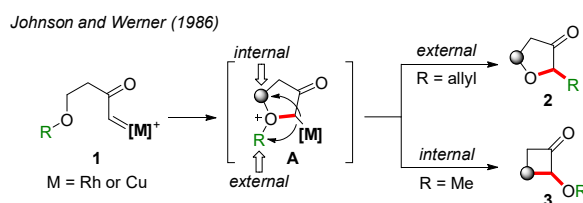


# Alkoxy migration onto $\alpha$ -Imino Gold Carbenes for Constructing Propellane-Type Indolines

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**Abstract:** We developed a new reaction entity of  $\alpha$ -imino gold carbenes involving alkoxy migration. The reaction would proceed through oxonium ylide formation by intramolecular addition of an alkoxy group, carbon–oxygen bond cleavage, and carbon–carbon bond formation. We achieved an efficient gold-catalyzed synthesis of indoline–propellanes via a one-pot sequence by using ethylene glycol as a trapping reagent.



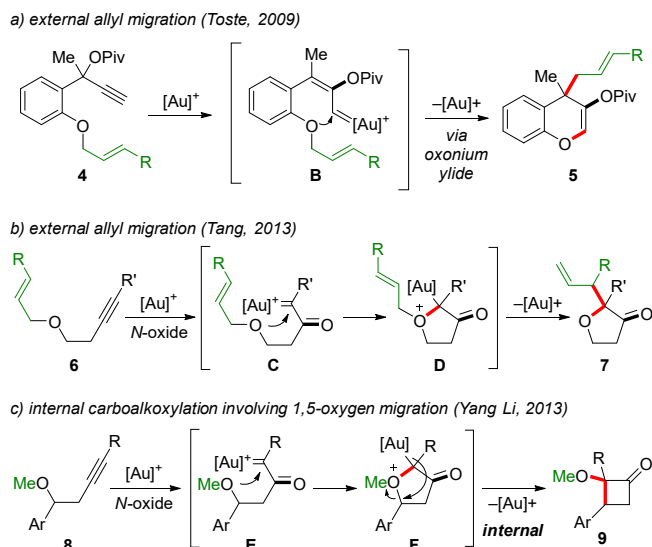
**Scheme 1.** External and internal oxonium ylide rearrangements via copper and rhodium carbenes.

## Introduction

High proportions of tetrahedral carbons and stereocenters correspond to high molecular complexity, which substantially enhances various physicochemical properties that are critical for drug discovery programs. Thus, synthetic strategies that can rapidly increase molecular complexity—leading to expansion of chemical space and opportunities to enhance physicochemical properties—are highly desirable.<sup>[1–4]</sup> Indoline-type propellane scaffolds are an attractive target in cascade strategies because of their three-dimensional architecture and diverse biological relevance.<sup>[5–9]</sup>

A special advantage of gold-catalyzed functionalization is the ability to assemble many elementary reaction steps in a highly efficient cascade sequence. Transformations that lead to rearrangements with a tethered nucleophilic functional group can rapidly generate multiple cyclic frameworks with high  $sp^3$ -content and an increasing number of stereocenters in a single operation. Such features render homogenous gold catalysis attractive for optimizing molecular complexity.<sup>[10–21]</sup> We expect that gold carbene chemistry in conjunction with rearrangement/migration offers an efficient approach to propellane-type scaffolds.

Johnson and Werner independently reported pioneering studies on transition metal carbene chemistry that include a rearrangement/migration step.<sup>[22,23]</sup> In one of their investigations, copper and rhodium carbenes were viable intermediates for intramolecular interception of a tethered allyl ether oxygen, affording oxonium ylide **A** ( $R = \text{allyl}$ ), which undergoes external rearrangement to afford furanone **2** (Scheme 1). When using methyl ethers ( $R = \text{Me}$ ), less reactive as the external migrating group, the alternate internal rearrangement affords cyclobutanones **3** via ring contractive C–C bond formation and oxygen migration (carboalkoxylation). To date, only limited examples of such internal migration have been reported.<sup>[24–26]</sup>

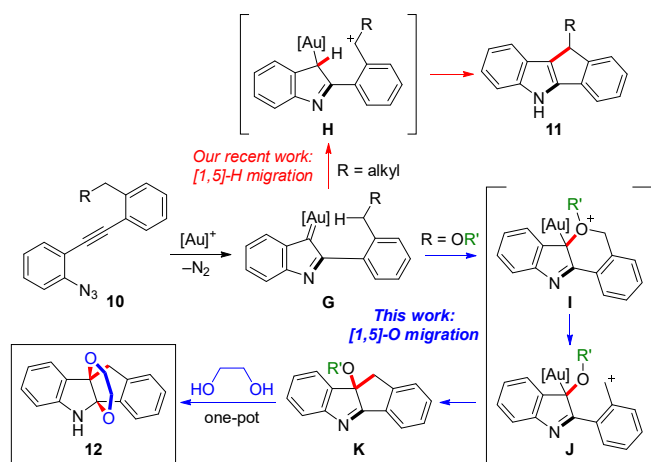


**Scheme 2.** Background for the reaction of ethers in the presence of gold carbenes.

Analogous migrations on gold carbenes are also exotic. Toste *et al.* obtained benzopyrans **5** from allyloxy-substituted phenyl propargyl esters **4** via gold carbene **B** (Scheme 2a). This carbene facilitates intramolecular trapping with the allylic ether oxygen as a nucleophile to form oxonium ylide, which undergoes external allyl transfer to afford **5**.<sup>[27]</sup> Tang and coworkers investigated a related reaction (Scheme 2b):<sup>[28]</sup> generation of an  $\alpha$ -oxo gold carbene **C** from homopropargyl allyl ethers **6** with an oxidant (such as 3,5-dichloropyridine *N*-oxide). After forming an oxonium ylide **D**, an external allyl migration afforded dihydrofuranones **7**. Notably, these reactions do not facilitate internal migration with an oxygen migrating step. On the other hand, Li and coworkers reported 1,5-oxygen migration onto gold carbenes via an internal

process (Scheme 2c). The  $\alpha$ -oxo gold carbene **E**, generated from homopropargylic ethers **8** and 8-ethyl quinoline *N*-oxide, afforded the corresponding substituted cyclobutanones **9** via rearrangement of oxonium ylide **F** bearing a methyl ether moiety.<sup>[29]</sup> However, oxygen migration on  $\alpha$ -imino gold carbenes is unprecedented to our best knowledge.

In our previous work, we reported that hydride migration on  $\alpha$ -imino gold carbenes is practical for generating polycyclic indoles **11** (Scheme 3).<sup>[30-32]</sup> Based on extensive research by Gagosz<sup>[33-35]</sup> and Davies,<sup>[36]</sup> introducing the oxygen functional group facilitates hydride transfer to electrophilic alkynyl gold complexes. Accordingly, we attempted to enhance the hydride transfer step on gold carbenes, via introducing an alkoxy group at the benzylic position, by stabilizing the benzylic cation species **H** (Scheme 3). However, based on a broad investigation by Toste and Rhee *et al.*,<sup>[37-43]</sup> carboalkoxylation of alkynyl gold complexes are also a viable pathway; thus, introducing a tethered alkoxy group could reveal a second reactivity pattern of  $\alpha$ -imino gold carbene complexes **G**: oxonium ylide **I** originating from a nucleophilic attack of the ether oxygen could facilitate oxygen migration to generate the tetracyclic product **K** through C–C bond formation from benzyl cation species **J**. In this study, we reveal that a gold-catalyzed reaction of azido alkynes **10** bearing an alkoxy group (R = OR') generates propellane-type indolines **12** involving unprecedented carboalkoxylation of  $\alpha$ -imino gold carbene **G**, followed by one-pot trapping of the corresponding 3*H*-indole intermediate **K** with glycol. Intramolecular entrapment with the preinstalled glycol ether (R' = CH<sub>2</sub>CH<sub>2</sub>OH) in a single cascade is also presented.



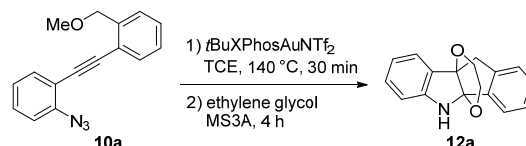
**Scheme 3.** Our works: 1,5-*H* migration and 1,5-*O* migration (this work).

## Results and Discussion

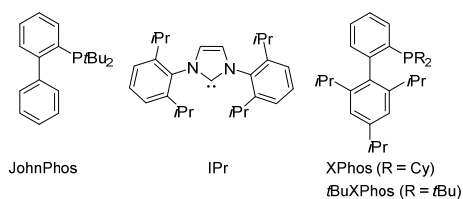
We chose benzyl methyl ether **10a** for optimizing the reaction conditions. Subjecting substrate **10a** to *t*BuXPhosAuNTf<sub>2</sub> in noncoordinating tetrachloroethane (TCE) for 30 min afforded full conversion; however, chromatographic purification led to decomposition of the product. Expecting that this unstable product would be the aforementioned imine **K**, we then considered trapping with a bis-nucleophile to form the aminal. Thus, after full consumption of starting material **10a**, we added ethylene glycol and MS3A (molecular sieves 3A) to the reaction mixture, leading to formation of propellane-type product **12a** in

58% yield after 3 h (Table 1, entry 1). Variation from the optimized conditions revealed that JohnPhos, *t*Bu<sub>3</sub>P, IPr, and XPhos were less effective; we observed decreased yields of **12a** (5% to 30%, entries 2–5). In contrast, bulky ligand *t*BuXPhos had a substantial impact on the reaction outcome, affording the desired product **12a** in a fair yield of 45% (entry 6). A brief investigation of the counter anion effect and reaction temperature revealed that using AgNTf<sub>2</sub> at 90 °C improved the yield to 51% (entry 8); the reaction at 140 °C was most effective (58%, entry 1). The reaction without using MS3A decreased the yield to 6% (entry 9), suggesting that MS3A facilitates the aminal formation step, presumably by trapping the generated methanol.

**Table 1.** Optimization of the reaction condition



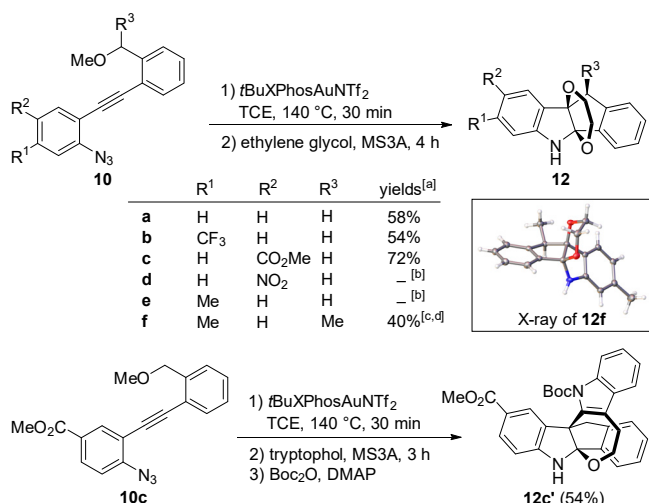
Entry <sup>[a]</sup>	Variation from entry 1	Yield (%) <sup>[b]</sup>
1	none (optimized conditions)	58 <sup>[c]</sup>
2	JohnPhosAuCl/AgSbF <sub>6</sub>	30 <sup>[d]</sup>
3	<i>t</i> Bu <sub>3</sub> PAuCl/AgSbF <sub>6</sub> , DCM	22
4	IPrAuCl/AgAbF <sub>6</sub> , DCM, rt	5 <sup>[d]</sup>
5	XPhosAuCl/AgSbF <sub>6</sub>	20
6	<i>t</i> BuXPhosAuCl/AgSbF <sub>6</sub> , DCM, rt	45
7	<i>t</i> BuXPhosAuCl/AgNTf <sub>2</sub> , DCM, rt	47
8	90 °C	51
9	without MS3A	6 <sup>[d]</sup>



[a] The ligand structures are shown above. [b] Yields were determined by <sup>1</sup>H-NMR analysis with triphenylmethane as an internal standard. [c] Isolated yield. [d] Concomitant black tar formation.

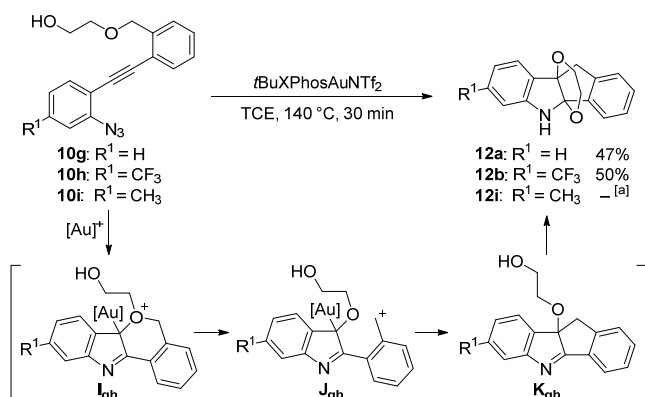
Based on the optimized conditions, we investigated the reaction scope (Scheme 4). When an electron-withdrawing CF<sub>3</sub> group was appended *meta* to the azido group (R<sup>1</sup> = CF<sub>3</sub>), the desired product **12b** formed in 54% yield. When introducing a moderately electron-withdrawing methoxycarbonyl group as R<sup>2</sup>, the yield improved to 72%, affording **12c**. However, appending a nitro group (R<sup>2</sup> = NO<sub>2</sub>) and a methyl group (R<sup>1</sup> = Me) on the aryl azide moiety resulted in a complex mixture without formation of the desired products **12d** and **12e**, respectively, even under milder reaction conditions (e.g. at room temperature); presumably because of rapid polymerization between the aryl group and gold carbene. Interestingly, simultaneous attachment of electron-donating methyl groups as R<sup>1</sup> and R<sup>3</sup> substituents afforded sterically congested **12f** in 40% yield, with a relative *cis*

configuration between the attached glycol and benzylic methyl group. We unambiguously determined the structure of **12f** by X-ray analysis (Scheme 4). Because the compound **12f** exhibited a disposition to decompose during the purification, we introduced an additional methyl group to determine the isolated yield of **12f**. The applicability of this reaction was demonstrated by using tryptophol as a C, O-bis-nucleophilic trapping reagent to afford an indole-fused indoline-type propellane **12c'** in 54% yield.



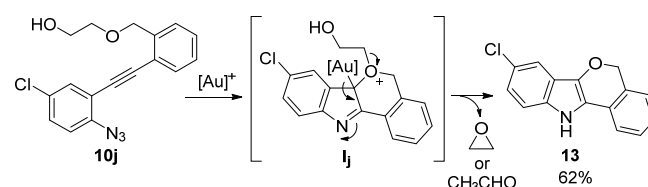
**Scheme 4.** Scope and limitations. [a] Isolated yields. [b] Black tar formation. [c] Isolated as the *N*-methylated form. [d] The relative stereochemistry was determined by X-ray analysis.

Next, we designed a cascade process that does not require adding ethylene glycol, by introducing ethylene glycol as the ether moiety (Scheme 5). The gold-catalyzed reaction of glycol-tethered substrates **10g** and **10h** afforded **12a** and **12b** in 47% and 50% yield, respectively, whereas the methylated derivative **10i** resulted in black tar formation. This cascade reaction would proceed through formation of oxonium ylide **I<sub>gh</sub>**, followed by C–C bond formation and amination through **J<sub>gh</sub>** and **K<sub>gh</sub>**. At the present stage, the possibility that the amination step proceeds from **I<sub>gh</sub>** or **J<sub>gh</sub>** cannot be excluded.



**Scheme 5.** Intramolecular cascade sequence for the indoline-type propellane formation reaction. [a] Black tar formation.

Surprisingly, attachment of a chlorine group *para* to the azide position (**10j**) afforded indole-fused benzopyran **13** in 62% yield,<sup>[44]</sup> without forming the desired propellane product **12** (Scheme 6). A rationale for this result can be found in the deaurative indole formation from **I<sub>j</sub>** being facilitated by the electron-withdrawing chlorine group at the *para* position of the imine nitrogen, concomitant with cleavage of the glycol moiety via deprotonation by an anionic indole species. This result supports the formation of oxonium ylides **I** in this reaction system.



**Scheme 6.** Reaction of chlorinated substrate **10j**. Reaction conditions: *t*BuXPhosAuNTf<sub>2</sub>, TCE, 140 °C, 30 min.

## Conclusion

In summary, we have demonstrated a new reaction entity of an  $\alpha$ -imino gold carbene that undergoes stepwise carboalkoxylation through addition of methyl ether and formation of oxonium ylide. These can be further functionalized in a one-pot or intramolecular cascade sequence to afford propellane-type indolines. The formation of oxonium ylides is supported by the production of indole-fused benzopyran when using a chlorine-substituted substrate. This method will contribute to covering chemical space of three-dimensional indole-based polycyclic compounds.

## Acknowledgements

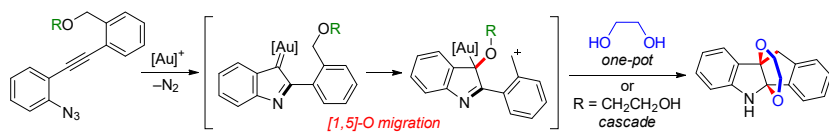
This work was supported by the JSPS KAKENHI (grant numbers 23H02603 and 22K19028), the Research Support Project for Life Science and Drug Discovery [Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)] from AMED (grant numbers JP22ama121034 and JP22ama121042), and the Naito Foundation.

**Keywords:** Carbene • Carboalkoxylation • Gold catalysis • Indoline • Propellane

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## Entry for the Table of Contents



Alkoxy migration onto  $\alpha$ -imino gold carbene: we developed an efficient gold-catalyzed synthesis of indoline-propellanes that proceeds through 1,5-alkoxy migration, cyclization, and external/internal trapping with ethylene glycol.