Universitat de Girona

Facultat de Ciències

Memòria del Treball Final de Grau

Exploring Oxidant-Free Au(I)-Catalyzed C-Heteroatom Cross-Coupling Reactions under CO Atmosphere

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ABSTRACT

Gold has been always considered a noble metal and traditionally, because of that, it had never been used in catalysis until about two decades ago, when first evidences of catalytic activity of some Au(I) complexes were reported. Since then, gold emerged as a late transition metal capable to catalyze reactions. Throughout the years, Au-based catalysis has experienced a fast growth and nowadays it is a promising field under deep investigation.

Taking inspiration from recently reported oxidant-free Au(I)-catalyzed C-O bond forming cross-coupling reactions and well-known Pd-catalyzed carbonylative cross-coupling reactions, this work wants to be a first approach to undergo oxidant-free gold-catalyzed carbonylative cross-coupling reactions. These reactions were performed using a well studied model aryl halide macrocyclic substrate synthesized in our research group, a variety of O-nucleophiles and catalytic amounts of a Au(I) complex under CO atmosphere. The desired products were not obtained but, in contrast, the corresponding Ar-Nu coupling products were. From a synthetic point of view, it should be pointed out the importance of having synthesized a phenol as a coupling product between the aryl halide substrate and hydroxide in water.

Moreover, in order to test the viability of performing carbonylative cross-coupling reactions using N-nucleophiles in a near future, we wanted to explore first the ability of gold to catalyze C-N bond forming cross-coupling reactions within the same model aryl halide substrate making use of N-nucleophiles. Here we report two N-nucleophiles (cyclohexylamine and *p*-nitroaniline) that did not afford the desired products and a third one (2-pyridone) that did. The corresponding coupling product had already been reported but it was synthesized via Cu(I)/Cu(III) catalysis so, to the best of our knowledge, this is the first time that this product is obtained via Au(I)/Au(III) catalysis within the macrocyclic platform.

The synthesis of the substrates and the catalyst was also carried out. These compounds, together with the products of the catalyzed reactions, were all characterized by ^{1}H-NMR and ESI-MS or ESI-HRMS.

RESUM

L'or sempre ha estat considerat un metall noble i tradicionalment, degut a aquest pensament, no s'havia intentat mai fer-lo servir en catàlisi fins fa unes dues dècades, que és quan van aparèixer les primeres evidències d'activitat catalítica d'alguns complexos d'Au(I). A partir de llavors, l'or ha esdevingut un metall de transició capaç de catalitzar reaccions. Amb el pas dels anys, la catàlisi basada en or ha experimentat un ràpid desenvolupament i avui en dia és un objecte d'estudi prometedor que està sent molt investigat.

Basant-se en reaccions publicades recentment d'acoblament creuat catalitzades per Au(I) lliures d'oxidants externs en què es formen enllaços C-O, així com també en les reaccions ben conegudes d'acoblament creuat carbonilatives catalitzades per pal·ladi, aquest treball vol ser un primer intent de dur a terme reaccions d'acoblament creuat carbonilatives catalitzades per or sense utilitzar oxidants externs. Aquestes reaccions es van dur a terme amb un halur d'aril macrocíclic com a substrat model sintetitzat i ben estudiat pel nostre grup de recerca, diversos O-nucleòfils i quantitats catalítiques d'un complex d'Au(I) en atmosfera de CO. Els productes desitjats no es van obtenir però, en canvi, sí que es van obtenir els corresponents productes d'acoblament Ar-Nu. Des d'un punt de vista sintètic, cal destacar la importància d'haver sintetitzat un fenol com a producte d'acoblament entre l'halur d'aril i hidròxid en aigua.

A més, per tal d'investigar en un futur proper la viabilitat de dur a terme reaccions d'acoblament creuat carbonilatives utilitzant N-nucleòfils, primer va voler investigar la capacitat de l'or de catalitzar reaccions d'acoblament creuat en què es formessin enllaços C-N utilitzant el mateix substrat model i fent servir N-nucleòfils. D'aquests, dos nucleòfils no van ser eficaços (ciclohexilamina i *p*-nitroanilina), en canvi, l'altre que es va utilitzar (2-piridona) sí que va donar el producte d'acoblament esperat. Aquest producte, de fet, ja havia estat sintetitzat anteriorment però mitjançant un cicle catalític de Cu(I)/Cu(III), per tant, segons el nostre coneixement, aquesta ha estat la primera vegada que s'ha obtingut el producte mitjançant una catàlisi de Au(I)/Au(III) fent servir el mateix substrat macrocíclic.

La síntesi dels substrats i del catalitzador també es va dur a terme. Aquests compostos, juntament amb els productes de les reaccions catalitzades, van ser tots caracteritzats per ^{1}H-RMN i ESI-MS o ESI-HRMS.

RESUMEN

El oro siempre ha sido considerado un metal noble y, por eso, tradicionalmente no se había probado nunca de utilizarlo en catálisis hasta que, hace unos veinte años, aparecieron las primeras evidencias de actividad catalítica de algunos complejos de Au(I). Desde entonces, el oro se ha convertido en un metal de transición capaz de catalizar reacciones. Con el paso de los años, la catálisis basada en oro ha experimentado un rápido desarrollo y hoy en día es un prometedor objeto de estudio que está siendo muy investigado.

Basándose en reacciones publicadas recientemente sobre acoplamiento cruzado catalizadas por Au(I) libre de oxidantes externos donde se forman enlaces C-O, así como en las reacciones bien conocidas de acoplamiento cruzado carbonilativas catalizadas por paladio, este trabajo quiere ser un primer intento de llevar a cabo reacciones de acoplamiento cruzado carbonilativas catalizadas por oro sin utilizar oxidantes externos. Estas reacciones se llevaron a cabo con un haluro de arilo macrocíclico como sustrato modelo sintetizado y bien estudiado por nuestro grupo de investigación, varios O-nucleófilos y cantidades catalíticas de un complejo de Au(I) en atmósfera de CO. Los productos deseados no se obtuvieron pero, en cambio, sí que se obtuvieron los correspondientes productos de acoplamiento Ar-Nu. Desde un punto de vista sintético, cabe destacar la importancia de haber sintetizado un fenol como producto de acoplamiento entre un haluro de arilo e hidróxido en agua.

Además, para poder investigar en un futuro la viabilidad de llevar a cabo reacciones de acoplamiento cruzado carbonilativas utilizando N-nucleófilos, primero se investigó la capacidad del oro de catalizar reacciones de acoplamiento cruzado donde se formasen enlaces C-N utilizando el mismo sustrato modelo y utilizando N-nucleófilos. Los nucleófilos ciclohexilamina y *p*-nitroanilina no fueron eficaces, en cambio, el otro que se utilizó (2-piridona) dio el producto de acoplamiento esperado. Este producto, de hecho, ya había sido sintetizado anteriormente mediante un ciclo catalítico de Cu(I)/Cu(III), por lo tanto, según nuestros conocimientos, ésta es la primera vez que se ha obtenido el producto mediante una catálisis de Au(I)/Au(III) utilizando el mismo sustrato macrocíclico.

La síntesis de los sustratos y del catalizador también se llevó a cabo. Estos compuestos, junto con los productos de las reacciones catalizadas, fueron todos caracterizados por ^{1}H-RMN y ESI-MS o ESI-HRMS.

LIST OF ABBREVIATIONS

AcOEt	Ethyl acetate
AcOH	Acetic acid
Ar	Aryl
calcd	Calculated
°C	Degree Celsius
DCM	Dichloromethane
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dt	Doublet of triplets
DMSO-d_6	Deuterated dimethyl sulfoxide
δ	Chemical shift
ΔG	Change in the Gibbs free energy
equiv.	Equivalent
ESI	Electrospray Ionization
ESI-MS	Electrospray Ionization Mass Spectrometry
ESI-HRMS	Electrospray Ionization High Resolution Mass Spectrometry
EtOH	Ethanol
g	Gram
h	Hour
^{1}H-NMR	Proton Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IPr	N,N’-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant
K	Kelvin
m	multiplet
M	Molar
mM	Millimolar
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mmol	Millimol
MS	Mass Spectrometry
µL	Microliter
m/z	Mass/charge
NBS	N-bromosuccinimide
Nu	Nucleophile
PhOH	Phenol
rt	Room temperature
s	singlet
t	triplet
td	triplet of doublets
TMB	1,3,5-trimethoxybenzene

1. INTRODUCTION

1.1. The importance of catalysis

The term “catalysis” was introduced for the first time in a report published by the Swedish chemist J. J. Berzelius in 1836.[1] Since then, catalytic phenomena started to be a topic of interest and to be more and more studied. Knowledge on catalysis has been increasing throughout the years but it is still a promising world to be exploited. It is especially of a great importance in organic, inorganic and organometallic chemistry.

Nowadays, we can find catalysis in many industrial processes. It is so widespread that about 90% of the manufactured chemicals are synthesized by a route where at least one step is catalyzed.

But what makes catalysis so interesting?

Catalysts are currently described as substances that increase the reaction rate because they make the reaction take place through a pathway made up of elemental reactions that has a low activation energy compared to that of the non-catalyzed reaction, and, in addition, they do not modify the ΔG of the reaction. The use of catalysts has several advantages apart from those included in the definition. One of them is that catalysts let us carry out reactions in a greener way compared to conventional methods, therefore catalysis is sustainable. This means that, thanks to catalysts, reactions with high atom economy can be performed, less residues are generated, less energy is consumed and lower amounts of solvents are needed.

Another advantage is that catalysts might be highly selective, so an important application of this feature is the obtention of value added chemicals in an easy way.

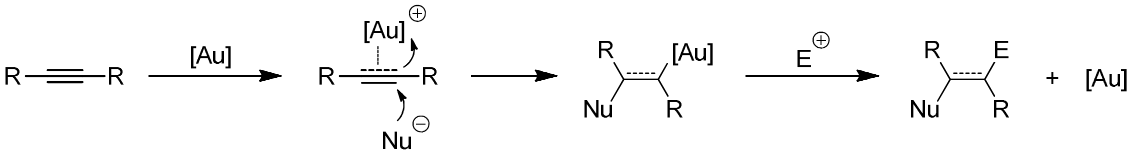
Moreover, catalysis enable the performance of reactions that otherwise, with stoichiometric reactants, would not be possible. Besides, once the products are formed, the catalyst is also regenerated and can be recovered. The combination of the elemental reactions that convert reactants into products accompanied with the regeneration of the catalyst is known as the catalytic cycle.

The advantage of catalytic cycles compared to stoichiometric reactions is that one molecule of catalyst can convert many molecules of reagent into products. So, little amount of catalyst (<20 mol %) is enough to promote the reaction. However, since a catalytic cycle involves many steps and intermediates the study of the mechanism of the global reaction is challenging and part of the investigation process is dedicated to its understanding.

Catalysts are commonly classified depending on the number of phases in which the catalyzed reaction takes place, although they can as well be classified depending on their nature or on the type of the catalyzed reaction. Homogeneous catalysts are those that are in the same phase as reactants (generally in solution) and heterogeneous catalysts are those that are found in a different phase (they are normally solid and the reactants are found in solution or in gas phase). This work is an example of homogeneous catalysis using a transition metal complex as a catalyst, in particular, a gold complex.

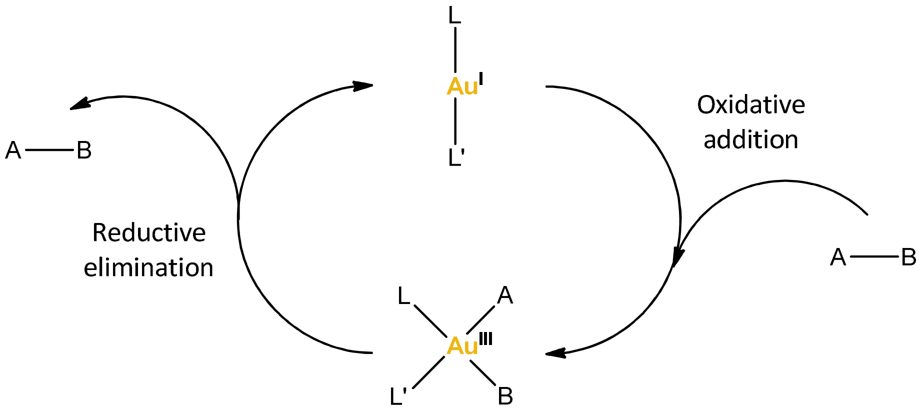
1.2. Gold(I) homogeneous catalysis

Traditionally, gold complexes were considered inactive species in catalysis. However, it was in the late 1990s when some catalytic activity was discovered.[2] At that time, it was thought that gold catalysis could occur thanks to the Lewis acid character of both Au(III) and Au(I) complexes. It was observed that they were highly carbophilic species that could activate C-C multiple bonds towards nucleophilic attacks.[3,4] So, at the beginning, gold catalysis was limited to π-activation chemistry in which the oxidation state of the metal does not change throughout the catalytic cycle (Scheme 1.1). It should be also pointed out that the interest and applicability of gold complexes has benefited from its moisture and air-stability.



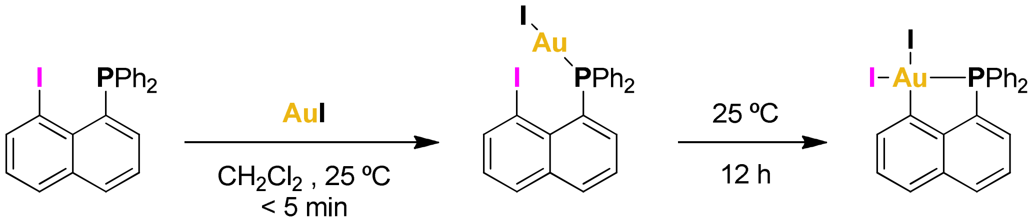
Scheme 1.1. General mechanism for the π-activation chemistry of gold.

Since then gold catalysis has evolved greatly during the past decades. In order to gain insight into the reactivity of gold beyond π-activation, 2-electron redox chemistry for gold complexes started to be investigated. This is a well-known chemistry of other late transition metals such as palladium, copper and nickel. Moreover, many catalytic cycles include elementary steps that require a metal centre able to undergo 2-electron redox transformations, that is, oxidative addition and reductive elimination (Scheme 1.2). Whilst nowadays there are extensive reports on the ability of Au(III) complexes to undergo reductive elimination,[5-7] the oxidative addition step has long been questioned.[8] Regarding that, several studies were carried out in order to obtain Au(III) complexes by an oxidative addition to a Au(I) complex. To date, oxidative addition of Au(I) in C(sp^3)-X bonds, C(sp^2)-X bonds and apolar σ-bonds such as Sn-Sn and Si-Si bonds has been achieved.[2]



Scheme 1.2. General scheme of oxidative addition and reductive elimination.

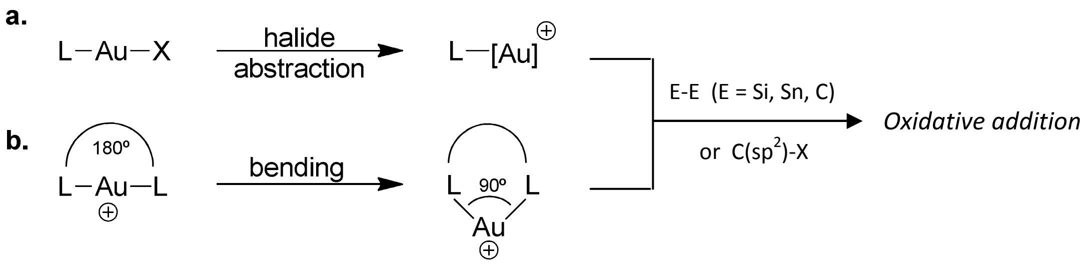
In 2014, Bourissou and co-workers provided evidence of the first oxidative addition of a C(sp^2)-X bond to a Au(I) center. They took advantage of the phosphine chelation assistance to obtain stable (P,C) cyclometalated gold (III) complexes (Scheme 1.3).[9]



Scheme 1.3. Coordination of the 8-iodo naphtyl phosphine to Au(I) followed by intramolecular oxidative addition of a C(sp^2)-I bond.

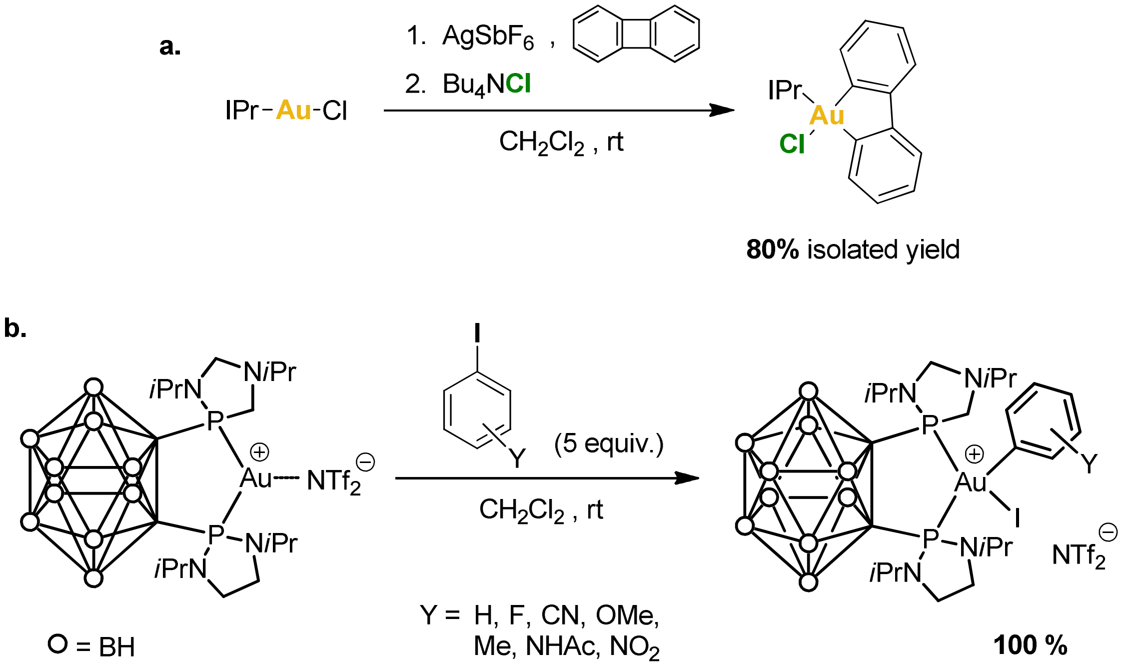
Thanks to this intramolecular chelation-assisted strategy, oxidative addition of apolar σ-bonds to Au(I) is also feasible.[10]

On the other hand, in order to trigger the reactivity of neutral ligand-quelated Au(I) complexes and achieve intermolecular oxidative addition, two strategies have been explored in the recent years: (I) The generation of highly electrophilic cationic monocoordiante species by halide abstraction (Scheme 1.4a), and (II) the design of bent dicoordinating ligands with the aim of reducing the deformation energy required in the activation process (Scheme 1.4b).



Scheme 1.4. Approaches to favour the oxidative addition to a Au(I) complex with no external oxidants.

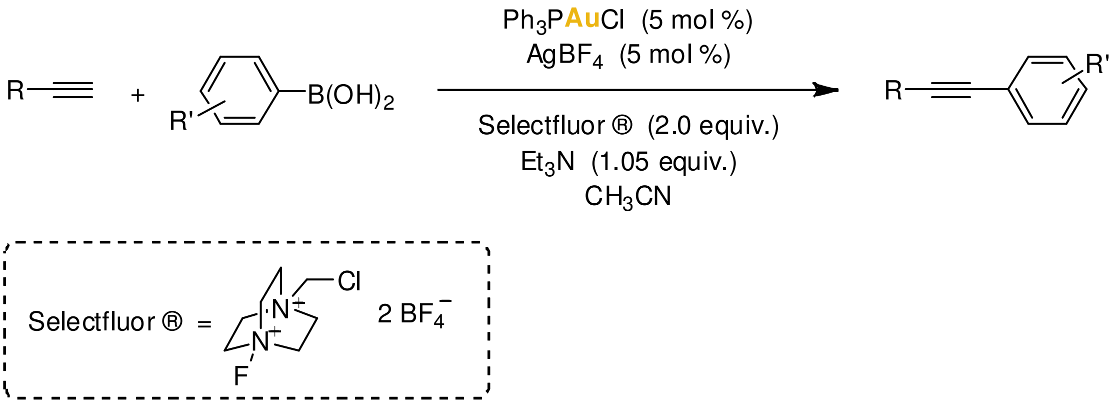
Following the first approach, Toste and co-workers reported the activation of C-C strained bonds in biphenylene after halide abstraction[11,12] (Scheme 1.5a), whereas Bourissou and co-workers took advantage of the ability of carborane diphosphines to chelate Au(I) with small P-Au-P bite angles.[13] The ensuing complex reacts readily with aryl iodides to form stable Au(III) complexes (Scheme 1.5b).



Scheme 1.5. a) Synthesis of a stable Au(III) complex via oxidative addition to a monocoordinate Au(I) complex. b) Oxidative addition of aryl iodides to a bent Au(I) complex.

Making use of these two strategies, stable Au(III) complexes have been obtained. However, despite the increasing number of works on the oxidative addition to gold(I) complexes, the implementation of 2-electron redox reactivity in a catalytic fashion remained a challenge until very recently.

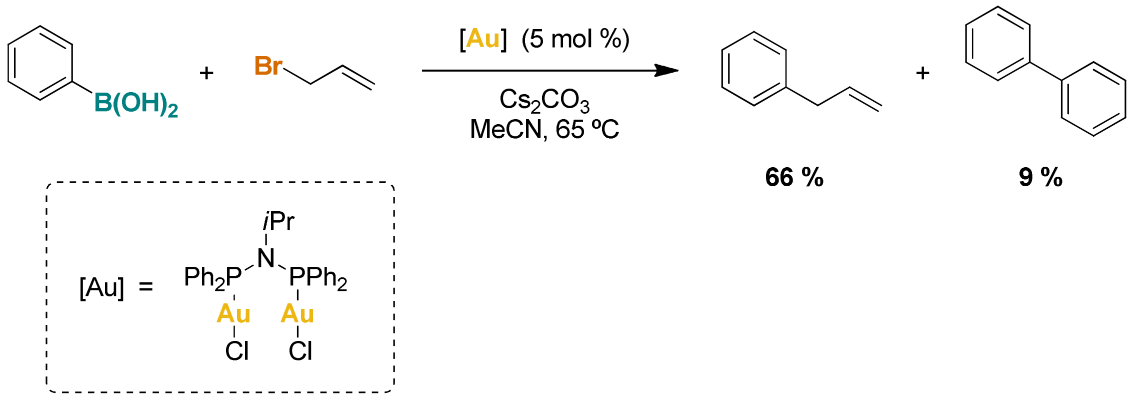
Since the redox potential of the Au(I)/Au(III) couple is very high ($E^0 = 1.41$ V)[14] compared to that of the isoelectronic Pd(0)/Pd(II) couple, the oxidation of Au(I) to Au(III) species in catalytic transformations has been usually promoted by the addition of stoichiometric amounts of strong external oxidants such as F^+ or I^{3+} sources.[2] By means of this strategy several cross-coupling reactions catalyzed by gold instead of palladium have been described[15,16] (Scheme 1.6).



Scheme 1.6. Au(I)/Au(III)-catalyzed Sonogashira coupling reaction of functionalized terminal alkynes with arylboronic acids under mild conditions.

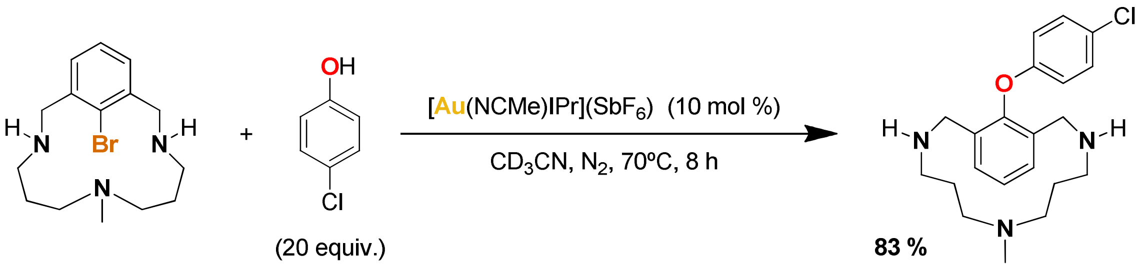
The use of strong oxidants to access a high-valent metal limits the functional group tolerance,[12] so the possibility of undergoing cross-coupling reactions in their absence has been investigated since 2014.

Toste and co-workers reported in 2014 a Suzuki cross-coupling reaction catalyzed by gold (I) complexes (Scheme 1.7).[17]



Scheme 1.7. Suzuki cross-coupling reaction catalyzed by gold.

In addition, Serra *et al.* reported in 2015 oxidant-free Au(I)-catalyzed halide exchange and C(sp^2)-O bond forming cross-coupling reactions using a model aryl halide substrate (Scheme 1.8).[18]



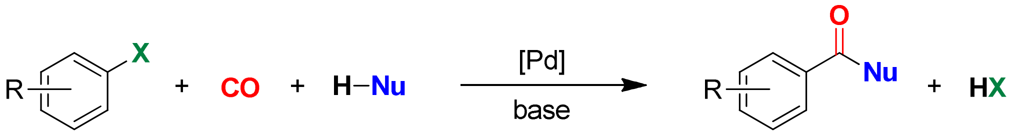
Scheme 1.8. C(sp^2)-O bond forming cross-coupling reaction catalyzed by gold.

In previous studies, this model aryl halide substrate had proved very useful in assisting the stabilisation of high-valent Cu(III) and Ag(IIII) species by chelation. Within this model system, two-electron Cu(I)/Cu(III) and Ag(I)/Ag(III) oxidative addition and reductive elimination steps were validated, and moreover the system also showed catalytic efficiency in C-C and C-heteroatom cross-coupling reactions.[19-21] In contrast, regarding the Au(I)-catalyzed reactions using the same substrate, Au(III) intermediates could not be seen. It is known that Au(III) species adopt a square-planar geometry, which cannot be properly stabilized by the macrocyclic environment. Despite that, the halide exchange and C(sp^2)-O bond forming cross-coupling reactions could be also performed using 2-(2-haloaryl)pyridines as substrates, suggesting that a single chelating group is enough for the catalysis to proceed.

1.3. Carbonylation reactions

Carbonylation reactions are those that incorporate a carbonyl moiety into a molecular structure. The use of carbon monoxide gas as a reactant has not been deeply studied maybe due to its high toxicity. Nevertheless, it seems to be a promising topic as it could be used as a C1 building block in new synthetic routes. In addition, since CO is commonly regarded as a waste gas, its re-utilization for synthetic protocols makes the carbonylation reaction a sustainable process.

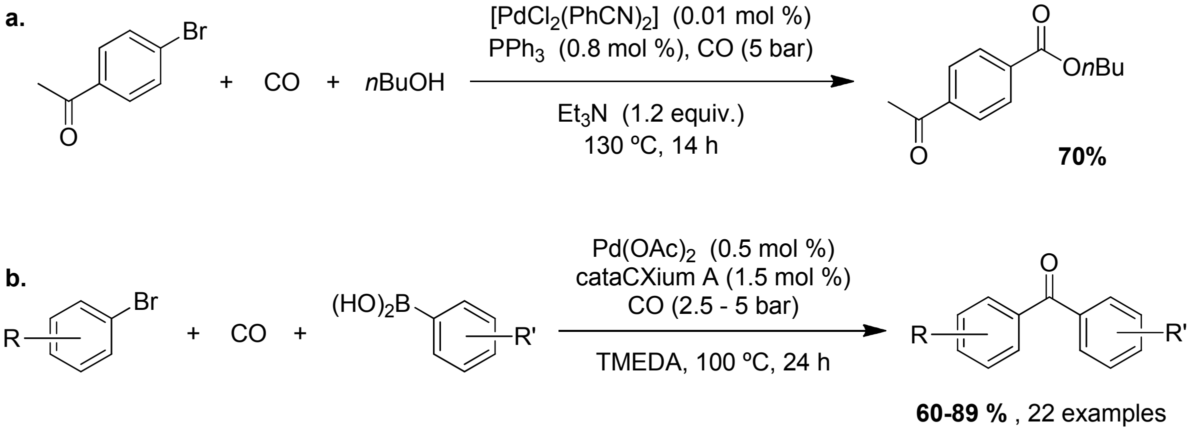
Since Heck and co-workers reported for the first time palladium-catalyzed carbonylation reactions of aromatic halides in the presence of nucleophiles in 1974,[22,23] carbonylation reactions have experienced a fast development and, nowadays, several palladium catalysts are known to undergo a variety of carbonylations. In order to perform this kind of reaction, the substrate, which is generally an aromatic halide, is treated under a CO atmosphere with a nucleophile and catalytic amounts of a palladium complex (Scheme 1.9).



X = Cl, Br, I, OSO_2R', N_2^+,...
Nu = OH, OR', NR'R'',...

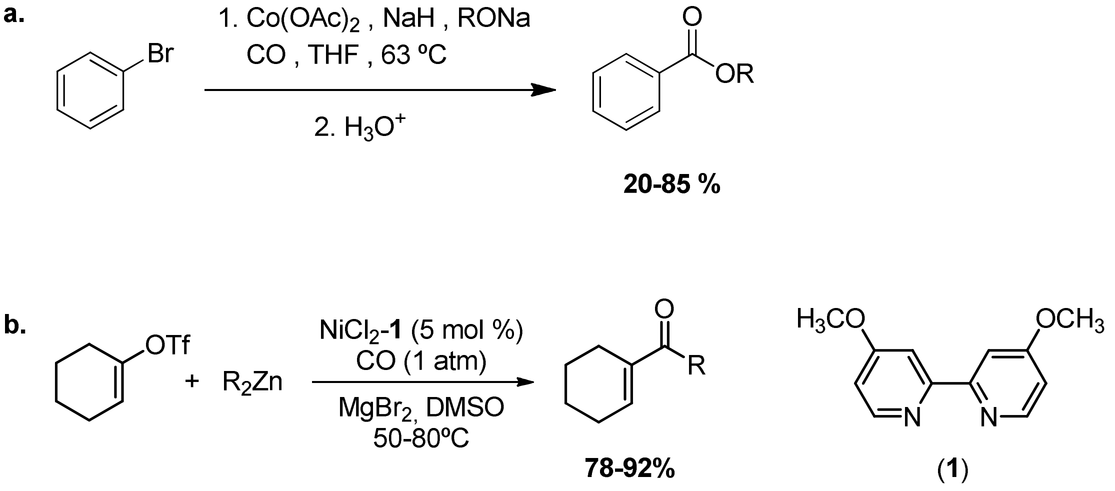
Scheme 1.9. General carbonylative coupling reaction between an aryl halide and a nucleophile.

The advantage of such carbonylative transformation is that many different products can be synthesized from the same substrate only by changing the nucleophile. For instance, Beller and co-workers reported in 2009 a review[24] in which several palladium-catalyzed carbonylation reactions afford different types of compounds such as carboxylic acid derivatives (esters and amides), carboxylic acids, ketones, aldehydes and carbonylative Suzuki and Sonogashira coupling products (Scheme 1.10). A very interesting application of these carbonylative cross-coupling reactions is the synthesis of symmetrical and unsymmetrical ketones.



Scheme 1.10. a) Palladium-catalyzed butoxycarbonylation of 4-bromoacetophenone.[25] b) Synthesis of diarylketones via Suzuki carbonylative coupling reaction.[26]

Aside from palladium, carbonylative cross-coupling reactions have also been transferred to cobalt and nickel (Scheme 1.11).[27,28] However, there are very few examples concerning these two metals and no mechanistic data is known for them.



Scheme 1.11. a) Carbonylative cross-coupling reaction catalyzed by a cobalt complex. b) Negishi reaction between an enol triflate and diorganozinc reagents under carbon monoxide atmosphere which affords α,β-unsaturated carbonyl compounds.

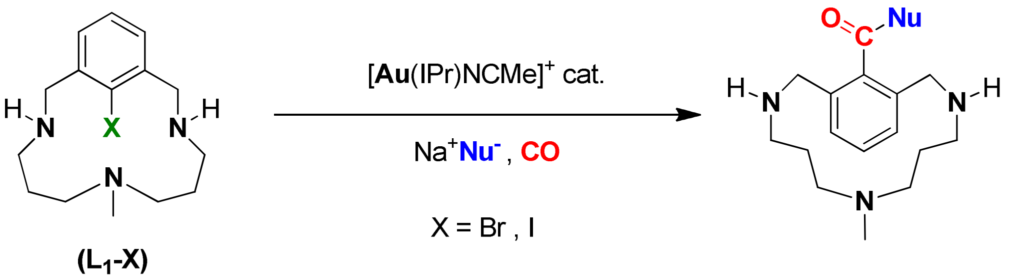
2. OBJECTIVES

As it has been said in the introduction, over the past five years the ability of gold complexes to undergo the elementary steps of the organometallic chemistry (the oxidative addition and the reductive elimination) has been evidenced, and Au(I)-catalyzed cross-coupling reactions without external oxidants have already been achieved using gold (I) catalysts. It should be again highlighted that this is a hot topic for its novelty, because cross-coupling reactions are very important in organic synthesis and because gold can now be considered as another late transition metal capable to catalyze a cross-coupling reaction.

Moreover, we have seen that carbonylative cross-coupling reactions, which are mainly catalyzed by palladium complexes, give access in a green way to a huge variety of compounds from aryl halide substrates only by changing the nucleophiles and performing the reaction under carbon monoxide atmosphere.

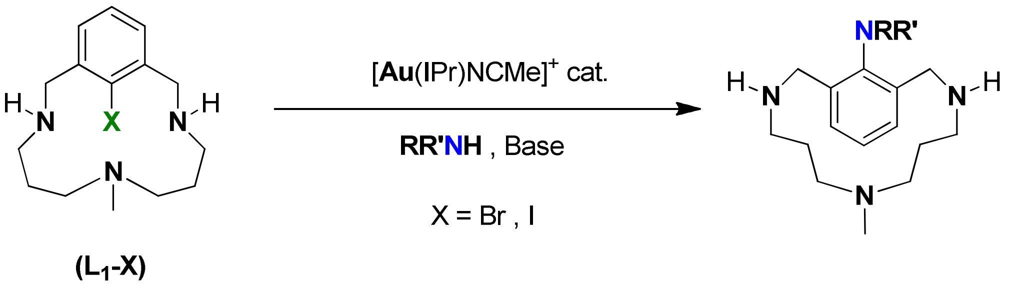
Thus, the aim of this work is to explore the ability of Au(I) complexes in performing carbonylative cross-coupling catalysis. For this purpose, we will use as platform the model aryl halide macrocyclic substrate synthesized in our research group, which has been successfully used in the previous studies on oxidant-free Au(I)-catalyzed transformations.[18]

Taking inspiration from this study reported by Serra *et al.*, the experimental approach will be focused on performing the carbonylative cross-coupling reactions using the aryl halide model macrocyclic substrate and a variety of O-nucleophiles under CO atmosphere in order to generate the corresponding esters or carboxylic acids (Scheme 2.1).



Scheme 2.1. Hypothetic Au(I)-catalyzed carbonylative cross-coupling reaction expected to be carried out.

Furthermore, we will also explore the possibility of expanding the scope of heteroatom nucleophilles within model macrocyclic substrates, focusing on Au(I)-catalyzed C(sp^2)–N bond-forming reactions using different N-nucleophiles such amines or amides (Scheme 2.2). These reactions will be carried out as a previous step before attempting carbonylative cross-coupling reactions using N-nucleophiles.

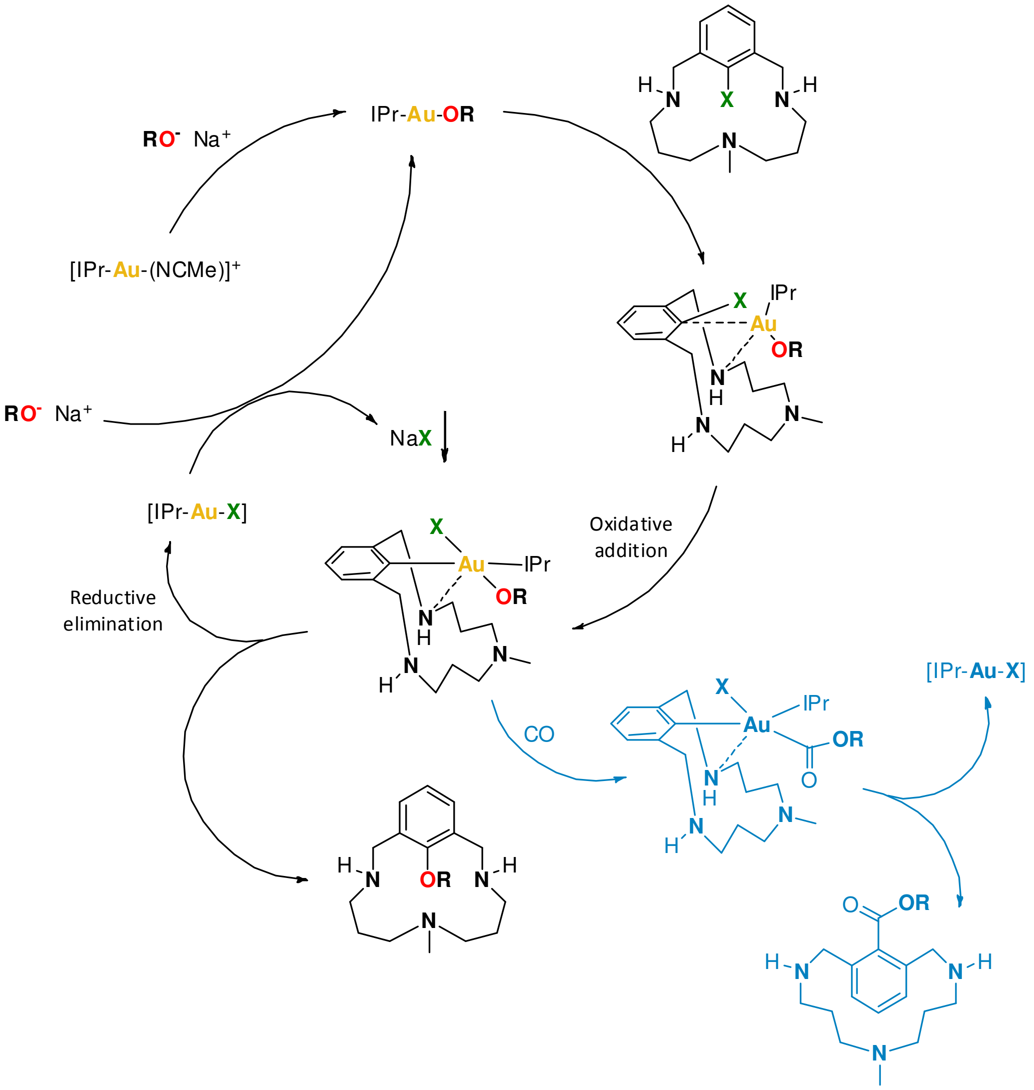


Scheme 2.2. Hypothetic Au(I)-catalyzed C(sp^2)-N bond forming cross-coupling reaction expected to be carried out.

3. RESULTS AND DISCUSSION

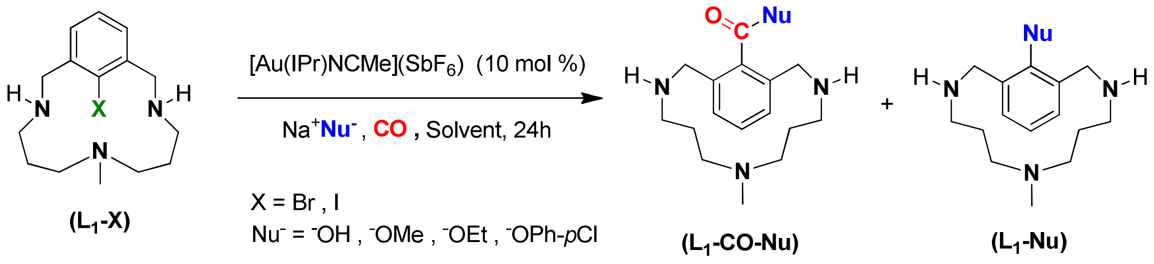
3.1. Carbonylative cross-coupling reactions using L_1-X and O-nucleophiles

In order to explore the ability of gold to undergo carbonylative cross-coupling reactions, we first aimed at screening the reaction conditions that play a role in this transformation: the temperature, the CO pressure, the solvent and the nature of both the substrate and the nucleophile. Carbonylative cross-coupling reactions were envisioned to occur through a variation of the Au(I)/Au(III) catalytic cycle previously proposed in our group (Scheme 3.1).[18]



Scheme 3.1. In black, catalytic cycle suggested by Serra *et al.*[18] for Au(I)-catalyzed C-O bond forming reactions. In blue, suggested variation of the cycle supposed to occur for carbonylative cross-coupling reactions.

Thus, a first attempt to achieve carbonylative coupling products was carried out employing a series of O-nucleophiles in the corresponding sodium salt form (Scheme 3.2).



Scheme 3.2. Expected reaction to obtain carbonylative coupling products using O-nucleophiles.

The reaction crudes were subsequently analyzed by both ^{1}H-NMR and MS experiments.

Table 3.1. Results of the reactions employing O-nucleophiles.

Entry	L_1-X	Na^+Nu^- (equiv.)	T (°C)	P_{CO} (bar)	Solvent	% yield L_1-CO-Nu	% yield* L_1-Nu	% starting material
1	L_1-Br	*p*Cl-PhONa (2.0)	40	5	CD_3CN	0	<99	0
2		*p*Cl-PhONa (2.2)	rt	5	CD_3CN	0	29[a]	71[a]
3		NaOEt (3.2)	40	10	EtOH	0	31[c]	30[c]
4		NaOMe (2.7)	40	10	MeOH	traces[d]	73	0
5		NaOH (1.7)	40	10	H_2O	0	0	<99
6	L_1-I	*p*Cl-PhONa (1.8)	rt	10	CD_3CN	0	37[b]	63[b]
7		NaOEt (2.7)	rt	10	EtOH	0	9	69
8		NaOMe (2.8)	rt	10	MeOH	traces[d]	66	10
9		NaOMe (2.4)	rt	20	MeOH	traces[d]	29	45
10		NaOH (2.0)	70	10	H_2O	0	70[e]	20[e]
11		NaOH (2.0)	90	0	H_2O	0	61[f]	-[g]

[*] Yield calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [a,b] Relationship of products in the crude. [c] Presence of ligand L_1-H as a side product in 2% yield. [d] Confirmed by ESI-MS. [e] Relationship of products in the crude. Presence of ligand L_1-H as a side product in 10% proportion. [f] Yield calculated from the mass obtained. The product's purity was around 86% as the other 14% corresponded to L_1-H. [g] Not measured.

Regarding the reaction using sodium *p*-chlorophenolate, the carbonylative coupling product L_1-CO-OPh-*p*Cl was not observed, while the coupling product L_1-OPh-*p*Cl without the insertion of CO was exclusively formed. When using L_1-Br as substrate (Table 3.1, entries 1 and 2), the role of temperature is reflected because whereas the reaction is completed at 40°C, at room temperature there is starting material still remaining in the crude after 24h. At room temperature, the conversion was almost maintained when L_1-I was used as substrate instead of L_1-Br , despite a weaker C-I bond. It must be highlighted that the conditions used in Table 3.1, entry 1 improve the yield of the coupling product compared to those reported by Serra *et al.*[18] (see Scheme 1.8).

For those reactions where sodium ethoxide was used as nucleophile, both the coupling product L_1-OEt and the starting material were found in the crude. When L_1-Br was the substrate and the reaction mixture was heated at 40°C, more coupling product seemed to be formed than when the substrate was L_1-I and the reaction took place at room temperature.

The two reactions performed with sodium methoxide at 10bar (Table 3.1, entries 4 and 8) gave the corresponding coupling product L_1-OMe and, surprisingly, when ESI-MS for both crudes was performed, a tiny peak at m/z=306.1 was observed, which may correspond to the [M+H$^+$] peak of the carbonylative coupling product L_1-CO-OMe (Figure 3.1). Having these results in hand, we decided to repeat the reaction with L_1-I but increasing the CO pressure up to 20bar (Table 3.1, entry 9). With this change, we wanted to explore if a higher concentration of CO would help optimizing the carbonylative reaction. Unfortunately, the reaction afforded less coupling product and the peak at m/z=306.1 remained very small. This result suggests that high concentrations of CO not only fail at enhancing the carbonylation reaction, but also are detrimental to the catalytic methoxide insertion.

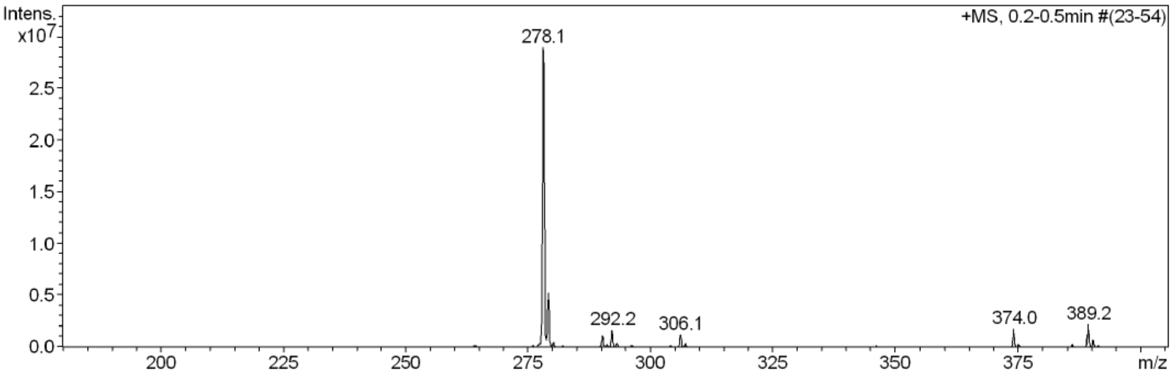


Figure 3.1. Mass spectrum of the crude reaction mixture corresponding to the reaction between L_1-I and NaOMe at 10 bar of CO pressure. m/z [IPr$^+$] =389.2, m/z [L_1-I + H$^+$] =374.0, m/z [L_1-COOMe + H$^+$] =306.1, m/z [L_1-OMe + H$^+$] =278.1. The peak at m/z = 292.2 seems to belong to [L_1-OEt + H$^+$], which was found in the previous analyzed sample.

In order to prove that the peak at m/z=306.1 corresponds to the carbonylative coupling product, a MS-MS of it was performed. It fragmented losing the mass of CO, 28, to give the peak at m/z=278.1, which corresponds to the mass of L_1-OMe + H^+, and several more that coincided with the fragmentation peaks of the MS-MS analysis of the m/z=278.1 peak (Figure 3.2). The facile loss of the CO moiety under ESI conditions seems to exclude the insertion and points towards the formation of a labile adduct between L_1-OMe and CO.

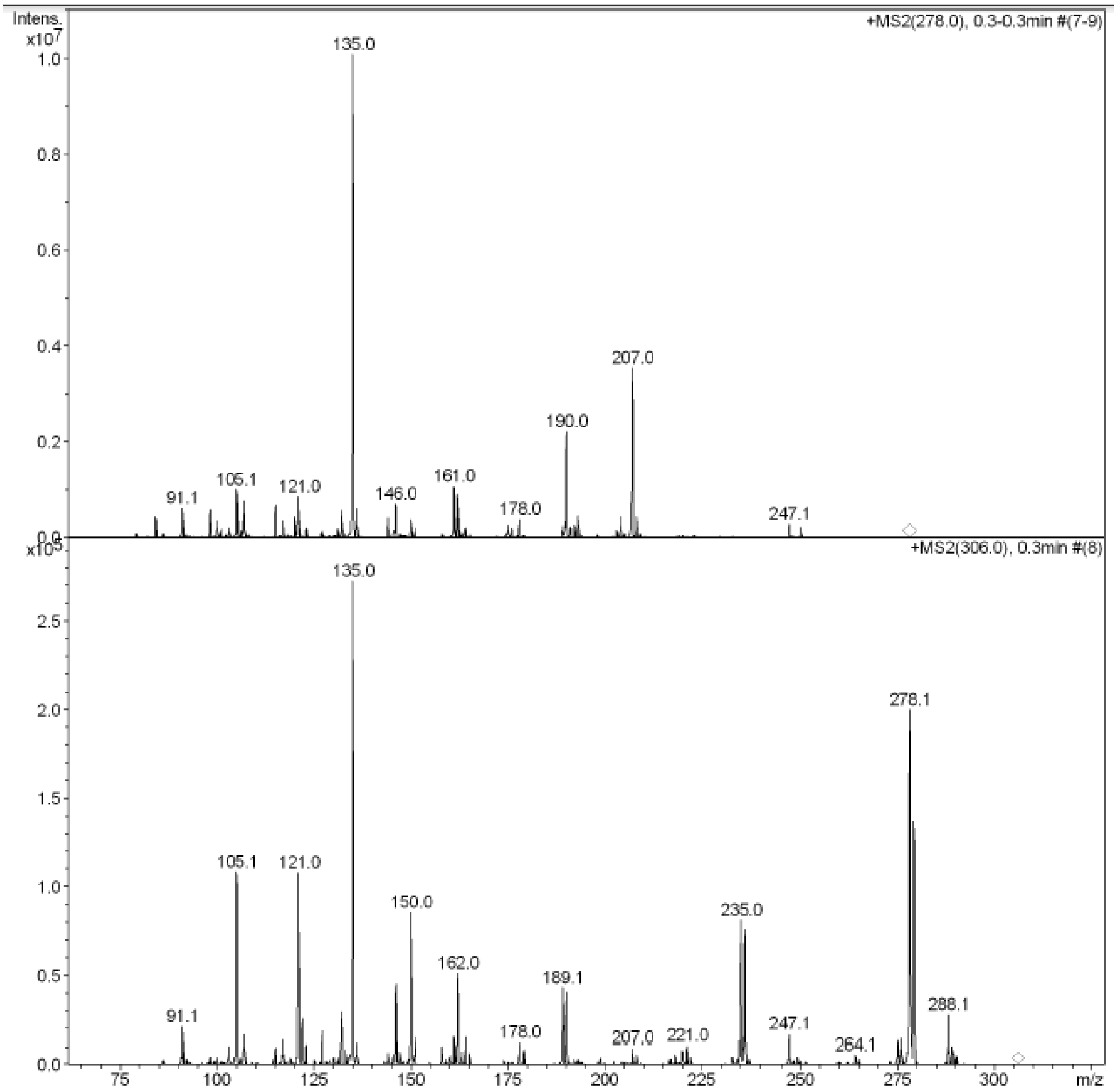


Figure 3.2. MS-MS analysis of the peaks at m/z =278.0 and m/z = 306.0 obtained in the mass spectrum of the reaction between L_1-Br and NaOMe. The fragmentation of both peaks is similar, suggesting that the carbonylative coupling product loses the CO moiety giving L_1-OMe plus the fragmented species that comes from the latter.

A ESI-HRMS of the crude of the reaction with L_1-I (Table 3.1, entry 8) was performed so as to corroborate that the m/z of the observed peak at 306.1 is exactly the expected for the carbonylative coupling product. The theoretical peaks coincided with the obtained experimentally (Figure 3.3).

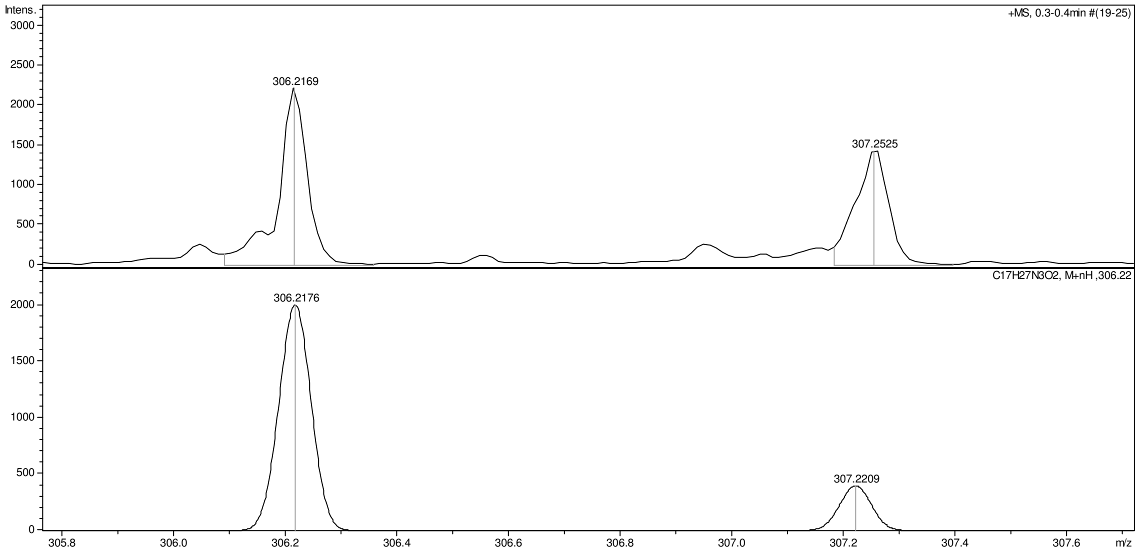


Figure 3.3. Coincidence between the peaks of the experimental mass spectrum (upper figure) and the theoretical peaks for the [$M+H^+$] carbonylative coupling product species (lower figure).

In order to have further information about whether the carbonylative coupling product was formed, a new reaction was performed at 40°C for 24h using L_1-Br, [Au(IPr)NCMe](SbF_6) (10 mol %) , sodium acetate (2.1 equiv.) as O-nucleophile and 0.5 mL glacial acetic acid as solvent in the absence of CO atmosphere. The aim of performing this reaction was to compare how the peak of the coupling product L_1-OAc fragmented relative to the fragmentation of the supposed carbonylative coupling product of L_1-CO-OMe, as both compounds have the same mass with different structures. By ESI-MS, a tiny peak at m/z=306.0 was observed corresponding to the coupling product L_1-OAc + H^+. The MS-MS of it was performed and fragmented differently (Figure 3.4). The peak corresponding to the loss of the acetate moiety was observed but the loss of CO was not.

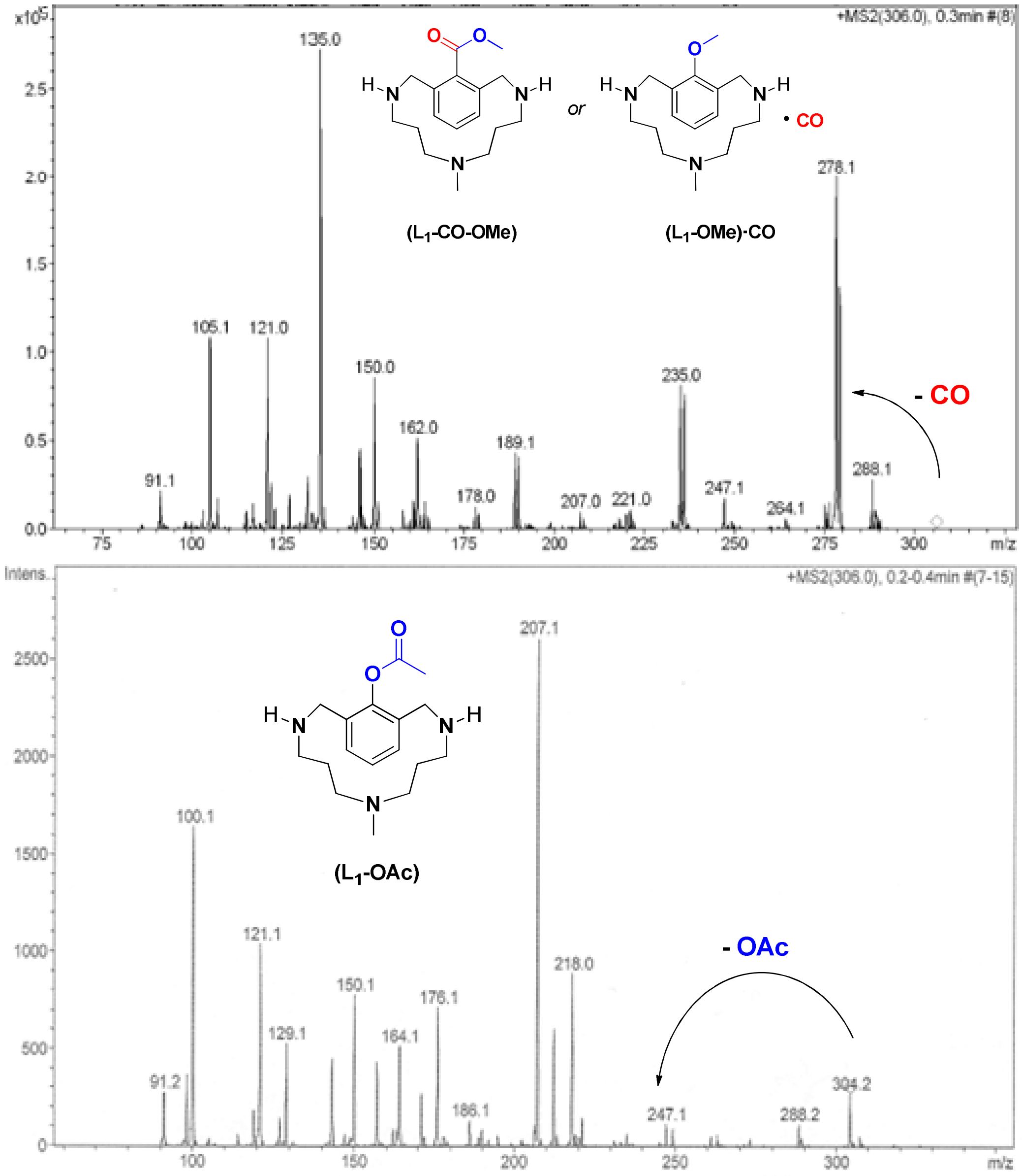


Figure 3.4. MS-MS analysis of the peaks at m/z = 306.0 corresponding to the supposed [L_1-CO-OMe + H^+] (upper spectrum) and the [L_1-OAc + H^+] (lower spectrum).

After trying to obtain information of the presumed carbonylative coupling product L_1-CO-OMe formation, this product is not likely to be formed because no evidences of getting the L_1-CO-Nu product have been seen for the rest of O-nucleophiles and because losing the CO moiety of an ester in a MS-MS analysis is quite strange, as this phenomenon is not observed for the L_1-OAc product. Further studies should be done to better characterize the species that gives a m/z = 306.1. Up to here, we can affirm that this species is not L_1-OAc as the mass spectrum is different, so we purpose that it should be an adduct between L_1-OMe and CO.

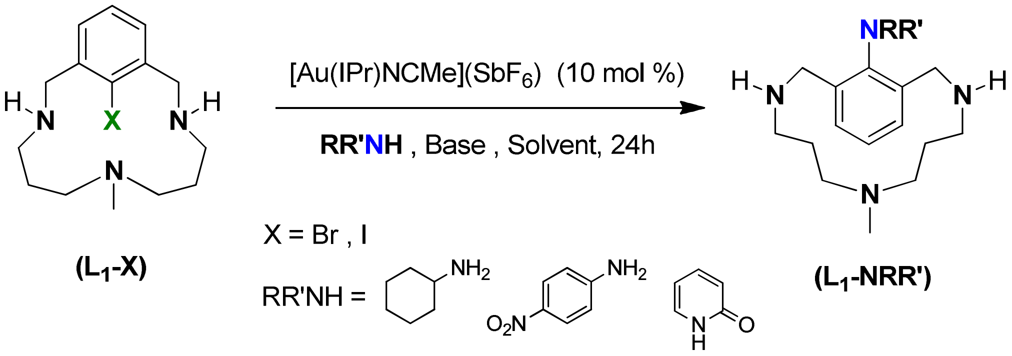
Then we moved on trying to synthesize the carboxylic acid L_1-CO-OH by performing the reaction depicted in Scheme 3.2 but using hydroxide as a nucleophile and water as solvent. No reaction took place when the substrate was L_1-Br at 40°C (Table 3.1, entry 5) as all the starting material was recovered in the crude. Nevertheless, when the temperature was increased and the substrate was changed to L_1-I (Table 3.1, entry 10), the coupling product L_1-OH was obtained. In this case, the influence of temperature and the ligand is obvious as the C-halogen bond is easier to break in L_1-I and temperature helps to achieve the transition state of the catalysis. The formation of the phenol L_1-OH in water represents a notorious advantage of Au(I) catalysis compared to Cu and Ag. Unreported studies done in our group reveal that L_1-OH cannot be synthesized using Cu or Ag catalysts due to the high basicity of the $^{-}$OH anions and the sensitivity of copper and silver towards water. L_1-OH was obtained as a novel coupling product, so it should be highlighted that a new method of synthesizing phenols has been discovered taking advantage of gold catalysis.

Pursuing the synthesis of L_1-OH in larger quantities, it was synthesized again in the absence of CO pressure (Table 3.1, entry 11) in order to be able to crystallize and characterize it by X-Ray Diffraction. The crystallization procedure followed was based on the one reported in the literature by Shannon S. Stahl and co-workers.[29] Unfortunately, the product did not crystallize so a work-up was carried out in order to obtain a good ^{1}H-NMR spectrum. Before adding $CDCl_3$ to do the resonance, the product was dried to know the mass and know the yield.

In addition, it should be pointed out the fact that some reactions (Table 3.1, entries 3, 10 and 11) yielded L_1-H as a byproduct, also detected in 2-electron Cu(I)/Cu(III) catalysis, because it suggests the involvement of Au-C_{aryl} intermediate.

3.2. Cross-coupling reactions using L_1-X and N-nucleophiles

Having seen that carbonylative coupling products are not obtained using O-nucleophiles, we focused on C(sp^2)-N bond formation cross-coupling reactions as a previous step to move towards carbonylative cross-coupling reactions with N-nucleophiles. A series of N-nucleophiles was used to test if the Au(I) complex could catalyze such reaction (Scheme 3.3).



Scheme 3.3. Expected reaction to obtain coupling products using N-nucleophiles.

Table 3.2. Results of the cross-coupling reactions employing N-nucleophiles.

Entry	L_1-X	RR'NH (equiv.)	Base (equiv.)	T (°C)	Solvent	% yield L_1-Nu	% starting material
1	L_1-Br	Cyclohexylamine (3.1)	^{t}BuOK (3.2)	70	DMSO-d_6	0	74
2		*p*-nitroaniline (4.1)	^{t}BuOK (4.5)	110	DMSO-d_6	0	67
3	L_1-I	Cyclohexylamine (5.7)	^{t}BuOK (3.0)	70	DMSO-d_6	0	69
4		Cyclohexylamine (5.5)	^{t}BuOK (6.1)	110	DMSO-d_6	0	12
5		*p*-nitroaniline (4.1)	^{t}BuOK (6.3)	110	DMSO-d_6	0	95
6		2-pyridone (4.2)	-	110	DMSO-d_6	100[a]	0[a]
7		2-pyridone (4.1)	-	110	DMSO-d_6	26[b]	-[c]

[a]Relationship of products in the crude. [b] Isolated yield. [c]Not measured.

^{1}H-NMR analysis of the reactions of L_1-Br and L_1-I using cyclohexylamine (Table 3.2, entries 1 and 3), indicated that the desired coupling product was not formed. ESI-MS confirmed the results since the two main peaks obtained corresponded to the L_1-Br or L_1-I and cyclohexylamine. Thus, we tried to increase the temperature to set some conversion using L_1-I as starting material (Table 3.2, entry 4). However, the reaction did not afford the coupling product either.

Unpublished studies carried out in our research group by Serra *et al.*[30] demonstrated that the acidity of the nucleophiles plays a key role in determining the reactivity trend they have. It was observed that more acidic nucleophiles give higher yields for the C-N cross-coupling reactions.

Therefore, *p*-nitroaniline was used under the same conditions for both L_1-Br and L_1-I. Since *p*-nitroaniline is an arylamine with a strong electron-withdrawing group in *para*-position, it is more acidic than cyclohexylamine. Thus, it should be expected to have better yields than the ones obtained with cyclohexylamine. Unfortunately, the corresponding coupling product was not obtained for any of the reactions (Table 3.2, entries 2 and 5).

Finally, 2-pyridone, an even more acidic N-nucleophile, was used. In this case, the nitrogen atom is part of a cyclic amide. 2-pyridone is in equilibrium with its tautomer 2-hydroxypyridine, so the presence of base was not required because nitrogen is already partially deprotonated. To our delight, this time the coupling product was obtained. A peak of the $[M+H^+]$ species of the coupling product was seen by ESI-HRMS at m/z=341.2346 and no starting material was found.

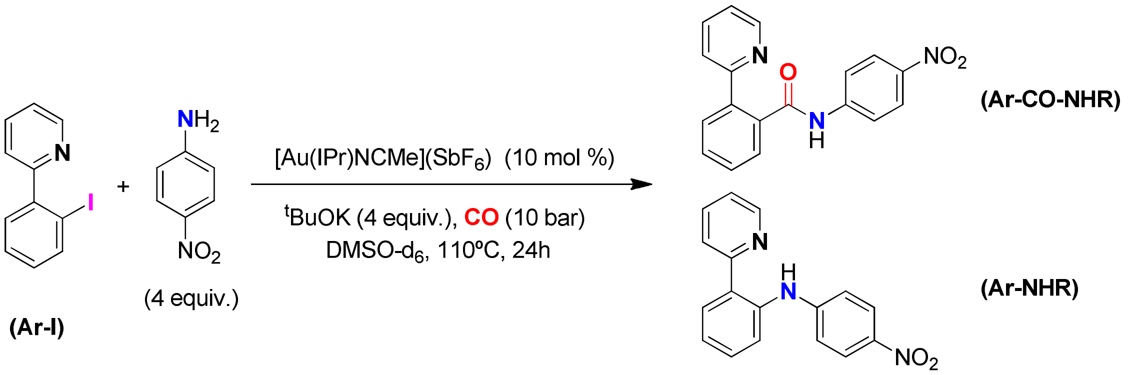
Catalyzed by Au(I) cross-coupling reactions between L_1-X and the N-nucleophiles tested did not afford the desired coupling products, with the exception of 2-pyridone. This is in agreement with the reactivity trend determined by the acidity of the nucleophiles (pK_a = 20.9 and 17.0 in DMSO for *p*-nitroaniline and 2-pyridone respectively).[31]

On the other hand, the product L_1-pyridone had already been synthesized taking advantage of copper catalysis and characterized.[20] However, in this work it has been demonstrated that this product can also be obtained via gold catalysis. Despite that, further optimization should be performed aimed at carrying out the reaction in the presence of base. Like in the case of L_1-OH, L_1-pyridone did not crystallize and X-Ray Diffraction analysis was not possible.

3.3. Attempt to synthesize an amide via carbonylative cross-coupling reaction

Studies made in our research group on Au(I)-catalyzed C-N bond forming cross-coupling reactions[30] demonstrated that *p*-nitroaniline affords the corresponding coupling product in high yields using 2-(2-iodphenyl)pyridine as substrate.

Taking inspiration from these studies, we finally tried to achieve the carbonylative cross-coupling reaction using 2-(2-iodophenyl)pyridine and *p*-nitroaniline (Scheme 3.4) so as to see if it would be a good method for synthesizing amides.

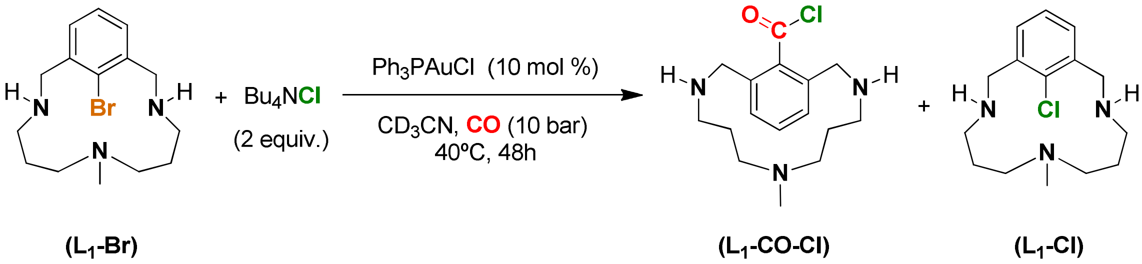


Scheme 3.4. Attempt to perform a carbonylative cross-coupling reaction employing a N-nucleophile.

The ^{1}H-NMR spectrum obtained did not have clear signals in the aromatic region, so ESI-MS was performed in order to identify the species present in the crude. Neither the coupling product nor the carbonylative coupling product were identified. However, little peaks corresponding to the starting material and to the homocoupling product were obtained. Despite this, the results show again that carbonylative cross-coupling reactions catalyzed by gold are unlikely to occur but, since only one reaction was carried out to test the viability of synthesizing amides via a carbonylative cross-coupling reaction, further studies should be carried out in the future regarding that.

3.4. Attempt to synthesize an acid chloride

Finally, a completely different reaction was performed in order to try to insert a CO molecule into the substrate. Based on the Au(I)-catalyzed halide exchange reactions reported by Serra *et al.,*[18] we wanted to make L_1-Br react with tetrabutylammonium chloride (TBACl) in the presence of the commercially available $(PPh_3)AuCl$ catalyst under CO atmosphere to see if an acid chloride could be synthesized (Scheme 3.5). The reason for changing the Au(I) source was the slower rates displayed by $(PPh_3)AuCl$ compared to $[Au(IPr)NCMe]SbF_6$, which might allow the CO moiety to insert between the coupling partners.



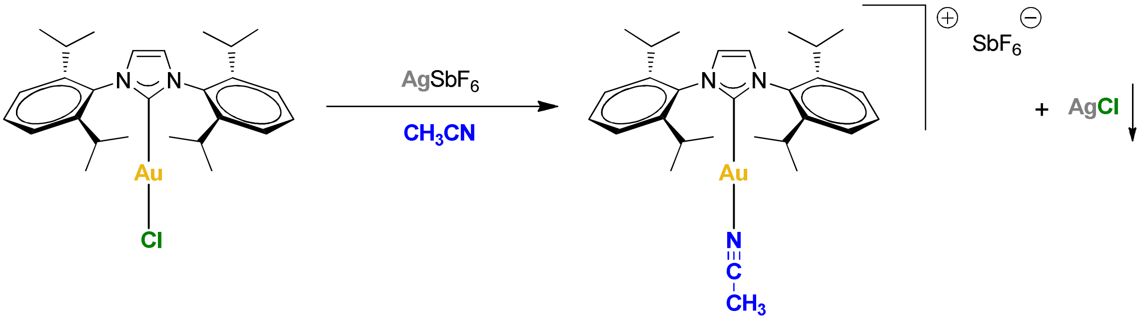
Scheme 3.5. Attempt to perform a carbonylative halide exchange reaction.

By ESI-HRMS, the peaks of [M+H$^+$] species for L$_1$-Br and L$_1$-Cl were observed but the peak expected for the acid chloride was not. Again, it is another example of reaction inhibition under high concentration of CO.

4. EXPERIMENTAL SECTION

4.1. Synthesis and characterization of catalyst [Au(IPr)NCMe]SbF_6

Catalyst [Au(IPr)NCMe]SbF_6 was synthesized from commercially available [AuCl(IPr)] as it is shown in Scheme 4.1 following a protocol found in the literature.[32]



Scheme 4.1. Synthesis of the catalyst [Au(IPr)NCMe]SbF_6.

In a vial, [AuCl(IPr)] (23.6 mg, 1 equiv., 0.04 mmol) is dissolved in 0.5 mL of CH_3CN and $AgSbF_6$ (13.7 mg, 1.05 equiv., 0.04 mmol) is added. The solution is stirred for 1 min. The solvent is then removed under vacuum and 0.5-1 mL of DCM are added. A filtration over a plug of Celite® is performed and then, the solvent is removed under vacuum. The resulting solid is the desired complex (28.8 mg, 88% yield).

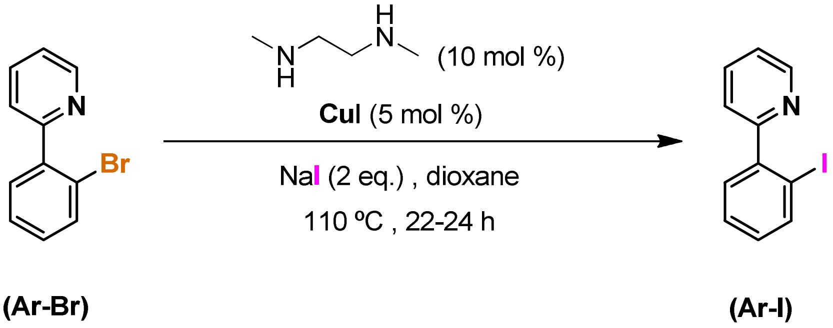
^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.59 (t, J = 8.0 Hz, 2H), 7.36 (d, J = 7.6 Hz, 4H), 7.32 (s, 2H), 2.45 (septuplet, J = 6.8 Hz, 4H), 2.34 (s, 3H), 1.31 (d, J = 6.8 Hz, 12H), 1.25 (d, J = 6.8 Hz, 12H).

HRMS (ESI) (CH_3CN, m/z) calcd for $[C_{29}H_{39}AuN_3]^+$: 626.2810, found: 626.2826

4.2. Synthesis and characterization of ligands

4.2.1. Synthesis and characterization of Ar-I

2-(2-iodophenyl)pyridine (Ar-I) is synthesized via the previously reported copper-catalyzed iodination of aryl bromides shown in Scheme 4.2.[33]



Scheme 4.2. Halide exchange reaction to obtain Ar-I from Ar-Br.

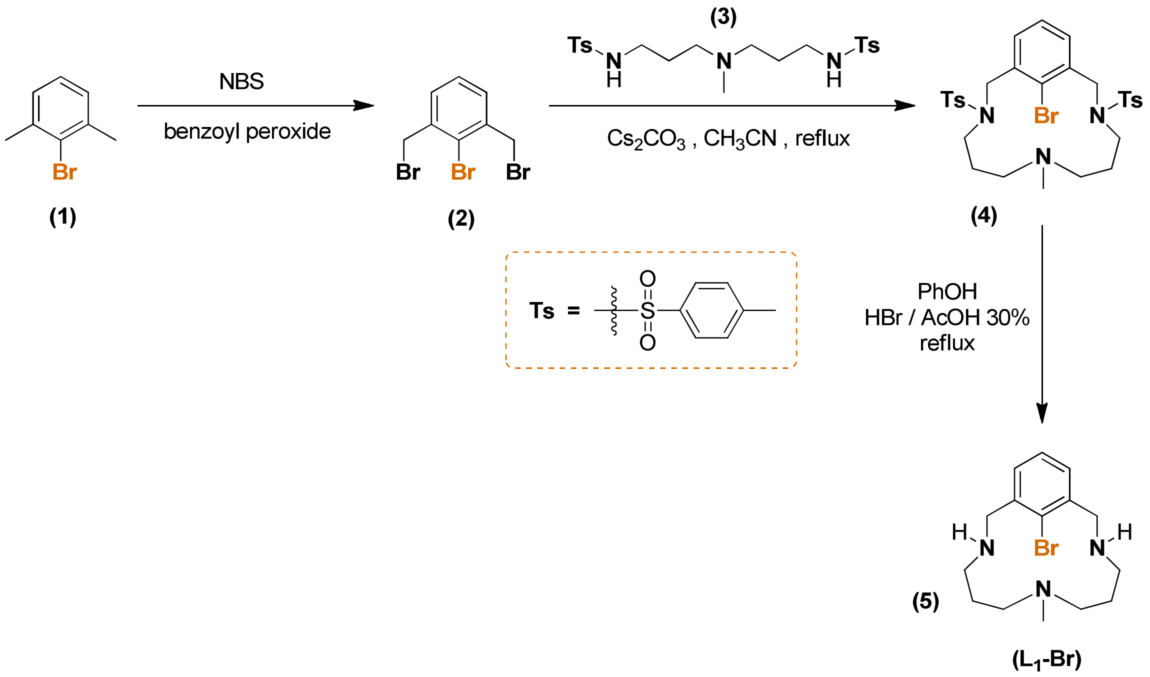
2-(2-bromophenyl)pyridine (261.1 mg, 1 equiv., 1.12 mmol) and NaI (333.9 mg, 2.00 equiv., 2.23 mmol) are added in a vial. In another vial, 1 mL of degassed dioxane is added. Both vials are entered in an inert-atmosphere glovebox. There, dioxane is transferred to the substrate-containing vial, and CuI (10.6 mg, 0.05 equiv., 0.06 mmol) and N,N'-dimethylethylenediamine (12 µL, 0.10 equiv., 0.11 mmol) are added as well. After that, the vial is hermetically sealed and heated at 110°C while stirred for 22-24h. The desired product is purified from the crude by column chromatography in silica gel using a solvent mixture of AcOEt:hexane (1:3) as a mobile phase. Eluted fractions containing the desired product are poured into a round-bottom flask and the solvent of the solution is removed under vacuum. 2-(2-iodophenyl)pyridine (Ar-I) is obtained as a pale yellow oil in 74% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.71 (ddd, J = 4.8 Hz, 1.8 Hz, 1.0 Hz, 1H), 7.97 (ddd, J = 8.0 Hz, 1.2 Hz, 0.4 Hz, 1H), 7.77 (td, J = 7.6 Hz, 1.6 Hz, 1H), 7.51 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 7.44 (m, 2H), 7.31 (ddd, J = 7.6 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.09 (ddd, J = 8.0 Hz, 6.8 Hz, 2.4 Hz, 1H).

HRMS (ESI) (CH_3CN, m/z) calcd for $C_{11}H_8IN$ [M+H$^+$]: 281.9780, found: 281.9791

4.2.2. Synthesis and characterization of L_1-Br

L_1-Br is synthesized as shown in Scheme 4.3.[19]



Scheme 4.3. Synthetic route towards L_1-Br.

A mixture of 2-bromo-1,3-dimethylbenzene (**1**) (6.95 g, 1 equiv., 37.53 mmol), NBS (13.36 g, 2.00 equiv., 75.06 mmol) and benzoyl peroxide (0.11 g, 0.01 equiv., 0.45 mmol) in 150 mL of $CHCl_3$ is heated under reflux for 24h at 70°C and then cooled down to room temperature. The orange solid obtained (succinimide) is removed by filtration. The solvent of the filtrate is evaporated under vacuum and the resulting solid is purified by column chromatography in silica gel using hexane:DCM (98:2) as a mobile phase, affording 1.30 g of 1,3-bis(bromomethyl)-2-bromobenzene (**2**) as a white solid in 10% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (d, J = 7.6 Hz, 2H), 7.29 (dd, J = 8.0 Hz, J = 7.2 Hz, 1H), 4.65 (s, 4H).

Compound **3** (1.70 g, 0.99 equiv., 3.75 mmol), which has already been synthesized following known procedures,[34,35] is dissolved in 50 mL of CH_3CN in a round-bottom flask. Then, Cs_2CO_3 (2.57 g, 2.08 equiv., 7.89 mmol) is added as a solid to the reaction mixture and the solution is heated under reflux at 90°C. Once the reflux is initiated, compound **2** (1.30 g, 1 equiv., 3.80

mmol) dissolved in 100 mL of CH_3CN is added dropwise to the reaction mixture. After refluxing for 24h, the reaction crude is cooled down to room temperature and filtered to remove the precipitate. The solvent of the filtrate is then evaporated under vacuum and the desired product (**4**) is obtained as an orange solid. The solid is purified by column chromatography in silica gel using a DCM:MeOH (90:10) mixture as a mobile phase. The reaction afforded 2.17 g of product **4** in 90% yield.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.74 (d, J = 8 Hz, 4H), 7.53 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 8 Hz, 4H), 7.34 (t, J = 7.6 Hz, 1H), 4.57 (d, J = 13.6 Hz, 2H), 4.39 (d, J = 13.6 Hz, 2H), 3.00 (m, 4H), 2.46 (s, 6H), 2.02 (m, 5H), 1.88 (m, 2H), 1.52 (m, 2H), 0.95 (m, 2H).

Compound **4** (2.17 g, 1 equiv., 3.42 mmol) and phenol (4.31 g, 13.39 equiv., 45.80 mmol) are added as solids into a flask. Then, 80 mL of HBr/AcOH 30% are also added and the resulting mixture is stirred and heated at 90°C for 24h. The brown crude is concentrated until the initial volume is reduced to the half. Afterwards, 50 mL of H_2O and 30 mL of HCl 2M are added to the crude and the aqueous phase is extracted using $CHCl_3$ (3 x 70 mL). The aqueous phase is made basic with NaOH pellets until pH 14 (it turns pink) and the resulting mixture is extracted again with $CHCl_3$ (3 x 70 mL). The organic phases are combined, dried with $MgSO_4$ and concentrated until a brown oil is obtained. The oil is purified by column chromatography in silica gel using a solvent mixture of DCM:MeOH:NH_4OH (90:10:3). Eluted fractions containing the desired product are gathered, dried with $MgSO_4$ and cleaned with activated carbon. The mixture is filtered and collected into a round-bottom flask. The solvent is then removed under vacuum. L_1-Br is obtained as a pale yellow solid (0.61 g, 55% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.14 (m, 3H), 4.38 (d, J = 14.4 Hz, 2H), 3.57 (d, J = 14 Hz, 2H), 2.40 (m, 4H), 2.28 (m, 2H), 2.00 (m, 2H), 1.85 (s, 3H), 1.45 (m, 4H).

HRMS (ESI) (CH_3CN, m/z) calcd for $C_{15}H_{24}BrN_3$ [M+H$^+$]: 326.1232, found: 326.1243

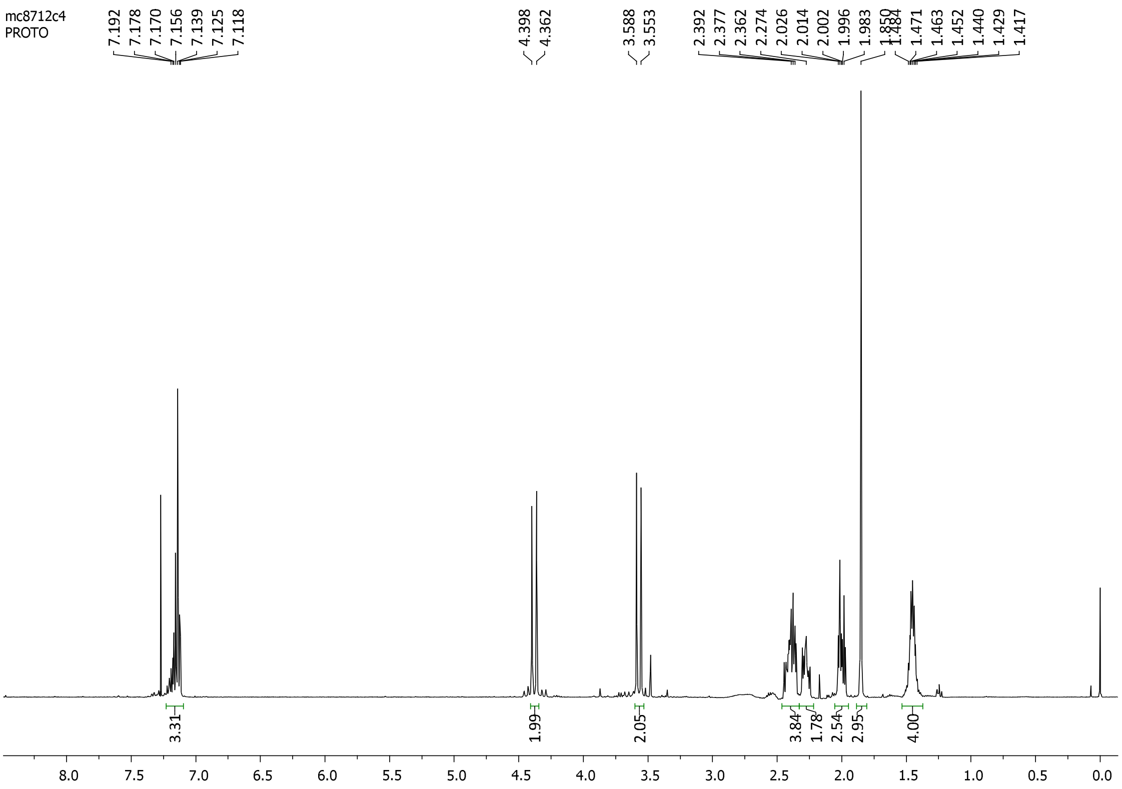
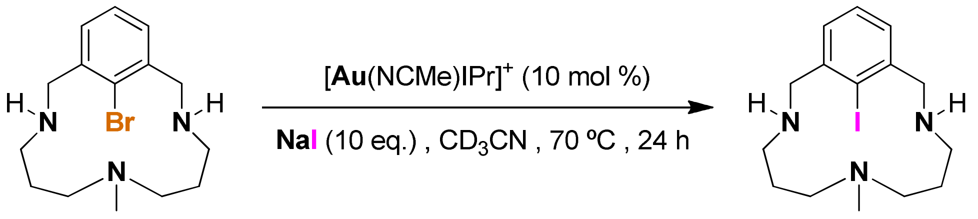


Figure 4.1. ^{1}H-NMR spectrum of L_1-Br in $CDCl_3$ at 298K.

4.2.3. *Synthesis and characterization of L_1-I*

As it is shown in Scheme 4.4, L_1-I is synthesized using L_1-Br as starting material following a Au(I)-catalyzed halide exchange reaction.[18]



(L_1-Br) **(L_1-I)**

Scheme 4.4. Halide exchange reaction to obtain L_1-I from L_1-Br.

L_1-Br (60.9 mg, 1 equiv., 0.19 mmol), [Au(IPr)NCMe]SbF_6 (16.1 mg, 0.10 equiv., 0.02 mmol) and NaI (290.9 mg, 10.35 equiv., 1.94 mmol) are added in a vial and dissolved in 1 mL CD_3CN. The vial is heated at 70°C for 24h. The reaction is monitored by ^{1}H-NMR until completion. Then, the crude is purified by column chromatography in silica gel using DCM:MeOH (90:10) as mobile phase. Eluted fractions containing the desired product are collected and poured into a round-bottom flask. After that, the solvent is removed under vacuum. NMR analysis of the solid obtained revealed that further purification was required. Therefore, extractions with $CHCl_3$ and NH_4OH (x3) were performed. Activated carbon and $MgSO_4$ were added to the organic phase and the mixture was filtered. All volatiles were then removed from the filtrates under vacuum and the desired product (L_1-I) was obtained as a yellowish oil, which was dissolved in the minimal amount of DCM and subsequently filtrated through a plug of Celite®. Solvent removal afforded the ligand L_1-I as a yellow solid (36.3 mg, 52% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.17 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 2H), 4.30 (d, J = 14.0 Hz, 2H), 3.66 (d, J = 14.4 Hz, 2H), 2.43 (m, 4H), 2.24 (m, 2H), 1.99 (m, 2H), 1.86 (s, 3H), 1.42 (m, 4H).

HRMS (ESI) (CH_3CN, m/z) calcd for $C_{15}H_{24}IN_3$ [M+H$^+$]: 374.1093, found: 374.1114

4.3. Gold-catalyzed cross-coupling reactions

L_1-X (X = Br, I), a nucleophile and catalyst [Au(IPr)NCMe](SbF_6) are weighted in a vial employing a precision balance. When cyclohexylamine and *p*-nitroaniline are used as N-nucleophiles, potassium *tert*-butoxide is also weighted since the presence of a base is required. Then, 0.5 mL of the corresponding solvent (CD_3CN, EtOH, MeOH, H_2O or DMSO-d_6) and a magnetic stirring bar are added.

For those reactions under a CO atmosphere, the vial is capped with a septum in which a needle is poked. The vial is then put inside a high pressure reactor connected to the carbon monoxide container and stirred for 24h. Depending on the experiment, the reactor is heated as well. On the contrary, if the reaction is going to be performed in the absence of CO (C-N bond forming cross-coupling reactions), the vial is hermetically sealed, heated and stirred for 24h.

After 24h of reaction, 40µL of a 20 mM TMB (1,3,5-trimethoxybenzene) solution in $CDCl_3$ are added to the crude reaction mixture. If the solvent of the reaction is a deuterated one (CD_3CN or DMSO-d_6), the resulting mixture is directly transferred to an NMR tube. If the solvent of the reaction is not deuterated (EtOH, MeOH or H_2O), the solvent is evaporated under vacuum and the resulting residue is dissolved in a deuterated solvent ($CDCl_3$ or CD_3CN). Then, the mixture is transferred to an NMR tube. The yield of the reaction is obtained by integration of the ^{1}H-NMR signals of the product relative to TMB as internal standard. Moreover, mass spectrometric experiments are carried out in order to further confirm the identity of the reaction products.

4.4. A note on sustainability

Apart from L_1-Br synthesis, which follows a typical organic route, the reactions that have been carried out in this work take advantage of catalysis. This means that we investigate new synthetic methods being conscious that chemistry should be done following the greenest possible way in order to reduce the environmental impact.

By performing catalytic processes, reactions with high atom economy are accomplished so less amount of reactants are needed and less residues are generated. Besides, little amount of catalyst is used since one molecule of it can react with many molecules of reagent. In addition, catalytic experiments have been performed using the minimum amount of solvent (0.5 mL). On the other hand, it must be said that significant amounts of solvent were used when it came to perform column chromatography and extractions.

Finally, recycling of wastes is performed by disposing them in the appropriate container which are found in the laboratory (halogenated solvents, non-halogenated solvents, halogenated solids, non-halogenated solids, aqueous bases, aqueous acids, needles, a bin for glass material and a bin for paper and plastic). Moreover, vials and NMR tubes are generally cleaned and reused so as to reduce waste and save money and material.

5. CONCLUSIONS AND OUTLOOK

We have investigated the ability of Au(I) complexes in catalyzing carbonylative cross-coupling reactions making use of L_1-X (X = Br, I) model aryl halide macrocyclic substrates and O-nucleophiles under CO atmosphere. In addition, we have also explored the ability of Au(I) complexes in incorporating a carbonyl moiety into the product of a halide exchange reaction and into the product of the C-N bond forming cross-coupling reaction using 2-(2-iodophenyl)pyridine and a N-nucleophile. On the other hand, we have also explored the possibility of catalyzing C-N bond forming cross-coupling reactions with gold, expanding the scope of nucleophiles that can react with the model aryl halide substrate.

Regarding the carbonylative cross-coupling reactions, the expected carbonylated products have not been obtained. Instead, the C-O coupling products L_1-Nu were observed, as well as L_1-Cl in the case of performing the halide exchange reaction under CO atmosphere. The reaction between the model aryl halide substrate and sodium *p*-chlorophenolate afforded the coupling product in higher yields that the ones reported in the literature. The reaction with sodium methoxide seemed to afford low quantities of the desired carbonylative coupling product but after trying to optimize the reaction and trying to provide further evidences of its formation, we suggested that an adduct between L_1-OMe and CO was formed. Moreover, we have also observed that at CO pressures above 10 bar the reactivity decreases. Finally, the obtention of the phenol L_1-OH using sodium hydroxide as nucleophile and water as solvent was interesting due to the impossibility of performing such reaction with Cu and Ag. Whereas all O-nucleophiles gave the corresponding coupling products (L_1-Nu), when we studied the cross-coupling reactions using N-nucleophiles we only obtained the desired product with 2-pyridone. This is due to the higher reactivity of more acidic nucleophiles. However, more N-nucleophiles should be used to perform cross-coupling reactions in order to have more knowledge for future work on carbonylative cross-coupling reactions with N-nucleophiles.

Overall, although our studies suggest that the model aryl halide macrocyclic system is not suitable for gold-catalyzed carbonylative cross-coupling reactions, we have found new patterns of reactivity in Au(I) homogeneous catalysis within this system. Future work will be focused on further analyzing the reaction conditions, with special interest in other substrates and nucleophiles. All in all, this work has contributed to gain insight in the possibilities of gold catalysis and we must keep working to find new applications.

6. REFERENCES

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