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Exploring the coordination properties of phosphonium-functionalized N-heterocyclic carbenes towards gold

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Abstract: Gold(I) complexes with N-heterocyclic carbene ligands functionalized with a pendant phosphonium moiety were synthesized by simple procedures. In particular, the simple addition of LiBr salt in the reaction media allows the formation of the NHC gold(I) mononuclear complexes, whilst in the absence of excess bromide ions the deprotonation of the methylene group in alpha position to the phosphonium group occurs, allowing the isolation of the dinuclear complexes with two C,C-bridging NHC-phosphonium ylide ligands. The complexes were characterized in solution with NMR spectroscopy and ESI-MS spectrometry, as well as in the solid state by means of single crystal X-ray diffraction analysis. Mononuclear gold(III) species were also isolated by Br₂ oxidative addition to the mononuclear gold(I) species and fully characterized. Preliminary results of the biological effects on MCF7 cancer cells are also reported.

Introduction

The interest towards N-heterocyclic carbenes (NHCs) is continuously growing driven by their application either as organocatalysts^[1–3] or as ligands in functional organometallics.^[4–7] NHC-metal complexes have shown indeed excellent performances in homogeneous catalysis, medicinal chemistry and material science.^[8–11] Consequently, there is a very intense research effort toward the design of novel NHC architectures with different moieties. In this view, a very common approach is the introduction of a second functionality at nitrogen wingtip group(s) or as a dangling substituent in the backbone of the heterocyclic ring. To date, several examples of backbone functionalized NHCs that feature neutral (like for example -OR, -NR₂, -PR₂, -SR, -SeR groups), anionic (like -O⁻, -NR⁻, -S⁻, -SO₃⁻, -COO⁻ groups) or even cationic (like -NR₃⁺, -PR₃⁺ groups) moieties have been

described.^[12–27] The exploitation of the second functionality allows for example to obtain polynuclear complexes,^[28,29] the anchoring of the complex to polymers,^[30] surfaces or nanoparticles.^[31] This also increases the robustness of the whole molecular system in the case of catalytic activity. It can also provide additional functionality, especially in medicinal chemistry, by seeking specific targeting.^[32]

In the series of functionalized NHCs, those bearing a phosphonium group have recently been extensively investigated by Canac and co-workers with particular interest towards palladium(II) and rhodium(I) centres.^[33–40] Importantly, this type of compounds can act as bidentate chelating ligands through the formation of a phosphonium ylide in addition to the NHC donor. Although phosphonium ylides are known since the early 20th century, there is now a renaissance in the study of their coordination properties.^[41,42] They formally have a negatively charged carbon atom directly attached to a positively charged phosphorus atom and behave as σ -donor ligands, stronger than NHCs.^[43,44]

A second benefit of the positive charge present on the phosphonium group is related to the possibility of using the obtained metal complexes in medicinal chemistry. Indeed since late 60s, triphenylphosphonium moieties have been shown to act perfectly as a delocalized lipophilic cation (DLC), allowing the functionalized compound to efficiently penetrate and accumulate in the mitochondria.^[45,46] In addition, the higher membrane potentials of cancer cells compared to normal cells, selectively promote the accumulation of DLCs in carcinoma cells.

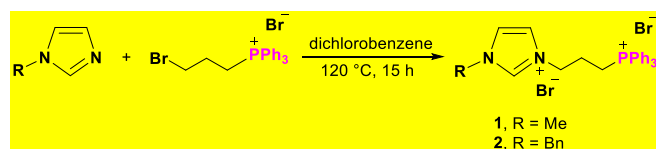
Considering both these aspects related to the use of phosphonium-functionalized NHC ligands, we report here a study on their coordinating properties towards gold. In particular, we show that the simple addition of LiBr salt in the reaction media allows the formation of a NHC gold(I) mononuclear complex, instead of a dinuclear complex, the two compounds having been

characterized by X-ray diffraction studies. Gold(III) species were also isolated and fully characterized. Preliminary results of the biological effects on MCF7 cancer cells are also reported.

Results and Discussion

Synthesis of phosphonium functionalized NHC proligands

A convenient access to the phosphonium functionalized NHC proligands **1** and **2** is the quaternization of the proper N-substituted imidazole via nucleophilic substitution using (3-bromopropyl)triphenylphosphonium bromide (Scheme 1).^[35]



Scheme 1. Synthesis of the phosphonium functionalized NHC proligands **1** (89% yield) and **2** (91% yield).

The ³¹P NMR spectra of the phosphonium salts in deuterated acetonitrile show a singlet at $\delta = 24.0$ and 24.1 ppm for **1** and **2**, respectively. The successful synthesis of these compounds was supported in the ¹H NMR spectra by the presence of a singlet at δ around 9.3–9.6 ppm associable to the acidic C2-H. Moreover, the molecular structure of compound **2** was determined by X-ray diffraction (Figure 1).

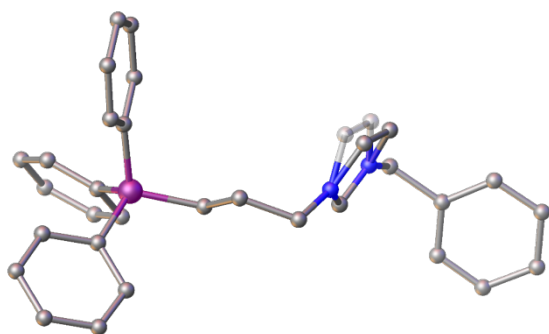


Figure 1. Crystal structure of **2**. Colour code: C, grey; P, purple; N, blue. H atoms, anions and solvent molecules omitted for clarity. Two carbon atoms in the imidazole ring are affected by positional disorder. Disordered moiety with minor occupation is displayed as translucent atoms.

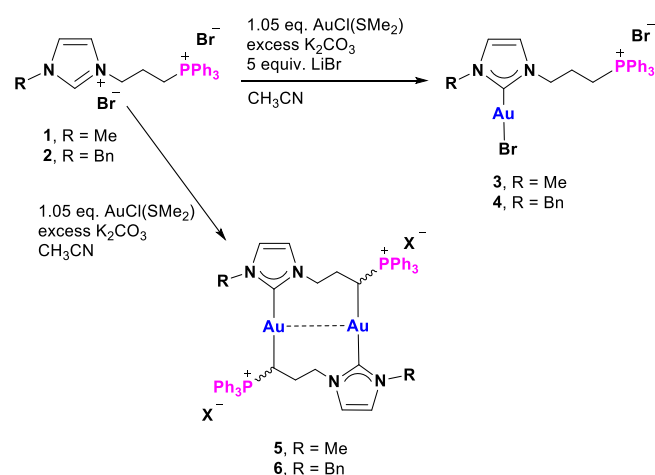
Gold(I) complexes bearing phosphonium functionalized NHC ligands

Starting from proligands **1** and **2**, two mononuclear gold(I) complexes were synthesized without by-products formation via the so-called weak base route (Scheme 2). Complexes **3** and **4** were isolated by using the proper proligand, 5 equiv. of K_2CO_3 and 5 equiv. of LiBr to avoid the formation of the *bis*(NHC) complex and heating the mixture in acetonitrile at 40 °C for ca. 5 hours.^[19]

The benzyl-substituted gold(I) complex **4** is stable and was isolated in excellent yield (86%). The successful coordination of

the carbene to the gold(I) centre was confirmed by means of ¹H NMR with the disappearance of the singlet assigned to the acidic C2-H of the imidazolium as well as by the presence of a signal at 173.1 ppm in the ¹³C NMR spectrum, which is the signature of the C2 carbene coordinated to the gold(I) centre.^[47] The chemical shift of the other functional groups both in the ¹H and ¹³C NMR spectra are similar to those observed in the starting imidazolium salt. The ³¹P NMR spectrum presents a signal at δ 23.5 ppm slightly shifted ($\Delta\delta +0.6$ ppm) in comparison with the analogous signal in the ligand precursor **2**. The ESI-MS spectrum shows a fragment at 737.20 *m/z* associable to the loss of the bromide, counter ion of the phosphonium moiety.

The analogous methyl-substituted gold(I) complex **3** was more difficult to isolate. The complex appeared stable in the reaction mixture (i.e. in the presence of LiBr and K_2CO_3), so that for example, colourless crystals of **3** suitable for single-crystal X-ray diffractometric (SC-XRD) analysis formed directly in the NMR tube containing a sample of the reaction mixture. The molecular structure of complex **3** together with selected bond distances and angles is shown in Figure 2 (see below for discussion). However, the complex undergoes decomposition after filtration of the inorganic salts and evaporation of the solvent under vacuum. In fact, during evaporation of the solvent, the colour of the solution turned yellow and a brown residue, attributed to the formation of metallic gold, formed at the bottom of the reaction flask. This residue was treated with deuterated acetonitrile, transferred into an NMR tube and the ¹H NMR spectra of this sample mixture were recorded after 1, 3, 5 and 8 days (Figure S7). A second set of signals, slightly downfield shifted with respect to the analogous set of the gold(I) complex, increases with time. The ESI-MS spectrum of the sample after 8 days displays two main fragments, one associable as the cation of the pristine gold(I) complex (fragment at 661.14 *m/z*, corresponding to loss of one bromide ion) and one to the species $[AuBr_3(L)]^+$ (822.83 *m/z*, attributed to the corresponding gold(III) complex with L=NHC ligand) (Figure S8). The partial formation of the gold(III) complex **7** and its characterisation were also confirmed by direct oxidative bromine addition experiments to the mixture, with the aim of isolating only the gold(III) species (see later in the text the section on gold(III) complexes). The partial oxidation of gold(I) to gold(III) could be the result of a partial disproportionation of the gold(I) complex. This type of reactivity has already been reported in the literature.^[48–52]



Scheme 2. Synthesis of the mononuclear gold(I) complexes **3** and **4** (86% yield), and of the dinuclear ones **5** (73% yield) and **6** (82% yield).

Complex **3** presents a linear coordination geometry, as expected for a metal center in a d^{10} electronic configuration, with one NHC and a bromide ligand coordinated to the gold(I) (C-Au-Br angle of 177.54° , see Figure 2). The Au-C and Au-Br bond distances are in agreement with literature data (1.984 Å and 2.3976 Å, respectively).^[19,53]

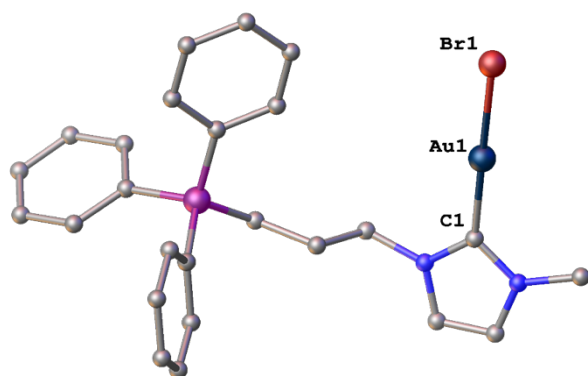


Figure 2. Crystal structure of complex **3**. Colour code: C, grey; Au, dark blue; P, purple; N, blue. H atoms and uncoordinated anions omitted for clarity. Selected bond lengths (Å) and angles ($^\circ$): Au1-Br1 2.3976(5), Au1-C1 1.984(4); C1-Au1-Br1 177.54(9).

Interestingly, we found that the result of the complexation on gold(I) strongly depends on the presence of LiBr. In fact, when the synthesis is carried out without an excess of bromide ions, two novel gold(I) complexes, **5** and **6**, could be isolated rather than the mononuclear ones **3** and **4**. Complexes **5** and **6** are dinuclear species, characterized by the coordination of two C,C-bridging NHC-phosphonium ylide ligands. The deprotonation of the methylene group in alpha position to the phosphonium group has been already reported in the literature for palladium(II) complexes with similar ligands.^[33–35,39] In our case, the formation of an ylide-metal bond was indeed suggested on the basis of the ^{31}P NMR spectrum, which exhibited two resonances around δ 29 ppm (29.6 (minor) and 29.5 (major) ppm for complex **5**; 29.6 (major) and 28.8 (minor) ppm for complex **6**) shifted of ca. 5 ppm to lower fields relative to phosphonium precursors or the gold(I) complexes **3** and **4**. The presence of two signals in the ^{31}P NMR spectrum can be justified by the occurrence of two conformational isomers in solution,^[54] characterised by different orientation of the bridge between the two donors or of two diastereoisomers due to the presence of the stereogenic ylidic carbon atoms.^[35,36,38–40]

Finally, the molecular structure of dinuclear complex **6** was definitively established by X-ray diffraction analysis on colourless crystals isolated by slow diffusion of diethyl ether into an acetonitrile solution of **6** (Figure 3).

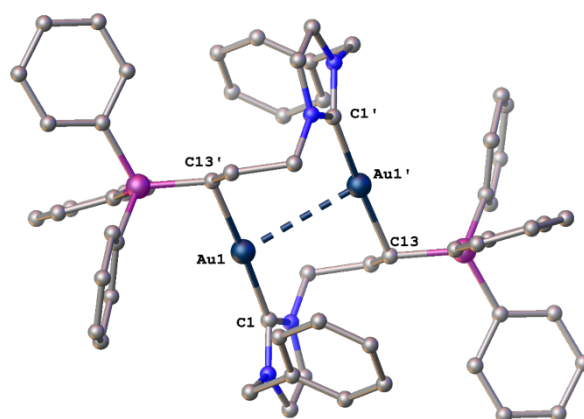


Figure 3. Crystal structure of complex **6**. Colour code: C, grey; Au, dark blue; P, purple; N, blue. H atoms and anions omitted for clarity. Selected bond lengths (Å) and angles ($^\circ$): Au1-Au1' 3.2265(4), Au1-C1 2.017(5), Au1-C13' 2.085(4); C1-Au1-C13' 176.78(16). Symmetry operation: ' 1-x,1-y,1-z.

Complex **6** is a dinuclear species with a head-to-tail bridging coordination of the two NHC-phosphonium ylide ligands. The stereochemical structure of complex **6** found in the crystal is the *meso* isomer. The gold(I) centres present an almost linear coordination geometry ($C_{\text{carbene}}\text{-Au-C}_{\text{ylide}}$ of 176.78°). The Au- C_{carbene} and Au- C_{ylide} bond distances (2.017 and 2.085 Å, respectively) are in agreement with literature data, with the Au- C_{ylide} bond slightly longer than the Au- C_{carbene} one.^[34,55] The Au \cdots Au distance (3.2265 Å) suggests the presence of aurophilic interactions, since the distance is shorter than the sum of van der Waals of two gold atoms (i.e. 3.32 Å from the 1.66 Å radii).^[56]

When crystals of complex **6** are dissolved in deuterated DMSO a singlet is observed (Figure S15) in the ^{31}P NMR spectrum at δ 28.8 ppm. The spectrum changes with time and after 72 h, it becomes superimposable to the one registered for the isolated solid at the end of the synthesis reaction (two signals at δ 29.6 and 28.8 ppm). This confirms the possibility of two isomers in equilibrium in solution. A change is also observed in the ^1H NMR spectrum (Figure S14), in which the most striking difference is the benzylic CH_2 group: in the just-dissolved sample an AB system is observed, whereas it becomes a singlet with time, suggesting an increase in mobility of the benzyl substituent.

Au^I-NHC complexes and their multi-metallic assemblies are known to display interesting and sometimes intense luminescence properties,^[57–61] in particular when short Au \cdots Au are present. Regrettably, complexes **5** and **6** display virtually absent photoluminescence very close to the detection limit of the in the solid state and no mechanochromic behavior.

Gold(III) complexes bearing phosphonium functionalized NHC ligands

Mononuclear gold(III) complexes **7** and **8** were isolated by oxidative addition of molecular bromine to gold(I) complexes (Scheme 3). We used complex **4** in its isolated pure form and complex **3** in solution and not purified because of its instability (*vide supra*). The ^1H NMR spectra of the two synthesized gold(III) complexes are similar to those observed for the pristine gold(I) complexes, except for a slight shift to higher ppm for all signals. In contrast, the ^{13}C NMR spectra show a signal for the carbene carbon around 136 ppm, in agreement with values reported in the

peak at 2.17 ppm. $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CD_3CN , 298 K, ppm) δ : 24.1 ppm.

Synthesis of the mononuclear gold(I) complexes 3 and 4

The proper imidazolium salt **1** or **2** (1 equiv.), the Au(I) precursor $\text{AuCl}(\text{SMe}_2)$ (1.05 equiv.), LiBr (5 equiv.) and an excess of K_2CO_3 (5 equiv.) were introduced into a two- or three-neck round bottom flask. Acetonitrile (15 mL) was then added via a syringe under inert atmosphere. The mixture was stirred at 40 °C for 5 hours, then filtered. Finally, the solvent was removed under vacuum giving a white solid. For complex **3**, the reported ^1H and ^{31}P NMR, as well as the ESI-MS, characterizations are based on a withdrawal from the reaction mixture, before the work-up for isolation of the solid, which causes decomposition of the compound. The most important ^{13}C signals were extrapolated from the 2D NMR spectrum of the mixture isolated after work-up.

3. ^1H NMR (300 MHz, CD_3CN , 298 K, ppm) δ : 3.29 (m, 2H, CH_2P), 3.76 (s, 3H, CH_3), 4.29 (t, $J = 7.0$ Hz, 2H, CH_2N), 7.11 (m, 2H, CH), 7.63 – 7.92 (m, 15H, Ph), the signal of the missing CH_2 is superimposed with the water peak at 2.16 ppm. ^{13}C NMR (75 MHz, CD_3CN , 298 K, ppm) δ : 38.5 (CH_3), 51.5 (CH_2N), 117.4–136.8 (C and CH arom), 174.8 (CAu). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CD_3CN , 298 K, ppm) δ : 23.6. ESI-MS (positive mode, m/z): 661.23 [**3-Br**] $^+$.

4. Yield 86%. ^1H NMR (300 MHz, CD_3CN , 298 K, ppm) δ : 3.30 (m, 2H, CH_2P), 4.32 (t, $J = 7.2$ Hz, 2H, CH_2N), 5.34 (s, 2H, CH_2Ph), 7.16 (d, $J = 2.0$ Hz, 1H, CH), 7.18 (d, $J = 2.0$ Hz, 1H, CH), 7.34 (m, 5H, Ph), 7.55 – 7.92 (m, 15H, Ph), the signal of the missing CH_2 is superimposed with the water peak at 2.16 ppm. ^{13}C NMR (75 MHz, CD_3CN , 298 K, ppm) δ : 18.7 (d, $J_{\text{PC}} = 53$ Hz, CH_2P), 23.3 (d, $J_{\text{PC}} = 3$ Hz, CH_2), 49.8 (d, $J_{\text{PC}} = 19$ Hz, CH_2N), 53.8 (CH_2Ph), 121.0 (CH_{im}), 121.3 (CH_{im}), 127.2 (CH), 127.8 (CH), 128.3 (CH), 129.9 (d, $J_{\text{PC}} = 12$ Hz), 133.1 (d, $J_{\text{PC}} = 11$ Hz), 134.7 (d, $J_{\text{PC}} = 3$ Hz), 135.9 (C), 173.1 (CAu), the ipso carbon around 117 ppm of the phosphonium group is partially superimposed with the solvent signal. $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CD_3CN , 298 K, ppm) δ : 23.5. ESI-MS (positive mode, m/z): 737.20 [**4-Br**] $^+$.

Synthesis of complexes 5 and 6

The proper imidazolium salt **1** or **2** (1 equiv.), the Au(I) precursor $\text{AuCl}(\text{SMe}_2)$ (1.05 equiv.) and an excess of K_2CO_3 (5 equiv.) were introduced into a two- or three-neck round bottom flask. Acetonitrile (15 mL) was then added via a syringe under inert atmosphere. The mixture was stirred at 40 °C for 5 hours, then filtered. Finally, the solvent was removed under vacuum giving a white solid.

5. Yield 73%. ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 2.06 (m, 2H, CH_2), 2.42 (m, 2H, CHP), 2.71 (m, 2H, CH_2), 3.09 (major species) and 3.37 (minor species) (s, 6H, CH_3), 4.30 and 4.81 (m, 2H, CH_2N), 7.50 – 7.85 (m, 34H, Ph and CH). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 29.5 (major), 29.6 (minor). ESI-MS (positive mode, m/z): 581.14 [**5-2Br**] $^{2+}$.

6. Yield 82%. ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 1.50 (m, 2H, CH_2), 1.87 (m, 2H, CHP), 2.61 (m, 2H, CH_2), 4.16–4.22 (m, 4H, NCH_2), 4.66 and 5.05 (AB system, 4H, CH_2Ph), 6.70 – 7.80 (m, 44H, Ph and CH). ^{13}C NMR (75.5 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 18.8 (d, $J_{\text{PC}} = 33$ Hz, CHP), 29.0 (CH_2), 52.1 (d, $J_{\text{PC}} = 22$ Hz, CH_2N), 52.9 (CH_2Ph), 119.7 (CH_{im}), 123.7 (d, $J_{\text{PC}} = 83$ Hz, CP), 123.8 (CH_{im}), 126.8 (CH), 127.8 (CH), 128.4 (CH), 129.7 (d, $J_{\text{PC}} = 11$ Hz, CH), 132.8 (d, $J_{\text{PC}} = 9$ Hz, CH), 133.5 (C), 137.4 (C), 184.8 (AuC). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 28.8. Crystals of complex **6** were obtained by slow diffusion of diethylether into an acetonitrile solution of the complex. The NMR spectra of complex **6** changes with time upon dissolution of a crystal in $\text{DMSO-}d_6$. The signals of the second isomeric species are: ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 2.02 (m, 2H, CH_2), 2.22 (m, 2H, CHP), 2.61 (m, 2H, CH_2), 4.30 and 4.90 (2m, 4H, NCH_2), 4.71 (s, 4H, CH_2Ph), 6.70 – 7.80 (m, 44H, Ph and CH). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, $\text{DMSO-}d_6$, 298 K, ppm) δ : 29.6. ESI-MS (positive mode, m/z): 657.21 [**6-2Br**] $^{2+}$, 1393.26 [**6-2Br**] $^+$.

Synthesis of complexes 7 and 8

The proper gold(I) complex was dissolved in acetonitrile (ca. 10 mL) under Argon atmosphere. A solution of bromine in acetonitrile was added to the solution of the gold(I) complex with a syringe (Au:Br $_2$ ratio 1:1.2). The

solution was left under stirring at room temperature for 2 hours. Finally, the solvent and the excess of bromine were removed at reduced pressure. The methyl-substituted gold(III) complex **7** was synthesised starting from the mixture of gold(I) and gold(III) complexes, isolated in the work-up reaction of **3**.

7. ^1H NMR (300 MHz, CD_3CN , 298 K, ppm) δ : 3.28 (m, 2H, CH_2P), 3.81 (s, 3H, CH_3), 4.39 (t, $J = 7.4$ Hz, 2H, CH_2N), 7.37 (m, 2H, CH), 7.63 – 7.95 (m, 15H, Ph), the signal of the missing CH_2 is superimposed with the water peak at 2.16 ppm. ^{13}C NMR (75 MHz, CD_3CN , 298 K, ppm) δ : 19.1 (d, $J_{\text{PC}} = 56$ Hz, CH_2P), 22.5 (CH_2), 49.3 (d, $J_{\text{PC}} = 20$ Hz, CH_2N), 37.1 (CH_3), 117.0 (d, $J_{\text{PC}} = 85$ Hz, CP), 123.6 (CH_{im}), 125.7 (CH_{im}), 129.9 (d, $J_{\text{PC}} = 12$ Hz), 133.2 (d, $J_{\text{PC}} = 10$ Hz), 134.8 (d, $J_{\text{PC}} = 3$ Hz, CH), 136.7 (AuC). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CD_3CN , 298 K, ppm) δ : 23.6. ESI-MS (positive mode, m/z): 822.80 [**7-Br**] $^+$.

8. Yield 67%. ^1H NMR (300 MHz, CD_3CN , 298 K, ppm) δ : 2.23 (m, 2H, CH_2), 3.32 (m, 2H, CH_2P), 4.44 (t, $J = 7.5$ Hz, 2H, CH_2N), 5.40 (s, 2H, CH_2Ph), 7.33 (d, $J = 2.0$ Hz, 1H, CH), 7.34 – 7.92 (m, 21H, Ph and CH). ^{13}C NMR (75 MHz, CD_3CN , 298 K, ppm) δ : 18.7 (d, $J_{\text{PC}} = 54$ Hz, CH_2P), 22.4 (d, $J_{\text{PC}} = 54$ Hz, CH_2), 49.7 (d, $J_{\text{PC}} = 21$ Hz, CH_2N), 53.7 (CH_2Ph), 117.0 (d, $J_{\text{PC}} = 86$ Hz, CP), 124.0 (CH_{im}), 124.5 (CH_{im}), 128.4–128.5 (3s, CH), 129.9 (d, $J_{\text{PC}} = 13$ Hz, CH), 133.2 (d, $J_{\text{PC}} = 10$ Hz, CH), 133.3 (C), 134.8 (d, $J_{\text{PC}} = 3$ Hz, CH), 136.7 (AuC). $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CD_3CN , 298 K, ppm) δ : 23.6 ppm. ESI-MS (positive mode, m/z): 896.82 [**8-Br**] $^+$.

X-ray crystal structure determination

Data were collected using an Oxford Diffraction Gemini E diffractometer, equipped with a 2K \times 2K EOS CCD area detector and sealed-tube Enhance (Mo) and (Cu) X-ray sources. A suitable single crystal was fastened on a nylon loop and measured at room temperature. Detector distance has been set at 45 mm. The diffraction intensities have been corrected for Lorentz/polarization effects as well as with respect to absorption. Empirical multi-scan absorption corrections using equivalent reflections have been performed with the scaling algorithm SCALE3 ABSPACK. Data reduction, finalization and cell refinement were carried out through the CrysAlisPro software. Accurate unit cell parameters were obtained by least squares refinement of the angular settings of strongest reflections, chosen from the whole experiment. The structures were solved with Olex2^[63] by using ShelXT^[64] structure solution program by Intrinsic Phasing and refined with the ShelXL^[65] refinement package using least-squares minimization. In the last cycles of refinement, non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated positions, and a riding model was used for their refinement. The structure of complex **6** contains a mixture of chloride and bromide anions occupying the same positions due to substitutional disorder. These atoms were split and modelled through EXYZ and EADP constrains. The unit cell contains circa 3 chloride and 1 bromide (Cl 2.9; Br 1.1). Details for each structure refinement are reported in the crystallographic table (Table S1). Deposition Numbers 2221949 (for **3**), 2221950 (for **6**) and 2221951 (for **2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe.

Cytotoxicity tests of NHC-gold(I/III) complexes

Cytotoxicity tests have been carried out at the "Institut de Chimie des Substances Naturelles CNRS - UPR2301, Gif-Sur-Yvette, France". Samples were prepared by dissolution of the compounds in DMSO (except for *cisplatin* that was dissolved in water since it rapidly decomposes in DMSO) at stock concentrations of 10 mM. MCF7 (breast cancer cells) cell lines were maintained as monolayers in RPMI 1640 medium supplemented with 10% fetal calf serum, in the presence of penicilline, streptomycine and fungizone in 75 cm 2 flask under 5% CO $_2$. Cells were plated in 96-well tissue culture plates in 200 μl complete medium at a density of 1000–2500 cells per well and treated 24h later with 2 μl of compounds using a Biomek 3000 automation workstation (Beckman-Coulter). Controls received the same volume of the appropriate vehicle (DMSO, EtOH or water, 1% final volume). After 72 h exposure, MTS reagent (CellTiter 96 $^{\text{®}}$ Aqueous One, Promega) was added and incubated for 3 h at 37 °C: the absorbance was monitored at 490nm and results expressed as the inhibition of cell proliferation calculated as the ratio [(1-

(OD490 treated/OD490 control) × 100] in triplicate experiments after subtraction of the blank without cells. Positive controls (cells incubated with a reference drug at its IC₅₀ concentration) were routinely added to check the responsiveness of cells. For IC₅₀ determination [50% inhibition of cell proliferation], cells were incubated for 72 h following the same protocol with compound concentrations ranged 5 nM to 100 μM in separate duplicate experiments. Values are given as means ± SD from at least three independent experiments performed in triplicate.

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- [1] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5655.
- [2] A. T. Biju, *N-Heterocycl. Carbenes Organocatalysis*, Wiley-VCH, **2018**.
- [3] D. M. Flanigan, F. Romanov-Michaillidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307–9387.
- [4] H. V. Huynh, *The organometallic chemistry of N-heterocyclic carbenes*, John Wiley & Sons, Inc, Hoboken NJ, **2017**.
- [5] H. M. Lee, C.-C. Lee, P.-Y. Cheng, *Curr. Org. Chem.* **2007**, *11*, 1491–1524.
- [6] S. P. Nolan, *N-Heterocyclic Carbenes, Effective Tools for Organometallic Synthesis*, Wiley-VCH, Weinheim, **2014**.
- [7] S. Diez-Gonzalez, *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, 2nd Edition, RSC Catalysis Series, RSC, Cambridge, **2017**.
- [8] L. Mercks, M. Albrecht, *Chem. Soc. Rev.* **2010**, *39*, 1903–1912.
- [9] L. Oehninger, R. Rubbiani, I. Ott, *Dalton Trans.* **2013**, *42*, 3269–3284.
- [10] S. A. Patil, A. P. Hoagland, S. A. Patil, A. Bugarin, *Future Med. Chem.* **2020**, *12*, 2239–2275.
- [11] C. A. Smith, M. R. Narouz, P. A. Lummis, I. Singh, A. Nazemi, C.-H. Li, C. M. Crudden, *Chem. Rev.* **2019**, *119*, 4986–5056.
- [12] L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Lapponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705–2733.
- [13] A. Neshat, P. Mastroianni, A. Mousavizadeh Mobarakeh, *Molecules* **2022**, *27*, 95.
- [14] D. Yuan, H. V. Huynh, *Molecules* **2012**, *17*, 2491–2517.
- [15] E. A. Baquero, G. F. Silbestri, P. Gómez-Sal, J. C. Flores, E. de Jesús, *Organometallics* **2013**, *32*, 2814–2826.
- [16] R. Taakilii, Y. Canac, *Molecules* **2020**, *25*, 2231.
- [17] M. E. Garner, W. Niu, X. Chen, I. Ghiviriga, K. A. Abboud, W. Tan, A. S. Veige, *Dalton Trans.* **2014**, *44*, 1914–1923.
- [18] M. Ruamps, N. Lugan, V. César, *Organometallics* **2017**, *36*, 1049–1055.
- [19] R. De Marco, M. Dal Grande, M. Baron, L. Orian, C. Graiff, T. Achard, S. Bellemin-Lapponnaz, A. Pöthig, C. Tubaro, *Eur. J. Inorg. Chem.* **2021**, *2021*, 4196–4206.
- [20] J. Egly, M. Bouché, W. Chen, A. Maise-François, T. Achard, S. Bellemin-Lapponnaz, *Eur. J. Inorg. Chem.* **2018**, *2018*, 159–166.
- [21] L.-A. Schaper, S. J. Hock, W. A. Herrmann, F. E. Kühn, *Angew. Chem. Int. Ed.* **2013**, *52*, 270–289.
- [22] C. Fliedel, G. Schnee, P. Braunstein, *Dalton Trans.* **2009**, 2474–2476.
- [23] C. Fliedel, P. Braunstein, *J. Organomet. Chem.* **2014**, *751*, 286–300.
- [24] S. Hameury, P. de Frémont, P. Braunstein, *Chem. Soc. Rev.* **2017**, *46*, 632–733.
- [25] T. Simler, P. Braunstein, A. A. Danopoulos, *Dalton Trans.* **2016**, *45*, 5122–5139.
- [26] S. Bellemin-Lapponnaz, S. Dagorne, R. Dümpelmann, P. Steffanut, *CHIMIA* **2014**, *68*, 500–500.
- [27] V. César, S. Bellemin-Lapponnaz, L. H. Gade, *Chem. Soc. Rev.* **2004**, *33*, 619–636.
- [28] P. Ai, K. Yu. Monakhov, J. van Leusen, P. Kögerler, C. Gourlaouen, M. Tromp, R. Welter, A. A. Danopoulos, P. Braunstein, *Chem. - Eur. J.* **2018**, *24*, 8787–8796.
- [29] T. Simler, P. Braunstein, A. A. Danopoulos, *Angew. Chem. Int. Ed.* **2015**, *54*, 13691–13695.
- [30] Q. Meng, H. Zhang, H. Chen, Q. Teng, *ChemistrySelect* **2021**, *6*, 5375–5380.
- [31] H. Shen, G. Tian, Z. Xu, L. Wang, Q. Wu, Y. Zhang, B. K. Teo, N. Zheng, *Coord. Chem. Rev.* **2022**, *458*, 214425.
- [32] S. Bellemin-Lapponnaz, *Eur. J. Inorg. Chem.* **2020**, *2020*, 10–20.
- [33] R. Taakilii, C. Barthes, A. Goëffon, C. Lepetit, C. Duhayon, D. A. Valyaev, Y. Canac, *Inorg. Chem.* **2020**, *59*, 7082–7096.
- [34] D. A. Valyaev, Y. Canac, *Dalton Trans.* **2021**, *50*, 16434–16442.
- [35] I. Benaissa, R. Taakilii, N. Lugan, Y. Canac, *Dalton Trans.* **2017**, *46*, 12293–12305.
- [36] I. Abdellah, N. Debono, Y. Canac, C. Duhayon, R. Chauvin, *Dalton Trans.* **2009**, *0*, 7196–7202.
- [37] C. Barthes, C. Bijani, N. Lugan, Y. Canac, *Organometallics* **2018**, *37*, 673–678.
- [38] R. Taakilii, C. Lepetit, C. Duhayon, D. A. Valyaev, N. Lugan, Y. Canac, *Dalton Trans.* **2019**, *48*, 1709–1721.
- [39] M. El Kadiri, A. Chihab, R. Taakilii, C. Duhayon, D. A. Valyaev, Y. Canac, *Organometallics* **2022**, *41*, 456–466.
- [40] R. Taakilii, C. Barthes, C. Lepetit, C. Duhayon, D. A. Valyaev, Y. Canac, *Inorg. Chem.* **2021**, *60*, 12116–12128.
- [41] S. Lapointe, A. Sarbajna, V. H. Gessner, *Acc. Chem. Res.* **2022**, *55*, 770–782.
- [42] A. Sarbajna, V. S. V. S. N. Swamy, V. H. Gessner, *Chem. Sci.* **2021**, *12*, 2016–2024.
- [43] M. Bayat, A. Sedghi, L. Ebrahimkhani, S. J. Sabounchei, *Dalton Trans.* **2016**, *46*, 207–220.
- [44] Y. Canac, *Chem. - Asian J.* **2018**, *13*, 1872–1887.
- [45] J. S. Modica-Napolitano, J. R. Aprile, *Adv. Drug Deliv. Rev.* **2001**, *49*, 63–70.
- [46] J. Zielonka, J. Joseph, A. Sikora, M. Hardy, O. Ouari, J. Vasquez-Vivar, G. Cheng, M. Lopez, B. Kalyanaraman, *Chem. Rev.* **2017**, *117*, 10043–10120.
- [47] A. Collado, A. Gómez-Suárez, A. R. Martin, A. M. Z. Slawin, S. P. Nolan, *Chem. Commun.* **2013**, *49*, 5541.
- [48] A. Nandy, T. Samanta, S. Mallick, P. Mitra, S. K. Seth, K. D. Saha, S. S. Al-Deyab, J. Dinda, *New J. Chem.* **2016**, *40*, 6289–6298.
- [49] J. Dinda, S. D. Adhikary, S. K. Seth, A. Mahapatra, *New J. Chem.* **2013**, *37*, 431–438.
- [50] S. K. Goetzfried, S. M. C. Koenig, C. M. Gallati, R. Gust, *Inorg. Chem.* **2021**, *60*, 8546–8553.
- [51] S. K. Goetzfried, P. Kapitza, C. M. Gallati, A. Nindl, M. Cziferszky, M. Hermann, K. Wurst, B. Kircher, R. Gust, *Dalton Trans.* **2022**, *51*, 1395–1406.
- [52] S. K. Goetzfried, C. M. Gallati, M. Cziferszky, R. A. Talmazan, K. Wurst, K. R. Liedl, M. Podewitz, R. Gust, *Inorg. Chem.* **2020**, *59*, 15312–15323.
- [53] P. de Frémont, R. Singh, E. D. Stevens, J. L. Petersen, S. P. Nolan, *Organometallics* **2007**, *26*, 1376–1385.
- [54] a) C. Tubaro, M. Baron, M. Costante, C. Graiff, G. Accorsi, *Dalton Trans.* **2013**, *42*, 10952–10963. b) T. P. Pell, B. D. Stringer, C. Tubaro, D. J. D. Wilson, P. J. Barnard, *Eur. J. Inorg. Chem.* **2017**, *2017*, 3661–3674. c) A. Biffis, M. Cipani, C. Tubaro, A. Venzo, C. Graiff, *New J. Chem.* **2013**, *37*, 4176–4184.
- [55] A. Johnson, I. Marzo, M. C. Gimeno, *Chem. - Eur. J.* **2018**, *24*, 11693–11702.
- [56] A. Bondi, *J. Phys. Chem.* **1966**, *70*, 3006–3007.
- [57] P. J. Barnard, L. E. Wedlock, M. V. Baker, S. J. Berners-Price, D. A. Joyce, B. W. Skelton, J. H. Steer, *Angew. Chem. Int. Ed.* **2006**, *45*, 5966–5970.
- [58] T. P. Pell, D. J. D. Wilson, B. W. Skelton, J. L. Dutton, P. J. Barnard, *Inorg. Chem.* **2016**, *55*, 6882–6891.
- [59] Y. Chen, G. Cheng, K. Li, D. P. Shelar, W. Lu, C.-M. Che, *Chem. Sci.* **2014**, *5*, 1348–1353.

- [60] R. Visbal, I. Ospino, J. M. López-de-Luzuriaga, A. Laguna, M. C. Gimeno, *J. Am. Chem. Soc.* **2013**, *135*, 4712–4715.
- [61] T. Li, D. G. Shlian, P. I. Djurovich, M. E. Thompson, *Chem. – Eur. J.* **2021**, *27*, 6191–6197.
- [62] M. Monticelli, S. Bellemin-Lapponnaz, C. Tubaro, M. Rancan, *Eur. J. Inorg. Chem.* **2017**, *2017*, 2488–2495.
- [63] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. a. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339–341.
- [64] G. M. Sheldrick, *Acta Crystallogr. Sect. Found. Adv.* **2015**, *71*, 3–8.
- [65] G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8.

