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Grau de Química

Treball Fi de Grau

Synthesis of gold(I) organometallic compounds with potential biological activity

Síntesis de compostos organometal·lics d'or(I) amb potencial activitat biològica

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Als meus pares, per el seu suport incondicional, ara i sempre. Als meus professors, a tots ells, perquè a més d'ensenyar-me tot el que sé m'han ensenyat el valor de l'esforç. A la Dra. Montserrat Ferrer i la Dra. Laura Rodríguez, per la seva direcció i per tot el que he pogut aprendre el seu costat durant aquest temps. I a tot el Departament de Química Inorgànica, per el seu suport com a col·lectiu.

Gràcies.

REPORT

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SUMMARY

One of the main interest of alkynylgold(I) compounds are their therapeutic properties, especially their activity as anticancer agents. This TFG focuses on the synthesis of water-soluble alkynylgold(I) organometallic derivatives that could present biological activity as anticancer agents.

Preliminary experiments with related compounds (derivatives with diphosphine ligands containing phenyl substituents), have shown promising results that could be improved by increasing the solubility in water of the complexes. The reason is that these present important water-solubility problems that preclude their use as drugs.

The introduction of polar functional groups on the ligands has been studied, to determine which functionalized phosphines show more promise as ligands for both water-soluble mononuclear and binuclear gold(I) complexes. Subsequently synthesis of monophosphine ligand Ph_2PCH_2OH (***1b***) and diphosphine [1,2-bis(hydroxymethylphenylphosphino)ethane] (hmppe) (***1a***) was undertaken with successful results.

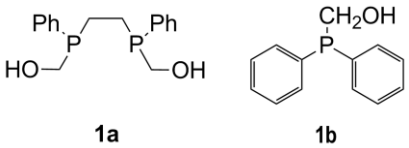


Figure 1.

Ligand Ph_2PCH_2OH was successfully synthesized, but hmppe which was also obtained could not be properly isolated. Purification of hmppe was undertaken using borane to form phosphine-borane, and the borane group was removed using morpholine. Instead of hmppe we obtained the morpholine derivative [1,2-bis(methylmorpholinephenylphosphino)ethane] (mmppe) through condensation. This aminomethylphosphine was pure; it does also contain side-chains with polar functional groups. Gold(I) compounds bearing this group might be water-soluble, as such derivatives usually are.

The synthesis of alkynylgold(I) compounds with phosphine ligand Ph_2PCH_2OH was attempted, by reaction of it with 4-ethynylpyridyinegold(I) polymer. Instead of a stable

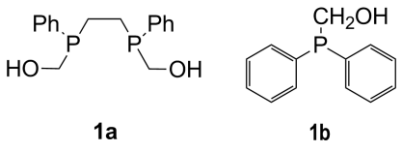
compound, the gold(I) compound decomposes into several species. It appears that some of them might be of polymeric nature, because a very insoluble solid is obtained from the reaction mixtures.

RESUM

Un dels principals interessos dels complexos organometàl·lics d'or(I) amb grups alquinil són les seves propietats terapèutiques, especialment per la seva activitat com a agents anticancerígens. Aquest Treball Final de Grau està enfocat a la síntesi de compostos organometallics d'alquinilor(I) solubles en aigua que presentin una potencial activitat biològica com a agents anticancerígens.

Experiments preliminars amb compostos relacionats (derivats amb lligands difosfina que contenen substituents fenílics) mostren resultats prometedors que podrien ser millorats incrementant la solubilitat en aigua d'aquest tipus de complexes. La raó és que aquests presenten problemes importants de solubilitat que dificulten el la seva aplicació com a medicaments.

S'ha estudiat la introducció de grups funcionals polars en lligands fosfina, per tal de determinar quines fosfines funcionalitzades són més prometedores tant per a la formació de compostos mononuclears com binuclears d'or(I) solubles en aigua. A continuació la síntesi del lligand monofosfina Ph_2PCH_2OH (***1b***) i del lligand difosfina [1,2-bis(hidroxialquilfenilfosfino)età] (hmppe) (***1a***) s'ha abordat amb resultats positius.



1a **1b**

Figura 1.

El lligand Ph_2PCH_2OH Ha estat sintetitzat amb èxit, però l'hmppe que també s'ha pogut obtenir no ha pogut ser aïllat. La purificació del hmppe s'ha dut a terme utilitzant adductes de borà, i el grup borà s'ha eliminat utilitzant morfolina. En lloc d'obtenir hmppe s'ha obtingut el derivat de morfolina [1,2-bis(metilmorfolinafenilfosfino)età] (mmppe) per condensació. Aquesta aminometilfosfina és pura, conté també cadenes laterals amb grups funcionals de caràcter polar. Complexes d'or(I) amb aquest grup podrien ser solubles en aigua, com es el cas de la majoria de derivats que contenen aquest grup.

La síntesi de compostos d'or(I) amb grups alquinil amb el lligand fosfina Ph_2PCH_2OH es va dur a terme, per reacció amb polímer de 4-etinilpiridinaor(I). En lloc d'un compost compost d'or(I) estable, al el compost d'or(I) obtingut descompon en diverses espècies diferents. Tot apunta a que algunes d'aquestes espècies pugin tenir naturalesa polimèrica, ja que un solid de naturalesa molt insoluble s'obté de la mescla de reacció.

INTRODUCTION

Metal alkynyl complexes have attracted the interest of the scientific community in the last decade and a half because of their versatile properties, concretely those of alkynyl complexes derived from gold(I) [1]. Research in the synthesis of this family of compounds began with Berthelot, who discovered in 1866 the explosive alkynylgold complex Au_2C_2. Coates and Parkin reported the synthesis of alkynylgold(I) phosphine complexes [Au(RC≡C)(PR'$_3$)] in 1962 [2]. They were obtained from the reaction of tertiary phosphines with polymeric $[AuC{\equiv}CR]_n$. In 1984 Cross reported the synthesis of mononuclear alkynylgold(I) complexes [Au(RC≡C)PPh_3] by reacting terminal acetylene with phosphinegold(I) chlorides [Ph_3PAuCl] in the presence of sodium ethoxide [3-4].

Gold(I) shows a clear preference towards linear coordination geometry (Figure 2). Because of this and because of the linearity and π-unsaturated nature of the acetylide units, alkynylgold(I) complexes are attractive building blocks [5]. Alkynylgold(I) complexes are especially interesting because of the wide spectrum of potential applications in fields such as luminescence, molecular recognition, molecular electronics, optical switches, catalysis and materials science [1].

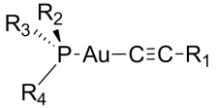


Figure 2. Basic structure of alkynylgold(I) phosphine complex with linear coordination.

Alkynylgold(I) complexes as units are able to build supramolecular structures based on their tendency to self-assembly through aurophilic interactions. Aurophilicity is that chemical property which refers to the tendency of gold complexes towards their aggregation due to the formation of weak Au···Au bonds or interactions. The polymetallic aggregates that form this way are stabilized by the presence of bridging ligands, of which polyphosphines are one of the most common kind. Chemical and physical properties of the compounds are determined by the nature of those ligands. Their electronic and especially steric properties have a decisive role in the design of supramolecular structures [6]. The possibility to switch 'on' and 'off' the emission of

alkynylgold(I) phosphine complexes by favoring or restricting Au···Au interactions has been explored in molecular sensing and optical switching devices.

Most of the catalytic properties of alkynylgold(I) complexes are because gold is not truly an inert metal, and as a transition metal has the ability to behave as a soft Lewis acid. Because of this, gold complexes can activate unsaturated functional groups such as alkynes, alkenes and allenes to form carbon-carbon and carbon-heteroatom bonds in extremely mild conditions even in water media [1].

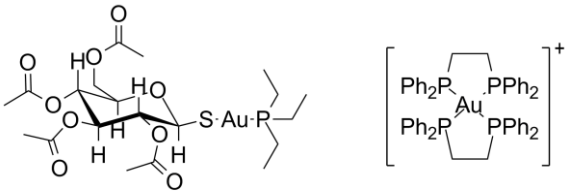
Another application of gold complexes of great historical importance and perhaps even greater repercussion is their potential therapeutic use [1][7-8]. Gold complexes have been extensively studied because of the clinically established antiarthritic properties of gold(I) thiolates such as Myocrisin (aurothiomalate), Solganal (aurothioglucose) o Auranofin ([(1-thio-β-D-glucopyranose-2,3,4,6-tetraacetato-S)(triethylphosphine)gold]). Rheumatoid arthritis is the most well-known disease treated with gold derivatives. Nonetheless, other afflictions such as asthma have been investigated in this regard and there have been successful results in treating malaria and cancer (Figure 3).

Gold complexes with cytotoxic properties are used in cancer treatment and have been found to strongly and selectively inhibit enzyme TrxR (Thioredoxine Reductase), which naturally defends genetic material from oxidative damage due to oxygen metabolism catalyzing reduction of disulphide bond between tioredoxin (TrxR) and other components. It is often found that overexpression of TrxR can be found in numerous tumor cell lines. Mechanism is supposedly based in the formation of a covalent bond between gold and a selenocysteine residue at the active center of the enzyme [9]. It must also be noted that they act as inhibitors of mitochondrial function in cancer cells.

Their pharmacological profile as drugs makes them eligible to substitute more classical platinum-based antitumor agents (e.g. cisplatin), because they interact with completely different biological targets. The therapeutic effect of cisplatin type drugs is based in metallation and adduct formation with DNA. Resistance development effects in cancer treatment can be avoided using gold(I) compounds because of their different cellular targets [10].

Derivatives of phosphinegold(I) have special interest as possible antitumor agents, as most biologically active gold drugs include phosphine ligands. There are apparently two types of gold(I) phosphine complexes that exhibit important activity against tumor cells [7]: complexes of

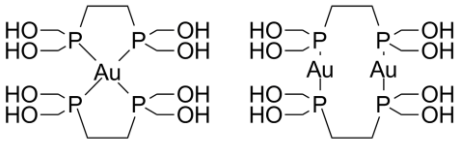
linear coordination and bis-quelated complexes with tetrahedral coordination geometry (e.g. $[Au(dppe)_2]^+$).



2a **2b**

Figure 3. Gold(I) complexes with antitumor activity: linear coordinated Auranofin (originally an antiarthritic drug) (2a), and tetrahedral coordinated $[Au(dppe)_2]^+$ (2b).

Studies indicate that in the series $[Au(Ph_2P(CH_2)_nPPh_2)_2]X$, to which lead compound $[Au(dppe)_2]^+$ belongs, antitumor activity is highest when bridging chain is at an optimal length of n = 2-3 carbon units [8][11]. The development of analogous complexes with functionalized diphosphines with hydroxymethyl groups has been undertaken with the intention of developing possible drugs that result in an increased water-solubility and better water-stability. Compound $[Au\{(HOH_2C)_2PCH_2CH_2P(CH_2OH)_2\}_2]Cl$ has been synthesized, along with the linear coordinated gold(I) complex $[Au_2\{(HOH_2C)_2PCH_2CH_2P(CH_2OH)_2\}_2]Cl_2$, and they both show stability in vivo with an elimination via the kidneys. Despite these results, the evaluation of their antitumor activity is still pending [12] (Figure 4).



2c **2d**

Figure 4. Gold(I) complexes with polar water-soluble phosphine ligands: (**2c**) $[Au\{(HOH_2C)2PCH_2CH_2P(CH_2OH)_2\}_2]Cl$ and (**2d**) $[Au_2\{(HOH_2C)_2PCH_2CH_2P(CH_2OH)_2\}_2]Cl_2$

Alkynylgold(I) complexes have been used to a much lesser extent in the research of therapeutic drugs. Recently, some complexes containing known antimalarial drug units (compounds 3a-c) (Figure 5) have been reported to be active against both cancer cells and *plasmodium falciparum* (the parasite responsible for malaria disease).

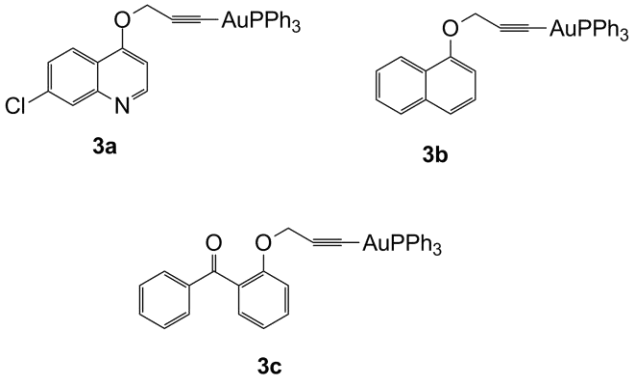


Figure 5. Some alkynylgold(I) complexes of therapeutic use.

Alkynylgold(I) complexes bearing water-soluble phosphine ligands such as PTA and DAPTA have also been synthesized. Water-soluble phosphines are of special interest in this context to try and prevent the marked instability and toxicity found in the traditional triphenylphosphine ligand (PPh_3) [1].

A new series of 4-etynylpyridinegold(I) complexes with different phosphine ligands have been recently synthesized [13] (Figure 6). These compounds are [Au(C≡CC_5H_4N)(PPh_3)] (compound 4a), [Au_2(C≡CC_5H_4N)$_2$(μ_2-diphosphine)] (compounds 4b-4j) in which diphosphine ligands are dppm, dppe, dppp, dppb, dppip, dppa, dppf, dcypm and dcypb, and [Au_3(C≡CC_5H4N)$_3$(μ_3-triphos)] (compound 4k).

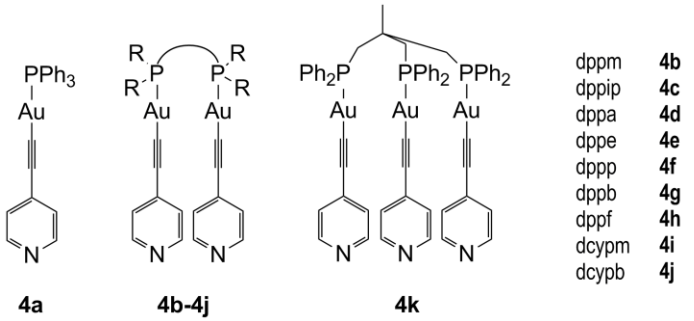


Figure 6. 4-etynylpyridinegold(I) complexes with mono-, di- and triphosphine ligands.

The synthesis of compounds with dcypm and dcypb ligands was undertaken to analyze the potentially different biological behavior of the compounds taking into account the different character of the diphosphines.

Preliminary results in enzymatic inhibition studies show that some of the above compounds are moderately active against tumor cell growth. In them, TrxR was used as the target enzyme, and GR (gluthatione reductase) was used as a control reference to evaluate selectivity of enzymatic inhibition (Table 1) [14]. Contrary to TrxR, GR does not contain a selenocysteine in its active site, but is otherwise structurally and functionally similar.

Ligand	TrxR EC_{50} (μM)	GR EC_{50} (μM)	TrxR/GR	MCF-7	HT-29
dppm ($Ph_2PCH_2PPh_2$)	>100	>1000	n.a.	0.7±0.1	1.2±0.1
dppb ($Ph_2P(CH_2)_4PPh_2$)	>100	>1000	n.a.	0.8±0.5	2.1±1.1
dcypm ($(C_6H_{11})_2PCH_2P(C_6H_{11})_2$)*	>100	>1000	n.a.	9.7±5.3	14.7±2.2
dcypb ($(C_6H_{11})_2P(CH_2)_4P(C_6H_{11})_2$)*	>100	>1000	n.a.	>40	>100
4-ethynylpiridine	>100	>1000	n.a.	>100	>100

Complex	TrxR EC_{50} (μM)	GR EC_{50} (μM)	TrxR/GR	MCF-7	HT-29
$[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dppm})]$	1.6±0,3	232±63	145	1.4±0.2	2.7±0.8
$[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dppb})]$	7.9±4,4	472±23	60	2.8±0.6	1.2±0.2
$[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dcypm})]$*	>50	>500	n.a.	1.1±0.3	0.6±0.2
$[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dcypb})]$*	>50	>500	n.a.	23.8±4.9	15.3±1.6

Table 1. Results for enzymatic inhibition studies on diphosphine ligands and gold(I) complexes: EC_{50} values for TrxR and GR, and antiproliferative studies with MCF-7 and HT-29 cells; *: major solubility problems were experienced during the biological assays; n.a.: not applicable.

The half maximal effective concentration (EC_{50}) is a measure of the potency of a drug. It refers to the concentration of a drug which induces a response halfway between the baseline and maximum after some specified exposure time. Both the gold(I) complexes with dppm and dppb turned out to be inhibitors of TrxR with EC_{50} values below 10μM. Simultaneously they show a good selectivity as they only inhibit GR at significantly higher concentrations. This makes these compounds good candidates as starting compounds for further development of binuclear gold alkynyl anticancer agents. Their activity, however was higher that several other mononuclear alkynylgold(I) phosphine complexes [15]. Complexes with dcypm and dcypp do not show any significant activity. This suggests that the presence of phenyl groups (C_6H_5) is directly

related to the activity of these series of compounds. Complex with dppm was more active than complex with dppb, and this might give a hint that shorter bridging ligands could be preferable as far as biological activity is concerned. None of the free diphosphine ligands, as well as 4-ethynylpyridine were active against TrxR or GR.

Antiproliferative effects were assessed in two cultured tumor cell lines (NCF-7 breast cancer, and HT-29 colon carcinoma cells), and were compared to the metal free ligands. Strong antiproliferative effects were observed in the range of 0.7 to 2.8 μM for the active TrxR inhibitors (gold complexes with dppm and dppb), and for their respective free phosphine ligands. Thus, while well-known, TrxR inhibition cannot be the only mechanism responsible for the cell growth inhibition effects of these complexes. In this case, complexes with dcypm and dcypb were also moderately active

The above study pointed that bridged dinuclear gold(I) alkynyl complexes have good potential potential for developing biologically active gold(I) complexes. Nonetheless, the main disadvantage observed for any potential use of these complexes as antitumor agents is their severe solubility problems in the assay conditions. Problematic solubility has already been reported recently for other dinuclear species [16]. It may significantly reduce enzymatic activity due to insufficient bioavailability. It is reasonable to think that thus, solubility could be an important parameter to be researched in regards to these complexes activity in aqueous media.

Equilibrium between lipophilicity and hydrophilicity in gold complexes with potential therapeutic use is a very important parameter in the optimization of their biodistribution, activity and selectivity. Specifically, selectivity of gold(I) diphosphine drugs for tumor tissue vs. normal tissue could be significantly improved by optimizing the lipophilic-hydrophilic balance of the complexes through the design of their ligands [10].

OBJECTIVES

The objective of this study is to investigate in the synthesis of 4-ethynylpyridinegold(I) complexes which may be soluble in water, or at least be more soluble in aqueous media that those previously synthesized with ligands such as dppe, dppp, etc. to improve the activity of the complexes already studied. These new complexes should be analogous to the series of compounds $[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-diphosphine})]$, or analogous to $[Au(C{\equiv}CC_5H_4N)(PPh_3)]$.

For this, a thorough research of the state-of-the-art in literature of functionalized phosphines and their methods of synthesis has been undertaken. It is intended that a greater solubility in gold(I) complexes may be achieved by modification of phosphine ligands, introducing polar functional groups in their structure.

RESULTS AND DISCUSSION

FUNCTIONALIZED PHOSPHINE LIGANDS

The first step in our approach to the synthesis of compounds of the series $[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-diphosphine})]$ which might be both hydrosoluble and biologically active is to select which phosphine ligand meets all requisites and shows better synthesis prospects. Preliminary information showed that compounds of the series $[Au_2(C{\equiv}CC_5H_4N)_2(Ph_2P(CH_2)_n PPh_2)]$ (**A**) had biological activity. In order to form analogous complexes of greater solubility, the possibility of introducing hydroxyalkyl groups in the phosphine ligand as shown in (**B**) and (**C**) (Figure 7) was envisaged. Hydroxyl functional groups were chosen to render the phosphine ligand more water-soluble. Sulfonated phosphines are water-soluble too, and are often used to form water-soluble complexes. Nonetheless, they are also not completely inert and may affect significantly the reactivity of a compound. Because of this our attention was directed only towards phosphines containing hydroxyl groups [17].

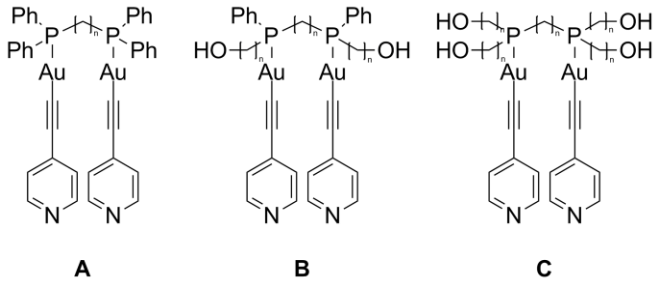


Figure 7. The series of complexes **A** are bioactive, but remarkably insoluble, and this potential drug's solubility problems could be improved by the synthesis of analogous compounds. Series **B** and **C** are the discussed options for the initial synthesis.

Synthesis of compounds of **C** series was discarded promptly because preliminary studies suggested that the presence of aromatic phenyl groups in the ligand was fundamental to biological activity. While gold(I) complexes with phenyl substituted diphosphine ligands $[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dppm})]$ and $[Au_2(C{\equiv}CC_5H_4N)_2(\mu_2\text{-dppb})]$ were active, those containing

cyclohexyl substituted diphosphine ligands [$Au_2(C{\equiv}CC_5H_4N)_2(\mu_2$-dcypm)] and [$Au_2(C{\equiv}CC_5H_4N)_2$ (μ_2-dcypb)] were not. Because of this, the series of complexes which synthesis has been studied are those of B series, with a diphosphine of with both aromatic and hydroxyalkyl substituents.

Hydroxyalkyl phosphine ligands are an important class of functionalized phosphines that combine chemical properties of electron donors and those of hydrophilic alcohols [18]. However, while literature on the synthesis and reactivity of diphosphines of the series $(HO(CH_2)_m)_2P(CH_2)_n P((CH_2)_mOH)_2$ is extensive enough, literature on mixed diphosphine ligands (Figure 8) is scarce and synthesis methods described show no contrastable data. Essentially, the synthesis of these compounds has been reported by Karasik et. al. [19-20] (2007-2008) and Meier [21] (2004) (Figure 8).

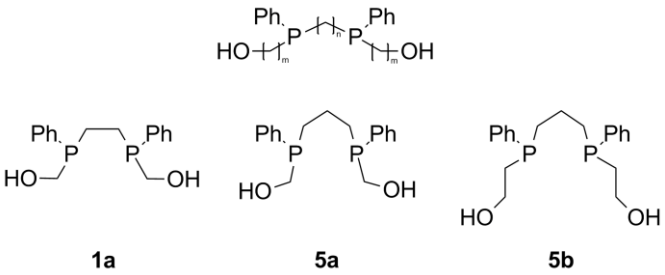


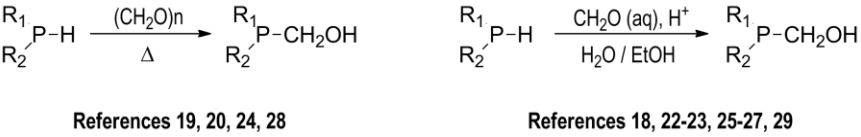
Figure 8. Mixed diphosphine ligands synthesized by Karasik et. al. (1a and 5a) and Meier (5b).

Based on the little information available on the topic, we chose to work on the synthesis of a diphosphine with a bridging chain of 2 carbon atoms. Extrapolating a parallelism between these complexes and other bis-quelated complexes with the same diphosphine ligands, which show maximum activity when bridging chain has *n* = 2 o 3 [9], we opted for the synthesis of a ligand with a 2 carbon atoms bridging chain.

To introduce the hydroxyalkyl groups in the phosphines, several methods exist which can introduce hydroxyalkyl groups in primary or secondary phosphines. One must be chosen depending on the number *m* of -CH_2- units of the alkyl chain.

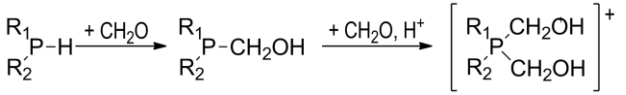
In particular, to introduce an hydroxyalkyl group with m = 1, the insertion of formaldehyde in the P-H bond of a primary or secondary phosphine is well documented. Phosphines *neat* (no solvent) react with paraformaldehyde or aqueous formaldehyde 35% (in which case it is necessary the use of a catalyst $K_2[PtCl_4]$) [18-20][22-29] (Scheme 1) to produce the desired

hydroxyalkylated derivative. This is by far the most commonly used method, and can be applied to all kinds of phosphines.



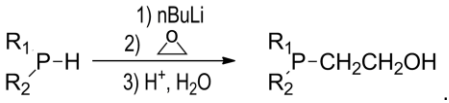
Scheme 1. Phosphine hydroxymethylation reaction (insertion of hydroxyalkyl groups *m* = 1).

Aqueous hydroxymethylation presents one main disadvantage, in weak acid media in which the reaction takes place there can be additional addition of formaldehyde units to form phosphonium salts [28] (Scheme 2).

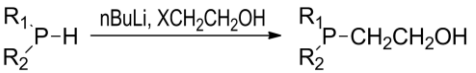


Scheme 2. Formation of phosphonium salts in acid media.

In order to introduce *m* = 2 groups in secondary phosphines two methods have been reported, one using ethylene oxide [21] and a 2-haloetanol (2-cloroetanol or 2-bromoetanol) [30]. The first method uses BuLi as a base to deprotonate the phosphine and form the corresponding organolithium species. Then, it reacts with ethylene oxide, and is later hydrolyzed (Scheme 3). The second method consists in treating a solution of phosphine and 2-haloetanol with BuLi (Scheme 4).



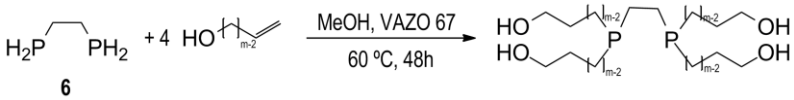
Scheme 3. Insertion of hydroxyalkyl groups *m* = 2 by the method described by Meier [21].



Scheme 4. Insertion of hydroxyalkyl groups *m* = 2 by the method described by Vargas [30].

The main discouraging feature of phosphines with m = 2 is that they possess hydrogen atoms in β positions and have a tendency to experience elimination reactions. Because of this they are highly unstable and decompose easily.

Hydroxyalkyl groups of larger alkyl chains (m > 2) are introduced by the means of allylic alcohols or primary olefinic alcohols [31-32]. These are radical reactions that take place in aqueous media (Scheme 5).



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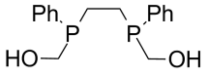
Scheme 5. Insertion of hydroxyalkyl groups -$(CH_2)_m$OH with m > 2.

Contrasting all the given information we chose to introduce a hydroxyalkyl chain with m = 1. Not only these type of phosphine hydroxyalkylation reactions are well-documented, but the functionalized phosphines are more stable. Additionally, the shorter alkyl side-chain the more polar character of the phosphine, which may result ideally for greater solubility. After all the arguments presented above, we decided to undertake the synthesis of [1,2-((hydroxymethyl) phenylphosphino)ethane] (hmppe) (Figure 9), to be used in the synthesis of the desired ethynylpyridinegold(I) complex.



1a

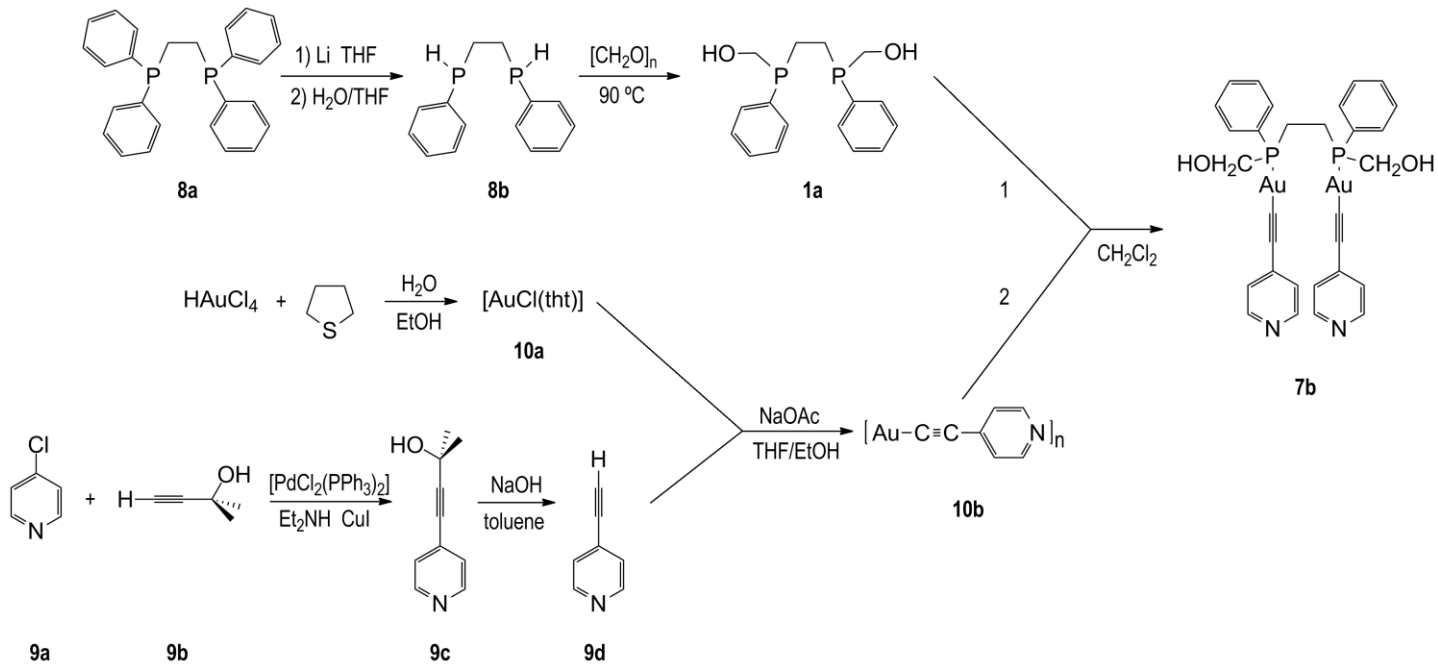
Figure 9. Ligand hmppe.

Focus was on synthesis of hmppe ligand, but also of (hydroxymethyl)diphenylphosphine (Ph_2PCH_2OH). Monophosphines are as susceptible as diphosphines to hydroxyalkylation. The introduction of hydroxymethyl groups is well-documented. Synthesis of this hydroxymethyl functionalized monophosphine was undertaken for comparative purposes.

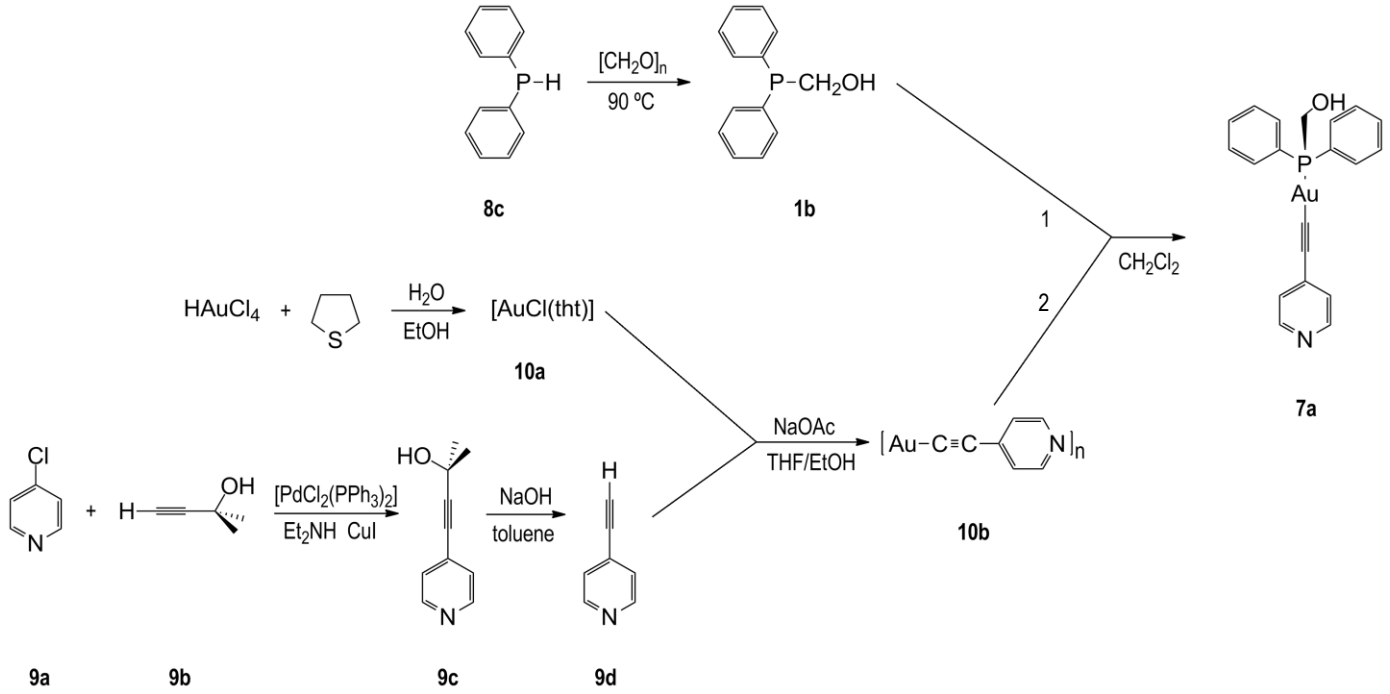
SYNTHESIS OF GOLD DERIVATIVES

We wanted to synthesize two hydroxymethyl phosphine ethynylpyridinegold(I) complexes (Figure 10). And a plausible synthesis route was mapped from data extracted from specialized literature. In both cases synthesis of hydroxymethyl phosphine ligands and synthesis of ethynylpyridinegold(I) polymer are carried out separately, and converge to form gold(I) organometallic complexes.

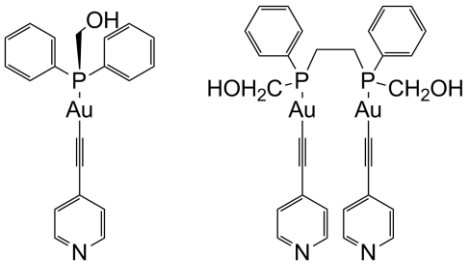
The proposed synthetic routes for complexes [$Au_2(C{\equiv}C\text{-}C_5H_4N)_2(\mu_2$-hmppe)] and [$Au(C{\equiv}C\text{-}C_5H_4N)(Ph_2PCH_2OH)$] are detailed in Schemes 6 and 7.



Scheme 6. Proposed synthesis route for $[Au_2(C{\equiv}C\text{-}C_5H_4N)_2(\mu_2\text{-hmppe})]$.



Scheme 7. Proposed synthesis route for [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)].



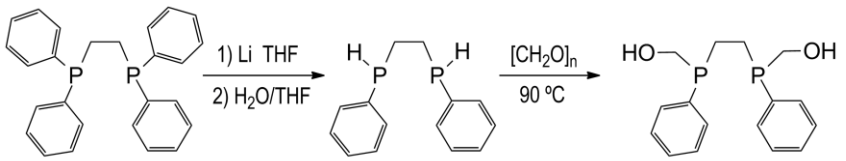
7a **7b**

Figure 10. Complexes [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)] (**7a**) and [Au_2(C≡C-C_5H_4N)$_2$(μ_2-hmppe)] (**7b**).

Synthesis of both ethynylpyridinegold(I) complexes takes place by reaction of ethynylpyridinegold(I) polymer with a phosphine ligand. Both reagents are obtained by previous separate synthesis. Hydroxymethyl phosphines are obtained by hydroxyalkylation with formaldehyde of secondary phosphines. Synthesis of 4-ethynylpyridine precedes the synthesis of the gold(I) polymer [Au(C≡C-C_5H_4N)]$_n$. In both cases the synthesis of gold(I) polymer was identical.

SYNTHESIS OF THE PHOSPHINE LIGAND HMPPE

The synthesis of hmppe has necessarily to be preceded by the synthesis of [1,2-bis(phenylphosphino)ethane] (mppe), as hydroxyalkylation reactions with paraformaldehyde reactions only take place upon primary and secondary phosphines. Thus, the synthesis of hmppe consists of two synthetic steps (Scheme 8). A phosphorus-carbon bond cleavage reaction was utilized for the synthesis mppe, the intermediate product. It was followed by a hydroxymethylation reaction upon mppe to give hmppe.

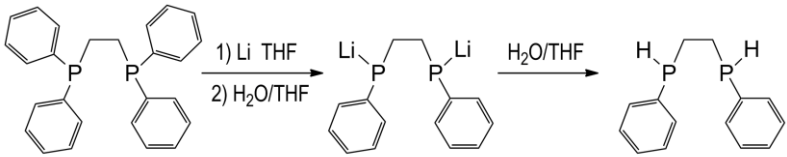


8a **8b** **1a**

Scheme 8. Synthetic route for hmppe synthesis.

Phosphorus-Carbon Bond Cleavage to produce mppe

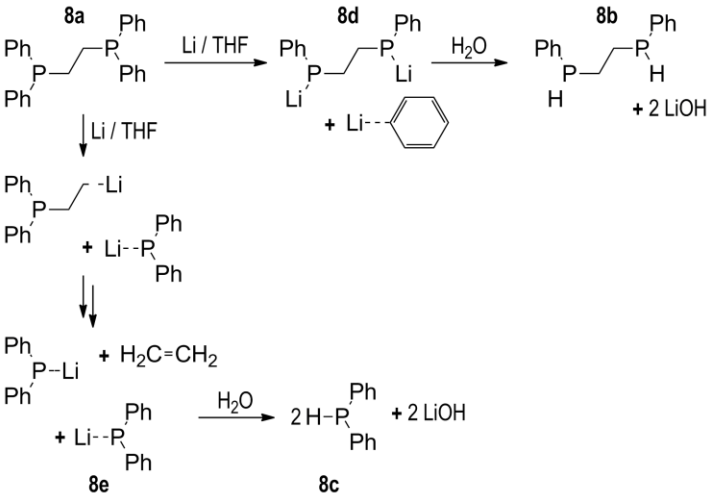
The phosphine ligand mppe is commercial only in the U.S.A. by the company Strem Chemicals Inc., but regulations force that in Europe it cannot be obtained with less than a year's notice. Because of this, we synthesized mppe by cleavage of Phosphorus-Carbon bonds from the commercial ligand [1,2-bis(diphenylphosphino)ethane] (dppe). The cleavage of P-C can be achieved by reaction with lithium in THF, and the resulting lithium phosphide species is protonated in a second step by addition of a mixture of water in THF.



Scheme 9. P-C cleavage reaction.

The preparation of disecondary phosphine (mppe) by the cleavage with lithium of the corresponding ditertiary phosphine (dppe) has been widely reported [33-40]. Unfortunately, this reaction often yields substantial amounts of alternative byproducts (mostly diphenylphosphine) owing to cleavage of a bridging chain P-CH_2 bond [33]. During the first step of the reaction, the di-lithium species $PhP(Li)CH_2CH_2P(Li)Ph$ and $LiPPh_2$ are produced through competitive cleavage of P-C bonds. It has been proposed that the key in this process lays in different leaving group preferences of P-C_{alkyl} and P-C_{aryl} bonds [35] (Scheme 10).

The cleavage step comprises of a thermodynamic equilibrium involving phosphinyl and alkyl/phenyl radicals and anions, followed by the irreversible formation of di-lithium phosphide salts [35]. When initial bond cleavage takes place at room temperature (or higher temperature) the reaction pathway that originates Ph_2PH is favored, and this by-product is obtained in larger proportions. At 0 ºC, solutions enriched in **8d** are obtained as the reaction pathway that leads to the formation of the di-lithium species becomes more favorable. Hydrolysis is another critical stage in the reaction, as when carried out at higher temperature significant amounts of Ph_2PH are generated in this step that do not originate from lithium phosphide species $Ph_2P(Li)$ product of the first step. Thus, both P-C bond cleavage and protonation step are both dependent on temperature.



Scheme 10. Competitive reactions that lead to formation of mppe and diphenylphosphine.

This prompted that earlier methods of synthesis involved a stirring mixture of dppe and lithium wire in THF at 0 ºC for a period of 7-18 days [33-34]. We dismissed this method of synthesis precisely for the long period of time which it needs in order to be carried out. This is a capricious method, and lower yielding but less-time consuming and more reliable routes were developed and reported [33][37], mostly optimized by means of trial and error. It is a matter of a carefully chosen compromise. The reaction mixture was stirred long enough at 273K to overcome the erratic induction of P-C_{aryl} cleavage and to diminish the formation of Ph_2PLi. Once formed, the di-lithium species is stable to heat, and reflux facilitates the decomposition of side-product PhLi, thus making the whole process less time-consuming. Protonation to form mppe has to be carried again slowly at 0 ºC. As indicated above this step is also crucial to the formation of undesired byproducts.

As both phosphine and lithium phosphide species are highly sensitive to O_2 and are easily oxidized to corresponding phosphine oxides, all experiments were carried out under N_2 atmosphere by standard *Schlenk* techniques. The reaction was monitored by $^{31}P\{^1H\}$ NMR Spectroscopy, which is a useful technique to assess purity because it has well-resolved signals. Integrations of $^{31}P\{^1H\}$ NMR Spectra are not useful. Nonetheless, when chemical shift difference, $\Delta\delta$, is small and we are working with mixtures of very similar compounds, integrations may be tentatively looked at to assess relative concentrations of some species. We

used this approximation to judge the production of both secondary phosphines mppe and Ph_2PH in our experiments.

We attempted the synthesis of mppe in two occasions. We varied both the concentration and the addition rate of dppe upon the lithium suspension on the first step; and both temperature and hydrolysis rate of the process in the protonation step following recommendations from literature sources [35].

In the first experiment (experiment 1) we added a solution 0.2 M of dppe in THF over a suspension of small pieces of Li, were dppe and Li were in a relative molar proportion of 1 to 10. The addition was carried out with a cannula at 0 ºC over 15 min, and the stirring mixture was left to react for 1h. To complete the reaction, the solution was refluxed at 80 ºC for 2h. After the pieces of Li were filtered, the resulting solution was cooled again to 0 ºC, and quenched with a mixture 1:3 H_2O/THF. The LiOH precipitate was filtered, and a cloudy yellow solution was obtained.

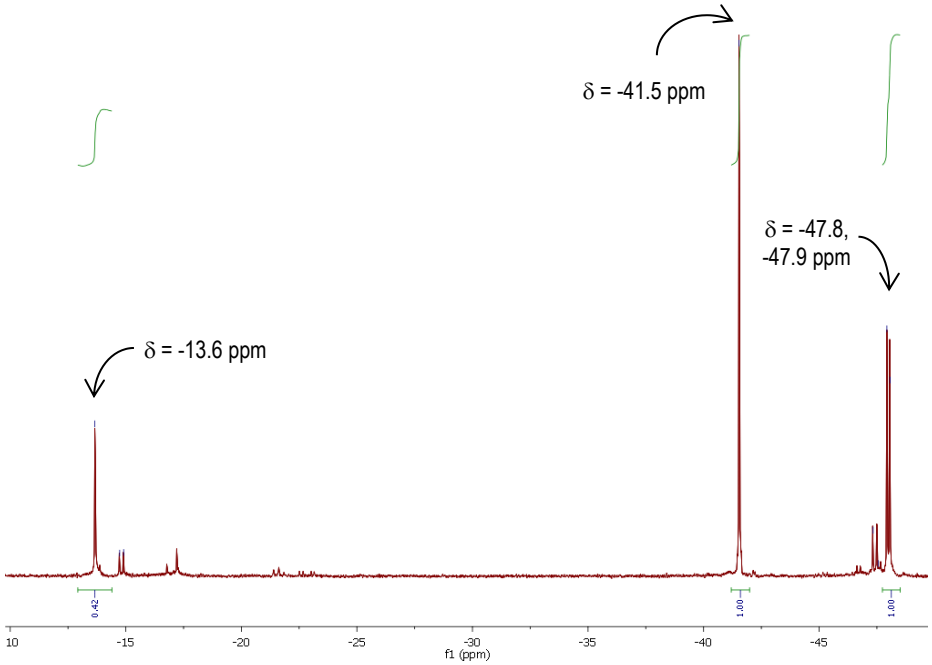


Figure 11. $^{31}P\{^1H\}$ NMR spectrum of reaction mixture after quenching (experiment 1)

After quenching, the resulting mixture of phosphines presented four characteristic peaks in the ^{31}P NMR spectrum (Figure 11). The desired product mppe appeared as two peaks at δ(THF, insert) = -47.8 and -47.9 ppm, corresponding each to the two possible diastereomers (R*,R*-(±)/R*,S*) which are formed in equal proportions. Diphenylphosphine (Ph_2PH) appeared at δ(THF, insert) = -41.5 ppm, and unreacted dppe appeared at δ(THF, insert) = -13.6 ppm. Selectivity (understood as the number of moles of desired product in relation to number of reacted moles) was found to be roughly 33% for mppe.

As selectivity was so poor, a second experiment was carried out (experiment 2). Two essential flaws were detected in experiment 1 that were corrected in experiment 2: the rate of dppe addition over the Li suspension was too high, and protonation of the dilithium phosphide species was too sudden. This favored too much the diphenylphosphine formation pathway of the reaction.

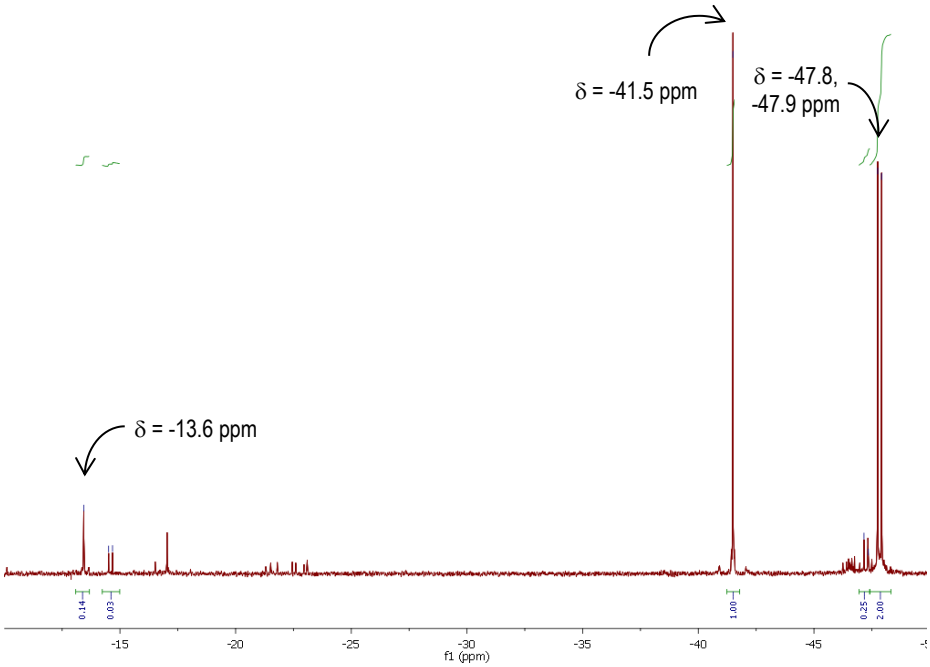


Figure 12. $^{31}P\{^1H\}$ NMR spectrum of reaction mixture after quenching (experiment 2)

In experiment 2, a 0.3 M solution of dppe in THF was added dropwise over a suspension of small Li pieces (relative molar proportion of 1 to 10) at 0 ºC over 4 h, instead of 15 minutes. The solution was refluxed at 80 ºC for 2h. Pieces of Li were filtered while hot, and the solution was cooled again to 0 ºC for 30 min. before being quenched with a mixture 1:3 H_2O/THF over another 30 min. The solution was extracted with Et_2O, and extracts were dried with Na_2SO_4.

Experiment 2 showed improved selectivity and conversion. ^{31}P {^1H} NMR spectra showed that the reaction mixture was enriched in mppe (Figure 12), because now selectivity was roughly 50%. Conversion in this case proved also higher, leaving a lower fraction of unreacted dppe in the reaction mixture.

Separation of the phosphine mixtures obtained proved to be a critical step in the process of obtaining mppe. Once all solvent was eliminated *in vacuo*, the phosphine mixture was a viscous yellow oil at room temperature. This liquid mixture was of difficult separation because of several reasons. Phosphines are extremely difficult to separate by chromatography because they are unstable to air. On the other hand, dppe, while solid at room temperature, proved to be highly soluble in the other liquid phosphines. Because of this, mppe was separated by means of vacuum distillation. The phosphines mppe and Ph_2PH have very different boiling points, 102 and 160 ºC respectively (0.1-0.07 mmHg), and dppe has a melting point of 140-145 ºC.

The oil obtained from experiment 1 was distilled using a Kugelrohr distillation apparatus (BUCHI Glass Oven B-580) (Figure 13), a short-path distillation apparatus typically used to distill relatively small amounts of compounds with high boiling points under reduced pressure. Vapors travel smaller distances in distillation, which helps reduce losses and speeds up collection.

This method proved to be inefficient for the separation of the present phosphine mixture. Fraction one collected was enriched in the more volatile Ph_2PH, but small amounts of mppe were also present (approximate ratio 5:2). Similarly, fraction 2 was significantly enriched in mppe, but there still was Ph_2PH in the distilled colorless mixture (approximate ratio 5:1). The distillation residue presented almost exclusively dppe. One of the main problems with this method was that while Kugelrohr distillation provided a short-enough distillation pathway to allow distillation to take place over a relatively short time-period, it was too short to render an adequate separation (Figure 14). The entire process of experiment 1 was low yielding; approximately 11% yield was obtained.

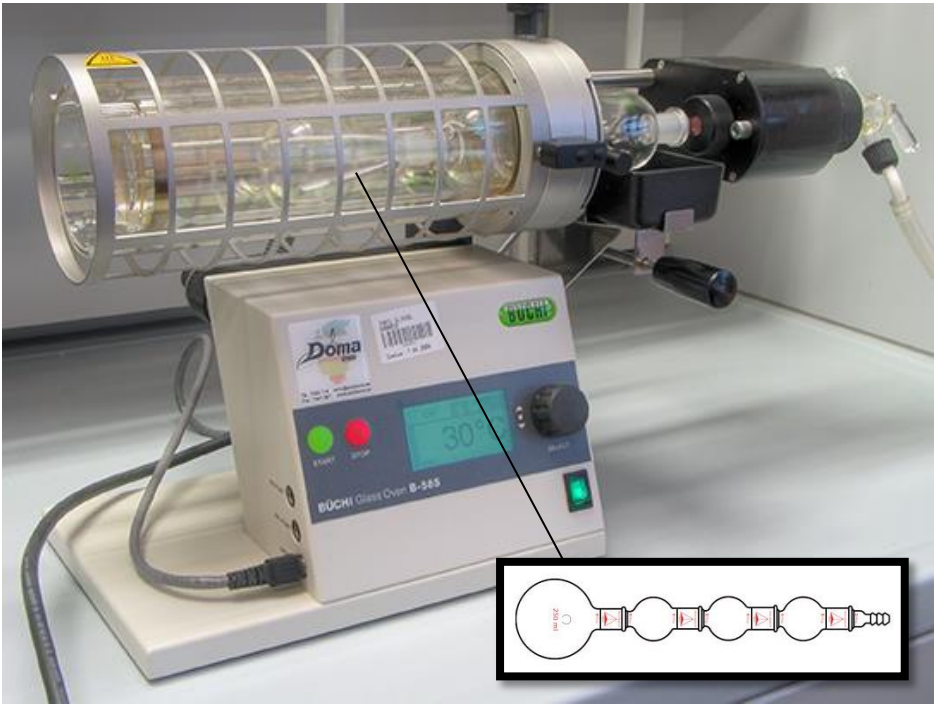


Figure 13. BUCHI Glass Oven B-580, Kugelrohr distillation apparatus. It consists of an electric heater with a digital thermostat, and two or more bulbs connected with ground glass joints. The compound to be distilled is placed in the last bulb. The other bulbs can be used to collect the distillates sequentially; when collecting each desired fraction, that bulb is cooled with ice to aid condensation. A motor drive is used to rotate the string of bulbs make distillation more efficient.

Experiment 2 was carried out in a larger scale and its distillation was achieved by fractional distillation *in vacuo*. Diphenylphosphine distilled at 102 ºC (0.07 mmHg). Once Ph_2PH was eliminated from the mixture, mppe was separated from dppe by simple distillation so the distance vapors had to travel was shorter and the distillation flask had to be heated to a lesser degree to achieve distillation in a reasonable amount of time. Phosphine mppe distilled at 160 ºC (0.07 mmHg) as a clear viscous oil that upon cooling turned into a gummy substance. Not all mppe present distilled, as when high temperatures are applied to the distillation flask it formed a viscous mass with fused dppe (which does not distill, as it has a much higher boiling point) and distillation stopped.

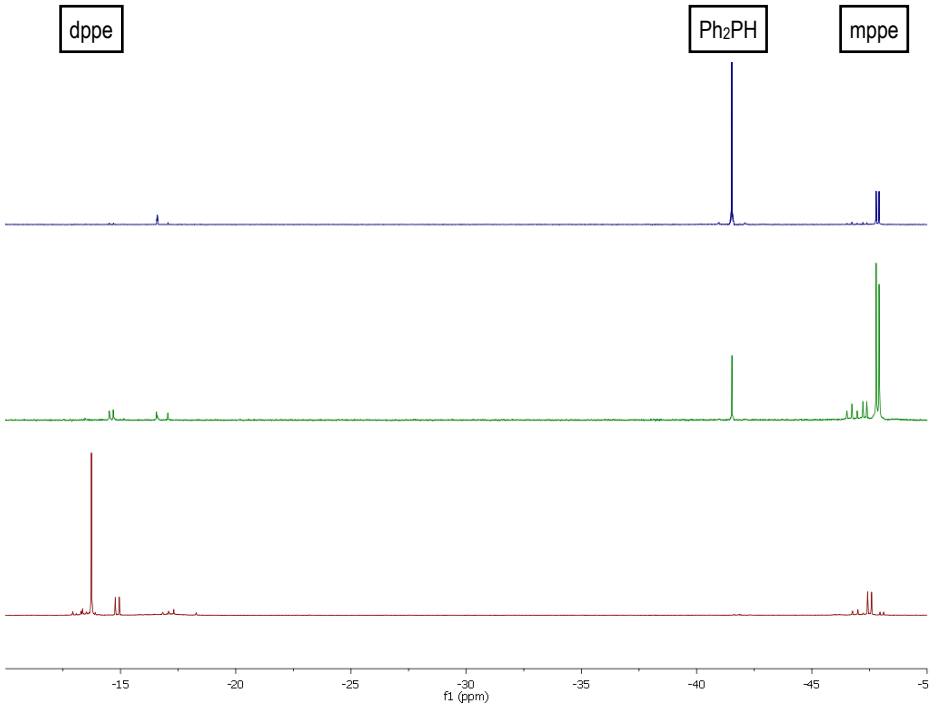


Figure 14. $^{31}P\{^{1}H\}$ NMR spectra of fractions 1 (top), 2 (middle) and residue (bottom) of Kugelrohr distillation of oil resulting from experiment 1.

This method of distillation proved to be more adequate for the separation of mppe, diphenylphosphine and dppe. Nonetheless, it was a more time-consuming method, and the phosphine mixture was heated for excessively long periods of time. By heating, the addition of oxygen to phosphine becomes more favorable. Even under N_2 atmosphere oxide $Ph_2P(O)H$ was formed during distillation. This too was observed in experiment 1, but to a much lesser extent. This phosphine oxide has a melting point of 48-53 ºC and distills at 102 ºC at 0.4 mmHg [41]. Diphenylphosphine oxide ($\delta(^{31}P\{^{1}H\}$ $CDCl_3$) = 21.4 ppm) distilled with Ph_2PH, and was initially eliminated from solution while diphenylphosphine was distilled. Heating to distill mppe was the cause that more diphenylphosphine oxide was formed. It became difficult to eliminate, as further heating to distillate only increased the amount of oxide present (Figure 15).

However, the overall yield of experiment 2 was higher than experiment 1 (approximately 32%), but mppe obtained contained a significant amount of diphenylphosphine oxide.

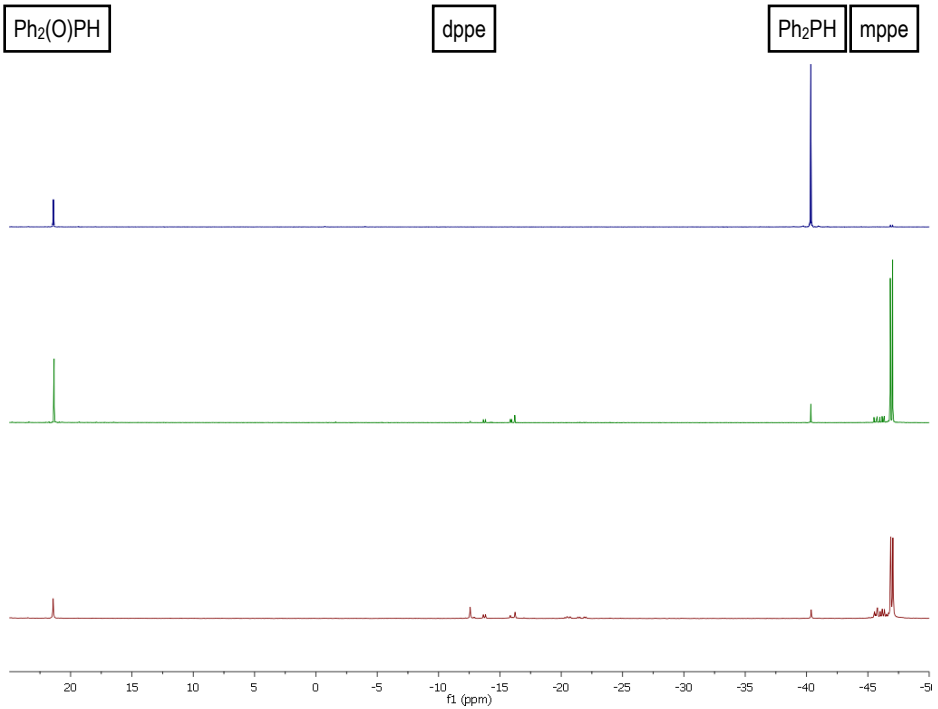
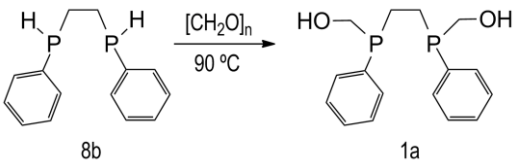


Figure 15. $^{31}P\{^{1}H\}$ NMR spectra of distilled Ph_2PH (top), mppe (middle) and residue (bottom) of fractional distillation from experiment 2.

Synthesis of hmppe: hydroxymethylation of mppe

Synthesis of hmppe was conducted with the sample of mppe obtained from experiment 2. As specified in literature method [19], secondary phosphine mppe neat reacted with solid formaldehyde after stirring for four hours at 90 ºC.



8b 1a

Scheme 11. Hydroxymethylation reaction of mppe.

A white semisolid substance was formed which contained white solid particles. This gummy substance was dissolved in THF and solid particles were separated from the solution. They

were characterized with IR Spectroscopy and found to be a mixture of various phosphorus oxides (stretching bands (P=O) at 1100-1200 cm^{-1}). $^{31}P\{^{1}H\}$ NMR Spectroscopy of the solution showed that the phosphines had become oxidized, and there was present a great variety of products, as shown by the big amount of peaks present in the spectrum (Figure16).

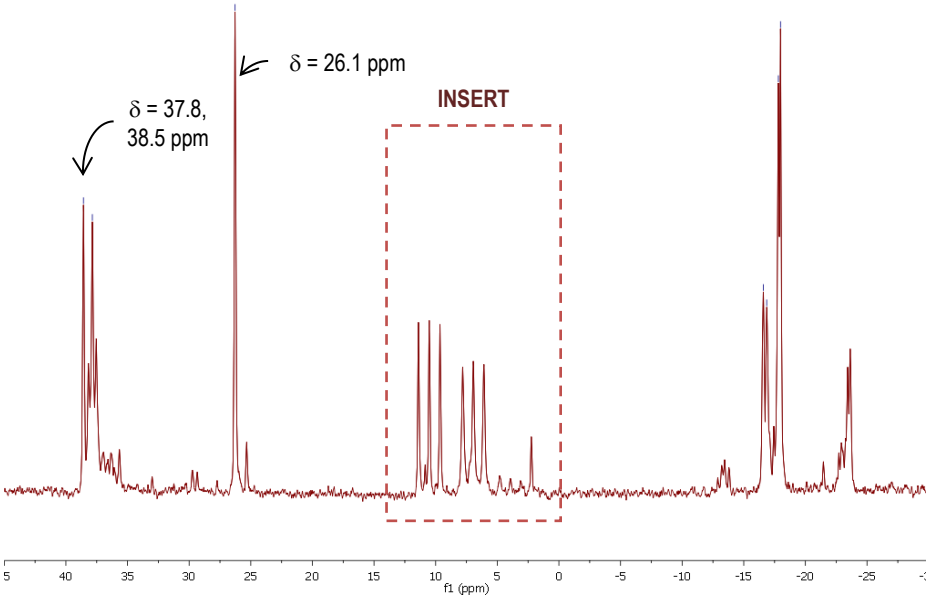


Figure 16. $^{31}P\{^{1}H\}$ NMR spectrum of the mixture obtained from the hydroxyalkylation of mppe.

Phosphines appear at negative shifts, as well as most species species with phosphorus(III). In this case, it becomes clear that we had not only hmppe, but some other phosphines too, which origin we are not quite yet ready to explain. At positive shifts, there are several peaks that correspond to phosphine oxides.

A literature search identified some of the oxides present in more significant proportions as can be seen in Figure16 [41-43]. The $^{31}P\{^{1}H\}$ NMR shifts of aforementioned phosphorus species registered in acetone-d_6 trimethylphosphite insert, and $CDCl_3$ if available, are included in Table 2. There have also been included all other phosphorus species relevant to phosphine ligands discussed in this report.

Compound	^{31}P {^{1}H} NMR Shifts ($CDCl_3$ 300MHz) (ppm)	^{31}P {^{1}H} NMR Shifts (insert 300MHz) (ppm)
$Ph_2PCH_2CH_2PPh_2$	-12.6	-13.6
$PhPHCH_2CH_2PHPh$	-46.8, -47.0	-47.8, -47.9
$Ph(CH_2OH)PCH_2CH_2P(CH_2OH)Ph$	-	-18.3, -18.7
$Ph((C_4H_8NO)CH_2)PCH_2CH_2P(CH_2(C_4H_8NO))Ph$	-32.7, -33.3	-33.8, -34.4
Ph_2PH	-40.3	-41.5
Ph_2PCH_2OH	- 11.7	-13.7
$Ph(CH_2OH)P(O)CH_2CH_2P(O)(CH_2OH)Ph$	-	37.8, 38.5
$Ph_2P(O)H$	21.4	21.4
$Ph_2P(O)CH_2OH$	31.1	26.1
$Ph(CH_2OH)P(BH_3)CH_2CH_2P(BH_3)(CH_2OH)Ph$	-20.0	-20.0

Table 2. NMR Characterization Data for different phosphorus species, both in NMR spectra registered in $CDCl_3$ and other solvents with an acetone-d_6 triphosphite insert for reference.

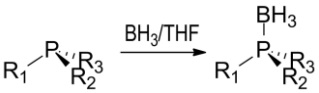
Given the great quantity of by-products generated by the hydroxyalkylation of mppe, we decided to try to separate the surviving phosphine form oxides and other species. Hmppe was purified using borane to form phosphine-borane adducts, this step served the purpose of both protecting the hydroxymethylated phosphine from oxidation and making it stable enough to allow separation.

Phosphine-boranes: protection and separation of phosphine ligands

Phosphine-borane complexes are very stable compounds. Their stability allows their use as intermediates in synthesis [44], and they can be used as effective protecting groups for active phosphorus species such as phosphines. It is common for borane to be used to protect phosphines by formation of hydroxyalkyldiphenylphosphine-borane complexes. These not sensitive to usual oxidizing agents, including atmospheric oxygen. Decomplexation using amines in mild conditions has been described [45].

In the role of borane-adducts as protecting group for phosphines, it is also common work with phosphine-boranes because purification of phosphines becomes easier. In most cases separation of phosphine oxides from phosphines is not feasible unless phosphines are previously protected. Phosphine-boranes may be separated from oxides by chromatographic methods.

In order to attempt to separate hmppe ligand from the phosphine oxides and other minor products in the mixture, the corresponding phosphine-boranes were formed. A solution of hydroxyalkylation products in THF was treated with BH_3 in THF (1M) (Scheme 12). A semisolid substance was obtained, which was washed several times with hexane.



Scheme 12. Phosphine-borane formation reaction.

$^{31}P\{^{1}H\}$ NMR spectrum of the resulting solution showed complete reaction of all phosphines (Figure 17). All peaks with negative chemical shifts disappeared. Instead, borane species appeared as one single broad signal at 20.0 ppm, as typical of most phosphine-borane adducts.

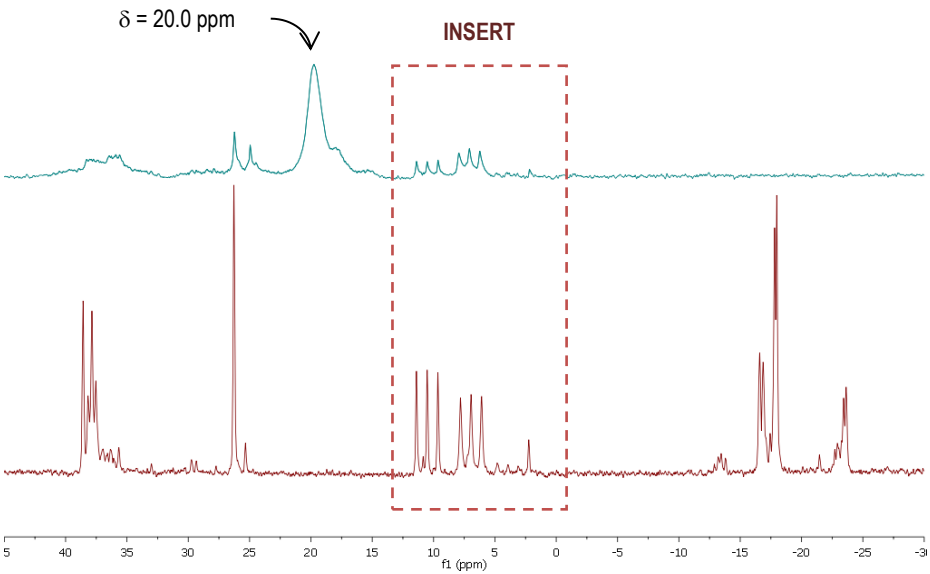


Figure 17. $^{31}P\{^{1}H\}$ NMR spectra before (bottom) and after (top) treatment with BH_3.

The phosphine-borane derived from hmppe was separated from various oxides by a chromatographic column of silica using CH_2Cl_2/MeOH as eluent. Different fractions contained mixtures of different oxides. Phosphine-borane ($Ph(CH_2OH)P(BH_3)CH_2CH_2P(BH_3)(CH_2OH)Ph$) was obtained pure (Figure 18) as a white semi-crystalline solid, insoluble in non-polar solvents.

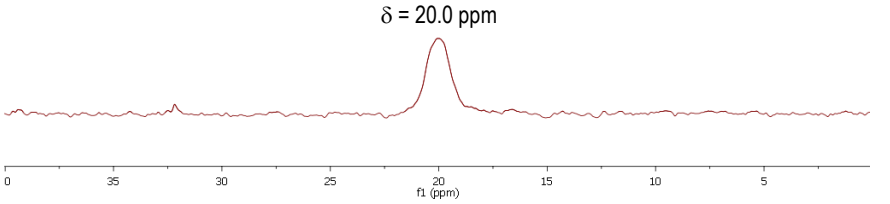
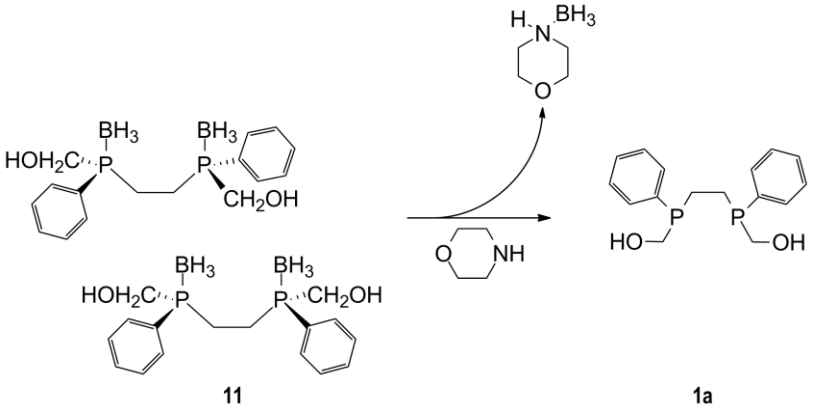


Figure 18. $^{31}P\{^{1}H\}$ NMR spectrum of $Ph(CH_2OH)P(BH_3)CH_2CH_2P(BH_3)(CH_2OH)Ph$.

The next step was deboronation of the phosphine-borane obtained from chromatographic purification, in order to obtain the free phosphine ready to be complexed. The method of choice was the treatment with a large excess of morpholine as it is rendered in Scheme 13.



Scheme 13. Deboronation of hmppe.

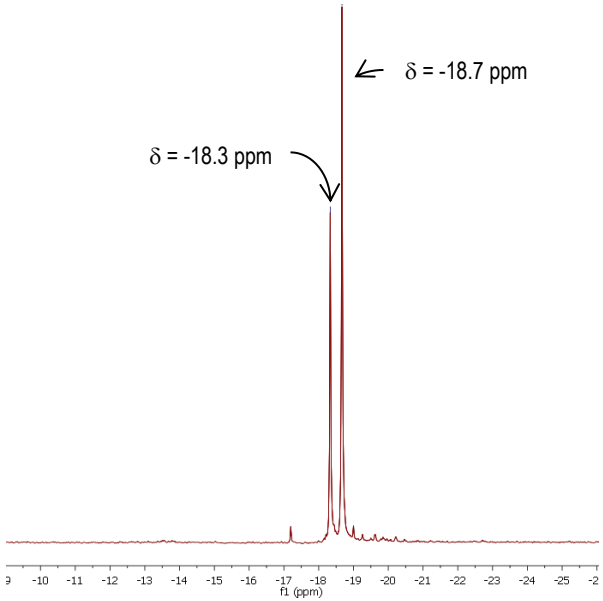


Figure 19. $^{31}P\{^{1}H\}$ NMR spectrum of phosphine recovered after deboronation.

Deboronation with morpholine at room temperature is a mild procedure. The completion of deboronation can be monitored with $^{31}P\{^{1}H\}$ NMR Spectroscopy, as with the removal of protecting borane group sharp well-defined peaks appear again with negative shifts, instead of wide broad band of borane species. Phosphine hmppe was successfully recovered mostly pure after 72h of reaction. Chemical phosphorus shifts assigned to (R*,R*-(±)) and (R*,S*) species were δ(morpholine, insert) = -18.29 and -18.69 ppm (Figure 19). The only drawback of this method is the high boiling point of morpholine (b.p 120 ºC) which makes difficult the elimination of morpholine excess.

Formation of mmppe

The morpholine solution containing diphosphine hmppe and the borane-morpholine adduct formed during deboronation was dried *in vacuum*, and a yellow semisolid was obtained. The crude mixture was filtered through a neutral alumina column, using toluene as eluent. The process was controlled through TLC, and $^{31}P\{^{1}H\}$ NMR Spectroscopy. We expected to recover pure hmppe, but instead we found that we had obtained a different phosphine with δ ($^{31}P\{^{1}H\}$ $CDCl_3$) = -32.7 and -33.3 ppm (Figure 20).

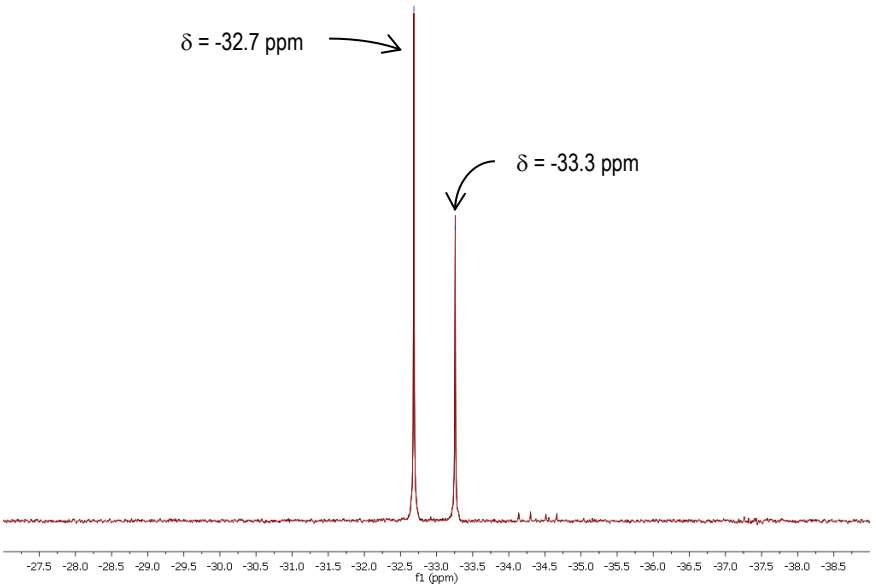


Figura 20. $^{31}P\{^{1}H\}$ NMR spectrum of diphosphine recovered after filtration through alumina column. Peaks correspond to morpholine derivative.

After drying *in vacuum* the recovered fractions, a white crystalline solid was obtained. It was characterized using IR, ^{1}H NMR and $^{31}P\{^{1}H\}$ NMR Spectroscopy and MS-ESI. We deduced that the resulting compound was [1,2-bis(methylmorpholinephenylphosphino)ethane] (mmppe) (Figure 21).

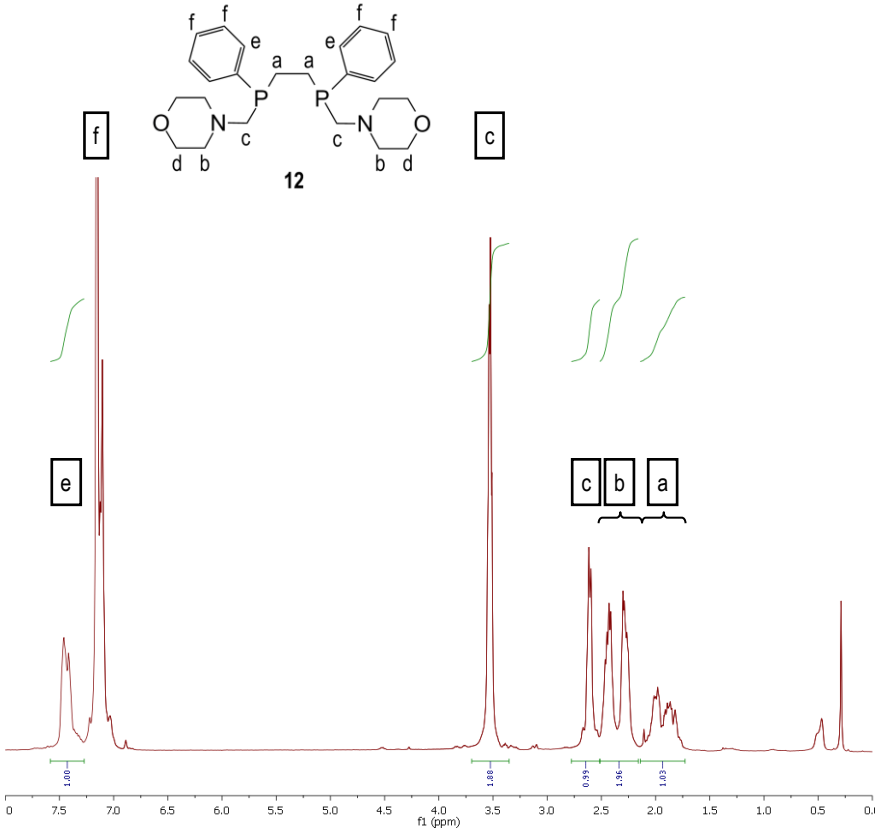
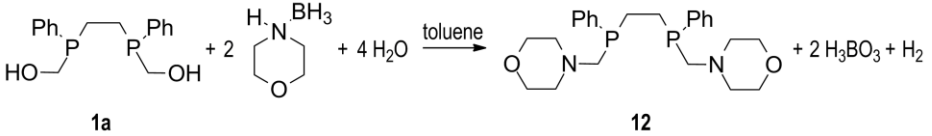


Figure 21. ^{1}H NMR spectrum of Ph((C$_4$H$_8$NO)CH$_2$)PCH$_2$CH$_2$P(CH$_2$(C$_4$H$_8$NO))Ph (mmppe), were both (R*,R*-(±)/R*,S*) configurations of the diphosphine are included. Splitting of the signal of **a** protons occurs because of a semi-rigid configuration where the proton at one side of the bridge-chain remains nearer the Ph substituent than the other. Splitting of **b** protons occurs because morpholine assumes a chair-like conformation, and in this case we can observe the different shifts for axial and equatorial protons in the position adjacent to N. Coupling of both a signals, of both b signals and between e and f signals was confirmed with a COSY spectrum.

It appears that by changing the polarity of the medium by introducing a solvent different to morpholine, a condensation reaction with morpholine begins in which morpholine acts as a nucleophile and substitutes the hydroxyl groups of the side-chains (Scheme 14). This morpholine comes from the BH_3-morpholine adduct present. The alumina, whose initial purpose was to filter the morpholine adduct, apparently acts as a catalyst for this reaction.



1a **12**

Scheme 14. Reaction with hmppe that leads to the formation of mmppe

A sample of the crude mixture of the diphosphine hmppe and the BH_3-morpholine adduct diluted in dichloromethane was analyzed with MS-ESI. Results effectively showed the presence both of hmppe (m/z (M^+) = 307) and protonated morpholine adduct (m/z ($M^+ + H^+$) = 102 u. It also showed, because of the introduction of another non-polar solvent, the presence of morpholine derivative mmppe (m/z (M^+) = 445).

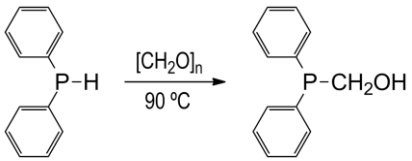
The synthesis of aminomethylphosphines does typically take place starting from hydroxymethylphosphines [46]. Although this reaction was not intended, and morpholine was only used as the common means for phosphine deboronation, mmppe can not be entirely dismissed.

Generally speaking methylmorpholinephosphines present several advantages over hydroxymethylphosphines. In the first place, while hmppe is reportedly an viscous oil, mmppe is a crystalline solid. Also, some morpholine derivatives are water-soluble, and their solutions in water and $CHCl_3$ are air-stable. Because of all these reasons, monophosphines bearing methylmorpholine substituents have been subject to studies about cytotoxic properties in the research for antibacterial drugs [46]. Although this methylmorpholinephosphine is not particularly water-soluble, it remains to be seen whether alkynylgold(I) complexes bearing mmppe would prove sufficiently soluble.

SYNTHESIS OF THE PHOSPHINE LIGAND Ph_2PCH_2OH

The synthesis of ligand Ph_2PCH_2OH was attempted for comparative purposes. Contrary to the synthesis of hmppe, this hydroxyalkylated phosphine is relatively common and has been well-studied. For this reason, synthesis of Ph_2PCH_2OH was attempted parallel to that of hmppe, utilizing initially the same reaction conditions.

Diphenylphosphine was treated with the stoichiometric quantity of solid paraformaldehyde to produce Ph_2PCH_2OH [28] in two separate experiments. The reaction time and temperature were different in both experiences. Initially diphenylphosphine obtained in the distillation process of mppe was used. The product was pure save for the small amounts of oxide developed. Diphenylphosphine reacted with paraformaldehyde for four hours at 90 ºC (as for hydroxyalkylation of mppe) (Scheme 15). In a second synthesis of Ph_2PCH_2OH, commercial diphenylphosphine reacted with paraformaldehyde for 40 min. at 100-110 ºC. Similar results were obtained in both instances.



8c **1b**

Scheme 15. Hydroxymethylation of diphenylphosphine.

In both cases a colorless clear liquid was obtained. The reaction had nearly quantitative yield, and control by $^{31}P\{^1H\}$ NMR showed that ligand Ph_2PCH_2OH was obtained pure $\delta(CDCl_3)$ = - 11.7 ppm ($\delta(CDCl_3)$ = -11.7 ppm according to literature sources too [47]). There was no oxide present in the mixture, neither $Ph_2P(O)H$, nor $Ph_2P(O)CH_2OH$.

It was later observed that in the space of hours to days, Ph_2PCH_2OH decomposed to form another unidentified phosphorus species ($\delta(CDCl_3)$ = -19.9 ppm) (Figure 22). The passing of time seemed to further degrade the phosphine samples, and increasing amounts of this second species could be detected.

In any case, this phosphorus species does not appear to be a phosphine oxide, and it isn't a phosphinite either, both based on its NMR chemical shift and its apparent later reactivity with

$[Au(C{\equiv}C\text{-}C_5H_4N)]_n$. Apparently this species does contain active phosphorus, but no P-O bonds. Separation of both species was not attempted.

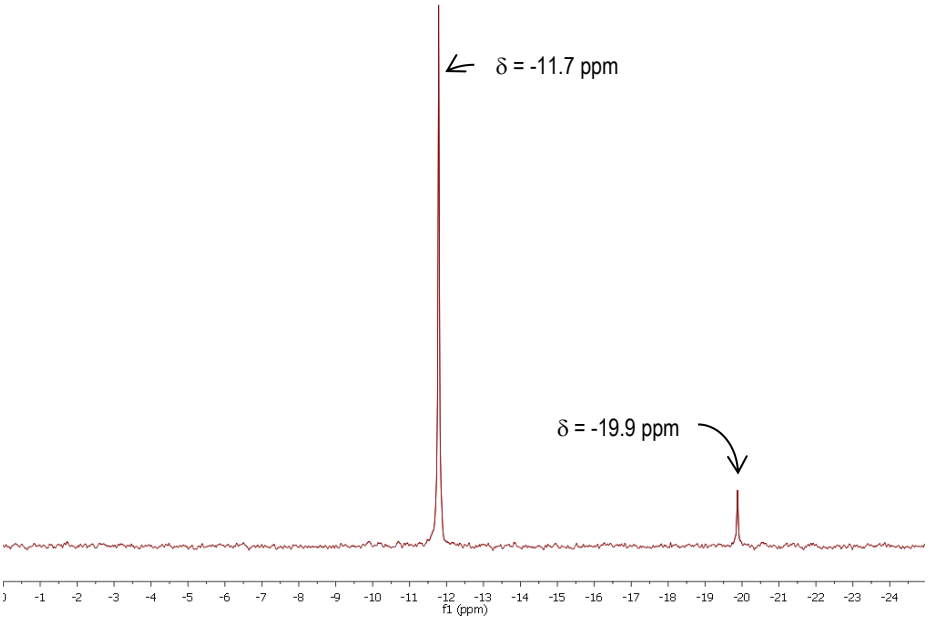


Figure 22. $^{31}P\{^1H\}$ NMR Spectra of Ph_2PCH_2OH ($\delta(CDCl_3)$ = - 11.7) sample after decomposition.

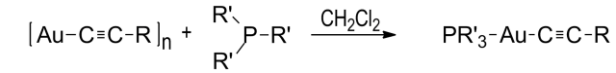
In order to elucidate the nature of the unidentified by-product gas chromatography-mass spectrometry (GC-MS) was performed on a sample of the reaction mixture. It did not provide any enlightening data in regards to the second phosphine species. On the other hand, the presence of the desired phosphine Ph_2PCH_2OH was confirmed as the main product. We also gleaned that Ph_2PCH_2OH was unstable at high temperature, as main chromatographic peak in the spectra was found to belong to Ph_2PH. $^{31}P\{^1H\}$ NMR clearly showed that reagent diphenylphosphine was not present when injected, but that Ph_2PCH_2OH fragmented to present a major peak at t = 10.14 s and m/z (M^+) = 186 Other minor peaks were t = 11.801 s and m/z (M^+) = 214, presumably $Ph_2PCH_2O^-$; at t = 14.787 s and m/z (M^+) = 215 appeared vestiges of Ph_2PCH_2OH, and a triphenylphosphine peak at t = 16.249 s and m/z (M^+) = 262.

Looking for a milder form of ionization in mass spectrometry, samples were analyzed with Electrospray Ionization-Mass Spectrometry (ESI-MS). Typically, ESI techniques are useful in producing ions from large molecules because it overcomes the propensity of said molecules to

fragment when ionized. ESI-MS confirmed that the obtained samples contained mainly Ph_2PCH_2OH (m/z $(M+H)^+$ = 217). Trimers of phosphorus(V) derived from the phosphine were also observed, along with peaks that showed the loss of a formaldehyde (m/z = 689, 659 and 629). However, it didn't provide any enlightening information in regards of the phosphine byproduct at lower negative phosphorus shifts.

SYNTHESIS OF THE GOLD(I) COMPLEX [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)]

For the synthesis of gold(I) complexes exist mainly two synthesis routes, as briefly expounded upon in the *Introduction*. The first one consists on the reaction of the polymer $[AuC{\equiv}CR]_n$ with a tertiary phosphine as described by Coates and Parkin [2] (Scheme 14).



Scheme 16. Scheme for reaction of gold(I) polymer and tertiary phosphines.

A second choice might be as describe by Cross [3-4] where phosphinegold(I) chlorides [Ph_3PAuCl] reacted with terminal acetylenes in basic media.

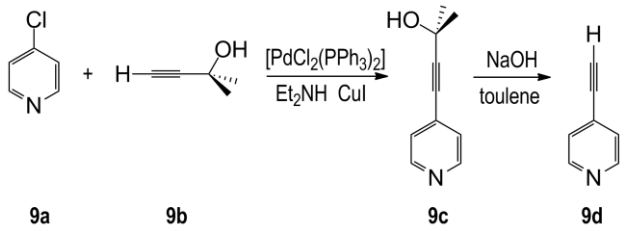
Scheme 17. Scheme for reaction of gold(I) phosphinegold(I) chlorides with alkynyl compounds.

In this instance, synthesis of [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)] was attempted only by way of the polymer-type reaction, as with the previously synthesized [Au(C≡C-C_5H_4N)(PPh_3)] [13].

Synthesis of the gold(I) polymer $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$

Synthesis of 4-ethynylpyridine

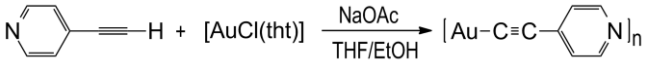
4-Ethynylpyridine was synthesized [48] by reaction of pyridyl bromide with 2,2-dimethyl-3-butyn-2-ol in basic media, a protected acetylene commercially available, in the presence of catalyst [$PdCl_2(PPh_3)_2$] and copper(I) iodide. In this manner, acetylide anion reacts with 4-bromopyridine hydrochloride by nucleophilic aromatic substitution forming a C-C bond. The removal of the protecting group as acetone is later accomplished by refluxing with sodium hydroxide in toluene.



Scheme 18. Schematic 4-ethynylpyridine synthesis.

Polymer Synthesis

The polymer $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$ was synthesized following a well-established method of synthesis [49], where solid [AuCl(tht)] (synthesis described in literature references [50]) reacted with 4-ethynylpiridine in basic media.



Scheme 19. Synthesis of alkynylgold(I) polymer of ethynylpyridine

Leaving group tht is displaced by acetylide anion in the early steps of the reaction. Then polymer $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$ is formed, a pale yellow fine solid that is highly insoluble. As expounded by Coates and Parkin [2] a polymer is formed, presumably by Φ and π interactions of acetylide triple bond with gold(I). Thus, it has been proposed that such gold(I) polymers have a structure such as in Figure 23.

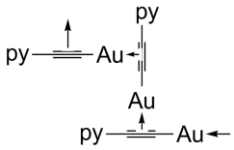


Figure 23. Most likely structure for $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$

Synthesis of $[Au(C{\equiv}C\text{-}C_5H_4N)(Ph_2PCH_2OH)]$

Synthesis of $[Au(C{\equiv}C\text{-}C_5H_4N)(Ph_2PCH_2OH)]$ was attempted, with different samples of previously synthesized Ph_2PCH_2OH. In each case, different amounts of unidentified phosphine ($\delta(CDCl_3)$ = -19.9 ppm) were present in Ph_2PCH_2OH sample.

Every time, Ph_2PCH_2OH was dissolved in CH_2Cl_2, and was added over a suspension of $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$ [13] in stoichiometric quantities. Reaction yielded almost immediately a pale yellow solution. An immediate $^{31}P\{^1H\}$ NMR analysis showed the presence of two species in solution presenting a phosphorus ligand. Typically 4-ethynylpyridinegold(I) complexes present phosphorus shifts around 50-40 ppm [51], whereas in this case phosphorus signals appeared at $\delta(CH_2Cl_2$, insert) = 33,1 and 29,8 ppm. This allowed us to determine that unfortunately both phosphine species had an phosphorus(III) atom, as they both apparently react with the ethynylgold(I) polymer (Figure 24).

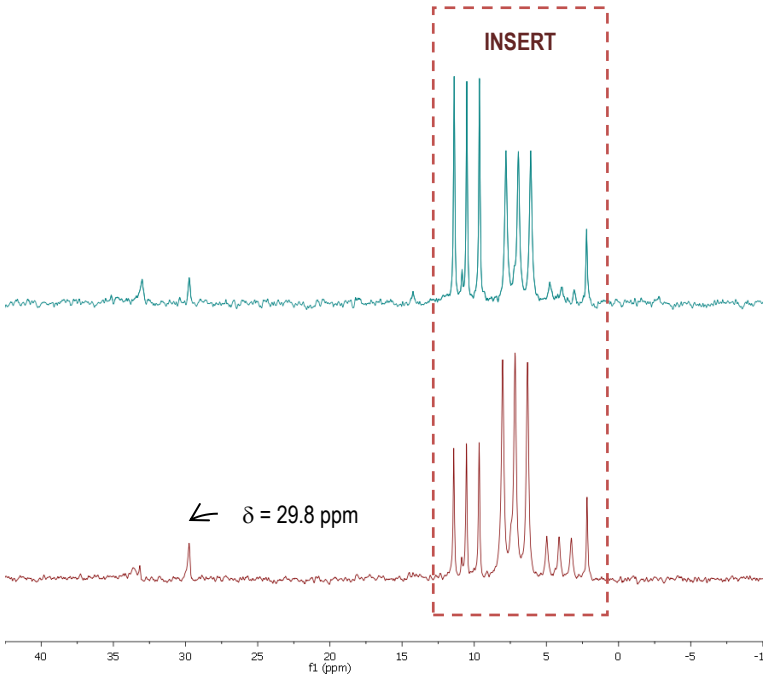


Figure 24. $^{31}P\{^1H\}$ NMR spectra of reaction mixture.

From the different intensity of the peaks corresponding to both species formed, we deduced that the peak at δ = 29.8 ppm could belong to $[Au(C{\equiv}C\text{-}C_5H_4N)(Ph_2PCH_2OH)]$. Second peak at δ = 33.05 ppm should belong to a gold(I) complex with the unidentified phosphine ligand.

Separation of both compounds by chromatography might have been attempted if said compounds had proved to be stable enough. But complex $[Au(C{\equiv}C\text{-}C_5H_4N)(Ph_2PCH_2OH)]$ has a very short half-life, and hours after reaction a white precipitate appeared. This white precipitate

is insoluble in all usual solvents. IR spectrum showed the presence of both phosphine and ethynyl ligands.

In the IR spectrum of ethynylgold(I) complexes the stretching frequency band of the triple bond attached to a gold(I) atom is about 2120 cm^{-1}, a shift of approximately 5-20 cm^{-1} over the stretching frequency band of the triple bond in 4-ethynylpyridine (ν(C≡C*H*) = 2095 cm^{-1}) [51]. This can be observed in the polymer $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$ where said band appears at (ν(C≡C*H*) = 2123 cm^{-1}. In this case, stretching frequency band of ethynylpyridine triple bond is 2106 cm^{-1}, a somewhat broad band. It is not clear whether 4-ethynylpyridine is coordinated to gold center or remains un-coordinated.

IR Spectra also presented several other bands demonstrating the presence of phosphine ligand: ν(C=C, Ph) 1587, 1473 and 1430 cm^{-1}, γ(CH) 739 cm^{-1}, ϕ(CC) 687 cm^{-1} and coordination sensitive bands at 509 and 482 cm^{-1}.

The compound formed is most assuredly a polymer, as all mononuclear gold(I) species known to date are soluble. The exact structure of said insoluble polymer could not be determined, as NMR characterization was not possible. Possibly, the formation of this polymer showed is due to the gold-oxygen interactions, because of hydroxyl group in the phosphine ligand.

This polymer was filtered from solution, and the remaining dichloromethane solution was concentrated *in vacuo*, and subsequently ether was added to precipitate the gold(I) complex [13]. A fine pale yellow solid was obtained on precipitation, which was filtered, but characterization was not possible because $^{31}P\{^1H\}$ and ^1H NMR analyses showed a dynamic behaviour.

The $^{31}P\{^1H\}$ NMR spectrum in chloroform did not present a fine well defined peak, as could be seen in the reaction mixture, and as is typical of $[Au(C{\equiv}C\text{-}C_5H_4N)(PPh_3)]$. Instead it presented a broad band, barely distinguishable from background noise, around δ ($CDCl_3$) = 50 ppm (Figure 25). Possibly this could be caused by a fluxional behavior of phosphine ligands. This phosphorus shift is in a range typical of ethynylpyridine(phosphine)gold(I) complexes.

^1H NMR Spectra was not well resolved, but happened to be identical in all experiments. Broad signals appeared at δ between 9 and 6 ppm, in the aromatic proton region. All peaks were ill-defined, wide and flat. This might actually support the existence of a dynamic process.

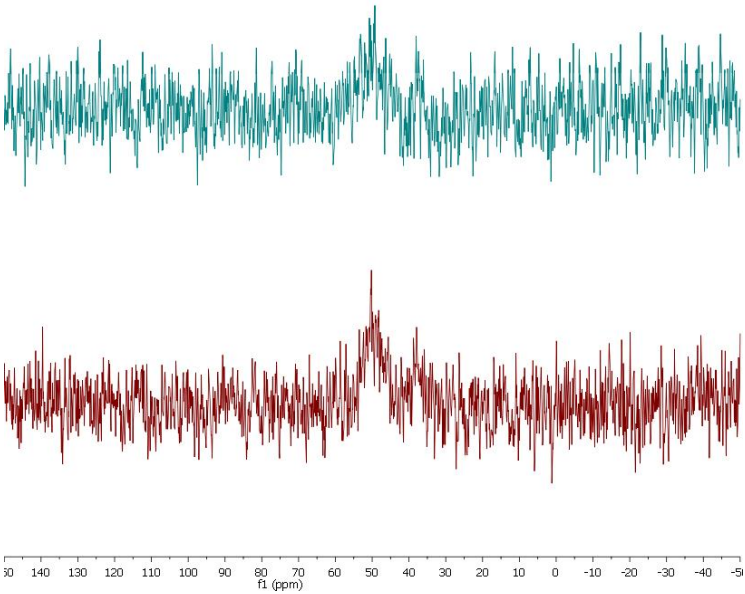


Figure 25. $^{31}P\{^{1}H\}$ NMR spectra of isolated yellow precipitate, on both experiments the same behavior was observed δ ($CDCl_3$) = 50 ppm.

IR spectra showed that the yellow precipitate contained no ethynylpyridine ligands as stretching band ν(C≡C*H*) was absent. Bands associated with phosphines could be observed: ν(C=C, Ph) 1430 cm^{-1}, coordination sensitive band at 1095 cm^{-1}, β(CH) 1022 cm^{-1}.

In any case, in solution of CH_2Cl_2 or $CDCl_3$ this complex [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)] rapidly forms more white solid precipitate. This compound is also sensitive to acid media, where gold(I) is immediately reduced to metallic gold.

Furthermore, in ether filtrate solution there were still large quantities of gold(I) complex as in dichloromethane reaction mixture. After solvent was removed *in vacuo* $^{31}P\{^{1}H\}$ NMR of the remaining cream-colored fine-powdered solid rendered identical shifts for compounds found initially in dichloromethane reaction mixture.

The amount of product that remained in ether solution was significant, and $^{31}P\{^{1}H\}$ NMR analysis showed the same species were present as after reaction in CH_2Cl_2. Analysis with ESI-MS allowed us to confirm that gold compound [Au(C≡C-C_5H_4N)(Ph_2PCH_2OH)] is present (m/z $(M+H)^+$ = 516 u). Other species resulting from the formation of phosphorus(V) adducts were

also present. There is, however, other species which we would be hard-pressed to identify, and appear also significantly in the registered spectrum.

Without entering further speculation, it was not possible to wholly characterize the gold(I) compounds obtained from this synthesis. It appears though that complex obtained from this synthesis route is both unstable and soluble in non-polar solvents.

CONCLUSIONS

The synthesis of the desired phosphine ligand, [1,2-bis(hydroxymethylphenyl-phosphino)ethane] (hmppe), has been successfully accomplished.

Although the cleavage of [1,2-bis(diphenylphosphino)ethane] (dppe) by lithium in THF has been reported to be a process largely dependent on both temperature and concentration, large amounts of [1,2-bis(phenylphosphino)ethane] (mppe) can be obtained lowering the temperature and the concentration at the earlier stages of cleavage reaction. Later, mppe must be separated from main side-product diphenylphoshphine by fractional distillation.

A mixture of phosphines and oxides was obtained as a result of the synthesis of hmppe by reaction of mppe with solid paraformaldehyde,. The reaction was not clean, and a purification method was devised. Borane-adducts were formed with BH_3/THF to protect active phosphorus, and thus, they were separated from phosphine oxides by column chromatography. Subsequent treatment with morpholine was undertaken in order to remove the borane group and obtain pure hmppe.

Although hmppe can be obtained, contact with other solvents, and filtering through a neutral alumina column to remove the morpholine adducts formed during deboronation, lead to the formation of a new diphosphine $Ph((C_4H_8NO)CH_2)PCH_2CH_2P(CH_2(C_4H_8NO))Ph$ (mmppe) through a condensation reaction. A white crystalline solid was obtained from this diphosphine that was fully characterized.

The synthesis of phosphine ligand Ph_2PCH_2OH was also successful, following strictly indications given in literature. Nonetheless results were anomalous as a decomposition of the phosphine was observed with time.

As hmppe could not be properly isolated, the synthesis of the corresponding 4-ethynylpyridinegold(I) complex was not attempted. The synthesis of 4-ethynylpyridinegold(I) complexes was attempted only with the phosphine ligand Ph_2PCH_2OH. It was not possible to ascertain whether the resulting complex is more soluble in aqueous media. Instead, we found that the complex formed from the reaction of Ph_2PCH_2OH with 4-ethynylpyridinegold(I) polymer is unstable in nature. Apparently, interaction of gold centers with the hydroxyl groups of the

functionalized phosphine lead to the formation of insoluble solids that we tentatively assigned to polymeric species that could not be fully characterized.

It appears that gold(I) has a strong affinity for oxygen, and this might lead to unpredictable results. A viable alternative would be to use ligands such as mmppe, as they do improve water-solubility, and have the advantage that are crystalline solids and more stable to oxidation when in contact with air (compared to hydroxyalkylphosphines).

For all that it is yet unknown the effect that these diphosphines might have upon the solubility of alkynylgold(I) compounds, they have the advantage of not presenting any free -OH groups. Thus it is less likely that they would lead to the formation of polymers in the same fashion as observed with Ph_2PCH_2OH. It would be of interest to be able to synthesize the gold(I) complex with mmppe to properly evaluate its water-solubility.

EXPERIMENTAL SECTION

GENERAL

Synthesis of most compounds described in this report was carried out under nitrogen atmosphere, making use of a high vacuum line (Schlenk Line) and standard Schlenk techniques.

Commercial reagents used to carry out the experimental section have been outlined below, detailing the company to which they were acquired from. All of them were used without prior purification: 4-bromopyridine hydrochloride (Sigma-Aldrich), 2-methyl-3-butyn-2-ol (Fluka), dppe (Aldrich), Ph_2PH (Aldrich), paraformaldehyde (Panreac), copper(I) iodide (Aldrich), Li (Fluka), anhydrous Na_2SO_4 (Probus), anhydrous $MgSO_4$ (Panreac), NaOAc (Probus), $HAuCl_4$ (Johnson Matthey), tht (Merck), NaOH (Panreac), BH_3/THF (Aldrich), morpholine (Fluka). Additionally dietylamine (Aldrich) was distilled under nitrogen atmosphere over sodium.

The following solvents were obtained from a Solvent Purification System (Innovative Technologies): tetrahydrofuran, diethyl ether, hexane, toluene and dichloromethane. Ethanol, methanol and ethyl acetate were used as received without further purification.

CHARACTERIZATION TECHNIQUES

Infrared spectroscopy

Infrared spectra were collected with a FT-IR AVATAR 330 THERMO NICOLET spectrophotometer in the interval comprised between 4000 and 400 cm^{-1}, using KBr as dispersing medium.

Nuclear Magnetic Resonance Spectroscopy

NMR Spectra of ^{1}H and $^{31}P\{^{1}H\}$ were registered using spectrometers Varian-Inova 300MHz and Varian-Mercury 400MHz. Chemical shifts (δ) are given in ppm an coupling constants (J) in Hz. All spectra were recorded at room temperature, and deuterated solvents used are indicated in parentheses en each case. In ^{1}H NMR spectroscopy, tetramethylsilane is used as a

reference. In $^{31}P\{^{1}H\}$ spectroscopy chemical shifts are measured relative to an aqueous solution of H_3PO_4 at 85%. In some cases, in which we worked with reaction mixtures with non-deuterated solvents, an insert of acetone-d_6 with trimethylphosphite was used as an internal reference.

Gas Chromatography-Mass Spectrometry

The chromatograms and MS spectra described in this report were registered with an 7820A GC System chromatograph (Agilent Technologies) equipped with a 5975 Series MSD mass spectrometry detector (Agilent Technologies). Chromatography gas was He. The heating program used had the sample at 100ºC for two minutes after injection, and after it increased 10 ºC every minute until it reached 280 ºC, were it remained for 15 min.

Electrospray Ionization-Mass Spectrometry

Mass Spectrometry with Electrospray ionization was registered with an LC/MSD TOF System form Agilent Technologies with an optically coupled ion detector, an apparatus designed for routine high-mass accuracy.

SYNTHESIS OF [1,2-BIS(PHENYLPHOSPHINO)ETHANE] (MPPE)

Experimental procedure used for synthesis of mppe is based on literature methods [35], but several modifications have been included. A suspension of finely divided lithium (3.5 g : 500 mmol) in 100 ml THF was cooled to 0ºC. Under vigorous stirring a solution of dppe (20 g : 50 mmol) in THF (160 ml) was added dropwise to the Li suspension over 4h. After completion of the addition, a brown solution was obtained. The reaction mixture was warmed to room temperature and heated under reflux for 2h at 80ºC. Solution acquired a darker shade of brown. The hot solution was separated from excess lithium with a cannula, and cooled to 0ºC over 30 min. Mixture was stirred vigorously as 20 ml aqueous THF (20% water) was added dropwise. Lithium hydroxide was deposited as a white precipitate. The THF was removed *in vacuo*, and 100 ml of water were added to the phosphine mixture. Three extractions of the aqueous phase with diethyl ether (3 x 50 ml) followed. The combined organic extracts were dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. An homogeneous air-sensitive yellow oil is obtained, which according to $^{31}P\{^{1}H\}$ NMR Spectroscopy contained mppe, diphenylphosphine and dppe. Diphenylphosphine distilled (fractional distillation) as a colorless oil having a boiling

point of 102ºC (0.1 mmHg). The mppe distilled (simple distillation) at 140ºC (0,07 mmHg), yielding 4.00 g of mppe (Yield of 32%).

$^{31}P\{^{1}H\}$ NMR (298K, $CDCl_3$): -46.8, -47.0 (R*,R*-(±)/R*,S*).

^{1}H NMR (298K, $CDCl_3$): 1.80-2.10 (m, 4H, CH_2), 3.94 (br s, 1H, PH), 4.65 (br s, 1H, PH), 7.27 (m, 6H, ArH), 7.48 (m, 4H, ArH).

SYNTHESIS OF [1,2-BIS(HYDROXYMETHYLPHENYLPHOSPHINO)ETHANE] (HMPPE)

Solid paraformaldehyde (980 mg : 32.6 mmol) was added to mppe oil (4 g : 16.3 mmol) and the reaction mixture was heated at 90ºC for 5h under vigorous stirring. A white rubber with suspended white solid was obtained. The rubber was dissolved in THF and the solid was filtered from solution with a cannula. The solution was concentrated *in vacuo* and 32 ml of a BH_3/THF 1M solution were added to form the respective borane-adducts with existing phosphine species. The excess BH_3 was eliminated *in vacuo*, and a white gummy solid was obtained. It was washed with hexane several times, and was purified with a silica chromatographic column (elution mixture was a 5% MeOH in CH_2Cl_2 solution). Corresponding fractions were dried *in vacuo*, and $Ph(CH_2OH)P(BH_3)CH_2CH_2P(BH_3)(CH_2OH)Ph$ was obtained as a white semi-crystalline solid (810 mg :2.45 mmol). It was dissolved in 10 ml morpholine, and deboronation process was monitored by $^{31}P\{^{1}H\}$ NMR Spectroscopy to completion (72 h).

$^{31}P\{^{1}H\}$ NMR (298K, $CDCl_3$): -18.3, -18.7 (R*,R*-(±)/R*,S*).

SYNTHESIS OF [1,2-BIS(METHYLMORPHOLINEPHENYLPHOSPHINO)ETHANE] (MMPPE)

Mixture of hmppe and morpholine-BH_3 in excess morpholine was dried *in vacuo*. A yellow semisolid was obtained containing all non-volatile components. The crude mixture was passed through a neutral alumina column and eluted with toluene. Process was monitored with TLC and $^{31}P\{^{1}H\}$ NMR, and all fractions containing the diphosphine were dried *in vacuo*. The entire process yielded a white crystalline solid.

IR (KBr cm^{-1}): 1550 (C=C st.), 1285 (β C-H), 1007 (β C-H), 869 (γ C-H), 741 (γ C-H).

$^{31}P\{^{1}H\}$ NMR (298K, C_6D_6): -32.7, -33.3 (R*,R*-(±)/R*,S*).

^{1}H NMR (298K, C_6D_6): 1.89 (m, 2H, P-C*H*H bridging chain), 2.00 (m, 2H, P-CH*H* bridging chain), 2.29 (m, 4H, N-C*H*H morpholine), 2.45 (m, 4H, N-CH*H* morpholine), 2.61 (m, 4H, P-CH_2-N), 3.54 (m, 8H, O-CH_2 cycle), 7.39 (m, 6H, ArH), 7,50 (m, 4H, ArH orto).

SYNTHESIS OF HYDROXYMETHYL(DIPHENYL)PHOSPHINE (Ph_2PCH_2OH)

Solid paraformaldehyde (200 mg : 6.66 mmol) was added to diphenylphosphine oil (1 ml : 6.66 mmol) and the reaction mixture was heated at 100-110ºC under vigorous stirring for 30 min. A clear oil was obtained in near quantitative yield.

$^{31}P\{^1H\}$ NMR (298K, $CDCl_3$): -11.7

^1H NMR (298K, $CDCl_3$): 2.55 (br s, 1H, OH), 4.30 (d, 2H, J_{P-H} = 7,96 Hz, CH_2), 7.2-7.4 (m, 10H, ArH).

SYNTHESIS OF 4-ETHYNYLPYRIDINE ($HC{\equiv}C\text{-}C_5H_4N$)

Experimental procedure used for synthesis of 4-ethynylpyridine is based on literature methods [47], but several modifications have been included. Initially, 2.52 g (12.86 mmol) of 4-bromopyridine hydrochloride were dissolved in 10 ml of recently distilled $NHEt_2$. Addition of 1.4 ml (14,33 ml) of 2-methyl-3-butyn-2-ol was followed cooling to 0 ºC in an ice bath. Then 85 mg (0.12 mmol) of $[PdCl_2(PPh_3)_2]$ and 14 mg (0,06 mmol) of CuI were added. After 15 min ice bath was retired. Resulting suspension was stirred all night, while protected from light with tinfoil. Then the suspension had acquired a greenish color and pasty quality, at which point it was dried *in vacuo*. The solid obtained was dissolved in CH_2Cl_2 (25 ml) obtaining an amber solution. Said solution was the washed with H_2O (2 x 10ml). Organic phase was dried with anhydrous $MgSO_4$, filtered and dried *in vacuo*. The solid obtained was filtered through a chromatographic column of silica gel (40 g), and eluted with hexane : ethyl acetate 1 : 4. They were obtained 683 mg of 2-methyl-4-(4-pyridyl)-3-butyn-2-ol (a yellow solid) with 33% yield.

Product obtained was dissolved in 25 ml toluene, and 0.17 g (4,23 mmol) of ground NaOH were added to solution. It was heated at reflux (111ºC) for two hours. The resulting brown solution was filtered from precipitate, and was dried *in vacuo*, obtaining a brown solid. Product was sublimated *in vacuo* (heating 40 ºC), and 164 mg of 4-ethynylpyridine (white crystalline solid) were obtained. Yield was 13%.

IR (KBr cm^{-1}): 3136 (st. C-H), 2095 (st. C≡C*H*), 1592, 1436 and 1404 (C=C, skeletal vibrations).

^1H NMR (298K, $CDCl_3$): 4.01 (s, 1H, C≡CH), 7.35 (d, J(H-H) = 5,8 Hz, 2H, $H_{\beta\text{-py}}$), 8.59 (d, J(H-H) = 5,8 Hz, 2H, $H_{\alpha\text{-py}}$).

SYNTHESIS OF [AuCl(tht)]

The synthesis of [AuCl(tht)] was carried out as in literature [50]. First, 4.65 g (13,69 mmol) of $HAuCl_4$ were dissolved in 8 ml of deoxygenated H_2O and 40 ml EtOH. Solution was orange at this point, and was stirred for 15 min. Then 2.1 ml (23.79 mmol) of tht were added dropwise to the solution, and it was stirred for 30 min. A white precipitate appeared, which was filtered and washed with EtOH. Process yielded 3.07 g of [AuCl(tht)] (70%).

SYNTHESIS OF $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$

In a mixture of THF/MeOH (42 ml, 1:1) 4-ethynylpyridine (150 mg : 1.40 mmol), [AuCl(tht)] (451 mg : 1.40 mmol) and sodium acetate (575 mg : 7.01 mmol) were dissolved. Flask was covered with tin foil to protect reaction mixture from light. After 40 min. the pale-yellow solid in suspension is filtered with a canula, and washed with THF/ MeOH 1:1. Solvent is removed *in vacuo*. Process yielded 280 mg of $[Au(C{\equiv}C\text{-}C_5H_4N)]_n$ (69%).

IR (KBr cm^{-1}): 2123 (st. C≡C*H*).

ABBREVIATIONS

DAPTA	3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane
dcypb	[1,4-bis(dicyclohexylphosphino)butane]
dcypm	[bis(dicyclohexylphosphino)methane]
dppa	[bis(diphenylphosphino)acetylene]
dppb	[1,4-bis(diphenylphosphino)butane]
dppe	[1,2-bis(diphenylphosphino)ethane]
dppf	[1,1'-bis(diphenylphosphino)ferrocene]
dppip	[bis(diphenylphosphino)isopropane]
dppm	[bis(diphenylphosphino)methane]
dppp	[1,3-bis(diphenylphosphino)propane]
GC-MS	Gas Chromatography-Mass Spectrometry
hmppe	[1,2-bis(hydroxymethylphenylphosphino)ethane]
IR	Infrarred
mmppe	[1,2-bis(methylmorpholinephenylphosphino)ethane]
mppe	[1,2-bis(phenylphosphino)ethane]
MS-ESI	Electrospray Ionization Mass Spectrometry
NMR	Nuclear Magnetic Resonance
PTA	l,3,5-triaza-7-phosphaadamantane
py	pyridine
tht	tetrahydrotiophene
triphos	[1,1,1-tris(diphenylphosphinometil)ethane]
TrxP	Tioredoxine reductase

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