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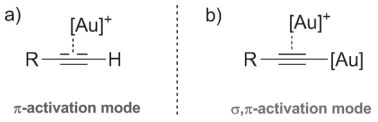
Gold Catalysis

Competitive Gold-Activation Modes in Terminal Alkynes: An Experimental and Mechanistic Study

Ana Gimeno, Ana B. Cuenca, Samuel Suárez-Pantiga, Carmen Ramírez de Arellano, Mercedes Medio-Simón,* and Gregorio Asensio[a]

Abstract: The competition between π- and dual σ,π-gold-activation modes is revealed in the gold(I)-catalyzed heterocyclization of 1-(*o*-ethynylaryl)urea. A noticeable effect of various ligands in gold complexes on the choice of these activation modes is described. The cationic $[Au(IPr)]^+$ (IPr = 2,6-bis(diisopropylphenyl)imidazol-2-ylidene) complex cleanly promotes the π activation of terminal alkynes, whereas $[Au(PtBu_3)]^+$ favors intermediate σ,π species.In this experimental and mechanistic study, which includes kinetic and cross-over experiments, several σ-gold, σ,π-gold, and other gold polynuclear reaction intermediates have been isolated and identified by NMR spectroscopy, X-ray diffraction, or MALDI spectrometry. The ligand control in the simultaneous or alternative π- and σ,π-activation modes is also supported by deuterium-labeling experiments.

Mechanistic proposals beyond the well-established π-activation mechanism for gold(I)-catalyzed reactions (Scheme 1 a) are currently gaining acceptance.[1] Toste and Houk et al., while investigating the mechanism of 1,5-allenyne cycloisomerization, proposed the concept of dual σ,π activation (Scheme 1 b) to depict a new model for the interaction between some gold(I)-complexes and terminal alkynes.[2] Later, the groups of Hashmi[3] and Zhang[4] independently applied this dual-activation concept to the cyclization of diynes.



Scheme 1. a) Canonical π-gold and b) dual σ,π-gold activation.

[a] *A. Gimeno, Dr. A. B. Cuenca, Dr. S. Suárez-Pantiga, Dr. C. R. de Arellano, Dr. M. Medio-Simón, Prof. Dr. G. Asensio*
Departamento de Química Orgánica, Universidad de Valencia
Avda. Vicent Andrés Estellés s/n 46100-Burjassot
Valencia (Spain)
Fax: (+34) 963544939
E-mail: Mercedes.Medio@uv.es

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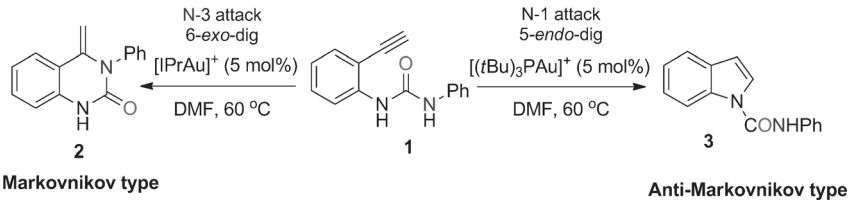
The presence of these σ,π-type complexes in $[Au]^+$-catalyzed reactions[5] and their formation in the course of certain gold–alkyne coordination studies[6] have recently received support by X-ray diffraction, NMR spectroscopy, and mass spectrometry studies. In addition, it has been shown that such species can act as efficient precatalysts in C–C-bond-forming reactions.[7] In this context, the gold(I)-catalyzed heterocyclization of 1-(*o*-ethynylaryl)ureas, recently reported by our group,[8] constitutes a simple model to study the effect of various ligands in gold complexes on the selection of π- or dual σ,π-activation modes. This reaction proceeds either in a 6-*exo*-dig (Markovnikov) or a 5-*endo*-dig (anti-Markovnikov) fashion, depending on the catalyst employed (Scheme 2). The cyclization to obtain indole **3** would entail an unfavorable build-up of positive charge at a terminal acetylenic carbon; a process that is difficult to regard as the major process if a π-acidic-activation mode is considered.

Herein, we report how the gold(I)-catalyzed heterocyclization of 1-(*o*-ethynylphenyl)urea **1** reveals a competition between the π- and σ,π-gold-activation modes. Characterization, by NMR spectroscopy and X-ray diffraction, of several aurated intermediates and the results of σ,π-gold cross-over and deuterium-labeling experiments are reported.

The [AuCl(L)]/$AgSbF_6$ (L = ligand) combination promotes, in DMF at 60 °C, the catalytic heterocyclization of **1** into either 4-methylene-3,4-dihydroquinazolin-2-one **2** or indole carboxamide **3**, depending on the ligand employed (Table 1, entries 1 and 2).

Specifically, 5 mol% of the bulky NHC-based (NHC = *N*-heterocyclic carbene) complex $[Au(IPr)]SbF_6$ (IPr = 2,6-bis(diisopropylphenyl)imidazol-2-ylidene) afforded exclusively the 6-*exo*-dig *N*-3-attack product **2** (>95%). In contrast, the use of $[Au(PtBu_3)]SbF_6$ led to indole **3** in 80% yield. The more common $[Au(PPh_3)]SbF_6$ afforded an almost equimolecular mixture of **2** and **3** (Table 1, entry 3). These results represent a general trend, in which the ancillary ligand has a significant influence on the selectivity of the reaction (see Table 1, entries 4–6).[9]

Complexation to a gold center perturbs the structure of the alkyne ligand by elongation of the C≡C bond and a concomitant deviation from linear geometry.[10,11] In the case of asymmetrically substituted alkynes, particularly terminal acetylenes, this interaction leads to a displacement of the gold center termed as the $\eta^2 \rightarrow \eta^1$ slippage.[12] This displacement, in turn, leads to an unsymmetrical activation of the acetylene towards nucleophilic attack.[13] The gold–alkyne coordination is also expected to lower the pK_a of the acetylenic C–H proton.[14]



Scheme 2. Gold(I)-catalyzed heterocyclization of urea **1**.

Table 1. Screening of ligands and conditions in the Au^{I}-catalyzed heterocyclization of **1**.

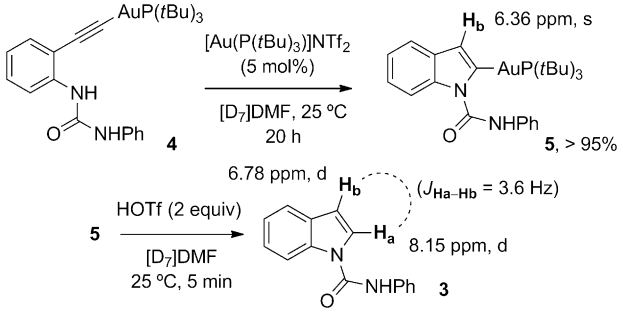
Entry	Catalytic S system [5 mol%]	**2** [%][a]	**3** [%][a]
1	$[Au(IPr)]SbF_6$	>**95**	<5
2	$[Au(PtBu_3)]SbF_6$	20	**80**
3	$[Au(PPh_3)]SbF_6$	53	47
4	$[Au(t\text{BuXPhos})]SbF_6$	>95	<5
5	$[Au(PMes_3)]SbF_6$	30	70
6	$[Au(L_{PO})]SbF_6$	>95	<5
7	$[Au(IPr)]SbF_6$/**Et_3N**[b]	–	**32**

IPr *t*BuXPhos L_{PO}

[a] ^{1}H NMR spectroscopy calculated **2**/**3** proportions. Complete conversion of **1** was observed in all cases. [b] 10 mol% of Et_3N was used. Mes = mesityl.

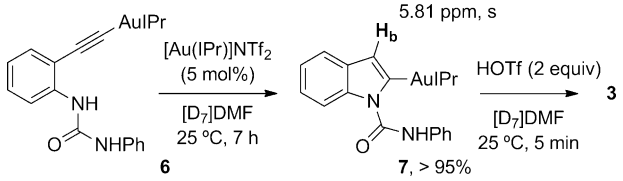
Exploring the latter phenomenon, we began by carrying out the catalytic heterocyclization of **1** in the presence of a base. Remarkably, for $[Au(IPr)]SbF_6$ (5 mol%), the cyclization in the presence of 10 mol% Et_3N afforded indole **3** as the sole product; a clear reversal from the base-free conditions (compare Table 1, entries 1 and 7). However, the reaction was sluggish, reaching only 32% conversion.

The acidity of the acetylenic C–H proton and the change in selectivity induced by the presence of a base raised the possibility of a gold–acetylide species as an intermediate in the 5-*endo*-dig ring closure of **1**. Therefore, the σ-gold complex of **1** was prepared and its behavior was evaluated. Tri-*tert*-butylphosphine gold–acetylide **4** was obtained by treating 2-ethynylaniline with $[AuCl(PtBu_3)]$ in the presence of Et_3N, followed by the reaction with phenylisocyanate. Complex **4** was stable in DMF and did not spontaneously undergo any reaction.[15] Nevertheless, in the presence of a catalytic amount of $[Au(PtBu_3)]NTf_2$[16] (NTf_2 = bis(trifluoromethanesulfonyl)imidate) in $[D_7]$DMF at 25 °C, complete conversion of **4** into new species **5** was observed. Compound **5** was identified by NMR spectroscopy as the 2-metalated indole (Scheme 3), which afforded **3** upon treatment with trifluoromethanesulfonic acid (HOTf).



Scheme 3. Synthesis of 2-aurated indole **5**.

The aurated indole **5** displays a ^{1}H signal at $\delta = 6.36$ ppm, assigned to the C3 hydrogen (H_b); the lack of H–H coupling for H_b was consistent with C2 metalation. No trace of compound **2** (or its aurated derivative) could be observed. To ascertain the involvement of two gold(I) entities in the formation of the indole ring, and to determine the order of the catalyst, a series of kinetic experiments[17] was carried out. The $[Au(PtBu_3)]NTf_2$-catalyzed reaction of urea **1** was, overall, second order with respect to gold.[18] For comparison, a similar kinetic study of the $[Au(IPr)]NTf_2$-catalyzed cyclization of **1** into dihydroquinazolin-2-one **2** was performed. Despite the reverse cyclization mode promoted by this later complex, the reaction showed the same order with respect to the catalyst (see the Supporting Information). To test whether the order of the catalyst is related to the activation mode of the $[Au(IPr)]NTf_2$ complex, σ-acetylide **6** was prepared. This acetylide could still progress into compound **2**, or the formation of indole **3** could prevail even in this case. It was found that acetylide **6** quantitatively provides the 2-aurated indole **7** (Scheme 4) in a similar fashion to the reaction of complex **4**. The identity of species **7** was confirmed by both NMR spectroscopy and X-ray diffraction (Figure 1; for color version, please see web).[19] Interestingly, the structure showed the expected linear coordination geometry (C-Au-C_{NHC} 176.7(3)°) and, in addition, a relatively short N1–H···Au distance that could be ascribed to an intramolecular N–H···Au hydrogen bond.[20]



Scheme 4. Synthesis of 2-metalated indole **7**

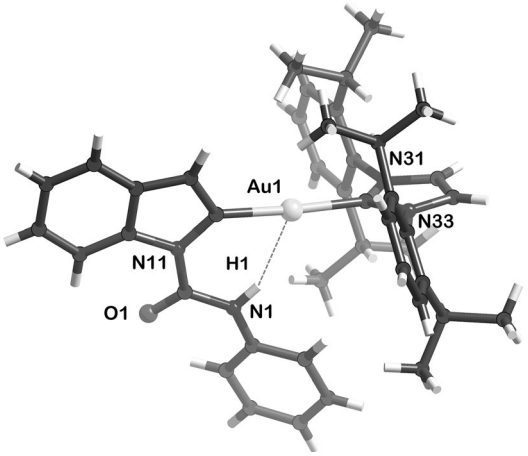


Figure 1. X-ray plot of one of the two independent molecules of **7** (H1···Au1 2.27(2) Å, N1···Au1 3.098(7) Å, and N1–H1···Au1 156(3)°).

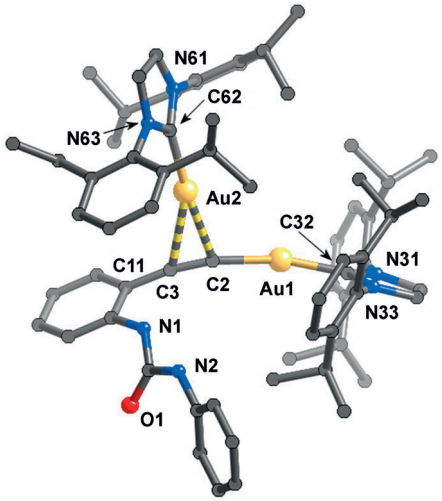


Figure 2. X-ray crystal structure of **8**, hydrogen atoms are omitted for clarity.

The experiments shown in Scheme 3 and 4 suggest that the intermediacy of a gold–acetylide[21] may indeed be responsible for the production of **3**, but involvement of this gold–acetylide in the formation of the quinazolin-2-one **2** appears to be unlikely. Moreover, these experiments also suggest that the classical π activation in the [Au(IPr)]NTf_2-catalyzed formation of **2** is not related to the rate-limiting step.[1b,3a,b,22–24]

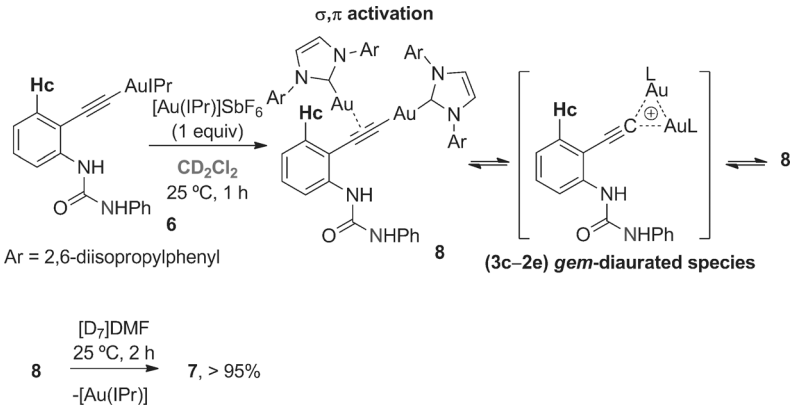
Next, we investigated whether the preformed gold–acetylides would undergo *N*-1 nucleophilic 5-*endo*-dig ring closure. In principle, the gold–acetylides should not undergo any nucleophilic attack, but coordination of a second cationic metal fragment[2,5b,7] is expected to generate a more electron-deficient σ,π-bimetallic species. This prompted us to study the role (if any) of **1**-σ,π-dinuclear species in the formation of compound **3**. A mixture of stoichiometric amounts of [Au(IPr)]SbF_6 and σ-acetylide **6** (selected for its higher stability) in CD_2Cl_2 cleanly afforded the bimetallic species **8**. This solvent appears to inhibit further evolution of **8** and allowed for its isolation (Scheme 5). Single crystals suitable for X-ray diffraction were obtained from the same solution at low temperature (Figure 2).[25]

The structure shows a dinuclear σ,π-acetylide gold compound, with a η^1,η^2-acetylide ligand σ bonded to one (IPr)Au fragment (Au1–C2 2.009(18) Å) and π bonded to a second (IPr)Au group (Au2–C2 2.21(3) Å, Au2–C3 2.44(3) Å).

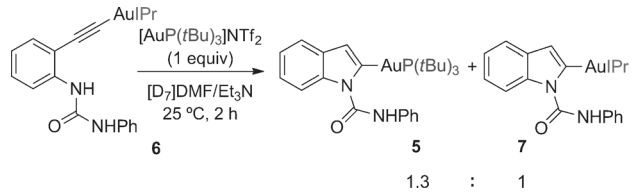
As with the previously described σ,π-gold complexes,[6] the two chemically distinct σ- and π-LAu fragments in complex **8** displayed, in CD_2Cl_2, a single set of ^1H and ^{13}C resonances, a fact attributable to their fast exchange, which might proceed via a more symmetrical *gem*-diaurated transition state. However, a solution of **8** in DMF afforded, after 2 h at 25 °C, > 95 % of the 2-aurated indole carboxamide **7**, lending support to the participation of the σ,π complexes in the formation of indole **3** (Scheme 5).

The conversion of **8** into the metalated indole **7** raised the possibility of tracing the fate of the individual LAu units in the cyclization process by means of a cross-over experiment.[26] Hence, IPrAu–acetylide **6** was subjected to one equivalent of [Au{P(*t*Bu)$_3$}]NTf_2 in [D_7]DMF at 25 °C, in the presence of Et_3N. After 2 h, full conversion of **6** into a 1.3:1 mixture of the 2-metalated indoles **5** and **7** was observed by ^1H NMR spectroscopy (Scheme 6). Despite the presence of a base, fast C3 protodeauration takes place at 25 °C. Once again, this result is taken as evidence of an exchange of the two LAu fragments, with the initially π-coordinated [Au(P*t*Bu$_3$)]$^+$ exchanging into the σ-acetylide position in the proposed σ,π species.

To prevent the rapid C3 protodeauration and to trap the possible C2,3-dimetallated indole, we followed a low-temperature (−30 °C) reaction involving acetylide **4** with [Au(P*t*Bu$_3$)]NTf_2 in the presence of Et_3N. After 4.5 h, the intensity of the signals corresponding to **4** diminished and

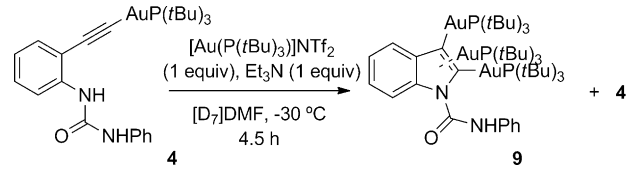


Scheme 5. Synthesis of σ,π-complex **8** and its conversion to aurated indole **7**.



Scheme 6. Cross-over experiment between acetylide **6** and [Au{P(*t*Bu)$_3$}]NTf$_2$.

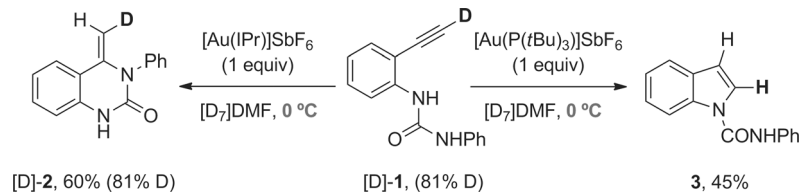
a new species **9**, with a similar NMR spectroscopy pattern to species **5**, was identified in the reaction mixture. This new species lacked protons at both the C2 and C3 positions. The presence of [Au(P*t*Bu$_3$)] at the C3 position of **9** reinforces the idea of the existence of an alternative non-*gem* evolution of the σ,π complex **8** into compound **3**.[27] It is worth noting that MALDI spectrometry revealed the presence of three LAu fragments (Scheme 7). Unfortunately, even though the X-ray structure of



Scheme 7. Newly identified polyaurated species in the low-temperature stoichiometric reaction of **4**.

9 also shows three gold atoms, all attempts to obtain a high-quality[28] single crystal of this complex failed.

The fate of the acetylenic C–H proton was determined by using urea [D]-**1** (81% D), deuterated at the terminal alkyne. Compound [D]-**1** was subjected to 5 mol% of [Au(P*t*Bu$_3$)]SbF$_6$ at 60 °C in DMF. In a similar fashion to the non-labeled substrate, the reaction gave a 1:4 mixture of **2** and **3** with no deuterium being incorporated into the products. A full D/H exchange was also observed in the [Au(IPr)]$^+$-catalyzed reaction. To address the possibility of the D-label loss through a misleading D/H scrambling with acidic protons in the medium, the reactions were repeated at 0 °C. Stoichiometric amounts of LAu$^+$ were employed to achieve measurable conversions. Indeed, when [D]-**1** was subjected to [Au(IPr)]SbF$_6$ at 0 °C, a 60% conversion into [D]-**2** (81% D), with full retention of the label, was observed. Conversely, the experiment carried out in the presence of [Au(P*t*Bu$_3$)]SbF$_6$ gave 40% of compound **3**, which exhibited complete loss of deuterium at both the C2 and C3 positions (Scheme 8).



Scheme 8. Low-temperature reactions with [D]-**1**.

These labeling experiments ascertain that π coordination of [Au(IPr)]$^+$ activates the alkyne in such a way that 6-*exo*-dig nucleophilic attack occurs faster than the formation of the σ gold–acetylide. Accordingly, the label is preserved in compound [D]-**2** and the intermediacy of an σ-acetylide species can be discarded in the formation of quinazolin-2-one **2**, as previously inferred from the reactivity of the preformed acetylide **6**. In contrast, when the alkyne is activated by [Au(P*t*Bu$_3$)]SbF$_6$, the loss of the acetylene C–H proton in the formation of the σ,π-gold complex becomes favored with respect to the direct nucleophilic attack, giving rise to the indole **3** as the major product.

A plausible explanation for the divergent reaction pathways found for [Au(IPr)]$^+$ and [Au(P*t*Bu$_3$)]$^+$ might have its origin in the different features of the corresponding initial π complexes. The bulky IPr ligand, with a high % V_{buried}[29] value (44.5) and a short gold–ligand distance (Au–$C_{carbene}$ 1.942 Å),[30] could interfere with the aryl terminus of **1** (Figure 3a), thus forcing

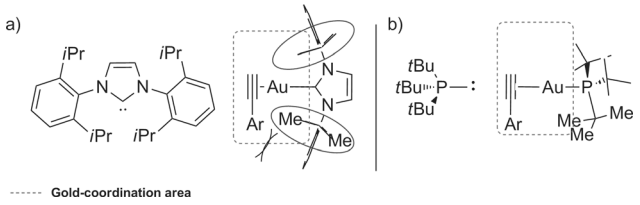


Figure 3. Comparative representation of the coordination of **1** to [Au(IPr)]$^+$ and [AuP(*t*Bu$_3$)]$^+$.

a more asymmetric alkyne activation, leading to a greater build-up of positive charge at the benzylic carbon in **1** and, consequently, a faster 6-*exo* attack with preferential formation of compound **2**. In contrast, the steric bulk of (P*t*Bu$_3$)[31] is located away from the alkyne coordination area (Figure 3b). This could result in a negligible slippage of the metal center and a diminished ability to accelerate the 6-*exo*-dig nucleophilic attack, thus allowing the formation of the dinuclear σ,π-gold complex.

Accordingly, other ligands that are highly hindered[32] or that have a high % V_{buried} value would be expected to display behavior similar to that of IPr. As proof of concept, *t*BuXPhos (XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) and tris(2,4-di-*tert*-butylphenyl)phosphite were tested. In both cases, the cyclization of **1** led to compound **2** with 96 and 92% yield, respectively. Indeed, the low-temperature (0 °C) reactions with [D]-**1** in the presence of these ligands proceeded through the 6-*exo*-dig cyclization[33] with retention of the deuterium label.

In summary, we have isolated and identified by NMR spectroscopy, X-ray diffraction, or MALDI spectrometry several aurated reaction intermediates (σ-gold, σ,π-gold, and other gold polynuclear species) involved in the

heterocyclization of 1-(*o*ethynylaryl)urea **1**. The behavior of these species and cross-over or deuterium-labeling experiments in the divergent 6-*exo*- or 5-*endo*-cyclization pathways of compound **1** reveal ligand control in the simultaneous or alternative π- and σ,π-activation modes of terminal alkynes in gold-catalyzed reactions. The results presented herein, including a preliminary kinetic study, contribute to a better understanding of the mechanisms of gold(I) catalysis. Work is in progress to determine the effect of different ligands and counterions on the kinetic behavior and reactivity of alkynes with cationic gold(I) complexes.

Acknowledgements

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Keywords: acetylides · alkynes · dual activation · gold intermediates · ligand effects

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[19] CCDC-953982 (**7**) and CCDC-953983 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[25] Relevant data for the crystal structures of **7** and **8** is given in the Supporting Information.

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[28] The structure of **9** shows three gold atoms bonded to the indole fragment, as proposed in Scheme 7; however, extensive disorder of a large part of the molecule rendered the structure unsatisfactory and, therefore, quantitative aspects are not discussed (see the Supporting Information for unit-cell details). The incorporation of three LAu cation units could result in the formation of the anticipated C2,3-diaurated indole

(through σ,π activation), followed by the coordination of an extra LAu owing to its high basicity.
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[33] In these two cases, the corresponding C_{sp}-deuterated benzoxazine derivative, the 6-*exo*-dig ring closure product of the urea oxygen, was also detected (see the Supporting Information for additional details).

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