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Effect of counterion on the catalytic activity of NHC-gold(I) in A^3 coupling reactions

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ABSTRACT

Synthetic A^3-coupling represents an efficient and environmentally convenient procedure for the production of propargylamines, relevant intermediates for the preparation of pharmacologically active substances. Gold(I) complexes of general formula NHC-Au-X have been synthesized, characterized, and tested in the A^3-coupling reaction of benzaldehyde, piperidine and phenylacetylene on varying the anionic fragment X as halogenide (Cl, Br, I), acetate (OAc), hexafluorophosphate (PF_6) or phenylacetylide (-C≡CPh), with 5-dichloro[N-methyl, N'(2-hydroxy-2-phenyl)ethyl imidazole-2-ylidene as NHC ligand. The kinetic profiles were interpreted with DFT (Density Functional Theory) studies on bond dissociation energies (BDE) of the counterion as well as on the relative stability of the neutral NHC-Au-X complexes with respect to their ionic forms $[Au(NHC)_2]^+[AuX_2]^-$.

Introduction

In recent years, gold-based catalysts have received considerable interest due to their ability to coordinate alkynes to promote reactions with electrophilic agents such as alcohols, enamines, imines, or iminium ions [1–6]. The latter can be produced by the condensation reaction of an aldehyde with an amine. The reaction of these electrophiles with the alkyne coordinated at the metal center produces propargylamines, reactivating the catalyst [7–9]. Since these syntheses are obtained by coupling of alkyne, aldehyde, and amine, the reaction is defined as A^3 [10]. The only byproduct of these reactions is water and the main products obtained are important scaffolds to obtain more complex molecules. Therefore, the low environmental impact of the synthesis and the interest in these molecules justifies the growing number of synthetic A^3-coupling procedures developed [11,12]. Propargylamines represent an important and versatile class of organic compounds characterized by an amino group in the β position with respect to a triple carbon–carbon bond. They are important intermediates for the preparation of a series of heterocyclic molecules such as oxazoles, pyrroles, and pyridines, and of pharmacologically active nitrogen-containing molecules such as polyfunctional amino derivatives, β-lactams, peptides, and oxotremorine analogs [13]. Some derivatives of propargylamine are used in the treatment of Alzheimer's and Parkinson's disease for their inhibitory actions against monoamine oxidase B (MAO-B) [14,15], as pargyline [16] (Trade name: Eutonyl), Rasagiline [17] (Trade name: Azilect) and Selegiline [18] (Trade name: Eldepryl or Zelapar). Furthermore, Selegiline and its analogs exhibit antiapoptotic activity, as reported by Boulton et al. [19], while Wunsch and collaborators reported, in 2017, on the inhibitory effect of histone deacetylase of propargyl scaffolds [20]. The discovery of the central role of the propargylamine moiety and its importance for the synthesis of compounds having these relevant therapeutic properties has further stimulated the study of these reactions [21–25].

The development of new, more active catalytic systems that can allow the reduction of the catalytic load as well as the use of green or the complete elimination of solvents represent an important goal given the interest in obtaining increasingly sustainable processes for the environment.

Recently, many gold complexes, having these peculiarities, have been synthesized and studied. Among them, those stabilized by N-heterocyclic carbene (NHC) ligands are particularly attractive [26–28]. NHCs are nucleophilic compounds with a strong coordination ability towards transition metals (M−NHC) [26], making them excellent ligands for the synthesis of metal complexes, involved in catalysis [29–31] and pharmaceutical applications [9,32–39].

Several gold complexes with NHC ligands having different substituents at the nitrogen atoms or on the backbone, have been reported in the literature. While the influence of the NHC architecture on the

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catalyst activity have been often investigated [40–43], only few studies have been reported on the effect of counterion [44–47], that possibly affects the kinetics of these complexes.

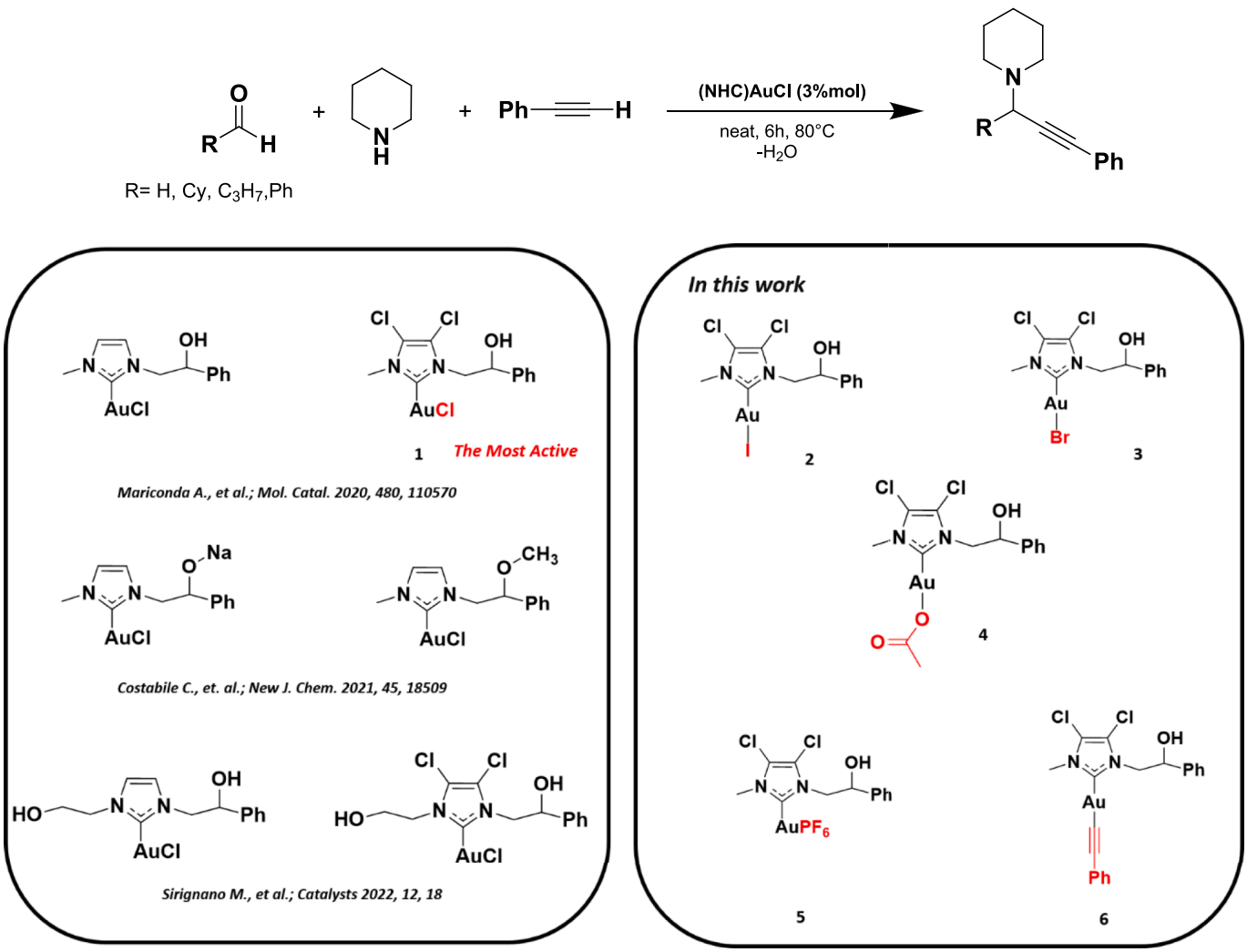
Recently, we reported on the synthesis, characterization, and catalytic activity of NHC-silver and -gold halogenide complexes tested in A^3-coupling reactions of piperidine, phenylacetylene, and an aldehyde such as paraformaldehyde, or butyraldehyde or cyclohexanecarboxaldehyde or benzaldehyde [7–9]. Most active catalyst bore as NHC-ligand the 4,5-dichloro [N-methyl, N'(2-hydroxy-2-phenyl)ethyl imidazole-2-ylidene], (NHC)AuCl, 1 in Scheme 1.

In this paper, the synthesis and characterization of some gold (I) complexes of general formula (NHC)AuX, having as NHC ligand the 4,5-dichloro[N-methyl, N'(2-hydroxy-2-phenyl)ethyl imidazole-2-ylidene and as anionic ligand (X) an halogenide (Br^- or I^-), acetate (AcO^-), hexafluorophosphate (PF_6^-) or phenylacetylide (-C≡CPh) (2–6 in Scheme 1) is reported. These complexes have been characterized and tested as catalysts in A^3-coupling reactions to obtain the kinetic profile. Density Functional Theory (DFT) studies were performed to interpret the role of the counterion during the reaction.

Experimental section

Materials and instruments

All manipulations were performed using standard Schlenk techniques under a nitrogen atmosphere. All chemicals were bought from TCI Chemicals and Merck-Life Science and were used as received. Solvents were dried according to the standard procedures, while deuterated solvents were degassed under a nitrogen atmosphere and stored with the exclusion of light, over activated molecular sieves (4 Å) in the glovebox. NMR spectra had been recorded on Brucker AM 300 spectrometer (300 MHz for ^{1}H; 75 MHz for ^{13}C) and Brucker AVANCE 400 spectrometer (400 MHz for ^{1}H; 100 MHz for ^{13}C, 377.35 MHz for ^{19}F, and 162.60 MHz for ^{31}P) using DMSO-d_6 as solvent. The ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR chemical shifts were referenced to $SiMe_4$ ($\delta = 0$ ppm) using the residual proton impurities of the deuterated solvents as an internal standard. The samples had been prepared by dissolving 15 mg of the compound in 0.5 mL of deuterated solvent. The spectrum multiplicities are abbreviated in this manner: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br), and septuplet (sept). Elemental analyses for C, H, and N were recorded with Thermo-Finnigan Flash EA 1112 and had been performed according to analytic procedures. Bromide, and iodide had been detected indirectly by the reaction of silver nitrate ($AgNO_3$) with halogen, and precipitation of AgX (X = Br, I), which was dissolved in $Na_2S_2O_3$. MALDI-MS were obtained using a Brucker SolariX XR Fourier transform ion cyclotron resonance mass spectrometer (Brucker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively shielded superconducting magnet (Brucker Biospin, Wissembourg, France). The laser power was 28 %, and 22 laser shots were used for each scan. The mass range was set to *m/z* 200–3000.



Scheme 1. NHC gold(I) complexes synthesized in this work and tested in A^3 coupling reaction.

The samples' spectra were recalibrated internally by matrix ionization (2,5-dihydroxybenzoic acid) to improve the measurement accuracy.

General procedures for the synthesis of halo and pseudo-halo analogues of NHC-Au-X

Bromide and iodide gold(I) NHC complex were synthesized following the literature procedure [44,48] by the reaction of the chloride gold(I) NHC complex with an excess of sodium or potassium halogenide salt in acetone. Acetate and hexafluorophosphate gold NHC complexes were obtained by metathesis reaction of counterion, by the reaction of chloride gold(I) NHC complexes with corresponding silver salt [49,50].

The alkynyl gold(I) complex was obtained following the published literature procedure [51,52], slightly modified by us, by the reaction of (1) with an excess of NEt_3 and phenylacetylene.

Synthesis of chloride gold complex [4,5-dichloro-(N-methyl-N'(2-hydroxy-2-phenyl) ethyl-imidazole-2-ylidene] (1)

The synthesis and characterization of 1 are reported in our published paper [7].

Synthesis of iodide gold complex [4,5-dichloro-[N-(methyl)-N'(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidene] (2)

A solution of chloro gold NHC complex 1 (0.050 g, 0.1 mmol, 1.0 eq) and NaI (0.140 g, 1.0 mmol, 10 eq) in acetone (10 mL), was stirred for 24 h at room temperature. After this time, the solvent was removed under reduced pressure, and it was added dichloromethane (10 mL). The resulting mixture was filtered and the complex 2 was recovered, as a white powder, by evaporation of the solvent (0.053 g, 0.093 mmol). Yield: 93 %.

^{1}H NMR (400 MHz, DMSO-d_6) *δ:* 7.4_0–7.3_4 (m, 5H, *Ph ring*); 5.9_5—5.7_5 (m, 1H, *OH group*); 5.1_8—5.1_7 (m, 1H, OC*H*); 4.3_9–4.0_5 (m, 2H, NCH_2); 3.8_1 (s, 3H, NCH_3).

^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 182.9 (N*C*N); 141.3 *(ipso aromatic carbon*, Ph-ring); 128.4, 128.0, 125.7 (*aromatic carbons*, Ph ring); 117.5, 116.6 (*backbone carbons*, N*C* = *C*N); 72.2 (O*C*H); 56.4 (NCH_2); 36.8 (NCH_3).

MALDI-ToF (*m/z*): 739.06311 Da attributable to a bis-carbene structure $[C_{24}H_{24}AuCl_4N_4O_2]^+$.

Elemental Analysis: calculated for $C_{12}H_{12}AuICl_2N_2O$ (595.011) C 24.22, H 2.03, N 4.71, I 21.33; Found C 24.02, H 2.01, N 4.91, I 21.04.

Synthesis of bromide gold complex [4,5-dichloro-(N-methyl-N'(2-hydroxy-2-phenyl) ethyl-imidazole-2-ylidene] (3)

At the solution of chloro gold NHC complex 1 (0.050 g, 0.1 mmol, 1.0 eq) in acetone (10 mL) was added an excess of LiBr (0.09 g, 1 mmol, 10 eq). The mixture was stirred for 24 h at room temperature. After, the solvent was removed at reduced pressure, and 10 mL of dichloromethane were added. The reaction mixture was filtered to remove the excess of LiBr and LiCl. Evaporation of the solvent has given the desirable product, as a white powder (0.049 g, 0.09 mmol). Yield: 90 %.

^{1}H NMR (300 MHz, DMSO-d_6) *δ:* 7.4_0–7.3_6 (m, 5H, *Ph ring*); 5.8_7 (br, 1H, *OH group*); 5.1_4 (m, 1H, OC*H*); 4.2_6–4.1_9 (m, 2H, NCH_2); 3.8_1 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6) *δ:* 173.9 (N*C*N); 141.2 *(ipso aromatic carbon*, Ph-ring); 128.5, 128.1, 125.8 (*aromatic carbons*, Ph ring); 117.4, 116.5 (*backbone carbons*, N*C* = *C*N); 72.1 (O*C*H); 56.5 (NCH_2); 37.0 (NCH_3).

MALDI-ToF (*m/z*): 739.03326 Da attributable to bis-carbene structure $[C_{24}H_{24}AuCl_4N_4O_2]^+$.

Elemental Analysis: calculated for $C_{12}H_{12}AuBrCl_2N_2O$ (548.011) C 26.30, H 2.21, N 5.11, Br 14.58; Found C 26.50, H 2.01, N 5.01, Br 14.39.

Synthesis of acetate gold complex [4,5-dichloro-(N-methyl-N'(2-hydroxy-2-phenyl) ethyl-imidazole-2-ylidene] (4)

The synthesis and characterization of 4 are reported in our published paper [39].

Synthesis of hexafluorophosphate gold complex 4,5-dichloro-[N-(methyl)-N'(2-hydroxy-2- phenyl)ethyl-imidazole-2-ylidene] (5)

A solution of silver hexafluorophosphate (0.030 g, 0.12 mmol, 1.2 eq) and chloro gold(I) NHC **(1)** (0.050 g, 0.1 mmol, 1.0 eq) in acetonitrile (10 mL) was stirred for 1 h at room temperature. Then, the mixture was filtered, and the solvent was removed in vacuo. The desirable gold (I) NHC complex was obtained as a grey powder (0.030 g, 0.05 mmol). Yield: 50 %.

^{1}H NMR (300 MHz, DMSO-d_6) *δ:* 7.4_0–7.2_9 (m, 5H, *Ph ring*); 5.90 (br, 1H, *OH group*); 5.10 (m, 1H, OC*H*); 4.3_3–4.3_0 (m, 2H, NCH_2); 3.80 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6) *δ:* 183.8 (N*C*N); 142.1 *(ipso aromatic carbon*, Ph-ring); 129.3, 128.9, 127.0 (*aromatic carbons*, Ph ring); 118.8, 118.5 (*backbone carbons* N*C* = *C*N); 72.3 (O*C*H); 57.6 (NCH_2); 37.8 (NCH_3).

^{19}F NMR (377.35 MHz, DMSO-d_6): *δ:* −69.9, −70.1 (d). ^{31}P NMR (162.60 MHz; DMSO-d_6) *δ:* −139.9 (sept).

MALDI-ToF (*m/z*): 739.03681 Da attributable to bis-carbene structure $[C_{24}H_{24}AuCl_4N_4O_2]^+$.

Elemental Analysis: calculated for $C_{12}H_{12}AuPF_6Cl_2N_2O$ (613.072) C 23.51, H 1.97, N 4.57.

Found C 23.59, H 2.09, N 4.42.

Synthesis of phenylacetylide 4,5-dichloro-[N-(methyl)-N'(2-hydroxy-2-phenyl)ethyl-imidazole-2-ylidene]gold(I) (6)

Phenylacetylene (0.010 g, 0.1 mmol, 1.0 eq) and NEt_3 (0.060 g, 0.6 mmol, 6.0 eq) were stirred in acetonitrile (10 mL) for 2 h. After, at mixture was added the 1 (0.050 g, 0.1 mmol, 1.0 eq) and the mixture was further stirred for another 8 h. Then, the mixture was filtered, and the complex (0.045 g, 0.08 mmol) was obtained by evaporation of the solvent in vacuo.

^{1}H NMR (400 MHz, DMSO-d_6) *δ:* 7.4_2–7.2_7 (m, 10*H*, *Ph rings*); 5.9_7 (br, 1H, *OH group*); 5.1_7 (m, 1H, OC*H*); 4.4_7–4.2_6 (m, 2H, NCH_2); 3.8_2 (s, 3H, NCH_3).

^{13}C NMR (100 MHz, DMSO-d_6) *δ:* 186.9 (N*C*N); 141.4 *(ipso aromatic carbon*, Ph-ring), 131.2–125.8 (*aromatic carbons*, Ph rings, and Au*C*≡C-Ph); 117.5, 116.6 (*backbone carbons,* N*C* = *C*N,), 104.0 (AuC≡*C*-Ph); 72.3 (O*C*H), 56.3 (NCH_2); 36.8 (NCH_3).

MALDI-ToF (*m/z*): 739.06311 Da attributable to a bis-carbene structure $[C_{24}H_{24}AuCl_4N_4O_2]^+$.

Elemental Analysis: calculated for $C_{20}H_{17}AuCl_2N_2O$ (569.236) C 42.20, H 3.01, N 4.92. Found C 42.40, H 3.21, N 4.72.

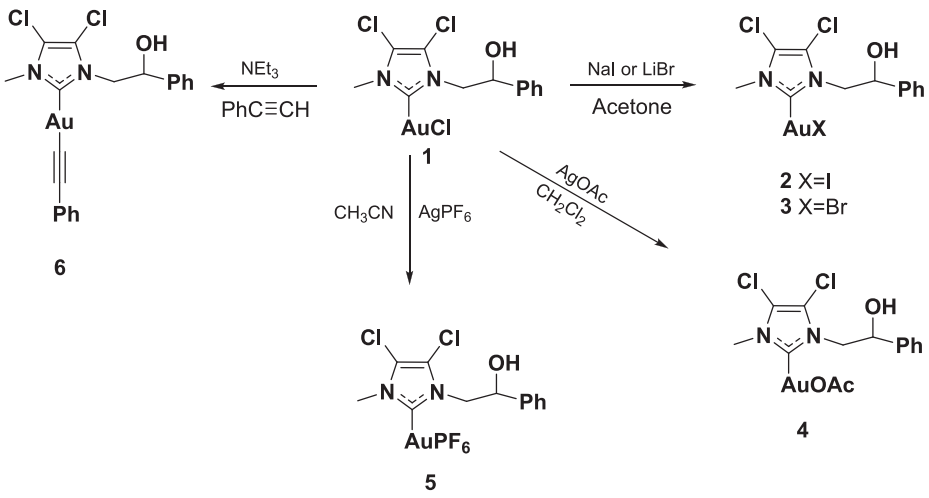
A^3coupling reaction: Kinetic activity

The kinetic studies were carried out according to ref. [7]. Aliquots were regularly withdrawn every 10 min for the first hour, while the others were taken after 2, 3, 4, 5 and 6 h and analyzed by ^{1}H NMR spectroscopy.

Results and discussion

Synthesis and characterization of gold(I) complexes

In Scheme 2, the steps for the synthesis of new complexes ((NHC)AuI, (NHC)AuBr, (NHC)AuPF_6, and (NHC)AuOAc) are summarized. By following the procedure reported by Baker [44], complexes 2–5 were obtained using counterion metathesis reaction on complex (NHC)AuCl, which was achieved as reported in the ref. [7]. Complex (NHC)AuC≡CPh (6 in Scheme 2) was obtained by reaction of 1 with phenylacetylene and an excess of NEt_3 [51,52].



Scheme 2. Synthetic routes to obtain new (NHC)Au(I)X complexes (2—6).

The iodide and bromide NHC complexes 2 and 3 were prepared in presence of acetone using an excess of NaI or LiBr, respectively, for 24 h at room temperature. The yield was nearly quantitative for both complexes (over 90 %). NHC acetate complex 4 and hexafluorophosphate complex 5 were obtained in good yields (80% and 50%) by metathesis reaction counterion, at room temperature for 12 hours. As shown in Scheme 2, the formation of the gold hexafluorophosphate complex 5 was carried out in acetonitrile, while the formation of complex 4 was carried out in dichloromethane[49]. The reaction between complexes 1 and phenylacetylene in the presence of NEt_3 (6 eq.), using acetonitrile as solvent, afforded the desired alkynyl specie 6 in very good yield (80 %) and under very mild conditions (8 h at room temperature).

The complexes were characterized by NMR, mass spectroscopy, and elemental analysis. ^{1}H NMR spectra of compounds 2 and 3 in DMSO-d_6 were almost overlapping, because the coordinated halide (I^- or Br^-) did not influence both the chemical shifts and the coupling pattern of the bound NHC ligand. The formation of the expected complexes was checked by ^{13}C NMR analyses, observing the downfield shifting of the carbene atom signal, bound to the gold atom *(vide infra)*. Complex 4 was synthesized by reaction of gold complex 1 with 1.2 equivalents of silver acetate [39]. ^{13}C NMR analysis of the acetate complex shows an upfield shift to 163.7 ppm with respect to complex 1 (C_{NHC} signal at 170.7 ppm) [39]. The gold complex (NHC)$AuPF_6$ was analogously synthesized: 1 was reacted with 1.2 equivalents of silver hexafluorophosphate in acetonitrile [49]. This process exploits the ability of silver ions to abstract halogen anions with consequent precipitation of the corresponding silver salt and the formation of the product. The reaction must be carried out in a coordinating solvent to avoid the risk of partial decomposition of the gold(I) complex to give colloidal gold(0). Considering the fundamental role of a coordinating solvent in the stabilization of NHC or phosphine complexes of gold (I), demonstrated by Nolan [42] and Echavarren [57], the counterion metathesis reaction was carried out in acetonitrile. The exchange of the anion was proved by precipitation of silver chloride, and by nuclear magnetic resonance characterization of compound. The ^{13}C NMR spectrum of hexafluorophosphate complex 5 showed a downfield shifting of the signal of the carbene C_{NHC} at 183.8 ppm. The formation of hexafluorophosphate complex 5 was supported by ^{19}F and ^{31}P spectroscopy analyses: in the ^{31}P spectrum, it was observed a septuplet at −139.9 ppm, due to the coupling constant J^1 (^{31}P-^{19}F) = 714.0 Hz, and a doublet in ^{19}F spectrum at −70.1 ppm.

The NHC gold(I) acetylide complex 6 was synthesized by following a procedure slightly modified with respect to that reported in the literature [51,52], using the reaction of phenylacetylene with a base such as triethylamine (NEt_3), to obtain the deprotonation of the alkyne. This leads to the corresponding acetylide binding to gold, producing the corresponding NHC gold (I) phenylacetylide complex, as observed by ^{1}H- and ^{13}C NMR spectroscopy characterization. ^{1}H spectra of 1 and 6 exhibit only differences in the aromatic region. As for the ^{13}C spectrum of 6 the triple carbon bond was observed through the signals at 128.7 ppm for *C*≡CPh and 104.0 ppm for C≡*C*Ph. Furthermore, the downfield shift of the carbene carbon atom bonded to the gold atom, which shift from 170.7 ppm of 1 to 186.9 ppm for acetylide gold complex, was relieved.

Chemical shift values of carbene carbon atoms of complexes 1–6, shown in Fig. 1 and summarized in Table 1, increase in the order 4 < 1 < 3 < 2 < 5 < 6.

A^3coupling reaction: Kinetic activity and molecular modeling studies

The catalytic activity of gold(I) complexes was evaluated in the coupling reaction of benzaldehyde, piperidine, and phenylacetylene carrying out the reactions in neat conditions for 6 h at 80 °C (see Scheme 3) [7]. The corresponding kinetic profiles are reported in Fig. 2, where the yield-time curves were determined by ^{1}H NMR spectroscopy using the internal standard method, with the integration of the signal of the two aromatic protons of internal standard (2-bromesitylene, δ_{CD2Cl2} = 6.89 ppm) and the methine proton (in α position to nitrogen atom) of propargylamine product at δ 4.79 ppm.

According to the kinetic profiles of Fig. 2, all complex reactions show an induction period and the complex activities are strongly influenced by the nature of the counterion. When X= Cl^-, Br^- and OAc^- we observe a similar induction period, but the activity decreases in the order Cl^- > OAc^- > Br^-. A slightly higher induction period was detected for X= I^-, whereas a 2 and a 5 hours induction periods were observed for X=-C≡CPh and PF_6^-, respectively. The slope of the kinetic profile for X = I^- and -C≡CPh are very similar to that of Br^-, indicating a comparable activity. In summary, the activity of the investigated catalysts decreases in the following order Cl^- > OAc^- > Br^- ≈ I^- ≈ C≡CPh > PF_6^-, in line with the trend published by Zou for NHC silver complexes [53].

Molecular modeling studies at the PBE0/6-311G(d,p) level of theory were conducted in order to interpret experimental observations. According to currently accepted mechanism [7,8,54] (Scheme 4), the formation of metal-acetylide from complexes **1**–**5** requires the break of the of the Au-X bond.

The counterion X^- can play a role in the initiation of the reaction, but also during the whole reaction as competitive species with respect to the alkyne substrate. In this framework, we modeled the starting monomeric complexes presenting X = Cl^-, Br^-, OAc^-, and PF_6^- (Fig. 3), and calculated the BDE (Bond-dissociation energies) of the counterion.

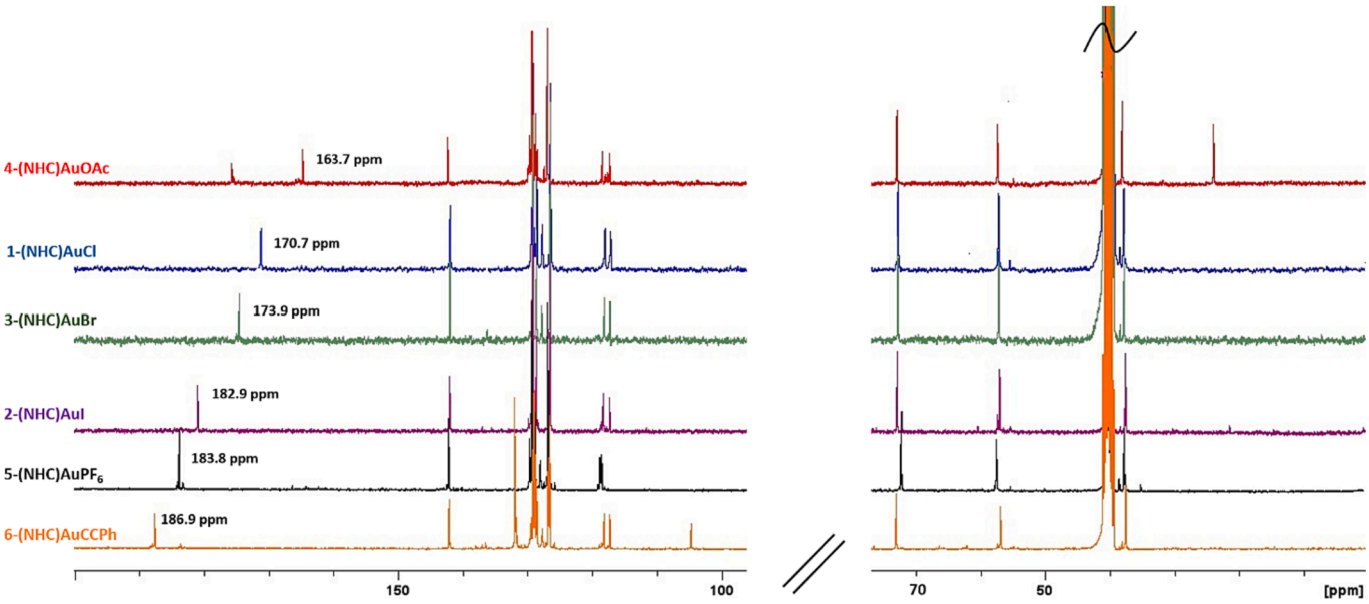


Fig. 1. Comparison of ^{13}C NMR spectra of (NHC)Au(I)X complexes 2–6 in DMSO-d_6.

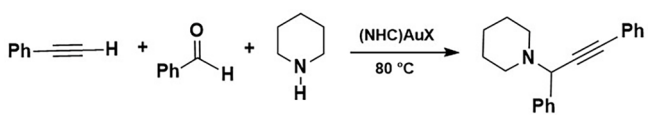
Table 1
Chemical shift of carbenic carbon of gold NHC complexes 1–6 (NHC)AuX.

Complex	X	δ_C (DMSO-d_6) Au-C (ppm)
4	AcO^-	163.7
1	Cl^-	170.7
3	Br^-	173.9
2	I^-	182.9
5	PF_6^-	183.8
6	PhC≡C-	186.9

As reported by Baker et al. [44] downfield shift of carbene carbons should increase with the σ-donor capacity of the counterion.

As reported in Table 2, BDE for halogens (Cl^- and Br^-) are equivalent. Indeed, the Au-Cl bond would possibly present a higher percentage of ionic character (as testified also by the Au charge reported in Table 2) and a shorter distance for the smaller chloride radius. On the other hand, the soft nature of gold would balance the unfavored higher Au-Br distance by a more favored soft–soft covalent interaction. The highest BDE was shown by complex 4, where acetate gives a strong interaction characterized by a short Au-O distance (2.06 Å) and a strong hydrogen bond (see Fig. 3). As expected, significantly low BDE was observed for complex 5, where PF_6^- reveals as a weak counterion, with a relatively high Au-F distance and a weaker hydrogen bond. It is worth noting that calculated BDE are coherent with NHC carbene carbon chemical shift observed by ^{13}C NMR (Table 1). The higher is the BDE the lower is the C_{NCN} chemical shift.

The nature of the metal-counterion interaction is not able so far to rationalize the experimental data on catalytic activity: acetate gold complex 4 showed to have an activity, intermediate among 1 and 3, and the efficiency of complex 5 was largely inferior with respect to other catalysts. Consequently, we considered a further factor able to influence the activity of these catalysts, which is the abundance of active species in



Scheme 3. The A^3 coupling reaction to give N-(1,3-diphenyl-2-propynyl) piperidine.

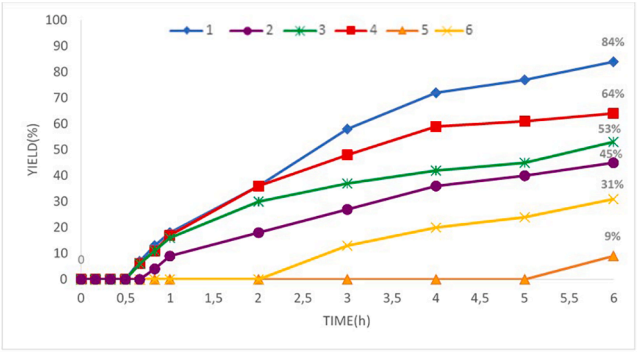
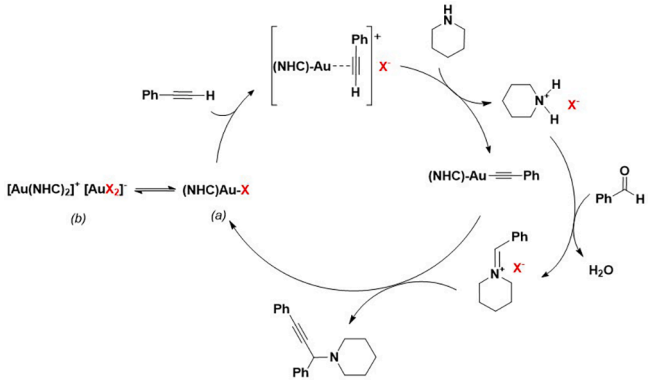


Fig. 2. Plot of yields versus time for the first 6 h of coupling among benzaldehyde, piperidine, and phenylacetylene.

the reacting medium. Indeed, it is widely accepted in the literature that the neutral NHC-Au-X complexes are generally in equilibrium when dissolved, with the ionic compound $[Au(NHC)_2]^+[AuX_2]^-$ Scheme 4, inactive in the catalysis process [7,8,55]. In this framework we calculated the free energy in benzaldehyde of the neutral NHC-Au-X species with respect to ionic compound $[Au(NHC)_2]^+[AuX_2]^-$, to evaluate its thermodynamical stability [56]. It is worth noting that, as for ionic compound $[Au(NHC)_2]^+[AuX_2]^-$, the calculations were run considering



Scheme 4. Metal catalyzed A^3 coupling mechanism.

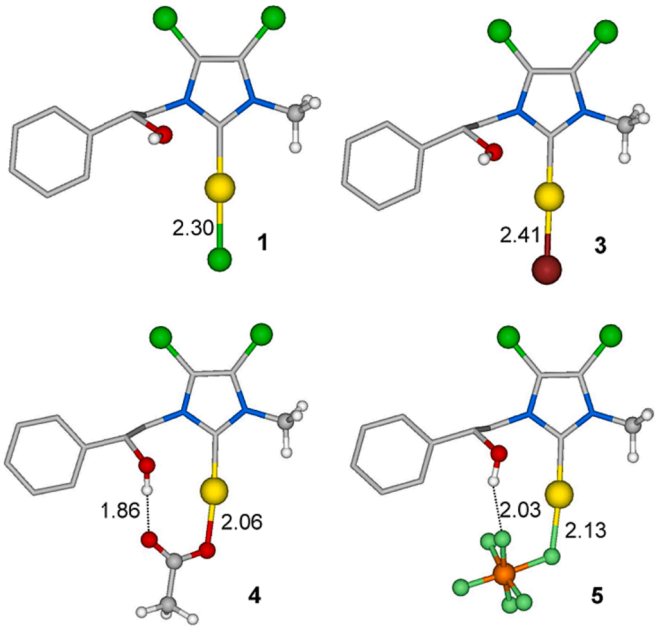


Fig. 3. Minimum energy structures of complexes 1, 3, and 5. Distances are in Å. Non-relevant hydrogens of the ligand skeleton were omitted for clarity.

Table 2
Bond-dissociation energies of counterion (BDE) and charge on the metal center.

Complex	BDE (counterion)[a]	Au charge [c]
1	146.2[b]	0.25549
3	146.2	0.19564
4	163.1	0.35888
5	106.7	0.42947

[a] Bond-dissociation energies (BDE) referred to the metal–halogen bond.
[b] See ref. [7].
[c] Au charges were obtained from NBO analysis.

the isolated cation and anion. In solution, ionic couples or small aggregates could be present. In our opinion, this approximation prevents from accepting the calculated free energy differences between the neutral NHC-Au-X species and the ionic compound $[Au(NHC)_2]^+[AuX_2]^-$ as absolute numbers. Nevertheless, we can compare the obtained ΔG to evaluate which complex has the highest tendency to produce in solution the neutral NHC-Au-X.

According to computational results collected in Table 3, chloride complex 1 exhibits ΔG more negative than the bromide complex 3. Consequently, the formation of the neutral NHC-Au-X species is more favored for the chloride than for the bromide complex. The higher abundance of the neutral active species for the chloride can explain the better performances of 1 with respect to 3 with equal BDE.

The acetate NHC complex 4 shows the highest stability with respect to its ionic analogous. This would imply a higher abundance of 4 as active neutral species NHC-Au-X with respect to gold halogenides. Therefore, the significantly high BDE of acetate can be partially balanced by the higher abundance of the neutral species NHC-Au-X. The activity of 4, intermediate among 1 and 3, could be rationalized by the coexistence of these two opposite factors: high BDE and neutral NHC-Au-X active species energetically favored.

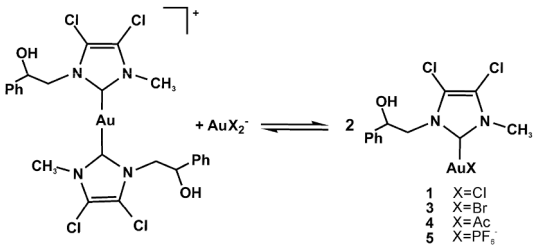
According to computational results, we still could not explain the dramatical low activity of hexafluorophosphate, which apparently presents the lowest BDE and a good stability neutral NHC-Au-X complex (ΔG = -12.1 kcal/mol) with respect to the ionic species.

These findings induced us to suppose a partial decomposition. Indeed, the Tyndall effect was observed by passing a beam of laser light through the solution made up of the reactants and the catalyst, confirming the presence of colloidal species, possibly corresponding to insoluble decomposition products. Finally, the low activity of catalyst 6 (X = -C≡CPh) can be rationalized by speculating on the catalytic mechanism: the very long induction time can be caused by the absence of a protonated piperidine at the beginning of the reaction, since the catalytic cycle must start from the acetylide, without the acetylene deprotonation. As well known, the formation of imine is catalyzed by acid ambient. In a neutral environment, the formation of the first imine is possibly very slow.

Conclusions

The synthesis and characterization of NHC gold complexes (1–6) with different counterions (Cl, Br, I, OAc, PF_6, -C≡CPh) have been described. A^3 coupling reactions of benzaldehyde, piperidine, and phenylacetylene, in the presence of 1–6 demonstrated the high relevance of the counterion in this kind of catalysis. Indeed, kinetic profiles indicate that catalyst activity, on varying the counterion, decreases in the order $Cl^- > OAc^- > Br^- \approx I^- \approx$ -C≡CPh $> PF_6^-$. According to computational studies, the observed trend is the sum of more than one factor. The

Table 3
Free energies in benzaldehyde of neutral NHC-Au-X species with respect to corresponding ionic compound $[Au(NHC)_2]^+[AuX_2]^-$.



Complex	ΔG (kcal/mol)[a]
1	−10.5
3	−8.7
4	−14.0
5	−12.1

[a] $\Delta G = 2G_{NHC\text{-}Au\text{-}X} - (G_{[M(NHC)2]+} + G_{[MX2]-})$. Minimum energy geometries of NHC-Au-X, $[M(NHC)_2]^+$, $[MX_2]^-$ were located at the PBE0/6-311G(d,p) level. Improved electronic energies were obtained by single-point calculations, on the gas phase optimized structures, using diffuse function basis set (6-311G++(d,p)) and solvent effects (see SI).

superior activity of Cl *vs* Br complex would be determined by the higher stability of the neutral active species NHCAuX toward the ionic compound $[Au(NHC)_2]^+[AuX_2]^-$. The reaction rate in the presence of complex 4 (X = OAc), intermediate between chloride and bromide complexes, would be due to the coexistence of the high BDE of the acetate (that would slow down the reaction) and the high stability of the neutral active species NHCAuOAc (that would accelerate the reaction).

The very low activity of PF_6 complex, apparently difficult to rationalize, is possibly due to a partial decomposition of the complex, whereas the unexpected long induction in the presence of 6 (X = -C≡CPh) is most probably associated to the lack of hydrogen (which generally comes from acetylene) in the very beginning of the reaction, essential for amine protonation.

CRediT authorship contribution statement

Marco Sirignano: Investigation, Methodology, Data curation. **Chiara Costabile:** Conceptualization, Methodology, Writing – review & editing, Supervision, Visualization. **Annaluisa Mariconda:** Conceptualization, Methodology, Writing – review & editing, Supervision, Visualization. **Pasquale Longo:** Conceptualization, Methodology, Writing – review & editing, Supervision, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2023.101198.

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