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New NHC- silver and gold complexes active in A^3-coupling (aldehyde-alkyne-amine) reaction.

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Abstract

Silver and gold complexes bearing unsaturated *N*-heterocyclic carbene ligands, with unsymmetrical *N*-substituents and hydrogen or chlorine on backbone, have been synthetized and their efficiency tested in A^3-coupling (aldehyde–alkyne–amine) reactions. Gold complexes showed higher activity than corresponding silver ones, even if the significant role of the backbone substituents should not be neglected. Indeed, complexes with chlorine substituted backbone were more efficient than hydrogen analogous. According to DFT calculations, electronic differences among complexes are able rationalize the different catalytic behavior, whereas steric properties play a minor part.

1. Introduction

The most efficient method for preparing propargylamines is the multicomponent reaction (MCR) commonly referred to as A^3-coupling (aldehyde–alkyne–amine) reaction [1,2] (see Scheme 1). The MCR is very interesting from an environmental point of view, as it allows the synthesis of complex molecules, reducing the total time necessary to obtain the desired product, by minimizing solvents and energy and

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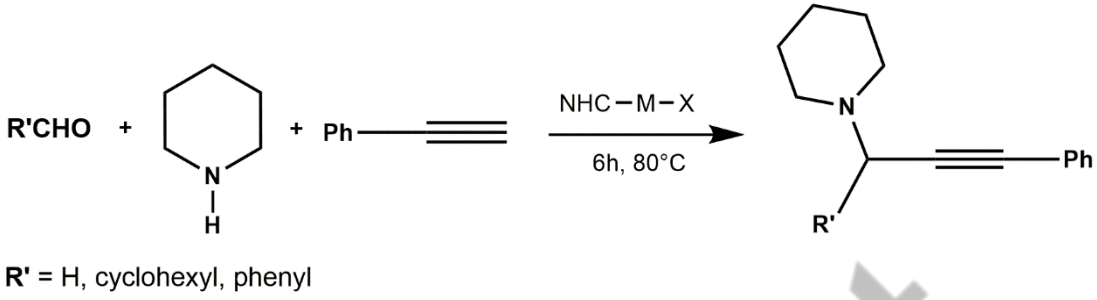
decreasing the production of by-products [3], since water is the only by-product with the desired compound.



Scheme 1. The A^3 reaction for the synthesis of propargylamines.

The propargylamines are versatile intermediates for the preparation of various nitrogen-containing compounds and important components of many biologically active pharmaceutical and natural products, such as Seleginine and Rasagiline, used to treat symptoms in early Parkinson's disease and Ladostigil as a neuroprotective agent [4-9].

Propargylamine can be prepared through addition of stoichiometric quantities of nucleophilic σ-alkyne organometallic reagents (acetylide) to electrophiles C=N groups (imines or their derivatives). The acetylides are prepared by reaction of terminal alkynes with strong bases such as alkylmetals, metallized amides, alkoxides or hydroxides [10]. However, these compounds are difficult to manage, and their reactions must be carried out at low temperatures and under anhydrous conditions. As an alternative to the use of stoichiometric amounts of metallized alkynes, it is possible to carry out this reaction by employing a catalytic amount of late transition metals. Several metallic compounds based on iron [11,12], cobalt [13], nickel [14], zinc [15,16], and mercury [17] showed significant activity in catalyzing this reaction, however, those which have proved to be the most interesting, are based on coin metals: copper, silver and gold [18-21]. These metals can coordinate terminal alkynes by forming π complexes, thereby increasing the acidity of the C–H bond. Because of this increased acidity, weak basic amines can deprotonate the CH bond and generate the desired organometallic alkynyl nucleophile [22]. The reaction

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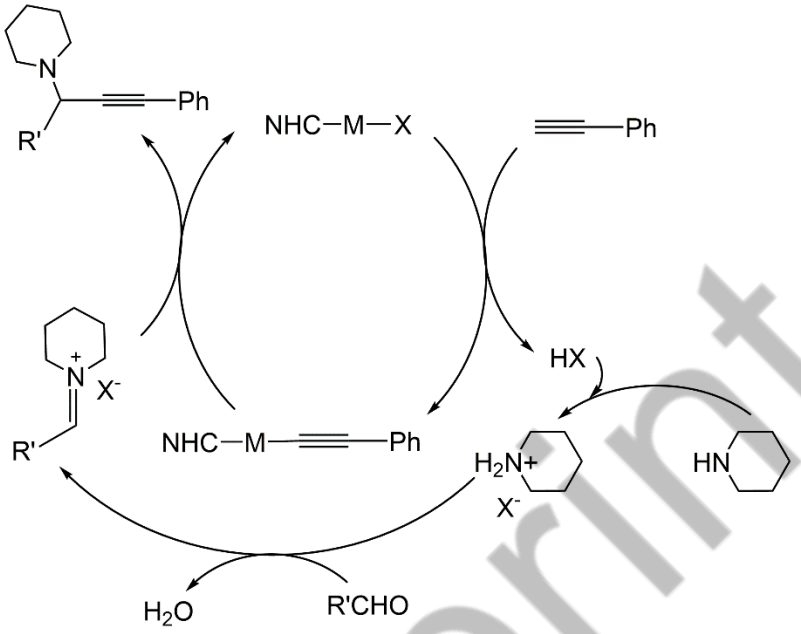
of this acetylide with iminio, which is obtained *in situ* by reaction of the aldehyde with the amine, produces the desired product and regenerates the catalyst (see Scheme 2) [22].



Scheme 2. Proposed mechanism for the A^3 coupling catalyzed by silver and gold NHC complexes.

Starting from the statement that many silver and gold complexes stabilized by *N*-heterocyclic carbene ligands are able to give this reaction [23] and considering our interest in these compounds, [24-26] we have explored the catalytic behavior of silver and gold NHC-metal complexes. More in detail, two novel complexes of silver and gold bearing 4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidine ligand (**1b** and **2b**) were synthetized and their catalytic activity compared with two analogous complexes with hydrogens on the backbone (**1a** and **2a**), recently synthesized by some of us [24-26] (Scheme 3).

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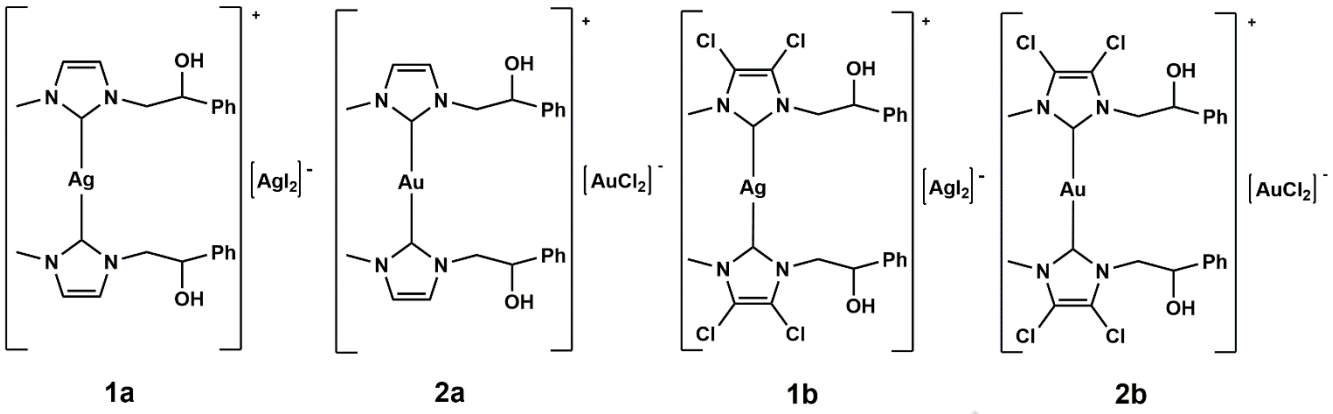

Scheme 3. Silver and gold complexes utilized as catalysts in A^3-coupling reactions.

2. Experimental part

2.1. Materials and methods

All reactions involving organometallic compounds were performed under an oxygen- and moisture-free atmosphere using standard Schlenk and glovebox techniques. All solvents were thoroughly deoxygenated and dehydrated under a nitrogen atmosphere by heating at reflux over suitable drying agents; whereas NMR deuterated solvents (Euriso-Top products) were kept in the dark over molecular sieves. Reagents were purchased from Sigma-Aldrich S.r.l. and TCI Chemicals and were used as received. NMR spectra were recorded on a Bruker AM 300 spectrometer (300 MHz for ^{1}H; 75 MHz for ^{13}C), a Bruker AVANCE 400 spectrometer (400 MHz for ^{1}H; 100 MHz for ^{13}C). NMR samples were prepared by dissolving about 10 mg of compounds in 0.5 mL of deuterated solvent. The ^{1}H NMR and ^{13}C NMR chemical shifts are referenced to $SiMe_4$ (δ=0 ppm) by using the residual proton impurities of the deuterated solvents as internal standards. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br) and overlapped (o). Elemental analyses for C, H, and N were recorded with a Thermo-Finnigan Flash EA 1112 and were performed according to standard microanalytical procedures. Chloride and iodide were determined indirectly by reaction of $AgNO_3$ with halogen, precipitation of AgX (X=Cl, I), which was dissolved in $Na_2S_2O_3$. The silver content in the

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solution was determined by flame atomic absorption spectroscopy (FAAS), and the halogen content was calculated by using the content of silver.

ESI-MS measurements of organic compounds were performed on a Waters Quattro Micro triple quadrupole mass spectrometer equipped with an electrospray ion source. ESI-FT-ICR measurements of complexes were performed on a Bruker Solaris XR instrument.

MALDI-MS: mass spectra were acquired using a Bruker SolariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively-shielded superconducting magnet (Bruker Biospin, Wissembourg, France). The samples were ionized in positive ion mode using the MALDI ion source (Bruker Daltonik GmbH, Bremen, Germany). The mass range was set to m/z 200 – 3000. The laser power was 28% and 22 laser shots were used for each scan. The mass spectra were calibrated externally using a mix of peptide clusters in MALDI ionization positive ion mode. A linear calibration was applied. To improve the mass accuracy, the sample spectra were recalibrated internally by matrix ionization (2,5-DHBA: 2,5-dihydroxybenzoic acid).

2.2 Synthesis of 4,5-dichloro-N-methyl-N'-(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidine

4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidine was prepared following the strategy proposed by Arnold and co-workers [27,28], and applying the procedures previously reported by us [24,26,29,30].

4,5-dichloroimidazole (3.00 g, 21.9 mmol) and styrene oxide (3.00 ml, 26.2 mmol) were stirred in 25 ml of CH_3CN at 80 °C for 12 h. The reaction mixture was cooled at room temperature and subsequently CH_3I (7 ml, 128 mmol) was added. The mixture was warmed up 80 °C for 8 h. The solvent was concentrated, the salt precipitated and washed with acetone (2·15 ml). Yield: 55%

^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.4_5 (s, 1H, NC*H*N), 7.4_0 (m, 5H, *Ph* group), 6.0_4 (d, 1H, O*H*), 4.9_7 (m, 1H, C*H*OH), 4.4_5 (dd, 1H, NCH_2CHOH), 4.3_3 (dd, 1H, NCH_2CHOH) 3.8_7 (s, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 140.3 (*ipso carbon* aromatic ring), 137.0 (N*C*N), 128.8, 128.4, 128.0, 127.2, 125.9 (*aromatic carbons*), 118.9 and 118.6 (N*C*Cl*C*ClN), 69.56 (CH_2*C*HOH), 54.7 (N*C*H_2), 35.0 (N*C*H_3).

ESI-MS (CH_3CN, m/z): 272.1 $[C_{12}H_{13}Cl_2N_2O]^+$.

Elemental Analysis: calculated for $C_{12}H_{13}Cl_2IN_2O$ (399.05) C, 36.12; H, 3.28; Cl, 17.77; I, 31.80; N, 7.02; O, 4.01. Found C, 36.87; H, 3.11; Cl, 18.02; I, 31.27; N, 6.86; O, 3.90.

2.3 Synthesis of silver complex bis-[4,5-dichloro-(N-methy-N'(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidene]silver(I)]$^+$[di-iodide-silver]$^-$ ***(1b)***

To a suspension of 4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidine (0.500 g, 1.25 mmol) in CH_2Cl_2 (20 ml) were added silver oxide (0.174 g, 0.750 mmol) and molecular sieves. The mixture was stirred for 1.5 h in darkness at room temperature. After filtration on pad celite, to eliminate AgI byproduct, the solvent was removed *in vacuo*. The product was obtained as white solid. Yield: 42%. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.3_9 (m, 5H, *Ph* group), 5.6_7 (d, 1H, O*H*), 5.0_3 (m, 1H, C*H*OH), 4.3_5 (m, 2H, NCH_2CHOH), 3.8_5 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 181.6 (N*C*N), 141.4, 128.3, 127.7, 127.3 125.9 (aromatic carbons), 117.2 and 116.6 (N*C*Cl*C*ClN), 71.8 (CH_2*C*HOH), 56.9 (N*C*H_2), 37.5 (N*C*H_3).

MALDI-MS (CH_2Cl_2, m/z): 555.06 Dalton attributable to $[C_{18}H_{18}N_4OCl_4]Ag^+$ derived from {$[(NHC)_2Ag]^+$-C_6H_5 -OH}, 271.03 Dalton referable to $(NHC)^+$.

Elemental Analysis**:** calculated for $C_{12}H_{24}AgCl_4IN_4O_2$ (777.06) C, 37.10; H, 3.11; Ag, 13.88; Cl, 18.25; I, 16.33; N, 7.21; O, 4.12 Found: C, 37.56; H, 3.01; Ag, 13.59; Cl, 18.12; I, 16.24; N, 7.69; O, 3.79.

2.4 Synthesis of gold complex bis-[4,5-dichloro-(N-methy-N'(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidene]gold(I)]$^+$[dichloro-gold]$^-$ ***(2b)***

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4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidine (0.500 g, 1.25 mmol) and Ag_2O (0.146 g, 0.629 mmol) were dissolved in 20 mL of dichloromethane and stirred for 3h at room temperature in darkness. Chloro(dimethylsulfide)gold(I) (0.368 g, 1.25 mmol) was added, the mixture was stirred for 6 hours at room temperature in darkness and it was filtered on pad celite, the solvent was removed under reduced pressure. The crude product was washed with hexane to give a yellow powder. Yield: 21%

^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.3_3 (m, 5H, *Ph* group), 5.8_8 (br, 1H, O*H*), 5.1_3 (m, 1H, C*H*OH), 4.2_3 (m, 2H, NCH_2CHOH), 3.8_2 (s, 3H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 170.7 (N*C*N), 141.2, 128.4, 127.8, 127.0, 125.7 (aromatic carbons), 117.3 and 116.4 (N*C*Cl*C*ClN), 72.0 (CH$_2$*C*HOH), 56.6 (N*C*H$_2$) 37.1 (N*C*H$_3$).

MALDI-MS (CH_2Cl_2, m/z): 739.03 Dalton attributable to $[C_{24}H_{24}N_4O_2Cl_4]Au^+$.

2.5 A^3-coupling (aldehyde-alkyne-amine) reaction: typical procedure of A^3-coupling reaction catalyzed by bis-(NHC)-M catalysts

Under nitrogen atmosphere, bis-(NHC)-M catalyst (3 mol %), aldehyde (1.00 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol) and internal standard (2-bromo mesitylene, 1.00 mmol), were added in a 10 mL Schlenk tube. The mixture was stirred at 80 °C for 6 hours, then it was cooled to room temperature and diethyl ether/dichloromethane were added. The organic portion was dried over $MgSO_4$ and filtered, concentrated and the degree of conversion was calculated by integrating the ^{1}H NMR signal at δ 6.89 of the two protons on aromatic carbons of the internal standard ~~(*i.e.*: 2-bromomesitylene)~~ and of protons on the carbon in α to acetylenic group of propargylamine: at δ 3.43, 2H for *N*-(3-phenyl-2-propynyl)piperidine), at δ 3.11, 1H for 1-(1-cyclohexyl-3-phenyl-2-propynyl) piperdine), at δ 4.79, ^{1}H for *N*-(1,3-diphenyl-2-propynyl) piperidine, respectively.

***N*-(3-phenyl-2-propynyl)piperidine**: ^{1}H NMR (300 MHz, CD_2Cl_2, δ ppm): 7.4_2 (m, 2H, CH_{Ar}), 7.3_0 (m, 3H, CH_{Ar}), 3.4_3 (s, 2H, NCH_2), 2.5_3 (t, 4H, NCH_2CH_2), 1.6_0 (m, 4H, NCH_2CH_2), 1.4_3 (m, 2H, NCH_2CH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 131.6, 128.1, 127.3 (3·s, 5C, C_{ar}), 123.5 (s, 1C, C_{ar}), 85.1 (s, 1C, C≡*C*-Ph), 84.9 (s, 1C, *C*≡C-Ph), 53.3 (s, 2C, N*C*H$_2$CH$_2$), 48.3 (s, 1C, N*C*H), 26.1 (s, 2C, NCH$_2$*C*H$_2$), 24.0 (s, 1C, NCH$_2$CH$_2$*C*H$_2$).

1-(1-cyclohexyl-3-phenyl-2-propynyl) piperdine: ^{1}H NMR (300 MHz, CD_2Cl_2, δ ppm): 7.4_2 (m, 2H, CH_{Ar}), 7.3_2 (m, 3H, CH_{Ar}), 3.1_1 (d, 1H, NC*H*), 2.6_4 (m, 2H), 2.3_3 (m, 2H), 2.0_7 (m, 2H), 1.8_6 (m, 2H), 1.6_7 (m, 6H), 1.5_6 (m, 2H), 1.4_3 (m, 3H), 1.1_0 (m, 2H).

^{13}C NMR (75 MHz, CD_2Cl_2, δ ppm): 132.0, 128.8, 128.2 (3·s, 5C, C_{ar}), 124.3 (s, 1C, C_{ar}), 88.4 (s, 1C, C≡*C*-Ph), 86.4 (s, 1C, *C*≡C-Ph), 64.8 (s, 1C, N*C*H), 51.2 (s, 2C, N*C*H$_2$CH$_2$), 40.1, 31.9, 30.8, 27.3 (4·s, 6C, Cyclohexyl), 26.6 (s, 2C, NCH$_2$*C*H$_2$CH$_2$), 25.3 (s, 1C,NCH$_2$CH$_2$*C*H$_2$).

***N*-(1,3-diphenyl-2-propynyl) piperidine** ^{1}H NMR (300 MHz, CD_2Cl_2, δ ppm) 7.8_9, 7.5_7, 7.5_0, 7.3_1, 7.2_4, 7.1_8 (m, 10H, CH_{ar}), 4.7_9 (s, 1H, NC*H*), 2.5_9 (s, 4H, NCH_2CH$_2$CH$_2$), 1.6_2 (m, 4H, NCH$_2$CH_2CH$_2$), 1.4_9 (m, 2H, NCH$_2$CH$_2$CH_2).

^{13}C NMR (75 MHz, $CDCl_3$-d_1, δ ppm): 138.6, 131.8, 128.5, 128.2, 128.0, 127.7, 123.3 (8·s, 12C, C_{ar}), 87.5 (s, 1C, C≡*C*-Ph), 86.1(s, 1C, *C*≡C-Ph), 62.4 (s, 1C, N*C*H), 50.5 (s, 2C, N*C*H$_2$CH$_2$), 26.2 (s, 2C, NCH$_2$*C*H$_2$CH$_2$), 24.3 (NCH$_2$CH$_2$*C*H$_2$).

3. Results and discussion

The complexes, reported in Scheme 3, are light and water stable. Hydrolysis tests performed in DMSO/D_2O (90/10) solution at room temperature showed unchanged ^{1}H NMR spectra after 24h.

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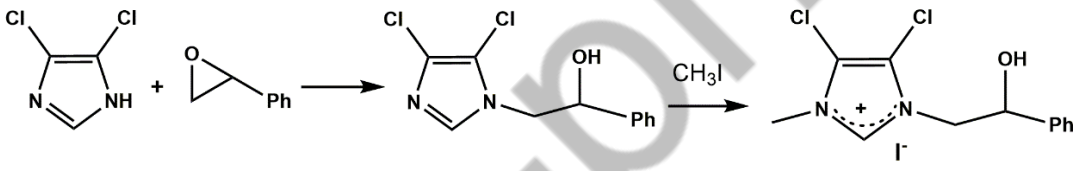
Complexes **1a** and **2a** were prepared according to ref. [24,26]. The ligand precursor of complexes **1b** and **2b** was prepared following the procedures previously reported by Arnold and co-workers [27,28], modified by us [25,29,30].

*3.1 Synthesis of proligand 4,5-dichloro-N-methyl-N'-(2-hydroxy-2-phenyl)ethyl-imidazolium-iodide, silver (**1b**) and gold (**2b**) complexes*

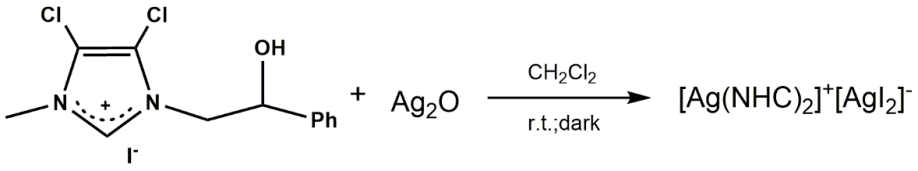
4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazolium-iodide was prepared by reaction of i) 4,5-dichloro-imidazole with 1,2-epoxyethylbenzene, this reaction, by opening of epoxy-ring, leads to the monoalkylated compound, and ii) addition of CH_3I that produces the imidazolium salt in a racemic mixture with 55 % of yield (Scheme 4) [24-30].



Scheme 4. Synthesis of 4,5-dichloro-*N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl-imidazolium-iodide**.**

The structure was confirmed by ^{1}H and ^{13}C NMR analysis, with the proton on cationic carbon showing the characteristic singlet at 9.45 ppm in ^{1}H NMR spectrum (all attributions are reported in the Experimental part).

The reaction of the salt with silver oxide (Ag_2O) produces the corresponding silver complex (**1b**, see scheme 5), which was characterized by ^{1}H and ^{13}C NMR, mass spectroscopy and elemental analysis.



Scheme 5. Synthetic scheme for preparation of **1b** Ag complex.

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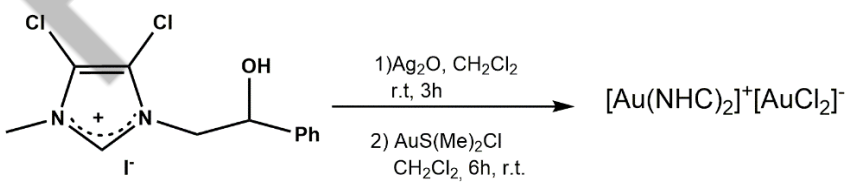
^{1}H and ^{13}C NMR spectra show the predictable signals that were attributed as reported in the Experimental part. The formation of the complex is confirmed by the diagnostic ^{13}C NMR sharp resonance of the carbene carbon at 181.6 ppm. According to elemental analysis, (see Experimental part) the ratio among ligand, silver and iodide is 1:1:1. The mass spectrometry spectrum (MALDI-MS, see Fig. S1A) shows more signals of different intensity around 555.06 Dalton attributable to $[C_{18}H_{18}N_4OCl_4]Ag^+$ derived from $\{[(NHC)_2Ag]^+\text{-}C_6H_5\text{-}OH\}$. MALDI-MS analysis were carried out in order to produce mass spectra with little fragmentation and mostly singly charged ions, thus facilitating identification. The multiplicity is due to the two silver and two chlorine isotopes: ^{107}Ag and ^{109}Ag of abundance nearly equal, and ^{35}Cl and ^{37}Cl of abundance 75% and 25%, respectively. According to the reported characterization, silver complexes **1a** and **1b** are ionic solids with $[(NHC)_2Ag]^+$ as a cation and $[AgI_2]^-$ as an anion. It is worth noting that, in solid-state, a similar silver complex showed an analogous structure as determined by X-ray diffraction [20].

A convenient way to synthesize gold-based metal complexes, by avoiding difficult workups and strong bases, is to use Ag-NHC as reagents for carbene transfer.

The complex **2b** was synthesized, according to a procedure already reported [25], by *trans*-metalation of the *situ* generated **1b** complex with the gold(I)-chloro-(dimethylsulfide) $[(Me_2S)AuCl]$ at room temperature in darkness (see scheme 6).



Scheme 6. Synthetic scheme for preparation of **2b** Au complex.

The **2b** complex was obtained as white powder, yields: 20%. The product was analyzed by NMR, mass spectroscopy and elemental analysis. The ^{1}H and ^{13}C NMR spectra reported in Fig. 1 show signals at

170.7 ppm attributable to carbene carbon, at 117.3 and 116.4 ppm for C-Cl unsatured carbons and signal at 72.0 ppm for methine carbon whose proton appears at 5.13 ppm.

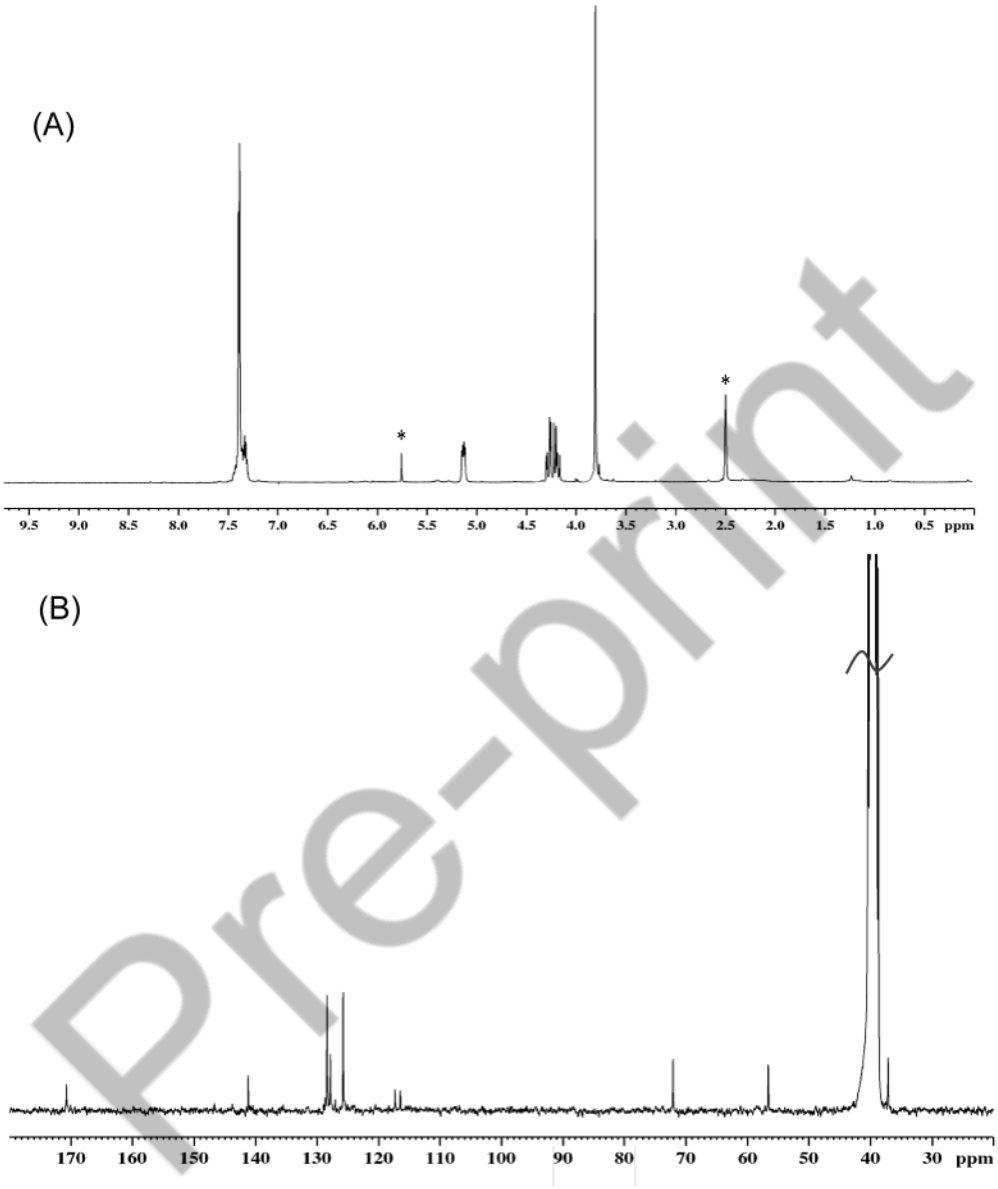


Fig. 1. Spectra (A) ^{1}H and (B) ^{13}C NMR of **2b** Au complex (starred peaks are due to solvents: dichloromethane and DMSO).

Also in this case, MALDI-MS data discloses a structure type $[(NHC)_2Au]^+[AuCl_2]^-$, showing signals around 739.03 Dalton attributable to $[C_{24}H_{24}N_4O_2Cl_4]Au^+$.

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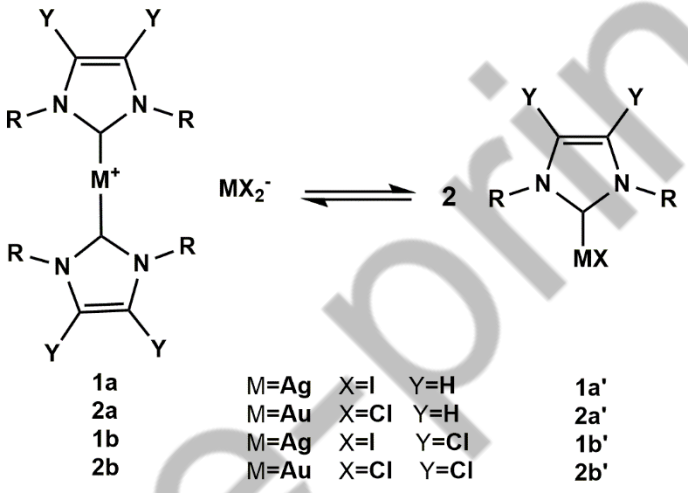
Conductivity measurements confirmed the electrolytic nature of both complexes (**1b** and **2b**). In fact, the conductance values, determined in CH_2Cl_2, showed concentration-dependence on the compounds (see Tables S1 and S2 of Supplementary Information). According to these results, it is possible to assume in solution the presence of an equilibrium among the ionic compound $[M(NHC)_2]^+[MX_2]^-$ [31] and the neutral species M(NHC)X (Scheme 7), that is usually considered responsible for the catalytic activity of these compounds [31].



Scheme 7. Solution structures of mono-NHC Ag(I) complexes.

3.2 Catalytic activity of complexes in A³coupling reactions

The catalytic behavior of **1a**, **1b**, **2a** and **2b** in the synthesis of propargylamines, via the A^3-coupling reactions of aldehyde, amine and alkyne (Scheme 1), was investigated. A comparison among catalysts was performed by reacting an aldehyde (*i.e.:* formaldehyde or paraformaldehyde or cyclohexyl-aldehyde or benzaldehyde) with piperidine and phenylacetylene, in absence of solvent or using dioxane as solvent. The results, in solvent-free reaction conditions, are reported in Table 1. In the experimental part the NMR data of the obtained propargylamines, perfectly coincident with those already reported in the literature for the same compounds, are detailed, [32,33] and in the Supplementary Information as an example the

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^{1}H and ^{13}C NMR spectra of product of run 7 is reported (Fig. S1). In all the runs the conversions were determined by ^{1}H NMR analysis, using as internal standard the 2-bromo mesitylene, which has the signals of two protons on aromatic carbons in an empty area of the spectrum ($\delta = 6.89$). The confirmation of the reliability of the data obtained was carried out by isolating the product from run 3. The choice to test our complexes in A^3-coupling reactions, using piperidine as amine, and phenylacetylene as alkyne, and changing only the aldehyde, has been done, in this preliminary work, to compare our data with the activities on these substrates already reported in literature [34,35].

Table 1. Solvent free synthesis of propargylamines via A^3-coupling reactions catalyzed by silver (1a and 1b) and gold (2a and 2b) NHC complexes.

Run[a]	Catalyst	Aldehyde	Conversion[b] (%)
1	**1a**	Formaldehyde solution (38%)	58
2		Paraformaldehyde	13
3		Cyclohexanecarboxaldehyde	99
4		Benzaldehyde	13
5	**2a**	Formaldehyde solution	96
6		Paraformaldehyde	99
7		Cyclohexanecarboxaldehyde	99
8		Benzaldehyde	83
9	**1b**	Formaldehyde solution	64
10		Paraformaldehyde	94
11		Cyclohexanecarboxaldehyde	99
12		Benzaldehyde	38
13	**2b**	Formaldehyde solution	81
14		Paraformaldehyde	99
15		Cyclohexanecarboxaldehyde	96
16		Benzaldehyde	86

[a]Reaction conditions: aldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), bis NHC-M catalyst (3 mol %), 80 °C, nitrogen atmosphere, 6 h.
[b]Conversions were determined by ^{1}H NMR analysis, using 2-bromo mesitylene as internal standard.

All complexes are able to perform A^3-coupling in screened reactions. By comparing runs 1-4 with runs 9-12 and runs 5-8 with runs 13-16, it is possible to observe that silver based catalysts were found to be much less performing than corresponding gold based compounds. Benzaldehyde showed to be the least

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reactive, whereas cyclohexanecarboxaldehyde was completely converted by all catalysts. Formaldehyde in aqueous solution was moderately reactive in the presence of silver complexes (run 1 and 9), while good reactivity was observed with gold-based complexes (run 5 and 13). Finally, paraformaldehyde showed to be very reactive in the presence of all complexes except **1a**.

The high conversions, observed in most of the runs, prevent a full comprehension of catalytic behavior differences among these complexes. Thus, the same reactions were performed in solution using dioxane as solvent, because as already reported in literature, [34,36] due to the lower concentration of the reagents, the activity in dioxane decreases, making any differences more evident. The results are reported in Table 2.

Table 2. Synthesis of propargylamines via A^3-coupling reactions catalyzed by silver and gold NHC complexes in the presence of dioxane as solvent.

Run[a]	Catalyst	Aldehyde	Conversion[b] (%)
17	**1a**	Formaldehyde solution	n.d.[c]
18		Paraformaldehyde	n.d.[c]
19		Cyclohexanecarboxaldehyde	71
20		Benzaldehyde	n.d.[c]
21	**2a**	Formaldehyde solution	65
22		Paraformaldehyde	67
23		Cyclohexanecarboxaldehyde	68
24		Benzaldehyde	22
25	**1b**	Formaldehyde solution	62
26		Paraformaldehyde	30
27		Cyclohexanecarboxaldehyde	99
28		Benzaldehyde	14
29	**2b**	Formaldehyde solution	99
30		Paraformaldehyde	71
31		Cyclohexanecarboxaldehyde	99
32		Benzaldehyde	68

[a]Reaction conditions: aldehyde (1.0 mmol), piperidine (1.2 mmol), phenylacetylene (1.5 mmol), bis NHC-M catalyst (3 mol %), dioxane (2.0 mL), 80 °C, nitrogen atmosphere, 6 h.
[b]Conversions were determined by ^{1}H NMR analysis, using 2-bromo mesitylene as internal standard.
[c] Not detectable

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According to results of Table 2, it is possible to depict a trend of reactivity as **2b** > **2a** > **1b** > **1a**, where gold complexes (**2a** and **2b**) show to be generally more performing than silver ones, and complexes bearing chlorines on NHC backbone (**1b** and **2b**) are more active than their analogous with backbone unsubstituted NHC.

It is generally well accepted in literature, that the active species involved in the catalytic cycle are of the type M(NHC)X (Scheme 7) [31]. Reactivity and stability of NHC-metal complexes are often related to the steric and electronic properties of the NHC ligands, that can be fine tuned to optimize the catalytic behavior (see for example refs [37-41]). As a consequence, to give a preliminary overview on factors influencing the catalytic activity of **1a**, **1b**, **2a** and **2b**, electronic and steric properties of NHCs presenting chlorine or hydrogen on the backbone were investigated by DFT calculations on M(NHC)X species **1a'**, **1b'**, **2a'** and **2b'** at the PBE0/6-311G(d,p) level of theory (see supporting information for computational details and Cartesian coordinates). Minimum energy structures are reported in Fig. 2.

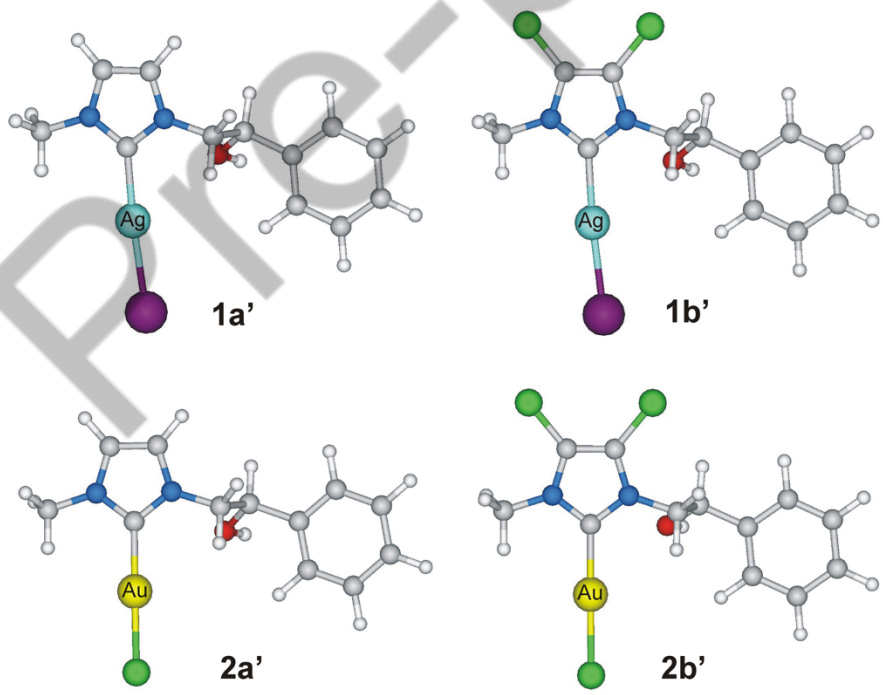

Fig. 2. Minimum energy structures of **1a', 1b', 2a'** and **2b'**.

In order to compare steric parameters of NHC ligands with hydrogens or chlorine substituted backbone the percent buried volumes (%V_{Bur}) were calculated and steric maps (Fig. 3) were obtained from the minimum energy structures relative to NHC-Ag-I complexes [42]. %V_{Bur} is a parameter, able to quantify the steric hindrance of NHC ligands, defined as the fraction of the total volume of a sphere centered on the metal occupied by a given ligand [43,44]. Both NHCs present %V_{Bur} = 30.4 and anisotropic hindrance that is more pronounced in the SE quadrant of the steric maps due to the presence of the phenyl group oriented toward the catalytic task. No meaningful differences could be appreciated among the chlorine substituted and hydrogen substituted NHCs.

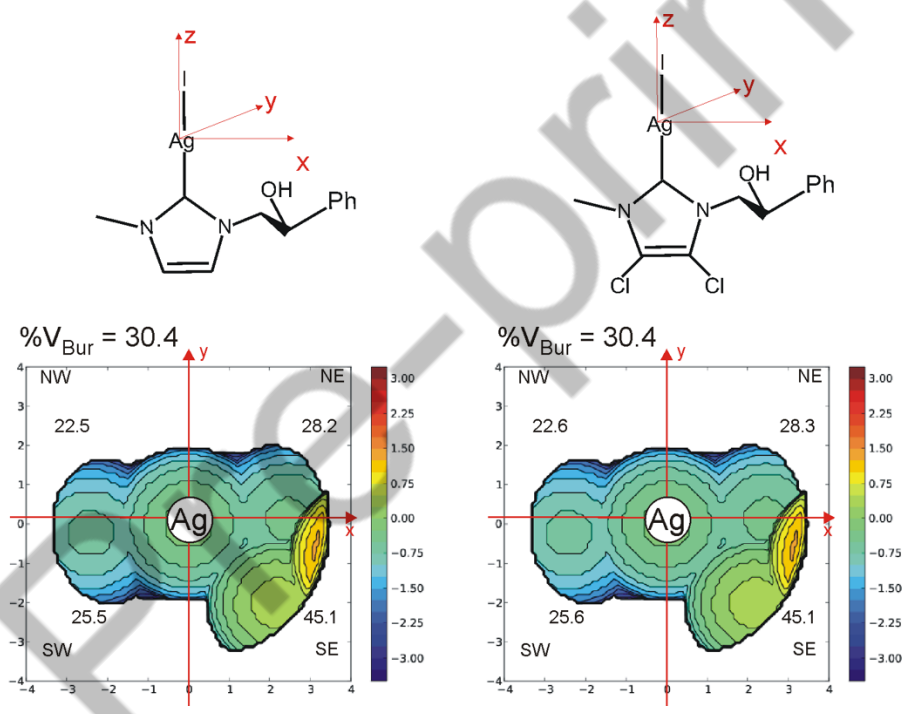

Fig. 3. Topographic steric maps of **1a', 1b'**. The iso-contour curves of steric maps are in Å. The maps were obtained starting from the minimum energy structures of complexes optimized by DFT calculations. The complexes are oriented according to the complex scheme. Overall %VBur and %VBur representative of each single quadrant are reported for each map.

Electronic properties were assessed by Mulliken charge and BDE analysis.

Mulliken analysis. According to Mulliken charges on the metal reported in Table 3, a more pronounced positive density charge were calculated for complexes with chlorine NHC substituted backbone (**1b'** and

2b') with respect to the analogous complexes presenting hydrogen substituted backbone (**1a'** and **2a'**). Indeed, it is not surprising that electron withdrawing groups on the NHC backbone decrease electron density on the metal.

Table 3. Mulliken charge on the metal and bond-dissociation energies (BDE) of NHC and halogen for **1a', 1b', 2a'** and **2b'.** Values obtained with DFT calculations using the PBE0/6-311G(d,p) basis set.

	Mulliken charge[a]	BDE(NHC)[b]	BDE(halogen)[c]
NHC(H)-Ag-I (**1a'**)	+0.151	55.2	116.0
NHC(Cl)-Ag-I (**1b'**)	+0.158	51.3	119.8
NHC(H)-Au-Cl (**2a'**)	+0.279	82.4	142.0
NHC(Cl)-Au-Cl (**2b'**)	+0.314	78.1	146.2

[a]Mulliken charges on the metal. [b]Bond-dissociation energies (BDE) referred to the metal–NHC bond. [c]Bond-dissociation energies (BDE) referred to the metal–halogen bond.

BDE analysis. BDE of NHCs for **1b'** and **2b'** are lower than BDE of the corresponding hydrogen substituted complexes (**1a'** and **2a'**), indicating a weaker bond among the metal center and chlorine substituted NHC ligands (Table 3). In addition, BDE of halogen in trans position with respect to NHC ligand gives indication on the nature of NHC-metal bond. More in detail, the higher halogen BDE, shown by complexes with chlorine substituted NHCs, indicates a weaker σ donation of these NHC ligands toward the metal.

In summary, according to DFT calculations, higher activity of chlorine substituted NHC complexes could be attributed to a more electrophile metal center, possibly able to easily coordinate nucleophiles such as alkynes at the very beginning of the catalytic cycle.

It is worth noting that the catalytic systems described in this paper, especially those gold-based, are among the most active reported in the literature [45-47].

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4. Conclusions

Silver and gold complexes with *N*-methyl-*N'*-(2-hydroxy-2-phenyl)ethyl substituted NHC ligands, bearing either hydrogen or chlorine at 4 and 5 positions of the imidazolium ring, were synthetized and their catalytic activities in A^3-coupling (aldehyde–alkyne–amine) reactions were compared. A^3-coupling reactions were conducted by reacting piperidine, phenylacetylene with four different aldehydes: formaldehyde, paraformaldehyde, cyclohexanecarboxaldehyde and benzaldehyde. All tested complexes gave complete conversion of cyclohexanecarboxaldehyde, while benzaldehyde showed to be the lowest reactive substrate. The catalyst activity was observed to be dependent on the metal as well as on the NHC backbone substituents. The gold complexes, in fact, exhibit higher activity than the corresponding silver ones and chlorine backbone substituents showed to have beneficial effects on catalysts performances. According to experimental results, it is possible to report the following trend of reactivity: **2b** > **2a** > **1b** > **1a**. To identify the main reason of the different catalytic behavior, steric and electronic properties of the supposed active species M(NHC)X were assessed for the four catalysts by DFT studies. Calculation of the percent buried volumes and extraction of steric maps showed that no significant differences can be appreciated for steric properties. On the other hand, Mulliken analysis disclosed a higher positive density charge for complexes with chlorine NHC substituted backbone (**1b'** and **2b'**) with respect to the analogous complexes presenting hydrogen substituted backbone (**1a'** and **2a'**), and BDE analysis indicates a weaker σ donation of chlorine substituted NHCs toward the metal.

In this light, the higher activity, observed for chlorine substituted NHC complexes, could be attributed to a more electrophile metal center, that possibly promotes the alkyne coordination at the beginning of the catalytic cycle.

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