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Grau de Química

Trabajo Fin de Grado

Synthesis and characterization of cyclometallated complexes of imines: 4-$ClC_6H_4CH=NCH_2(4'-FC_6H_4)$ and 2,3-$F_2C_6H_3CH=NCH_2(4'-FC_6H_4)$. Expanding the scope of cyclopalladations.

Síntesis y caracterización de los complejos ciclometalados de las iminas: 4-$ClC_6H_4CH=NCH_2(4'-FC_6H_4)$ y 2,3-$F_2C_6H_3CH=NCH_2(4'-FC_6H_4)$. Ampliando horizontes en el ámbito de las ciclopaladaciones.

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January 2019

Universitat de Barcelona

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We think there is color, we think there is sweet,
we think there is bitter, but in reality
there are atoms and a void.

Democritus

Aunque no lo parezca, estas líneas han sido de las más difíciles de redactar de todo el TFG, pues no es fácil expresar en palabras, y menos aún en media hoja, todos estos sentimientos hacia la gente que ha hecho posible que hoy concluya una etapa de mi vida.

En primer lugar, quiero agradecerle al Dr. Granell por todo su tutelaje y paciencia a lo largo de este proyecto. He tenido la oportunidad de trabajar para uno de los mejores investigadores de los que la UB dispone. También hay que decir que, debido a ello, ha sido duro mantener el listón siempre alto para no defraudarle. Gracias a él he podido llegar a ver la punta del iceberg de la química de los ciclopaladados, ver cómo es el funcionamiento en un laboratorio de investigación y aprender cómo es el trabajo de un científico en busca de nuevos productos. También quería agradecer al Dr. Albert el hecho de que en el laboratorio siempre estuvo dispuesto a debatir cuestiones de los ciclometalados y así ayudarme a impregnarme e interesarme aún más sobre el tema. Por supuesto, no podrían faltar mis padres, por aguantarme durante todo este tiempo, por confiar siempre en mí y nunca tirar la toalla. Ha sido una historia larga en la que, por desgracia, ha habido más bajadas que subidas y sin ellos este día nunca habría llegado. A mi pareja, Alicia, por ayudarme a presentar un trabajo con el menor número de erratas posibles y por pulirlo, aunque debido a ello haya tenido que leer casi unas 40 hojas de cosas que le sonaban a chino. A mis amigos más cercanos porque ellos también han estado ahí apoyándome… a su manera. También quería tener un par de agradecimientos con todos los docentes con los que me he encotnrado a lo largo de la carrera porque, exceptuando a un par, he tenido la oportunidad de toparme con grandes profesionales, sin los cuales hoy no estaría aquí.

REPORT

CONTENTS

1. SUMMARY

The treatment of 4-fluorobenzylamine with 4-chlorobenzaldehyde or 2,3-difluorobenzaldehyde in acetone at 80ºC afforded the corresponding imines (**1**), 4-$ClC_6H_4CH{=}NCH_2(4'\text{-}FC_6H_4)$ and 2,3-$F_2C_6H_3CH{=}NCH_2(4'\text{-}FC_6H_4)$ respectively, which were isolated in a yield >90%. The same reaction was performed in milder conditions obtaining similar results. The imines (**1**) reacted with a stoichiometric amount of $Pd(OAc)_2$ in acetic acid affording the corresponding acetato-bridged five-membered *ortho*-cyclopalladated dimers (**2**) in 44-69% yield. The reaction was reproduced in different conditions to improve the yield, obtaining the best results at 85ºC for 1h. Compounds **2** were converted by a metathesis reaction with an excess of LiCl and LiBr in acetone into the corresponding chloro- or bromo-bridged dinuclear cyclopalladated compounds. The stoichiometric amount of PPh_3 and dppe was added to the halogen-bridge compounds to obtain the mononuclear compounds *trans*-N,L-[Pd{$RHC{=}NCH_2(4'\text{-}FC_6H_4)$}(X)(L)] [**3-A** (R= 4-$ClC_6H_4$, X= Br, L= PPh_3); **3-B** (R= 2,3-$F_2C_6H_3$, X = Br, L = PPh_3); **4-A** (R= 4-ClC_6H_4, X= Cl, L= PPh_3); and the dinuclear compounds **5-A** (R= 4-ClC_6H_4, X= Br, L= dppe); **5-B** (R= 2,3-$F_2C_6H_3$, X= Br, L= dppe)] in 50-90% yield. The compounds obtained were characterized by ^1H NMR, ^{31}P NMR spectroscopy –in $CDCl_3$ solution–, elemental analyses, mass spectrometry, and IR spectroscopy.

Some tendencies have been found in this work: i) the *E* isomer of the imine was isolated in all reactions; ii) the *ortho*-fluoro atoms show an interaction with the imine proton; iii) the *endo*-palladacycle is the thermodynamic control isomer; iv) the aromatic protons of the metallated ring are high field shifted in compounds containing phosphines, showing a *trans* arrangement between the phosphines and the nitrogen atom in agreement with the transphobia; v) the methinic proton signal in proton NMR spectra is displaced toward high fields confirming the nitrogen-metal bond.

Keywords: Cyclopalladated compound, imine, CH activation, phosphines

2. RESUMEN

La reacción de la 4-fluorobencilamina con 4-clorobenzaldehído o con 2,3-difluorobenzaldehído en acetona a 80ºC da lugar a las iminas (**1**), 4-$ClC_6H_4CH{=}NCH_2(4'\text{-}FC_6H_4)$ y 2,3-$F_2C_6H_3CH{=}NCH_2(4'\text{-}FC_6H_4)$, que se aislaron con un rendimiento >90%. Cuando la misma reacción se realizó en condiciones más suaves se obtuvieron similares resultados. Las iminas (**1**) reaccionaron con la cantidad estequiométrica de $Pd(OAc)_2$ en ácido acético, produciendo los correspondientes compuestos *orto*-ciclopaladados (**2**) de cinco miembros con puente acetato con un rendimiento del 44-69%. La reacción se reprodujo en diferentes condiciones para mejorar el rendimiento, y se obtuvieron los mejores resultados a 85ºC durante 1h. El compuesto (**2**) se transformó mediante una reacción de metátesis, con un exceso de LiCl o LiBr en acetona, en los correspondientes compuestos ciclopalados con puente cloro o bromo. La reacción de los compuestos ciclopaladados con puente halógeno con una cantidad estequiométrica de PPh_3 o dppe dio lugar a la formación de los compuestos mononucleares *trans*-N,L-[Pd{$RHC{=}NCH_2(4'\text{-}FC_6H_4)$}(X)(L)] [**3-A** (R= 4-$ClC_6H_4$, X= Br, L= PPh_3); **3-B** (R= 2,3-$F_2C_6H_3$, X = Br, L = PPh_3); **4-A** (R= 4-ClC_6H_4, X= Cl, L= PPh_3); y dinucleares **5-A** (R= 4-ClC_6H_4, X= Br, L= dppe); **5-B** (R= 2,3-$F_2C_6H_3$, X= Br, L= dppe)] con unos rendimientos del 50-90%.

Los compuestos se caracterizaron por RMN de ^1H y de ^{31}P, en solución de $CDCl_3$, por análisis elemental, espectrometría de masas y espectroscopia IR. Se han encontrado algunas tendencias en este trabajo: i) el isómero *E* de la imina se aisló en todas las reacciones; ii) los átomos *orto*-flúor muestran una interacción con el protón imina; iii) la formación del *endo*-palladociclo como un isómero de control termodinámico; iv) en los compuestos que contienen fosfinas los protones aromáticos del anillo metalado están desplazados hacia campos altos, mostrando una disposición *trans* entre las fosfinas y el átomo de nitrógeno de acuerdo con la transfobia; v) el desplazamiento de la señal de protón metínico a campos altos en los espectros de RMN de protón confirma el enlace nitrógeno-metal.

Palabras clave: Compuesto ciclopaladado, imina, activación CH, fosfinas

3. INTRODUCTION

Organometallic chemistry is the study of chemical compounds containing at least one chemical bond between a carbon atom of an organic molecule and a metal. The first work about this type of chemistry were made by Louis-Claude Cadet de Gassicourt in 1757[1]. In 1827, the first examples of a transition metal alkene complex were discovered by William Christopher Zeise, and therefore this complex was subsequently named after him –Zeise's salt. In 1890-1990, L. Mond discovered the process to extract and purify nickel and Grignard discovered the Grignard reaction. In 1951, Pauson-Miller prepared unintentionally the ferrocene. It was not until 1963 that Kleiman[2] reported the first work about cyclometallation.

The cyclometallated term was introduced by Trofimenko[3] to describe reactions of transition metal complexes in which the ligand undergoes intramolecular metalation with the formation of a chelate ring. These organometallic metallacycles complexes contain an E-M-C sequence of sigma bonds, where E is usually a donor group atom, M is a metallic centre and C is a sp^2 or sp^3 carbon atom. Cyclometallation reactions, which allow the activation of C-H, C-C or C-F bonds, are noteworthy since these bonds present a large energy of dissociation and therefore a very limited chemical reactivity**.**

The facile redox interchange between Pd (II) and Pd (0) and his compatibility with most functional groups gave palladium a very rich chemistry. The first palladacycles were isolated and characterized from azobenzene derivates in 1965[4]. Since then, the intramolecular C-H activation reactions at Pd (II) complexes have been extensively studied reaching a great variety of fields: organic synthesis, the design of new metallomesogenes, photoactive compounds, molecular receptors, antitumoral drugs, organometallic polymers and homogenous catalysis [5].

3.1. TYPES OF PALLADACYCLES

Palladacycles can be divided into two types: anionic four-electron donor or six-electron donor, CY and YCY, respectively (Chart 1). CY type usually exists as halogen or acetate bridged dimers, as two geometric isomers (*cisoid* and *transoid* conformations, Chart 2).

CY-Type YCY-Type

Chart 1

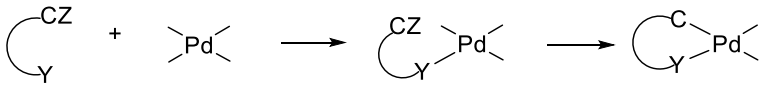
Transoid-palladacycle *cisoid*-palladacycle

Chart 2

CY-type palladacycles can be neutral or monomeric, cationic or anionic depending on the nature of the other X ligands. The metalated carbon is usually an aromatic sp^2 carbon and less commonly a sp^3 carbon (aliphatic or benzylic) or a sp^2 vinylic carbon. A great number of organic molecules have been metalized such as: azobenzenes, amines, imines, pyridines, thioketones, amides, amidines, oxazolines, phosphorus and thioethers and ethers. The most common palladacycles are derived from tertiary amines and imines and are usually five- or six-membered rings. Conversely, cyclopalladated complexes derived from primary amines, are rather rare. The metalated ring of CY-type palladacycles can vary between 3 and 11 members. It is noteworthy that three-and four-membered palladacycles are not usually stable. YCY pincer-type palladacycles are usually symmetrical (two equivalent five- and, less commonly, six-membered rings) or are unsymmetrical (mixed, five- and six-membered)[5].

3.2. METHODS OF PREPARATION

There are several methods for the synthesis of palladacycles, affording the formation of five- or six-membered chelates. In these processes, a stable Pd-C bond is formed by the assistance of a two-electron donor ligand that previously coordinated the metal (Chart 3).

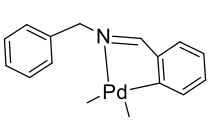


Y=NR_2, SR, PR_2, etc.
CZ= CH, CX, CM, C=C, C≡C

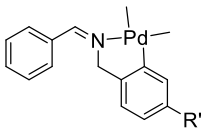
Chart 3

3.2.1. C-H BOND ACTIVATION

The C-H activation is the simplest and most direct method for making the cyclopalladation reaction, activating the *ortho*-C-H bound, also termed *ortho*-palladation. Cyclopalladation reactions are caused by a variety of mechanisms and the aromatic cyclopalladation occurs by a simple electrophilic aromatic substitution. There is some evidence that the C-H bond is only activated within the coordination plane of the metal center. The cyclopalladation of imines is usually a very regioselective process because there is a strong tendency to form the *endo* derivate. It is probable that the *endo*-palladacycle (structural isomers which contain the C=N inside the metallacycle) is the thermodynamic isomer, since in some cases the *exo*-cyclic (structural isomers which contain the C=N outside the metallacycle) analogue can be isolated and undergoes isomerization[5] (Chart 4).



endo-palladacyle



exo-palladacyle

Chart 4

3.2.2. OXIDATIVE ADDITION

The oxidative addition of aryl halides and alkyl halides is a useful method for the generation of palladacycles that cannot be obtained by C-H activation like the formation of three- and four-membered rings and for the obtention of palladacycles with reactive functionalities. These palladacycles are useful starting materials for the synthesis of these derivatives and heterobimetallic systems using the activity of the C-H bound. The major drawback of the

oxidative addition methodology is the accessibility of the halo starting material, which in many cases is prepared by a multistep procedure[5].

3.2.3. TRANSMETALATION

Transmetalation reactions are used for the generation of palladacycles using organomercury and organolithium reagents. Bis-cyclopalladated compounds are easily prepared by transmetalation with organolithium or mercurial N- and O- palladacycles with halogen dimer. The transmetalation reaction via organo-mercurial compounds is useful for the generation of planar chiral cyclopalladated complexes containing the $Cr(CO)_3$ moiety. Transmetalation reactions are also an interesting method for the generation of halogen dimer palladacycles that are not accessible through other methods, such as those containing a labile $SiMe_3$ group located at the metalated carbon.

In the case of transmetalation or oxidative addition processes, it is possible that the initial step does not involve coordination of the donor group to the metal, and indeed an *ortho* substituent decelerates such an addition through both steric and electronic effects[5].

3.2.4. ALKOXY- AND CARBOPALLADATION OF ALKENES

The reaction proceeds through a coordination of the donor group and the C=C bond to the electrophilic Pd(II) center followed by nucleophilic addition to the unsaturated carbon, leading to the more stable palladacyclic, five-membered over six-membered rings. Terminal allyl or homoallyl alkenes are better than internal alkenes. Hard nucleophilic reagents tend to attack the metal center, leading to Pd-alkoxide species that decompose to metallic palladium[5].

3.3. STRUCTURAL ASPECTS

The Pd-C bond distance is between 1.985 and 2.295 Å depending upon various structural and electronic aspects such as the nature of the palladated carbon, the nature of the donor group or the size of the ring. Dimeric pallacycles can adopt two isomeric forms, *cisoid* and *transoid*, that can be in equilibrium in solution[6]. Halogen dimer palladacycles, usually adopt the *transoid* geometry. The Pd-halogen bond located *trans* to Pd-C is longer than the one located in the *cis* position due to the stronger *trans* influence imposed by carbon compared with the heteroatom ligand. In acetate-bridged palladacycles, adopting an “open-book” structure that lead to three more structural isomers besides the *cisoid* and the *transoid* conformations; *in-in,*

out-in and *out-out*, depending on the nature of the ligand. Most monomeric palladacycles formed through the bridge splitting reaction with L-type ligands such as pyridines or phosphines, have the L ligand located *cis* to the Pd-C bond, more stable isomer because of the thermodynamic control of the reaction[5].

3.4. APPLICATIONS

Nowadays there are many areas of research of cyclopalladated compounds that have promoted some interesting applications including organic synthesis, homogeneous catalysis, the design of new metallomesogenses, antitumor drugs, asymmetric synthesis...

Chiral cyclopalladated compounds are used for the asymmetric synthesis to determine the enantiomeric excess of various species in solution as chiral ligands such as amino acids. Also, these compounds are used as resolution agents. These cyclopalladated compounds can exist in different enantioenriched forms (Chart 5): the stereogenic center can be directly bound to palladium as an asymmetrically substituted donor group such as an amine, phosphine, or thioether (**A**). The stereogenic center cannot be directly bound to the metal but it is elsewhere in the metalated ligand(**B**); these types of complexes are often conformationally very stable. A planar chirality can usually be found in a ferrocenyl or η^6-chromium carbonyl moieties(**C**). These types of complexes are becoming more popular and have many impressive applications in asymmetric synthesis. A stereogenic carbon atom directly σ-bonded to the metal is not very common(**D**)[5].

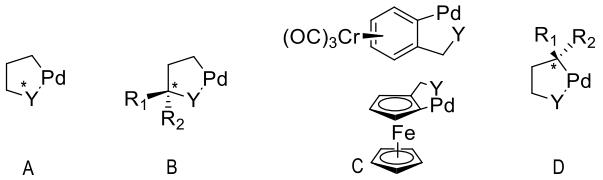


Chart 5

Due to the functionalization of Pd-C bound, cyclopalladated are used in stoichiometric functionalization including acylations and isotope exchanges. A stoichiometric insertion of carbon monoxide into the Pd-C bond of palladacycles enables the carbonylation reaction. The behaviour of isocyanides (the isomer of the related cyanide (-C≡N) reflects that of the

isoelectronic carbon monoxide. Insertion also can be done by allenes, dienes, alkenes and alkynes[5].

The use of palladacycles as catalyst precursors started with the hydrogenation of C=C bonds and it was followed by the selective reduction of nitro-aromatic compounds, nitro-alkenes, nitriles, alkynes, alkenes and aromatic carbonyl compounds. The possibility of C-C coupling reactions such as Heck- and Suzuki-type gave a special attraction to these organo-palladium compounds, besides other cross-couplings reactions and oxidation chemistry. What's more, C-C coupling reactions have been used as a precursor of the selective catalysis. However, in the vast majority of these cases the palladacycles serve as a reservoir of catalytically active Pd(0) species. Most of the catalytic reactions follow a cyclic model mechanism[5].

Over the past decades, luminescent organic and organometallic compounds have attracted a great deal of attention. The reason behind this is the strong spin-orbit coupling of heavy metal ions that allows efficient intersystem crossing between singlet and triplet excited states. As a result, high quantum efficiency is obtained. The luminescent palladacycles are exceptions if compared with the innumerous analogous platinum and iridium compounds, and it is often found that the palladation of luminescent ligands causes a drastic decrease in luminescence. Nonetheless, palladacycles can serve as model compounds for OLEDs, for comparative purposes (structural and photophysical properties) with analogous cyclometalated platinum and iridium compounds[5].

Mesogenic palladacycles, compounds showing liquid crystal properties, present interest proprieties. These palladium liquid crystals are dimeric or monomeric five-membered *ortho*-palladated complexes, in most cases. These new compounds show high thermal stability and a variety of geometries. The metalation reaction of a particular ligand is commonly performed, aiming to improve some desired property, such as reaching some particular mesophase, conductivity, or redox behaviour. However, no practical applications have yet been reported, in particular due to their high melting point temperatures and significant decomposition during prolonged heating[5].

The discovery of cisplatin (*cis*-$PtCl_2(NH_3)_2$) anti-cancer properties promoted the investigation of alternative metal-containing complexes, especially since the former can give rise to toxic side effects and has a narrow spectrum of activity, being tumour cells well-known to develop resistance. Palladium derivatives have been studied as an alternative to platinum-based

compounds since the platinum (II) and palladium (II) complexes have analogous structure and thermodynamics. However, the hydrolysis of the palladium (II) compounds is much faster, which makes their research more complicated for pharmacological purposes. Even so, cyclopalladated complexes are less toxic, so they are promising compounds for antitumor applications. Palladacycle complexes can lead to possible alternative modes of cytotoxic action, such as intercalative DNA lesion, as opposed to the *cis*-platin-induced intrastrand guanine. Particularly cyclopalladated compounds display cytotoxicity against several different cancer cell lines, and some of them are also effective against cells that are resistant to cisplatin. Although some cyclopalladated complexes have been reported to interact with DNA, there are also other cellular sites interactions like mitochondrial membrane or inhibition of some enzymes implicated in some diseases, that contribute in cytotoxic activity[5].

4. OBJECTIVES

The aim of this work is the preparation and characterization of some metallacycles of palladium. The specific objectives are:

- The synthesis of aromatic imines as ligands from aldehydes and primary amines by a condensation reaction.
- The synthesis of the acetate-bridged cyclopalladated compounds by C-H aryl bond activation using palladium acetate as a metalation agent.
- The synthesis of halogen-bridged cyclopalladated compounds through a metathesis reaction from acetate-bridged compounds.
- The synthesis of neutral mononuclear cyclopalladated compounds by splitting reactions of halogen-bridged compounds with phosphines.
- The improvement of the purity of the products by a column chromatography or recrystallization.
- The characterization of products by elemental analysis, IR spectra, ^{1}H and ^{31}P NMR spectra and MS-ESI^{+}.

5. EXPERIMENTAL SECTION

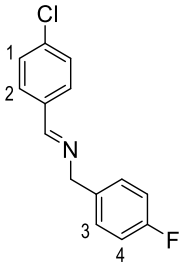
5.1. MATERIALS AND METHODS

Infrared spectra were recorded on a Nicolet Impact-400 spectrophotometer using pressed discs of dispersed samples of the compounds in KBr and bands are given in cm^{-1}. ^{1}H NMR spectra at 400 MHz were recorded in $CDCL_3$ at 298K with Mercury 400 spectrometer and $^{31}P\{^{1}H\}$ at 121.4 MHz were recorded with Bruker 400 Avance III HD. Chemical shifts are giving in δ values (ppm) relative to $SiMe_4$ (^{1}H) and H_3PO_4 ($^{31}P\{^{1}H\}$). Coupling constants are given in Hz and the multiplicity of signals are indicated as: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad signal). ESI-(+) spectra were acquired on a LC/MSD-TOF mass spectrometer, using 1:1 H_2O:CH_3CN as eluent. Elemental analysis of C, H, and N were performed with an Eager 1108 microanalyzer.

5.2 SYNTHESIS

5.2.1 Synthesis of 4-$ClC_6H_4CH=NCH_2(4'-FC_6H_4)$, 1-A

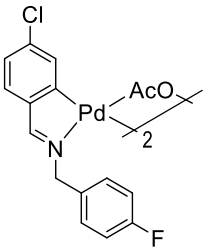
Compound 4-$ClC_6H_4CH=NCH_2(4'-FC_6H_4)$, was obtained after stirring at 90ºC for 1.5 hours a solution containing 308 mg (220 mmol) of 4-chlorobenzaldehyde and 275 mg (220 mmol) of 4-fluorobenzylamine in 20 mL of acetone. After completion of the reaction the solvent was evaporated under reduced pressure to obtain an oily material**.** Yield: 502 mg (92%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.34 (s, 1H, H=CN), 7.70 (d, J_{H-H}= 8.5, 2H, H^2), 7.40 (d, J_{H-H}= 8.5 Hz, 2H, H^1), 7.30 (dd, J_{H-H}=8.2 Hz, J_{H-F}= 5.4 Hz, 2H, H^3), 7.03 (t, J_{H-H}= 8.7 Hz, J_{H-F}= 8.7 Hz, 2H, H^4), 4.77 (s, 2H, CH_2N).

5.2.2 Synthesis of {Pd(μ-AcO)[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)]}$_2$, 2-A

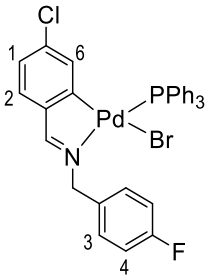
Compound {Pd(μ-AcO)[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)]}$_2$, was obtained after stirring at 83ºC for 1 hour a solution containing 209 mg (0.85 mmol) of compound **1-A** and 189 mg (0.84 mmol) of palladium acetate in 20 mL of acetic acid. The black precipitate was filtered, discarded and the resulting solution was evaporated under reduced pressure. Ethanol absolute was added, a yellow precipitate was formed and filtrated. The solid was filtrated. Yield: 214 mg (61%).



MS-ESI-(+) *m/z:* 821.9 (calc. 820.92) [M+H]$^+$, 352.0 (calc. 351.95) [(M/2)-AcO]$^+$. IR (cm^{-1}): 1582 (st asym COO), 1415 (st sym COO). ^{1}H NMR (400 MHz, CDCl$_3$, 298 K), δ (ppm): 7.10-6.9 (m, 14H, Ar-H+HC=N), 4.55-4.00 (ABq, 4H, CH$_2$N), 2.18 (s, 6H, acetate *transoid*). EA (calc. for C$_{32}$H$_{26}$Cl$_2$F$_2$N$_2$O$_4$Pd$_2$): C: 45.4% (46.63%); H: 3.3% (3.18%); N: 3.4% (3.40%)

5.2.3 Synthesis of {PdBr[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)](PPh$_3$)}, 3-A

Compound {PdBr[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)](PPh$_3$)}, **3-A** was obtained after stirring at room temperature for 1 hour 100 mg (0.12 mmol) of compound **2-A** with 65 mg (0.75 mmol) of lithium bromide in 20 mL of acetone. In a second step, 63 mg (0.24 mmol) of triphenylphosphine were added. The white precipitate formed was filtrated, and the solution was evaporated under reduced pressure. The yellow product obtained was crystallized with diethyl ether. Yield= 162 mg (97%).

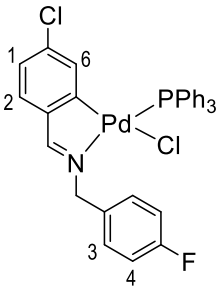


MS-ESI-(+) *m/z:* 614.0 (calc.614.04) [M+Br], 263.1 (calc.623.09) [PPh$_3$+H]$^+$. IR (cm^{-1}): 1620 (st C=N), 1097 (q-X-sensitive of PPh$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 298 K), δ (ppm): 7.9 (d, J_{H-P}= 8.0, 1H, HC=N), 7.7 (dd, J_{H-P}= 11.2 Hz, J_{H-H}= 7.2 Hz, 6H, *ortho*-H PPh$_3$), 7.5 (m, 11H, H-Ar+H^3), 7.1 (m, 3H, H^2+H^4), 6.8 (dd, J_{H-H}= 8.0 Hz, J_{H-H}= 1.9 Hz, 1H, H^1), 6.2 (dd, J_{H-P}= 6.2 Hz, J_{H-H}= 1.9 Hz, 1H, H^6), 5.40 (s, 2H, CH$_2$N). ^{31}P NMR (161.98 MHz, CDCl$_3$, 298 K), δ(ppm): 41,4 (s). EA (calc. for C$_{33}$H$_{28}$ClFNPPd): C: 54.8% (55.28%); H: 3.6% (3.62%); N: 2.0% (2.01%)

5.2.4 Synthesis of {{PdCl[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)](PPh$_3$)}, 4-A

Compound {PdCl[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)](PPh$_3$)}$_2$ was obtained in a two steps process. In a first step a chlorine bridged compound was made after stirring at room temperature for 1 hour 147 mg (0.18 mmol) of compound **2-A** with an excess of 45 mg (1.08 mmol) of lithium chloride in 20 ml of acetone. The white precipitate was filtrated, and the solution was evaporated under reduced pressure. The yellow product obtained was crystallized with ethanol and then filtrated. Yield: 97 mg (70%).

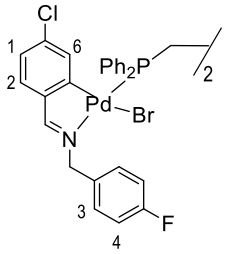
In a second step, a mixture of 69 mg (0.09 mmol) of chlorine bridged compound and 47 mg (0.18 mmol) of triphenylphosphine in 20 mL of acetone was left stirring at room temperature for 1 hour. The yellow solution was filtrated and evaporated under reduced pressure. The product obtained was crystallized with diethyl ether. Yield: 87 mg (74%).



MS-ESI-(+) *m/z*: 616.0 (calc. 614.04) [M+Cl], 263.1 (calc. 263.09) [(PPh$_3$+H]$^+$. IR (cm^{-1}): 1621 (st C=N), 1097 (q-X-sensitive of PPh$_3$). ^{1}H NMR (400 MHz, CDCl$_3$, 298 K), δ (ppm): 7.83 (d, J_{H-P}= 8.0 Hz, 1H, HC=N), 7.77 (dd, J_{H-P}= 11.8 Hz, J_{H-H}= 8.3 Hz, 6H, *ortho*-H PPh$_3$), 7.46 (m, 11H, H-Ar+H^3), 7.13 (m, 3H, H^2+H^4), 6.89 (dd, J_{H-H} = 8.0 Hz, J_{H-H} = 1.9 Hz, 1H, H^1), 6.27 (dd, J_{H-P}= 5.9 Hz, J_{H-H}= 2.0 Hz, 1H, H^6), 5.14 (s, 2H, CH$_2$N).

5.2.5 Synthesis of {PdBr[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)]}$_2$-μ-[Ph$_2$P(CH$_2$)$_2$PPh$_2$], 5-A

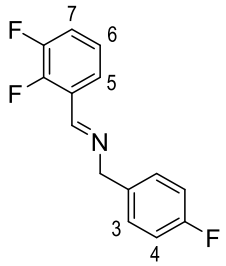
Compound {PdBr[4-ClC$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$)]}$_2$-μ-[Ph$_2$P(CH$_2$)$_2$PPh$_2$], was obtained after stirring at room temperature for 2 hours a mixture of 150 mg (0.18 mmol) of compound **2-A** and 101 mg (1,17 mmol) of lithium bromide. In a second step 73 mg (0.18 mmol) of 1,2-bis(diphenylphosphino)ethane (dppe) was added and the pale-yellow precipitate was filtrated. The solution was evaporated under reduced pressure and the yellow solid was crystallized with ethyl ether. Yield= 161 mg (81%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 7.88 (br, 1H, HC=N), 7.80 (dd, J_{H-P}= 11.6 Hz, J_{H-H}= 6.8 Hz, 4H, *ortho*-H PPh_3), 7.44 (m, 8H, H-Ar), 7.08 (t, J_{H-H}= 8.4 Hz, J_{H-F}= 8.4 Hz, 2H, H^4), 7.06 (d, J_{H-H}= 8.0 Hz, 1H, H^2), 6.85 (dd, J_{H-H}= 8.0 Hz, J_{H-H}= 1.9 Hz, 1H, H^1), 6.21 (br, 1H, H^6), 5.32 (s, 2H, CH2-N), 3.09 (s, 2H, CH_2 dppe). ^{31}P NMR (161.98 MHz, $CDCl_3$, 298 K), δ(ppm): 36.74 (s).

5.2.6 Synthesis of 2,3-F$_2$C$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$), 1-B

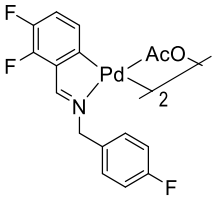
Compound 2,3-F$_2$C$_6$H$_3$CH=NCH$_2$(4'-FC$_6$H$_4$) was obtained after stirring at reflux for 2 hours a solution containing 203 mg (1.43 mmol) of 2,3-difluorobenzaldehyde and 178 mg (1.420 mmol) of 4-fluorobenzylamine in 20 mL of ethanol. After completion of the reaction the solvent was evaporated under reduced pressure to obtain an oily material. Yield: 349 mg (99%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.68 (s, 1H, HC=N), 7.78 (ddt, J_{H-H}= 7.7 Hz, $J_{H-Fmeta}$= 5.9 Hz, $J_{H-Fpara}$= 1.7 Hz, 1H, H^{5-6}), 7.30 (dd, J_{H-H}= 8.2 Hz, J_{F-H}= 5.4 Hz, 2H, H^3), 7.23 (m, 1H, H^{5-6}), 7.12 (m, 1H, H^7), 7.04 (t, J_{H-H}= 8.5 Hz, J_{H-F}= 8.5 Hz, 2H, H^4) 4.82 (s, 2H, CH_2N).

5.2.7 Synthesis of {Pd(μ-AcO)[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)$]}$_2$, 2-B

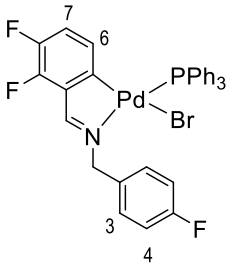
Compound {Pd(μ-AcO)[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)$]}$_2$ was obtained after stirring at 80ºC for 2 hours a solution containing 124 mg (0.5 mmol) of compound **1-B** and 113 mg (0.5 mmol) of palladium acetate in 20 mL of acetic acid. The black precipitate was filtered, and the solution was evaporated under reduced pressure. Ethanol absolute was added, a yellow-orange precipitated was obtained and filtrated. Yield: 129 mg (63%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 7.56 (s, 1H, CH=N), 7.01 (m, 5H, Ar-H), 6.81 (m, 1H, Ar-H) 4.55-4.00 (ABq, 2H, CH_2N), 2.18 (s, 3H, acetate *transoid*). EA (calc. for $C_{32}H_{24}F_6N_2O_4Pd_2$): C: 45.9% (46.45%); H: 3.1% (3.92%); N: 3.4% (3.39%)

5.2.8 Synthesis of {PdBr[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)](PPh_3)$}, 3-B

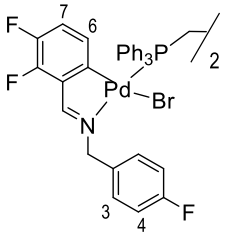
Compound {PdBr[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)](PPh_3)$} was obtained after stirring at room temperature for 1 hour 129 mg (0.16 mmol) of compound **2-B** with 100 mg (1.16 mmol) of lithium bromide in 27 mL of acetone. In a second step 84 mg (0.32 mmol) of triphenylphosphine were added. The white precipitate was filtrated, and the solution was evaporated under reduced pressure. The yellow product obtained was crystallized with diethyl ether. The solid was filtrated. Yield= 113 mg (52%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.33 (s, 1H, HC=N), 7.72 (dd, J_{H-P}= 11.8 Hz, J_{H-H}= 7.2 Hz, 6H, *ortho*-H PPh_3), 7.70-7.30 (m, 11H, H-Ar+H^3), 7.08 (t, J_{H-F}= 8.6 Hz, J_{H-H}= 8.6 Hz 2H, H^4), 6.41 (dt, J_{F-H}= 10.7 Hz, J_{H-H}= 8.3 Hz, 1H, H^7), 5.99 (br, 1H, H^6), 5.41 (s, 2H, CH_2N).

5.2.9 Synthesis of {PdBr[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)]\}_2$-μ-[$Ph_2P(CH_2)_2PPh_2$], 5-B

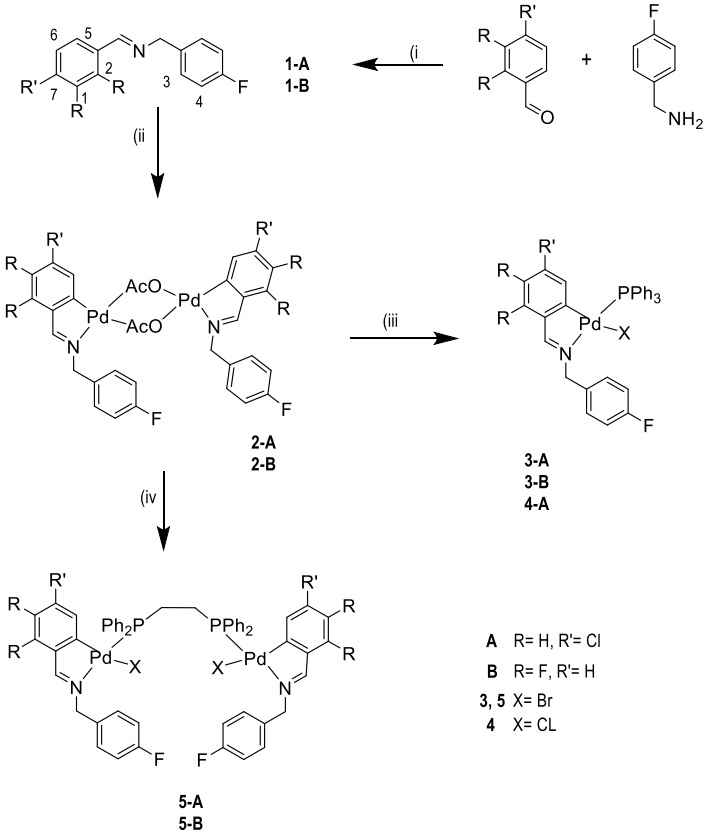
Compound {PdBr[2,3-$F_2C_6H_2CH=NCH_2(4'-FC_6H_4)]\}_2$-μ-[$Ph_2P(CH_2)_2PPh_2$] was obtained after stirring at room temperature for 2 hours a mixture of 119 mg (0.14 mmol) of compound **2-B** and 96 mg (1.12 mmol) of lithium bromide in 20 mL of acetone. In a second step 56 mg (0.14 mmol) of 1,2-bis(diphenylphosphino)ethane (dppe) was added and the pale-yellow precipitate was filtrated. The solution was evaporated under reduced pressure and the yellow solid was recrystallize with ethyl ether. Yield= 146 mg (64%).



^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ (ppm): 8.27 (br, 1H, HC=N), 7.83 (dd, J_{H-P}= 12.4 Hz, J_{H-H}= 6.6 Hz, 4H, *ortho*-H PPh_3), 7.40 (m, 8H, H-Ar), 7.08 (t, J_{H-H}= 8.4 Hz, J_{H-F}= 8.4 Hz, 1H, H^4), 6.40 (dt, J_{H-P}=10.6 Hz, J_{H-H}= 8.3 Hz, 1H, H^6), 5.91 (br, 1H) 5.35 (s, 2H, CH_2-N), 3.00 (s, 2H, CH_2 dppe). ^{31}P NMR (161.98 MHz, $CDCl_3$, 298 K), δ(ppm): 38.10 (s).

6. RESULTS AND DISCUSSIONS

Scheme 1 outlines the methods of preparation of the compounds under study and gives their numbering, and that of their hydrogen atoms for the discussion that follows.



Scheme 1. Reagents and conditions: (i) EtOH, 90ºC, 1h 30min for **1-A** or reflux, 2h for **1-B**; (ii) $Pd(AcO)_2$, HAcO, 85ºC for 1h; (iii) LiBr or LiCl (excess), acetone, PPh_3, r.t. for 1h; iv)) LiBr (excess), acetone, dppe, r.t. for 2h.

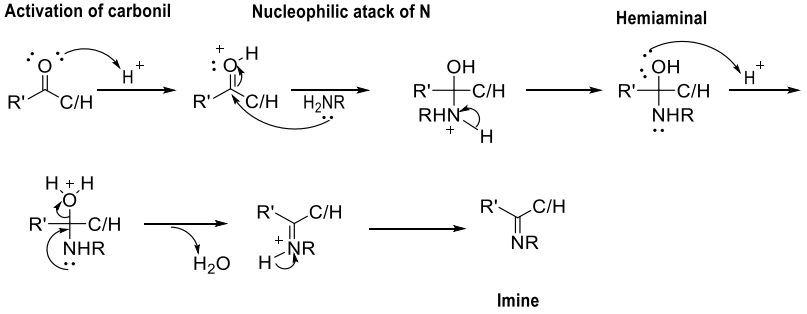
Imines **1-A** and **1-B** were synthesized by a condensation reaction between equimolecular amounts of 4-chlorobenzaldehyde and 4-fluorobenzylamine for imine **1-A** and 2,3-difluorobenzaldehyde and of 4-fluorobenzylamine for imine **1-B**. The acetato bridge cyclopalladated compounds, **2,** were prepared by a cyclopalladation reaction between equimolecular amounts of $Pd(OAc)_2$ and imine **1**. A metathesis reaction between compound **2**

and an excess of LiBr was carried out to produce the bromo bridge cyclopalladated complexes which were subsequently treated with triphenylphosphine to obtain complexes **3** and with 1,2-bis(diphenylphosphino)ethane (dppe) to obtain complexes **5**. To obtain complex **4**, compound **2** was treated with an excess of LiCl to prepare the chloro bridge complex, which was afterwards treated with triphenylphosphine. Compound were characterized by IR, ^{1}H MNR and ^{31}P MNR spectroscopy, elemental analysis and mass spectroscopy ESI-(+).

6.1 SYNTHESIS OF IMINE COMPOUNDS 1-A AND 1-B

Imines are formed when any primary amine reacts with an aldehyde or ketone. Imine formation requires an acid catalyst.

The electrophilic carbon atoms of aldehydes and ketones can be targets of nucleophilic attack by primary amines. The end result of this reaction is a compound in which the C=O double bond is replaced by a C=N double bond by an elimination of water. Amine nitrogen acts as a nucleophile, attacking the carbonyl carbon by a nucleophilic addition giving a hemiaminal -C(OH)(NHR)- intermediate. This is closely analogous to hemiacetal and hemiketal formation. The nitrogen is deprotonated, leaving as a C=N double bond (an imine) and forming a water molecule[7] (Scheme 2).

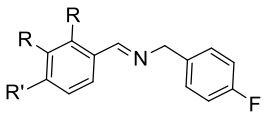


Scheme 2. Imine reaction mechanism.

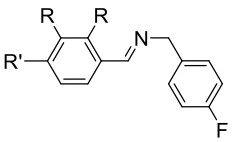
Imine **1-A** was prepared by a condensation reaction between equimolecular amounts of 4-chlorobenzaldehyde and 4-fluorobenzylamine at 90 ºC in ethanol for 1.5h. **1-A** was isolated as a colourless oil; however, the precipitation of the compound can be forced by keeping it at low temperature for a few hours. The white solid was soluble in $CDCl_3$, and in solution in this solvent afforded a set of signals in the ^{1}H NMR. In the ^{1}H NMR, **1-A** presented a single set of signals,

which indicated that it consisted of only one stereoisomer out of the two possibilities, *E* or *Z* (Chart 6). The methinic proton appeared at 8.34 ppm as a singlet and the CH_2N appeared at 4.77 as an A_2 system. The aromatic protons appeared in the interval of 7.01-7.71 ppm. Furthermore, the value of the coupling constant and the integration of the signals allows a complete assignment. The two upfield doublets are the *ortho*- and *meta*- protons in relation to chloro atom and the two downfield signals are the *ortho*- and *meta*- protons in relation to flour atom. Coupling values support the assignation proposed: the doublet of doublets at δ= 7.30 with a coupling constant J_{H-F} of 5.4 Hz can be assigned the *meta*- hydrogen (H^3) and the triplet at δ= 7.03 with a coupling constant J_{H-F} of 8.7 represents the *ortho*- hydrogen (H^4)[8]. The H^2 proton in the vicinity of iminic function, an electron withdrawing group, was deshielded and appeared at the chemical shift value 7.70 (Figure 1).

The synthesis of imine **1-A** was also carried out in the mild conditions previously reported[9]. The reaction was performed at r.t. for 2h. ^{1}H NMR afforded the same signals. The only difference was that a small signal at 10.00 ppm was obtained, showing impurities of aldehyde that had not reacted.



Isomer E



Isomer Z

Chart 6

Imine **1-B** was prepared by a condensation reaction between equimolecular amounts of 2,3-difluorobenzaldehyde and 4-fluorobenzylamine. This imine has not been reported before and the reaction was made at reflux in ethanol for 2h**. 1-B** was isolated as a colourless oil; however, the precipitation of the compound can be forced by keeping it at low temperature for a few hours. The white solid was soluble in $CDCl_3$, and in solution in this solvent afforded a set of signals in the ^{1}H NMR. The methinic proton appeared at 8.68 ppm as a singlet and the aromatic zone integrates 7 protons**.** The difference shifts of the methinic proton in **1-A** (8.34 ppm) and **1-B** (8.68 ppm) can be explained by the position of the fluor group**.** Several studies[10]–[12] have concluded that compounds bearing an halogen substituent (Cl, F) at the C_2 position of the aryl

ring show a downfield shift of the imine resonance which is consistent with a NCH···X (X= Cl, F) interaction between the imine proton and the fluor atom, reinforcing the planarity of the compound.

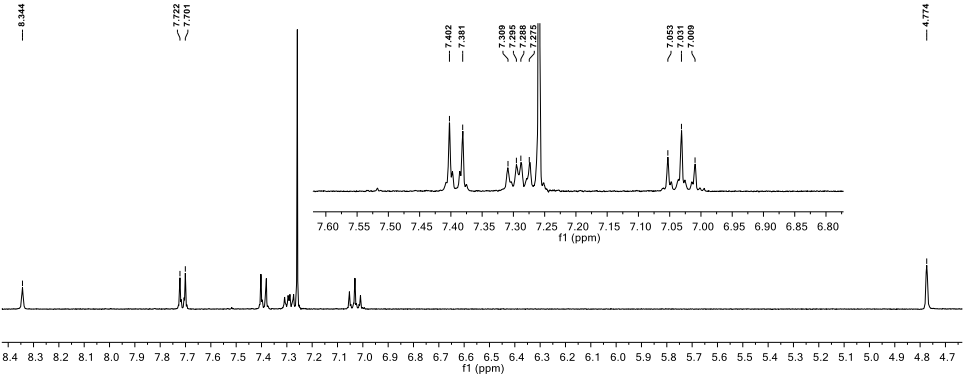


Figure 1. ^{1}H NMR spectrum of compound **1-A**.

Even though imine formation requires an acid catalyst, in these cases it was not required. Also, both imines **1-A** were obtained in a good yield (>90%) verifying the reaction condition made in Aneja's[9] study. The reaction conditions used in the synthesis of **1-B** were satisfactory enough to obtain the new imine.

6.2 SYNTHESIS OF COMPOUNDS 2 AND CHLORO BRIDGED COMPOUND

Reaction between imines and palladium acetate in acetic acid solution to perform the metalation is a rather complex process in which several different reactions, such as acidolysis of Pd-C and C=N bonds and substitution on the acetato bridging positions take place[13]. But in general, the following trends are accepted: an intramolecular electrophilic attack of Pd (II) at the carbon atom; a strong tendency to form five membered metallacycles; a preferential activation of aromatic versus benzylic C-H bonds.

From these ligands, *endo* and *exo* metallacycles can be obtained according to the carbon atom metalated. The formation of one type or another depends on the isomeric form adopted by the ligand. Compounds **1** were formed as single isomers which are assumed to have the most stable *E* stereochemistry about the C=N bond. As shown in Chart 7, from the *E* form both *endo*- and *exo*-cycles can be formed, while only *exo*-cycles are possible for the *Z* form[14].These

acetate-bridged compounds are usually dinuclear, but there is also evidence for the formation of trinuclear or even polynuclear species[15], [16].

Treatment of imine **1** with $Pd(OAc)_2$ in acetic acid in a 1 to 1 molar ratio afforded the dimeric acetato-bridged five-membered *ortho*-cyclopalladated compound. In order to optimise the yield of compounds **2**, the reaction between **1** and $Pd(OAc)_2$ was carried out in acetic acid under different reaction conditions. Table 1 summarises the yield obtained under the different reaction conditions. In all the experiments, the final mixture of reaction was concentrated under vacuum.

E form *Z* form

Chart 7

Addition of a minimum volume of diethyl ether to the resulting oily material produced the crystallisation of compound **2** as a powder whose colour ranged from yellow to orange. The best results were obtained when **1** and $Pd(AcO)_2$ were treated at 85 ºC in acetic acid for 60 min (Table 1). In this way, compound **2** was isolated in 69% yield. In addition, **2-A** was easily transformed by a metathesis reaction with LiCl into the corresponding chloro bridged cyclopalladated dimer which was isolated in 70% yield. The replacement of bridging acetate by the chloro/bromo bridge proceeds easily, according to the HSAB principle formulated by R.G. Pearson, which predicts that the palladium (II) center has greater affinity for the chloro or bromo ligand than for the oxygen of the ligand acetate. They were air-stable solids ranging from yellow to orange, soluble in chloroform and in acetone. The acetate derivates present a satisfactory ^1H NMR, IR, ESI-(+) mass spectrum and elemental analysis**.**

In the IR spectra of compound **2-A**, the asymmetric and symmetric stretching of the carboxylate functions produced broad intense bands at 1582 and 1415 cm^{-1}, indicating that the acetato ligands of the compound presented a bridging coordination mode[17]. The C=N stretching was not observed since it was occluded inside the broad and strong signals corresponding to the asymmetric stretching of the carboxylate functions. For chloro bridged cyclopalladated derivate the C=N stretching appeared at 1613 cm^{-1} as an intense band shifted

to lower wave numbers in relation to the free imine, according to the coordination of the iminic nitrogen to the palladium(II) centre[18].

The ESI-(+) mass spectrum of **2-A** produced the most abundant peaks at 822 corresponded to the molecular monopositive cations [M+H$^+$]. Also it can be observed that the [M/2-AcO]$^+$ defragmentation peaks at 351, characteristic of acetate-bridge palladacycles for being a quite labile function in agreement with their dinuclear structure with acetato bridge ligands[19].

In the ^{1}H NMR spectra (Figure 2) the CH_2N protons appeared as an AB quartet, showing that these protons are diastereotopic. This is consistent with a folded structure that have been described for acetato-bridged cyclopalladated dimers, usually named open book structure. This is also confirmed by the X-ray diffraction studies of some cyclopalladated acetate-bridge dimers[20]. The coordination μ-acetate-κO:κO' can give rise to two geometric isomers (*cisoid* and *transoid*) (Chart 8).The protons of the acetate ligands produced a singlet at 2.18 ppm which indicates a *trans* folded structure belonging to C_2 point group and the bridge coordination of the acetate group between two palladium centers. The *cisoid* isomer possesses non-equivalent methyls due to the symmetry C_s of the complex[21]. The methinic proton is overlapped with aromatic protons that integrate 14 protons as a multiplet at 7.10-6.90 ppm. The shielded methinic proton confirms the *endo* form of the complex and the coordination of iminic nitrogen with the palladium center. In the endocyclic derivatives, it undergoes a shielding with respect to the free imine –between 0.3-1,3 ppm, according to the derivative. However, the *exo* metalacycles exhibit a remarkable deshielding of the signal from the methinic proton as long as the imine adopts the *Z* form, whereas if it adopts the *E* configuration of the *exo* complex, this signal is hardly affected[22], [23]**.**

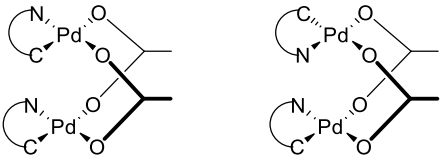
Table 1

Reaction conditions and yield of isolated 2

Entry	Temperature [ºC]	Time [min]	Yield [%]
1[a]	90	60	60
2[a]	90-76	60	62
3[b]	50-60	70	44
4[b]	r.t.	60	48
5[a]	73	120	47
6[a]	85	60	69
7[a]	85	120	53

[a] Formation of palladium (0) was observed under these reaction conditions.

[b] Non-reacted palladium acetate was observed under these reaction conditions.



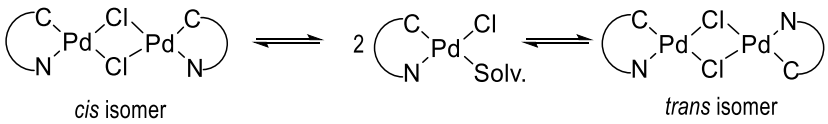
transoid *cisoid*

Chart 8

In the ^{1}H NMR of **2-B** acetato proton signals and the CH_2N protons shows the same pattern of **2-A** showing the *trans* arrangement relative to the Pd2(μ-AcO)$_2$ and the fold structure of the acetato-bridge. The methinic proton appeared at 7.56 ppm as a singlet and the aromatic zone integrate 6 protons as a multiplet. A small broad signal can be seen at 6.80 corresponding to minor *cis* configuration compound.

The ^{1}H NMR of chloro bridged cyclopalladated produced one set of signals, most of them broad, except the methinic protons, which afforded a singlet at 7.70 ppm. The broadening of the proton NMR signals of dinuclear cyclopalladated compounds with chloro bridge ligands in $CDCl_3$ has been ascribed to a dynamic equilibrium between their *cis* and *trans* isomers (Scheme 3)[24]. For this reason, it cannot be assigned any signal.

Product **2-A** was eluted by a column chromatography with silica gel and a solution of CH_2Cl_2/MeOH (100:2) as eluent and followed by TLC to see the relation of the fractions, in order to purify it. Two fractions were obtained (Fr2-6 and Fr7-10) and the ^{1}H NMR spectrum was recorded. It is noteworthy to mention that new signals, not present in the sample before the column chromatography was carried out, were detected in both fractions. Some interaction was occurring in the column that was supposed to be inert.



cis isomer *trans* isomer

Scheme 3. Dynamic equilibrium between the *trans* and *cis* isomers of the cyclopalladated chloride bridge compound

Data showed that only the *endo*-derivative was formed, which is consistent with reports of the strong tendency of imines to form *endo*-metallacycles[25]–[27]. Also, a decrease in yield is observed because small part of the palladium acetate did not react, at low temperature, whereas at high temperature, an improvement in yield can be perceived since all the palladium acetate reacted**.** However, a long reaction time can result in a decrease of the yield by the palladium reduction. Column chromatography shows internal interactions of the column cause a loss of yield.

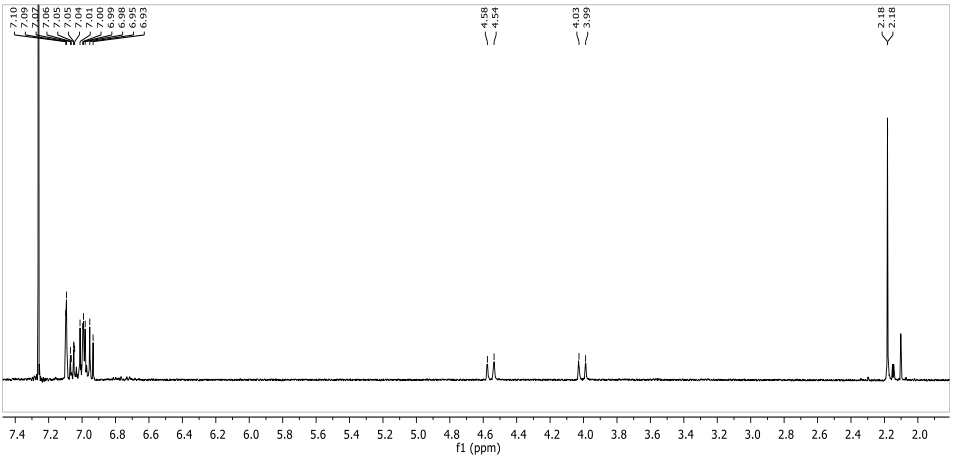


Figure 2. ^{1}H NMR spectrum of compounds **2-A**.

6.3 SYNTHESIS OF COMPOUNDS 3 AND 4-A

The reaction of compounds **2** with an excess of LiBr and in a second step with PPh_3 in a 2:1 mol relation in acetone afforded the mononuclear derivatives **3,** a pale-yellow solid. Compound **2-A** was also reacted in a first step with an excess of LiCl and in a second step with PPh_3 in a 2:1 mol relation in acetone producing the mononuclear derivate **4-A,** a pale-yellow solid. All these compounds have the triphenylphosphine in *trans* position to iminic nitrogen according to the antisymbiotic effect *"two soft ligands in mutual trans position will have a destabilizing effect on each other when attached to class d metal atoms"* [28]. This was confirmed by the ^{1}H NMR**.** Compounds **3** and **4** were quite soluble in $CDCl_3$ and produced satisfactory ^{1}H NMR, **3-A** and **4-A** produced satisfactory mass spectra and IR and for **3-A** elemental analysis and ^{31}P NMR also was made.

The ESI-(+) mass spectrum of **3-A** and **4-A** had the base peak that corresponded to the molecular fragments $[M-X]^+$ (where X is Br for compound **3-A** and Cl for compound **4-A**) at *m/z* 614 and *m/z* 616 respectively. Also, in both cases the fragmentation of the triphenylphosphine [PPh_3+H] at 263 can be observed.

The IR spectra presented the characteristic bands of the coordinated ligands. Sharp signals of medium intensity at 1621 cm^{-1} and 1620 cm^{-1} assigned to the C=N stretching were observed for compound 4-A and 3-A respectively. Furthermore, both compounds showed an intense band at 1097 cm^{-1} assigned to the q mode of sensitive vibrations of the PPh_3, according to Whiffen's notation[29] —triphenylphosphine had similar bands[30], so the same notation is adopted. The X-sensitive modes are useful to elucidate the structure of complexes, since the coordination of the ligand causes a shift of the X-sensitive bands towards higher energies —the q mode of the free PPh_3 is at 1089 cm^{-1}. This shift towards higher wave number values is consistent with a contribution of Kross and Fassel[31], where the movement of this band is related to the increase in the electronegativity of the X substituent when coordinated to the metal. Also, Y-sensitive modes can be observed at 532, 514 and 492 cm^{-1} for both compounds. The shape of these Y-sensitive nodes permits to deduce the existence of a single triphenylphosphine ligand in the coordination sphere of the palladium center[32] (Figure 3).

^1H NMR data for the mononuclear compounds for all three compounds were consistent with their proposed stereochemistry, in which the PPh_3 ligand is in *trans* to the iminic nitrogen and the X ligand (X= Br for compounds **3** and X= Cl for **4-A**) in *trans* position to the palladated carbon atom (Scheme 1). This arrangement is referred as *trans*-N,L stereochemistry[33]. This stereochemistry causes a remarkable shielding effect on the metallated phenyl, showing a great

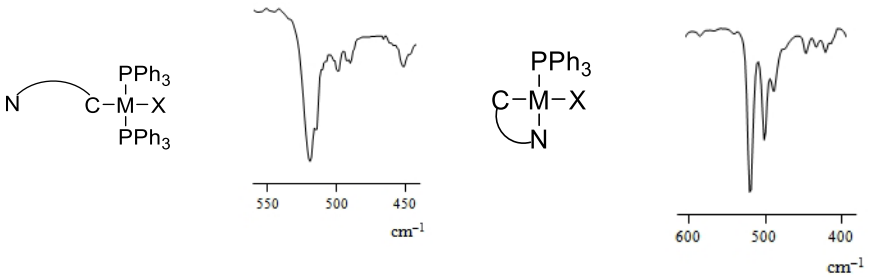


Figure 3. Shape of Y-sensitive bands due to the coordination sphere.

high-field in the aromatic protons signal —between 7.50 and 5.99 ppm—, in relation to the other aromatic protons. This high-field is especially pronounced for the aromatic proton in *ortho* to the metalated carbon. The expected influence of the aromatic ring anisotropy makes possible to explain these high-field resonances (Figure 4). In addition, for compounds **3-A** and **4-A**, the methinic proton and the aromatic *ortho*-proton to the metaled carbon atom (H^6) showed a heteronuclear coupling H-P of 7.9 Hz and 8.0 Hz for the methinic and 6.2 Hz and 5.9 Hz for the *ortho*-proton, respectively. The value of this coupling constant confirms the *trans*-N,P stereochemistry[19].

Even though in compound **3-B** the coupling H-P of methinic proton cannot be seen, the high-field of the metalled aromatic protons and the broad signal of the hydrogen in *ortho*-proton to the metaled are consistent with an endocyclic *trans*-N,L stereochemistry. It is also remarkable the downfield shift of the methinic proton in comparation to **3-A** and **4-A** caused by the interaction between the imine proton and the fluor atom, reinforcing the planarity of the compound. Similar types of shifts have been previously observed for compound **1-B**.

Further indication of the *trans*-N,P stereochemistry of compounds **3-A** was given by the chemical shift of their $^{31}P\text{-}\{^1H\}$ NMR, which were in 41.37 ppm. This chemical shifts was in the range expected —40-43 ppm— for mononuclear cyclopalladated compounds of general formula *trans*-N,P-[Pd(C-N)(X)(PPh3)] (X= OAc, Cl, Br, I) that contain a five-membered palladacycle where a Csp_2-H has been activated[34].

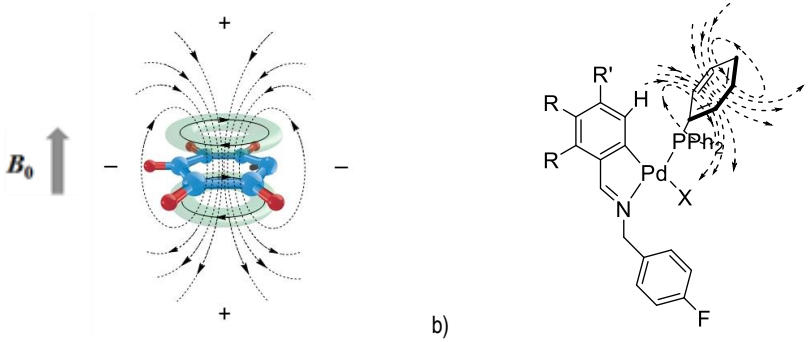


Figure 4. a) Induced field originated in benzene after applying a magnetic field B_0 (solid line). The aromatic ring current induces a local magnetic field around the molecule (dotted line), reinforcing the applied magnetic field (indicated by the sign -) in the periphery of the ring and weakening it inside, above and below the plane of the molecule (+ sign); b) Bigger shielding effect on the *ortho* metalated carbon.

Taking this into consideration, the proton assignment remains as follows (Figure 5): a signal appeared at 7.90, 8.31 and 7.83 ppm of the methinic proton for **3-A**, **3-B** and **4-A** respectively. Around 7.77 ppm the *ortho*-hydrogen of the triphenylphosphine with a coupling constant H-P can be observed. The other aromatic signals and H^3 appeared over the zone of 7.4 ppm. For compound **3-A** and **4-A** at 7.1 ppm, the H^2 and H^4 with overlapping signals appeared, being the H^1 a dd at 6.80 ppm and the *ortho*-proton to the metaled (H^6) at 6.17 ppm. While in compound **3-B** at 7.08 and 6.41 ppm the H^4 and H^7 appeared with a coupling constant H-F respectively, and the *ortho*-proton to the metaled carbon atom (H^6) appeared at 5.99 ppm.

The yield obtained were 97% and 74% for compound **3-A** and **4-A** respectively. For compound **3-A**, traces of impurity were detected in the first MNR, therefore it was recrystallized. In a first step it was dissolved in dichloromethane and then it was added diethyl ether in a minimum quantity. It was evaporated under vacuum until half volume and the sample was cooled. Finally, after its filtration, it was dried in a Schlenk line. For compound **3-B**, a 52% of yield was obtained. The decrease of yield stems from the crystallization process. It was quite soluble in diethyl ether and the sample required a cooling process.

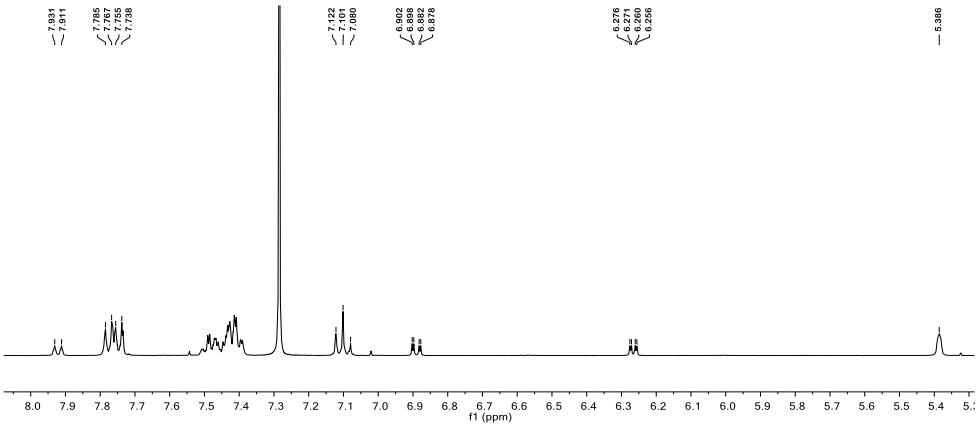


Figure 5. ^{1}H NMR spectrum of compounds **3-A**.

6.4 SYNTHESIS OF COMPOUNDS 5

The reaction of compound **2** with an excess of LiBr and in a second step with dppe in an equimolar ratio in acetone afforded the mononuclear derivatives **5,** a pale-yellow solid. **5-A** was quite insoluble in methanol, moderately soluble in ethyl acetate and quite soluble in acetone and $CDCl_3$. While **5-B** was moderately soluble in chloroform and $CDCl_3$, a little soluble in methanol and quite insoluble in ethyl acetate. Both compounds produced a satisfactory, ^1H and ^{31}P NMR spectra. Mass spectra was performed only for compound **5-A.** Despite the great tendency of dppe to act as a chelate ligand, complexes **5** were obtained with high performance presenting a bis(monodentate) coordination when working in an equimolar ratio.

The ^1H NMR spectra show that these compounds present a molecular structure with an apparent centre of inversion which divides the molecules into two symmetrical parts, which implies the bis(monodentate) coordination of the dppe. This is in agreement with the structures proposed for these compounds with symmetric L_2 ligands bridging the two palladium (II) centres and coordinated to the cyclopalladated units with *trans*-N,L stereochemistry[19]. Both ^1H NMR spectra exhibited a signal assignable to the resonance of the methinic proton at 7.87 ppm for compound **5-A** (Figure 6) and at 8.26 ppm for compound **5-B**. This signal is displaced towards high fields with respect to the iminic proton of the free imine, which confirms the presence of the nitrogen-metal bond. It is noteworthy that the resonance of the proton CH=N in the derivatives with bridge phosphines is a broad signal, as a result of the coupling with the two phosphorus atoms of the dppe[19]. The signal of the proton H^6 is shifted upfield shift towards low frequencies in relation to the free ligand at 6.21 ppm for compound **5-A** and at 5.91 ppm for compound **5-B** –in agreement with the *cis* arrangement of the phosphine and the metalled ring,

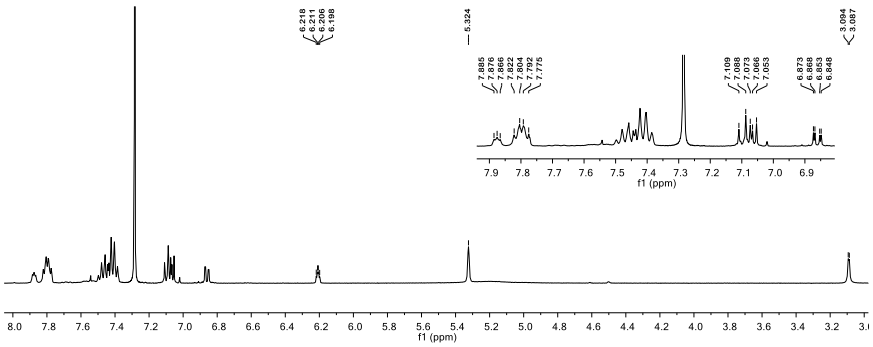
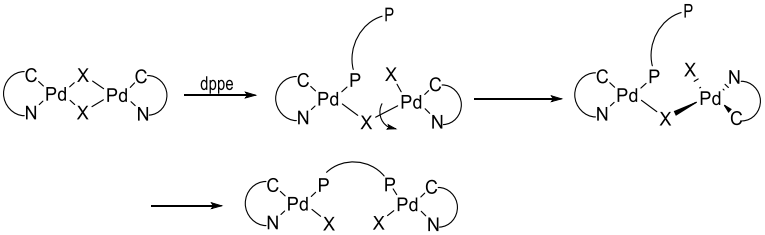


Figure 6. ^1H NMR spectrum of compound **5-A**.

and thus, a *trans* disposition of phosphorus and nitrogen atoms. That is consistent with the presence of aromatic rings in the vicinity of H^6. Note that the H^6 proton signal had a coupling constant J_{H-P}, for compound **5-B**, showing the existence of a coupling with the phosphorus atoms of the relevant bridge diphosphine. The broad signal of compound **5-A** for H^6 suggest also this coupling. For both compounds the *ortho*-hydrogen of the aromatic rings of the dppe appeared at 7.80 and at 7.44 the others aromatic protons. Also, H^4 appeared at 7.08ppm with a coupling constant J_{H-F} of 8.4 Hz. For compound **5-A** the H^2 is overlapped with H^4 but can be assigned due the coupling constants[17]. H^1 appeared at 6.85 ppm. The aliphatic P–CH_2 protons appeared as an apparent doublet around 2.97 ppm, can be noted that this signal shows a coupling with the phosphorus atom. The CH_2-N proton appeared around 5.33 ppm for both compounds. Concerning to the $^{31}P-\{^1H\}$ NMR the spectra the chemical equivalence of the two phosphorus atoms in the compounds **5-A** and **5-B** led to a singlet signal at 37 ppm, as expected for the proposed structures, a dinuclear cyclometallated structure in which the two palladium atoms are bridged by the diphosphine with the phosphorus atoms *trans* to the nitrogen atom[19].

Mass spectroscopy was performed for compound **5-A**, giving rise to a signal corresponding to the ion $[M-Br]^+$ and the $[M-2Br]^+$ at *m/z* 1180 and 1102 respectively which confirms the existence of the dinuclear species.

The relatively easy preparation of these dinuclear cyclometallated species with bridging dppe is remarkable because dppe usually chelates[35]. The preparation of such species can be explained by the dinuclear structure of the cyclometalled starting materials and by the stability of the metallacycles. When one of the phosphorus atoms attacks the cyclometalled compound, breaking one of the Pd-X-Pd bridging bonds, there is another Pd-X-Pd bond keeping the other palladium atom in a suitable position to be attacked by the second phosphorous atom of the dppe[36] (scheme 4).



Scheme 4. Proposed mechanism for dppe attack on cyclopalladated compounds[36].

7. CONCLUSIONS

New cyclopalladated compounds (**2**-**6**) were satisfactorily prepared, increasing the scope of the cyclopalladation reaction. All the products were fully characterized by the standard techniques. ^{1}H NMR spectra was the most useful technique to characterise it. The other techniques were used to complete the characterization.

The synthesis of the two imines did not required acid catalysis. Despite this, a good yield was obtained (>90%). **1-A** was isolated in good yield, also, when the reaction was performed at room temperature. It was showed that palladium acetate was a good metalation agent to obtain the cyclopalladated compound. It was also found that the optimal conditions for this reaction were 80ºC for 1h. The formation of the endo five-membered compound concluded in the formation of the *E* isomer of the imines. The *ortho*-halogen products produced a downfield shift in the iminic proton signal showing a N=CH····X interaction that reinforced the planarity of the compound. The dimeric acetato bridge compound gave a *trans* folded structure of the bridge. Also, it was observed that the chromatography column is not a good purifying method for these complexes since it was not inert when faced with the acetate-bridged compounds. Triphenylphosphine split the dinuclear bridge compounds to afford the corresponding mononuclear complexes. And the reaction between dinuclear bridge compounds and dppe, in a 1/1 relation, afforded the dppe-bridge derivatives. The aromatic protons of the metallated ring are high field shifted in compounds containing phosphines, showing a *trans* arrangement between the phosphines and the nitrogen atom in agreement with the transphobia effect.

8. REFERENCES AND NOTES

[1] D. Seyferth, "Cadet's Fuming Arsenical Liquid and the Cacodyl Compounds of Bunsen," *Organometallics*, vol. 20, no. 8, pp. 1488–1498, 2001.

[2] J. P. Kleiman and M. Dubeck, "The preparation of cyclopentadienyl [*o*-(phenylazo)phenyl] nickel," *Journal of the American Chemical Society*, vol. 85, no. 10. pp. 1544–1545, 1963.

[3] S. Trofimenko, "Some Studies of the Cyclopalladation Reaction," *Inorg. Chem.*, vol. 12, no. 6, pp. 1215–1221, 1973.

[4] A. C. Cope and R. W. Siekman, "Formation of Covalent Bonds from Platinum or Palladium to Carbon by Direct Substitution," *J. Am. Chem. Soc.*, vol. 87, no. 14, pp. 3272–3273, 1965.

[5] J. Dupont, C. S. Consorti, and J. Spencer, "The potential of palladacycles: More than just precatalysts," *Chemical Reviews*, vol. 105, no. 6. American Chemical Society, pp. 2527–2571, 2005. And references therein.

[6] J. Albert, R. Bosque, L. D'Andrea, J. A. Durán, J. Granell, M. Font-Bardia, and T. Calvet, "Synthesis and crystal structure of the dinuclear cyclopalladated compounds of methyl (E)-4-(benzylideneamino)benzoate with acetato and chlorido bridge ligands: Study of their splitting reactions with pyridine," *J. Organomet. Chem.*, vol. 815–816, pp. 44–52, 2016.

[7] P. Y. Bruice, *Organic Chemistry, Seventh Edition*. 2014.

[8] E. Pretsch, T. Clerc, J. Seibl, and W. Simon, *Tablas para la elucidación estructural de compuestos orgánicos por métodos espectroscópicos*, [1a. ed.]., vol. 44. Madrid: Alhambra, 1980.

[9] B. Aneja, M. Irfan, M. I. Hassan, A. Prakash, U. Yadava, C. G. Daniliuc, M. Zafaryab, M. M. A. Rizvi, A. Azam, and M. Abid, "Monocyclic β-lactam and unexpected oxazinone formation: synthesis, crystal structure, docking studies and antibacterial evaluation," *J. Enzyme Inhib. Med. Chem.*, vol. 31, no. 5, pp. 834–852, 2016.

[10] M. Crespo, J. Granell, X. Solans, and M. Font-Bardia, "Preparation of metallacycles with anionic terdentate [C,N,N'] ligands by intramolecular oxidative addition of C-X (X= Br, Cl) bonds to $[Pt(dba)_2]$. An unexpected effect of chloro substituents," *Organometallics*, vol. 21, no. 23, pp. 5140–5143, 2002.

[11] M. Crespo and X. Solans, "Cyclometalated Platinum(II) Compounds with Fluorinated Iminic Ligands: Synthesis and Reactivity Tuning. Crystal Structures of the Compounds $[PtMe(RCH{:}NCH_2C_6H_5)(PPh_3)]$ (R= 2,3,4-C_6HF_3 and 2,3-$C_6H_2F_2$)," *Organometallics*, vol. 14, no. 1, pp. 355–364, 1996.

[12] R. M. Ceder, J. Granell, and G. Muller, "Nickel organometallic compounds containing optically active Schiff bases. A chiral carbon atom as a sensor of structural features," *J. Chem. Soc. Dalt. Trans.*, no. 6, pp. 1047–1052, 1998.

[13] M. Gómez, J. Granell, and M. Martinez, "Mechanisms of cyclopalladation reactions in acetic acid: Not so simple one-pot processes," *Eur. J. Inorg. Chem.*, vol. 2000, no. 1, pp. 217–224, 2000.

[14] J. M. Thompson and R. F. Heck, "Carbonylation Reactions of *Ortho*-Palladation Products of α-Arylnitrogen Derivatives," *J. Org. Chem.*, vol. 40, no. 18, pp. 2667–2674, 1975.

[15] J. Granell, J. Sales, J. Vilarrasa, J. P. Declercq, G. Germain, C. Miravitlles, and X. Solans, "Synthesis and characterization of cyclometallated complexes of benzalazines. Crystal and molecular structure of $[\{Pd(p\text{-}ClC_6H_3CH{:}N\text{–})Cl(PEt_3)_2\}_2]$," *J. Chem. Soc. Dalt. Trans.*, no. 11, pp. 2441–2446, 1983.

[16] M. Pfeffer, E. Wehman, and G. Van Koten, "The metallation of N,N-dimethylaminotoluene by palladium acetate. Evidence for a trinuclear species," *J. Organomet. Chem.*, vol. 282, no. 1, pp. 127–131, 1985.

[17] K. Nakamoto, *Infrared and Raman Spectra of Inorganic and Coordination Compounds: Part A: Theory and Applications in Inorganic Chemistry: Sixth Edition*. Hoboken, NJ, USA: John Wiley & Sons, Inc., 2008.

[18] H. Onoue and I. Moritani, "*ortho*-Metalation reactions of N-phenylbenzaldimine and its related compounds by palladium(II) acetate," *J. Organomet. Chem.*, vol. 43, no. 2, pp. 431–436, 1972.

[19] J. Albert, R. Bosque, L. D'Andrea, J. Granell, M. Font-Bardia, and T. Calvet, "Synthesis of cyclopalladated derivatives of (*E*)-N-Benzylidene-2-(2,6- dichlorophenyl)ethanamine and their reactivity towards monodentate and symmetric bidentate lewis bases," *Eur. J. Inorg. Chem.*, no. 24, pp. 3617–3631, 2011.

[20] J. L. Garcia-Ruano, I. Lopez-Solera, J. R. Masaguer, C. Navarro-Ranninger, J. H. Rodriguez, and S. Martinez-Carrera, "Cyclometalation of N-(4-methoxyphenyl)-α-benzoylbenzylideneamine with palladium(II) acetate. Evidence for a new kind of diastereoisomerism," *Organometallics*, vol. 11, no. 9, pp. 3013–3018, 1992.

[21] J. Albert, L. D'Andrea, J. Granell, R. Tavera, M. Font-Bardia, and X. Solans, "Synthesis and reactivity towards carbon monoxide of an optically active *endo* five-membered *ortho*-cyclopalladated imine: X-ray molecular structure of *trans*-(μ-Cl)$_2$[Pd(κ^2-C,N-(R)-C$_6$H$_4$-CH:N-CHMe-Ph)]$_2$," *J. Organomet. Chem.*, vol. 692, no. 14, pp. 3070–3080, 2007.

[22] J. Albert, R. M. Ceder, M. Gómez, J. Granell, and J. Sales, "Cyclopalladation of N-Mesitylbenzylideneamines. Aromatic versus Aliphatic C-H Activation," *Organometallics*, vol. 11, no. 4, pp. 1536–1541, 1992.

[23] J. Albert, M. Gómez, J. Granell, J. Sales, and X. Solans, "Five- and Six-Membered *Exo*-Cyclopalladated Compounds of N-Benzylideneamines. Synthesis and X-ray Crystal Structure of [cyclic] [PdBr{*p*-MeOC$_6$H$_3$(CH$_2$)$_2$N:CH(2,6-Cl$_2$C$_6$H$_3$)}(PPh$_3$)] and [PdBr{C$_6$H$_4$CH$_2$N:CH(2,6-Cl$_2$C$_6$H$_3$)}(PEt$_3$)$_2$]," *Organometallics*, vol. 9, no. 5, pp. 1405–1413, 1990.

[24] D. C. R. Hockless, P. A. Gugger, P. H. Leung, R. C. Mayadunne, M. Pabel, and S. B. Wild, "Facile interconversion between diastereomers of chloro-bridged palladium(II) dimers of orthometallated (±)-dimethyl[1-(1-naphthyl)ethyl]amine," *Tetrahedron*, vol. 53, no. 11, pp. 4083–4094, 1997.

[25] R. Bosque, C. López, and J. Sales, "Schiff bases derived from aminomethylferrocene and their cyclopalladated derivatives," *J. Organomet. Chem.*, vol. 498, no. 2, pp. 147–154, 1995.

[26] M. Gómez, J. Granell, and M. Martinez, "Variable-temperature and -pressure kinetics and mechanism of the cyclopalladation reaction of imines in aprotic solvent," *Organometallics*, vol. 16, no. 12, pp. 2539–2546, 1997.

[27] M. Gómez, J. Granell, M. Martinez, C. Navarro-Ranninger, J. H. Rodríguez, S. Martínez-Carrera, E. P. Carreño, G. González, and M. Martinez, "Solution behaviour, kinetics and mechanism of the acid-catalysed cyclopalladation of imines," *J. Chem. Soc. Dalt. Trans.*, no. 1, pp. 37–44, 1998.

[28] R. G. Pearson, "Antisymbiosis and the *Trans* Effect," *Inorg. Chem.*, vol. 12, no. 3, pp. 712–713, 1973.

[29] D. H. Whiffen, "Vibrational frequencies and thermodynamic properties of fluoro-, chloro-, bromo-, and iodo-benzene," *J. Chem. Soc.*, pp. 1350–1356, 1956.

[30] R. Faggiani, H. E. Howard-Lock, C. J. L. Lock, and M. A. Turner, "The reaction of chloro(triphenylphosphine)gold(I) with 1-methylthymine," *Can. J. Chem.*, vol. 65, no. 7, pp. 1568–1575, 1987.

[31] R. D. Kross and V. A. Fassel, "The Infrared Spectra of Aromatic Compounds. III. The 1045-1185 Cm^{-1} Vibration in Mono-substituted Benzenes," *Journal of the American Chemical Society*, vol. 77, no. 22, pp. 5858–5860, 1955.

[32] L. D'Andrea, "Síntesis y reactividad de iminas y diiminas ciclopaladadas. Una aproximación a los metalaciclos hidrosolubles," *TDX (Tesis Dr. en Xarxa)*, 2013.

[33] J. Albert, S. García, J. Granell, A. Llorca, M. V. Lovelle, V. Moreno, A. Presa, L. Rodríguez, J. Quirante, C. Calvis, R. Messeguer, J. Badía, and L. Baldomà, "Cyclopalladated benzophenone imines: Synthesis, cytotoxicity against human breast adenocarcinoma cell lines and DNA interaction," *J. Organomet. Chem.*, vol. 724, pp. 289–296, 2013.

[34] A. Fernández, D. Vázquez-García, J. J. Fernández, M. López-Torres, A. Suárez, R. Mosteiro, and J. M. Vila, "Cyclopalladated compounds with a bidentate [C, N]/terdentate [C, N, S] benzylidenethiophene imine ligand. Crystal and molecular structures of [Pd{2,3-$(MeO)_2C_6H_2C(H):NCH_2(C_4H_3S)$}$(\mu$-OAc)$]_2$, [Pd{2,3-$(MeO)_2C_6H_2C(H):NCH_2(C_4H_3S)$}-(Cl)·$(PPh^3)$]," *J. Organomet. Chem.*, vol. 654, no. 1–2, pp. 162–169, 2002.

[35] D. M. A. Minahan, W. E. Hill, and C. A. McAuliffe, "An investigation of the chelate effect: The binding of bidentate phosphine and arsine chelates in square-planar transition metal complexes," *Coord. Chem. Rev.*, vol. 55, no. 1–2, pp. 31–54, 1984.

[36] R. Bosque, J. Granell, J. Sales, M. Font-Bardía, and X. Solans, "Reactivity of cyclometallated compounds of N-benzylideneamines. Synthesis and X-ray crystal structure of [Pd{1-CH_2-2-$(CHN\text{-}C_6H_5)$-3,5-$(CH_3)_2C_6H_2$} (2,4-$Me_2C_5H_3N$)]ClO_4," *J. Organomet. Chem.*, vol. 453, no. 1, pp. 147–154, 1993.

9. ACRONYMS

AcO: Acetate Group

Ar: Aromatic

br: broad signal

d: doublet

dd: doublet of doublets

DNA: Desoxyribonucleic Acid

dppe:1,2-Bis(diphenylphosphino)ethane

EA: Elemental analysis

IR: Infrared spectroscopy

$J_{A\text{-}B}$: Coupling constant between atom A and B

L: Neutral Ligand

m: multiplet

MS-ESI+: Electrospray ionization time-of-flight mass spectrometry

NMR: Nuclear Magnetic Ressonace

q: quadruplet

s: singlet

t: triplet

TLC: Thin-layer chromatography

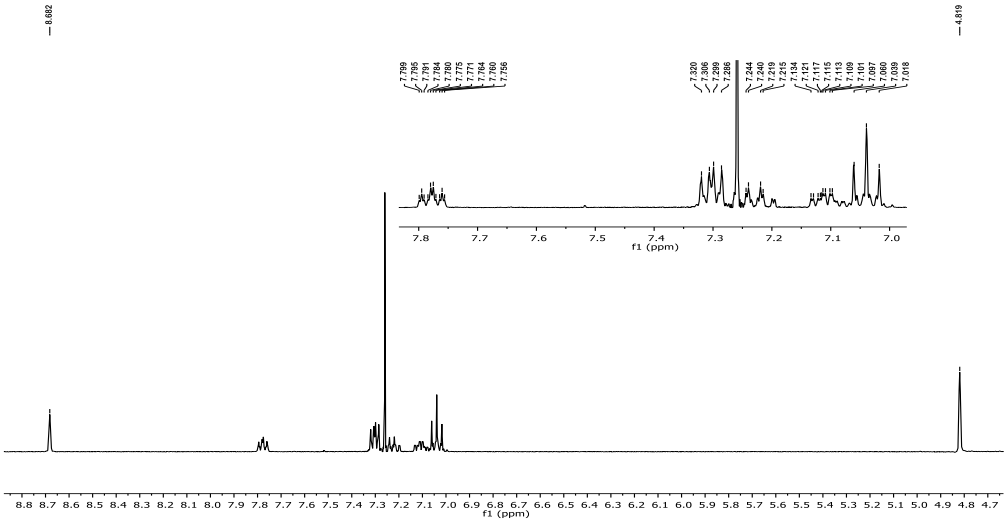
X: Halogen Group

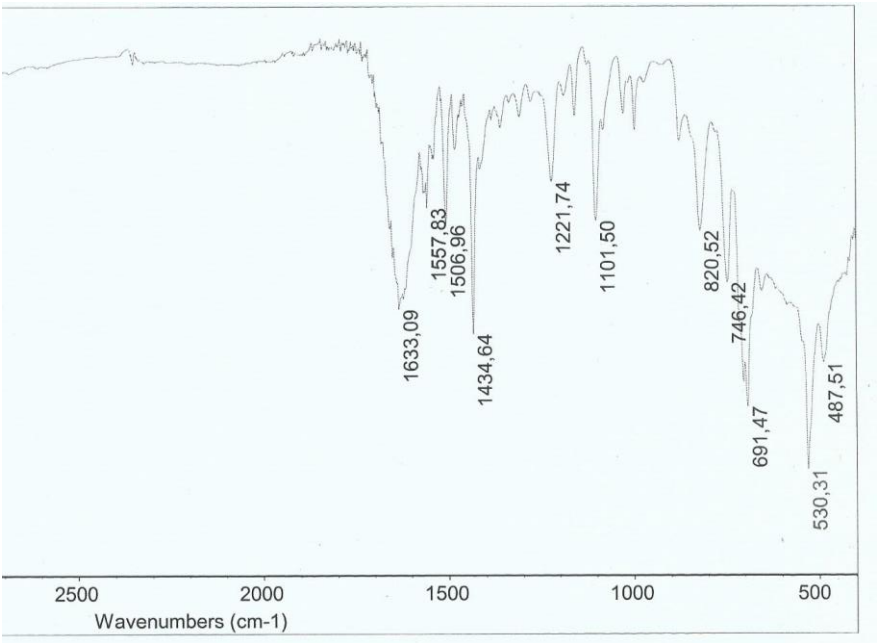
δ: chemical shift

μ: Bridged ligand

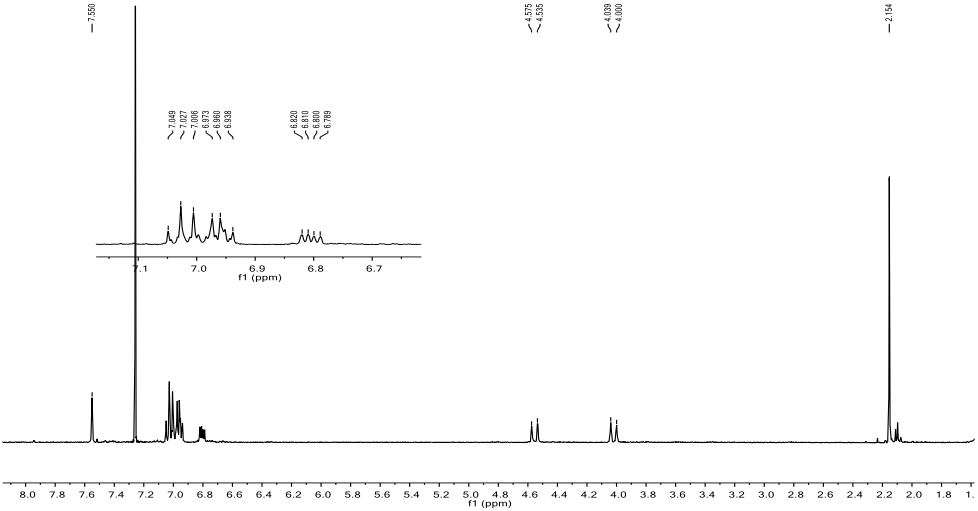
APPENDIXES

APPENDIX 1: IR SPECTROSCOPY AND ^{1}H NMR OF 1-B



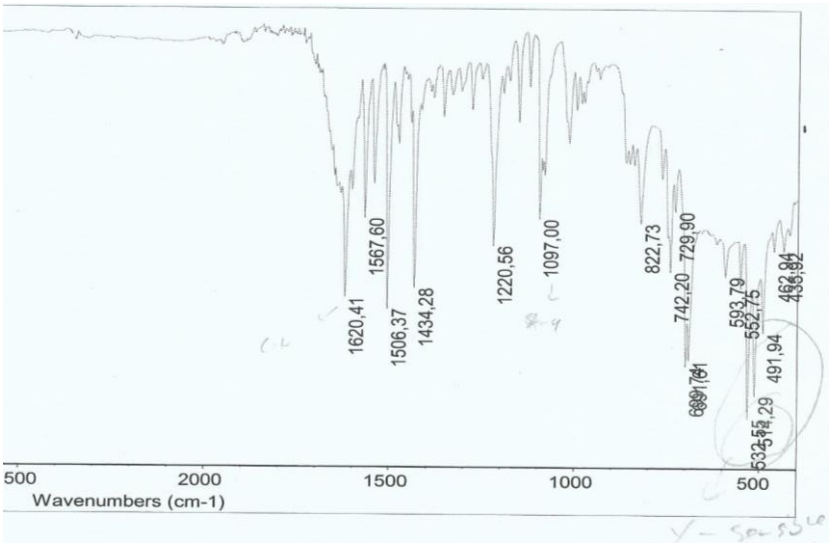


APPENDIX 2: ^{1}H NMR OF 2-B

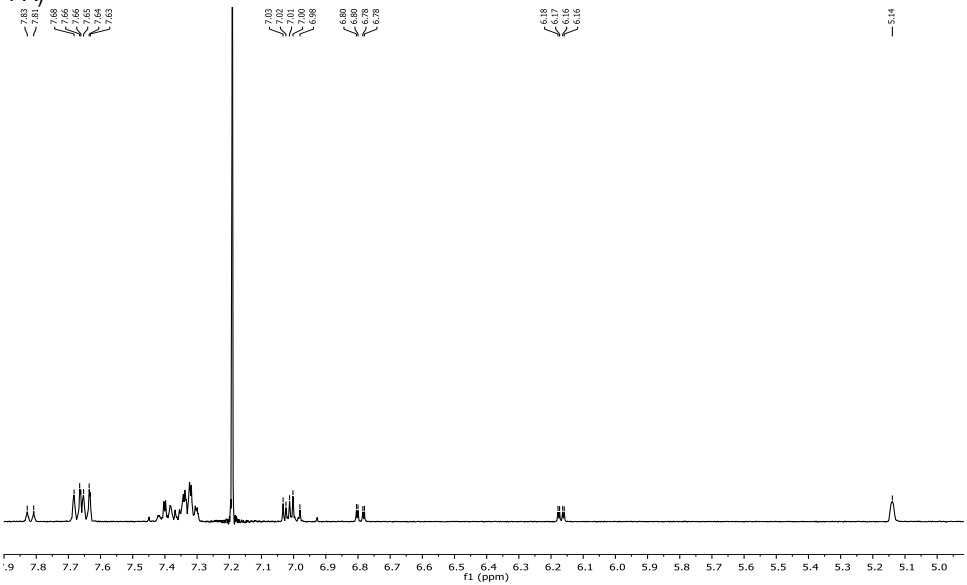


APPENDIX 3: IR SPECTROSCOPY AND ^{1}H NMR OF 3-B AND 4-A

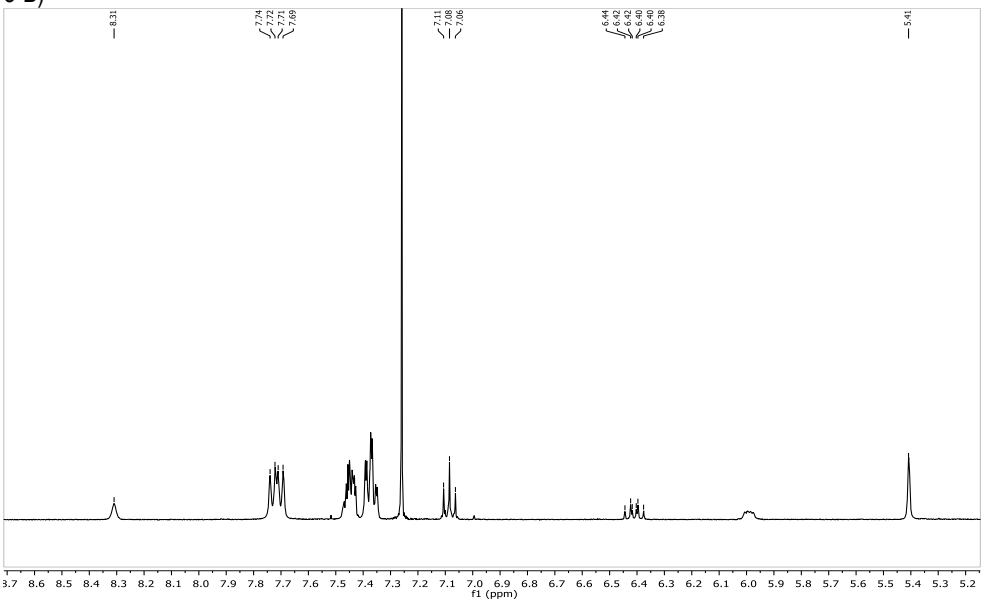
IR of 3-B



4-A)


7.83
7.81
7.68
7.66
7.66
7.65
7.64
7.63
7.03
7.02
7.01
7.00
6.98
6.80
6.80
6.78
6.78
6.18
6.17
6.16
6.16
5.14
f1 (ppm)

3-B)


8.31
7.74
7.72
7.71
7.69
7.11
7.08
7.06
6.44
6.42
6.42
6.40
6.40
6.38
5.41
f1 (ppm)