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# Access to the Parent Tetrakis(pyridine)gold(III) Trication, Facile Formation of Rare Au(III) Terminal Hydroxides, and Preliminary Studies of Biological Properties

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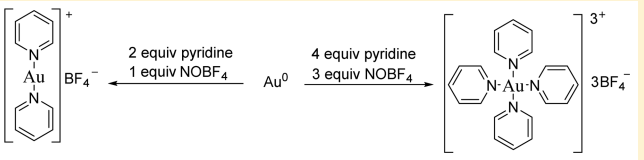
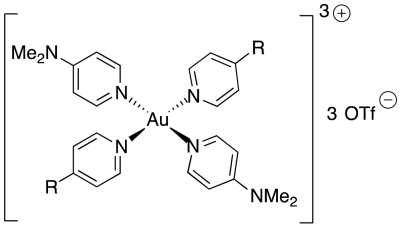
Supporting Information

**ABSTRACT:** In this paper we report on the use of $[NO][BF_4]$ to access tricationic tetrakis(pyridine)gold(III) from Au powder, a species inaccessible using the more traditional (tetrahydrothiophene)AuCl route. It is then demonstrated that this family of compounds can be used to access new terminal Au(III) hydroxides, a challenging class of compounds, and the first crystallographically characterized examples employing bidentate ligands. Finally, preliminary biological studies indicate good activity for derivatives featuring polydentate ligands against the HeLa and PC3 cell lines but also strong inhibition of primary HUVEC cells.




## INTRODUCTION

The renaissance of organometallic gold chemistry, driven by the 1998 publication of Teles and co-workers, was initially associated with catalysis using the Au(0)/Au(I) redox couple.[1] In more recent times, the Au(I)/Au(III) couple has seen increasing use in catalysis,[2] with particular effectiveness in oxidative coupling of nonactivated arenes.[3−7] Au(III) compounds also often have desirable emissive properties.[8−10] Two very recent reviews by the groups of Bochmann[11] and Bourissou[12] highlight the most recent important advances in catalytic and stoichiometric applications of Au(III). We recently reported a new class of Au(III) compounds, namely, salts of Au(III) trications bound only by monodentate pyridine-type ligands (**1R**).[13] Initial studies demonstrated that these complexes provide ready access to the challenging terminal Au(III)−OH functional group using only water as a reagent.




1R; R = -$NMe_2$, -CN, -H

Here we present a substantially improved synthesis of the **1R** class of molecules, which most importantly provides access to the parent $[Au(pyridine)_4]^{3+}$ trication, which cannot be synthesized via the original method. Additionally, we demonstrate the formation of novel Au(III) terminal hydroxides and report preliminary studies of the cytotoxic properties of these molecules against representative cancer cell lines.

## RESULTS AND DISCUSSION

Our previously reported synthesis (Scheme 1) involved two separate manifolds based on the synthesis of Au(I) and I(III) precursors.[13] The Au(I) half required the preparation of the salt $[Au(4\text{-DMAP})_2][OTf]$ (4-DMAP = 4-(dimethylamino)-pyridine). Au powder was converted to $HAuCl_4$ using aqua regia and then to (tht)AuCl (tht = tetrahydrothiophene) using standard methods. A modified procedure from Lin and co-workers was then used, reacting (tht)AuCl with 2 equiv of 4-DMAP and excess KOTf to give **2NMe$_2$**.[14] The I(III) half involved the reaction of commercially available $PhI(OAc)_2$ with 2 equiv of trimethylsilyl triflate (TMSOTf), generating highly reactive PhI(OAc)(OTf) in situ,[15,16] to which 2 equiv of the pyridine-based ligand was added. This gave isolatable but highly moisture-sensitive dications **3R**.[17−20] Finally, the reaction of **2NMe$_2$** with **3R** gave the homoleptic or pseudohomoleptic Au(III) trication. Wasted species in the synthesis (not including solvent) include aqua regia (which must be removed via a tedious distillation), 3 equiv of tht, KCl, 2 equiv of TMSOAc, and PhI. Significantly, the literature report on the cationic bis(4-DMAP)gold(I) starting material **2NMe$_2$** does not mention the parent pyridine species,[14] and in our hands we

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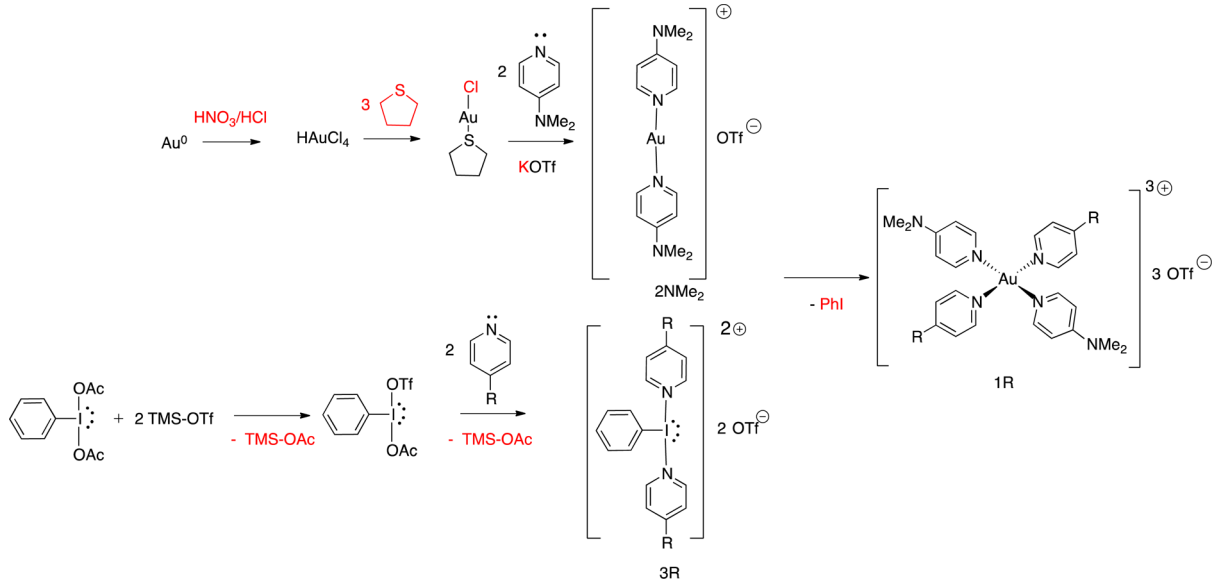
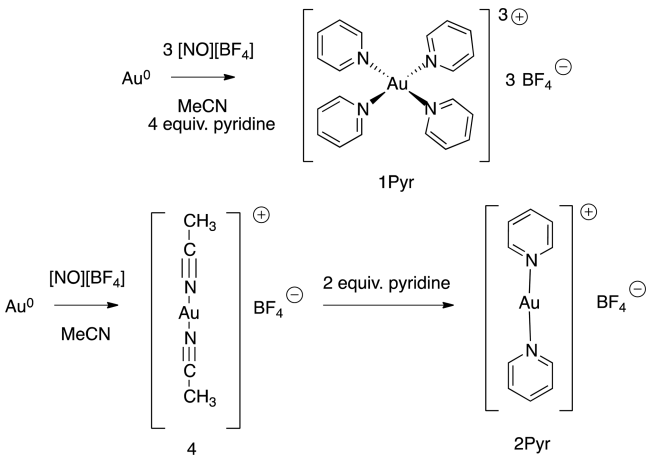
**Scheme 1. Original Synthesis of 1R Shown from the Commercially Available Starting Compounds Used (Species Shown in Red Are Waste)**




were unable to synthesize the pyridine analogue using the methods outlined. Since pyridine is unable to displace 4-DMAP in ligand exchange reactions, this left the parent compound inaccessible.

The reaction of $[NO][BF_4]$/acetonitrile with elemental transition metals is a popular method of forming highly reactive acetonitrile complexes of metal cations, which then offer access to a wide variety of complexes via displacement of MeCN.[21] The bis(acetonitrile)gold(I) cation has been synthesized via this method, although there are only a handful of reports of its use.[22−31] Wildgoose and co-workers recently described the generation of the radical cation $[N(4\text{-}BrC_6H_4)_3]^+$ from $[NO][PF_6]$ and $N(4\text{-}BrC_6H_4)_3$ and showed that it is also effective for accessing Au(III) trications, with cleaner results than using $[NO]^+$ itself.[31] We viewed this apparently underutilized Au(I) starting material as a potential pathway to access the parent tetrakis(pyridine)gold(III) trication (**1Pyr**) (Scheme 2).

**Scheme 2. Synthesis of the Complexes Tetrakis(pyridine)gold(III) (1Pyr) and Bis(pyridine)gold(I) (2Pyr)**




The reaction of 3 equiv of $[NO][BF_4]$ with Au powder in acetonitrile resulted in a colorless solution. After 12 h of stirring, an excess of pyridine was added, and a short workup gave a colorless powder. A sample redissolved in $CD_3CN$ for $^1H$ NMR studies revealed the presence of one pyridine-containing compound. The colorless nature of the material suggested the likelihood that it was an Au(I) species. However, X-ray structural studies on colorless crystals obtained from a concentrated solution demonstrated that the material was the target homoleptic Au(III) trication **1Pyr**. The reaction conditions suggested the possibility that we had generated the unknown tetrakis(acetonitrile)gold(III) complex, which then reacted with the added pyridine. To probe this, we added 1 and 3 equiv of $[NO][BF_4]$ to Au powder in $CH_3CN$, allowed the solutions to stir for 12 h, and obtained their $^1H$ NMR spectra. In both cases the signal arising from "bound" $CH_3CN$ was found at the same chemical shift. This indicates that **1Pyr** likely arises from pyridine displacement of acetonitrile from Au(I) in bis(acetonitrile)gold(I) cation (**4**). The bis(pyridine) complex is then susceptible to further oxidation and ligation of the final two pyridine ligands.

Addition of pyridine to a reaction mixture containing 1 stoichiometric equivalent of $[NO][BF_4]$ and gold power allowed the isolation and crystallographic characterization of the previously inaccessible bis(pyridine)gold(I) cation (**2Pyr**) (Figure 1). The ease with which these two reactions were carried out indicates that the use of complex **4** generated in situ from Au powder and $[NO][BF_4]$ is an underutilized technique in gold chemistry. The Au−N bond lengths in **1Pyr** (Figure 1) range from 2.015 to 2.030 Å, essentially the same as in the other compounds in the **1R** family. The closest secondary interaction with the Au center is a contact of 2.942 Å with the F of a $[BF_4]^-$ counterion, directly in the axial direction of the complex (N−Au−F = 88°). The Au−N bond lengths in **2Pyr** are similar at 2.022 and 2.019 Å (cf. 2.008(3) and 2.016(3) Å in **2NMe$_2$**). There is a Au···Au aurophilic interaction of 3.0535(7) Å, as would be expected for a sterically uncongested Au(I) cation.



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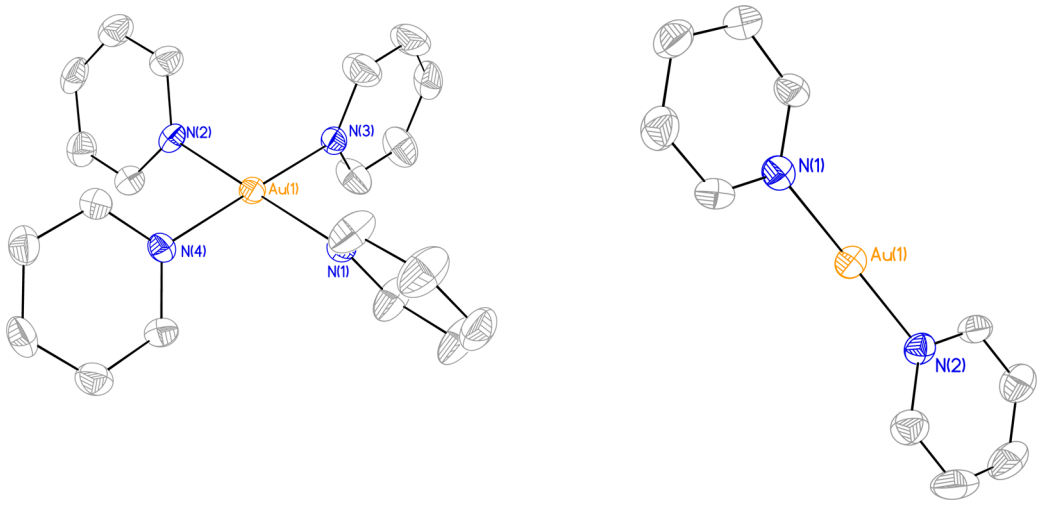


**Figure 1.** Solid-state structures of the trication **1Pyr** and the cation **2Pyr**. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å) in **1Pyr**: Au(1)−N(1) 2.030(4), Au(1)−N(2) 2.015(4). In **2Pyr**: Au(1)−N(1) 2.022(6), Au(1)−N(2) 2.019(6).

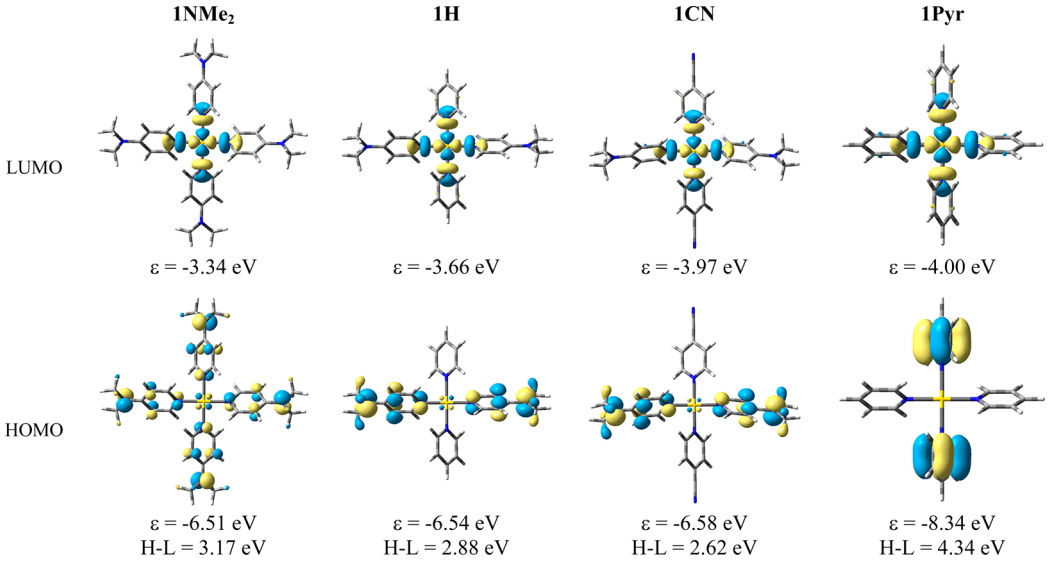


**Figure 2.** Plots and energies of B3LYP/def2-TZVP (SMD acetonitrile solvent)-calculated HOMOs and LUMOs of complexes **1NMe$_2$**, **1H**, **1CN**, and **1Pyr**.

We did find, however, that the success of this route is dependent on the pyridine ligand. Attempts to directly synthesize **1NMe$_2$** using Au powder and 3 equiv of $[NO][BF_4]$ met with failure, as did attempts to generate **1CN** from **2NMe$_2$**, 2 equiv of $[NO][BF_4]$, and 2 equiv of 4-cyanopyridine. Wildgoose and co-workers noted that formation of nitrosylated terpyridines interfered with their chemistry,[31] which is also possible in our case. We also found that attempted oxidations of **2NMe$_2$** using the radical cation $[N(4\text{-}BrC_6H_4)_3]^+$ (as the commercially available $[SbCl_6]^-$ salt) in the presence of 4-DMAP or 4-cyanopyridine resulted in no reaction. However, the generation of **2NMe$_2$** from Au powder, 1 equiv of $[NO][BF_4]$, and 2 equiv of 4-DMAP does proceed cleanly using the same procedure as was employed for **2Pyr**. This means that the tedious generation of (tht)AuCl may be avoided in accessing all of the Au compounds we describe. In the Au(III) chemistry using **2NMe$_2$** as the Au(I) starting material described below, the I(III) manifold is still required, but this chemistry may be carried out from start to finish in one pot within minutes.

To explain the unexpectedly colorless nature of the tetrakis(pyridine) complex **1Pyr**, we conducted a combination of theoretical calculations and UV/vis spectroscopic studies. The electronic transition responsible for the color is a weak $\pi-\sigma^*$ transition centered at 392 nm for **1NMe$_2$**. For the previously reported pseudohomoleptic compounds containing two 4-DMAP ligands and either two 4-DMAP, two pyridine (**1H**), or two 4-cyanopyridine (**1CN**) ligands, the trend was for the HOMO−LUMO gap to narrow as less basic pyridine ligands were introduced. There was a corresponding red shift in the $\pi-\sigma^*$ transition, which reached a maximum of 461 nm for **1CN**, with **1H** having an intermediate absorption at 427 nm. Following this trend, we expected the calculated HOMO−LUMO gap for **1Pyr**, having four pyridine ligands, to be decreased relative to that of **1H** (2.88 eV, cf. **1NMe$_2$** 3.17 eV, **1CN** 2.62 eV). On the basis of the calculated HOMO−LUMO gaps, $\lambda_{max}$ for the absorption can be computed as 474 nm for **1CN** and 431 nm for **1H**, in reasonable agreement with experiment. Similarly, the HOMO−LUMO gap corresponds to a $\lambda_{max}$ of 391 nm for **1NMe$_2$**. The calculated HOMO−LUMO


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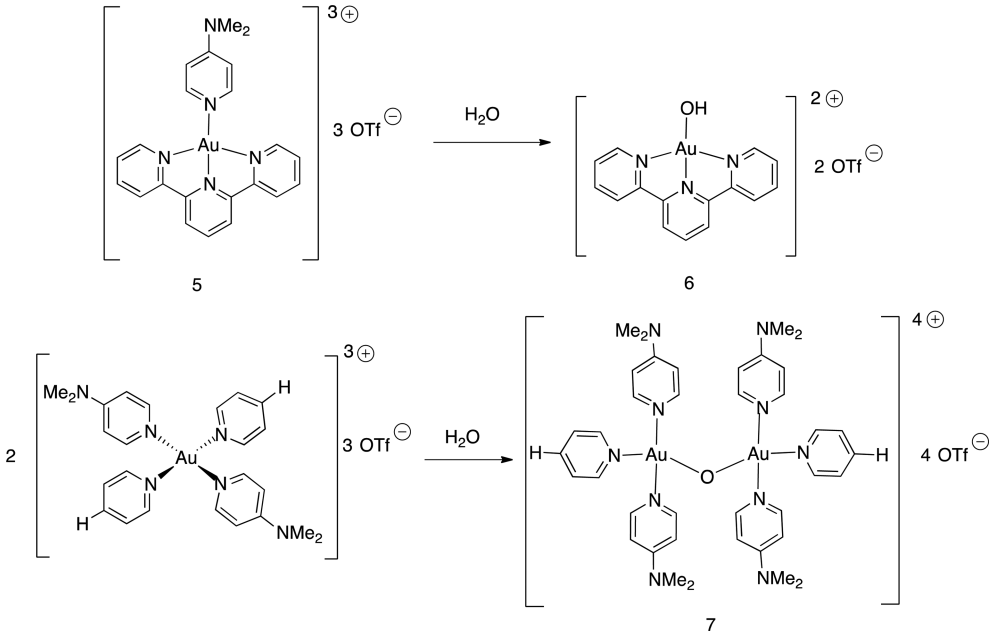
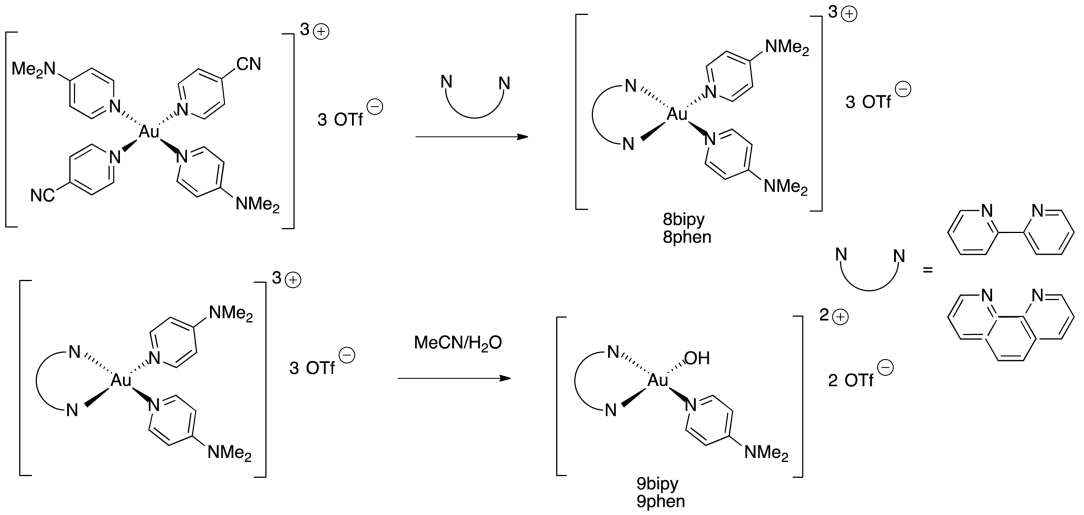
**Scheme 3. Reactions of Au(III) Reagents with Water To Form 6 and 7**




**Scheme 4. Synthesis of Au(III) Terminal Hydroxides 9bipy and 9phen via 8bipy and 8phen**




gap for **1Pyr** is 4.34 eV, which corresponds to a $\lambda_{max}$ of 286 nm in the UV region of the spectrum, consistent with the colorless nature of the compound. Experimentally, the wavelength for the $\pi-\sigma^*$ transition in **1Pyr** could not be determined because of an absorbance overlap with the strong $\pi-\pi^*$ transition, the tail of which extends to 300 nm. An examination of the frontier molecular orbitals for the different compounds may be used to explain this apparent discrepancy in the trend (Figure 2). For the trication bearing four 4-DMAP ligands (**1NMe$_2$**), the HOMO is based primarily on the $\pi$ system of the 4-DMAP ligands. The contribution from the amine is antibonding with respect to the pyridine ring, destabilizing the orbital. The HOMOs for **1H** and **1CN** are similar in that they are primarily based on the 4-DMAP ligands containing the amine antibonding interaction rather than on the pyridines. The HOMO for **1Pyr** is primarily based on pyridine (in this case localized) as a result of the absence of any 4-DMAP ligands, and the lack of the antibonding interaction arising from the amino group additionally results in a more stabilized (lower-energy) HOMO. The LUMOs for all four complexes (including **1Pyr**) are similar, being largely $\sigma$-antibonding with respect to the Au−pyridine bonds. That is, differences in the characteristics of the HOMOs are predominantly responsible for the difference in the HOMO−LUMO gaps of the complexes.

**New Au(III) Hydroxides from Bidentate Analogues.** One of the advances in our original report was the facile synthesis and isolation of a terminal Au(III)−OH, of which there were previously only two crystallographically characterized examples, with Bochmann having shown the Au(III)−OH functionality is a versatile synthon in Au(III) chemistry.[32−34] There were also two further examples that were not crystallographically characterized, including one supported by the bipyridine ligand.[35,36] Our synthesis (Scheme 3) was accomplished by adding a drop of water to a solution of **5**. A 4-DMAP ligand is displaced by water and in turn deprotonates the bound water, giving the terminal hydroxide **6**. This specific cation in **6** was one of the previously known examples of a



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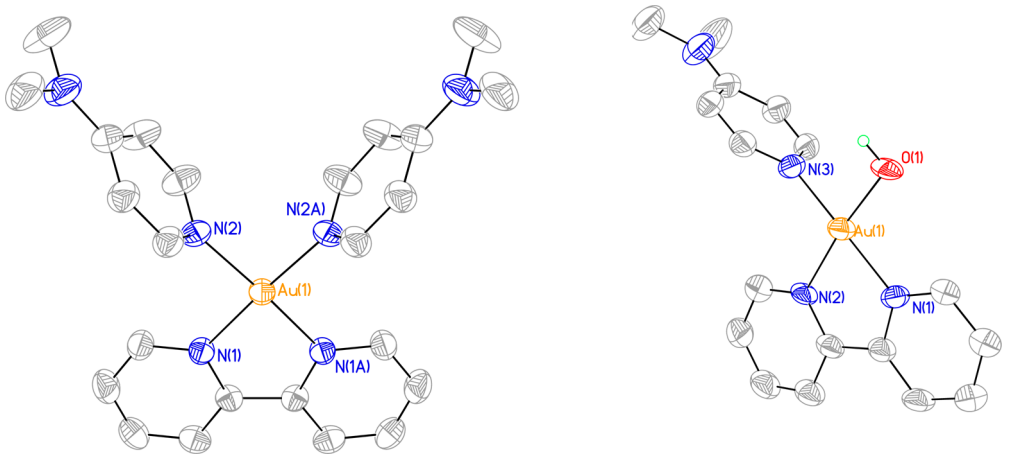


**Figure 3.** Solid-state structures of the trication **8bipy** and dication **9bipy**. Thermal ellipsoids are drawn to 50% probability. The solid-state structures of **8phen** and **9phen** are shown in the Supporting Information. Selected bond lengths (Å) in **8bipy**: Au(1)−N(1) 2.019(4), Au(1)−N(2) 1.994(4). In **9bipy**: Au(1)−O(1) 1.968(5), Au(1)−N(1) 2.011(6), Au(1)−N(2) 2.018(6), Au(1)−N(3) 1.991(6).

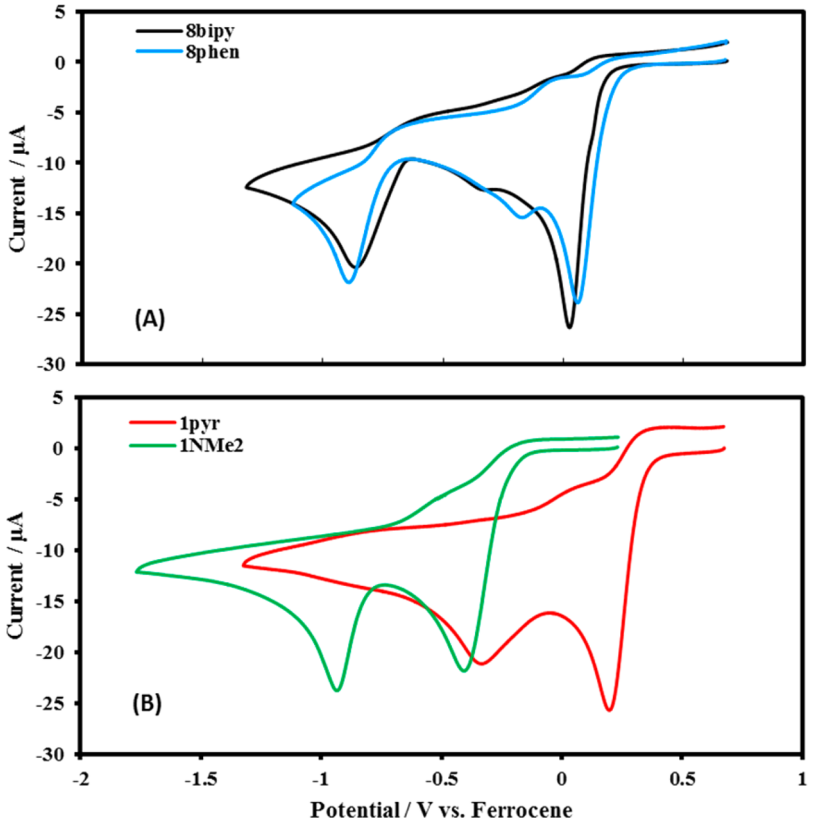


**Figure 4.** Cyclic voltammetric responses at 0.1 V $s^{-1}$ for (A) **8bipy** and **8phen** and (B) **1Pyr** and **1NMe$_2$** using a a glassy carbon disk working electrode (Ø = 3 mm). The concentration of each compound was 1 mM, dissolved in acetonitrile containing 0.1 M $[Bu_4N][PF_6]$ as the supporting electrolyte.

terminal Au(III)−OH moiety (paired with $[ClO_4]^-$ in that instance),[32] which might indicate that the terpyridine (terpy) framework is specifically amenable to the Au(III)−OH functionality (in the original synthesis, activation of (terpy)-AuCl using $AgClO_4$ followed by addition of KOH was used). For example, the same reaction of water with **1H** gave the bridged bis(Au(III))($\mu$-oxo) complex **7**, a well-established class of molecule,[37−39] while **1NMe$_2$** did not react with water at all.

To investigate whether novel Au(III)−OH complexes could be formed using our system, we aimed to synthesize derivatives based on bidentate anchors (Scheme 4). To this end, 1 equiv of 4,4′-bipyridine (bipy) was added to **1CN** in MeCN, and the solution was stirred for 12 h. After a short workup, a red solid was obtained. The $^1$H NMR spectrum of the worked-up material showed a set of signals consistent with the presence of 1 equiv of bipy and 2 equiv of 4-DMAP. Single crystals suitable for X-ray diffraction studies were grown via vapor diffusion of $Et_2O$ into an MeCN solution, and the solid-state structure was indeed the target trication **8bipy** (Figure 3). Using 1,10-phenathroline rather than bipy gave essentially identical results for the ligand exchange reaction, yielding **8phen**. The crystal structures of both trications are as expected, with Au−N bond


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Inorg. Chem. XXXX, XXX, XXX−XXX

lengths of 1.992(5) Å (Au−$N_{DMAP}$) and 2.019(5) Å (Au−$N_{bipy}$) for **8bipy**. The Au−N bond lengths in **8phen** are nearly identical. In **8bipy** there are no interactions with the Au center within van der Waals distances, but for **8phen** there are contacts with OTf counterions at the axial positions with Au−O distances of 2.79 and 2.82 Å.

Water (10 μL, 3 stoichiometric equivalents) was added to a 5 mL solution of **8bipy** in MeCN, and the resulting mixture was stirred for 12 h. After a short workup, a yellow crystalline material was obtained. The $^1$H NMR spectrum of the isolated solid now indicated that the complex contained bipy and 4-DMAP in a 1:1 ratio, and a signal at 5.19 ppm integrating to 1H was also evident. Crystals suitable for X-ray analysis were grown via vapor diffusion of $Et_2O$ into an MeCN solution, and structural studies indicated that the isolated compound contained the targeted novel Au(III)−OH complex **9bipy** (Figure 3). An identical strategy was employed for **8phen** to obtain the Au(III)−OH complex **9phen**.

An examination of the local solid-state environment about the Au−hydroxide in **9bipy** indicated a 2.09 Å hydrogen bond with a triflate counterion as the most important secondary bonding interaction, and no evidence of any bridging interaction with an adjacent Au center was found. The H atom could be located and refined for **9bipy**; this was not the case for **9phen**, where no electron density was apparent, but the Au−O···O−$SO_2$−$CF_3$ separation and vector were identical to those in **9bipy**, therefore making it likely that the Au−OH environment is the same in this derivative. The Au−O bond lengths in the two complexes are 1.968(5) and 1.953(3) Å for **9bipy** and **9phen**, respectively. The anionic OH ligand appears to have a virtually identical trans influence as neutral 4-DMAP, since the opposite Au−N bonds have nearly identical distances in both complexes.

A semiquantitative study of the effect of the water concentration on the rate of conversion to the hydroxide was carried out on **8phen** via $^1$H NMR studies in $CD_3CN$, and the results indicated that an associative mechanism is most likely, as expected for a square-planar 16-electron metal center, with a clear dependence of the rate on the concentration of water. At $t$ = 75 min, the conversions from **8phen** to **9phen** were 56%, 79%, and 100% for the additions of 25, 50, and 100 μL of $H_2O$, respectively, to 40 mg of **8phen** in 2 mL of $CD_3CN$. Even with the large excess of water, monitoring of the reactions over a period of days did not indicate any further reaction that might lead to, for example, bis(hydroxo) compounds.

Figure 4 and Table 1 show the results of a cyclic voltammetry investigation of **1R**, **8bipy**, and **8phen**. The electrochemical properties of **1NMe$_2$**, **1H**, and **1CN** were disclosed in our initial report[13] but are included here for purposes of comparison with those of **1Pyr**. For each complex there are two main reduction processes, which are chemically irreversible over a wide range of scan rates. The first redox process in each case is attributable to the two-electron reduction of the trication, and the second peak is due to the further reduction to the Au(0) species. As shown by the data in Table 1, the trications **1R** are moderately oxidizing, with potentials for the Au(III)/Au(I) process ranging from −0.41 to +0.20 V vs Fc/Fc$^+$. The potentials for the reduction of the Au(III) species increase in the order **1NMe$_2$** < **1H** < **1CN** < **1Pyr**. The electrochemical potentials for the reduction of the pseudohomoleptic 4-DMAP-containing complexes follow the same trend as the calculated LUMO energies, with **1CN** easiest to reduce with a measured Au(III)/Au(I) reduction potential of −0.04 V vs Fc/Fc$^+$, **1H** next easiest at −0.22 V vs Fc/Fc$^+$, and **1NMe$_2$** the least oxidizing at −0.41 V vs Fc/Fc$^+$. The Au(III)/Au(I) reduction potential for **1Pyr** is +0.20 V vs Fc/Fc$^+$, indicating that this derivative is more oxidizing than any of the **1NMe$_2$**-bearing species, more in line with the trend that might be expected from the UV/vis absorptions. The electrochemical reduction product of the pseudohomoleptic nonchelate Au(III) species is taken to be the Au(I) precursor **2NMe$_2$**. This is supported by the quantitative isolation of **2NMe$_2$** via chemical reduction of **1NMe$_2$** in the presence of reduced glutathione. The Au(III)/Au(I) reduction of **1Pyr** is then expected to generate **2Pyr**. This is supported by the observation that the Au(I)/Au(0) reduction potential of **2Pyr** is within 0.1 mV of the Au(I)/Au(0) reduction potential for **1Pyr**. This indicates that the bis(pyridine)gold(I) cation **2Pyr** is slightly more oxidizing than the Au(III) trication **1NMe$_2$**. **8bipy** and **8phen** are relatively easy to reduce, with Au(III)/Au(I) reduction potentials of about 0 V vs Fc/Fc$^+$, indicating that the chelating nature of these ligands about Au(III) does not provide substantial protection from reduction.

**Table 1. Reduction Potentials (vs Fc/Fc$^+$) for the Newly Reported Au(III) Trications and Selected Examples from the Previous Report**

| | $E_{p,red}$ (V vs Fc/Fc$^+$) | |
|---|---|---|
| complex | Au(I)/Au(0) | Au(III)/Au(I) |
| **1NMe$_2$** | −0.93 | −0.41 |
| **1H** | −0.87 | −0.22 |
| **1CN** | −0.87 | −0.04 |
| **1Pyr** | −0.34 | 0.20 |
| **2Pyr** | −0.44 | – |
| **8bipy** | −0.86 | 0.03 |
| **8phen** | −0.89 | 0.06 |

**Biological Studies.** The past decade has seen a surge of interest in the anticancer properties of Au(III) complexes, due in part to their similarities (isoelectronic and isostructural) to well-known Pt(II) drugs such as cisplatin and oxaliplatin.[40,41] Most Au(III) compounds are reductively unstable under biological conditions and are easily reduced to their Au(I) counterparts, and a large number of Au(I) complexes are also known to possess anticancer properties.[40] Good biological activity against a variety of cancer cell lines as been previously reported for (pyridine)(oxo/hydroxo)gold(III) complexes related to those investigated here.[41−48] It is important to note that the success rate for the translation of metal complexes that show promising anticancer properties in vitro to the clinic has been extraordinarily low, but in view of the often serendipitous nature of medicinal chemistry, it is nevertheless a worthwhile endeavor to evaluate novel compounds.

Preliminary studies were undertaken to investigate the anticancer activities of **1NMe$_2$**, **8phen**, and **5** (representing derivatives with monodentate, bidentate, and tridentate motifs, respectively) against three human cancer cell lines and two primary human cell lines, namely, cervical cancer (HeLa), melanoma (MM170), prostate cancer (PC3), human dermal fibroblast (AHDF), and human umbilical vein endothelial (HUVEC) cells, respectively (Table 2). All of the compounds tested were water-soluble, and the solutions were prepared in deionized water and left to stand overnight. On the basis of our findings on the behavior of these complexes with water, both previously reported[13] and described above, **8phen** and **5** are converted to the respective hydroxyl species **9phen** and **6** while


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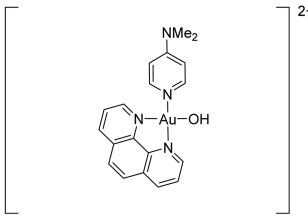
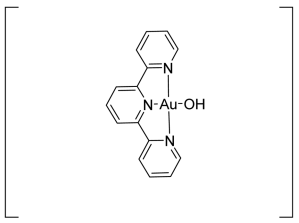
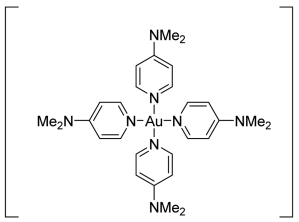
Table 2. MTT Assay Results for Au(III) Trications

| Test Compound | Structure | $IC_{50}$ value (μM)[a] | | | | |
|---|---|---|---|---|---|---|
| | | HeLa | MM170 | PC3 | AHDF | HUVEC |
| **9phen** |  | 19.15 ±2.38 | 47.44 ±2.77 | 4.31 ±0.60 | 82.22 ±7.58 | 6.34 ±0.79 |
| **6** |  | 5.60 ±0.30 | 12.20 ±1.93 | 2.27 ±0.31 | 36.26 ±2.54 | 5.84 ±1.35 |
| **1NMe$_2$** |  | 148.20 ±26.96 | 92.41 ±5.26 | 121.50 ±17.40 | 179.13 ±35.11 | 26.68 ±1.70 |

[a]Amounts of compound required to retard the growth of the HeLa, MM170, PC3, AHDF, and HUVEC cell lines by 50% in 48 h.

**1NMe$_2$** remains intact prior to addition to the biological system. After a 48 h exposure, the cytotoxicity of each compound was assessed by the MTT cell viability assay. Among the three gold(III) complexes investigated, **1NMe$_2$** showed poor toxicity toward all of the cell lines. Conversely, **6** and **9phen** had higher toxicities, both displaying low-micromolar $IC_{50}$ values against HeLa and PC3 cells and lower activities against MM170 cells. Micromolar $IC_{50}$ values (0.2−60) have been reported for a range of N-ligated Au(III) compounds against a variety of cancer cell lines, including HeLa.[49−51] Importantly, however, when complexes **6** and **9phen** were tested against primary cells, it was evident that they are highly toxic toward HUVEC cells, with low-micromolar $IC_{50}$ values. These can be compared with that for cisplatin, with a reported $IC_{50}$ of 92.4 ± 3.8 against this cell line.[52] In view of the intravenous delivery method used for platinum-containing drugs, this high toxicity against HUVEC cells indicates that these complexes are not viable for further exploration for therapeutic applications.

All of the tested Au(III) complexes are rapidly reduced within minutes by stoichiometric glutathione (GSH), as monitored by complete conversion of GSH to the GSSG dimer by $^1$H NMR spectroscopy in $D_2O$, indicating that the active species in these assays is likely Au(I). For **1NMe$_2$**, the reduction product is **2NMe$_2$**. For **9phen**, protonated 4-DMAP is produced immediately upon reduction, as determined by $^1$H NMR spectroscopy. The identity of the Au(I) product could not be ascertained from mass spectrometry studies. A key difference between the less toxic complex **1NMe$_2$** and **6**/**9phen** is the hydroxide moiety, and it was found that the reduction product from **1NMe$_2$** (**2NMe$_2$**) reacts only slowly in $D_2O$. After 2 full days of standing in $D_2O$, 50% of **2NMe$_2$** remains along with protonated 4-DMAP, without any other intermediates observed.

## CONCLUSIONS

We have shown that [NO][$BF_4$] is an effective reagent for the generation of pyridine-ligated Au(I) and Au(III) cations directly from Au powder, the most economical starting material for Au chemistry, and suggest that this method should be more widely investigated in Au chemistry. We have also generated new Au(III) terminal hydroxides, the first structurally characterized examples in which the Au(III) center is supported by anything other than a tridentate ligand. Finally, biological studies have indicated that while the tri- and bidentate-based complexes display good activities against a variety of cancer cell lines, their high toxicity against primary HUVEC cells would likely preclude any real applications. It was determined that for all of the compounds we have reported, Au(I) is likely rapidly produced under cellular conditions on the basis of their rapid reduction by glutathione.

## EXPERIMENTAL DETAILS

All of the reactions involving $NOBF_4$ were performed using standard Schlenk techniques or in a nitrogen-filled glovebox. Subsequent Au(III) products were found to be moisture-sensitive, and therefore, reaction workups and characterizations were also performed in an inert atmosphere.

Dichloromethane, tetrahydrofuran, MeCN, $Et_2O$, *n*-pentane, and *n*-hexane were obtained from Caledon Laboratories and dried using an Innovative Technologies solvent purification system with dual columns packed with solvent-appropriate drying agents. The dried solvents were stored under a nitrogen atmosphere over 3 Å molecular sieves in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Inorg. Chem. XXXX, XXX, XXX−XXX

the glovebox. Solvents for NMR spectroscopy ($CDCl_3$ $CD_3CN$, $C_6D_6$) were purchased from Cambridge Isotope Laboratories and dried by stirring for 3 days over $CaH_2$, distilled prior to use, and stored in the glovebox over 3 Å molecular sieves. Reagents were purchased from Alfa Aesar, Aldrich, or Precious Metals Online (Au powder) and used as received.

Cyclic voltammetry experiments were performed using a μAUTOLAB (type II) electrochemical potentiostat (MEP Instruments, North Ryde, NSW, Australia) with Nova 1.8 software. In an oxygen-free glovebox, 1 mM compound was dissolved in oxygen-free acetonitrile, and $[Bu_4N][PF_6]$ was added to give a concentration of 0.1 M as the supporting electrolyte. A conventional three-electrode cell configuration was used, consisting of a silver wire in 0.1 M electrolyte as a quasi-reference electrode, a platinum wire as the auxiliary electrode, and a 3 mm diameter glassy carbon disc shrouded in Teflon (CH Instruments, Austin, TX, USA) as the working electrode. The working electrode was polished in a 0.3 μm alumina slurry on a felt pad, rinsed with Milli-Q water followed by acetone, sonicated in acetonitrile for 10 s followed by a final rinse in acetonitrile, and dried with a stream of $N_2$. Potentials were referenced to the ferrocene/ferrocenium couple measured in situ at a concentration of 1 mM, (0.389 ± 0.016 vs SCE).

**1CN** was synthesized by our previously reported method.[13] **$2NMe_2$** was prepared by a variation on the literature method for preparing the corresponding $PF_6$ salt[14] or alternatively via the method described below.

**Synthesis of 2pyr.** To a suspension of Au powder (100 mg, 0.51 mmol) in $CH_3CN$ (50 mL) was added $NOBF_4$ (60 mg, 0.51 mmol). The reaction mixture was then stirred for 3 h in the absence of visible light with a positive nitrogen flow. The reaction mixture was filtered to remove unreacted Au(0) powder. Pyridine (0.041 mL, 0.51 mmol) was then added, and the reaction mixture was stirred for a further 30 min. The resulting solution was concentrated under reduced pressure, and the addition of $Et_2O$ gave **2Pyr** as a fine white solid (237 mg, 89% yield). Single crystals of **2Pyr** were grown using slow vapor diffusion of $Et_2O$ into a $CD_3CN$ solution. Decomposition at 47−50 °C; ESI-MS $[M]^+$ $m/z$ 355.0 $[Au(pyr)_2]^+$; $^1H$ NMR ($CD_3CN$, ppm) 8.65 (d, 4H, $J$ = 5.0 Hz, $o$-H of pyr), 8.14 (t, 2H, $J$ = 5.0 Hz, $p$-H of pyr), 7.83 (t, 4H, $J$ = 5.0 Hz, $m$-H of pyr); $^{13}C$ NMR ($CD_3CN$, ppm) 153.9, 143.1, 128.6.

**Synthesis of $2NMe_2$ via $NOBF_4$ Oxidation.** To a stirred solution of Au powder (94 mg, 0.48 mmol) in $CH_3CN$ (30 mL) was added $NOBF_4$ (60 mg, 0.51 mmol). The reaction mixture was stirred for 3 h. Unreacted Au(0) powder was removed by filtration. 4-DMAP (2 equiv) was then added, and the reaction mixture was stirred for a further 20 min. The solvent volume was reduced under vacuum, and addition of $Et_2O$ afforded **$2NMe_2$** as a fine white solid (110 mg, 49% yield).

**Synthesis of 1Pyr.** To a suspension of Au powder (120 mg, 0.609 mmol) in $CH_3CN$ (50 mL) was added 1 equiv of $NOBF_4$ (78 mg, 0.67 mmol). The reaction mixture was stirred for 3 h in the absence of visible light with a positive nitrogen flow, giving a clear solution. Pyridine (0.054 mL, 1.22 mmol, 2 equiv) was then added, and the reaction mixture was stirred for a further 30 min before the addition of an additional 2 equiv of $NOBF_4$ (156 mg, 1.34 mmol). The reaction mixture was left to stir for 3 h before the addition of a final 2 equiv of pyridine. The reaction mixture was concentrated under reduced pressure and upon the addition of $Et_2O$ yielded **1Pyr** as a fine white solid (399 mg, 85% yield). Single crystals of **1Pyr** for X-ray diffraction analysis were grown using slow vapor diffusion of $Et_2O$ into a $CD_3CN$ solution. Mp 205−210 °C; ESI-MS $[M]^+$ $m/z$ 355.0 $[Au(pyr)_2]^+$; $^1H$ NMR ($CD_3CN$, ppm) 8.80 (d, 8H, $J$ = 5.7 Hz, $o$-H of pyr), 8.34 (t, 4H, $J$ = 5.7 Hz, $p$-H of pyr), 7.85 (t, 8H, $J$ = 5.7, $m$-H of pyr); $^{13}C$ NMR ($CD_3CN$, ppm) 150.5, 146.9, 131.7.

**Synthesis of 8bipy.** A solution of 2,2-bipyridine (13 mg, 0.085 mmol) in $CH_3CN$ (5 mL) was added to a solution of **1CN** (93 mg, 0.085 mmol) in $CH_3CN$ (10 mL). The reaction mixture was then stirred for 12 h at room temperature. The solution was then concentrated under reduced pressure, and addition of $Et_2O$ yielded **8bipy** as a bright-red solid (70 mg, 79% yield). Single crystals of **8bipy** were grown using slow vapor diffusion of $Et_2O$ into a $CD_3CN$ solution. Mp 235−245 °C; $^1H$ NMR ($CD_3CN$, ppm) 8.63 (m, bipy), 8.35 (d, 4H, $J$ = 7.8 Hz, $o$-H of 4-DMAP), 7.94 (m, 4H, bipy), 6.92 (d, 4H, $J$ = 7.8, $m$-H of 4-DMAP), 3.19 (s, $N(Me)_2$); $^{13}C$ NMR ($CD_3CN$, ppm) 157.4, 157.3, 149.5, 147.6, 146.0, 131.0, 127.6, 112.1, 40.6.

**Synthesis of 8phen.** A solution of 1,10-phenanthroline (25 mg, 0.14 mmol) in $CD_3CN$ (5 mL) was added to a solution of **1CN** (153 mg, 0.14 mmol) in $CH_3CN$ (10 mL). The reaction mixture was stirred for 12 h at room temperature. The solution was then concentrated under reduced pressure, and addition of $Et_2O$ yielded **8phen** as deep-red solid (114 mg, 76% yield). Single crystals of **8phen** were grown using slow vapor diffusion of $Et_2O$ into a $CD_3CN$ solution. Mp 242−246 °C; $^1H$ NMR ($CD_3CN$, ppm) 9.21 (d, 2H, $J$ = 8.4 Hz), 8.35 (m, 5H), 8.33 (d, 2H), 8.19 (m, 3H), 6.96 (d, 4H), 3.22 (s, 12H, $N(Me)_2$); $^{13}C$ NMR ($CD_3CN$, ppm) 157.5, 150.9, 147.4, 146.6, 146.2, 134.0, 130.4, 128.7, 112.2, 40.6.

**Synthesis of 9bipy.** To a solution of **8bipy** (115 mg, 0.085 mmol) in $CH_3CN$ (5 mL) was added deionized water (0.010 mL, 0.555 mmol). The reaction mixture was then stirred for 12 h at room temperature in the absence of visible light. The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The rude orange solid was then washed with hot $CHCl_3$ (3 × 15 mL) to give **9bipy** as a pale-orange solid (34 mg, 51% yield). Single crystals of **9bipy** for X-ray diffraction analysis were grown using slow vapor diffusion of $Et_2O$ into a $CD_3CN$ solution. Melts with decomposition at 77−80 °C; $^1H$ NMR ($CD_3CN$, ppm) 9.10 (d, 1H, $J$ = 5.9 Hz), 8.51 (m, 5H), 8.18 (d, 2H, $J$ = 4.8 Hz, $o$-H of 4-DMAP), 8.12 (m, 1H), 8.04 (m, 1H), 7.95 (m, 1H), 7.88 (t, 1H, $J$ = 6.7 Hz), 6.97 (d, 2H, $J$ = 4.8 Hz, $m$-H of 4-DMAP), 5.12 (s, 1H, Au−OH), 3.23 (s, 6H, $N(Me)_2$); $^{13}C$ NMR ($CD_3CN$, ppm) 156.5, 154.2, 147.8, 147.0, 146.2, 145.5, 145.2, 130.0, 128.9, 126.2, 126.1, 110.0, 106.92, 39.4; IR (KBr, $cm^{-1}$) 3451 (Au−OH).

**Synthesis of 9phen.** To a solution of **8phen** (194 mg, 0.182 mmol) in $CH_3CN$ (5 mL) was added deionized water (0.010 mL, 0.555 mmol). The reaction mixture was then stirred for 12 h at room temperature in the absence of visible light. The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude orange solid was then washed with hot $CHCl_3$ (3 × 15 mL), yielding **9phen** as a pale-orange solid (71 mg, 48% yield). Single crystals of **9phen** for X-ray diffraction analysis were grown from a concentrated solution in $CD_3CN$ at −30 °C. Melts with decomposition at 108−112 °C; $^1H$ NMR ($CD_3CN$, ppm) 9.35 (d, 1H, $J$ = 4.6 Hz), 9.19 (d, 1H, $J$ = 8.3 Hz), 9.13 (d, 1H, $J$ = 7.4 Hz), 8.45 (d, 1H, $J$ = 4.6 Hz), 8.41 (m, 3H), 8.27 (d, 2H, $J$ = 7.6 Hz), 8.16 (m, 1H), 7.00 (d, 2H, $J$ = 7.6 Hz, $m$-H of 4-DMAP), 5.25 (s, 1H, Au−OH), 3.25 (s, 6H, $N(Me)_2$); $^{13}C$ NMR ($CD_3CN$, ppm) 157.5, 150.0, 148.3, 147.8, 146.1, 145.2, 133.5, 133.4, 130.0, 129.6, 128.8, 128.2, 127.8, 120.5, 111.1, 40.5.

**Investigation of the Mechanism of Formation of Au(III) Hydroxide 9phen.** Three 20 mL reaction vials were charged with **8phen** (40 mg, 0.068 mmol). To each reaction vial were then added 2 mL of $CD_3CN$ and either 0.025, 0.050, or 0.100 mL of $H_2O$, and reactions were monitored by $^1H$ NMR spectroscopy.

**Computational Methods.** All of the calculations were carried out using the Gaussian 09 package.[53] All of the geometries were optimized in the gas phase by density functional theory using the M06-L functional.[54] The def2-TZVP basis set was used in all of the calculations.[55] Stationary points were characterized as minima by calculating the Hessian matrix analytically at this level of theory. Molecular orbital analysis was carried out with the B3LYP functional[56,57] and the def2-TZVP basis set at the optimized gas-phase geometries using an ultrafine integration grid. Solvent effects were included using the integral equation formulation of the polarizable continuum model (IEFPCM)[58−60] with a $CH_2Cl_2$ solvent and the SMD solvation model.[61]

**MTT Cell Viability Assay.** Mammalian cells were seeded at various densities from 3 × $10^3$ to 1 × $10^4$ cells/well of a 96-well plate and incubated at 37 °C for 24 h under a humidified atmosphere containing 5% $CO_2$/95% air. Cancer cell lines (HeLa, PC3, and MM170) were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum and penicillin streptomycin (Gibco). ADHF cells were cultured


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Inorg. Chem. XXXX, XXX, XXX−XXX

in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum and penicillin streptomycin (Gibco), and HUVEC cells were cultured in EGM-2 Bulletkit (Lonza). Cells were then treated for 48 h with an equal volume of Au(III) compound, diluted serially in the appropriate medium. The solutions of Au(III) cations were prepared in deionized water and left to stand overnight. Then 1 mg/mL 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) (Sigma-Aldrich) in serum-free medium was added, and the cells were incubated for 3 h. Formazan crystals were solubilized in dimethyl sulfoxide, and the absorbance was measured at 570 nm. Cell viability was normalized to no-treatment controls (assigned 100% viability), and the $IC_{50}$ values (i.e., the Au(III) trication concentrations needed to inhibit 50% of cell growth) were determined using OriginPro software version 8.1.13.88 (OriginLab Corporation, Northampton, MA).

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b02667.

$^{1}$H and $^{13}$C NMR spectra, IR spectrum of **9bipy**, cyclic voltammograms of **1pyr** and **2pyr**, crystallographic details, and Cartesian coordinates of the optimized geometries (PDF)

Crystallographic data for **1pyr**, **2pyr**, **8bipy**, **8phen**, **9bipy**, and **9phen** (CIF)

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### Notes

The authors declare no competing financial interest.

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