Universitat de Girona

Facultat de Ciències

Final degree project

Carbon-carbon cross-coupling reactions with aryl-Ag(III) and aryl-Cu(III) species

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CONTENTS

ABSTRACT

In this project we describe a direct comparison between the different reactivity of well-defined aryl-Ag(III) and aryl-Cu(III) compounds. Special attention has been devoted to the carbon-carbon cross-coupling reactions, which are currently of great interest in organic chemistry. These transformations have been studied with two different types of substrates, arylboronic acids and arylsilanes.

As already known, the chemistry of palladium highlights are related to the variety of the important products obtained and the versatility in the reaction conditions. The mechanism that is generally proposed is a Pd(0)/Pd(II) two-electron redox catalytic cycle. Other transition metals have appeared more recently as an alternative to palladium, which are much more abundant and less toxic, and might become a substitute for palladium. This refers to copper, which might follow a two-electron redox catalytic cycle similar to palladium. Silver has been recently capable to perform this type of transformations following a Ag(I)/Ag(III) redox cycle. Aryl-Ag(III) and aryl-Cu(III) species have been identified unequivocally as intermediate catalytic cycle and direct evidence of aryl halide oxidative addition and carbon-carbon or carbon-oxygen bond-forming reductive elimination steps has been provided. The different reaction conditions under each of these two complexes react has become a good opportunity to investigate different selectivities that have both and, therefore, it has led to the development of synthetic strategies in an orthogonal way.

Herein, various macrocylic ligands had been used to synthesize the corresponding aryl-Ag(III) and aryl-Cu(III) compounds. A study of the different transformations with arylboronic acids and arylsilanes has been undertaken, obtaining a number of products which were characterized by Nuclear Magnetic Resonance (NMR) and Electrospray Ionization in a high-resolution mass spectrometer (Q-TOF).

RESUM

En aquest projecte es porta a terme una comparativa directa entre la diferent reactivitat dels compostos aril-Ag(III) i aril-Cu(III) ben definits. S'ha dedicat especial atenció a les reaccions d'acoblament carboni-carboni, les quals són de gran interès actualment en la química orgànica. Aquestes transformacions s'han estudiat amb dos tipus de substrats diferents, els àcids borònics i els silans.

Tal i com ja es coneix, la química del pal·ladi destaca degut a la gran varietat i importància dels productes obtinguts i a la versatilitat en les condicions de reacció. El mecanisme que generalment es segueix és un cicle catalític redox Pd(0)/Pd(II). Altres metalls de transició han aparegut més recentment com a alternativa al pal·ladi, els quals són molt més abundants i menys tòxics i es poden utilitzar com a substïtut d'aquest. Aquí es fa referència al coure, el qual pot seguir un cicle catalític redox semblant al del pal·ladi. Recentment s'ha descobert que la plata ha estat capaç de realitzar aquest tipus de transformacions seguint un cicle catalític redox Ag(I)/Ag(III). S'han identificat de manera inequívoca espècies aril-Ag(III) i aril-Cu(III) com a intermedis del cicle catalític i s'ha obtingut evidències directes d'una addició oxidativa d'un halur d'aril i la formació d'enllaços carboni-carboni o carboni-oxígen en l'etapa de l'eliminació reductiva. Les diferents condicions de reacció sota les quals reaccionen cadascun d'aquests dos complexes ha esdevingut una bona oportunitat per investigar les diferents selectivitats que presenten ambdós i, per tant, ha donat peu a desenvolupar estratègies sintètiques de manera ortogonal.

En el projecte en qüestió s'han utilitzat diferents lligands macrocíclics per tal de sintetitzar els corresponents compostos aril-Ag(III) i aril-Cu(III). S'ha realitzat un estudi de les diferents transformacions amb àcids borònics i silans, obtenint una sèrie de productes els quals han estat caracteritzats mitjançant Ressonància Magnètica Nuclear (RMN) i Ionització per Electroesprai en un espectròmetre de masses d'alta resolució (Q-TOF).

RESUMEN

En este proyecto se lleva a cabo una comparativa directa entre la diferente reactividad de los compuestos de aril-Ag(III) y aril-Cu(III) bien definidos. Se ha dedicado especial atención a las reacciones de acoplamiento carbono-carbono, las cuales son de gran interés actualmente en la química orgánica. Estas transformaciones se han estudiado con dos tipos de sustratos diferentes, los ácidos borónicos y los silanos.

Tal y como ya se conoce, la química del paladio destaca debido a la gran variedad e importancia de los productos obtenidos y la versatilidad en las condiciones de reacción. El mecanismo que generalmente se sigue es un ciclo catalítico redox Pd(0)/Pd(II). Otros metales de transición han aparecido más recientemente como alternativa al paladio, los cuales son mucho más abundantes y menos tóxicos y se pueden utilizar como sustitutos de éste. Aquí se hace referencia al cobre, el cual puede seguir un ciclo catalítico redox parecido al del paladio. Recientemente se ha descubierto que la plata es capaz de realizar este tipo de transformaciones siguiendo un ciclo catalítico redox Ag(I)/Ag(III). Se han identificado de forma inequívoca especies aril-Ag(III) y aril-Cu(III) como intermedios del ciclo catalítico y se ha obtenido evidencias directas de una adición oxidativa de un haluro de arilo y la formación de enlaces carbono-carbono o carbono-oxígeno en la etapa de eliminación reductiva. Las diferentes condiciones de reacción bajo las que reaccionan cada uno de estos dos complejos se ha convertido en una buena oportunidad para investigar las diferentes selectividades que presentan ambos y, por tanto, ha dado pie a desarrollar estrategias sintéticas de manera ortogonal.

En el proyecto en cuestión se han utilizado diferentes ligandos macrocíclicos a fin de sintetizar los correspondientes compuestos aril-Ag(III) y aril-Cu(III). Se ha realizado un estudio de las diferentes transformaciones con ácidos borónicos y silanos, obteniendo una serie de productos que han sido caracterizados mediante Resonancia Magnética Nuclear (RMN) e ionización por Electroespray en un espectrómetro de masas (Q-TOF).

GLOSSARY OF ABBREVIATIONS

AcOH	acetic acid
Ar	aryl
bb	broad band
cat.	catalytic
CH_3CN	acetonitrile
CH_3OH	methanol
COSY	Correlation Spectroscopy
C-C	carbon-carbon
C-O	carbon-oxygen
d	doublet
dd	doublet of doublets
DMSO	dimethylsulfoxide
ESI-MS	Electrospray Ionization Mass Spectrometry
Equiv.	equivalents
h	hours
HBr	hydrobromic acid
HRMS	high resolution mass spectrometer
HSQC	Heteronuclear single-quantum Correlation Spectroscopy
L	ligand
M	molar
m	multiplet
min	minutes
mM	millimolar
m/z	mass/charge
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nuc	nucleophile
rt	room temperature
s	singlet
THF	tetrahydrofuran
t	triplet
TMB	1,3,5-trimethoxybenzene
X	halogen

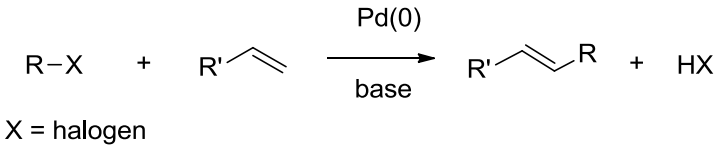
1. INTRODUCTION

1.1. General overview

Carbon is one of the few elements that can form long chains of its own atoms, a property called catenation. This coupled with the strength of the carbon-carbon (C-C) bond gives rise to an enormous number of molecular forms, many of which are important structural elements of life, so carbon compounds have their own field of study: organic chemistry. C-C bond-forming reactions are organic reactions in which a new C-C bond is formed[1]. They are important in the production of many man-made chemicals such as pharmaceuticals[2], plastics and other new materials. Moreover, other C-heteroatom couplings have become very important in recent years.

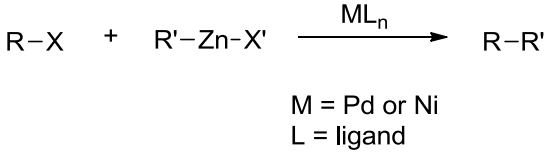
A cross-coupling reaction in organic chemistry is a general term for a variety of reactions where two hydrocarbon fragments are coupled with the aid of a metal catalyst[3]. In one model reaction type a main group organometallic compound of the type RM (R = organic fragment, M = metal) reacts with an organic halide of the type R'-halogen with the formation of a new C-C bond. Among the various transition metals able to carry on C-C or C-heteroatom cross-coupling reactions, palladium is the most useful due to its high catalytic activity and its high selectivity[4,5]. There are several cross-coupling reactions involving palladium as a transition metal: Mizoroki-Heck[6-8], Negishi[4,9], Suzuki-Miyaura[4,8,10], Stille[4,8,11], Sonogashira[4,12], Hiyama[13], Kumada[14] and others. These reactions are briefly explained as follows:

The Mizoroki-Heck reaction is the chemical reaction of an unsaturated halide with an alkene in the presence of a base and a palladium catalyst to form a substituted alkene. This reaction was the first example of a C-C bond-forming reaction that followed a Pd(0)/Pd(II) catalytic cycle.



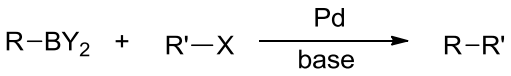
Scheme 1. Mizoroki-Heck cross-coupling reaction.

The Negishi coupling is a widely employed transition metal catalyzed cross-coupling reactions. This reaction couples organic halides with organozinc compounds forming C-C bonds. For this case a Pd(0) complex is generally used as the metal catalyst too, though nickel is sometimes used.



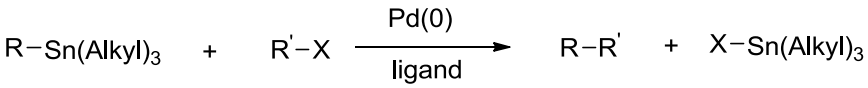
Scheme 2. Negishi cross-coupling reaction.

The Suzuki-Miyaura is a cross-coupling reaction between a boronic acid with a halide catalyzed by a Pd(0) complex. In this case a Pd(0)/Pd(II) catalytic cycle also takes place.



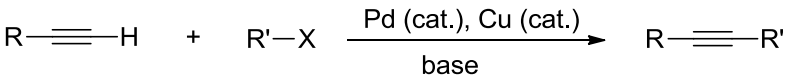
Scheme 3. Suzuki-Miyaura cross-coupling reaction.

The Stille reaction, also known as the Migita-Kosugi-Stille coupling, is a chemical reaction widely used in organic synthesis which involves the coupling of an organotin compound (or organostannanes) with a variety of organic electrophiles via palladium-catalyzed cross-coupling reaction.



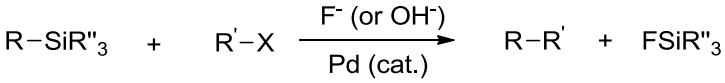
Scheme 4. Stille cross-coupling reaction.

The Sonogashira reaction is a cross-coupling reaction used in organic synthesis to form C-C bonds too. In this case it is also employed a palladium catalyst to form C-C bond between a terminal alkyne and an aryl or vinyl halide.



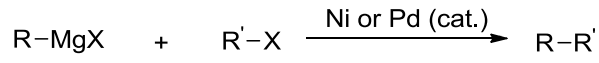
Scheme 5. Sonogashira cross-coupling reaction.

The Hiyama reaction is a palladium-catalyzed cross-coupling reaction of organosilicons (or organosilanes) with organic halides in the presence of an activating agent such as fluoride (F^-) or hydroxide (OH^-) to form C-C bonds.



Scheme 6. Hiyama cross-coupling reaction.

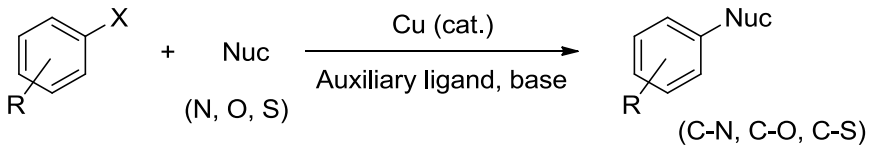
The Kumada coupling is another cross-coupling reaction useful for generating C-C bonds by reaction of a Grignard reagent and an organic halide. This reaction uses transition metal catalysts, typically nickel or palladium.



Scheme 7. Kumada cross-coupling reaction.

1.2. Copper as a catalyst in Ullmann-type couplings

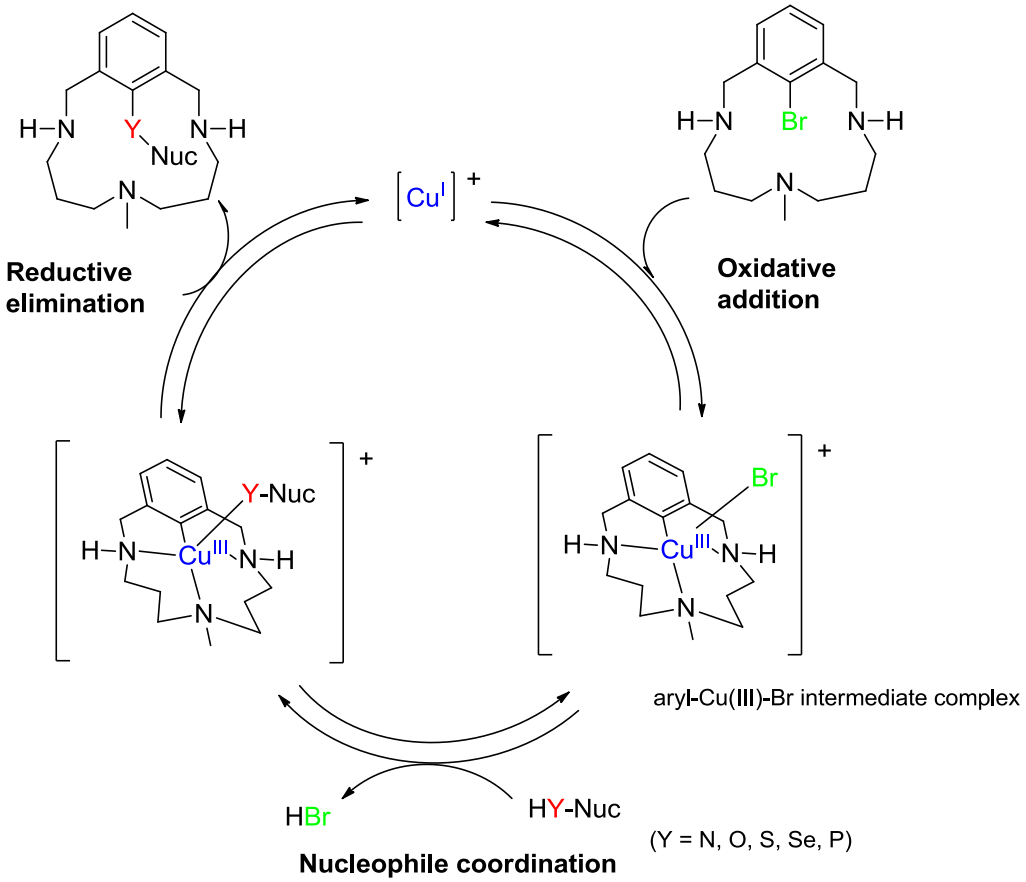
In order to develop more sustainable methods of synthesis it was investigated the possibility of replacing the palladium for metals of the first transition series, more abundant, less expensive and less toxic. Thus the development of cross-coupling reactions catalyzed by copper have become of huge interest as an alternative to palladium catalyzed. Nowadays it is known that copper catalysis in organic transformations is one of the most successful and useful strategies to effect C-heteroatom bond formation[15,16], and becoming important in C-C bond formation. These copper catalysts are mainly interesting because it is an economical element and also because of its compatibility with functional groups and their low toxicity. All these reasons have led to the study and optimization of these processes and their implementation in the industry. One of the reactions known where copper is used as a catalyst in order to carry out cross-coupling reactions is the Ullmann-Goldberg reaction[17,18] to C-N, C-O or C-S bond-forming.



Scheme 8. General Ullmann-type catalytic reactions.

It should be mentioned that several kinds of mechanisms have been proposed to explain the reaction observed in the reactivity of Ullmann-Goldberg cross-coupling reactions, but the theory that possess more experimental evidence is that which proposes a Cu(I)/Cu(III) catalytic cycle. This catalytic cycle involves oxidative addition and reductive elimination steps, highly similar to the reactions which have been discussed previously, where a Pd(0)/Pd(II) catalytic cycle takes place with a oxidative addition and subsequent reductive elimination.

The detection of intermediates in this Cu(I)/Cu(III) catalytic cycle is very challenging due to its very short-living nature. Although aryl-Cu(III) complexes have been often proposed, until 2010 there were no direct evidences of Cu(III) species. Ribas and Stahl's groups provided the first direct observation of the fundamental oxidative addition and reductive elimination steps at a Cu(I) complex (see Scheme 9) and Ribas' group proposed a new strategy to synthesize a well-defined aryl-Cu(III) complex[19-22].

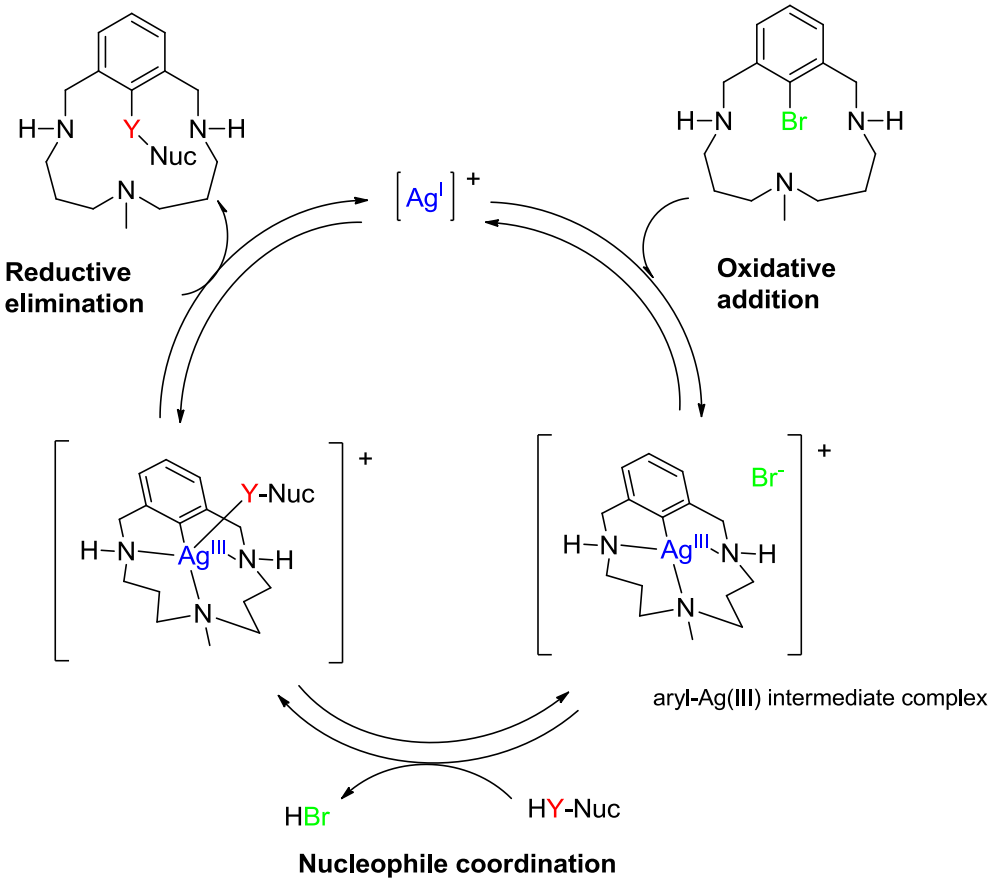


Scheme 9. Cu-catalyzed C-heteroatom cross-coupling reaction using a model aryl halide substrate.

1.3. Silver as a catalyst in Ullmann-type couplings

In recent years also it has been studied the silver as a catalyst in order to carry out C-C or C-heteroatom cross-coupling reactions. Silver has been the most unexplored chemistry from a few years ago and its redox chemistry it has been the least understood[23,24]. It is well known that Ag(I) salts were commonly employed in organic transformations, highlighting the following properties: they are able to activate C-C unsaturations due to its Lewis acid character[24]; the insolubility of their corresponding halide salts (halogenophilicity)[24]; and as a sacrificial oxidant by promoting the one-electron oxidation of the metal catalyst[23].

Since recently, it was generally accepted that silver involves exclusively one-electron redox chemistry, in contrast to copper and gold. However, recently it has been found that silver can show a Ag(I)/Ag(III) two-electron redox catalytic cycle for C-C and C-O cross-coupling reactions, and it has been possible to synthesize an aryl-Ag(III) complex[25].

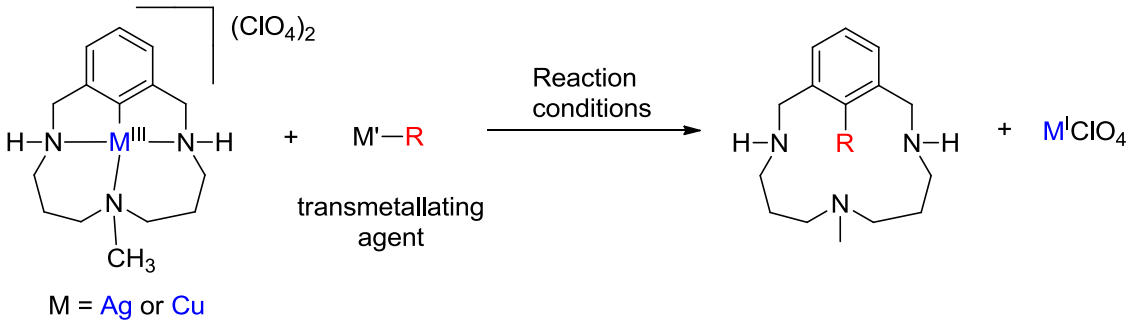


Scheme 10. General proposed mechanism of Ag(I)-catalysed cross-coupling reactions through the intermediacy of an aryl-Ag(III) complex using a model aryl halide substrate.

2. OBJECTIVES

The aim of this work is to the study of C-C bond-forming cross-coupling reactions in model systems of well-defined aryl-Cu(III) and aryl-Ag(III), which have been previously reported by the group of research QBIS-CAT[17,19,20,25], to prove their plausibility as reaction intermediates in C-C cross-coupling reactions. For both model systems we study the reactivity in the presence of two types of substrates: arylboronic acids and arylsilanes. In addition, a redox catalytic cycle Ag(I)/Ag(III) is considered for C-C cross-coupling reactions, in a parallelism with the known Cu(I)/Cu(III) and Pd(0)/Pd(II) catalytic cycle[27]. Therefore, synthetic strategies are developed to investigate the different intrinsic reactivities of silver and copper in these transformations.

The model cross-coupling reaction stoichiometric to be studied using different transmetallating agents (arylboronic acids and arylsilanes) with the aryl-Ag(III) and the aryl-Cu(III) complex is depicted below:



Scheme 11. Stoichiometric coupling of arylboronic acids and arylsilanes (transmetallating agents) with aryl-Ag(III) and aryl-Cu(III) complex.

3. EXPERIMENTAL SECTION

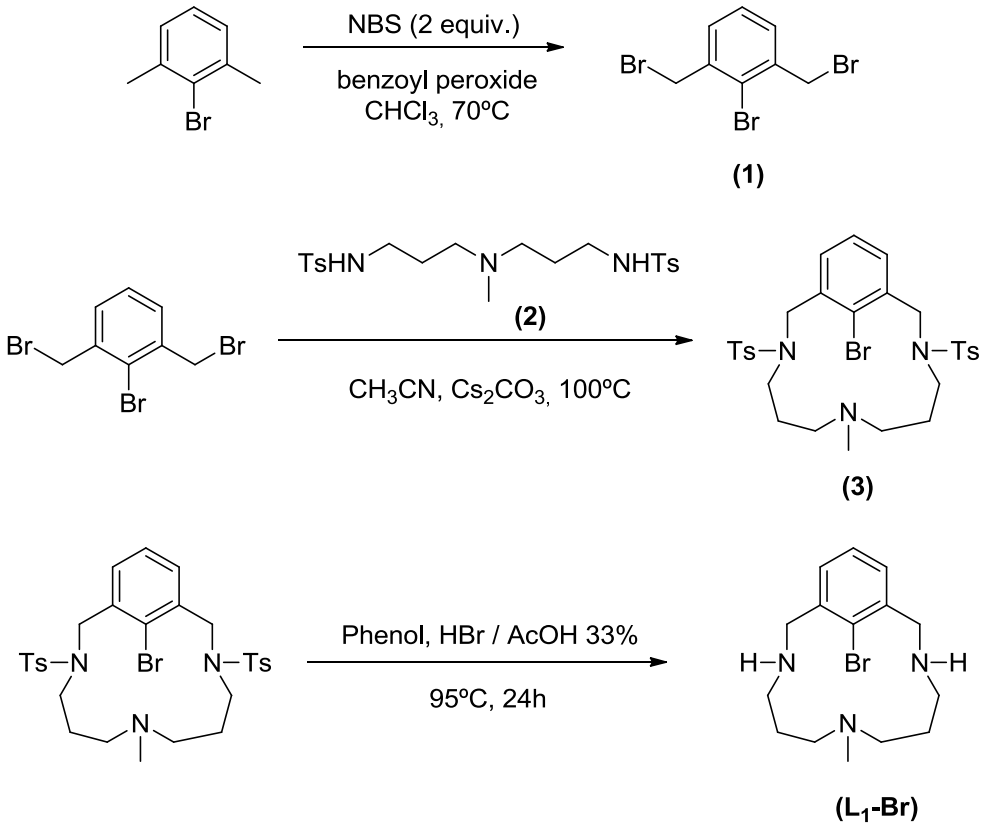
3.1. Instrumentation

Nuclear Magnetic Ressonance: ^{1}H-NMR, ^{13}C-NMR, COSY, NOESY and HSQC spectra were performed in a Bruker Ultrashield Advance III400 and Ultrashield DPX300 spectrometers.

Mass Spectrometry: Mass spectra were performed by electrospray ionization in a high-resolution mass spectrometer Bruker micrOTOF QII (Q-TOF) with a quadrupole analyzer with positive and negative ionization modes; and by MS^n Bruker Daltonics Esquire 6000 Ion Trap.

3.2. Synthesis and characterization of ligand L_1-Br

The ligand **L_1-Br** has been synthesized following the adaptation of a protocol described by Ribas et. al[21,26,28]. Its synthetic route was performed following three steps:



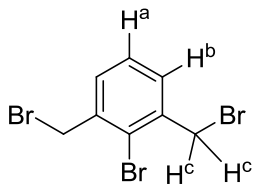
Scheme 12. Synthetic strategy followed for the **L_1-Br** ligand.

3.2.1. Dibromination stage

A mixture of 2-bromo-1,3-dimethylbenzene (15.28 g, 82 mmol), NBS (29.3 g, 115 mmol) and benzoyl peroxide (0.2353 g, 1 mmol) in 750 mL of chloroform is heated to 70ºC under reflux for

24 hours and monitored by TLC[28]. Then cooled down the crude reaction to room temperature and the white solid formed (succinimide) is removed by filtration. The solvent is evaporated under vacuum and the resulting solid is purified by column chromatography in silica gel, using as mobile phase a hexane:dichloromethane (96:4) mixture, affording the product 1,3-bis(bromomethyl)-2-bromobenzene (**1**) as a white solid in 29% yield.

Compound 1: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.42 (d, *J*=7.6 Hz, 2H, H^b), 7.31 (dd, *J*=7.6 Hz, 1H, H^a), 4.65 (s, 4H, H^c).

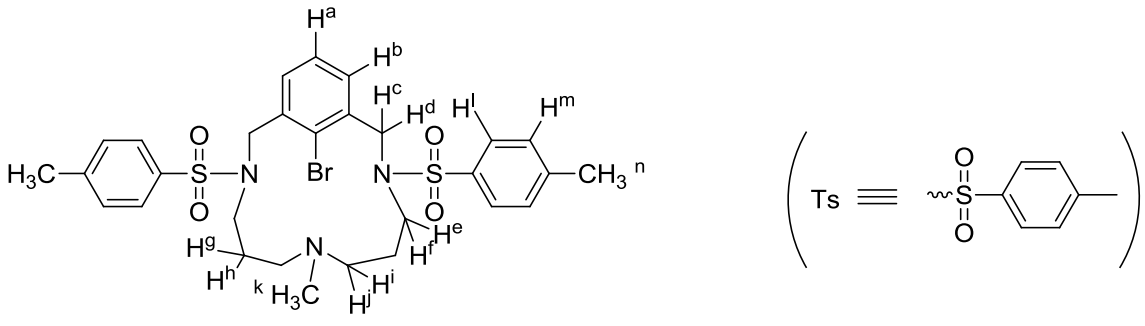


(1)

3.2.2. Cyclization stage

The amine $TsNH(CH_2)_3$-NMe-$(CH_2)_3$-NHTs (**2**) (10.12 g, 22.3 mmol), which is prepared from known protocols found in the literature[26] , is dissolved in CH_3CN in a round bottom-flask. Then cesium carbonate (18.88 g, 45 mmol) is added to the reaction mixture, and the solution is refluxed at 100ºC. When reflux is initiated, 1,3-bis(bromomethyl)-2-bromobenzene (**1**) (5.98 g) dissolved in 250 mL of CH_3CN is added dropwise to the reaction mixture. After heating for 24 hours under reflux, the crude is cooled down to room temperature and filtered to remove residual cesium carbonate. The solvent of the filtrate is evaporated under vacuum and the resulting solid is purified by column chromatography in silica gel using a dichloromethane:methanol (90:10) solvent mixture as mobile phase, affording the desired product (**3**) in 60% yield.

Compound 3: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.75 (d, *J*=7.92 Hz, 4H, H^l), 7.52 (d, *J*=7.6 Hz, 2H, H^b), 7.36 (d, *J*=7.92 Hz, 4H, H^m), 7.32 (t, *J*=7.6 Hz, 1H, H^a), 4.59 (d, *J*=13.6 Hz, 2H, H^c or H^d), 4.36 (d, *J*=13.6 Hz, 2H, H^c or H^d), 3.01 (m, 4H, H^e and H^f), 2.45 (s, 6H, H^n), 2.06 (s, 3H, H^k), 2.06 (m, 2H, H^i or H^j), 1.93 (m, 2H, H^i or H^j), 1.54 (m, 2H, H^g or H^h), 0.96 (m, 2H, H^g or H^h).

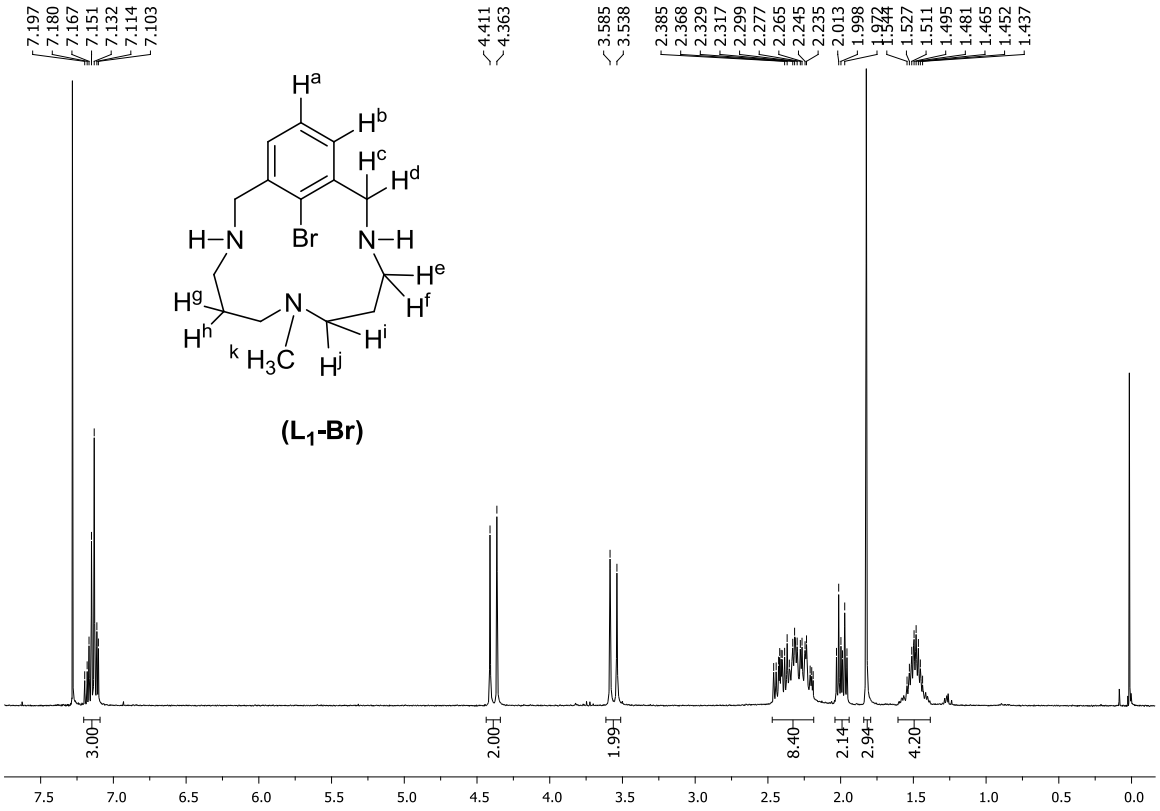


(3)

3.2.3. Detosylation of amines

The ligand synthesized previously (**3**) is added into two 250 mL flasks (2.01 g and 2.00 g, respectively). Then, 79 mL of HBr/AcOH 33% are added to each of the flasks and the resulting mixture is vigorously stirred and heated under reflux at 95ºC for 24 hours. The assembly includes an acid trap to catch hydrobromic acid vapors generated during the reaction. After heating for 24 hours under reflux, the two reactions are cooled down to room temperature and then the crude is concentrated until the initial volume is reduced to the half part. Afterwards, a mixture of dichloromethane:water (3x50 mL) are added to the crude and the aqueous phase is extracted using chloroform (3x70 mL). The aqueous phase is basified with sodium hydroxide until pH 14, and the resulting mixture is extracted again with chloroform (3x70 mL). The organic phases are separated, dried with magnesium sulfate and concentrated. The obtained oil is purified by column chromatography in silica using a solvent mixture of dichloromethane:methanol:ammonia (90:10:2). The product is stirred in presence of activated carbon during 5 minutes and then it is filtrated using Celite®. Finally, after the solvent was removed under vacuum, the desired product (**L_1-Br**) was obtained in 23.8% yield.

L_1-Br: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.19-7.10 (m,3H, H^a and H^b), 4.38 (d, *J*=18.8Hz, 2H, H^c or H^d), 3.56 (d, *J*=18.8Hz, 2H, H^c or H^d), 2.46-2.18 (m, 8H, H^i ,H^j , H^e and H^f), 1.82 (s, 3H, H^k), 1.57-1.39 (m, 4H, H^g and H^h).

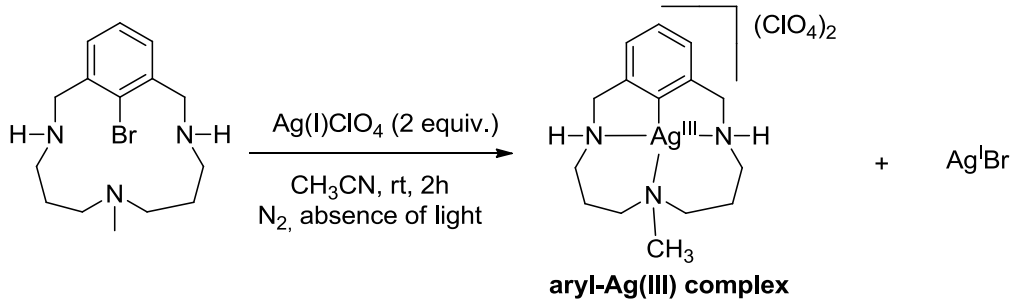


Scheme 13. ^{1}H-NMR spectrum of **L_1-Br**. Experiment performed in $CDCl_3$, 300 MHz, at 298 K.

3.3. Synthesis and characterization of aryl-Ag(III) complex

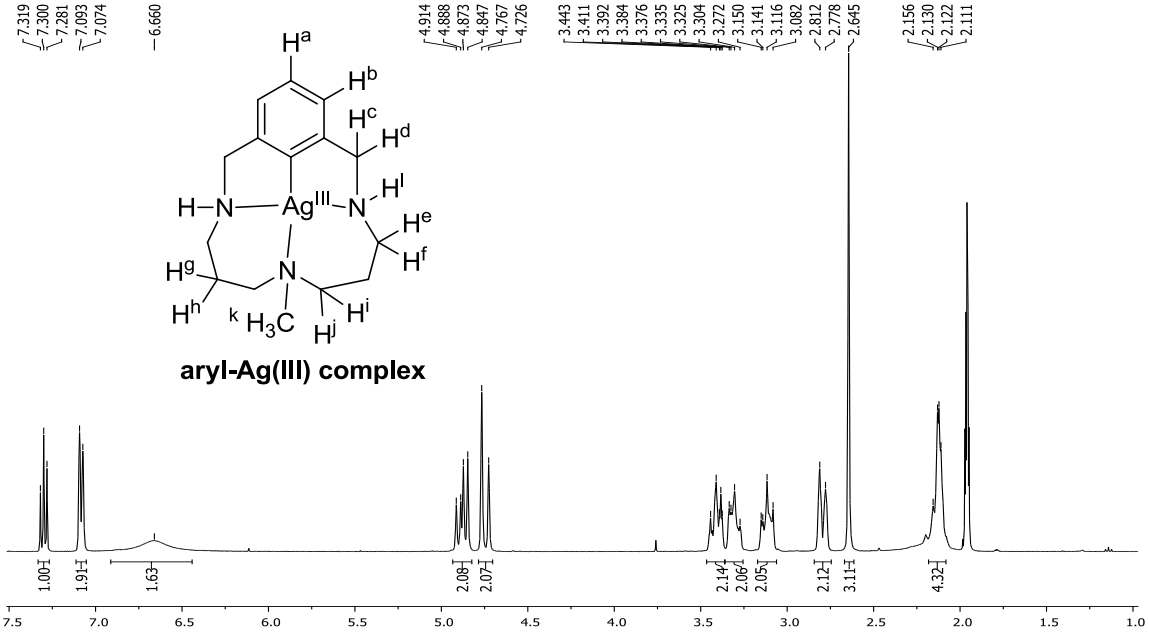
The aryl-Ag(III) complex, $\mathbf{1_{ClO4}}$, was synthesized by reacting the model aryl-halide ligand $\mathbf{L_1}$**-Br** (see section 3.1) with 2 equiv. of silver perchlorate affording $\mathbf{1_{ClO4}}$ (63% yield) and silver bromide that precipitates from the solution[25].

To an amber vial which contains a solution of ligand $\mathbf{L_1}$**-Br** (20 mg, 0.0613 mmol) in CH_3CN, 2 equiv. of silver perchlorate (25.4 mg, 0.1226 mmol) dissolved in 1 mL of CH_3CN was added under an inert-atmosphere glove box. The mixture reaction was stirred at room temperature for 30 min. Afterwards, the crude reaction was centrifuged and the resulting supernatant was filtrated with an Acrodisc® filter and concentrated. Finally, the desired product was obtained as yellow crystals by slow diffusion of diethyl ether.



Scheme 14. Synthesis of the aryl-Ag(III) complex ($\mathbf{1_{ClO4}}$).

Aryl-Ag(III) complex: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.30 (t, *J*=7.6Hz, 1H, H^a), 7.08 (d, *J*=7.2Hz, 2H, H^b), 6.66 (bb, 2H, H^j), 4.88 (dd, *J*=16.4Hz, *J*=10.4Hz, 2H, H^c or H^d), 4.74 (d, *J*=16.4Hz, 2H, H^c or H^d), 3.44-3.41 (m, 2H, H^e or H^f), 3.39-3.37 (m, 2H, H^e or H^f), 3.15-3.08 (m, 2H, H^i or H^j), 2.79 (d, *J*=13.6Hz, 2H, H^i or H^j), 2.64 (s, 3H, H^k), 2.19-2.11 (m, 4H, H^g or H^h).

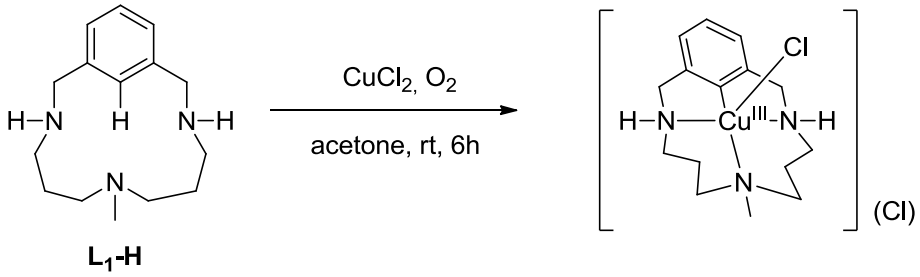


Scheme 15. ^{1}H-NMR spectrum of **aryl-Ag(III) complex**. Experiment performed in $CDCl_3$, 400 MHz, at 298 K.

3.4. Synthesis and characterization of aryl-Cu(III) complex

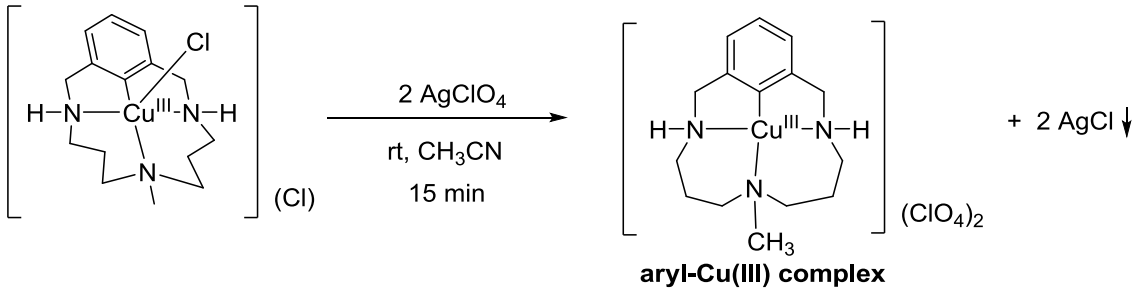
A protocol defined by Casitas et. al.[28] was carried out for synthesize the aryl-Cu(III) complex.

The ligand **L_1-H** (0.0735 g, 0.297 mmol) dissolved in 15 mL of acetone was added to a round-bottom flask. Then a solution of copper(II) chloride (0.0363 g, 0.27 mmol) was added dropwise to the reaction mixture while stirred under oxygen atmosphere for 6 h. Finally, the red precipitate formed was centrifuged to separate it from the supernatant.



Scheme 16. Synthesis of the corresponding aryl-Cu(III)-halide species.

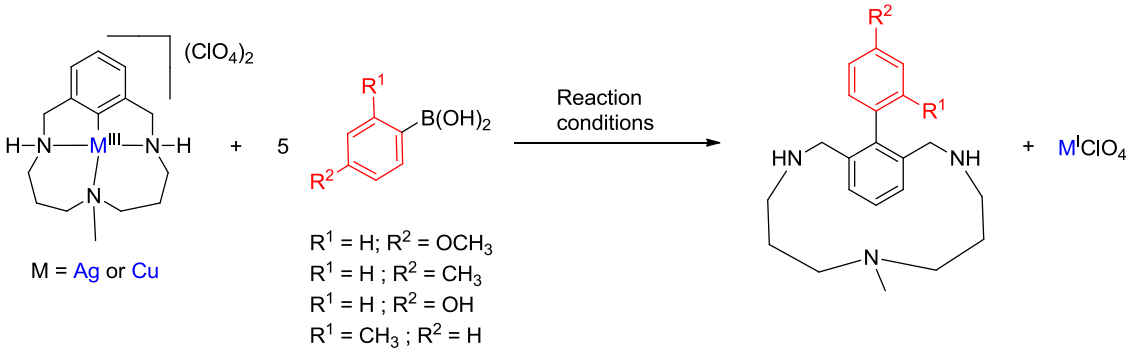
Afterwards, the complex synthesized (0.078 g, 0.204 mmol) was dissolved in CH_3CN and a solution of silver perchlorate (0.0849 g, 0.409 mmol) was added dropwise on the complex. The mixture was stirred for 15 minutes and the resulting solution was centrifuged and filtrated through an Acrodisc® filter. Finally, the solution was concentrated and the product was obtained as orange crystals by slow diffusion of diethyl ether in 52% yield.



Scheme 17. Exchange counteranions reaction.

Aryl-Cu(III) complex: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.25(t, *J*=8Hz,1H), 6.93 (d, *J*=8Hz, 2H), 6.29 (m, 2H), 4.62 (d, *J*=16.02Hz, 2H), 4.47 (d, *J*=16.02Hz, 2H), 3.17 (m, 2H), 3.05 (m, 2H), 2.96 (m, 2H), 2.66 (s, 3H), 2.56 (dt, *J*=13.15Hz, *J*=2.9Hz, 2H), 2.13 (m, 2H), 1.95 (m, 2H).

3.5. Synthesis and characterization of the coupling products of arylboronic acids with aryl-Ag(III) or aryl-Cu(III) complex

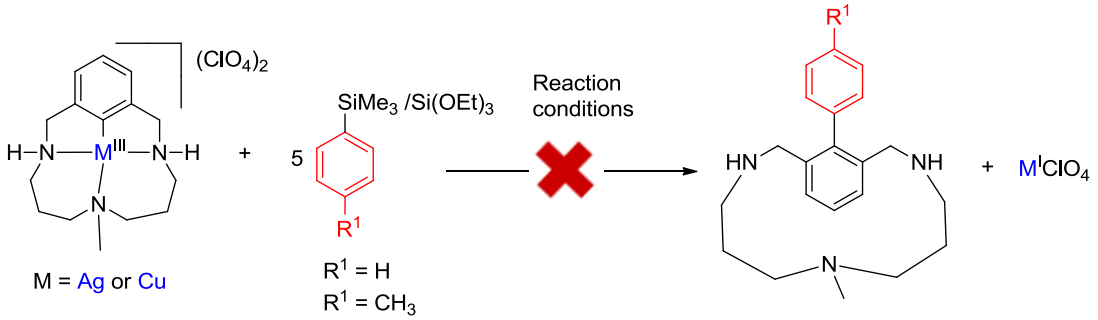


Scheme 18. Cross-coupling reactions stoichiometric of arylboronic acids with aryl-Ag(III) or aryl-Cu(III) complex.

A sample of aryl-Ag(III) or aryl-Cu(III) complex (13.3 mg, 0.024 mmol or 12.2 mg, 0.024 mmol, respectively) was dissolved in the corresponding solvent (0.9 mL) and 0.1 mL of a solution of 1,3,5-trimethoxybenzene (TMB) was added as internal standard. Then, a portion of this solution (0.35 mL) was loaded into a NMR tube and 5 equiv. of the corresponding arylboronic acid was added to the tube (0.35 mL, 0.12 M). The final concentrations: [aryl-Ag(III) or aryl-Cu(III) complex] = 12 mM, [arylboronic acid] = 60 mM. Finally, the tube was sealed with a septum; and the reaction was carried out at 70ºC. It was monitored by ^{1}H-NMR spectroscopy until completion. ^{1}H, ^{13}C, COSY, NOESY, ^{1}H-^{13}C HSQC NMR spectra and Electrospray Ionization in a high-resolution mass spectrometer (Q-TOF) were obtained without isolation of the C-C coupling product.

The reaction yields were obtained by integration of the ^{1}H-NMR spectrum of the crude reaction mixtures relative to the internal standard (TMB). For the case of aryl-Ag(III) complex the reaction were performed in absence of light into an amber NMR tube. And all the reactions were performed under an inert-atmosphere glove box.

3.6. Attempts to synthesise the coupling products of arylsilanes with aryl-Ag(III) or aryl-Cu(III) complex



Scheme 19. Cross-coupling reactions stoichiometric of arylsilanes with aryl-Ag(III) or aryl-Cu(III) complex. Note that the C-C bond-forming is not obtained in any case and the C-O bond-forming is obtained (see section 4.3).

Similarly to the previously methodology, a portion of aryl-Ag(III) or aryl-Cu(III) (13.3 mg, 0.024 mmol or 12.2 mg, 0.024 mmol, respectively) was dissolved in the corresponding solvent (0.9 mL) and 0.1 mL of a solution of TMB was added as internal standard. Afterwards, a portion of this solution (0.35 mL) was loaded into a NMR tube and 5 equiv. of the corresponding arylsilane was added to the tube (0.35 mL, 0.12 M). The final concentrations: [aryl-Ag(III) or aryl-Cu(III) complex] = 12 mM, [arylsilane] = 60 mM. Finally, as before, the tube was sealed with a septum and the reaction was allowed to proceed at 70ºC and it was monitored by ^{1}H-NMR spectroscopy until completion. ^{1}H, ^{13}C, COSY, NOESY, ^{1}H-^{13}C HSQC NMR spectra and ElectroSpray Ionization in a high-resolution mass spectrometer (Q-TOF) were obtained without isolation of the C-C coupling product.

The ^{1}H-NMR spectrum of the crude reaction mixtures did not show the formation of the desired C-C coupling products, and the reagents were recovered. For the case of the aryl-Ag(III) complex the reactions were performed in absence of light into an amber NMR tube. And all the reactions were performed under an inert-atmosphere glove box.

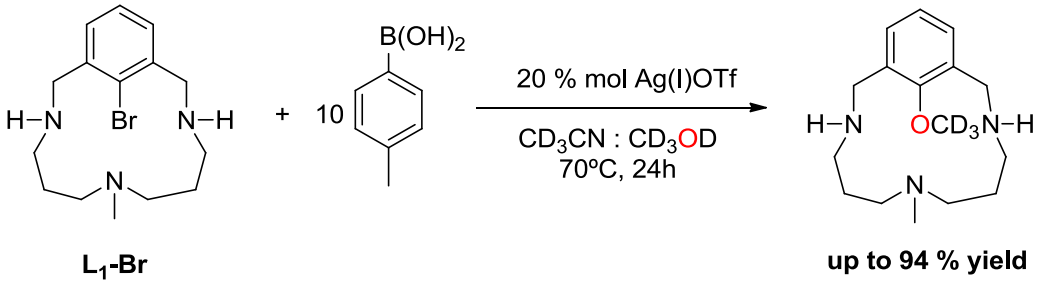
3.7. Silver-catalyzed cross-coupling reactions via aryl-Ag(III) complex

A representative experiment of catalytic C-O bond-forming reaction with ligand **L_1-Br** using 20% mol of silver(I) triflate (AgOTf) and 10 equivalents of an arylboronic acid is hereby explained.

A portion of ligand **L_1-Br** (7.83 mg, 0.024 mmol) was dissolved in CD_3CN (0.8 mL) and 0.1 mL of a solution of TMB was added as internal standard. A solution of silver(I) triflate (6.4 mg, 0.0168 mmol) was added too. Then, a portion of this solution (0.35 mL) was loaded into an amber NMR tube and 10 equiv. of the corresponding arylboronic acid dissolved in CD_3OD were added to the tube (0.35 mL, 0.24 M). The final concentrations: [**L_1-Br**] = 12 mM, [arylboronic acid] = 120 mM, [catalyst] = 2.4 mM. Finally, the tube was sealed with a septum and the reaction was carried out in absence of light and heated to 70ºC. It was monitored by ^{1}H-NMR spectroscopy until completion. An Electrospray Ionization Mass Spectrometry (ESI-MS) was obtained without isolation of the C-C coupling product.

The reaction yield was obtained by integration of the ^{1}H-NMR spectrum of the crude reaction mixtures relative to the internal standard (TMB). The reaction was performed under an inert-atmosphere glove box.

For this experiment we demonstrate that a Ag(I)/Ag(III) catalytic cycle is not operative in model C-C cross-coupling reactions, but in contrast it is operative in model C-O cross-coupling reactions due to the presence of methanol as a solvent (see section 4.4).

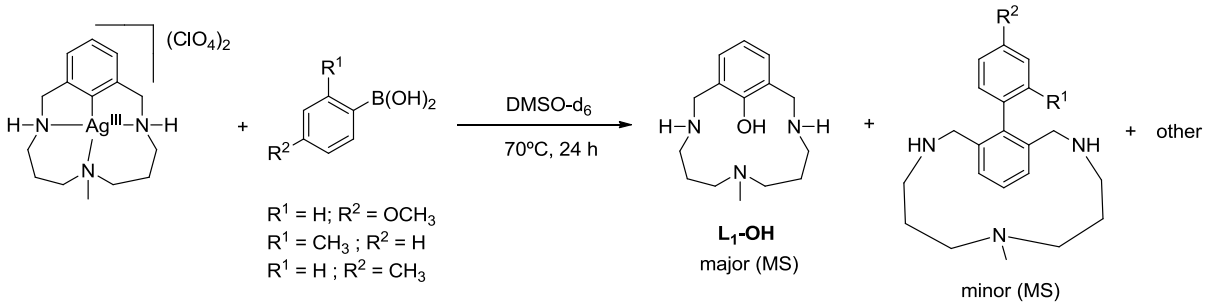


Scheme 20. A silver-catalysed C-O bond-forming cross-coupling reaction with **L_1-Br** model substrate.

4. RESULTS AND DISCUSSION

4.1. C-C cross-coupling reactions of arylboronic acids with aryl-Ag(III) complex

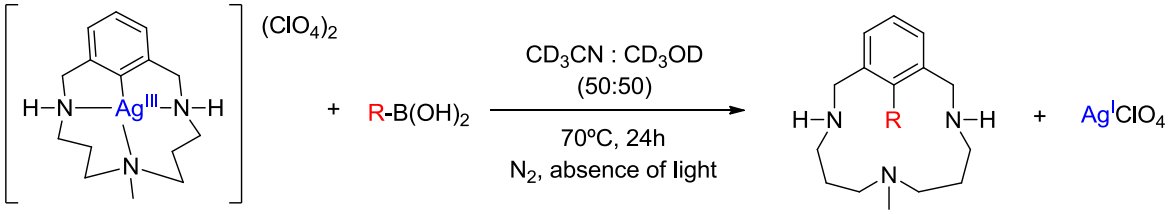
First of all, C-C cross-coupling reactions were studied using aryl-Ag(III) complex with different arylboronic acids in DMSO-d_6. For that case, the desired C-C coupling product was not obtained and, in contrast, the hydroxylation product (**L_1-OH**) was obtained in all cases (see Scheme 21). Mixtures of CD_3CN:THF-d_8 and acetone-d_6 were also tested with aryl-Ag(III) complex and arylboronic acids. But in none of these cases the desired coupling product was obtained.

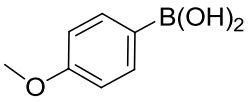
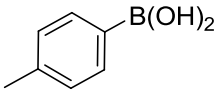
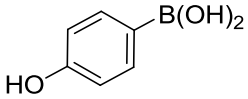
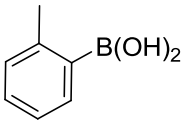


Scheme 21. Reactions between aryl-Ag(III) complex and arylboronic acids in DMSO-d_6. The hydroxylation product (**L_1-OH**) was obtained due to traces of H_2O in DMSO.

The reaction worked properly for the case where a mixture of CD_3CN:CD_3OD (50:50) was used, and the C-C coupling products were obtained in excellent yields (see **Table 1**, products **P1**, **P2**, **P3-OH/OD** and **P4**). These reactions were performed during 24 hours at 70ºC, using four different arylboronic acids (transmetallating agents). In all the cases it is observed the presence of the product (**P5**) resulting from the insertion of deuterated methanol (solvent), which acts as a nucleophile.

Table 1. Stoichiometric coupling of different arylboronic acids with aryl-Ag(III) complex.



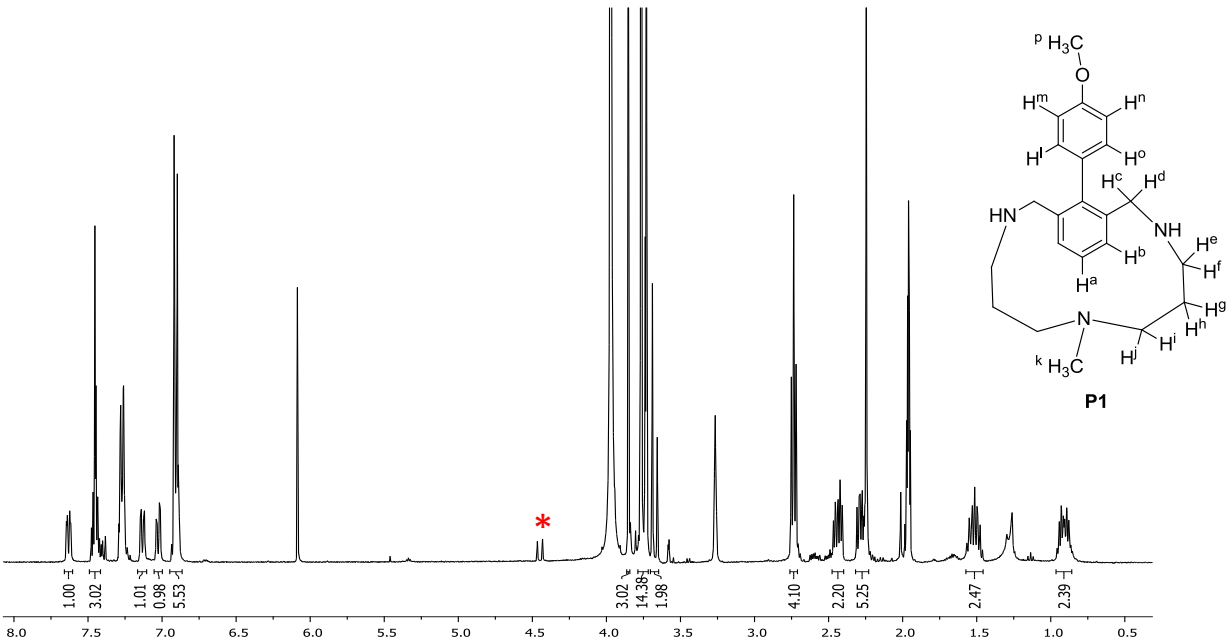
Entry	Arylboronic acid	Equiv.	Yield*
1		5	91% (**P1**)
2		5	85% (**P2**)
3		5	92%** (**P3-OH/OD**)
4		5	87% (**P4**)[25]

* Calculated by ^{1}H-NMR spectroscopy using 1,3,5-trimethoxybenzene (TMB) as internal standard.
For the coupling product **P3-OH/OD the yield is approximate.

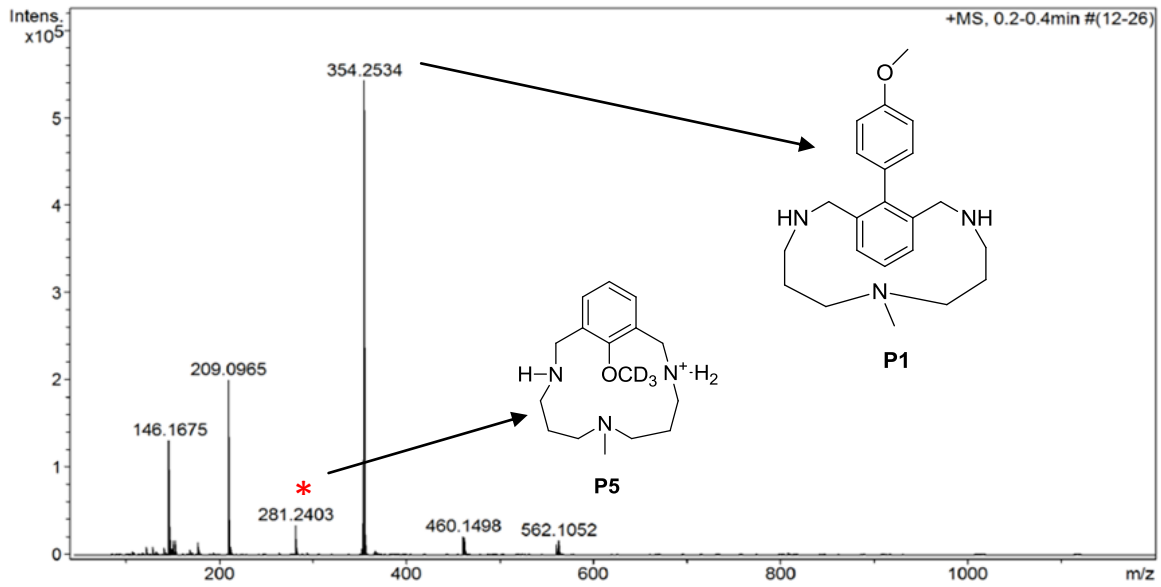
Descriptions of ^{1}H-NMR spectra of the C-C coupling products shown in **Table 1** are presented below:

P1: ^{1}H-NMR (400MHz, CD_3CN:CD_3OD) δ (ppm): 7.63 (dd, *J*=8.48 Hz, *J*=2.2 Hz, 1H, H^{o}), 7.48-7.42 (m, 3H, H^{a} and H^{b}), 7.27 (dd, *J*=7.88 Hz, *J*=0.96 Hz, 1H, H^{n}), 7.13 (dd, *J*=8.52 Hz, *J*=2.68 Hz, 1H, H^{m}), 6.92-6.89 (m, 1H, H^{l}), 3.85 (s, 3H, H^{p}), 3.76-3.73 (m, 2H, H^{c} or H^{d}), 3.67 (d, *J*=13.12 Hz, 2H, H^{c} or H^{d}), 2.73 (t, *J*=6.28 Hz, 4H, H^{e} and H^{f}), 2.47-2.40 (m, 2H, H^{i} or H^{j}), 2.31-2.25 (m, 5H, H^{i} or H^{j} and H^{k}), 1.57-1.46 (m, 2H, H^{g} or H^{h}), 0.96-0.86 (m, 2H, H^{g} or H^{h}).

HRMS (ESI-TOF, $[M-H]^{+}$) *m/z* calculated for $C_{22}H_{32}N_3O^{+}$, 354.2545, found: 354.2534.



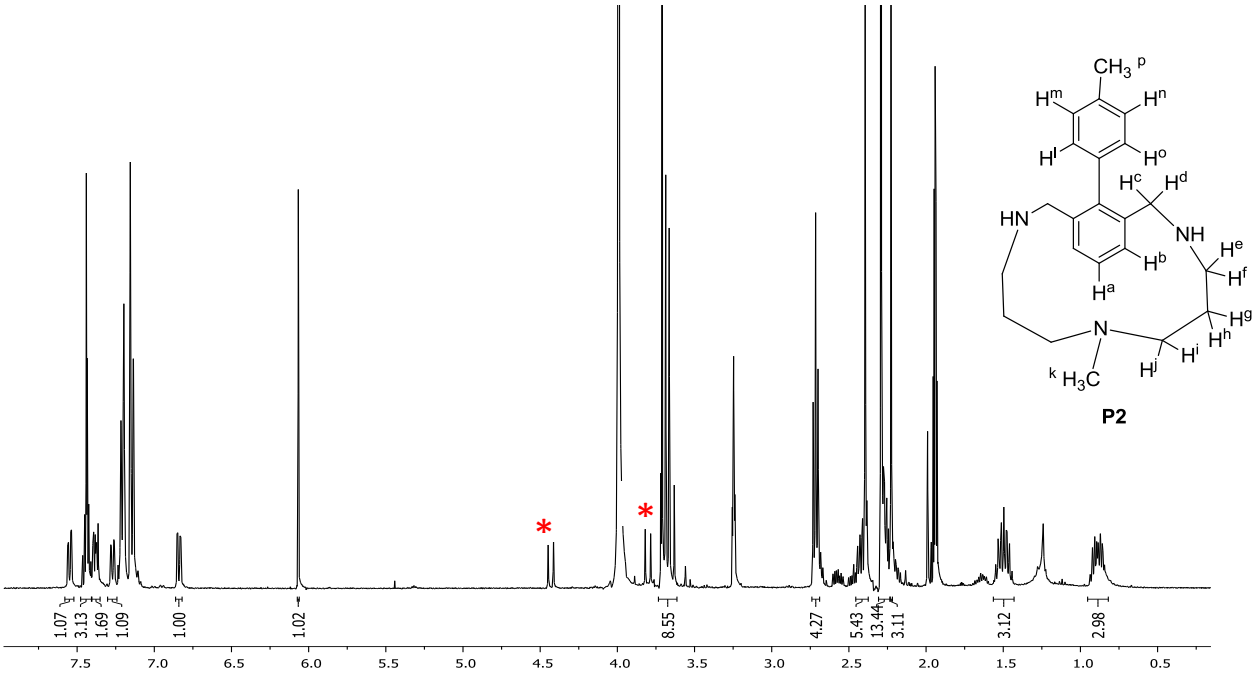
Scheme 22. ^{1}H-NMR spectrum of compound **P1**. Experiment performed in CD_3CN:CD_3OD, 400 MHz, at 298 K. *Impurities due to the product (**P5**) resulting from the insertion of deuterated methanol (solvent), that acts as a nucleophile (see section 4.3., where product **P5** is characterized).



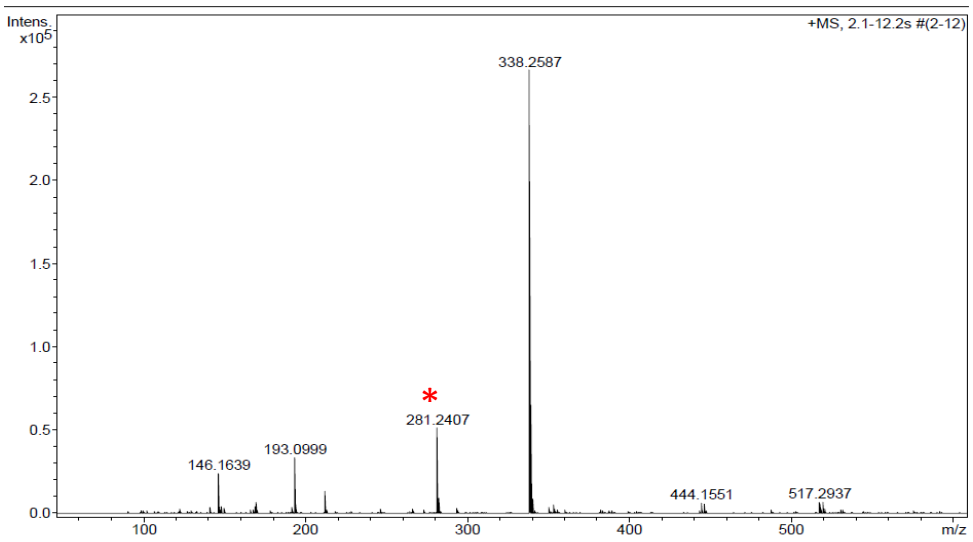
Scheme 23. HRMS (ESI-MS) spectrum of the product **P1**. Experiment performed in CD_3CN. *The peak of *m/z* = 281.2403 corresponds to **P5**.

P2: ^{1}H-NMR (400MHz, CD_3CN:CD_3OD) δ (ppm): 7.55 (dd, *J*=7.8 Hz, *J*=1.96 Hz, 1H, H^o), 7.46-7.41 (m, 3H, H^a and H^b), 7.38 (dd, *J*=7.88 Hz, *J*=4.04 Hz, 1H, H^n), 7.27 (d, *J*=7.84 Hz, 1H, H^m), 6.84 (dd, *J*=7.76 Hz, *J*=2 Hz, 1H, H^l), 3.72-3.63 (m, 4H, H^c and H^d), 2.72 (t, *J*=6.36 Hz, 4H, H^e or H^f), 2.45-2.38 (m, 5H, H^i or H^j and H^p), 2.29-2.24 (m, 2H, H^i or H^j), 2.23 (s, 3H, H^k), 1.55-1.44 (m, 2H, H^g or H^h), 0.94-0.84 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]**$^+$) *m/z* calculated for $C_{22}H_{32}N_3^+$, 338.2596, found: 338.2587.



Scheme 24. ^{1}H-NMR spectrum of compound **P2**. Experiment performed in CD_3CN:CD_3OD, 400 MHz, at 298 K. *Impurities due to the product (**P5**) resulting from the insertion of methanol (solvent), that acts as a nucleophile (see section 4.3, where product **P5** is characterized).

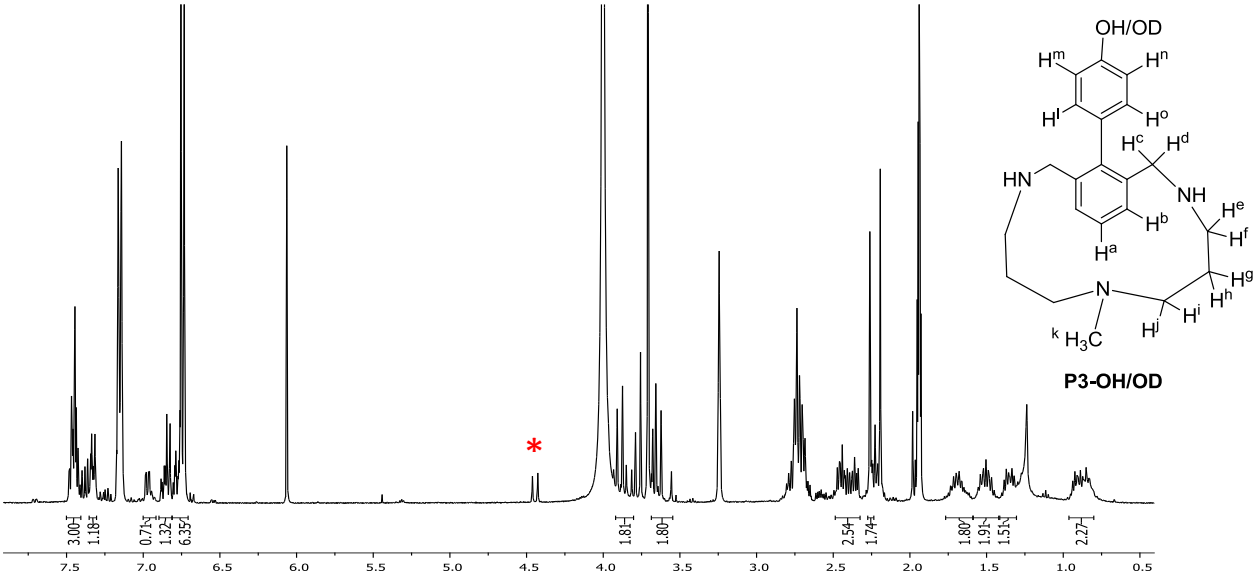


Scheme 25. HRMS (ESI-MS) spectrum of the product **P2**. Experiment performed in CD_3CN. *The peak of *m/z* = 281.2407 corresponds to **P5**.

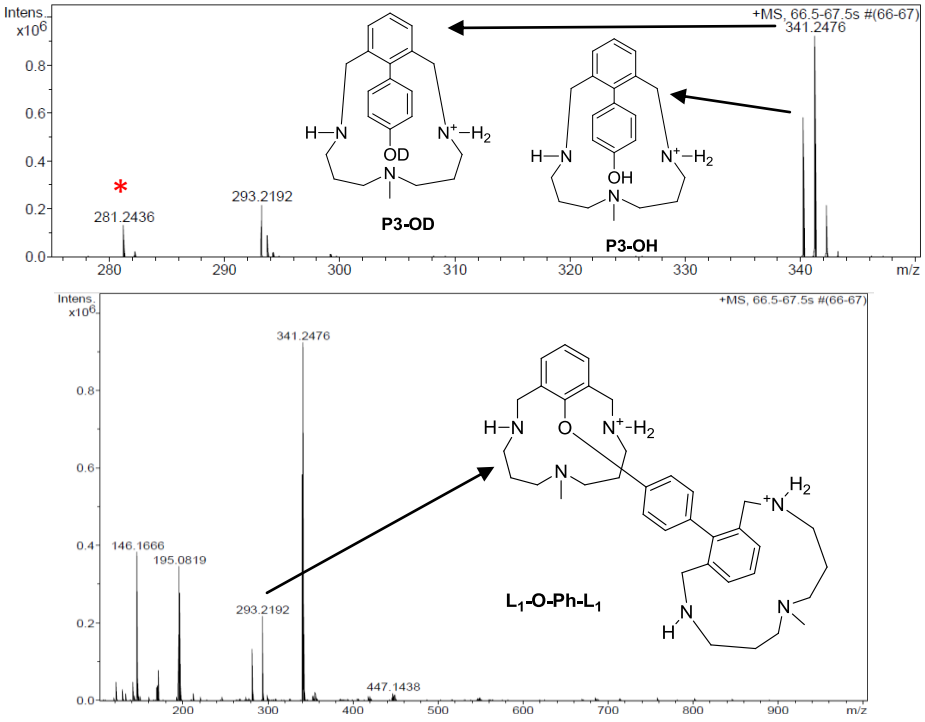
The reaction with the 4-hydroxyphenylboronic acid, which is a bifunctional substrate, resulted interesting since the reaction can takes place by the alcohol or by the arylboronic acid moiety. This reaction (Table 1, entry 3) resulted in the formation of C_{aryl}–C (major) coupling product, although the yield of the reaction was difficult to calculate due to the overlap of the bands in the ^{1}H-NMR spectrum (see Scheme 26). This was because other species (such as **L_1-O-Ph-L_1**) were formed in addition to the desired coupling product, as observed in the ESI-MS spectrum (see Scheme 27). An exchange between a proton and a deuterium in the alcohol moiety of the desired coupling product occurs.

P3-OH/OD: ^{1}H-NMR (400MHz, CD_3CN:CD_3OD) δ (ppm): 7.50-7.41 (m, 3H, H^a and H^b), 7.33 (dd, *J*=8.08 Hz, *J*=2.48 Hz, 1H, H^o), 6.97 (dd, *J*=8.36 Hz, *J*=2.64 Hz, 1H, H^n or H^m or H^l), 6.88-6.77 (m, 2H, H^n or H^m or H^l), 3.78 (d, *J*=13.08 Hz, 2H, H^c or H^d), 3.64 (d, *J*=13.76 Hz, 2H, H^c or H^d), 2.48-2.35 (m, 4H, H^e and H^f), 2.27 (s, 3H, H^k), 1.72-1.66 (m, 2H, H^i or H^j), 1.54-1.47 (m, 2H, H^i or H^j), 1.40-1.30 (m, 2H, H^g or H^h), 0.94-0.83 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]$^+$**) *m/z* calculated for $C_{21}H_{29}DN_3O^+$, 341.2446, found: 341.2476.



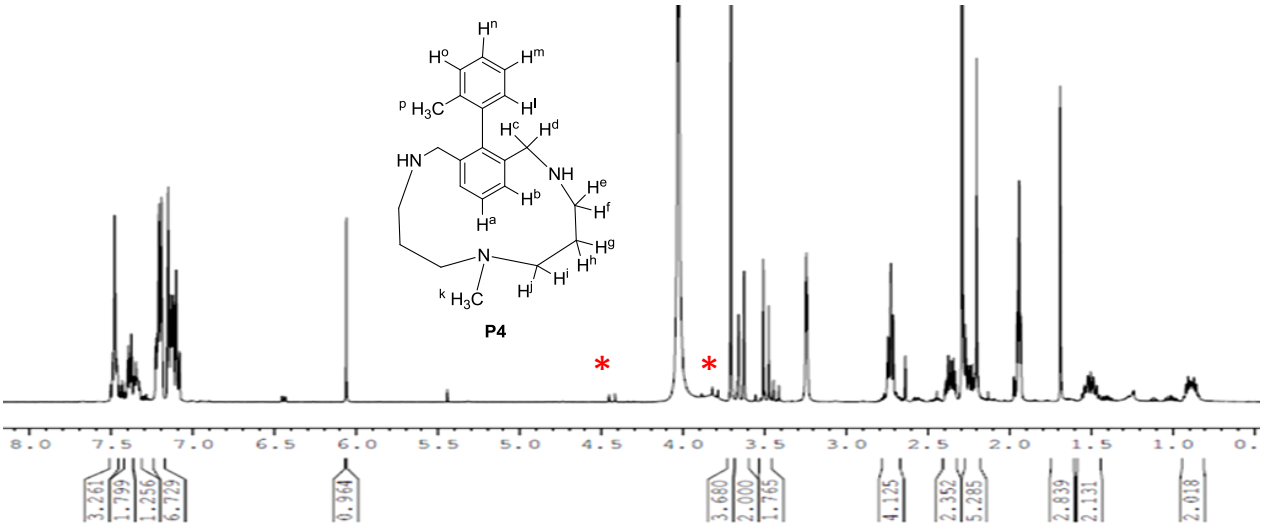
Scheme 26. ^{1}H-NMR spectrum of compound **P3-OH/OD**. Experiment performed in CD_3CN:CD_3OD, 400 MHz, at 298K. *Impurities due to the product (**P5**) resulting from the insertion of methanol (solvent), that acts as a nucleophile (see section 4.3, where product **P5** is characterized).



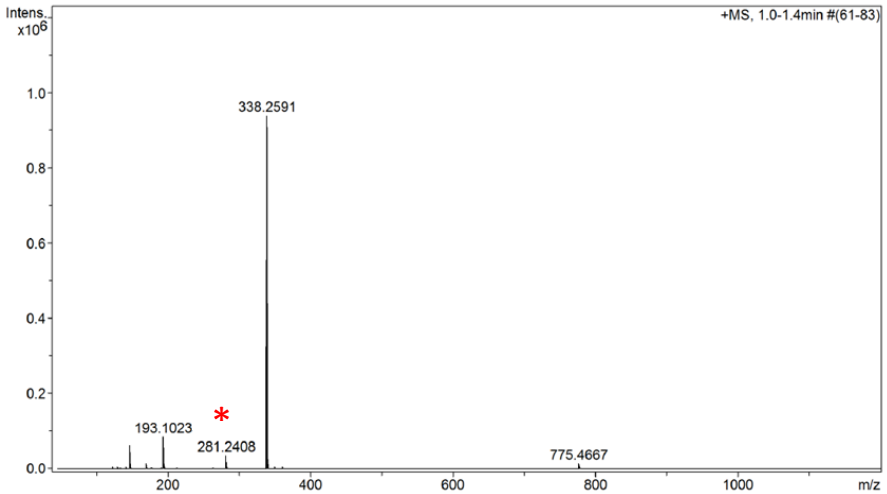
Scheme 27. HRMS (ESI-MS) spectrum of the product **P3-OH/OD** and **L_1-O-Ph-L_1**. Experiment performed in CD_3CN. *The peak of m/z = 281.2436 corresponds to **P5**.

P4: ^{1}H NMR (400 MHz, CD_3CN:CD_3OD) δ (ppm): 7.50-7.43 (m, 3H, H^a and H^b), 7.40-7.37 (m, 2H, H^m and H^n), 7.36-7.33 (m, 1H, H^o), 7.22-7.19 (m, 1H, H^l), 3.64 (d, 2H, *J* = 13.16 Hz, H^c or H^d), 3.49 (d, 2H, *J* = 13.12 Hz, H^c or H^d), 2.75-2.71 (m, 4H, H^e and H^f), 2.39-2.33 (m, 2H, H^i or H^j), 2.27-2.20 (m, 5H, H^i or H^j and H^k), 1.69 (s, 3H, H^p), 1.56-1.45 (m, 2H, H^g or H^h), 0.93-0.84 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]$^+$**) *m/z* calculated for $C_{22}H_{32}N_3^+$, 338.2591, found: 338.2591.



Scheme 28. ^{1}H-NMR spectrum of compound **P4**. Experiment performed in CD_3CN:CD_3OD, 400 MHz, at 298 K. *Impurities due to the product (**P5**) resulting from the insertion of methanol (solvent), that acts as a nucleophile (see section 4.3, where product **P5** is characterized).

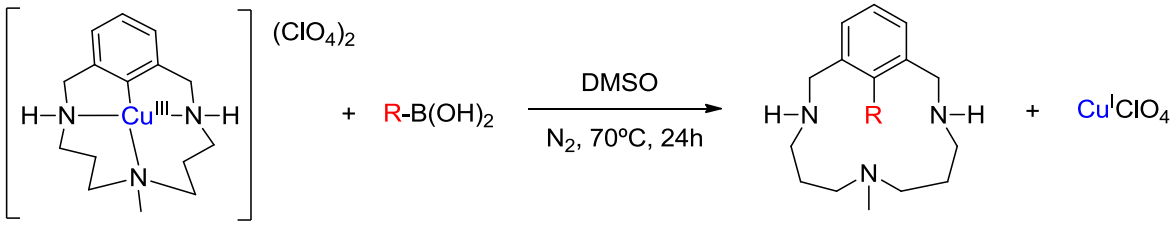


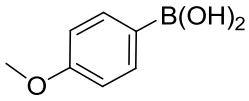
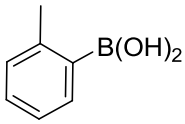
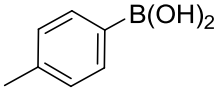
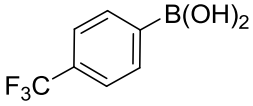
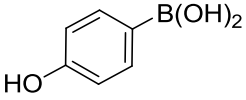
Scheme 29. HRMS (ESI-MS) spectrum of the product **P4**. Experiment performed in CD_3CN. *The peak of m/z = 281.2408 corresponds to **P5**.

4.2. C-C cross-coupling reactions of arylboronic acids with aryl-Cu(III) complex

C-C cross-coupling reactions were studied using aryl-Cu(III) complex with three different arylboronic acids, obtaining in all three cases the desired coupling product in moderate yield. The different arylboronic acids tested are shown in the next table (**Table 2**, products **P1**, **P2** and **P3-OH**). The reactions were performed with DMSO as a solvent, during 24 hours at 70ºC. C-C bond-forming cross-coupling reactions takes place using copper, contrary to C-O bond-forming cross-coupling reactions when silver was used in DMSO-d_6, where the hydroxylation product (**L_1-OH**) was obtained (see section 4.1).

Table 2. Stoichiometric coupling of different arylboronic acids with aryl-Cu(III) complex.



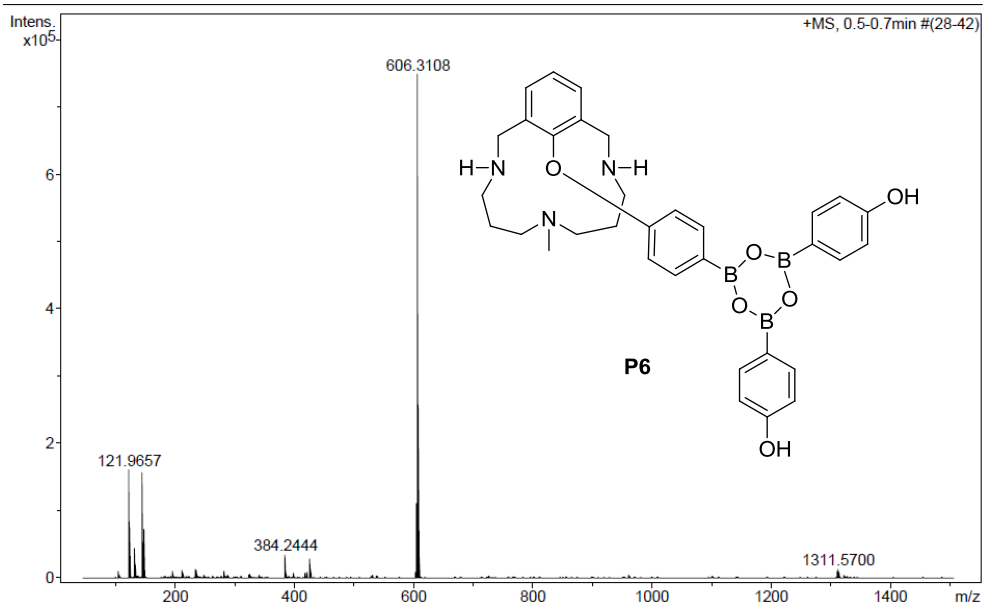
Entry	Arylboronic acid	Equiv.	Yield*	Entry	Arylboronic acid	Equiv.	Yield*
1		5	42% (**P1**)	4		5	- (**L_1-CN**)**
2		5	49% (**P2**)	5		5	-
3		5	46% (**P3-OH**)				

* Calculated by ^{1}H-NMR spectroscopy using TMB as internal standard. It is only indicate the yield values of that reactions in which the desired coupling product was obtained. ****L_1-CN** was detected by HRMS.

Note that the crude ^{1}H-NMR in DMSO-d_6 showed broad bands and the yields were impossible to calculate. So after the reaction was finished, DMSO-d_6 was distilled and CD_3CN (0.7 mL) was added to get the ^{1}H-NMR spectrum.

The reaction of arylboronic acids with aryl-Cu(III) complex resulted in the formation of C-C coupling products in poor yields (**Table 2**, products **P1**, **P2** and **P3-OH**), in any case exceeding 50% yield. In the case of using the sterically hindered o-tolylboronic acid the desired product was not obtained (**L_1-CN** was detected by HRMS) (Table 1, entry 4). The desired coupling product was not obtained with the 4-(trifluoromethyl)phenylboronic acid using DMSO (Table 1, entry 5), either. For the latter, CD_3CN as solvent was tested too, but the desired coupling product was not obtained.

The reactions were tested with DMSO because all of these arylboronic acids were soluble in this solvent. But in the case of 4-hydroxyphenylboronic acid (Table 1, entry 3), which is a bifunctional arylboronic acid, the reaction was tested with CD_3CN too. This substrate was interesting because the reaction can takes place by the alcohol or by the arylboronic acid moiety. **P6** was obtained, which was characterized by HRMS (see Scheme 30).The ^{1}H-NMR spectrum showed broad bands that prevented the proper characterization.



Scheme 30. HRMS (ESI-MS) spectrum of the product **P6**. Experiment performed in CD_3CN.

In this particular reaction the C-O bond-forming cross-coupling reaction takes place, forming an adduct (**P6**). Then we tried to break the B-O bond formed with fluorides, adding tetramethylammonium fluoride (NMe_4F), but it was not achieved satisfactorily.

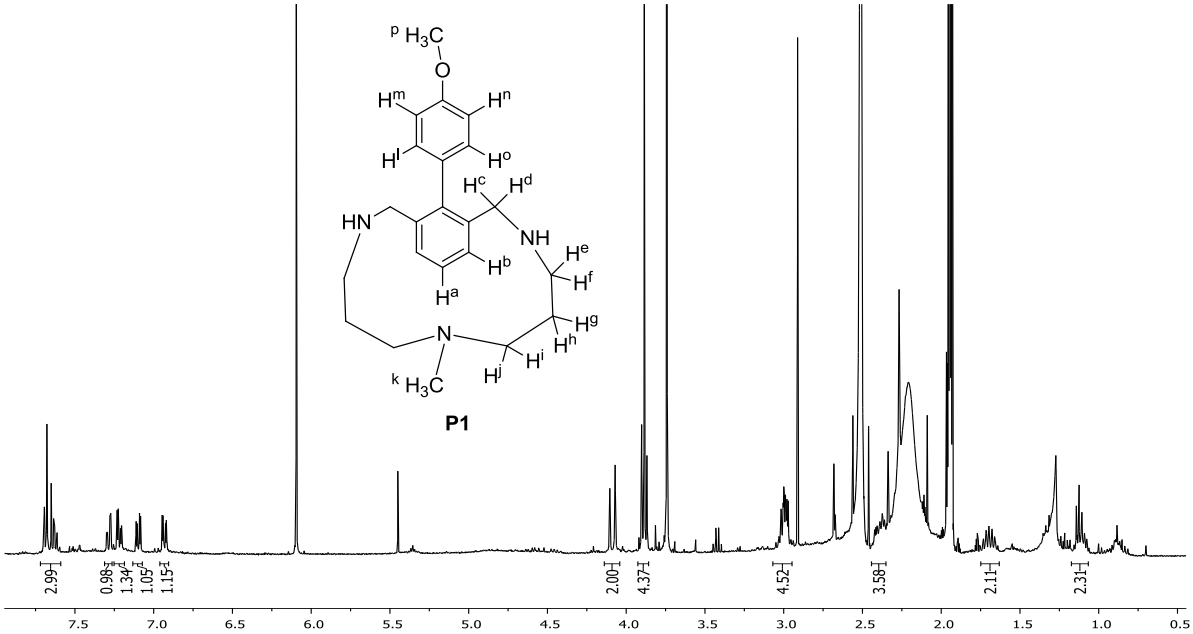
As a conclusion, in the case of aryl-Cu(III) complex the C-O bond-forming cross-coupling reactions take place when CD_3CN was used. However, C-C bond-forming cross-coupling reactions occurred when DMSO was used. The generality of this solvent-dependent selectivity needs to be further explored.

Descriptions of ^{1}H-NMR spectra of the C-C coupling products shown in **Table 2** are presented below. Note that these spectra are somewhat different compared with those obtained in the case

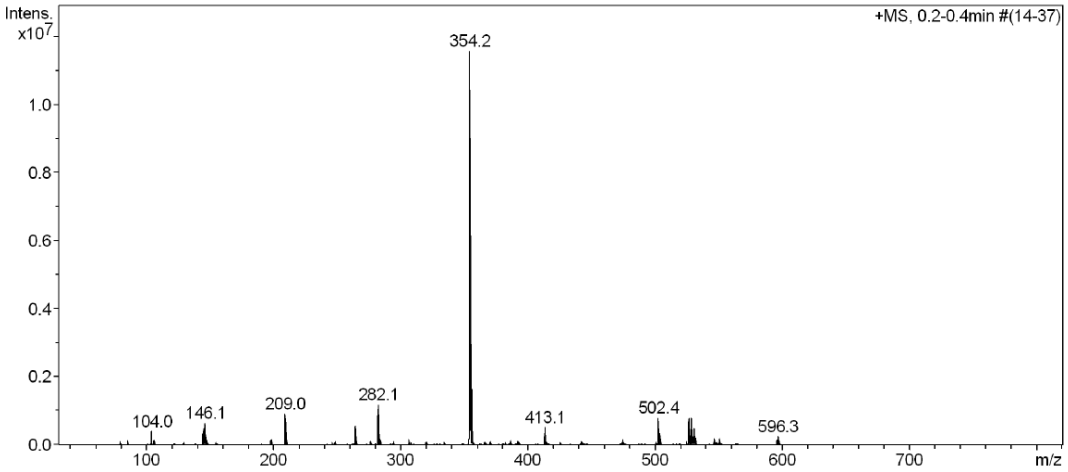
where the aryl-Ag(III) complex was used (see section 4.1), probably due to the presence of Cu(I) or Ag(I) in the crude solutions.

P1: ^{1}H-NMR (400MHz, CD_3CN) δ (ppm): 7.69-7.61 (m, 3H, H^a and H^b), 7.28 (dd, *J*=8.44Hz, J=2.28Hz, 1H, H^l or H^o), 7.22 (dd, *J*=8.44Hz, *J*=2.68Hz, 1H, H^l or H^o), 7.09 (dd, *J*=8.52Hz, *J*=2.72Hz, 1H, H^n or H^m), 6.93 (dd, *J*=8.52Hz, *J*=2.2Hz, 1H, H^n or H^m), 4.09 (d, *J*=13.48Hz, 2H, H^c or H^d), 3.88 (d, *J*=13.48Hz, 2H, H^c or H^d), 3.88 (s, 3H, H^p), 3.02-2.97 (m, 4H, H^e and H^f), 2.42-2.36 (m, 2H, H^i or H^j), 2.32-2.24 (m, 2H, H^i or H^j), 2.27 (s, 3H, H^k), 1.73-1.66 (m, 2H, H^g or H^h), 1.16-1.08 (m, 2H, H^g or H^h).

ESI-MS (**[M-H]$^+$**) *m/z* calculated for $C_{22}H_{32}N_3O^+$, 354.3, found: 354.2.



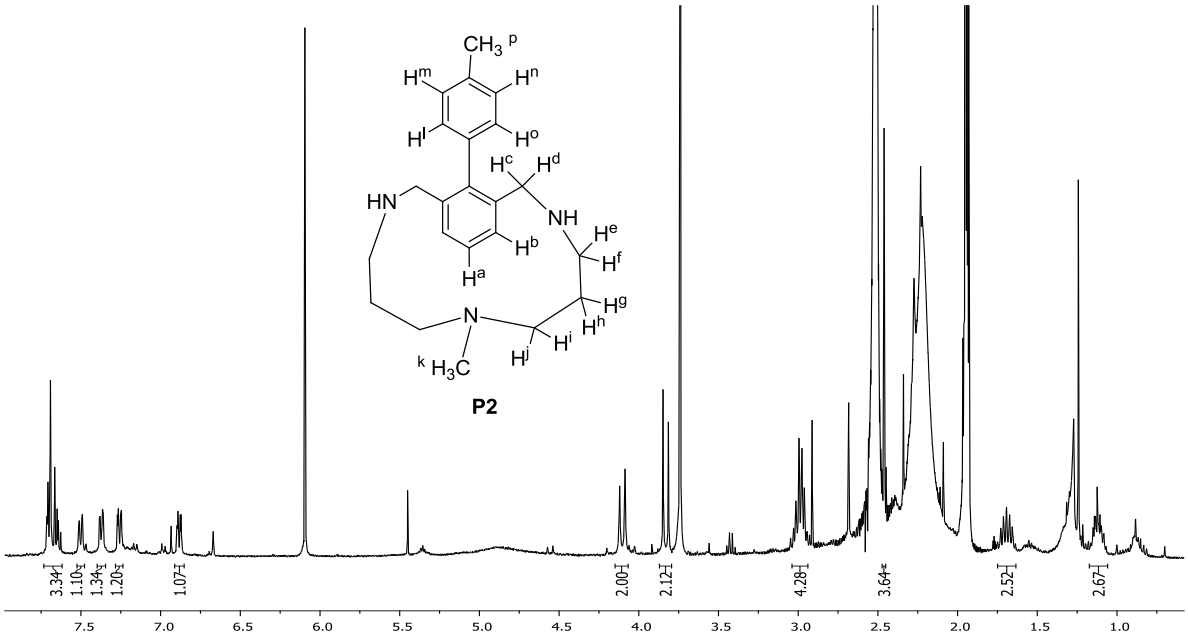
Scheme 31. ^{1}H-NMR spectrum of compound **P1**. Experiment performed in CD_3CN, 400 MHz, at 298 K.



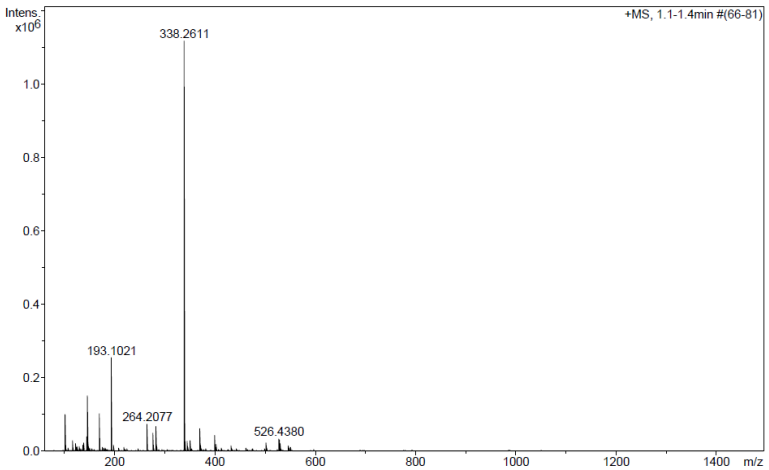
Scheme 32. ESI-MS spectrum of the product **P1**. Experiment performed in CD_3CN.

P2: ^{1}H-NMR (400MHz, CD_3CN) δ (ppm): 7.71-7.62 (m, 3H, H^a and H^b), 7.50 (d, *J*=7.8Hz, 1H, H^m or H^n), 7.37 (d, *J*=6.48Hz, 1H, H^m or H^n), 7.26 (dd, *J*=7.76Hz, *J*=2Hz, 1H, H^l or H^o), 6.88 (dd, *J*=7.8Hz, *J*=2Hz, 1H, H^l or H^o), 4.10 (d, *J*=13.56Hz, 2H, H^c or H^d), 3.83 (d, *J*=13.52Hz, 2H, H^c or H^d), 3.05-2.93 (m, 4H, H^e and H^f), 2.48-2.38 (m, 2H, H^i or H^j), 2.46 (s, 3H, H^p), 2.36-2.26 (m, 2H, H^i or H^j), 2.27 (s, 3H, H^k), 1.77-1.66 (m, 2H, H^g or H^h), 1.15-1.08 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]$^+$**) *m/z* calculated for $C_{22}H_{32}N_3^+$, 338.2518, found: 338.2611.



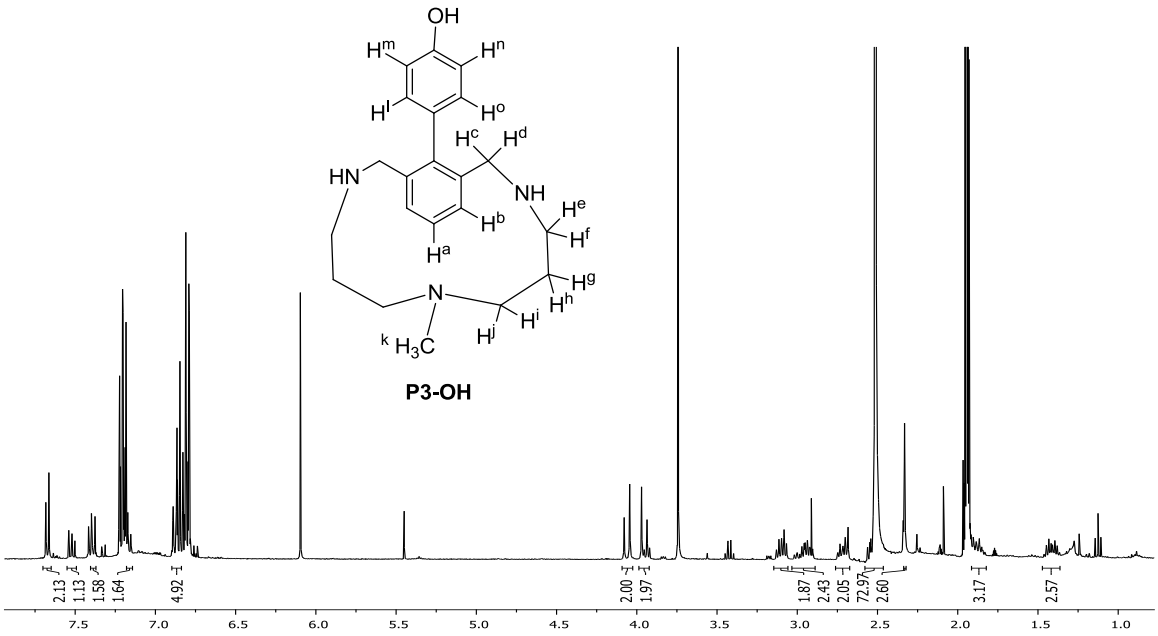
Scheme 33. ^{1}H-NMR spectrum of compound **P2**. Experiment performed in CD_3CN, 400 MHz, at 298 K.



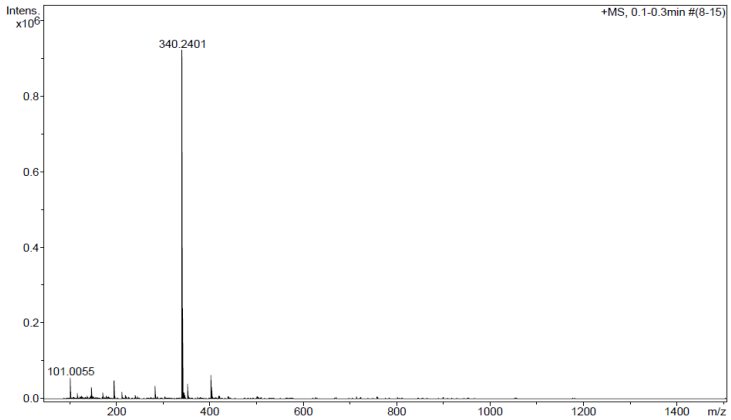
Scheme 34. HRMS (ESI-MS) spectrum of the product **P2**. Experiment performed in CD_3CN.

P3-OH: ^{1}H-NMR (400MHz, CD_3CN) δ (ppm): 7.67 (d, *J*=7.6Hz, 2H, H^b), 7.51 (t, *J*=7.28Hz, 1H, H^a), 7.39 (dd, *J*=8.68Hz, *J*=7.36Hz, 1H, H^o), 7.23-7.16 (m, 1H, H^n), 6.89-6.77 (m, 2H, H^l or H^o and H^m or H^n), 4.05 (d, *J*=13.68Hz, 2H, H^c or H^d), 3.94 (d, *J*=13.76Hz, 2H, H^c or H^d), 3.12-3.06 (m, 2H, H^e or H^f), 2.96-2.89 (m, 2H, H^e or H^f), 2.75-2.68 (m, 2H, H^i or H^j), 2.58-2.53 (m, 2H, H^i or H^j), 2.32 (s, 3H, H^k), 1.90-1.84 (m, 2H, H^g or H^h), 1.44-1.38 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]$^+$**) *m/z* calculated for $C_{21}H_{29}N_3O^+$, 340.2389, found: 340.2401.

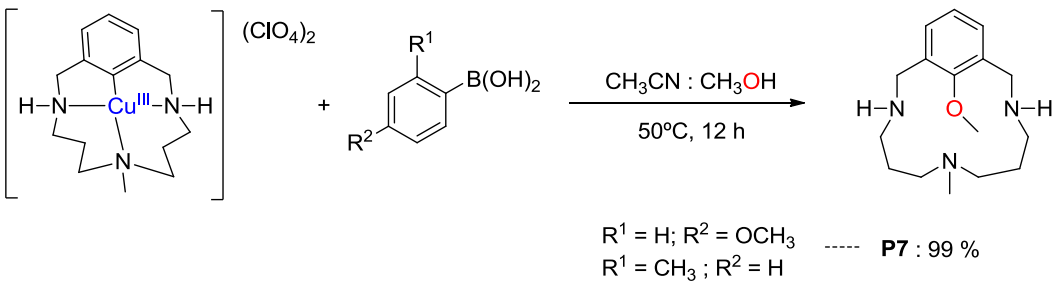


Scheme 35. ^{1}H-NMR spectrum of compound **P3-OH**. Experiment performed in CD_3CN, 400 MHz, at 298 K.



Scheme 36. HRMS (ESI-MS) spectrum of the product **P3-OH**. Experiment performed in CD_3CN.

Other experiments tested with the aryl-Cu(III) complex were using a mixture of CD_3CN:CD_3OD (50:50), in the same way it had been tested with aryl-Ag(III) complex. In that case, always the C-O bond-forming cross-coupling reaction takes place, due to the presence of methanol (solvent) that acts as a nucleophile (see Scheme 37)[22]. Mixtures of CD_3CN:THF-d_8 and acetone-d_6 were also tested with aryl-Cu(III) complex and arylboronic acids, but in none of these cases the desired coupling product was obtained.

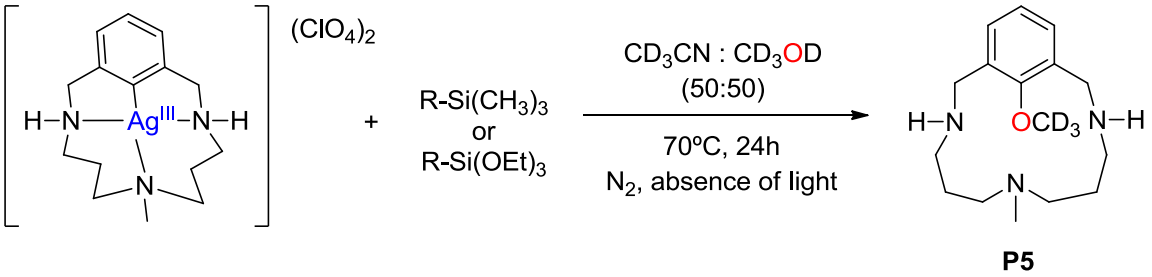


Scheme 37. C-O bond-forming cross-coupling reaction catalyzed by aryl-Cu(III) complex.

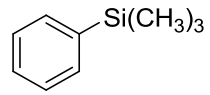
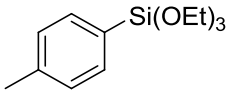
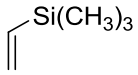
4.3. Attempts to obtain C-C cross-coupling reactions of arylsilanes with aryl-Ag(III) complex

Here we wanted to study stoichiometric couplings of arylsilanes with the aryl-Ag(III) complex, in the same conditions previously tested with arylboronic acids (see section 4.1). However, we find that it was not possible to obtain C-C bond-forming cross-coupling reactions. Despite this, a C-O bond-forming was obtained in all the cross-coupling reactions.

Table 3. Stoichiometric coupling of different arylsilanes with aryl-Ag(III) complex.



P5

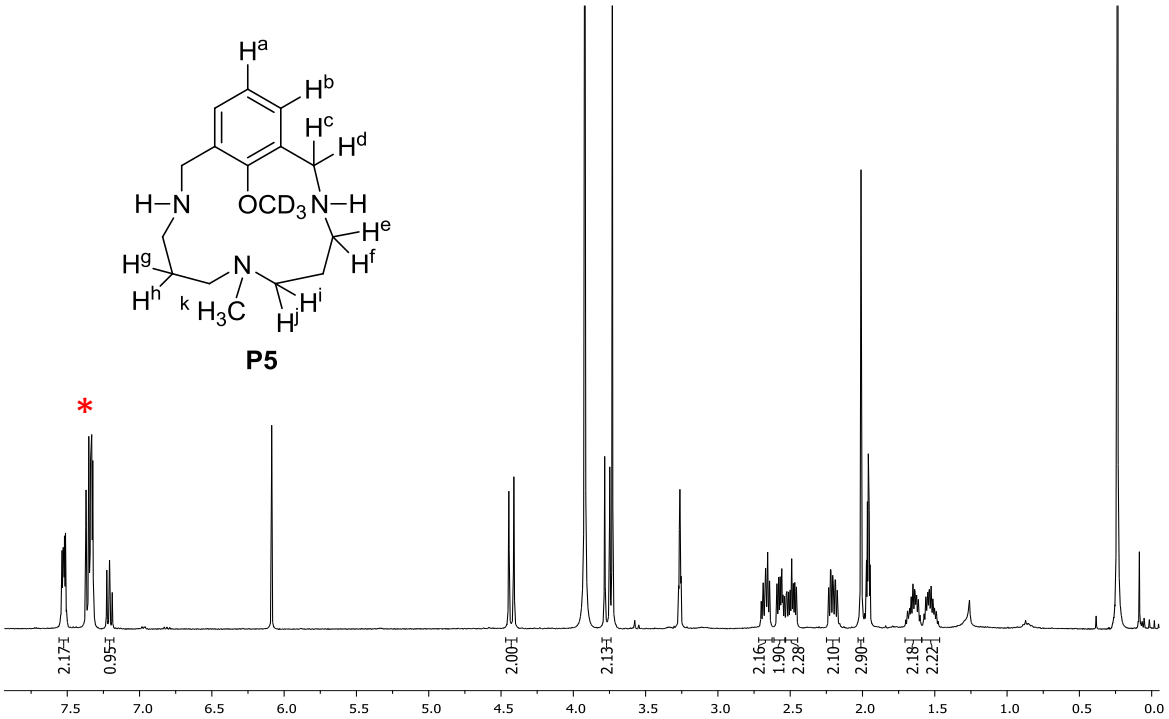
Entry	Arylsilanes	Equiv.	Yield*
1		5	99% (**P5**)
2		5	99% (**P5**)
3		5	84% (**P5**)

* Calculated by ^{1}H-NMR spectroscopy using TMB as internal standard.

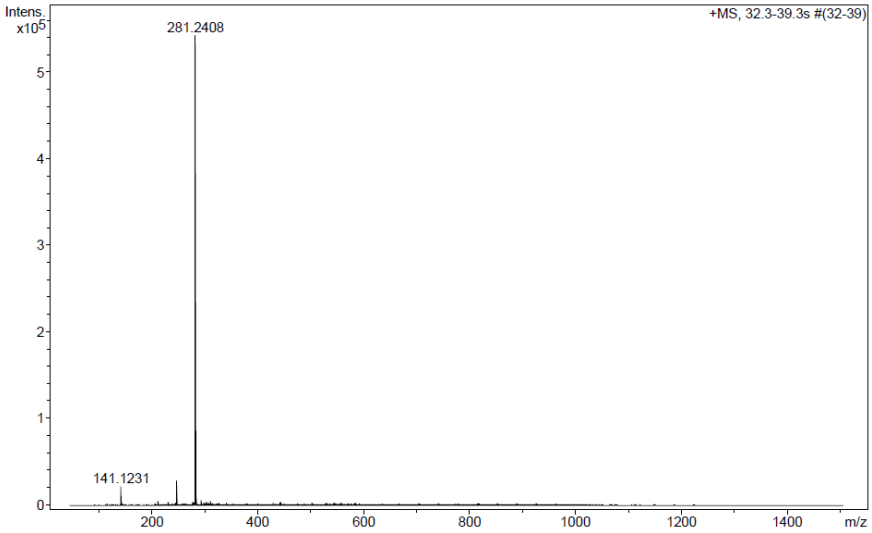
The product **P5** was obtained due to the presence of deuterated methanol as a solvent in the reaction, which acts as a nucleophile. This product was characterized by ^{1}H-NMR spectroscopy and Electrospray ionization in a high-resolution mass spectrometer (Q-TOF).

P5: ^{1}H-NMR (400MHz, CD_3CN:CD_3OD) δ (ppm): 7.53 (m, 2H, H^b), 7.20 (t, *J*=7.52 Hz, 1H, H^a), 4.43 (d, *J*=13.96 Hz, 2H, H^c or H^d), 3.78 (d, *J*=14 Hz, 2H, H^c or H^d), 2.70-2.64 (m, 2H, H^e or H^f), 2.59-2.54 (m, 2H, H^e or H^f), 2.53-2.46 (m, 2H, H^i or H^j), 2.23-2.17 (m, 2H, H^i or H^j), 2.01 (s, 3H, H^k), 1.69-1.61 (m, 2H, H^g or H^h), 1.56-1.49 (m, 2H, H^g or H^h).

HRMS (ESI-TOF, **[M-H]$^+$**) *m/z* calculated for $C_{16}H_{25}D_3N_3O^+$, 281.2421, found: 281.2408.



Scheme 38. ^{1}H-NMR spectrum of compound **P5**. Experiment performed in CD_3CN:CD_3OD, 400 MHz, at 298 K using trimethyl(phenyl)silane as a transmetallating agent (Table 3, entry 1). *Impurities due to the excess of the arylsilane.



Scheme 39. HRMS (ESI-MS) spectrum of the product **P5**. Experiment performed in CD_3CN.

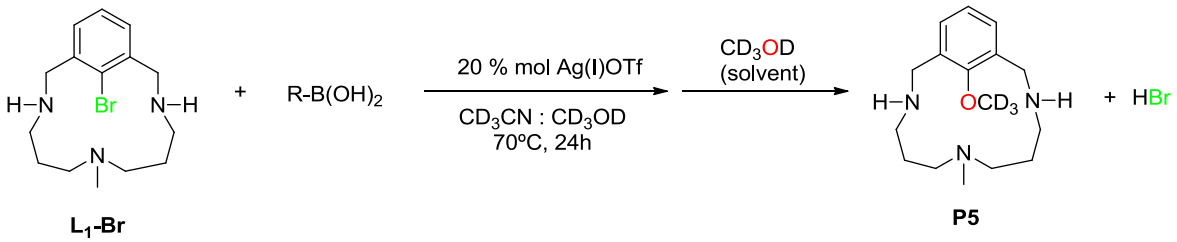
These reactions were performed with other solvent conditions, specifically with a mixture of CD_3CN:Acetone-d_6, or only with CD_3CN, although without success. Reactions were also tested using the aryl-Cu(III) complex with arylsilanes using DMSO-d_6 as a solvent (as in section 4.2. where arylboronic acids are used), but no C-C coupling was obtained.

Attempts to synthesize the C-C coupling product of arylsilanes with the aryl-Ag(III) complex was using fluorides (tetrabutylammonium fluoride) to activate the arylsilane. Upon addition of the fluoride source, the solution rapidly turns deep orange, indicating some degree of deprotonation of the aryl-Ag(III) complex as a consequence of the basic character of the fluorides[25].

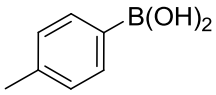
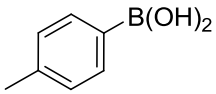
4.4. Catalytic cross-coupling reactions via aryl-Ag(III) complex.

Initially we wanted to show that a Ag(I)/Ag(III) catalytic cycle is operative in model C-C cross-coupling reactions using arylboronic acids. The positive results obtained for the C-C cross-coupling reactions stoichiometric in silver prompted us to explore the catalytic version of these processes. Strikingly, the catalytic cycle was effective not for C-C cross-coupling but for C-O cross-coupling reactions, obtaining **P5** product quantitatively (**Table 4**).

Table 4. Catalytic cross-coupling reactions via Ag(III) species with L_1-Br model substrate.



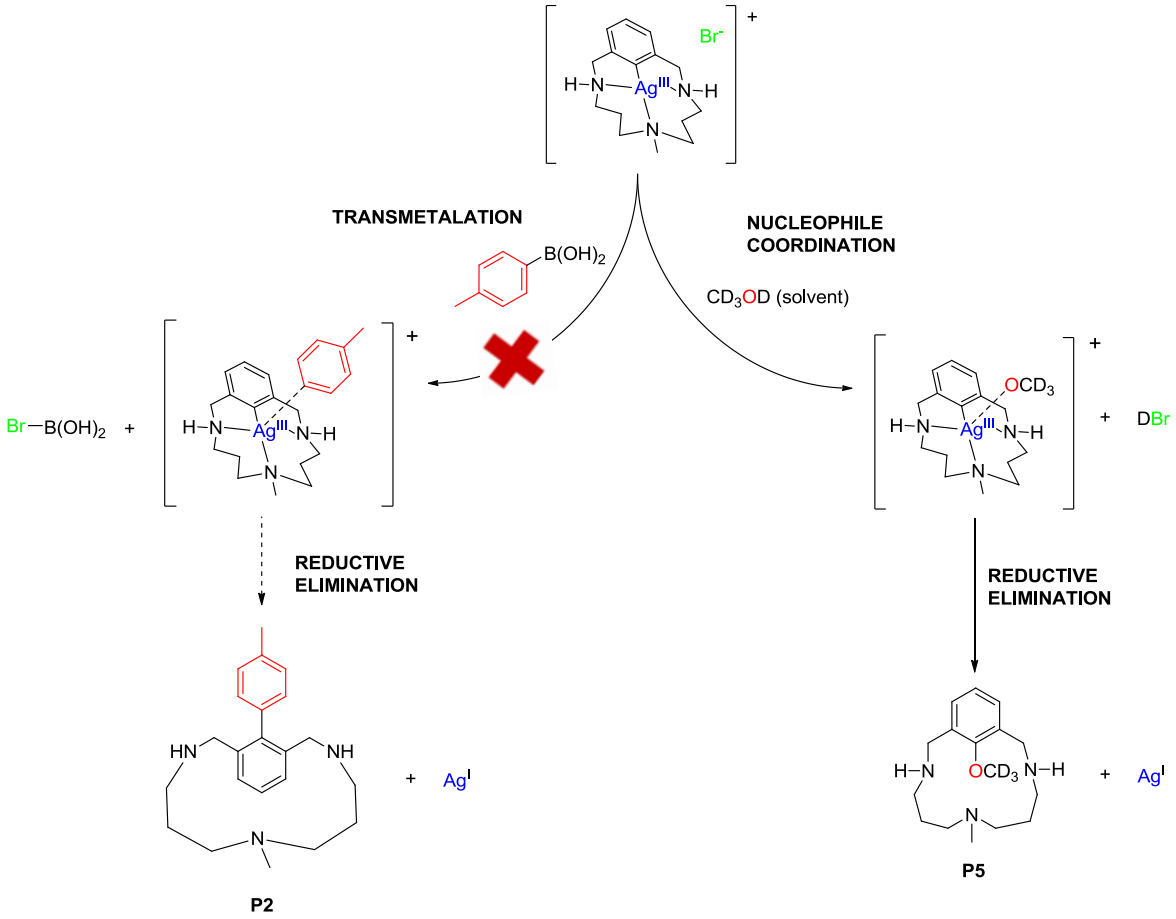
L_1-Br P5

Entry	Arylboronic acid	Proportion of solvents (CD_3CN:CD_3OD)	AgOTf (mol%)	P5 (% Yield)*
1		50:50	20	94
2		90:10	20	-

* Calculated by ^{1}H-NMR spectroscopy using TMB as internal standard. It is only indicate the yield values of that reactions in which the desired coupling product was obtained.

The conceived catalytic strategy for achieving transmetalation consisted in the addition of a catalytic amount (20 mol%) of an Ag(I) source (AgOTf). We studied the p-tolylboronic acid coupling with the bromide ligand (**L_1-Br**). Surprisingly C-C bond-forming did not occur, contrary to what occurred with stoichiometric cross-coupling reactions (see section 4.1). This is explained by the presence of the bromine that prevents the insertion of the arylboronic acid, and in contrast, the insertion of deuterated methanol (solvent) is favored, acting as a nucleophile (see Scheme 40). We tested these reactions with a mixture of solvents (CD_3CN:CD_3OD), so the presence of deuterated methanol causes the C-O cross-coupling reactions. For the experiment performed with a proportion of CD_3CN:CD_3OD of 90:10 (Table 4, entry 2) only traces of the C-O coupling product was obtained, because the deuterated methanol proportion was too little.

In the case of stoichiometric cross-coupling reactions there is not presence of bromine because for these reactions we started with the aryl-Ag(III) complex synthesized (see section 3.2), so the C-C bond-forming cross-coupling reactions occurs successfully in that case (see section 4.1).



Scheme 40. Proposed mechanistic scheme for a Ag(I)-catalysed cross-coupling reaction. Nucleophile coordination of deuterated methanol (solvent) occurs, obtaining the final coupling product **P5**. The transmetalation of the arylboronic acid is not achieved satisfactorily.

5. CONCLUSIONS AND OUTLOOK

In this project we have explored the chemistry of silver and copper in cross-coupling reactions. For both elements it has been shown that two-electron redox Ag(I)/Ag(III) and Cu(I)/Cu(III) catalytic cycles are followed in model systems in the same way that the well-known chemistry of palladium.

It has been possible to synthesize and characterize an aryl-Ag(III) and an aryl-Cu(III) complex for the study of C-C cross-coupling reactions. Then, we have optimized the reaction conditions for the different C-C cross-coupling reactions tested and it has been concluded that complexes of both metals have a different reactivity.

On the one hand, while the aryl-Cu(III) complex provides the desired C-C coupling product by making it react with arylboronic acids as transmetallating agent with DMSO as a solvent, similar reactions with the aryl-Ag(III) complex do not progress and in contrast, in this last case the hydroxylation product (**L_1-OH**) was obtained due to the presence of water traces in DMSO. On the other hand, the aryl-Ag(III) complex provides the desired C-C coupling product by reacting with arylboronic acids using a mixture of solvents (CD_3CN:CD_3OD). When these conditions are applied to the aryl-Cu(III) complex only the C-O bond-forming cross-coupling reaction with CD_3OD as nucleophile took place. Therefore, the different reactivity of well-defined aryl-Ag(III) and aryl-Cu(III) complexes in front arylboronic acids as transmetallating agents in cross-coupling transformations has been demonstrated.

For the cross-coupling reactions tested with arylsilanes, we could conclude that in any case the C-C bond-forming has been obtained. For the case of using the aryl-Ag(III) complex, we tested the reaction with the same conditions that worked with the arylboronic acids (CD_3CN:CD_3OD), but in that case we obtained the C-O coupling product due to the deuterated methanol that acts as a nucleophile. Then we tested the cross-coupling reaction of arylsilanes with the aryl-Cu(III) complex in DMSO, but neither C-C nor the C-O coupling product were obtained.

Finally, catalytic cross-coupling reactions via aryl-Ag(III) complex with arylboronic acids were tested aiming at obtaining C-C coupling products through a Ag(I)/Ag(III) catalytic cycle. These experiments were tested with a CD_3CN:CD_3OD mixture, but in this case the results were negative, and we conclude that the Ag(I)/Ag(III) catalytic cycle was not operative in model C-C cross-coupling reactions in this specific case. Nonetheless, a C-O bond-forming was obtained, in contrast to what have been obtained on the stoichiometric couplings in these same conditions. This is explained by the presence of bromine in the aryl-Ag(III) intermediate complex, which prevents the insertion of the arylboronic acid and the insertion of deuterated methanol is favored, acting as a nucleophile.

In summary, we have demonstrated that the aryl-Ag(III) and the aryl-Cu(III) complex have a different reactivity in front arylboronic acids, and this reactivity is also different in the case of cross-coupling reactions with arylsilanes. In addition, the aryl-Ag(III) complex has a different reactivity when the catalytic version of these processes is performed. Therefore, this study opens the door to further explore orthogonal selectivities of both species.

6. REFERENCES

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