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Photoreduction of Thioether Gold(III) Complexes: Mechanistic Insight and Homogeneous Catalysis

Zhen Cao,[a] Dario M. Bassani,[a] and Brigitte Bibal*[a]

Abstract: Complexes formed between $AuCl_3$ and thioether ligands undergo a photo-induced reductive elimination under homogeneous conditions in dichloromethane and toluene solutions to afford the corresponding Au(I) complexes. All gold(III) complexes were rapidly reduced to the gold(I) chloride complexes under a 365-nm irradiation or ambient light while being thermally stable below 55°C. The mechanism of photoreduction through Cl_2 elimination is discussed based on a kinetic study and the chemical traping of chlorine species: Cl_2, radical $Cl^{\bullet}$ and possibly Cl^{+}. The catalytic activity of gold(III) chloride complexes and the corresponding gold(I) ones obtained by *in situ* reduction was evaluated in the cyclization of *N*-propargylic amides to oxazoles. The merits of such photoreducible complexes in homogeneous gold catalysis are illustrated by a cascade reaction catalyzed by thioether gold complexes affording a *4H*-quinolizin-4-one in high yields.

Introduction

Since 1986, homogeneous gold(I) catalysis has played a considerable role in the development of synthetic transformations and the construction of complex molecular architectures.[1],[2] In contrast, the use of gold(III) catalysts is less common, despite the description of some remarkable examples using $AuCl_3$.[3] Three main limitations still exist for the exploitation of gold(III) complexes in catalysis: (i) the preparation of gold(III) complexes from $AuCl_3$ is facile when using pyridine ligands[4] but less convenient with phosphine and *N*-heterocyclic carbene (NHC) ligands requiring the formation of the corresponding Au(I) complexes followed by an oxidation step, (ii) the formation of cationic Au(III) species by chloride exchange is not controlled,[5] and (iii) the reduction of $AuCl_3$ species into the corresponding AuCl complexes is scarcely documented in organic solvents despite their importance in catalytic processes (*vide infra*). Currently, the rationalization of the properties of new gold catalysts distinguishes between their oxidation state (Au^{III} or Au^{I}) and the nature of their substituents on the gold center, with the notion of precatalysts (neutral gold chloride) and active species (cationic gold).[6]

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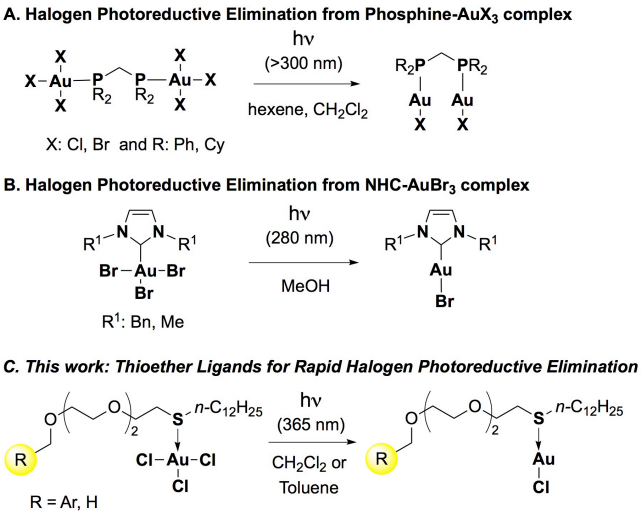
Recently, interest in the reduction of gold(III) complexes has increased following the report of two new catalytic pathways: (i) the known reductive elimination of organogold(III) complexes elegantly exploited in advanced transformations[7] and (ii) the redox Au(I)/Au(III) catalytic cycle implemented in the presence of a sacrificial oxidant[8]. The latter redox cycle was also successfully achieved in several radical reactions with aryl diazonium, diaryliodonium salts or bromoalcanes using gold catalysis in the presence of photosensitizers[9] or by simply using light to directly activate the gold species[10].

Concerning the reductive elimination from $AuCl_3$ complexes, the process seems to depend on the nature of the ligands (Scheme 1). Mono- and di- phosphine ligands enabled a slow photoreduction of $AuCl_3$ into AuCl in the presence of alkenes, as a chemical trap.[11] NHC ligands were reported to favor rapid photoreduction of $AuBr_3$ into AuBr in methanol under UV light (280 nm).[12] It was proposed that these photoreductions proceed through a ligand-to-metal charge transfer (LMCT) state that results in the direct elimination of X_2.



Scheme 1. Photoreduction of gold(III) halide complexes depending on ligand: (A) Mono- or di- phosphine, (B) *N*-heterocyclic carbenes, and (C) dialkylthioether.

Another plausible mechanism for X_2 elimination during gold(III) reduction was proposed earlier by Kochi[7a–b] for dialkyl- and trialkyl- gold(III) phosphine complexes and later, for NHC[13] complexes of AuX_2R (R: Me, Ar). It consists in the initial loss of an halide substituent from the gold atom to generate a three-coordinate intermediate that is more prone to undergo a

reductive elimination than the former square-planar saturated gold(III) center. Of note, the catalytic properties of these gold(I) complex obtained by photoreduction were not reported.

We previously described a 9,10-diphenylanthracene (DPA) derivative **L1** (Fig. 1) with two thioether groups as coordinating sites that allowed facile preparation of a $AuCl_3$ complex, through liquid-liquid extraction.[14] The corresponding gold complex is directly soluble in hydrophobic solvents such as dichloromethane and toluene, thereby avoiding the two-step procedure typically used to prepare $AuCl_3$ complexes with ligands other than pyridine.[4] Importantly, the liquid-liquid extraction procedure guarantees that the **L1**.2$AuCl_3$ complex is confined to the organic phase and that it is not exposed to additional reduction processes as observed in other reported protocoles. For example, the preparation of (tht)AuCl or (Me_2S)AuCl is based on the *in situ* redox reaction between the neat organic ligand (tht or Me_2S) and an aqueous solution of $HAuCl_4$.[15]

The photoreduction of **L1**.2$AuCl_3$ complex into **L1**.2AuCl in dichloromethane or toluene at 365 nm is fast and can lead to the formation of gold nanocrystals in the presence of water. However, in anhydrous media, this interesting example of a photoreducible thioether complex of $AuCl_3$ remains under-exploited with respect to its catalytic properties at either oxidation state (+III) or (+I) and the mechanism of the photoreduction still requires additional clarifications. We envisioned that not only **L1**, but other dialkylthioether compounds would be useful ligands for $AuCl_3$ with the ensuing complexes reduced *in situ* into Au(I) complexes in a controlled fashion. Both gold species can thus contribute to homogeneous gold catalysis. Herein, we report a series of lipophilic dialkylthioether ligands for $AuCl_3$ coordination, appended with (**L1** – **L2**) or without (**L3** – **L4**) a chromophore in order to elucidate the exact role of the photosensitizing anthracene moiety in **L1**. Ligands **L3** – **L4** were chosen as reference thioether ligands that do not absorb light between 365 and 600 nm.

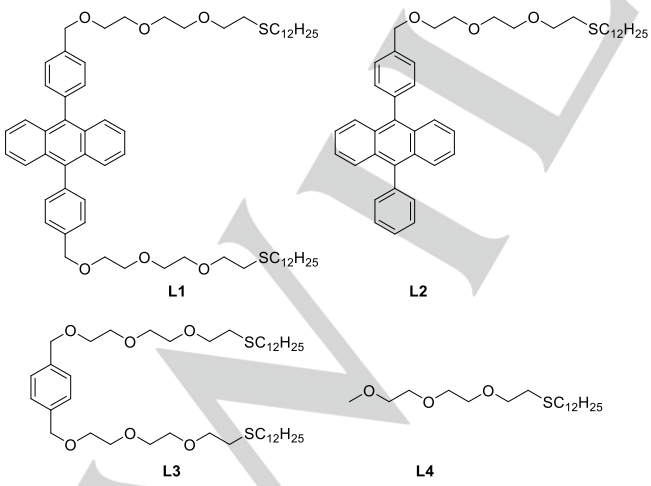


Figure 1. Dialkylthioether ligands **L1**–**L4** designed for $AuCl_3$ and AuCl coordination in dichloromethane or toluene: **L1**–**L2** absorb visible light absorption whereas **L3**–**L4** are transparent to 365–600 nm irradiation.

The corresponding gold(III) chloride complexes underwent photo- and thermal reductions to generate Au(I) chloride complexes. The mechanism of these reductions was investigated to define the impact of the ligand, *i.e.* its nature and its number of coordination sites. Interestingly, the observation of chlorinated side-products arising from the trapping of different halogen species provides indirect support for the heterolytic cleavage of the Au–Cl bond. Finally, the catalytic properties of these $AuCl_3$ and *in situ* generated AuCl complexes were evaluated under homogeneous conditions in both a model cyclization reaction and in new one-pot cascade reaction for the construction of a fused polyaromatic compound.

Results and Discussion

Complexes between thioethers L1–L4 and $AuCl_3$

New ligands **L2**–**L4** were prepared through straigthforward routes in high yields (see supporting information, SI) and the synthesis of **L1** was achieved according to our previous procedure.[14] The complexes between thioethers **L*n*** (n = 1–4) and $AuCl_3$ were prepared by liquid-liquid extraction in the dark by dissolving the desired ligand in the organic phase and shaking with an aqueous solution of $KAuCl_4$. This procedure takes advantage of the solubility of the ligands and gold complexes in low polarity solvents such as dichloromethane or toluene while free Au(III) is confined to the aqueous phase. Another benefit of this protocol is that the solution of gold complex can be directly prepared in common solvents for the further use in organic synthesis.

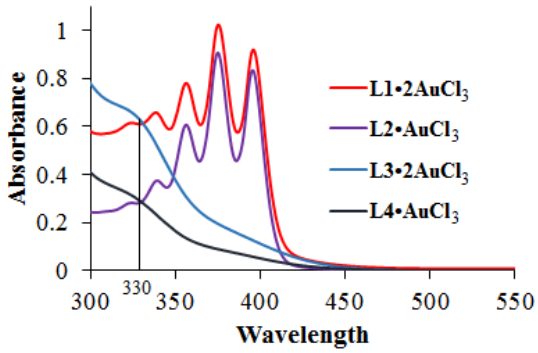


Figure 2. UV-Visible spectra of $AuCl_3$ complexes (c = 60 µM, toluene) and the gold(III) contribution at 330 nm.[9]

For each complex, the stoichiometry in solution was determined by UV–Visible spectroscopy by monitoring the absorbance at 330 nm due mainly to the contribution of gold(III) (Figure 2). Despite a small absorption by ligands **L1** and **L2**, the spectra unambiguously indicated a (Ligand: $AuCl_3$) stoichiometry of 1 : 2

for **L1** and **L3**, whereas a 1 : 1 value was found for **L2** and **L4**. Each dialkylthioether group therefore contributes to the coordination of one $AuCl_3$ species.

All gold(III) complexes were characterized by NMR ($CDCl_3$) and mass spectroscopy. Interestingly, their ^{1}H NMR spectra featured a series of distinct signals for the aliphatic protons (CH_2) near the thioether group due to metal coordination of the sulfur atom (Figure 3). Concerning the mass spectra, complex **L1**•2$AuCl_3$ and complex **L2**•$AuCl_3$ were clearly identified by FD technique, along with reduced complexes containing AuCl, obtained through an *in situ* reductive elimination of Cl_2. For the complexes without a DPA chromophore *i.e.* **L3**•2$AuCl_3$ and **L4**•$AuCl_3$, their mass spectra showed several reduced species such as [**L3**.$AuCl_2$]$^+$ and [**L4**.2Au]$^+$, indicating a lower stability under different analysis conditions (Figures S3–4). The occurrence of reduced species and unusual ionic complexes reflects the lability of these gold complexes under mass spectrometry operating conditions.

Finally, the strong fluorescence emission of 9,10-diphenylanthracene is quenched in **L1**•2$AuCl_3$ and **L2**•$AuCl_3$ complexes due to an intramolecular energy transfer from the polyaromatic ligand to the gold(III) atom, as previously evidenced.[14] The classical emission of anthracene is recovered after photoreduction to the corresponding **L1**•2AuCl and **L2**•AuCl complexes, as Au(I) species do not absorb at 260-600 nm (Figures S18, S20).

Photoreduction towards AuCl complexes

L*n*•x$AuCl$ gold(I) complexes were obtained by irradiating the corresponding solutions of **L*n***•x$AuCl_3$ (4.8 µmol, 6.0 mM) in dichloromethane (0.8 mL) for 1h using a 365-nm UV lamp (6W). The photoreduction was monitored by UV–Visible spectroscopy (Figure 4A). The absorbance at 330 nm decreases due to the transformation of the more highly absorbing gold(III) chloride into the weakly absorbing gold(I) chloride. This process is fast (about 30 min) and does not require any additive such as alkenes which were previously employed to achieve the photoreduction of gold complexes with phosphines[11]. A pseudo-first-order kinetics was observed over the first 7–10 minutes of the process (Table 1), which is consistent with the photoreductive elimination mechanism proposed in the literature (*see vide infra*).[11],[12]

Following photoreduction, all **L*n***•x$AuCl$ complexes (n = 1 – 4, x = 1 – 2) were characterized by proton NMR which revealed upfield shifts for protons next to the sulfur atom, when compared to the corresponding $AuCl_3$ complexes (Figure 3). Mass spectroscopy indicated that the expected reduced gold(I) complexes were formed (Figures S11–14). As observed for gold(III) complexes, gold(I) complexes with thioether ligands appeared to be labile under mass spectrometry operating conditions.

Remarkably, all solution of **L*n***•x$AuCl_3$ complexes are stable in the dark but sensitive to ambient visible light. We found that solutions of $AuCl_3$ complex exposed to daylight inside the laboratory were prone to be photoreduced to Au(I) at rates similar to samples exposed to the 365-nm irradiation (Table 1). However, a closer inspection revealed that the catalytic activity was somewhat lower for gold(I) complexes obtained by daylight photoreduction *versus* 365-nm irradiation (77–80% conv. *vs.* 93-95% respectively, see Table 3, entry 2). Accurate analysis of cyclization products further indicated that gold(I) complexes obtained through daylight exposure lead to side-products in higher proportion than those obtained using catalysts prepared by 365-nm irradiation (Table S3).

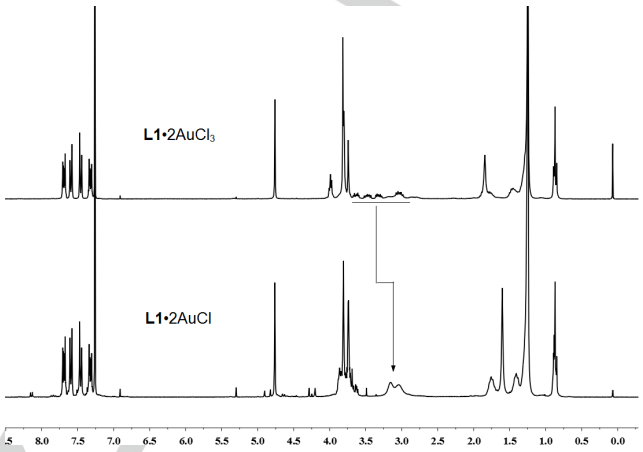


Figure 3. ^{1}H NMR spectra ($CDCl_3$) of **L1**•2$AuCl_3$ before (up) and after (down) photoreduction towards the corresponding **L1**•2AuCl complex, showing shifted thioether protons due to the change in oxidation state of gold chloride.

Thermal reduction

In the dark, the **L1**•2$AuCl_3$ complex is thermally stable up to 55°C (See Figure S21). To further investigate the impact of temperature, a solution of **L1**•2$AuCl_3$ in toluene was monitored by UV–Visible spectroscopy at 80 °C in the dark over several hours (Figure 4B).

The decrease in gold(III) absorption at 330 nm was similar to that observed during photoreduction (Figure 4A), but much slower (12 hours *vs*. 30 min). Therefore, it can be concluded that background thermal reduction is negligible under irradiation conditions.

The ^{1}H NMR spectra of crude product(s) after the thermal treatment presented the signature of the expected gold(I) complexes and several signals that could be attributed to degradation of the aliphatic chains belonging to the ligands (Fig. S23–24). Notably, the catalytic properties of **L1**•2AuCl and **L2**•AuCl complexes obtained by thermal reduction were far lower than those of the same complexes prepared by photoreduction (40–67% conv. *versus* 93–95%, see Table 3, entry 2). For the sake of preparation and effectiveness, the following studies were focused on gold(I) complexes obtained by photoreduction.

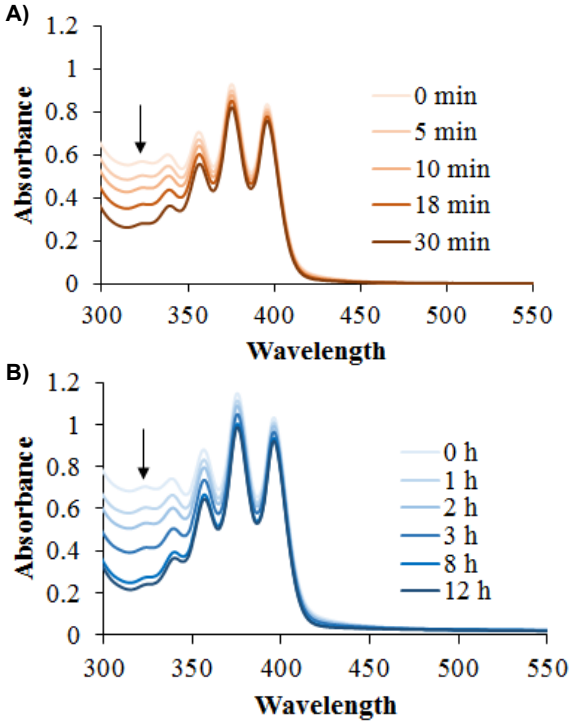


Figure 4. Reductions of **L1**•2AuCl$_3$ in toluene monitored by UV-Visible spectroscopy: (**A**) Photoreduction (c = 60 µM) using a TLC lamp at 365 nm; (**B**) Thermal reduction (c = 70 µM) at 80°C.

Mechanistic aspect of AuCl$_3$ photoreduction:

Previously, we showed that an intramolecular energy transfer occurs within the **L1**•2AuCl$_3$ complex upon excitation of the DPA chromophore at 365 – 400 nm. We proposed that this energy transfer might accelerate the rapid and clean reduction into **L1**•2AuCl.[14] To better understand the photoreduction mechanism of gold(III) thioether complexes, we further investigated the role of the diphenylanthracene chromophore, taking into account the plausible reductive elimination pathway.[7a–b],[11–13]

The kinetics of reduction were investigated under irradiation at 365 nm or ambient daylight by monitoring the absorption of the gold(III) species. For each **L*n***•xAuCl$_3$ (n = 1–4, x = 1–2) complex, the decrease in absorbance was fitted to a pseudo-first-order reaction over the first ten minutes of irradiation (Table 1), with similar rates observed upon irradiation at 365 nm (k^{365} = *ca.* 0.06–0.08 min^{-1}) and under ambient daylight ($k^{daylight}$ = *ca.* 0.05–0.08 min^{-1}). The nature of the dialkylthioether ligand, *i.e.* the presence of diphenylanthracene, aryl or alkyl, substituents, does not impact the rate of the photoinduced process. This is in agreement with our previous finding[14] of near-quantitative energy transfer from the excited DPA to the gold(III) center since, under these experimental conditions, all incident light is absorbed either by the DPA or by the gold(III).

Comparing complexes with one or two gold atom(s), the photoreduction of **L1**•2AuCl$_3$ and **L3**•2AuCl$_3$ were found to be faster than those of **L2**•AuCl$_3$ and **L4**•AuCl$_3$ complexes, as observed for phosphine-based complexes[11]. In the latter, it was suggested that reductive elimination in the case of binuclear gold complexes might be facilitated through the formation of short-lived halide-bridged intermediates that weaken the Au–Cl bond.

Table 1. Pseudo-first-order rate constants for photoreduction of gold(III) complexes under 365 nm irradiation and daylight.[a]

Gold(III) Complexes	k^{365} (min^{-1})[b]	$k^{daylight}$ (min^{-1})[c]
L1•2AuCl$_3$	0.0802	0.0733
L2•AuCl$_3$	0.0571	0.0539
L3•2AuCl$_3$	0.0836	0.079
L4•AuCl$_3$	0.0644	0.0673

[a] All rate constants were determined for solutions of gold(III) complex (60 µM) in toluene at room temperature. [b] Irradiation under a xenon-mercury lamp at 365 nm. [c] Indoor daylight in a sunny day.

To explore the elimination of dichlorine, the photoreduction of each **L*n***•xAuCl$_3$ complex (*ca.* 20–30 mM in CH_2Cl_2) was conducted in the presence of cyclohexene (380 mM) as a chemical trap (Table 2). The crude mixture was analyzed by GC–MS, which revealed the presence of chlorocyclohexane and 1,2-dichlorocyclohexane, as well as 2-chlorocyclohexanol (see Figures S25–S28). This result suggests that Cl_2 and $Cl^{\bullet}$ were released following the photoexcitation of the gold(III) complex (Figure 6). In the presence of alkene, the excitation of the LMCT band was shown to induce the ejection of $Cl^{\bullet}$ to give an Au(II) intermediate that was further reduced.[16] On the contrary, the *in situ* dichlorine formation is characteristic of a non–radical reductive elimination mechanism in agreement with Kochi's proposed mechanism or a direct *cis*-elimination process.[11],[13b] Therefore, both radical and non–radical photoreduction pathways appear to be operating during the reduction of gold(III) chloride thioether complexes. Surprisingly, the GC-MS analysis of the crude photoreducted gold(III) complexes indicated that 2-chlorocyclohexanol was also formed. This compound may be generated from cyclohexene and electrophilic Cl^+ in the presence of residual water. To the best of our knowledge, this is the first time that the cleavage of Au^{III}–Cl bond into $^{-}Au^{III}$ and Cl^+, was indirectly observed through a chemical trap.

Table 2. Outcome of chlorinated species during photoreduction of gold(III) complexes in toluene under 365-nm irradiation (UV lamp).[a]

Conditions	GC-MS Analysis of products[c]
Ln•xAuCl$_3$ + cyclohexene[b]	chlorocyclohexene, 1,2-dichlorocyclohexene, 2-chlorocyclohexanol
Ln•xAuCl$_3$	benzaldehyde, benzyl chloride, *o*- and *p*- chlorotoluene

[a] All **Ln**•xAuCl$_3$ complexes (20-30 µM, toluene; n = 1–4, x = 1–2) revealed similar GC-MS analysis after 4h of irradiation at room temperature. [b] cyclohexene concentration was 300 µM. [c] for detailed analysis, see S.I.

In the absence of cyclohexene, the analysis of the crude irradiated gold(III) chloride complexes revealed the presence of benzaldehyde and species resulting from the chlorination of toluene, *i.e.* benzyl chloride and *ortho*- and *para*- chlorotoluene (Table 2). These products could be obtained from reaction of toluene: oxidation by Cl_2 (PhCHO), radical substitution by radical $Cl^{\bullet}$ ($PhCH_2Cl$) and electrophilic substitution by Cl^+ ($Cl\text{-}C_6H_4\text{-}CH_3$). The formation of the chloronium ion is unexpected, although supported by the formation of both 2-chlorocyclohexanol and *o*/*p*-chlorotoluene. It may arise from an ionic pathway that is reminiscent of the mechanism initially proposed by Kochi (Figure 6). This ionic pathway would imply the formation of a chloronium cation and a tricoordinated gold(III) $[\mathbf{L}n\bullet x AuCl_2]^-$ species. The reactive Cl^+ reacts with toluene to form *o*- and *p*- chlorotoluene. If the chloronium is not captured by toluene, then $[\mathbf{L}n\bullet x AuCl_2]^-$ can undergo a reductive elimination of Cl_2 followed by a recombination with Cl^+ to lead to the expected **L*n***•xAuCl complex.

The use of toluene as solvent is thus beneficial for the protection of the catalyst during its photoreduction as it captures any reactive halogenated species that are generated. Indeed, when dichloromethane was employed as a solvent for photoreductions, some degradation of dialkylthioether ligands was noticed, presumedly due to their reactivity towards $Cl^{\bullet}$ and/or Cl^+.

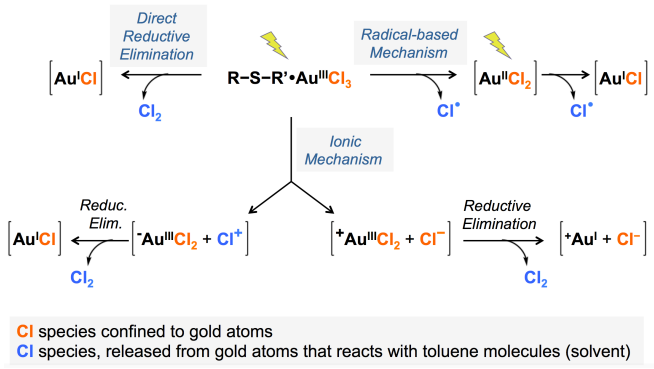


Figure 6. Plausible pathways for the photoreduction of complexes between dialkylthioether and $AuCl_3$ in solution: a radical-based mecanism induced by excitation of the LMCT band (release of $Cl^{\bullet}$), a direct reductive elimination through a concerted mechanism (release of Cl_2) and two ionic pathways through transient tricoordinated Au(III) ions (negatively or positively charged) that undergo a reductive elimination. Each reactive chlorinated species ($Cl^{\bullet}$, Cl_2, Cl^+) can be trapped by cyclohexene or toluene (solvent) molecules.

Gold catalysis

The catalytic properties of thioether-based complexes of $AuCl_3$ and AuCl (obtained by *in situ* photoreduction) were exploited in two model reactions.

In a first example, the cyclization of *N*-propargylic amides developed by Hashmi was chosen as a model reaction.[17] Two different isomers were prepared depending on the nature of the catalyst. An oxazole (compounds **5a** – **7a**) was isolated in the presence of $AuCl_3$, due to a a 5-*exo*-dig cyclization followed by an isomerization of the allyl group towards the aromatic compound. Meanwhile, in the presence of cationic Au(I) catalyst, the product of 5-*exo*-dig cyclization *i.e* alkylidene oxazoline (compounds **5b** – **7b**) was observed. Our study was focused on three different propargylic amides appended with aliphatic (**5**), phenyl (**6**) and electron-rich thiophene (**7**) substituents (Table 3). The catalytic activities of **L*n***•x$AuCl_3$ (termed gold(III) chloride), the corresponding **L*n***•xAuCl (gold(I) chloride) obtained by *in situ* photoreduction at 365 nm and the cationic **L*n***•x$AuNTf_2$ complexes (obtained from the latter **L*n***•xAuCl in the presence of $AgNTf_2$) were compared to PPh_3AuNTf_2, an efficient gold(I) phosphine complex for homogeneous catalysis.

Amides **5**–**7** were converted to the aromatic 2,5-disubstituted oxazoles **5a**–**7a** using either the gold(III) chloride catalysts (85–99% conv.), or the gold(I) chloride catalysts (80–99% conv.) in a similar fashion as $AuCl_3$. To the best of our knowledge, this is the first report that complexes of AuCl can also catalyze this transformation. Slightly lower conversions for amide **5** might be result from steric hindrance between the catalyst and the reactant.

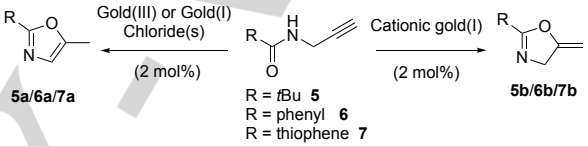
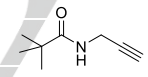
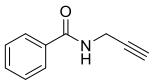
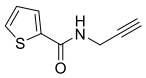


Table 3. Catalytic activity of gold(III) chlorides and gold(I) catalysts obtained by photoreduction.[a],[b]

Substrates	Entry	Catalyst	Conversion,[c] Product
 5	1	Gold(III) chloride	85–90 %, **5a**
	2	Gold(I) chloride	80–92 %, **5a**
		Gold(I) chloride[d] (daylight)	77–80 %, **5a**
		Gold(I) chloride[e] (thermal reduction)	40–67 %, **5a**
	3	Gold(I) chloride/$AgNTf_2$[f]	85–93 %, **5b**
	4	PPh_3AuNTf_2[g]	95 %, **5b**
 6	5	Gold(III) chloride	96–99 %, **6a**
	6	Gold(I) chloride	96–99 %, **6a**
	7	Gold(I) chloride/$AgNTf_2$[f]	91–96 %, **6b**
	8[	PPh_3AuNTf_2[g]	94 %, **6b**
 7	9	Gold(III) chloride	95–99 %, **7a**
	10	Gold(I) chloride	90–99 %, **7a**
	11	Gold(I) chloride/$AgNTf_2$[f]	79–95 %, **7b**
	12	PPh_3AuNTf_2[g]	96 %, **7b**

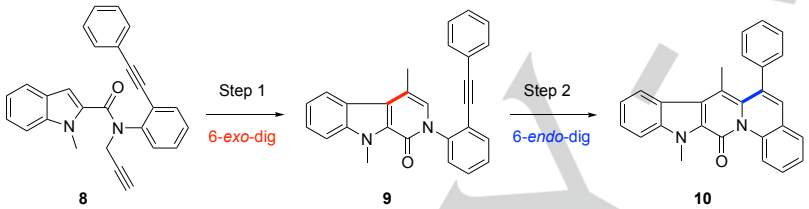
[a] Unless specified, all the reactions were carried out in the dark an NMR tube ($CDCl_3$) without stirring, using an amide substrate (0.11 mmol), **L*n***.x$AuCl_3$ or **L*n***.xAuCl (formed by 365 nm irradiation of the precursor using a TLC lamp) as a catalyst (n = 1–4, x = 1–2; 2 mol% loading), at room temperature in the dark. Reactions were monitored by ^{1}H NMR for 24-30h until full conversion was

reached. [b] For detailed experiments depending on the ligand nature, see supporting information, Table S2. [c] Determined by ^{1}H NMR. [d] Obtained through photoirradiation by ambient daylight. [e] Obtained by thermal reduction. [f] Prepared by mixing gold(I) chloride complex and $AgNTf_2$ for 1h. [g] reaction performed in a 10 mL vial with stirring.

As expected, dihydrooxazoles **5b**–**7b** were obtained by employing cationic **L*n***•x$AuNTf_2$ complexes (79–96% conv.) or commercially available PPh_3AuNTf_2 (94–96% conv.)[17c] through a 5-*exo*-dig cyclization without further isomerization. The model cyclization of *N*-propargylic amides can thus be readily controlled by employing **L*n***•x$AuCl_3$ and **L*n***•xAuCl gold chloride catalysts or cationic gold(I) catalyst, **L*n***•x$AuNTf_2$.

In a second example of the catalytic properties of dialkylthioether gold complexes, a more sophisticated one-pot reaction was developed to transform amide **8** with two alkyne groups into indolino-*4H*-benzoquinolizin-4-one **10**. In principle, the two sequential chemioselective cyclizations are catalyzed by different gold species: the monosubstituted alkyne is activated by the gold(III) chloride catalyst whereas the disubstituted alkyne reacts in the presence of cationic gold(I). Step 1 is a 6-*exo*-dig cyclization followed by isomerization leading to the new β–carbolinone **9**. A similar electrophilic activation of monoalkynes by gold(III) was described by A. Padwa using $AuCl_3$.[18] Step 2 is a novel 6-*endo*-dig cyclization towards *4H*-quinolizin-4-one **10**, inspired by the synthesis of a related regioisomer[19]. Straightforward routes to *4H*-quinolizin-4-ones are rare and mainly based on Pd or Rh catalysis.[20] The development of new synthetic pathways is thus of interest as these π-extended *N*-heteroarenes exhibited biological activities with potential applications against Alzheimer's disease, Type 2 diabetes and as antibiotics.[21] Herein, we propose a cascade strategy towards model substrate **10** that can be attained using gold catalysts at different oxidation states: either Au(III) or Au(I) that is obtained from photoreduction of the corresponding Au(III) complex.

Table 4. One-pot cascade cyclization of a propargylindole **8** towards fused polyheteroaromatic compound **10** catalyzed by gold(III) or gold(I) catalysts.



8 **9** **10**

Entry[a]	Catalyst	*Step 1*		*Step 2*		Yield, Product[d]
		Time	Conversion (**9**)[b]	Irradiation (365 nm)[c]	Additive	
1	$AuCl_3$	16 h	–[e]	–	–	trace
2	**L1**•2$AuCl_3$	5 h (48 h)	99 % (99 %)	–	–	93 %, **9**
4	**L2**•$AuCl_3$	12 h	99 %	–	–	90 %, **9**
5	**L3**•2$AuCl_3$	12 h	99 %	–	–	95 %, **9**
6	**L4**•$AuCl_3$	12 h	99 %	–	–	92 %, **9**
7	**L1**•2AuCl[f]	16 h	99 %	–	AgOTf	80 %, **10**
8	**L2**•AuCl[f]	16 h	99 %	–	AgOTf	71 %, **10**
9	AgOTf	16h	99%	–	–	n.d.[g], **9**
10	**L1**•2$AuCl_3$	16 h	99 %	–	AgOTf	76 %, **10**
11	**L2**•$AuCl_3$	16 h	99 %	–	AgOTf	72 %, **10**
12	**L1**•2$AuCl_3$	12 h	99 %	Yes	AgOTf	83 %, **10**
13	**L2**•$AuCl_3$	12 h	99 %	Yes	AgOTf	72 %, **10**
14	**L3**•2$AuCl_3$	12 h	99 %	Yes	AgOTf	80 %, **10**
15	**L4**•$AuCl_3$	12 h	99 %	Yes	AgOTf	73 %, **10**

[a] Unless specified, all the reactions were performed in dry dichloromethane at ambient temperature and in the dark, in the presence of a catalyst (2 mol%), amide **8** (0.1 mmol) and when necessary, AgOTf (6 mol%) was added after the completion of step 1 (except entry 9). [b] monitored by TLC. [c] TLC lamp (6W) irradiation for 2h. [d] Isolated yield. [e] Compound **9** was not detected by TLC. [f] Freshly prepared through irradiation of the corresponding gold(III) complex at 365 nm . [g] n.d.: not determined.

Indole-based compound **8** was synthesized in four steps with a 37 % overall yield (see SI). This model substrate possesses both an *N*-propargyl amide and an *N*-diphenylacetylene group to successively allow the formation of a pyridone (step 1) and a quinolizin-4-one ring (step 2).

Initially, the reaction was tested using $AuCl_3$ as catalyst (Table 4, entry 1). Several products were observed by TLC but the expected cyclization product was not detected. The smooth transformation of amide **8** to **9** (step 1) was seen when thioether gold(III) chlorides **L*n*•**x$AuCl_3$ (n = 1–4, Table 4, entries 2–6, 90–95% yield) or the corresponding gold(I) catalyst **L*n*•**xAuCl obtained by photoreduction at 365 nm (n = 1–2, entries 7–8, 99% conversion) were used as catalysts.

Notably, indole **9** can be obtained with 99% conversion within 5h in the presence of **L1**•2$AuCl_3$, and this product was isolated in 93 % yield (Table 4, entry 2). As noticed for the catalyzed cyclization of propargylic amides, the synthesis of indole-pyridone **9** is catalyzed by thioether complexes with gold(III) chloride or gold(I) chloride. To catalyze the second cyclization and obtain the desired quinolizin-4-one **10** (step 2), the higher activity of a cationic gold species is required. The classical cationic Au(I) species obtained from **L*n*•**xAuCl complexes in the presence of silver salts were explored first (Table 4, entries 7–8).[22] The sequential cyclization product **10** is obtained in excellent yield (71–80 %, entries 7–8) by tuning the Au(I) catalysts over the two sequential steps: Au(I) chloride complex was used in the first step (99% conv.) whereas, in the second step, the corresponding cationic Au(I) complex was *in situ* generated by the addition of AgOTf in the reaction medium. Along step 2, the role of silver triflate was shown to be restricted to chloride exchange, as no catalytic activity was detected when using the silver salt alone (entry 9).

We then decided to try an alternative catalytic system, composed of **L*n*•**x$AuCl_3$ complexes in the presence of silver salts, in the absence or presence of irradiation during step 2. This complex system is composed of cationic gold(III) species and possibly traces of cationic gold(I). The catalytic effect of Au(III) chloride complexes (**L1**•2$AuCl_3$ and **L2**•$AuCl_3$) alone for the first step and in the presence of a silver triflate for the second step, allowed the synthesis of compound **10** in excellent yield (72–76 %, entries 10–11). It should be noted that several Au(III) active species can co-exist and no data was available concerning their nature under our homogeneous reaction conditions. We also cannot exclude the occurence of Au(I) traces (through undesired photoreduction) that might participate to the final cyclization.

To better investigate the possible effect of *in situ* reduction of Au(III) into Au(I), we proceed to the final cyclization using gold(III) chloride complexes in the presence of AgOTf and under a 365-nm irradiation (entries 12–15). Compound **10** was isolated in excellent yields (72–82 %) that are similar to those determined in the dark. The catalytic system composed of AgOTf and complexes based on thioether ligands **L3** – **L4** and Au(III) chloride are therefore efficient gold species for the cyclization of disubstituted alkynes, with a similar performance to that of cationic Au(I) catalysts.

Conclusion

Homogeneous gold(III) complexes with well-defined stoichiometry are readily obtained by liquid-liquid extraction using lipophilic dialkylthioether ligands and the resulting complexes are stable in the dark below 55°C. Independently of the ligand nature (anthracene, phenyl, alkyl), the gold(III) chloride complexes are rapidly photoreduced to the corresponding gold(I) chloride complexes using a 365-nm irradiation. The course of this photoreduction was more rapid (30 min) than thermal reduction at 80°C (12h). The photoreduction under a conventional TLC lamp (365 nm) also induces the formation of Au(I) exhibiting a higher catalytic activity than those obtained by daylight exposure or heating.

Under our conditions, we found no variation in the rate of photoreduction ascribable to the presence of the diphenylanthracene chromophore. A possible antenna effect resulting from efficient intramolecular energy transfer from the organic chromophore to the gold center would presumably become more pronounced under low light absorption conditions. The photoreductive elimination of X_2 seems to occur under 365 nm or daylight irradiation as evidenced by the formation of chlorinated organic by-products. In the case of the dialkylthioether gold complexes, reductive elimination might be triggered through a direct excitation on the gold center and/or through a ligand-to-metal charge transfer (LMCT), possibly accompanied by the formation of a chloronium ion.

The catalytic properties of gold complexes at different oxidation states were evaluated in cyclization reactions of alkynes under homogeneous reaction conditions for single and sequential double cyclization(s). All Au(III) chloride and *in situ* generated Au(I) chloride complexes showed excellent efficiency (high yield, reasonnable reaction times). The corresponding cationic Au(I) complexes obtained in the presence of AgOTf were also active. Interestingly, the catalytic system composed of the Au(III) chloride catalyst and AgOTf (in the dark) showed a similar activity to classical cationic Au(I) catalysts. The complexes of thioethers and $AuCl_3$ are therefore highly versatile complexes with the possibility to prepare and tailor their catalytic activity by using light to control the oxidation state and silver salts to modify the coordination sphere of the gold center.

Experimental Section

The synthesis of ligands **1**–**4** and indole **8** is detailed in the supporting information. *N*-propargylic amides **5**–**7** were prepared according to the literature.[17c]

Preparation of $AuCl_3$ complexes: in an oven-dried glass centrifuge tube (50 mL), were charged a solution of $NaAuCl_4$•$2H_2O$ (4.0 equiv. for ligands **1** and **3**; 2.0 equiv for ligands **2** and **4**) in MilliQ water (10 mL)

and a solution of thioether ligand **L*n*** (n= 1-4, 1.0 equiv) dissolved in toluene (12 mL) was added. After shaking in the dark for 1 to 2 hours and centrifugating at 3000 rpm for 15 min, the upper golden organic phase was collected, concentrated under vacuum and dried.

Photoreduction of $AuCl_3$ complexes: a solution of **L*n*•**$AuCl_3$ complex (n = 1–4, 60 µM) in dry dichloromethane or toluene (20 mL) was irradiated at 365 nm, using either an optical bench equipped with a xenon-mercury lamp and a high-intensity monochromator, or a TLC lamp (6 W). The photoreduction process was monitored by UV-Visible spectroscopy.

Thermal reduction: a solution of **L*n*•**$AuCl_3$ complex (n = 1–4, 70 µM) in dry toluene (10 mL) was placed in a sealed glassware equipped with a cuvette (l = 1 cm) and a round flask (25 mL). The solution was heated at different temperatures (25–80°C). The experiment was monitored by UV-Visible spectroscopy.

β–Carbolinone 9: to a solution of 2-amido-indole **8** (17 mg, 44 µmol) in dichloromethane (2 mL) was added a solution of **L1•**2$AuCl_3$ catalyst (2.2 µmol, 5 mol%) in dichloromethane (0.5 mL). The reaction was stirred at room temperature for 40 h. After concentration under vacuum, the residue was purified by column chromatography on silica gel (eluent: petrol ether/AcOEt, 1:1). Compound **9** was isolated as a white solid (93 % yield). m.p. 163.7 °C; FTIR (NaCl): ν 2923, 2854, 2219, 1663, 1590, 1331, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.70-7.72 (m, 1H), 7.42-7.58 (m, 5H), 7.27-7.33 (m, 1H), 7.08-7.22 (m, 5H), 6.93 (d, *J* = 0.88 Hz, 1H), 4.35 (s, 3H), 2.63 (d, *J* = 0.88 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 142.7, 141.2, 132.9, 131.5, 129.1, 128.6, 128.5, 128.4, 128.2, 126.8, 126.7, 126.5, 125.0, 122.9, 122.8, 122.3, 122.2, 120.2, 111.9, 110.3, 94.7, 85.5, 31.5, 17.0; HRMS (ESI): *m/z* calculated for $C_{27}H_{21}N_2O$ $[M+H]^+$: 389.1654; found: 389.1638.

General procedure for one-pot cyclizations: to a solution of 2-amido-indole **8** (17 mg, 44 µmol) in dichloromethane (2 mL) was added a solution of gold catalyst (2.2 µmol, 5 mol%) in dichloromethane (0.5 mL). The reaction was stirred at room temperature for 8 h. Then silver trifluoromethanesulfonate (1.0 mg, 7 mol%) was added and the reaction was stirred for 4 hours.

Indolino-*4H*-benzoquinolizin-4-one 10: following the general procedure with catalyst **L3•**2$AuCl_3$, the reaction medium was finally concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH, 50:1). Compound **10** was isolated as yellow sticky oil (80 % yield): FTIR (NaCl): ν 2925, 2854, 1630, 1525, 1334, 1266, 1030, 756, 637 cm^{-1}; ^{1}H NMR (300 MHz, CD_3CN) δ 8.41 (s, 1H), 8.31 (d, *J* = 7.95 Hz, 1H), 8.06 (d, *J* = 8.28 Hz, 1H), 7.96 (d, *J* = 7.62 Hz, 1H), 7.62-7.82 (m, 5H), 7.40-7.53 (m, 4H), 6.96 (s, 1H), 3.91 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 146.2, 144.6, 141.4, 134.8, 133.3, 132.9, 132.7, 2.1, 131.4, 130.3, 129.6, 129.4, 126.8, 126.1, 125.2, 124.2, 123.9, 123.5, 122.8, 122.2, 121.1, 119.9, 119.6, 112.3, 111.3, 34.0, 17.3; HRMS (ESI): *m/z* calculated for $C_{27}H_{21}N_2O$ $[M+H]^+$: 389.1654; found: 389.1648.

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Keywords: gold • photoreduction • homogeneous catalysis • thioether ligand • mechanism

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[22] Under UV-Visible irradiation, in the presence or absence of gold(III) or gold(I) chloride complexes, compound **9** showed an uncontrolled reactivity as several spots were observed by TLC. No trace of product **10** was detected. Only cationic gold catalysts successfully lead to the 6-*endo*-dig product. As a consequence, no *in situ* photoreduction of gold(III) complexes can be conducted in the presence of **9**, to achieve a *in situ* Au(III)/Au(I) sequential catalysis.

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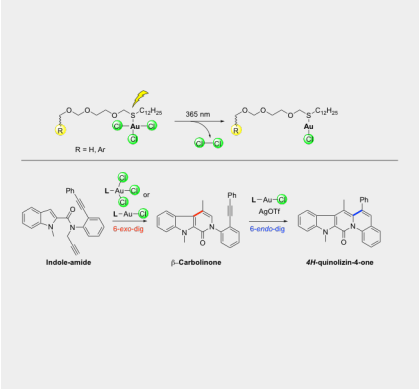
FULL PAPER

Four homogeneous dialkylthioether gold(III) complexes undergo a rapid halogen photoreductive elimination process into the corresponding gold(I) complexes. The catalytic properties of these gold chlorides at different oxidation states were evaluated in the cyclization of propargylamines and a one-pot cascade reaction towards a fused heteropolycyclic compound.



*Zhen Cao, Dario M. Bassani, Brigitte Bibal**

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Photoreduction of Thioether Gold(III) Complexes: Mechanistic Insight and Homogeneous Catalysis