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Grau de Química

Treball Final de Grau

Synthesis of imine cyclopalladated compounds.
Síntesi de compostos ciclopal·ladats d'imines.

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Universitat de Barcelona

B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

Life is like riding a bicycle. To keep your balance, you must keep moving.

Albert Einstein

Gracias al grupo de recerca de *Síntesi i Aplicacions dels Compostos Ciclometal·lats* por ayudarme siempre cuando lo he necesitado. En especial al Dr. Joan Albert Mach, que ha sido mi tutor durante estos meses y su dedicación e involucración por el proyecto, no hacía más que motivarme. Un 10 como persona y profesor.

Muchas gracias a mi familia, por estar ahí a pie de cañón, siempre apoyándome, entendiendo cuando tenía un día malo en el laboratorio, y alegrándose cuando volvía con una sonrisa. Incluyo en familia también, a los amigos y compañeros de esta Facultad, pequeños confidentes con los cuales hemos compartido el estrés que conlleva este trabajo.

Para finalizar, agradezco a todo aquel que se tome la molestia en leer mi TFG. Mi inglés no es el más perfecto, pero espero que se entienda todo. Y lanzo un mensaje a las nuevas generaciones que lean esto: no pasa nada si va mal una síntesis y se pierde el trabajo de la semana, canaliza esa frustración en algo positivo y haz que cada error valga la pena.

REPORT

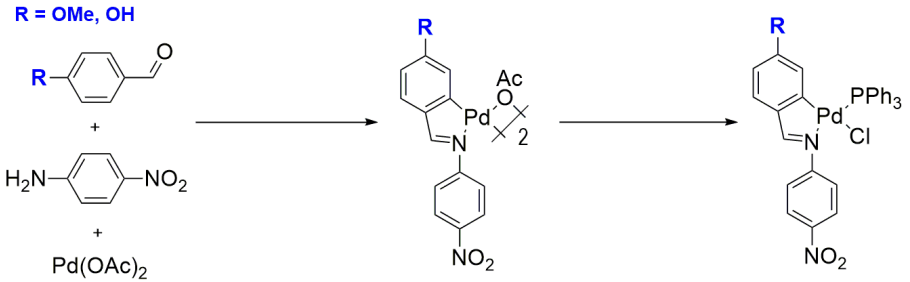
CONTENTS

1. SUMMARY

Since the clinical discovery in the mid-60s of cis-platin, as one of the most powerful antitumor agents, the existence of a cyclometallated compound that could have similar or better properties has been investigated. [1] The results found up to now show that the cis-platinum has not no competition. However, in previous studies, by means of "in vitro" and others "in vivo" tests [2, 3], it has been found that, there are cyclopalladated compounds with anticancer activity and these produce fewer side effects than cis-platinum. [4]

For this reason, the *Research Group on Synthesis and Applications of Cyclometallated Compounds* of the *Department of Inorganic Chemistry* from the *University of Barcelona*, continues to study new cyclometallated compounds. Thus, in this project, the synthesis of new cyclopalladated compounds, from imines, are proposed.

As part of this project, the synthesis of these compounds, and subsequent characterization by IR, ^{1}H NMR, will be performed. A ^{31}P-{^{1}H} NMR will be done too for those compounds that contain phosphorus atoms. More techniques, such as Elemental Analysis and X-ray diffraction, will be used for the characterization. The scheme below summarizes the synthetic route performed.



Scheme. Example of the compounds that were synthesised.

For each **R** the same series of reactions will be carried out. Therefore, there will be two series of reactions, where the formation of five-membered rings (orthopalladation) is studied with acetato as a bridge ligand, the reaction of metathesis with chlorido ligand, and the formation of mononuclear compounds with triphenylphosphane.

Keywords: cyclometallation, imine, palladium(II), synthesis, aromatic.

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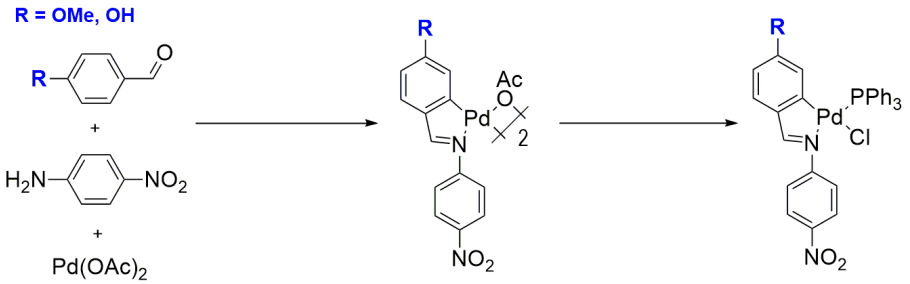
2. RESUM

Des del descobriment clínic del cis-platí a mitjans dels anys 60, com un dels més potents agents antitumorials, s'ha estat investigant si pot existir cap compost ciclometal·lat amb propietats semblants o millors. [1] Els resultats, però, demostren que de moment el cis-platí no te competidor; no obstant, en estudis anteriors mitjançant proves "in vitro" i altres "in vivo" [2, 3] , s'ha comprovat que hi ha compostos ciclopal·ladats amb activitat anticancerígena i que produeixen menys efectes secundaris que el cis-platí. [4]

Per aquest motiu, el grup de recerca de *Síntesi i Aplicacions dels Compostos Ciclometal·lats* del Departament de Química Inorgànica de la Universitat de Barcelona, segueix estudiant nous compostos ciclometal·lats. Així, en aquest treball es proposa la síntesi nous compostos ciclopal·ladats a partir d'imines.

Durant aquest treball es realitzarà la síntesis d'aquest compostos i posterior caracterització per IR, RMN ^{1}H, i RMN ^{31}P-$\{^{1}H\}$ en compostos que continguin fòsfor. També es valorarà si cal analitzar amb altres tècniques com l'espectrometria de masses o la difracció de raigs X. L'esquema següent mostra de forma resumida la ruta sintètica realitzada.



Esquema. Exemple de la sèrie de compostos sintetitzats.

Per a cada **R** es realitza la mateixa sèrie de reaccions, per tant, es realitzaran dues sèries on s'estudia la formació d'anells de cinc baules (ortopal·ladació) amb l'acetat com a lligand pont, la reacció de metàtesis amb lligand pont clorur i la formació de compostos mononuclears amb trifenilfosfina.

Paraules clau: ciclometal·lació, imina, pal·ladi (II), síntesis, aromàtic.

3. INTRODUCTION

Organometallic chemistry places itself in the border of organic and inorganic chemistry, it is the study of the molecules with carbon atoms bonded to a metal atom. Organometallic compounds are species that at least, contain, one bond between a metal centre and a carbon atom, where the carbon is part of an organic molecule. If an organometallic complex contains metallacycles with a sequence of σ bonds **E-Metal-Carbon**, where **E** is a donor heteroatom, the specie is called cyclometallated compound.

Many methods are widely developed to synthesize these cyclometallated compounds: *cyclometallation reaction, oxidative addition, transmetallation, external attack by nucleophiles to coordinate ligands, etc.* The cyclometallation reaction is the most interesting of these methods. It consists in the intramolecular activation of a σ bond between C-X, where X is a non-metallic atom, usually a hydrogen, and the formation of a new bond M-C, resulting in the cyclometallated compound.

Figure 1. Formation of the bond M-C

Cyclometallation reactions will be studied during this project, using palladium (II) acetate as a metallating agent, leading to a cyclopalladated compounds.

3.1. CYCLOPALLADATED COMPOUNDS

When the metallic centre present in the cyclometallated compound is palladium(II), the complex is known as cyclopalladated or palladacycle. This compound contains at least one Pd-C bond intramolecularly stabilized by a donor atom, such as nitrogen or phosphorus. [5] The metallated carbon atom usually is a sp^2 or sp^3.

The most common palladacycles come from tertiary amines and imines. [5] In this research project, eight different cyclopalladated compounds were synthesized using two different imines. The cyclometallation of these compounds could lead to two different isomers, depending on whether the ring formed contains the C=N bond or not. Palladacycles that contain the C=N bond in the ring are called *endo*, and *exo* when C=N bond is not contained.

Figure 2 shows the two possible isomers structures of the compound generated during this project.

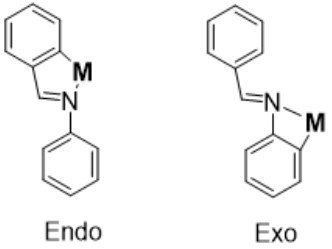


Figure 2. Example of endo and exo isomers

Endo product is more stable than exo, because a five-membered ring is thermodynamically favoured compared to a four-membered ring. So, it is expected that all the products of this research would be in the endo form.

The cyclopalladated compound can be neutral, anionic or cationic, and it can be found with a dinuclear, mononuclear or bis-cyclopalladated structure.

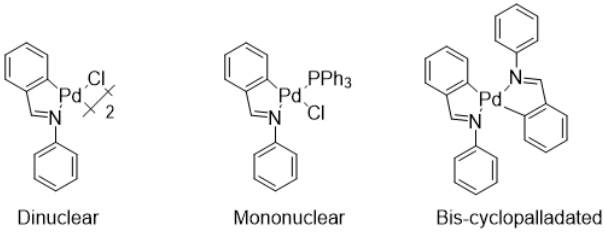


Figure 3. Example of palladacycles' structure

The dinuclear structure usually exists as acetato or halogeno bridged dimers, and it has two geometrical isomers: cisoid and transoid.

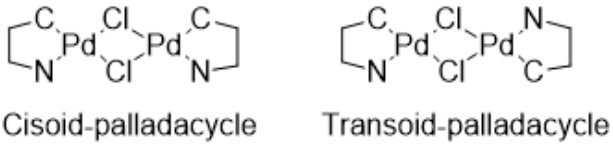


Figure 4. Example of the isomers

In addition, if one dinuclear palladacycle specie is in front of a better nucleophile ligand for the palladium(II) than the ligand which acts as bridge, this ligand is coordinated with the Pd(II) and the dinuclear compound is broken. This process is called splitting reaction (**Figure 5**) and it usually uses triphenylphosphine as the ligand. [6]

This bonded ligand can be entering to the palladium atom in a cis or trans position in front of the donor atom of the palladacycle. According to Pearson's theory, it is known that the ligand PPh_3 is considered a soft base, while the nitrogen of the cyclometallated compound is a hard base. Anyway, the PPh_3 is coordinated at the trans position regarding the nitrogen atom. This behaviour is called antisymbiotic effect. [7]

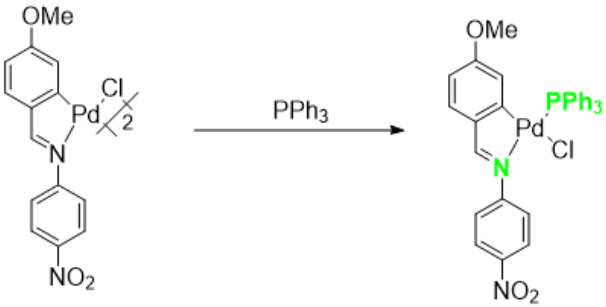


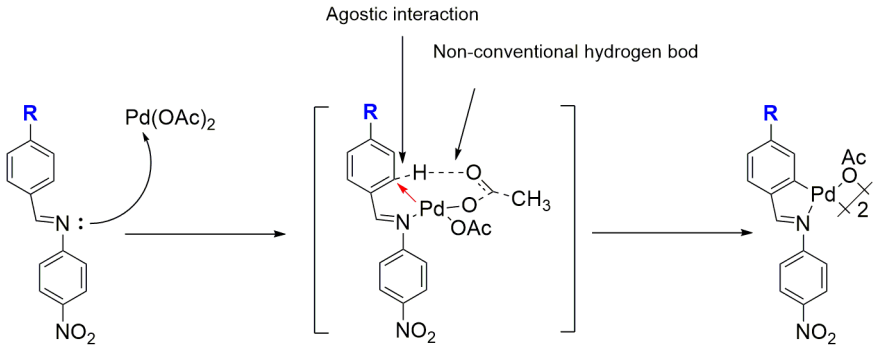
Figure 5. Splitting reaction

3.2. METHODS TO SYNTHESIZE A CYCLOPALLADATED COMPOUND

A variety of methods are available for the synthesis of palladacycles. The most distinguishable are the intramolecular C-H activation (also called cyclopalladation reaction), oxidative addition and transmetallation.

For the intramolecular C-H activation, the most common palladation agents are tetrachloropalladate(II) salts and palladium(II) acetate. The latter is the agent used for the synthesis of cyclopalladated compounds in this project.

The mechanism of this reaction is not thoroughly understood. It is suggested a fast-initial coordination to the palladium through the donor atom. The formation of the transition state which activated the C-H by means of an agostic interaction, and a non-conventional hydrogen bond in a concerted process. [8]



Scheme 1. Resumed mechanism of the C-H activation

Scheme 1 above an example of the mechanism of the C-H activation, using the same imine ligand that will be used in this memory. The regioselectivity for the palladation of imines is directional, forming the endo-palladacycle.

The other methods are used in case the first one does not work. The oxidative addition consists in the oxidation of palladium (0) compounds by aryl and alkyl halides and the formation of cyclometallated compound. In transmetallation reactions, either organolithium or organomercurial reagents are used, which exchange its alkyl or aryl ligands with a halido-bridged cyclopalladated compound.

3.3. APPLICATIONS OF CYCLOPALLADATED COMPOUNDS

Among the wide variety of catalytic application of palladium for organic synthesis; the cyclopalladated compounds can also be very helpful as a precursors catalyst. Nowadays, it is not a surprise that some palladacycles are used in reactions that involve bonds formation like C=C, in the Heck reaction [9] or the Suzuki coupling. [10] These studies with palladium catalysts and the formation of C-C bonds, led Heck, Suzuki and Negishi to win the Nobel Prize in 2010, due to the importance in the medicine world.

Nevertheless, the organometallic branch is submerged in the synthesis of new palladacycles, since the fact that these compounds have antitumoral properties was found out. [2, 3] The mechanism of this anticancer activity is still unclear. For instance, there are some compounds, that induce cancer cell apoptosis through interactions with organelle membrane thiol-groups, which led to the permeabilization of the membrane. [11] The point of these N-donor cyclopalladated compounds lies in the ambiguous character in front of water. A molecule of these compounds has a hydrophilic and lipophilic group. This property, makes it capable to go through cellular membranes and eliminate the tumour cells. [12]

One of the options to improve the behaviour of the cyclopalladated compounds is to lengthen the chain of the substituted imine using different synthesis. To do so, it is necessary to synthesize a cyclopalladated with reactive groups, like hydroxyl or ether groups. For instance, a hydroxyl group is easy to oxidize and makes the chain lengthen with aldolic reactions. The best option to do that, begins with getting a few compounds with high purity, which is the aim of this project.

4. OBJECTIVES

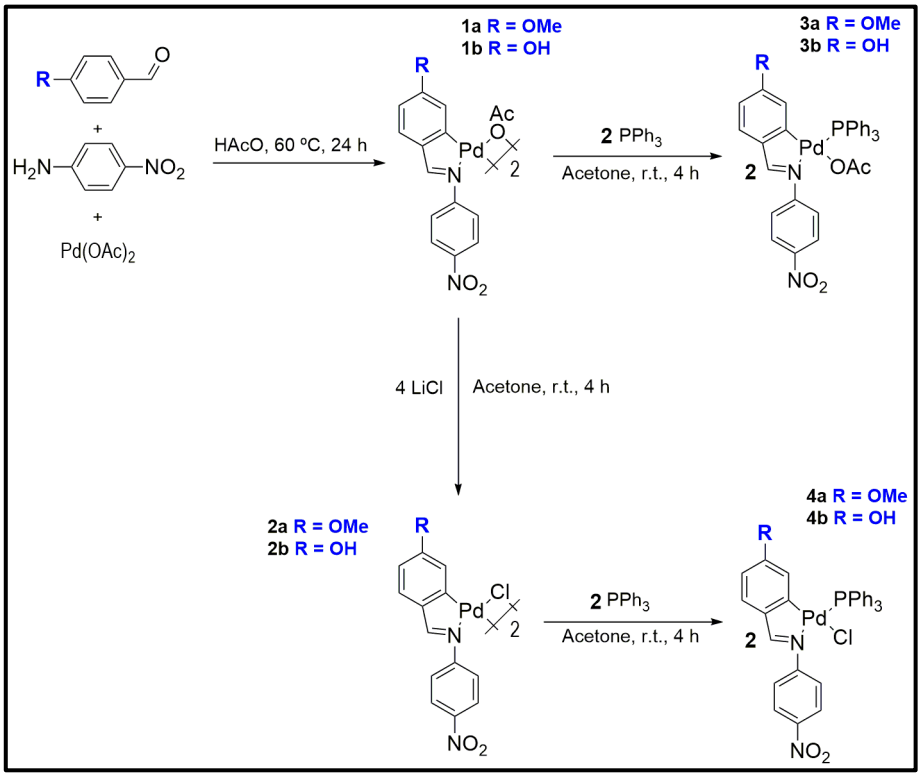
The target of this work is to synthesize the compounds proposed. Therefore, eight different compounds derived from imines by the condensation between 4-nitroaniline and 4-metoxibenzaldehide or 4-hidroxibenzaldehid will be prepared according to the literature consulted previously. [13, 14] Once these compounds are prepared, they will be characterized by IR and ^{1}H NMR. In addition, when necessary, a characterization by ^{31}P $\{^{1}H\}$ NMR, Elemental Analysis and X-Ray Diffraction will be done.

It is expected that, in the future, the antitumoral activity of these compounds would be studied. To do that, it is necessary to synthesize high-purity products.

5. RESULTS AND DISCUSSIONS

The following scheme (**Scheme 2**) collect all the reaction conditions, and the eight compounds that had been synthesized during this study. Following the numbers; we can know for what compound we are talking about all the time.

We decide to put the number **1** to those compounds that have an acetato-bridged, the number **2** is for those that have a chlorido-bridged, **3** for those that are mononuclear and have a PPh_3 and an acetato as a ligand, and **4** for those that are mononuclear and have a PPh_3 and a chlorido as ligands.



Scheme 2. Synthetic path followed

5.1. SYNTHESIS OF ACETATO-BRIDGED COMPOUNDS

In previous years, the synthesis path to get the imine cyclopalladated compound, was first, to synthesize the imine through a condensation reaction between an aldehyde and an amine. Then, to isolate it, and make it to react by a cyclometallation reaction with a palladating agent, such as $Pd(OAc)_2$. To optimise this reaction, the imine is generated "in situ", that means, the imine is synthetized in the same medium, where the palladation agent takes place. This change generated higher yields.

The reaction that involves the formation of compounds **1a** and **1b** is called ortho-palladation and it occurs by C-H activation. One of the reasons of $Pd(OAc)_2$ is used, is due to its good electrophile behaviour in front of aromatic compounds. The C-H bond is activated giving the endo five-membered ring compound.

Compounds **1a** and **1b** were orange and yellow, respectively. Compound **1a** was soluble in deuterated chloroform and ethyl acetate. It was obtained with a yield of 82 %, but after the purification by column chromatography this yield was reduced till 63 %. Compound **1b** was insoluble in most deuterated compounds ($CDCl_3$, metanol-d_4, acetone-d_6), only was soluble in DMSO-d_6. That was a disadvantage, because in the NMR spectrum it was observed two signals systems, since the DMSO was coordinated to palladium centre, breaking the acetato-bridge and forming mononuclear compounds. Compound **1b** couldn't be purified by column chromatography, so the time of reaction was increased in 3 days to obtain the compound as pure as possible, the yield was 95%.

^1H NMR spectra of both compounds showed a singlet corresponding to the methinic proton (the proton bonded to the C_{sp^2} of the imine) at 7.72 and 8.12, respectively. The chemical shift of this methinic proton indicates that the coordination to palladium is established through the lone pair of N. [15] The signal corresponding to the proton of the OH group of compound **1b** apparently was not observed. The aromatic protons of both compounds were clearly observed and assigned.

IR spectra of both compounds showed a middle-intense C=N band at 1606 and 1610 cm^{-1} respectively, which indicates that the imine was generated. [16] The asymmetric and symmetric stretching of the carboxylic group produced broad intense bands at 1527 and 1410 cm^{-1} for the compound **1a** respectively; and for the compound **1b**, the asymmetric band appeared at 1521 cm^{-1} and the symmetric stretching of the carboxylic group was it observed at 1416 cm^{-1}, these

bands indicate that the acetato ligands presented a bridging coordination mode. [6, 17] It is remarkable the band at 2835 cm^{-1} which is characteristic for ethers groups, corresponding the stretching of $O\text{-}CH_3$. This band is repeated for each compound of the **A Serie**.

X-ray diffraction (XRD) is an important method to analyse the structure of the compounds, in which, the crystalline atoms cause the diffraction of the incidents X-rays into many directions. A crystallographer can use the angles and intensities of these diffracted beams and produce a three-dimensional picture of the density of electrons inside of the crystal. During the progress of this work, it was obtained mono-crystals of the compound **1a**. Suitable crystals for an X-ray diffraction were studied by this technique.

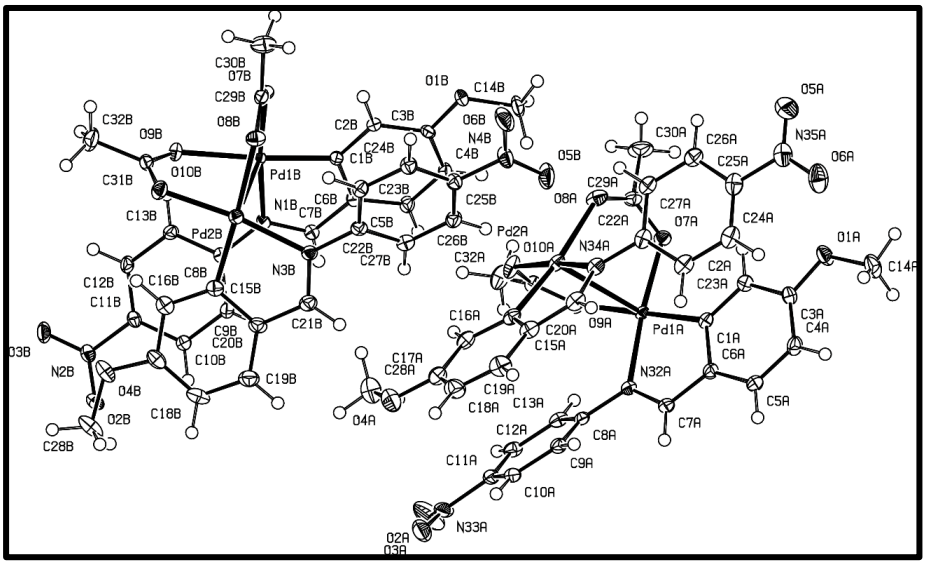


Figure 6. The X-ray structure of compound **1a**

As seen in **Figure 6**, it is possible to recognize the whole structure of compound **1a**. In addition, two structures are distinguishable, but both structures belong at the same compound. The difference between these structures is the torsion angle for one of the benzene rings.

Compound **1b** was also characterized by elemental analysis. This technique consists of a process where the sample is analysed for its elemental composition. Elemental analysis can be qualitative (we can know what elements are present) or it can be quantitative (we can know how much of each element are present). Compound **1b** was determinate using a C, H, N, S combustion analyser. The sample is burned in an excess of O_2 and the products of the combustion were collected in a gas phase: CO_2, H_2O (g), NO_x (g). The masses of these combustion products can be used to calculate the composition of the sample.

The results of the elemental analysis for C, H and N atoms are showed in the following table (**Table 1**).

Experiment	%C	%H	%N
1	42.16	3.48	5.83
2	42.23	3.64	5.82
3	42.20	3.62	5.81

Table 1. Results of the elemental analysis of the compound **1b**

Compound **1b** has a molecular formula of $C_{30}H_{24}N_4O_{10}Pd_2$, theoretically the composition of C is 44.30%, of H is 2.97% and of N is 6.89%. The results obtained in the elemental analysis were unclear to proof whether it was the compound or not. It can possible that the compound was not completely dry, because it has more % of H than the expected. So, we can say that we have a hydrated compound.

In both products, there was no evidence in the characterization, that there were any residues of free aldehyde or amine. It is possible to affirm that this method to synthesize this palladacycles were good, at least, for these compounds.

5.2. SYNTHESIS OF CHLORIDO-BRIDGED COMPOUNDS

To obtain the chlorido-bridged compounds, a metathesis reaction was done for compounds **1a** and **1b**. This reaction consists in an exchange of cations and anions, so, what we wanted was the exchange of the acetato bridge ligand and substituted then, by chlorido bridge ligands. Compounds **1a** and **1b** reacted with an excess of lithium chloride, the details are explaining in the experimental section.

Compounds **2a** and **2b** were yellow and mustard respectively. Both compounds were only soluble in DMSO, so the ^{1}H NMR were recorded using DMSO-d_6 as the solvent. Due to the insolubility in front of other solvents, none of the compounds were purified.

^{1}H NMR spectra confirmed that compound **2a** and **2b** were obtained. The signal corresponding to the protons of the acetato bridge were not in the spectra, this is what we expected, because these compounds had a chlorido-bridged ligand. The aromatic protons were significant to reinforce the idea that products were synthetized, or at least, to be the majority compound. It is necessary to mention, that the signals of the protons from carbons 1, 2 and 3 (**Figure 7**) are broad and looked different than the other aromatic protons. This fact could be explained for the interaction of the coordination of the DMSO to the Pd centre forming mononuclear compounds, bonded at trans position respected to the nitrogen atom and coordinated to the Pd centre with the sulphur atom. There is an exchange between free and coordinated DMSO.

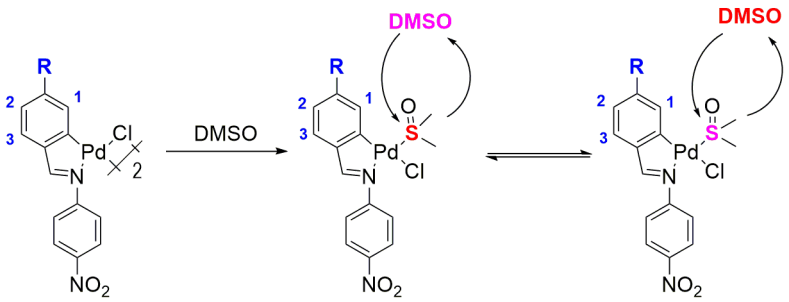


Figure 7. Dynamic coordination of the DMSO

This dynamic system, made the chemical environment different for the protons 1, 2 and 3 in comparison with the other aromatic protons. All the NMR spectra are placed in the **Annexes** section.

In the IR spectra it was observed, for both products, that the bands corresponding at the asymmetric and symmetric stretching of the carboxylate group, were not in the spectra, due to the loss of the acetato-bridge. Both spectra showed the characteristic band of the C=N, the imine group, at 1603 cm^{-1} for compound **2a** and 1610 cm^{-1} for **2b**. Compound **2a** showed a band at 2835 cm^{-1}, typical for the ether group that it has.

5.3. SYNTHESIS OF MONONUCLEAR ACETATO LIGAND COMPOUNDS

Concurrently, we made compounds **1a** and **1b** undergo a splitting reaction, which consisted in the divide of the acetato bridged through a reaction with one ligand that could be break the bridge, forming a mononuclear compound. The ligand used was triphenylphosphine. As it is explained in the introduction, the PPh_3 was bonded at trans position respected the nitrogen, due to the antisymbiotic effect.

Compounds **3a** and **3b** were pale yellow and yellow respectively. Compound **3a** was soluble in $CDCl_3$ so the ^1H NMR spectrum was recorded in this solvent. Compound **3b**, as all the **b serie**, was only soluble, but partially, in DMSO.

For the ^1H NMR of the compound **3a**, a doublet at 8.15 ppm was assigned to the methinic proton, due to the coupling with the phosphorus atom. We could know that the coupling of the methinic proton and the phosphorus atom was produced because the value of the *J*, known as *coupling constant*. The values for *J* of the coupling between aromatic protons were in 9 – 8 Hz. But in this spectrum, the methinic proton (**H4**) has a coupling constant of 6.3 Hz, this value is only explained with the coupling of this proton with another nucleus of I = 1/2, like the phosphorus atom. All the characterization and the values of this constant are in the section 6 **Experimental Section**.

As the PPh_3 has many aromatic protons, in the spectrum is it observed different signals in the aromatic zone shift, but the aromatic protons of the imine still were distinguishable. The $^{31}P-\{^1H\}$ NMR spectrum showed three different signals; one was the signal of the reference compound for the NMR, the $OP(OMe)_3$, at 2.39 ppm, and the other signals appeared at 42.31 and 44.36 ppm. For this determination, is it expected to observe only one signal, aside the reference signal, but in this case, it is observed two signals, this fact could be to the presence of an isomer of the compound. This reason explains the similar ppm that both signals had. This spectrum confirms that we have the PPh_3 coordinated only at trans position of the nitrogen atom, and not coordinated in other positions.

For compound **3b** the ^1H NMR was recorded using DMSO-d_6, the only dissolvent that this product was partially soluble, due to this, the spectrum showed the product at a low concentration. The methinic proton was assigned at 8.46 ppm as a doublet for the coupling with the phosphorus atom. A few aromatic protons of the imine were overlapped with the aromatic protons of the PPh_3.

The use of triphenylphosphine, is not only useful for the formation of mononuclear compounds, is it use too because is relatively easy to characterise if a compound has or not this ligand, at least, using the IR, due to the characteristic band, which name is q.X. sensitive vibration. [18] For compounds **3a** and **3b** this band were founded at 1100 cm^{-1}. Other bands were also characteristic, as the stretching of C=N, at 1606 for compound **3a** and 1603 for **3b** or the asymmetric and antisymmetric stretching of the group nitro.

5.4. SYNTHESIS OF MONONUCLEAR CHLORIDO LIGAND COMPOUNDS

Compounds **2a** and **2b** reacted with PPh_3 in a splitting reaction, to obtain mononuclear compounds with a chlorido as a terminal ligand instead of a bridge one. Compounds **4a** and **4b** were both yellow and soluble in $CHCl_3$.

Compound **4a** was obtained with a yield of 56 %, but after the column chromatography this yield is reduced till 34 %. The ^1H NMR spectrum of **4a** was recorded in $CDCl_3$. A doublet at 8.21 ppm was assigned to the methinic proton, due to the coupling with the phosphorus atom. Many signals that were presented with a multiplet in the aromatic zone were to the presence of

triphenylphosphane, where it was distinguishable what protons were the ortho, meta and para for the PPh_3. The ^{31}P-{^1H} spectrum show 3 signals: one for the reference compound $OP(OMe)_3$ at 2.39 ppm and the other two at 44.37 and 23.27 ppm in a relation of 5:1 respectively. We can say that the signal at 44.37 is due to the phosphor atom because is the majority signal. The other signal at 23.27 ppm could be an impurity, which this fact is difficult to happen because this compound was purified by column chromatography. Other option to explain this signal could be the coordination of another phosphor atom in the compound, but with a less quantity due to the intensity of the signal is five times lower than the other. It is not easy try to answer why have appeared a second signal, but the second option could be the best explanation for this fact. In the IR spectrum we can observed the bands produced for the C=N bond of the imine formed at 1603 cm^{-1}, and other important bands like the characteristic q.X.sens band of the PPh_3 at 1100 cm^{-1}, the asymmetric and symmetric bands of the NO_2 substituent, and the characteristic band of the ether group at 2835 cm^{-1} which indicates the stretching of the bond between O-CH_3.

Compound **4b** was soluble in $CDCl_3$, but the ^1H NMR was done using DMSO-d_6 because this solvent was used during all the **B Serie** for the characterization. In this spectrum we can observed the signal corresponding to the proton of the hydroxy group at 9.73 ppm, this the first time that we distinguished this signal. A broad signal at 8.43 ppm was assigned to the methinic proton. This signal is so broad that it is not observed the coupling with the phosphor atom and it had the appearance of a singlet. The aromatic protons of the imine were assigned, but the protons **5** and **3** are overlapped with the signals of the aromatic protons of the PPh_3, which these were distinguishable in ortho, para and meta. The ^{31}P {^1H} NMR spectrum showed two signals: the reference signal of the $OP(OMe)_3$ at 2.39 ppm and a singlet at 43.44 corresponding to the phosphor atom. That means that compound **4b** has only one phosphor atom and it is coordinated to the palladium at trans position respected the nitrogen atom. The IR spectrum showed a band at 3176 cm^{-1} that created confusion because, in theory, compound **4b** didn't have a group that produced a band in this zone, so we have the idea that this band could be an impurity. The other bands that we had seen during the others IR spectra of the products, were in this too: the C=N stretching at 1603 cm^{-1} which means that we have the imine, the symmetric and antisymmetric bands for the group nitro, and the characteristic band of the PPh_3 at 1097 cm^{-1}.

In a summary way, the following table (**Table 2**) explains some information of the eight compounds that were synthesised during this work. The reagents and the conditions of each compound were prepared are in the next section of this memory.

Compound	Formula	Colour	Molecular Weight (g/mol)	Yield (%)
1a	$C_{32}H_{28}N_4O_{10}Pd_2$	Orange	841.43	63
1b	$C_{30}H_{24}N_4O_{10}Pd_2$	Yellow	813.38	93
2a	$C_{28}H_{22}Cl_2N_4O_6Pd_2$	Yellow	794.25	83
2b	$C_{26}H_{18}Cl_2N_4O_6Pd_2$	Mustard	766.19	84
3a	$C_{34}H_{29}N_2O_5PPd$	Pale yellow	683.01	72
3b	$C_{33}H_{27}N_2O_5PPd$	Yellow	668.98	64
4a	$C_{32}H_{26}ClN_2O_3PPd$	Pale yellow	659.41	34
4b	$C_{31}H_{24}ClN_2O_3PPd$	Pale yellow	645.39	73

Table 2. The cyclometallated compounds

6. EXPERIMENTAL SECTION

This section will elucidate how the reactions are done, the reagents used, the experimental conditions, and the characterization of the products by the basics techniques of analysis.

6.1. MATERIALS AND METHODS

^{1}H NMR and ^{31}P-{H} NMR spectra were recorded in a Varian Mercury 400 MHz and a Bruker 400 MHz Advance III, respectively. Chemical shifts were measured relative to TMS for ^{1}H NMR and to $OP(OMe)_3$ for ^{31}P NMR. Chemical shifts were reported in ppm and coupling constants in Hz. IR spectra were collected with a Thermo Nicolet 5700 spectrometer using KBr discs analysis. For the X-ray crystallographic analysis, the X-ray intensity data were measured on a D8 Venture system equipped with a multilayer monochromator and a Mo microfocus (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. C, H and N were analyzed at Scientific and Technological Centers of the University of Barcelona, using an elemental organic analyzer Thermo EA Flash 2000.

6.2. PREPARATION OF THE COMPOUNDS (SERIES A AND B)

6.2.1. Preparation of acetato-bridge compounds

Synthesis of compound 1a

A solution formed by 4-methoxybenzaldehyde (0.164 g, 1.205 mmols), 4-nitroaniline (0.167 g, 1.209 mmols) and palladium(II) acetate (0.271 g, 1.207 mmols) in 5 mL of acetic acid was heated to 60 °C for 24 hours. The solid obtained was filtered and dried under vacuum line. The product was purified by column chromatography using a mixture of CH_2Cl_2:MeOH in a relative volume ratio of 100:2, as a mobile phase and silica-60 as stationary phase. (**Figure 8**)

Figure 8. Purification of compound **1a**

The orange band was collected in fractions and studied by TLC to know if each one was corresponding to the same product (**Figure 9**). The fractions that showed the same spot patron in the TLC, were collected and concentrated in a rotary evaporator. The solid was treated with diethyl ether (3 mL) and dried under the vacuum line (0.320 g, 63 % yield).

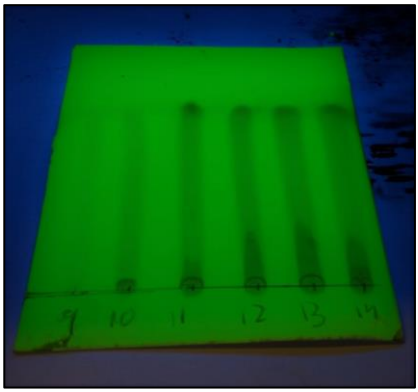
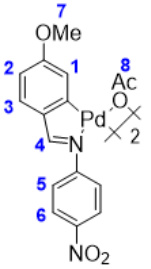


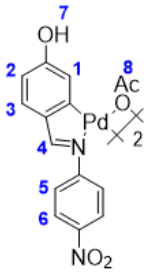
Figure 9. TLC of compound **1a**



Orange solid. IR (cm^{-1}): 3113, 3069 (st aromatic C-H); 2965, 2927 (st aliphatic C-H); **2835 (O-CH_3)**; 1606 (st C=N); 1575 (as st $NO_{2)}$; 1527 (as st bridge carboxylic function; 1410 (s st bridge carboxylic function); 1340 (s st NO_2); 1135, 1109 (as st C-O-C). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J = 9.0 Hz, 2H, **6**); 7.72 (s, 1H, **4**); 7.30 (d, J = 8.4 Hz, 1H, **3**); 6.87 (d, J = 9.0 Hz, 2H, **5**); 6.64 (d, J = 8.4 Hz, 1H, **2**); 5.89 (s, 1H, **1**); 3.56 (s, 3H, **7**); 1.97 (s, 3H, **8**).

Synthesis of compound 1b

A solution formed by 4-hydroxybenzaldehyde (0.082 g, 0.671 mmol), 4-nitroaniline (0.093 g, 0.673 mmol) and palladium(II) acetate (0.155 g, 0.690 mmol) was heated in 5 mL of acetic acid to 60 °C for 72 hours. During the first day of the reaction, the solution's colour was changing between brown, red, orange, till it kept this last colour. The solid obtained was filtered and dried under vacuum line (0.254 g, 93 % yield).

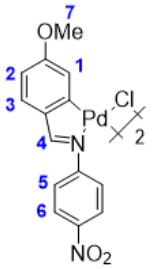


Yellow solid. IR (cm^{-1}): 3401 (st O-H); 3110, 3069 (st aromatic C-H); 2977, 2923 (st aliphatic C-H); 1610 (st C=N); 1571 (as st NO_2); 1521 as st bridge carboxylic function); 1416 (s st bridge carboxylic function); 1344 (s st NO_2). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.12 (s, 1H, **4**); 7.94 (d, J = 9.0 Hz, 2H, **6**); 7.29 (d, J = 8.3 Hz, 1H **3**); 6.99 (d, J = 8.9 Hz, 2H, **5**); 6.44 (dd, J = 8.1, 2.3 Hz, 1H, **2**); 5.69 (d, J = 2.3 Hz, 1H, **1**); 1.89 (s, 3H, **7**).

6.2.2 Preparation of chlorido-bridge compounds

Synthesis of the compound 2a

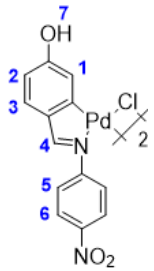
0.100 g of compound **1a** (0. 119 mmol) reacted with 0.033 g of lithium chloride (0.778 mmol) in 5 mL of acetone for 4 hours at room temperature. The product of the reaction is transfered to a 100 mL baker using 20 mL of acetone and, 60 ml of water were added in order to dissolve the excess of lithium chloride. The suspension was filtered and the solid was dried under vacuum line (0.078 g, 83 % yield).



Yellow solid. IR (cm^{-1}): 3107, 3066 (st aromatic C-H); 2965, 2939 (st aliphatic C-H); **2835 (O-CH_3)**; 1603 (st C=N); 1578 (as st NO_2); 1344 (s st NO_2); 1138, 1109 (as st C-O-C). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.43 (s, 1H, **4**); 8.24 (d, J = 8.6 Hz, 2H, **6**); 7.58 (d, J = 8.6 Hz; 2H, **5**); 7.49 (s, 1H, **3**); 7.21 (s, 1H, **2**); 6.72 (s, 1H, **1**); 3.78 (s, 3H, **7**).

Synthesis of the compound 2b

0.200 g of compound **1b** (0.246 mmol) reacted with an excess of LiCl (0.050 g, 1.180 mmols). The work-up after the reaction was exactly equal, as for compound **2a**. The solid obtain was dried under vacuum line (0.158 g, 84 % yield).

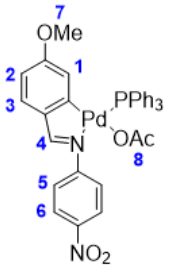


Mustard solid. IR (cm^{-1}): 3348 (st O-H); 3107, 3069 (st aromatic C-H); 2990, 2930 (st aliphatic C-H); 1610 (st C=N); 1581 (as st NO_2); 1344 (s st NO_2). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.35 (s, 1H, **4**); 8.25 (d, J = 8.5 Hz, 2H, **6**); 7.57 (d, J = 8.5 Hz, 2H, **5**); 7.39 (s, 1H, **3**); 7.13 (s, 1H, **2**); 6.50 (s, 1H, **1**).

6.2.3 Preparation of mononuclear compounds with terminal acetato ligand

Synthesis of compound 3a

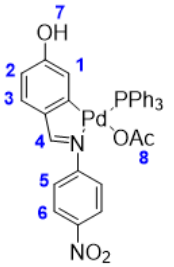
0.107 g of compound **1a** (0.127 mmol) reacted with 0.066 g of triphenylphosphane (0.252 mmol) in 5 mL of acetone for 4 hours at room temperature. The colour of the suspension during the reaction is pale yellow. The suspension was filtered and the solid obtained was dried under vacuum line (0.123 g, 72 % yield).



Pale yellow solid. IR (cm^{-1}): 3104, 3063 (st aromatic C-H); 3003, 2933 (st aliphatic C-H); **2835 (O-CH_3)**; 1606 (st C=N); 1584 (as st NO_2); 1518 (as st bridge carboxylic function); 1435 (s st bridge carboxylic function); 1344 (s st NO_2); 1198 (as st C-O-C); 1100 (q. X. sens. PPh_3). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 9.0 Hz, 2H, **6**); 8.15 (d, J = 6.3 Hz, 1H, **4**); 7.84 – 7.78 (m, 6H, **PPh_3 ortho**); 7.51 (d, J = 8.9 Hz, 2H, **5**); 7.47 – 7.43 (m, 3H, **PPh_3 meta**); 7.42 – 7.36 (m, 6H, **PPh_3 para**); 7.35 (s, 1H, **3**); 6.47 (d, J = 8.4 Hz, 1H, **2**); 6.04 (d, J = 6.2 Hz, 1H, **1**); 3.04 (s, 3H, **7**); 0.97 (s, 3H, **8**). ^{31}P {^1H} NMR ($CHCl_3$, 400 MHz): δ 44.35; 42.30.

Synthesis of compound 3b

0.100 g of compound **1b** (0.123 mmol) was mixed with 0.064 g of triphenylphosphane (0.244 mmol) in 5 mL of acetone for 4 hours at room temperature. During the reaction, a suspension was formed. The suspension was filtered in order to obtain the solid and it was dried under vacuum line (0.105 g, 64 % yield)



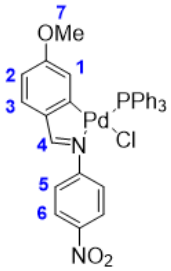
Yellow solid. IR (cm^{-1}): 3439.58 (st O-H); 3053 (st aromatic C-H); 3006, 2923 st aliphatic C-H); 1603 (st C=N); 1581 (as st NO_2); 1518 (as st bridge carboxylic function); 1439 (s st bridge carboxylic function); 1340 (s st NO_2); 1097 (q. X. sens. PPh_3). ^1H NMR (DMSO-d_6, 400 MHz): δ 8.48 (d, J = 4.8 Hz, 1H, **4**); 8.21 (d, J = 8.8 Hz, 2H, **6**); 7.70 (m, 6H, **PPh_3 ortho**); 7.61 – 7.49 (m, 4H, **PPh_3 meta**); 7.46 (m, 6H, **PPh_3 para**); 6.35 (d, J = 8.5 Hz, 1H, **2**); 5.84 (d, J = 6.1 Hz, 1H, **1**); 4.04 (s, 3H, **8**). ^{31}P {^1H} NMR (DMSO, 400 MHz): δ 41.85.

6.2.4 Preparation of mononuclear compounds with terminal chlorido ligand

Synthesis of compound 4a

A solution formed by 0.102 g of compound **2a** (0.128 mmol) and 0.069 of triphenylphosphane (0.263 mmol) in 5 mL of acetone reacted for 4 hours at room temperature. The compound **2a** is partially soluble in acetone, but when it was added the PPh3, the solution became insoluble and the colour of the suspension turned orange/brown.

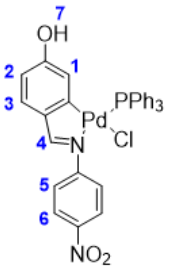
The suspension was filtered and the solid obtained was purified by column chromatography using a mixture of CH_2Cl_2:MeOH in relative 100:2 of volume, as a mobile phase and silica-60 as stationary phase. The solid was treated with diethyl ether (3 mL) and dried under the vacuum line (0.057 g, 34 % yield).



Yellow solid. IR (cm^{-1}): 3085, 3047 (st aromatic C-H), 2968, 2930 (st aliphatic C-H); **2835 (O-CH_3)**; 1603 (st C=N); 1578 (as st NO_2); 1344 (s st NO_2); 1270 (as st C-O-C); 1100 (q. X. sens. PPh_3). ^1H NMR (1_3, 400 MHz): δ 8.21 (d, J = 3.3 Hz, 1H, **4**); 8.20 (s, 2H, **6**); 7.81 – 7.71 (m, 6H, **PPh_3 ortho**); 7.51 (s, 2H, **5**); 7.49 – 7.44 (m, 3H, **PPh_3 meta**); 7.41 – 7.38 (m, 6H, **PPh_3 para**); 7.36 (d, J = 2.2 Hz, 1H, **3**); 6.52 (dd, J = 8.3, 2.4 Hz, 1H, **2**); 6.07 (dd, J = 6.7, 2.3 Hz, 1H, **1**); 3.02 (s, 3H, **7**). ^{31}P {^1H} NMR ($CHCl_3$, 400 MHz): δ 44.38; 23.27.

Synthesis of compound 4b

0.152 g of compound **2b** (0.198 mmol) was mixed with 0.104 g of triphenylphosphane (0.397 mmol) using 5 mL of acetone, for 4 hours at room temperature. Compound **2b** is partially soluble in acetone, but when it was added the PPh_3, the mix became a suspension. The colour of the suspensions was orange/brown due to the formation the formation of a solid precipitated. This solid is filtered and dried under vacuum line (0.186 g, 73 % yield).



Yellow solid. IR (cm^{-1}): 3459 (st O-H); 3060 (st aromatic C-H), 2923 (st aliphatic C-H); 1603 (st C=N); 1584 (as st NO_2); 1347 (s st NO_2); 1096 (q. X. sens. PPh_3). ^1H NMR (DMSO-d_6, 400 MHz): δ 9.73 (s, 1H, **7**); 8.43 (s, 1H, **4**); 8.22 (d, J = 8.8 Hz, 2H, **6**); 7.61 (m, 6H, **PPh_3 ortho**); 7.52 – 7.43 (m, 4H, **PPh_3 meta**); 7.41 (m, 6H, **PPh_3 para**); 6.34 (s, 1H, **2**); 5.95 (s, 1H, **1**). ^{31}P {^1H} NMR (DMSO, 400 MHz): δ 43.44.

7. CONCLUSIONS

Following the synthetic route, stablished in previous papers, a successful synthesis and characterization of the compounds was achieved. All the preparations given by the reactions followed, resulted in a solid, which was easy to filter and study by analysis techniques.

On one hand, the compounds of the **A Serie** (**1a**, **2a**, **3a**, **4a**) had an easy characterization, those gave ^{1}H NMR and IR spectra, with apparently, only the signals corresponding to the atoms of the product, which means, the spectra showed barely signals of impurities. In fact, those compounds can be studied for their antitumoral properties, especially compounds **1a** and **4a**, which were synthesized and purified by column chromatography and almost considered pure for these studies.

On the other hand, the **B Serie** needs to be studied in more detail, since the products showed spectra with, apparently, few incoherence, due to the dynamic processes when those were in solution. For instance, compounds **3a** and **3b** did not show the characteristic intense broadband of the O-H stretching on the IR, or compounds **3a**, **3b**, and **3c** did not show the proton of the hydroxyl group on the ^{1}H NMR. Those compounds were considered pure, but not enough to be studied for their antitumoral properties.

8. REFERENCES AND NOTES

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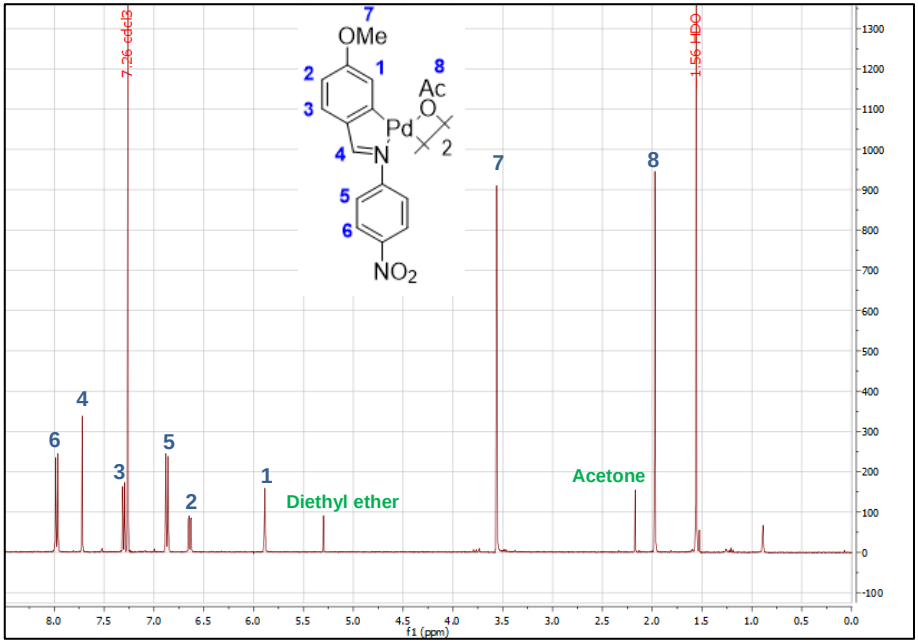
9. ACRONYMS

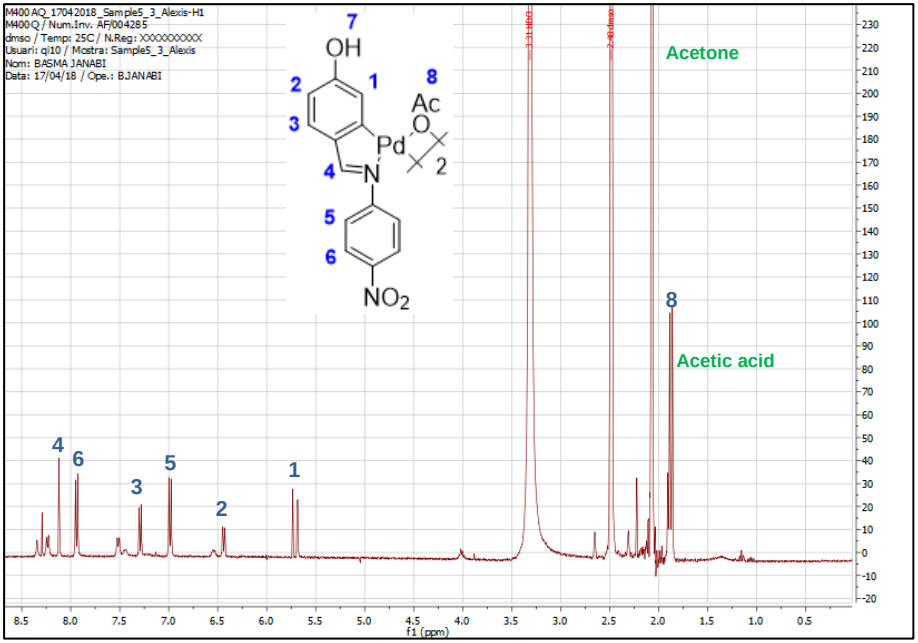
IR	Infrared Spectroscopy
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{31}P-{^{1}H} NMR	Phosphorus-31 Decoupled from proton Nuclear Magnetic Resonance
$CDCl_3$	Deuterated Chloroform
TMS	Tetramethylsilane
DMSO	Dimethyl Sulfoxide
$OP(OMe)_3$	Trimethyl Phosphate
s	Singlet
d	Doublet
t	Triplet
m	Multiplet
dd	Doublet of doublets

APPENDICES

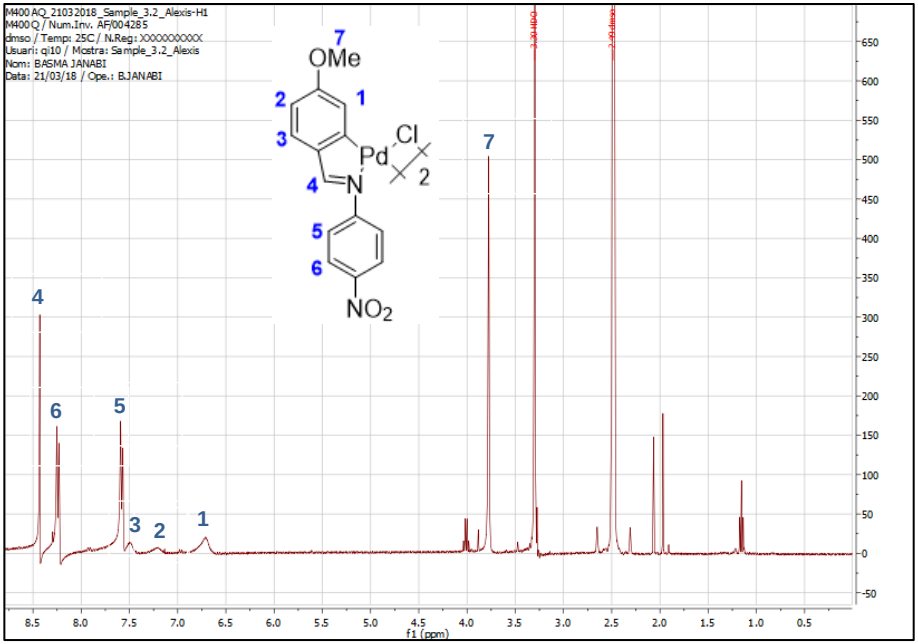
APPENDIX 1: ^{1}H NMR SPECTRA



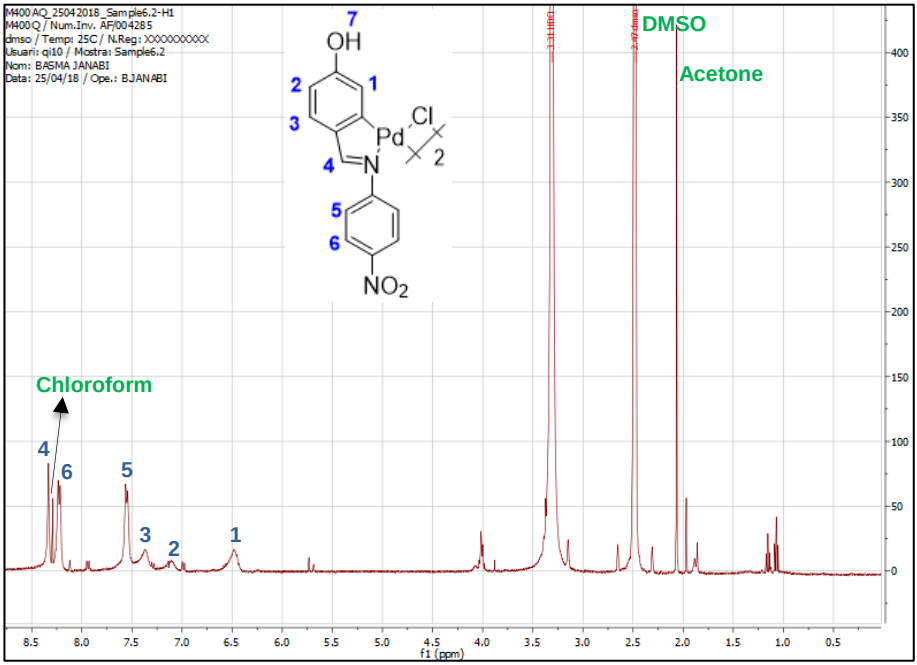
^{1}H NMR spectrum of compound **1a**



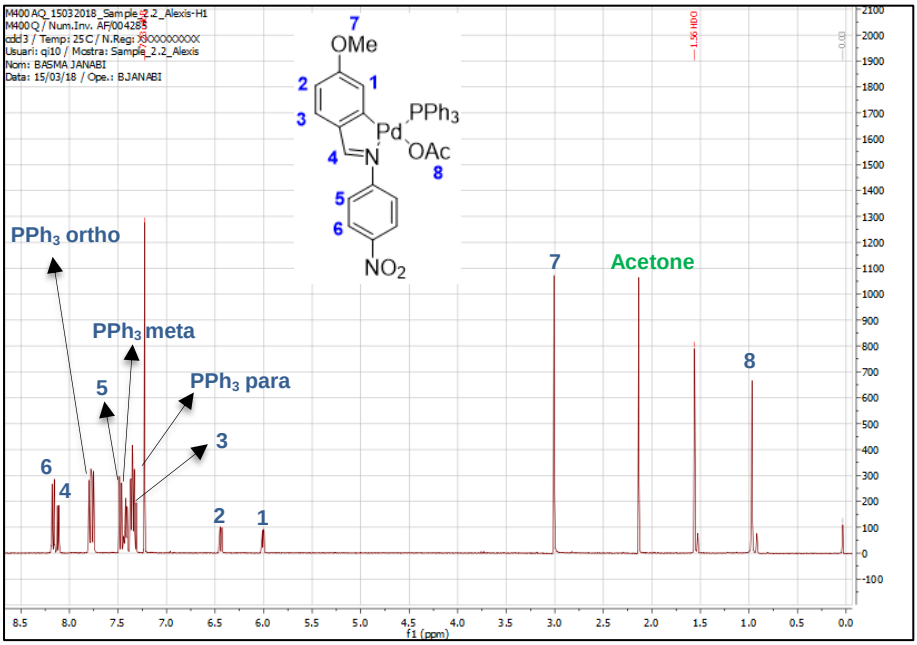
^{1}H NMR spectrum of compound **1b**



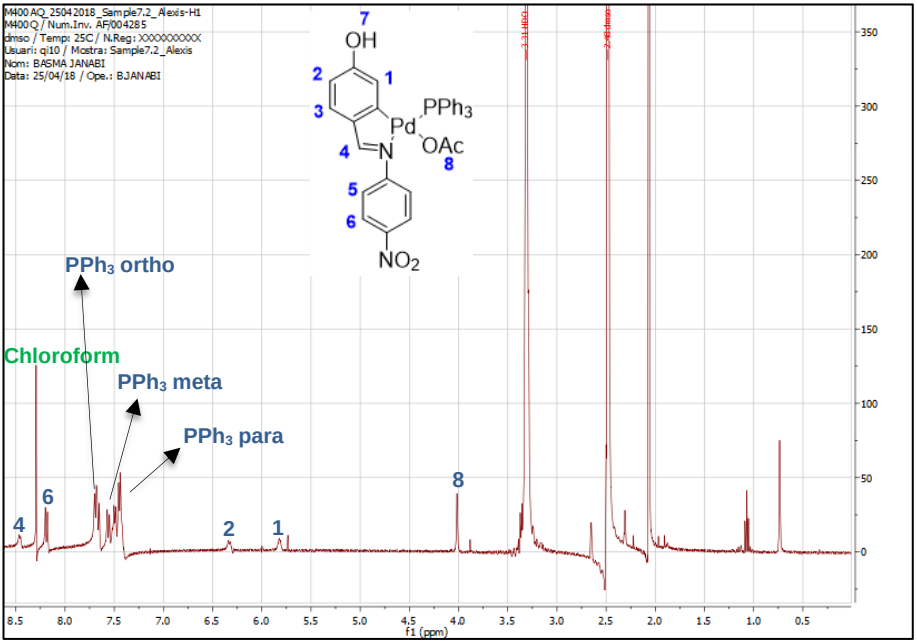
^{1}H NMR spectrum of compound **2a**



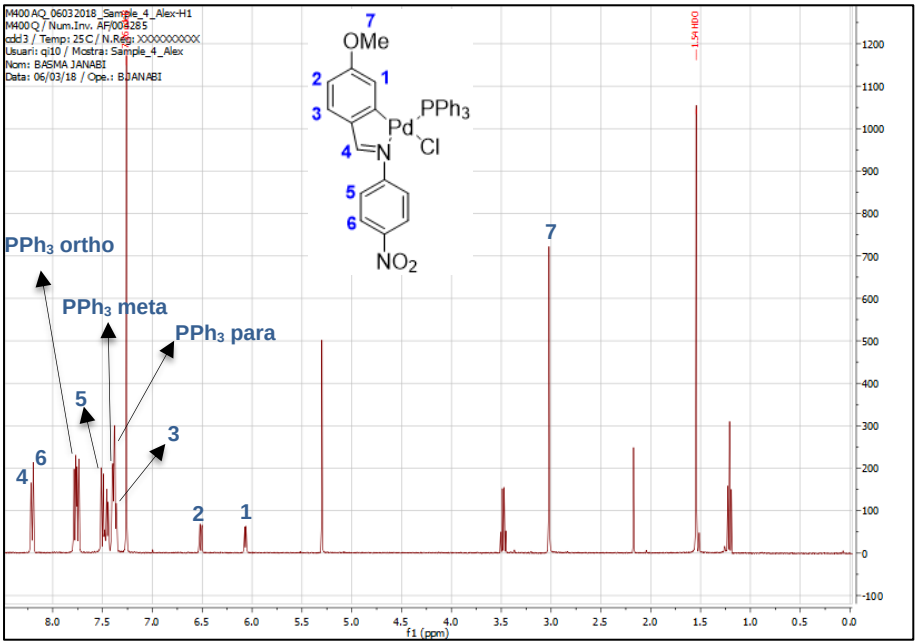
^{1}H NMR spectrum of compound **2b**



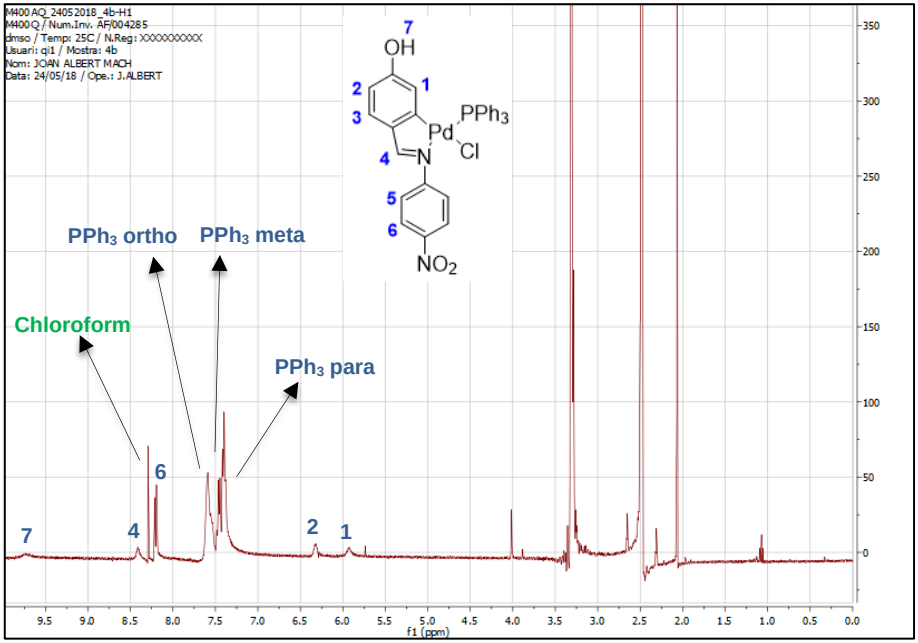
^{1}H NMR spectrum of compound **3a**



^{1}H NMR spectrum of compound **3b**

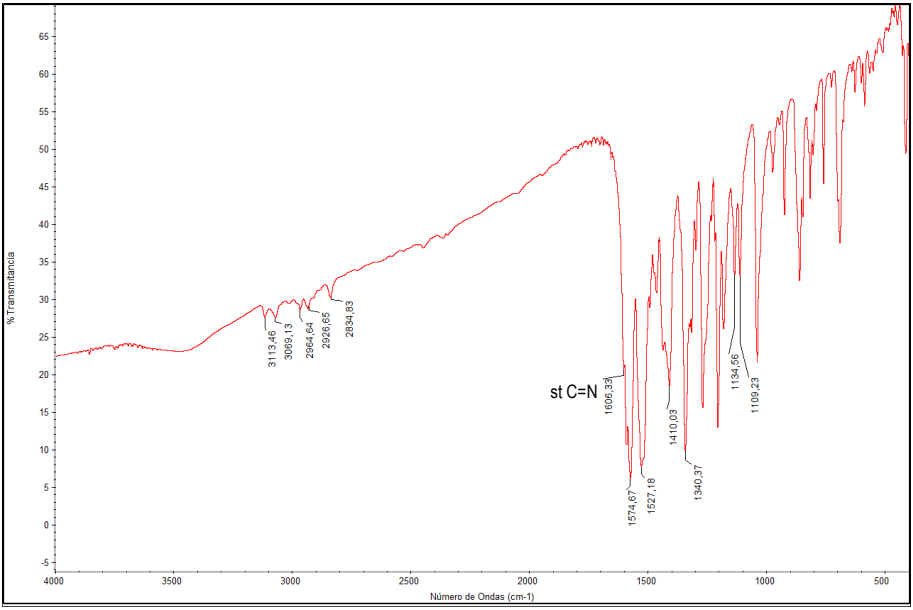


^{1}H NMR spectrum of compound **4a**

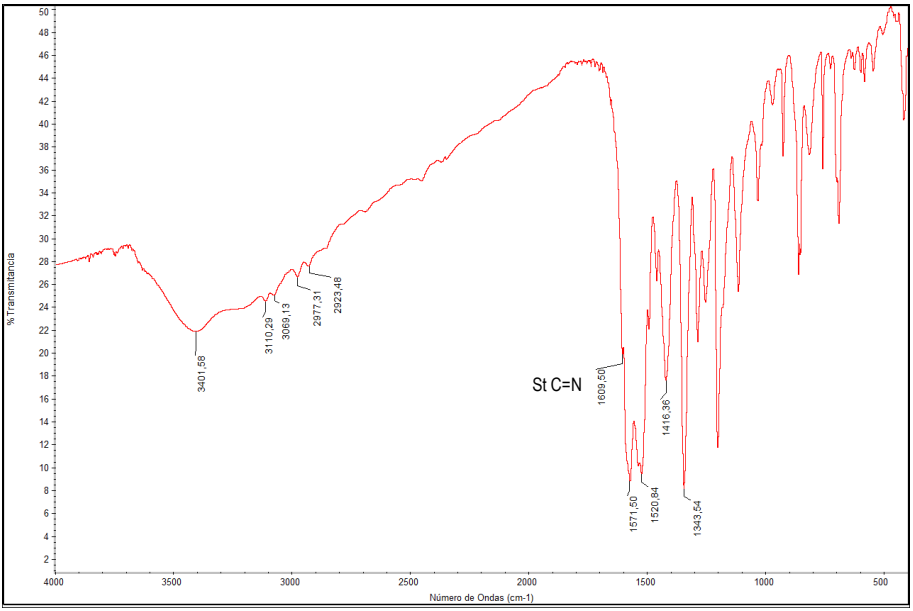


^{1}H NMR spectrum of compound **4b**

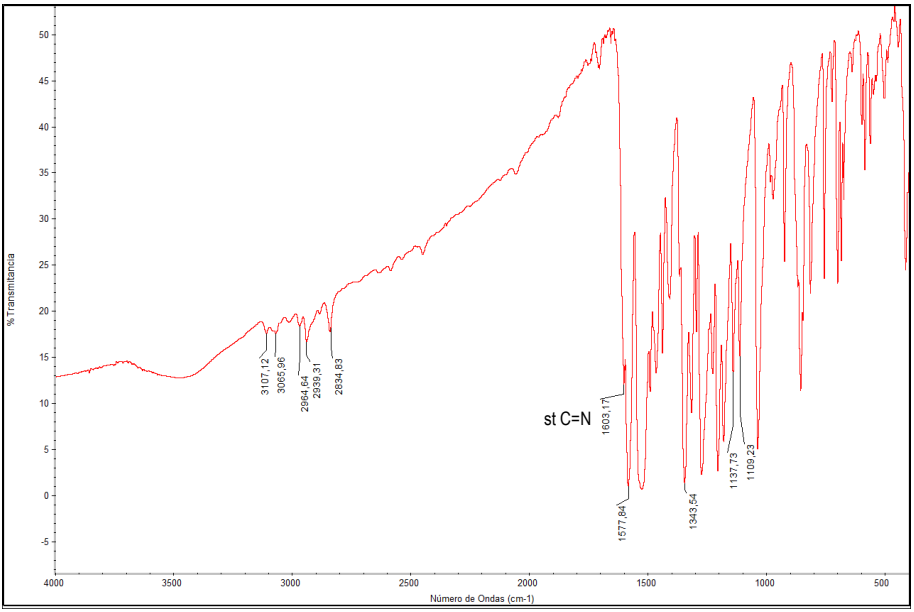
APPENDIX 2: IR SPECTRA



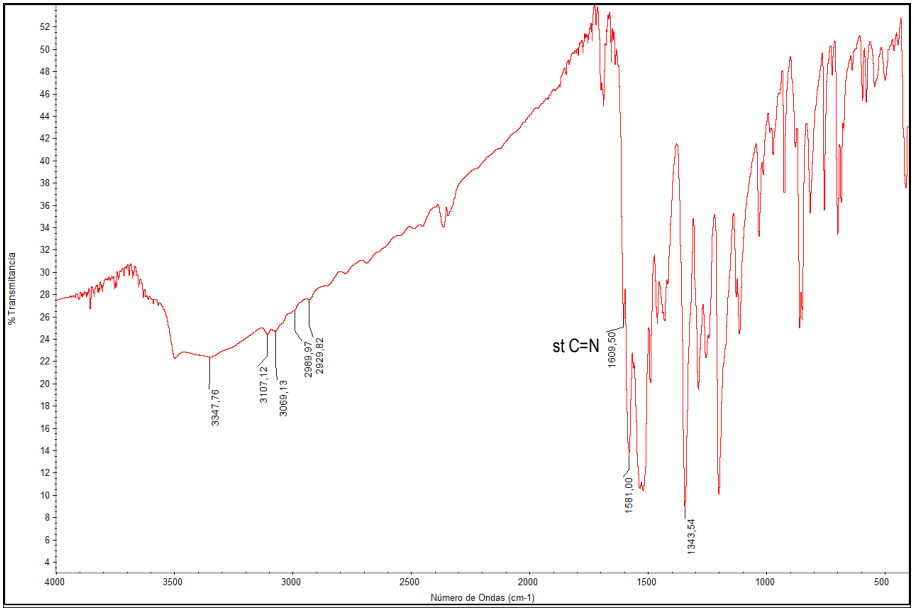
IR spectrum of compound **1a**



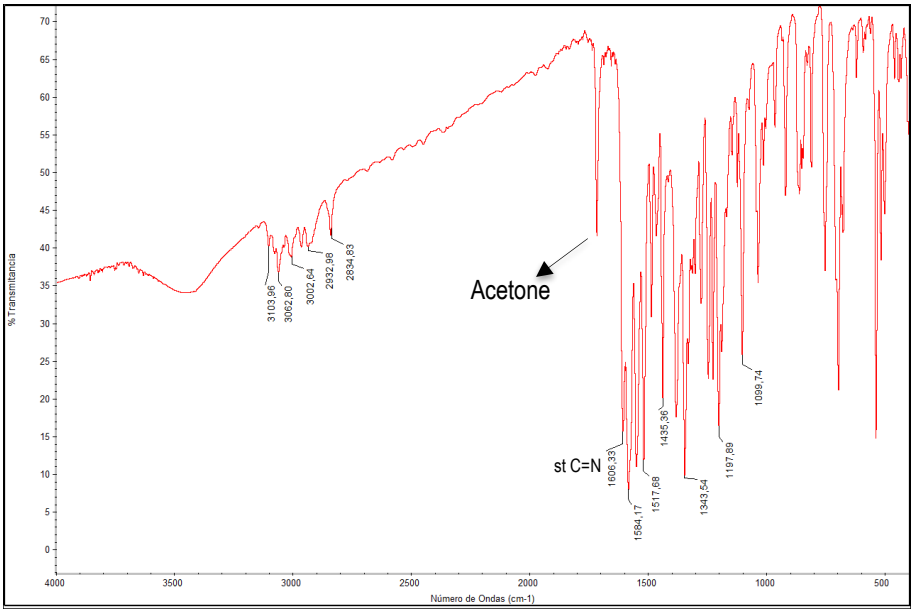
IR spectrum of compound **1b**



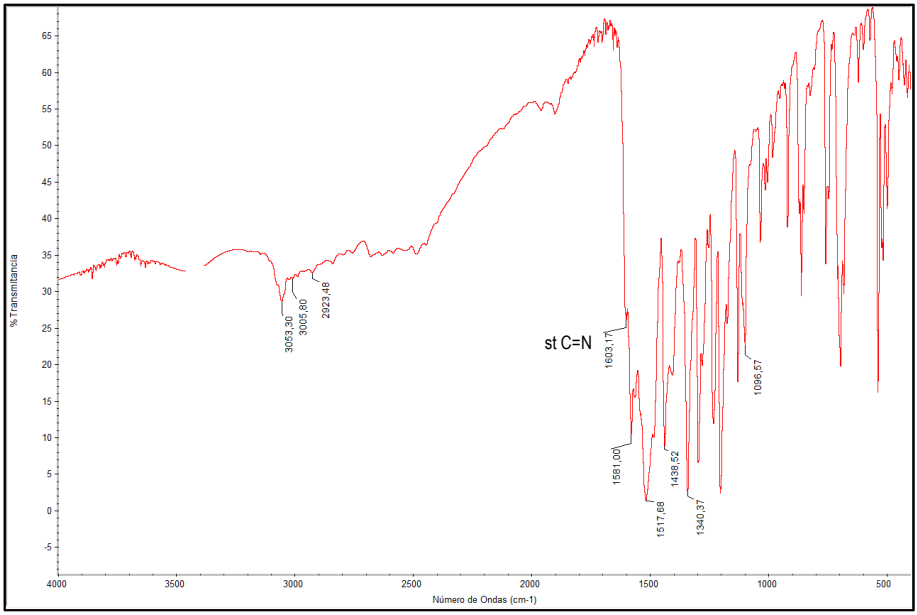
IR spectrum of compound **2a**



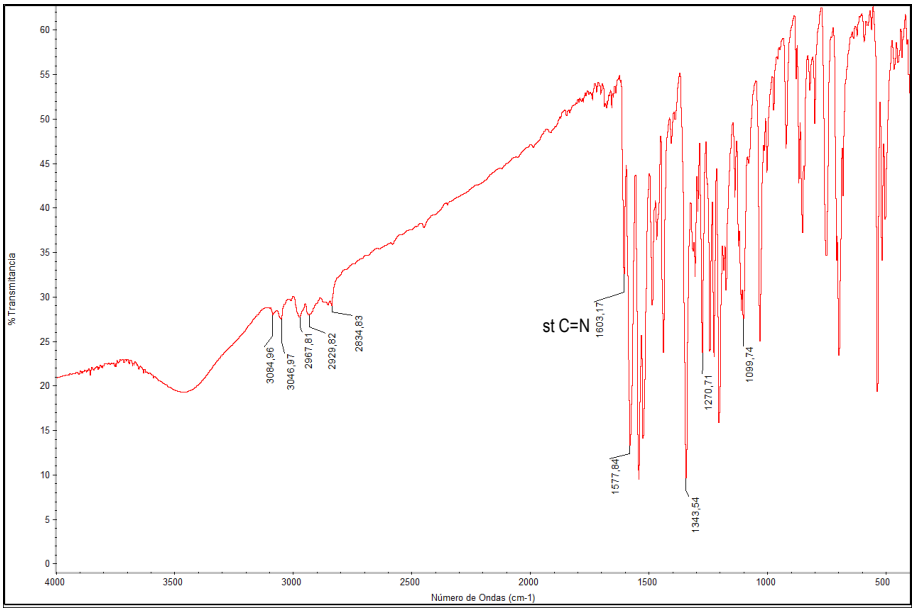
IR spectrum of compound **2b**



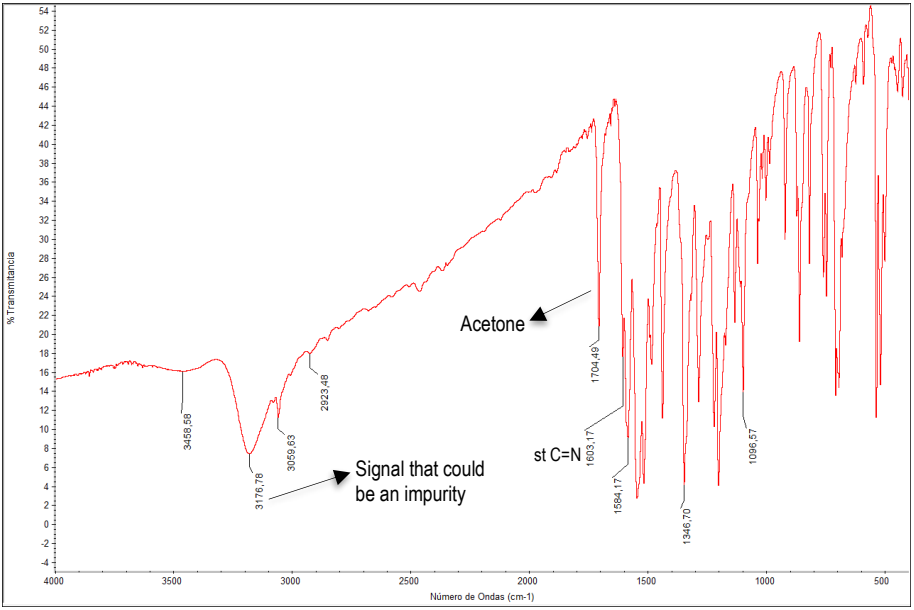
IR spectrum of compound **3a**



IR spectrum of compound **3b**

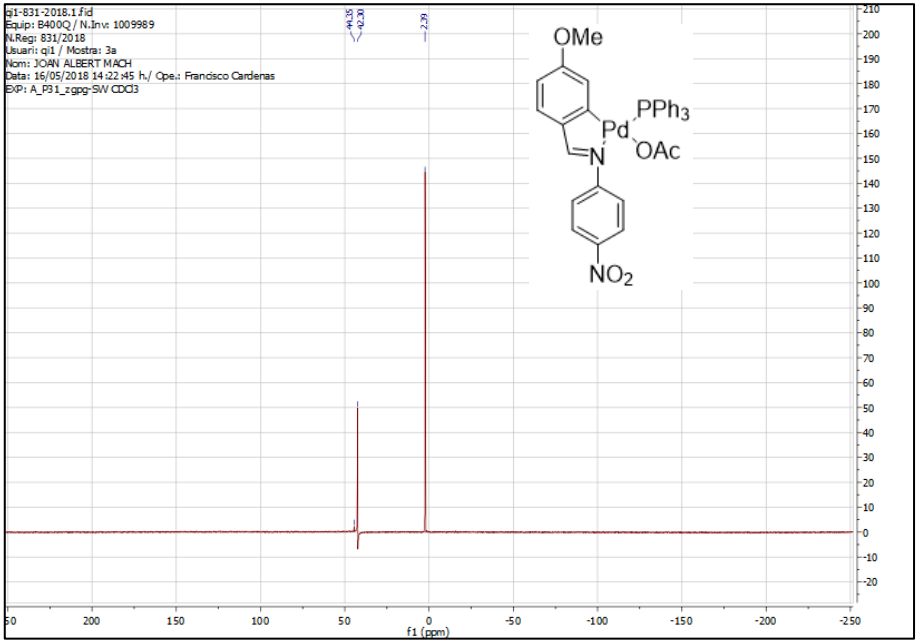


IR spectrum of compound **4a**

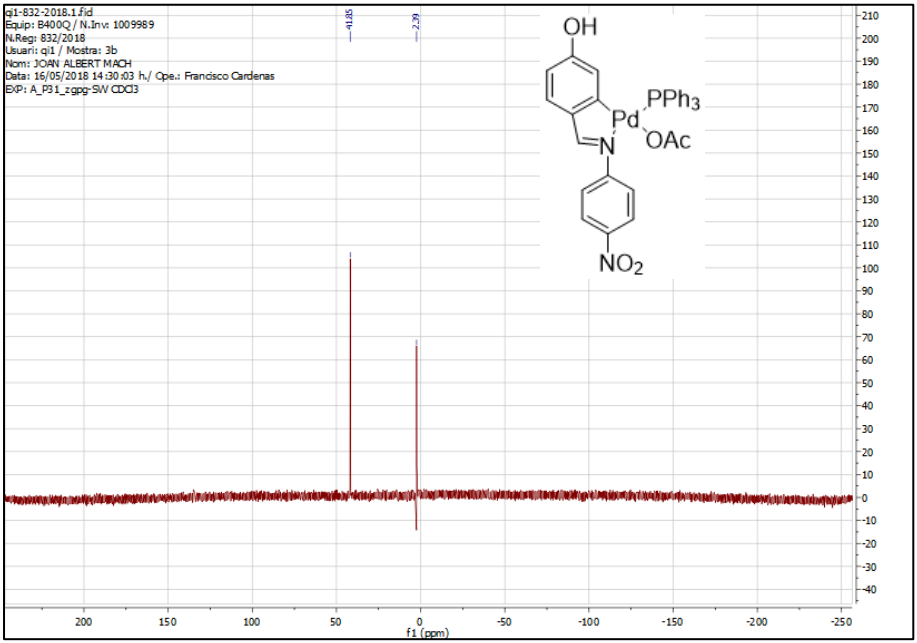


IR spectrum of compound **4b**

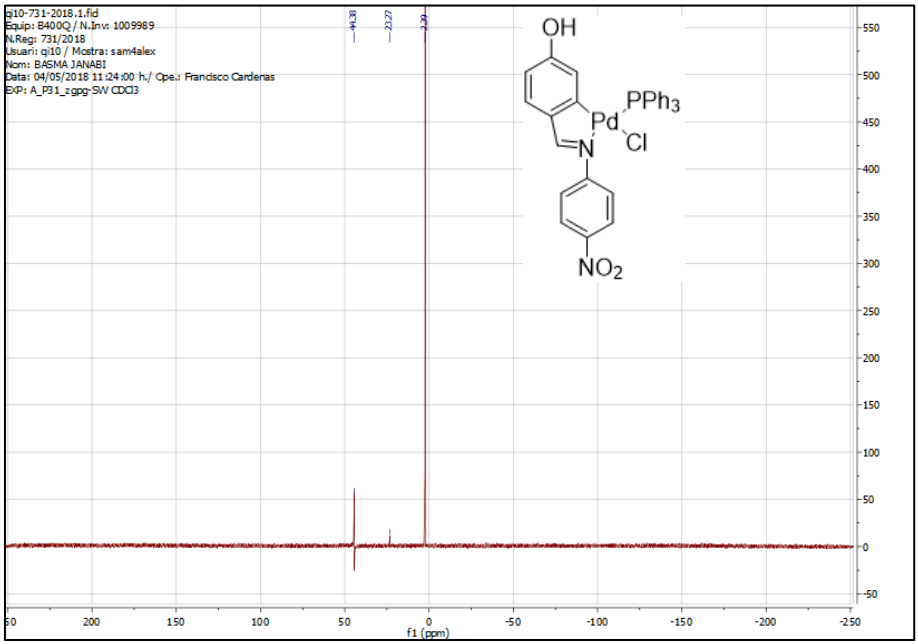
APPENDIX 3: ^{31}P-{^{1}H} NMR SPECTRA



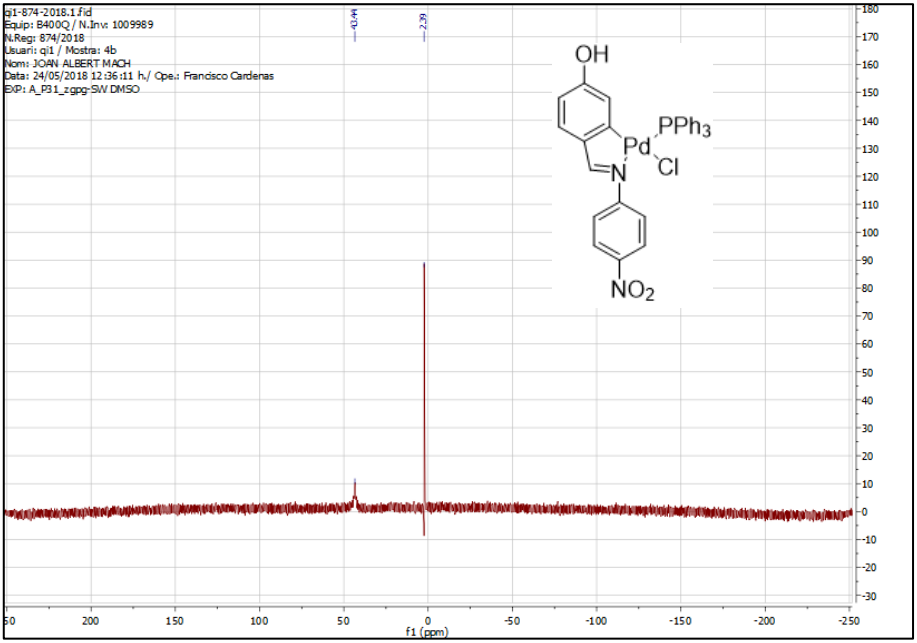
^{31}P-{^{1}H} NMR spectrum of compound **3a**



$^{31}P\text{-}\{^{1}H\}$ NMR spectrum of compound **3b**



$^{31}P\text{-}\{^{1}H\}$ NMR spectrum of compound **4a**



^{31}P-{^{1}H} NMR spectrum of compound **4b**