



**Versatile Synthesis of Cationic N-Heterocyclic Carbene-Gold(I) Complexes Containing a Second Ancillary Ligand. Design of Heterobimetallic Ruthenium-Gold Anticancer Agents**

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## Versatile Synthesis of Cationic N-Heterocyclic Carbene-Gold(I) Complexes Containing a Second Ancillary Ligand. Design of Heterobimetallic Ruthenium-Gold Anticancer Agents.

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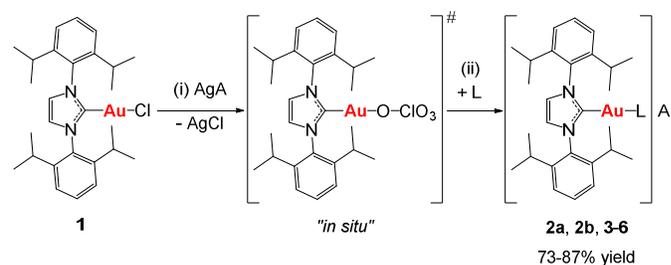
We describe a versatile and quick route to cationic gold(I) complexes containing N-heterocyclic carbenes and a second ancillary ligand (such as phosphanes, phosphites, arsines and amines) of interest for the synthesis of compounds with potential catalytic and medicinal applications. The general synthetic strategy has been applied to the preparation of novel cationic heterobimetallic ruthenium(II)-gold(I) complexes that are highly cytotoxic on renal cancer Caki-1 and colon cancer HCT 116 cell lines while showing a synergistic effect and being more selective than their monometallic counterparts.

The chemistry of gold(I) complexes containing N-heterocyclic carbenes<sup>1</sup> has developed rapidly in the past decade with the findings of their relevant applications as homogeneous catalysts<sup>1-7</sup> and their potential as anticancer and antimicrobial agents<sup>7-14</sup> (including some heterometallic complexes<sup>15,16</sup>). The beneficial effects of a second ligand in processes catalyzed by gold(I)-N-heterocyclic compounds have been described.<sup>17</sup> Cationic gold(I) N-heterocyclic carbene complexes containing phosphanes of the type [(NHC)AuPR<sub>3</sub>]<sup>+</sup> (NHC = 1,3-diethylbenzimidazol-2-ylidene) have been described recently by Ott *et al.* as very efficient enzyme inhibitors with promising potential as anticancer chemotherapeutics.<sup>18,19</sup>

The preparation of these complexes involves the addition of

NaCO<sub>3</sub> to the N-heterocyclic imidazolium iodide at 50 °C followed by addition the corresponding chlorido(phosphane) gold(I) derivatives with reactions times ranging from 8 to 60 hours, and subsequent purification by extraction in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O.<sup>18,19</sup> This method limits the nature of the anion to that present in the imidazolium salt precursor. A second method developed by Nolan *et al.* for the preparation of [(IPr)Au(PR<sub>3</sub>)]<sup>+</sup> compounds involves protonolysis of [(IPr)Au(OH)] derivatives with appropriate PR<sub>3</sub>.HBF<sub>4</sub> salts (RT and reaction times of 14 hours).<sup>20</sup>

We describe here a simple and efficient synthetic method to obtain gold(I)-N-heterocyclic carbenes with a second ancillary ligand by abstraction of the chloride with silver perchlorate in compounds [(NHC)AuCl]<sup>21</sup> and subsequent addition of the ancillary ligand (Scheme 1, total reaction time 30 min). The reaction scheme is quite general and different phosphanes such as PPh<sub>3</sub> and PEt<sub>3</sub> can be used. We also synthesized cationic complexes containing NHC and a phosphite P(OEt)<sub>3</sub>, triphenylarsine AsPh<sub>3</sub> and bipyridine (bipy) as second ligand.



**Scheme 1** Preparation of gold complexes [(IPr)Au(L)]A, L = PPh<sub>3</sub>, A = ClO<sub>4</sub><sup>-</sup> (**2a**), A = CF<sub>3</sub>SO<sub>3</sub><sup>-</sup> (**2b**), A = ClO<sub>4</sub><sup>-</sup>, L = PEt<sub>3</sub> (**3**), L = P(OPh)<sub>3</sub> (**4**), L = AsPh<sub>3</sub> (**5**), L = bipy (**6**). (i) AgClO<sub>4</sub> or AgOSO<sub>2</sub>CF<sub>3</sub> (1 eq.), CH<sub>2</sub>Cl<sub>2</sub>/Diethyl ether 1:1, from 0 °C to RT, 15'. (ii) L (1 eq.), CH<sub>2</sub>Cl<sub>2</sub>/Diethyl ether 2:1, RT, 15 min.

Gold(I) compounds with hydrogen-bond-supported heterocyclic carbene (HBHC) and nitrogen acyclic carbene (NAC) of the type [(carbene)Au(AsPh<sub>3</sub>)] [SbF<sub>6</sub>]<sup>-</sup> have been described by Espinet *et al.* by one pot reaction of gold

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Electronic Supplementary Information (ESI) available: Experimental section (general information, instrumentation and synthetic procedures), NMR, IR, UV-Vis and MS-ESI+HR spectra, crystallographic data, interaction with plasmid pBR322 DNA, cell culture and cell viability assays and inhibition of thioredoxin reductase. See DOI: 10.1039/x0xx00000x

precursors [(carbene)AuCl] and AgSBF<sub>6</sub>/AsPh<sub>3</sub> (2-5 h reactions).<sup>17</sup> Cationic gold(I) compounds of the type [(NHC)Au(α-diimine)]X (X = BF<sub>4</sub><sup>-</sup>, SbF<sub>6</sub><sup>-</sup>) have also been reported by Braunstein *et al.* by one pot reaction of [(NHC)AuCl]/α-diimine and TlPF<sub>6</sub> or AgX (24 h reaction).<sup>21</sup>

For different synthetic/catalytic purposes it may be relevant to separate the AgCl formed in the abstraction reaction before addition of the second ancillary ligand. We have demonstrated that the use of a silver salt containing an anion that can be covalently coordinated to gold, allows for the separation of solutions (after filtration of AgCl) containing *in situ* generated [(NHC)AuOClO<sub>3</sub>] species that are stable for at least 72h at 5 °C, and during 2 hours at RT. The covalent nature of the OClO<sub>3</sub><sup>-</sup> group in the intermediate has been confirmed by IR spectroscopy (spectra and explanations in the ESI). The addition of different ancillary ligands to these solutions leads to immediate formation of stable cationic species (**2-6**) that precipitate in the reaction media in high yields and that can be separated by filtration without further purification (Scheme 1). The reaction can also be performed with silver triflate (AgOSO<sub>2</sub>CF<sub>3</sub>) (**2b**). It should be noted that compound **4** is a stable precursor to the phosphane derivatives by displacement of the more labile AsPh<sub>3</sub>.

We have used this general synthetic method to incorporate a phosphane fragment containing a second metal center and generate new cationic heterobimetallic ruthenium-gold complexes. Our group has been involved in the preparation of heterometallic complexes containing gold(I) phosphane moieties as potential cancer chemotherapeutics.<sup>23-26</sup> The hypothesis is that the incorporation of two active metals in the same molecule may improve their activity as anti-tumor agents due to interaction of the different metals with multiple biological targets (cooperative effect) or by the improved chemophysical properties of the resulting heterometallic compound (synergism). We have prepared a number of titanocene-gold derivatives with high efficacy in ovarian and prostate cancer *in vitro*<sup>23</sup> and in renal cancer both *in vitro*<sup>24</sup> and *in vivo*.<sup>25</sup> We and others have also reported recently on the design of heterometallic ruthenium-gold complexes with relevant *in vitro* properties against HCT 116 colon cancer cell lines (**7** and **8** in Chart 1).<sup>26</sup> We found in most cases a synergistic effect of the heterometallic compound when compared to its monometallic counterparts (either alone or in combination).<sup>23-26</sup>

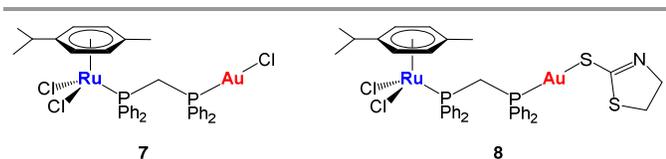
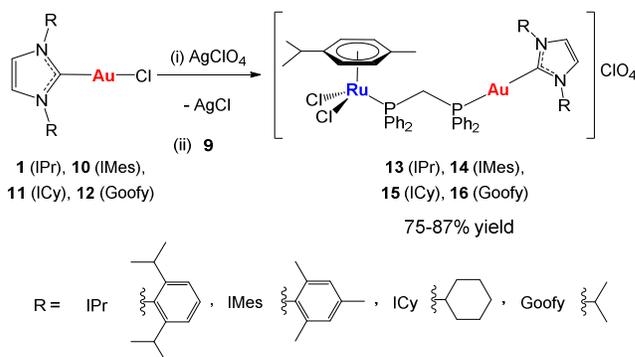


Chart 1 Previous heterometallic Ru-Au complexes synthesized in our group.<sup>26</sup>

We aimed to incorporate gold(I)-N-heterocyclic fragments to [Ru(*p*-cymene)Cl<sub>2</sub>(η<sup>1</sup>-dppm)] **9** species to improve the pharmacological profile of previously reported heterometallic complexes **7** and **8**. Gold NHC complexes display strong

antimitochondrial effects, which can be attributed to both their cationic and lipophilic characters.<sup>27,28</sup> Combining the potential antimetastatic/cytotoxic properties of [Ru(*p*-cymene)Cl<sub>2</sub>(η<sup>1</sup>-dppm)] **9**<sup>29</sup> and the antimitochondrial/TrRx inhibition effects of [(NHC)Au]<sup>+</sup> and [(NHC)Au(PR<sub>3</sub>)]<sup>+</sup> species<sup>10,18,19</sup> may give rise to potent cancer chemotherapeutics.

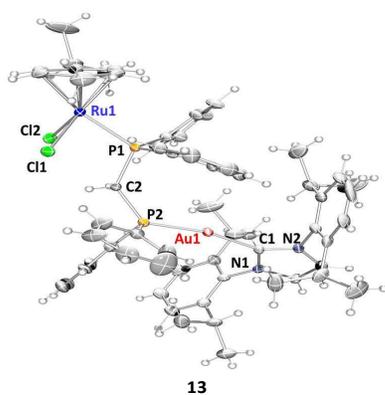


Scheme 2 Preparation of heterometallic ruthenium-gold complexes [Ru(*p*-cymene)Cl<sub>2</sub>(μ-dppm)Au(NHC)]ClO<sub>4</sub>. (i) AgClO<sub>4</sub> (1 eq.), CH<sub>2</sub>Cl<sub>2</sub>/Diethyl ether 1:1, from 0 °C to RT, 15 min. (ii) [Ru(*p*-cymene)Cl<sub>2</sub>(η<sup>1</sup>-dppm)] **9** (1 eq.), CH<sub>2</sub>Cl<sub>2</sub>/Diethyl ether 2:1, RT, 15 min.

Following the general reaction scheme reported here we obtained cationic heterobimetallic Ru-Au complexes (**13-16**) with four different N-heterocyclic carbenes in high yields (Scheme 2). These compounds could not have been prepared following any of the previously reported methods.<sup>17-20,22</sup> The new heterometallic compounds (see ESI for detailed synthetic procedure and characterization) are soluble in DMSO/H<sub>2</sub>O, DMSO/PBS or DMSO/media (1:99) mixtures at micromolar concentrations, which is relevant for subsequent biological testing.

Compounds **13-16** were characterized unambiguously by <sup>31</sup>P{<sup>1</sup>H}, <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR and IR spectroscopy, MS ESI spectrometry and by elemental analysis (see experimental section in ESI). In addition, the ionic nature of the compounds can be ascertained by conductivity measurements that confirm that they are 1:1 electrolytes. The anionic nature of the ClO<sub>4</sub><sup>-</sup> is also confirmed by IR spectroscopy (ESI). The <sup>31</sup>P{<sup>1</sup>H} NMR spectra in CDCl<sub>3</sub> of the heterometallic complexes show two distinct doublets at 26.7/20.0 ppm (**13**), 25.3/21.1 ppm (**14**), 28.7/21.5 (**15**) and 28.1/21.4 ppm (**16**) due to coordination of the dppm ligand to the Au(I) and Ru(II) centers respectively. Moreover, the signals corresponding to the carbons of the imidazolium ring show a doublet in all cases due to the coupling between the carbenic (<sup>2</sup>J<sub>PC</sub> ~ 128Hz) and the ethylenic (<sup>4</sup>J<sub>PC</sub> ~ 3Hz) carbons and the phosphorous of the dppm ligand bound to the gold center.

Single crystals of compounds **13** and **14** were isolated as bright orange needles in mixtures of dichloromethane/Et<sub>2</sub>O. The structure of **13** is depicted below along including selected angles and distances. The structure of **14** is collected in the ESI along with crystallographic data and tables of selected distances and angles for both **13** and **14** (quite similar).



**Figure 1.** ORTEP view of the molecular structures of **13** showing the labelling scheme. Labelling for hydrogen and carbon atoms is omitted for clarity. A drawing of the molecular structure containing relevant carbon atoms labelled is provided in the ESI. Selected distances (Å) and angles ( $^{\circ}$ ): Au(1)-P(2) = 2.228(7), Au(1)-C(1) = 2.052(12), Ru(1)-P(1) = 2.352(3), Ru(1)-Cl(1) = 2.409(3), Ru(1)-Cl(2) = 2.422(3), Ru(1)-Z\* = 1.719; P(2)-Au(1)-C(1) = 165.3(4), Cl(1)-Ru(1)-Cl(2) = 87.65(11), Cl(1)-Ru(1)-P(1) = 85.39(10), Cl(2)-Ru(1)-P(1) = 86.80(10), Ru(1)-P(1)-Z\* = 132.32. Z\* = centroid of *p*-cymene ring.

Coordination bond lengths and angles of the two metal ions in **13** and **14** (ESI) are in agreement with those found for similar complexes retrieved in a search in the CSD (v. 1.16)<sup>26,30</sup> and in the structure of previously described [Ru(*p*-cymene)Cl<sub>2</sub>( $\mu$ -dppm)AuCl] (**7**).<sup>26</sup> The bond lengths Au(1)-P(2) and Au(1)-C(1) are respectively 2.228(7) and 2.052(12) Å while the angle P(2)-Au(1)-C(1) is 165.3(4) $^{\circ}$  showing a stronger deviation of the linearity preferred by gold(I) and being considerably smaller than the angle of 177.88(9) $^{\circ}$  found for heterobimetallic **7**.<sup>26</sup> The ruthenium(II) ion exhibits the expected pseudo octahedral three legged piano-stool arrangement common for half-sandwich Ru(II) phosphine complexes and as found in **7**.

The stability of the new heterometallic compounds **13-16** was evaluated by <sup>31</sup>P{<sup>1</sup>H} and <sup>1</sup>H NMR spectroscopy in DMSO-*d*<sub>6</sub>, and by UV-vis spectroscopy in DMSO/PBS solution. NMR experiments were performed in neat DMSO-*d*<sub>6</sub> due to the low solubility of the compounds in mixtures of DMSO-*d*<sub>6</sub>/D<sub>2</sub>O in concentrations larger than 100 micromolar. The compounds are stable in DMSO-*d*<sub>6</sub> with half-life times ranging from 2 to 15 days. The UV-vis spectra of selected compound **15** (micromolar concentration) in 1:99 DMSO/PBS solution did not change in 24 h, with a half-life >72 h (see ESI) indicating the stability of these complexes in physiological media.

The cytotoxicity of the heterometallic complexes [Ru(*p*-cymene)Cl<sub>2</sub>( $\mu$ -dppm)Au(NHC)]ClO<sub>4</sub> (**13-16**) and monometallic gold(I) complexes [(NHC)AuCl] (**1, 10-12** in Scheme 2) was assayed by monitoring their ability to inhibit cell growth using the BluePresto<sup>TM</sup> assay (see details in the ESI). In this assay, human renal Caki-1 and human colon HCT 116 and DLD1 cancer cell lines and non-tumorigenic human embryonic kidney cell lines HEK-293T were incubated with the indicated compound for 72 hours and compared for sensitivity to cisplatin, and [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta^1$ -dppm)] **9**. The results are summarized in Table 1 (a complete Table including data on the DLD1 cell line and the combination of monometallic **9** and

**1,10-12** can be found in the ESI). The heterometallic compounds are more toxic to the renal cancer cell line (Caki-1 cells) and colon HCT 116 than cisplatin, and monometallic [(NHC)AuCl] (**1, 10-12**) and [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta^1$ -dppm)] **9**.<sup>29</sup> Importantly, all heterometallic RuAu complexes are considerably less toxic to the non-tumorigenic human embryonic kidney cell line (HEK-293T) than cisplatin and [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta^1$ -dppm)] **9**. Monometallic [(NHC)AuCl] have also IC<sub>50</sub> values above 100 micromolar for the HEK cell line but are less toxic to the renal cancer cell line Caki-1. We studied the effect of the combination of monometallic gold **1, 10-12** and ruthenium **9** compounds (1:1 equivalents) in Caki-1 cell lines at 72 h which in all cases gave IC<sub>50</sub> values larger than those of the bimetallic compounds (ESI). This fact supports the idea that there is indeed a synergistic effect for the heterometallic complexes in their *in vitro* activity on the renal cancer cell line.

**Table 2** IC<sub>50</sub> values ( $\mu$ M) in human cell lines were determined with monometallic [(NHC)AuCl] **1, 10-12** monometallic [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta^1$ -dppm)] **9**, and new heterometallic Ru-Au compounds (**13-16**).<sup>a</sup>

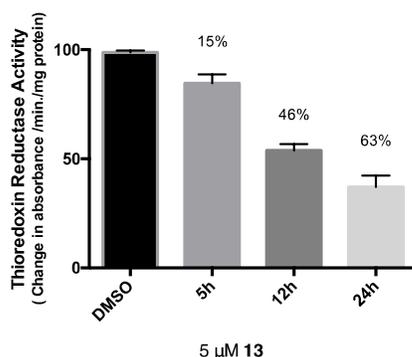
	Caki-1	HEK-293T	HCT 116
[(NHC)AuCl]			
<b>1</b>	27.1 $\pm$ 2.0	61.5 $\pm$ 5.1	39.7 $\pm$ 4.9
<b>10</b>	21.2 $\pm$ 1.6	>100	31.2 $\pm$ 3.2
<b>11</b>	58.8 $\pm$ 3.9	>100	59.1 $\pm$ 5.8
<b>12</b>	17.5 $\pm$ 2.2	>100	27.7 $\pm$ 4.9
[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ( $\eta^1$ -dppm)] <b>9</b>	35.6 $\pm$ 3.7	81.6 $\pm$ 3.0	18.2 $\pm$ 2.2
New cationic Ru-Au			
<b>13</b>	5.2 $\pm$ 0.9	73.2 $\pm$ 2.5	8.1 $\pm$ 1.8
<b>14</b>	14.1 $\pm$ 1.9	>100	5.22 $\pm$ 0.7
<b>15</b>	3.8 $\pm$ 0.6	>100	6.4 $\pm$ 1.0
<b>16</b>	12.7 $\pm$ 2.7	>100	9.6 $\pm$ 3.1
cisplatin	29 $\pm$ 4.11 <sup>b</sup>	3.27 $\pm$ 0.13 <sup>b</sup>	---

<sup>a</sup>All compounds were dissolved in 1% of DMSO and diluted with water before addition to cell culture medium for a 72 h incubation period. Cisplatin was dissolved in H<sub>2</sub>O. <sup>b</sup>Values from reference 24.

We analyzed the interactions of **13-16** with representative DNA molecules. Specifically, we carried out gel electrophoresis studies to disclose the effects of the new heterobimetallic compounds on plasmid (pBR322) DNA (ESI). Compound [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta^1$ -dppm)] **9** weakly reduced supercoiling in plasmid DNA although it was able to bind DNA in a non-intercalative fashion.<sup>31</sup> Most Gold(I)-N-heterocyclic carbene complexes (unless designed to target DNA quadruplexes) are known to not interact or interact only weakly with DNA.<sup>10</sup> Treatment with increasing amounts of heterometallic RuAu derivatives **13-16** did not affect the mobility of the faster-running supercoiled form (Form I) even at the highest molar ratios (ESI). The lack of interaction between the heterobimetallic compounds and plasmid (pBR322) DNA (already observed for previously described [Ru(*p*-cymene)Cl<sub>2</sub>( $\mu$ -dppm)AuX] compounds, X = Cl **7**, thiazoline **8**) points out that other biomolecular targets are probably implicated in the cell death pathway.

Changes in cell anti-oxidant capacity are a characteristic of many chemo-resistant cancers, and overexpression of

thioredoxin reductase (TrRx) is among the key defense and survival mechanisms of cisplatin-resistant cells. We have reported on the inhibition of TrRx in Caki-1 cells by Auranofin and heterometallic titanocene-gold complexes.<sup>25</sup> Since Au-NHC compounds are known to inhibit TrRx, we measured the activity of thioredoxin reductase in Caki-1 cells, following incubation with compounds **13**, **1** and **9**. We found thioredoxin reductase activity to be lower in cells treated with 5  $\mu$ M of **1**, **9**, **13**, with an observed inhibition of 17%, 44% and 63% respectively after a 24 hour incubation (Figure 2 and see figures for all compounds in the ESI). This experiment clearly showed that the inhibition of TrRx is more efficient for the heterometallic complex **13** [Ru(*p*-cymene)Cl<sub>2</sub>( $\mu$ -dppm)Au(IPr)]ClO<sub>4</sub> when compared to monometallic [(IPr)AuCl] derivative **1** and [Ru(*p*-cymene)Cl<sub>2</sub>( $\eta$ <sup>1</sup>-dppm)] **9**.



**Figure 2.** Thioredoxin reductase activity in **13** treated Caki-1 cells. Activity of endogenous Caki-1 thioredoxin reductase from soluble whole cell lysates following incubation with 5  $\mu$ M of compound **13** or 0.1% DMSO for 5, 12 and 24 hours.

In conclusion, the general synthetic strategy described here may be used for the preparation of cationic gold(I)-N-heterocyclic carbene complexes containing a second neutral ligand. The mild reaction conditions and the complete separation of silver salts before the addition of the second ligand, has allowed for the preparation of novel heterometallic RuAu complexes that have resulted highly active *in vitro* against renal and colon cancer cell lines while being more selective and active than the monometallic counterparts (either alone or in combination). The biological activity of these new derivatives is currently being further explored.

We envision that the versatility of this method will enable the synthesis of a broad range of compounds (e.g. multimetallic systems, polymers, nanocarriers) for which the incorporation of [Au(NHC)] species may improve their biological or catalytic applications.

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