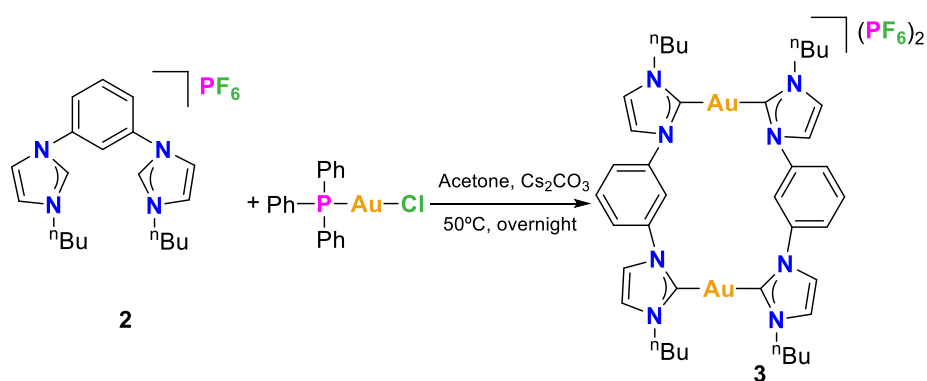


Figure 16. Synthesis of gold(I) complex.

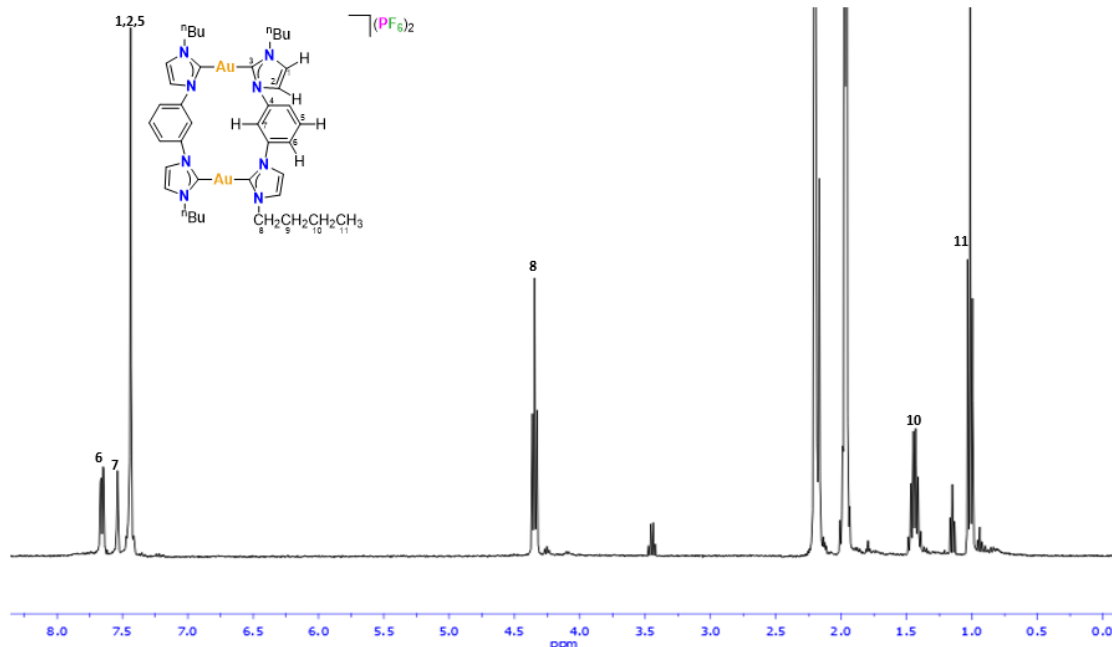


Figure 17. $^1\text{H-NMR}$ of compound **3** in CD_3CN .

Complex **3** was characterized by ESI-MS, ^1H and ^{13}C NMR. The first indication that confirms the formation of the complex was observed in its $^1\text{H-NMR}$ spectrum, due to the signal of the NCHN was not observed, and the signal of the $-\text{NCH}_2-$ fragment was slightly shifted to downfield.

In principle we were interested in obtaining a gold(III) pincer complex, engaging simultaneously the two NHC coordination and formation of the aryl-Au(III) via C-H activation. Therefore, we decided to oxidize complex **3** with bromine (Figure 18). The reaction was easily carried out in dichloromethane at room temperature overnight. The product was precipitated by adding hexane to the reaction mixture, affording complex **4** was isolated in good yield, reaching 85 %. The characterization of this complex (see below) clearly showed a bimetallic Au(III) nature instead of the monometallic pincer Au(III) complex.

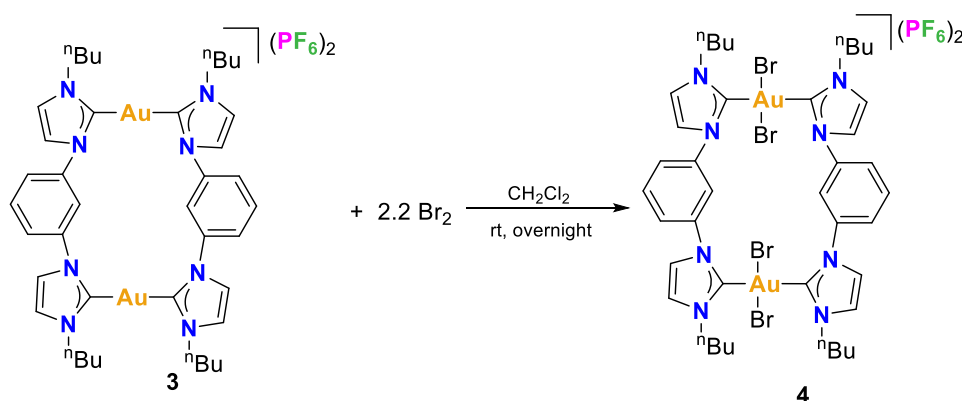


Figure 18. Oxidation of gold(I) with bromine.

Complex **4** was characterized by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, ESI-MS and XRD. Figure 19 shows the $^1\text{H-NMR}$ spectrum of complex **4**, which is very similar to that recorded for complex **3** (Figure 17). The signal of the acidic proton (NCHN) between 9.5-10 ppm was not observed, either. The resonances due to the diastereotopic protons of the $-\text{NCH}_2-$ moiety are displayed between 4.2 and 4.5 ppm. The rests of the signals were assigned by HSQC and HMBC 2D-NMR experiments.

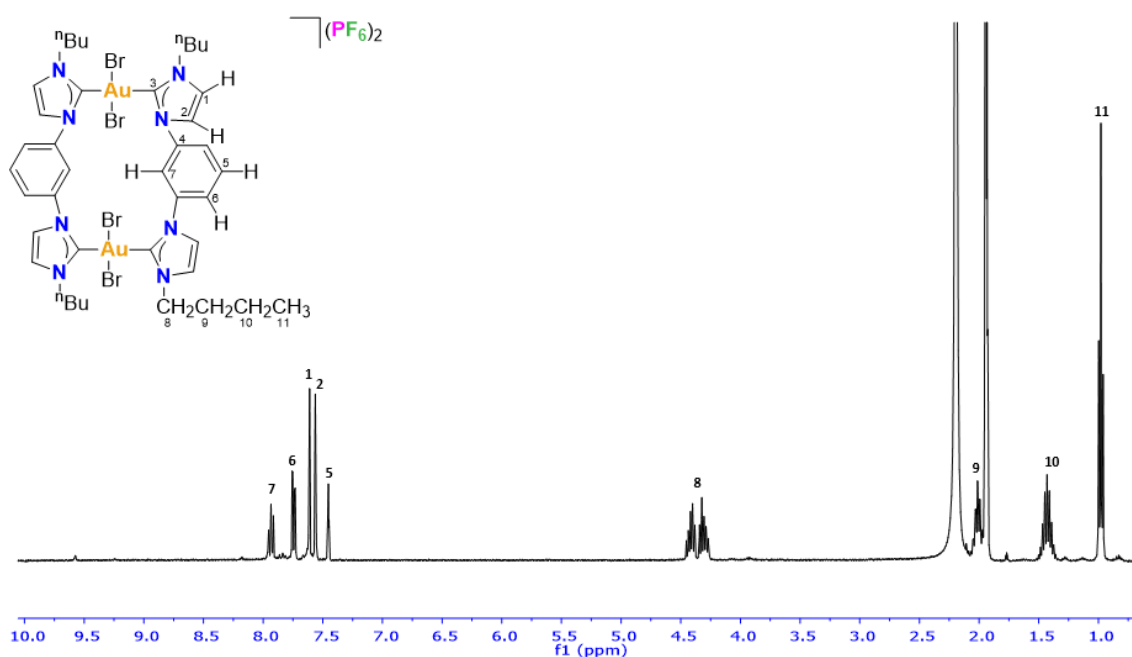


Figure 19. $^1\text{H-NMR}$ of the compound **4** in CD_3CN .

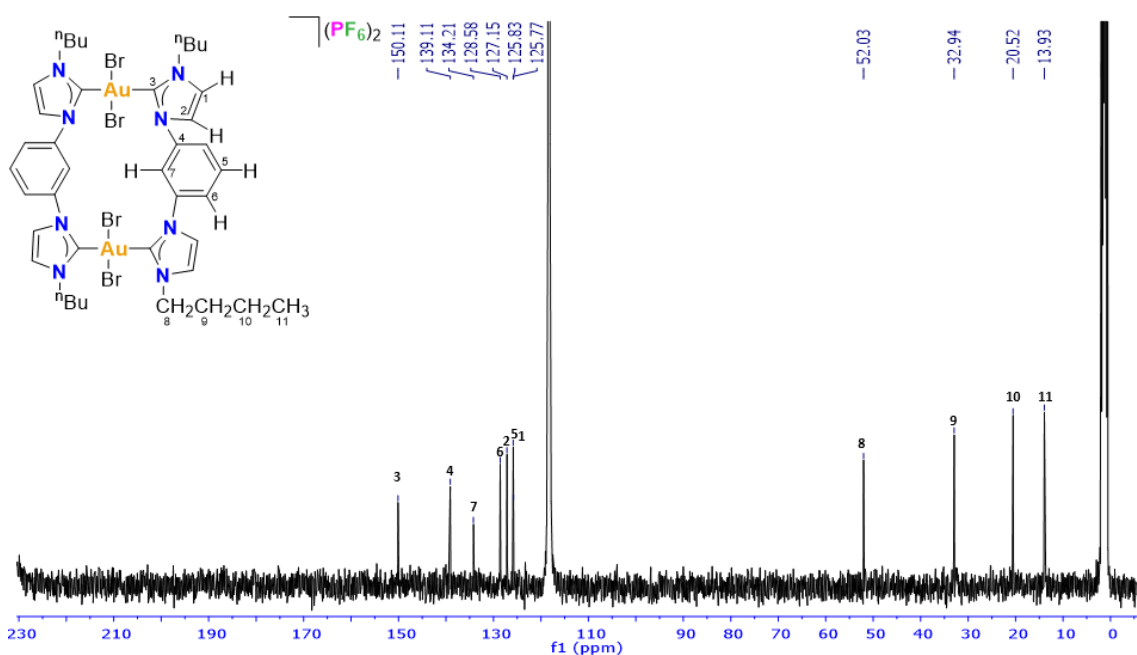


Figure 20. ^{13}C -NMR of the compound **4** in CD_3CN .

Moreover, crystals of complex **4** suitable for X-ray diffraction analysis were obtained by slow diffusion of hexane into a dichloromethane solution of the compound. The molecular structure of **4** confirms the bimetallic nature of the compound (Figure 21). The each bis-NHC ligand is coordinated to two gold fragments, which completes their coordination sphere with two bromine ligands, affording the expected square-planar geometry for a Au(III) center. The Au-Br distance is 2.42 Å, while the Au-C_{carbene} is shorter, 2.03-2.02 Å.

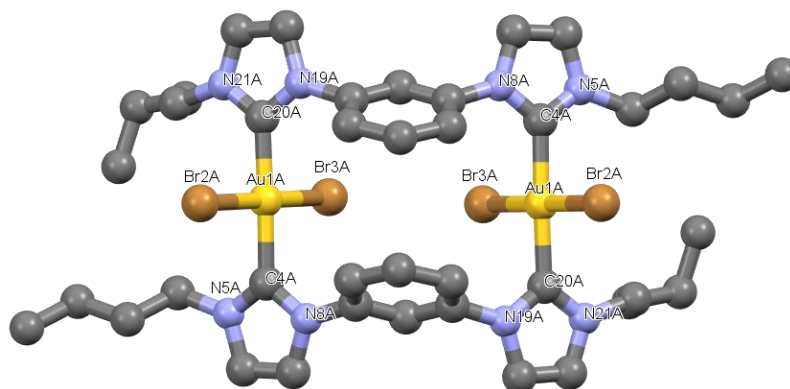


Figure 21. Crystal structure of **4**. Ellipsoids are at 30% probability. Hydrogen atoms and PF_6^- counteranions have been omitted for clarity.

3.2. Reactivity studies of bimetallic Au(III)-NHC complex **4**

First we tried to react compound **4** with AgSbF_6 , in neat pyridine, expecting to change the bromine ligands by pyridine and the precipitation of AgBr (Figure 22). The coordination of the pyridine may strain the structure, and consequently the complex might form a new structure. The reaction was left for four days at room temperature and constant stirring. During this time the color of the mixture was yellow.

Afterward, the reaction was filtrated and washed with hexane to eliminate the pyridine, the obtained solid residue was white and insoluble. However, in the $^1\text{H-NMR}$ we could not observe the expected results and complex **5** was not formed. ESI-MS shows peaks corresponding to **4**.

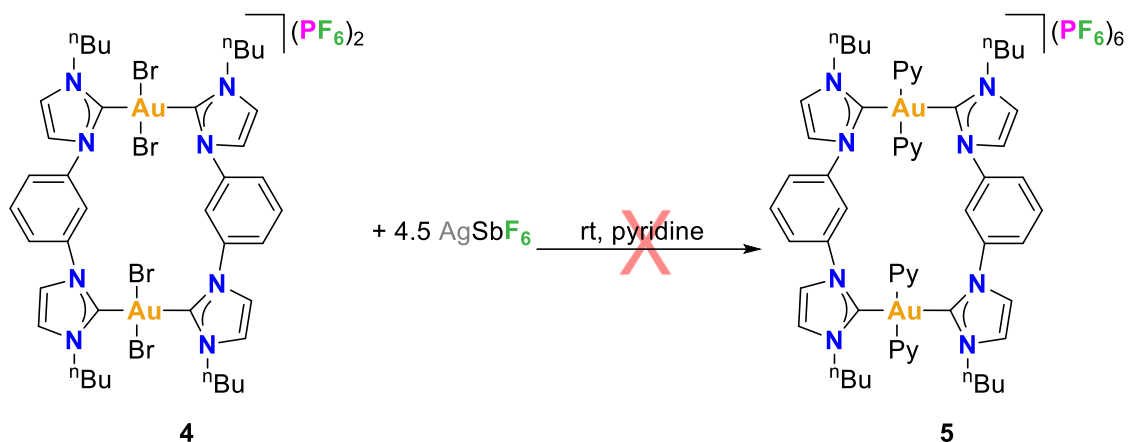


Figure 22. Attempt to exchange the Br^- anion for Py to obtain complex **5**.

Moreover, we tried to coordinate benzoic acid to gold instead of two bromine atoms. The reaction was performed in two stages. The first one was the deprotonation of the benzoic acid with potassium carbonate (*Figure 23*), and in the other the bromine atoms were removed from compound **4** with AgSbF_6 . Then, both solutions were mixed together. This procedure was carried out under anhydrous condition in the glovebox. Nevertheless, the ESI-MS showed that the reaction did not take place, instead the counteranion PF_6^- was changed by SbF_6^- only.

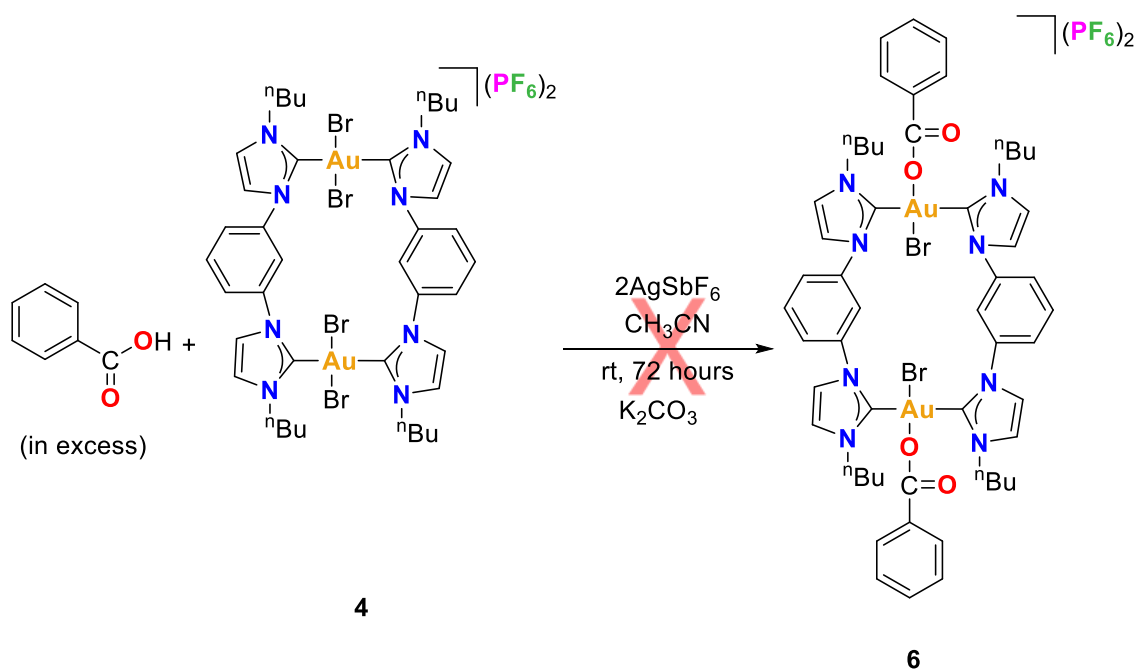


Figure 23. Attempt to exchange Br^- anions by benzoate to obtain **6**.

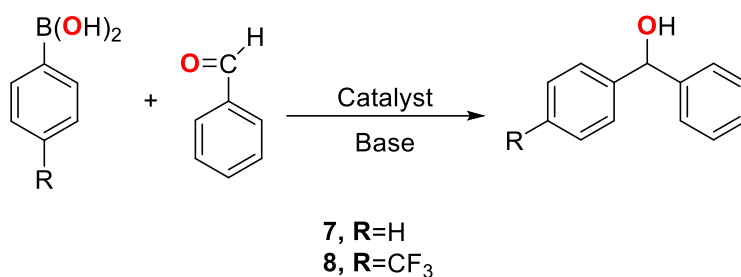
3.3. Catalytic evaluation of bimetallic Au(III) complex 4

Despite the lack of reactivity of complex **4**, we tried to perform some catalytic reactions. In the next paragraphs are summarized some of them.

Arylation of aldehydes

The arylation of aldehydes was performed with phenyl boronic acid and benzaldehyde in the presence of complex **4** in catalytic amounts. *Table 1* shows some tested reaction conditions. In all the catalytic reactions was used 10 % mmol of catalyst and the reactions were carried out for 24 hours. Also, we tried with different solvents and temperatures. However, the products **7** and **8** that we were expecting was not formed in any case.

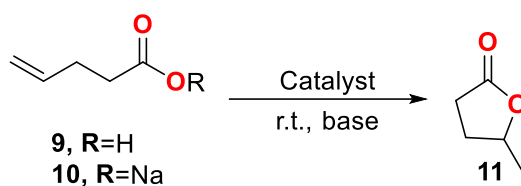
Table 1. Different reaction conditions studied for the arylation of aldehydes using the compound **4**.



| Entry | R | Base | Solvent | T (°C) | Product 7 |
|-------|-----------------|------------------------------------|----------------------|--------|-----------|
| 1 | H | — | DMSO d ₆ | 150 | ND |
| 2 | H | KOC(CH ₃) ₃ | DMSO d ₆ | 150 | ND |
| 3 | H | K ₂ CO ₃ | DMSO d ₆ | 150 | ND |
| 4 | H | KOC(CH ₃) ₃ | <i>Tert</i> -butanol | 100 | ND |
| 5 | H | KOC(CH ₃) ₃ | <i>Tert</i> -butanol | 80 | ND |
| 6 | H | KOC(CH ₃) ₃ | CD ₃ CN | 80 | ND |
| 7 | CF ₃ | KOC(CH ₃) ₃ | <i>Tert</i> -butanol | 80 | ND |

Cycloisomerization of 4-pentanoic acid

Another gold catalysis described in literature was the cycloisomerization of an unsaturated acid with Au(III). So, we tried to perform the reaction in different conditions *Table 2*, with 5 mol% of the catalyst **4**.¹³ Firstly, we carried out the reaction of 4-pentanoic acid in acetonitrile, however we did not observe the formation of the desired product. Then, we decided to start with the corresponding salt of the acid. Thus, previous to the catalytic reaction, we performed the reaction of 4-pentanoic acid with sodium hydride in THF under N₂ atmosphere (inside the glovebox). Unfortunately, the formation of the lactone was not observed in any case.

Table 2. Cycloisomerization of 4-pentanoic acid using compound **4**.

| Entry | R | Time (hours) | Solvent | Product 12 |
|----------|----|--------------|---------------------------------------|-------------------|
| 1 | H | Overnight | CH ₃ CN | ND |
| 2 | Na | 48 h | CH ₃ CN | ND |
| 3 | Na | Overnight | CH ₃ CN/CH ₃ OH | ND |

4. CONCLUSIONS

In this project, it was demonstrated that is possible to synthesize complex **4**, which is a dimeric NHC-gold(III) complex with two PF_6^- as counteranions. The synthesis of this complex was carried out in different steps, and each reaction could be followed by $^1\text{H-NMR}$ to determine if the intermediate species were formed. Moreover, complex **4** was fully characterized by different spectroscopic techniques, and its molecular structure was unambiguously determined by X-ray diffraction analysis.

Complex **4** is very stable because under the different tested reaction conditions we were not able to remove or exchange any bromine ligands. Furthermore, we did not observed any product formation in reactions catalyzed by this complex, i.e. arylation of aldehydes or cycloisomerizations of 4-pentanoic acid, which is most likely due to the stability conferred by the coordinated bromides.

The sought monometallic pincer Au(III) complex could not be obtained and more efforts should be devoted to achieve this goal.

5. EXPERIMENTAL SECTION

5.1. Materials

Solvents and reagents used during this project are commercially available and were used as received.

5.2. Instrumentation

Nuclear magnetic resonance (NMR): ^1H -NMR and ^{13}C -NMR spectra were performed in a Bruker Ultrashield Advance III400.

Mass spectrometry (MS): Mass spectra were performed using electrospray ionization source (ESI) on a Bruker Daltonics Esquire 6000 spectrometer.

XRD: Monocrystal X-Ray diffraction was performed with a Bruker D8 QUEST ECO diffractometer.

5.3. Synthesis of gold complexes

Synthesis of the bis-azolium salt

Compound 1,3-di-(imidazol)benzene was synthesized following a procedure described in literature (Figure 24) (Yield: 75 %).¹ ^1H -NMR (400 MHz, CDCl_3) δ (ppm): 7.93 (s, 2H, NCHN), 7.63 (t, 1H, H_{Ar}), 7.48 – 7.43 (m, 2H, H_{Ar}), 7.43 – 7.40 (m, H_{Ar}), 7.35 (s, 2H, H_{Im}), 7.27 (s, $J = 5.7$ Hz, 2H, H_{Im}).

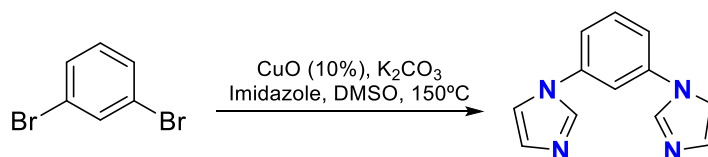


Figure 24. Synthesis of 1,3-di-(imidazole)benzene.

A vial was charged with 1,3-di(imidazole)benzene (300 mg, 1.4 mmol), 1-iodobutane (0,6 mL, 5.3 mmol), and CH_3CN (1 mL) under N_2 atmosphere. The resulting solution was heated at 110 °C overnight. Then, the reaction was cooled to room temperature, and the addition of diethyl ether produced the precipitation of a solid. This product was used without an extra purification in the next step. To a concentrated methanol solution of compound **1** (0.52 mmol) was added NH_4PF_6 (0.2020 g, 1.3 mmol) (Figure 25). The solution was stirred at room temperature overnight. Then, the formed solid was filtered and washed with methanol and diethyl ether. (Yield: 43 %) The spectroscopic data was similar to that described in the literature.¹ ^1H -NMR (400 MHz, DMSO-d_6) δ (ppm): 9.91 (s, 2H, NCHN), 8.39 (br s, 2H, H_{Im}), 8.33 – 8.26 (m, 1H, H_{Ar}), 8.12 (s, 2H, H_{Im}), 8.04 – 7.93 (m, 3H, H_{Ar}), 4.29 (t, $J = 7.2$ Hz, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.89 (q, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.36 (sx, 4H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.95 (t, $J = 7.4$ Hz, 6H, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

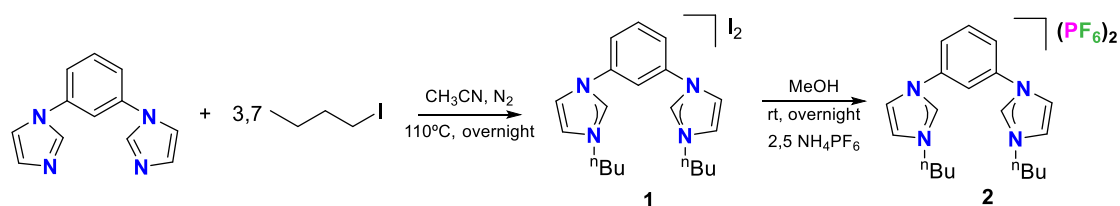


Figure 25. Synthesis of the bis-azolium salt **2**.

Synthesis of complex **3**

A solution of the bis-azolium salt (50 mg, 0.03 mmol), chloro(triphenylphosphine)gold(I) (52.5 mg, 0.1 mmol) and cesium carbonate (76 mg, 0.16 mmol) was heated at 50 °C overnight (*Figure 26*). Then, the solution was cooled to room temperature, filtered through Celite®, and all volatiles were removed under high vacuum (yield: 88 %). The solid residue was washed with diethyl ether several times, and dried under high vacuum. The spectroscopic data was similar to that described in the literature.² ¹H-NMR (400 MHz, CD₃CN) δ (ppm): 7.69 – 7.62 (m, 4H), 7.56 – 7.51 (m, 2H), 7.48 – 7.40 (m, 10H), 4.35 (t, J = 7.1 Hz, 8H), 1.53 – 1.33 (m, 8H), 1.05 – 0.96 (m, 12H).

ESI-MS (m/z): $[M-PF_6]^+ = 1183.3$, $[M-2PF_6]^{2+} = 519.2$

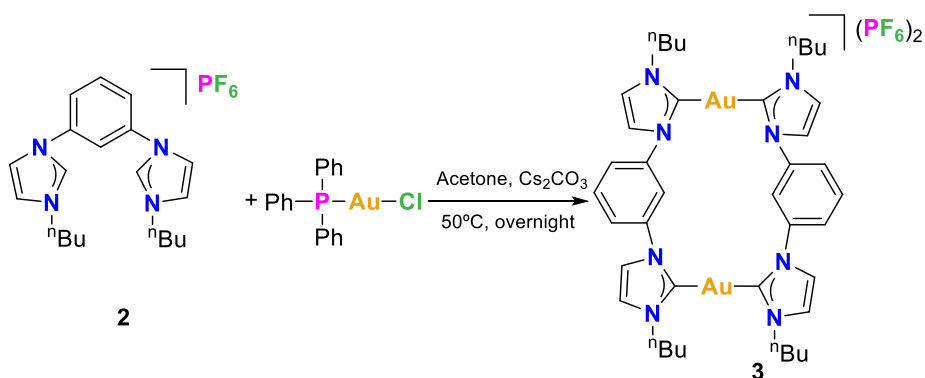


Figure 26. Coordination of the gold(I) to the structure.

To a dichloromethane (2mL) solution of complex **3** (25.7mg, 0.02 mmol) was added dropwise bromine (2.19 μ L, 0.04 mmol). The solution was stirred at room temperature overnight (Figure 27). Then, the addition of hexane produced the precipitation of the desired product, which was filtered and washed with diethyl ether. Yield: 85 %.

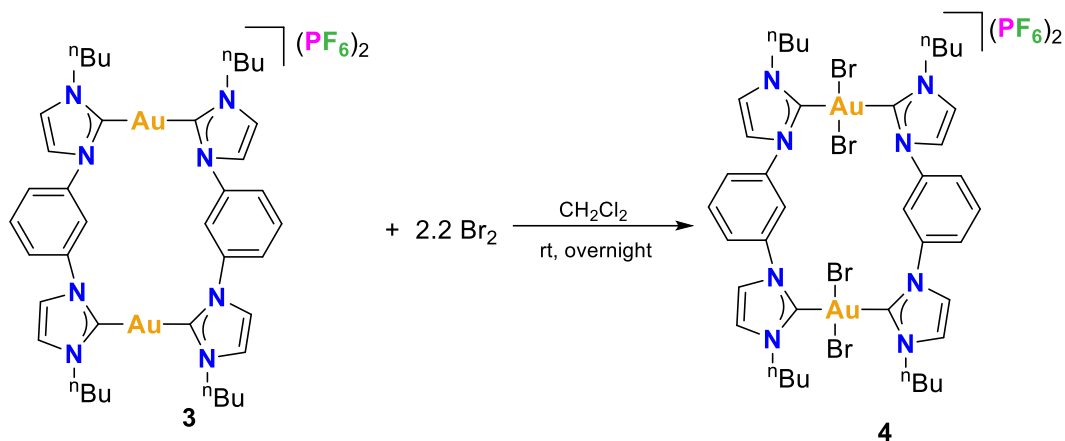


Figure 27. Oxidation of the complex 4 with bromine.

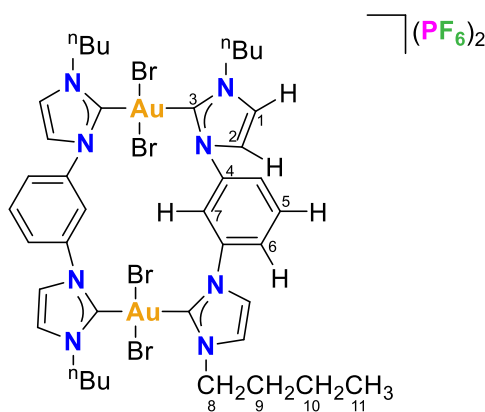


Figure 28. Structure complex 4.

$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ (ppm): 7.98 – 7.88 (m, 2H, H_7), 7.78 – 7.71 (m, 4H, H_6), 7.65 – 7.60 (m, 4H, H_1), 7.60 – 7.54 (m, 4H, H_2), 7.45 (t, $J = 2.0$ Hz, 2H, H_5), 4.50 – 4.23 (m, 8H, H_8), 2.07 – 1.96 (m, 8H, H_9), 1.56 – 1.31 (m, 8H, H_{10}), 0.98 (t, $J = 7.4$ Hz, 12H, H_{11}).

$^{13}\text{C-NMR}$ (101 MHz, CD_3CN) δ (ppm): 150.1 C_3 , 139.1 C_4 , 134.2 C_7 , 128.6 C_6 , 127.2 C_2 , 125.8 C_5 , 125.8 C_1 , 52.0 C_8 , 32.9 C_9 , 20.5 C_{10} , 13.9 C_{11} .

ESI-MS (m/z): $[\text{M-PF}_6]^+ = 1502.8$, $[\text{M-2PF}_6]^{2+} = 679.0$

Reactivity of complex 4

To coordinate the Au-NHC complex with pyridine, structure **4** is mixed with AgSbF_6 and 1 mL of pyridine is added. This reaction was carried out for 48 hours at room temperature (*Figure 22*). The solid was filtered and washed with hexane, but the complex **5** was not obtained and starting complex **4** was detected by ESI-MS.

Coordination of Au-NHC complex with benzoic acid

This reaction was made in two vials in the glovebox. In the first one, the benzoic acid (1.5 mg, 0.01 mmol) was deprotonated using potassium carbonate (1.7 mg, 0.01 mmol) in 1 mL of acetonitrile. In the second vial complex **4** (10 mg, 0.006 mmol) was dissolved with 1 mL of acetonitrile and AgSbF_6 was added (4.2 mg, 0.01 mmol). This is filtered in the first vial to eliminate the AgBr . The reaction was performed inert atmosphere, at room temperature and for 72 hours (*Figure 23*). The desired product was no obtained.

5.4. Gold catalysis

Aldehyde arylation

In a vial was added the complex **4** (3 mg, 10 mmol%), the corresponding boronic acid (0.02 mmol), the benzaldehyde (2.29 μL , 0.02 mmol), the corresponding base (0.02 mmol) and 1mL of solvent. The temperature was varied for the different reaction between 80 and 150 $^\circ\text{C}$ (*Table 1*). However, all of them were done for 24 hours. The desired products were not obtained.

Cycloisomerization of 4-pentanoic acid

For this catalysis, to the corresponding acid, gold (III) catalyst was added (10 mg, 5 mmol%) as well as 1 mL of the corresponding solvent. The reaction took place at room temperature (*Table 2*). Entry 1 and 3 was overnight however entry 2 was 24 hours reacting. The entry 3 before to add the product to the catalyst was solved in methanol.

5.5. Crystallographic data

Table 3. Crystal data and structure refinement for complex 4.

| | |
|---|---|
| Identification code | SE16-Complex 4 |
| Empirical formula | C ₁₂₄ H ₁₆₄ Au ₆ Br ₁₂ Cl ₈ F ₃₆ N ₂₄ P ₆ |
| Formula weight | 5284.92 |
| Temperature/K | 100.(2) |
| Crystal system | monoclinic |
| Space group | C2/c |
| a/Å | 37.48(4) |
| b/Å | 21.46(3) |
| c/Å | 24.07(3) |
| α/° | 90 |
| β/° | 105.00(2) |
| γ/° | 90 |
| Volume/Å ³ | 18700.(40) |
| Z | 4 |
| ρ _{calc} /cm ³ | 1.876 |
| μ/mm ⁻¹ | 7.499 |
| F(000) | 10080.0 |
| Crystal size/mm ³ | 0.270 × 0.200 × 0.110 |
| Radiation | Mo Kα (λ = 0.71076) |
| 2θ range for data collection/° | 4.96 to 56.68 |
| Index ranges | -50 ≤ h ≤ 50, -28 ≤ k ≤ 28, -32 ≤ l ≤ 32 |
| Reflections collected | 416371 |
| Independent reflections | 23203 [R _{int} = 0.1049, R _{sigma} = 0.0432] |
| Data/restraints/parameters | 23203/82/1000 |
| Goodness-of-fit on F ² | 1.140 |
| Final R indexes [I >= 2σ (I)] | R ₁ = 0.0992, wR ₂ = 0.2363 |
| Final R indexes [all data] | R ₁ = 0.1696, wR ₂ = 0.3041 |
| Largest diff. peak/hole / e Å ⁻³ | 9.23/-4.95 |

5.6. Ethical and sustainability criteria

The use of catalysts helps to minimize the waste produced in a synthetic process, allowing the development of more eco-friendly routes. Halogenated solvents were not used in excess during this project, and used, disposed in the correct tanks for selective recycling or destruction. However, we may try to change cesium carbonate by potassium hydroxide, in a similar way that is described in some reports found in literature.³ The residues obtained were handled correctly.

In this project all the information is cited correctly in the bibliography, and the results that I presented has no modified or falsified.

5.7. Gender criteria

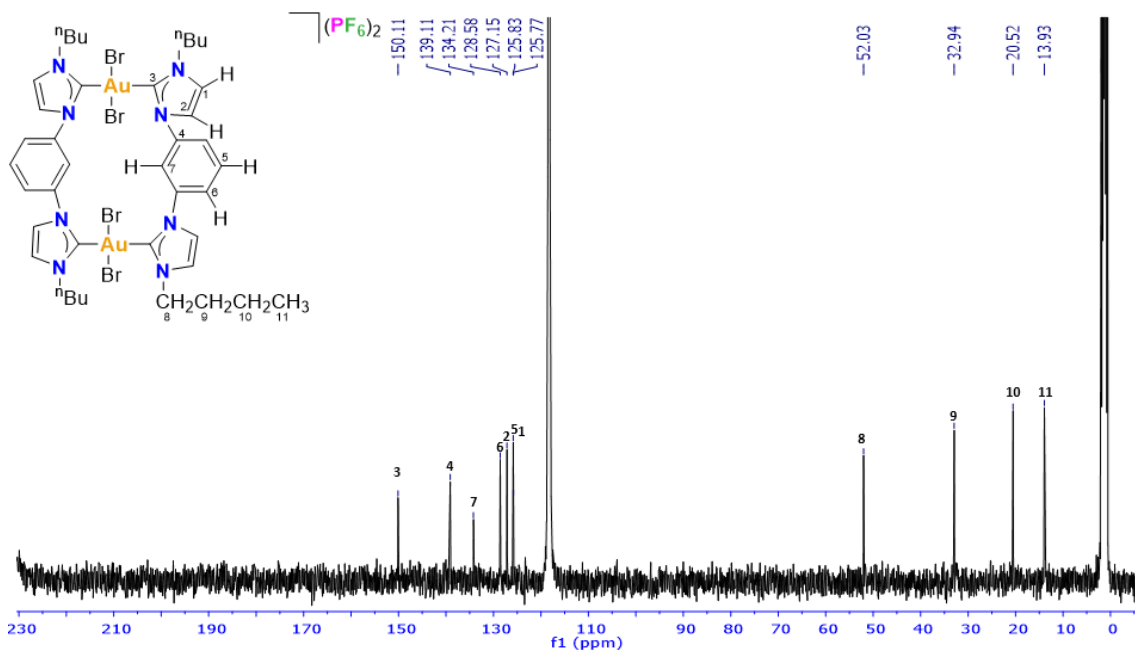
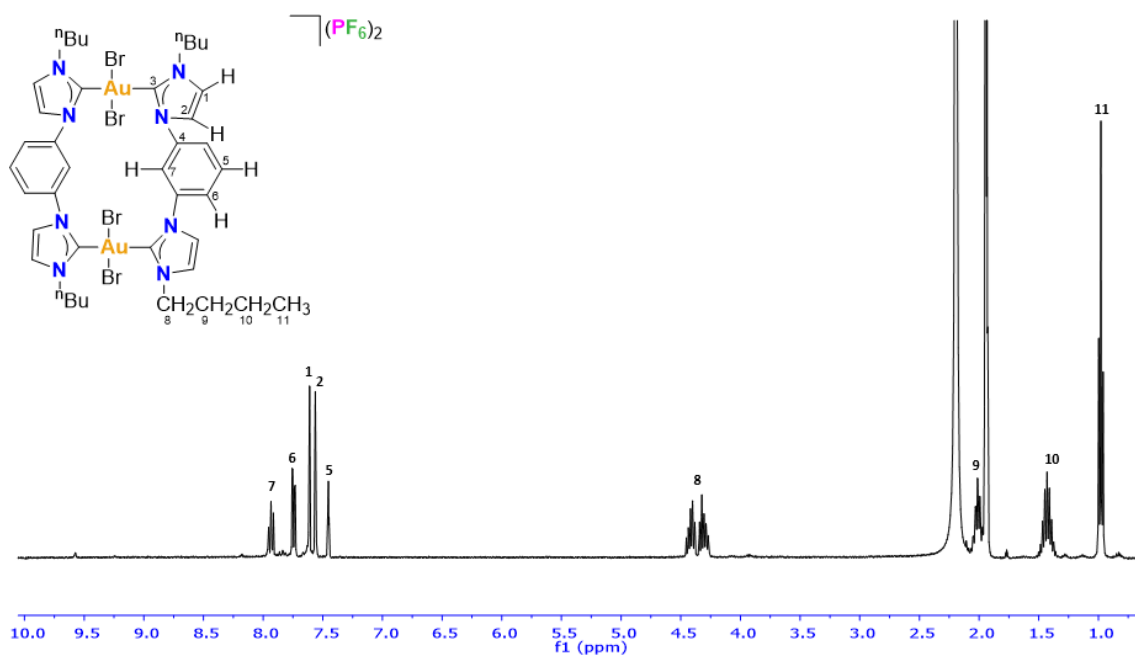
During the years of my degree I could notice that there are more men than women in science. Also from my point of view I have not been in any situation where the gender was important or makes the difference in results. I expect that in the future this gap between men and women, will be significantly reduced as for instance in my promotion, a huge difference between men and women could not be observed.

In the group where I was doing my final project, I could observe equality among all the students of both genders (PhD and post doc students). I am aware that in a several situations the number of men is higher than women and they are in the highest positions. Obviously, I do not find thus appropriate, however I hope that with the generations that are coming this can be changed.

From the bibliography some of the papers used were written by women although it is not easy to find one.

6. ANNEX

Characterization of the complex **4**:



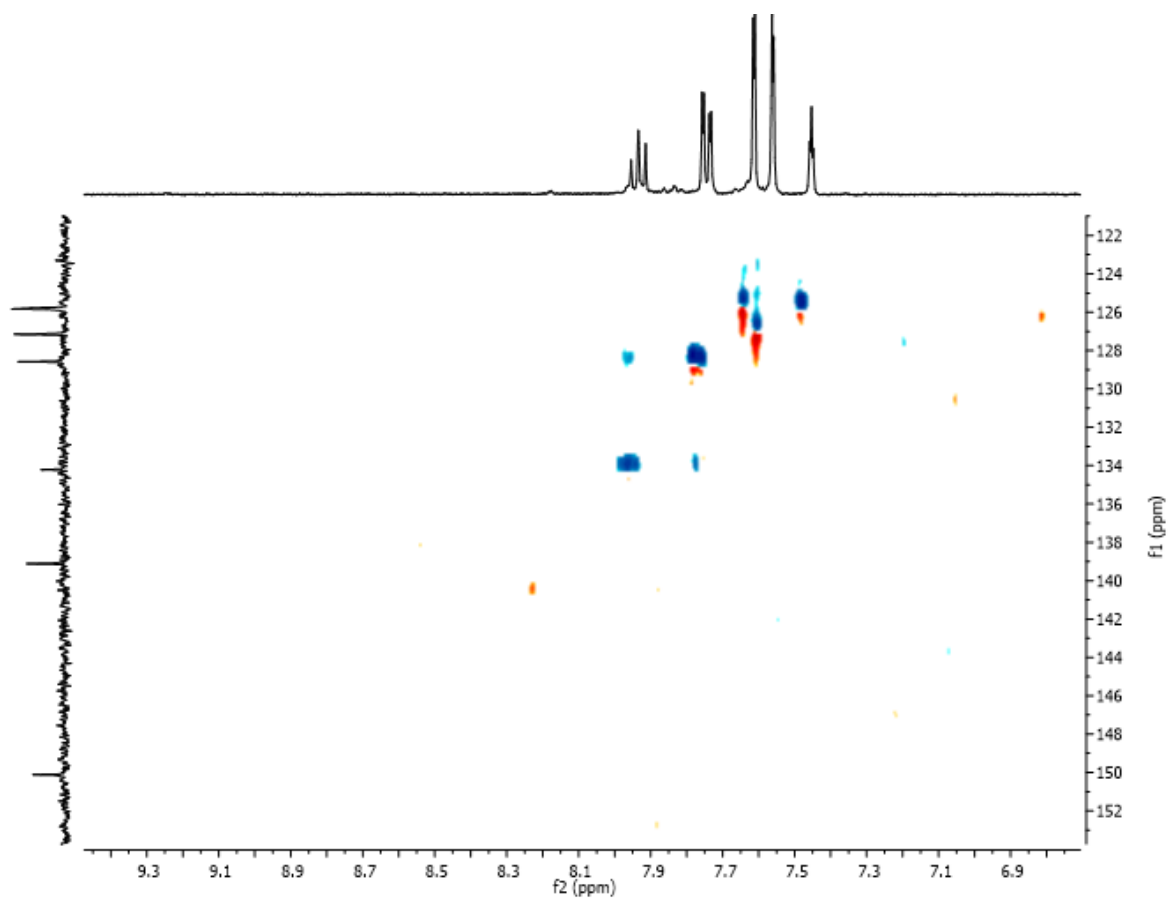


Figure 31. HSQC of the structure **4** in CD₃CN.

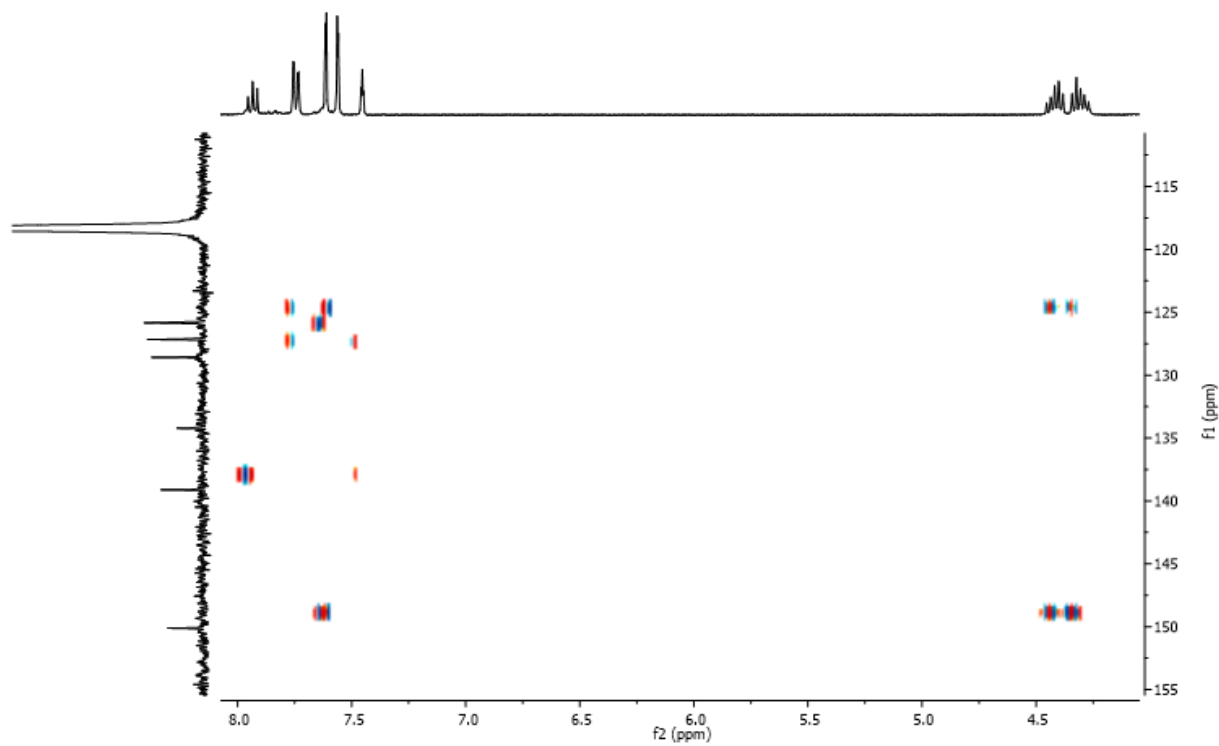


Figure 32. HMBC of the structure **4** in CD₃CN.

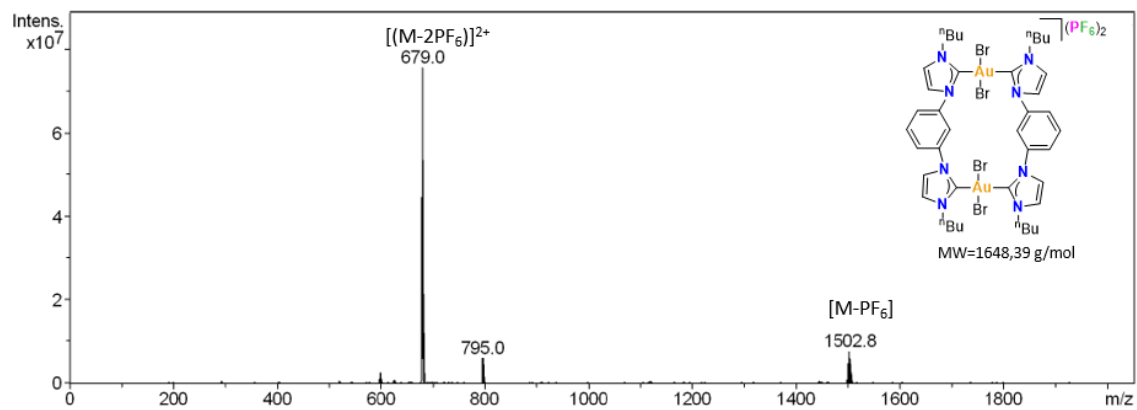


Figure 33. ESI-MS of the structure 4.

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