Gold(I)-Catalyzed Benzylic C(sp^3)-H Functionalizations: Divergent Synthesis of Indole[*a*]- and [*b*]-Fused Polycycles

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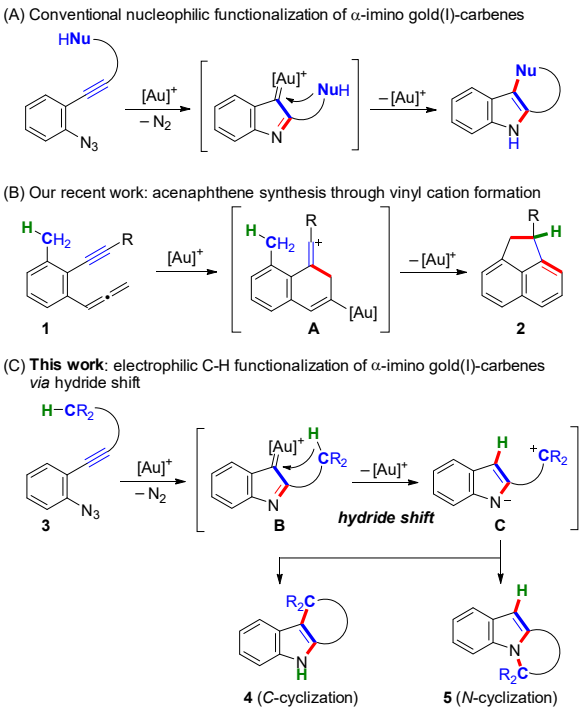
Supporting information: Reaction optimization and experimental procedures, including characterization data, for all new compounds.

Abstract: Phenyl azides substituted by an (alkylphenyl)ethynyl group facilitate benzylic sp^3(C-H) functionalization in the presence of a JohnPhosAu catalyst, resulting in indole-fused tetra- and pentacycles via divergent *N*- or *C*-cyclization. The chemoselectivity is influenced depending on the counter-anion, the electron density of the α-imino gold(I) carbene, and the alkyl groups stabilizing the benzylic carbocation originating from a 1,5-hydride shift. An isotopic labeling experiment demonstrates the involvement of an indolylgold(I) species resulting from a tautomerization that is much faster than the deauration. The formation of a benzylic sp^3(C-H) functionalization leading to an indole-fused seven-membered ring is also demonstrated.

Studies of C(sp^3)-H functionalizations have experienced a phenomenal growth in the field of organic synthesis. A key advantage of these transformations is found in their high atom economy originating from the omission of pre-functionalization steps to form new C–C or C–X (X = N, O, or halogen) bonds. Their integration in cascade processes is of high synthetic value for the construction of complex molecules, which allows access to untapped chemical space.[1-8] Although the development of cascade reactions involving hydrogen atom transfer[9-12] or carbene/nitrene insertion[13,14] is making great strides, functionalizations via hydride abstraction in an internal redox process are developing at a comparatively sluggish rate.[15-21]

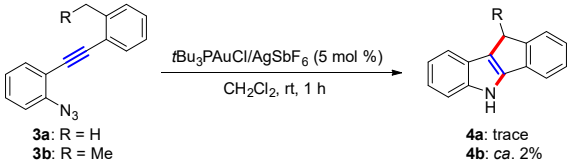
The emerging growth of gold catalysis has played an important role in cascade reactions involving a C(sp^3)-H functionalization step.[22] In addition to the high π-acidity of gold with an extraordinary selectivity towards alkyne activation for diverse nucleophilic addition reactions, the ability of gold to engage in electron back-donation for the stabilization of cationic intermediates results in dual reactivity modes.[23-30] In 2005, Toste and co-workers demonstrated that exposing homopropargyl azides to a gold catalyst causes the formation of highly electrophilic α-imino gold carbenes to yield substituted pyrroles via a 1,2-hydride shift.[31] This concept was further extended by Gagosz and Zhang to cascade cyclizations,[32,33] in which an umpolung reactivity for indole was established for unusual nucleophilic functionalizations at the C3 position. Based upon this reactivity, multiple polycyclic indole syntheses have been reported by the groups of Ye,[34-38] Xu,[39] Hashmi,[40,41] and by our group[42-47] (Scheme 1A).[48] Although the involvement of C-H functionalization via a 1,5-hydride shift-based internal redox process has been observed for gold complexes with keteniminium,[49] furyl,[50] allenyl,[51,52] alkynyl,[53-56] vinyl cation,[57] unfunctionalized carbene,[58] and oxo carbene species,[59] these processes are unprecedented among α-imino gold carbenes.[60-62] The occurrence of 1,5-migrations onto gold carbene centers remains disproportionately rare compared with the occurrence of 1,2-migrations.[63]

In our ongoing endeavors in reaction development using gold catalysis,[42-47] we previously reported the synthesis of acenaphthenes **2**, which can be rationalized by a 1,5-hydride shift on a vinyl cationic gold complex **A** generated from allenynes **1** (Scheme 1B).[64,65] From this vantage point, we envisioned that a 1,5-hydride shift leading to electrophilic α-imino gold carbene functionalization should also be conceivable in gold-catalyzed electrophilic C-H functionalization, leading to fused indoles such as **4** (Scheme 1C), which often exhibit biologically intriguing properties.[21] Herein we present our research to show that alkynylated arylazides are suitable substrates for gold-catalyzed cascade cyclizations to form indeno[*b*]-type fused indoles **4** via a 1,5-hydride shift on α-imino gold carbenes and *C*-cyclization. The selective formation of indeno[*a*]-type fused indoles **5** through *N*-cyclization is also presented.



Scheme 1. Related research and this work.

At the outset of our investigation, the reaction of **3a** (R = H) with *t*Bu$_3$PAuCl/AgSbF$_6$ was investigated. We expected that a methyl group adjacent to the phenyl-alkyne would induce sufficient benzylic activation for a 1,5-hydride shift (Scheme 2). Unfortunately, the crude ^{1}H NMR spectrum displayed the characteristics of a polymer, whereas only a trace amount of the desired product **4a** was suspected. To enhance the hydride donor reactivity, we attempted to stabilize the corresponding benzylic cation with an additional methyl group. Indeed, when the ethylbenzene-type substrate **3b** was exposed to the gold catalyst, the desired product **4b** was obtained, although in approximately 2% yield.



3a: R = H
3b: R = Me

4a: trace
4b: *ca.* 2%

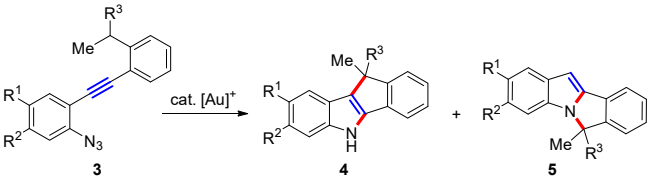
Scheme 2. Initial investigations.

Encouraged by these results, we next optimized the reaction conditions for the synthesis of tetracyclic indoles using **4b** and several ligands including XPhos, JohnPhos, DavePhos, IPr, BrettPhos (see Table 1 footnote), and found that the reaction of **3b** using JohnPhosAu(MeCN)SbF$_6$ (5 mol %) in 2 mM tetrachloroethane (TCE) at 90 °C for 0.5 h gave the *C*-cyclization product **4b** and an additional *N*-cyclization product **5b** with a 63% combined isolated yield and a product ratio of **4b**:**5b** = 85:15 (for optimization process, see the Supporting information).

We moved on to explore the reaction scope (Table 1). The application of the electron-donating methoxy group **3c** resulted in a pronounced decrease of the yield (**4c**, 20%), with concomitant amounts of insoluble black tar originating from intermolecular processes (entry 3). The introduction of an electron-withdrawing chlorine group for R^1 led to the emergence of the dominant *N*-cyclization (**4d**:**5d** = 45:55) in a combined yield of 55% (entry 4). The structure of **4d** was unambiguously confirmed by X-ray analysis (Figure 1). Similarly, the introduction of the CF_3 group **3e** gave 53% of an isomeric mixture with a product ratio of **4e**:**5e** = 43:57 (entry 5). While optimizing the reaction conditions, we suspected that NaBARF induced the formation of the *N*-cyclization product (entry 2). Indeed, this anticipation was verified by an altered product ratio (**4e**:**5e** = 30:70) with good yield (81%, entry 6). An analogous result with an increased *N*-cyclization selectivity was observed when the electron-withdrawing NO_2 derivative was used (**4f**:**5f** = 42:58, entry 7) in 70% yield. The introduction of an NO_2 group for R^2 (**3g**) had a comparable effect on the yield (65%) and selectivity (**4g**:**5g** = 34:66, entry 8) as the use of **3f** did. In the presence of NaBARF, this ratio shifted to 1:>99; however, this shift in selectivity occurred at the expense of the yield (15%) and the reaction rate (entry 9).

Next, improvement of the *N*-cyclization was attempted. Exposure of the derivative **3h** to an isopropylbenzene moiety as the hydride donor (entry 10) has proven to be significantly advantageous for the *N*-cyclization, giving a ratio of **4h**:**5h** = 18:82 in 65% combined yield. Excellent chemoselectivity (**4h**:**5h** = 1:>99) and 57% yield was eventually accomplished when JohnPhosAuCl/NaBARF was employed, highlighting the impact of the counter-anion effect (entry 11). Exposure of the chlorine derivative **3i** to JohnPhosAuCl/NaBARF gave **5i** in 80% yield with striking 1:>99 selectivity (entry 12). The trifluoromethyl derivative **3j** was likewise chemoselectively converted to the *N*-cyclization product **5j** with 76% combined yield (entry 13). When the electron-withdrawing NO_2 group was inserted for R^2, the selectivity for the C–N bond remained outstanding (**4k**:**5k** = 1:>99, entry 14), with a prolonged reaction time of 3 h. The solid-state structure of **5k** confirmed the molecular connectivity (Figure 1). A prolonged reaction time was also observed for **3g** in the presence of NaBARF, suggesting that a decreased electron density of the substrate might reduce the interaction with the JohnPhosAuBARF complex, and/or the nucleophilicity required for the second cyclization to decrease the reaction rate. In light of these results, we concluded that the combined effects of electron-withdrawing groups on the aryl moiety, weakly coordinating counter-anions, and inductive stabilization of the carbocation contributed incrementally to a selective *N*-cyclization. In essence, these multi-causal factors affect the reactivity of the end groups.

Table 1. Substrate scope.[a]



3 **4** **5**

Entry	Subst.	R^1	R^2	R^3	Yield[b]	Ratio[c]
1	**3b**	H	H	H	63	85 : 15
2[d]	**3b**	H	H	H	50	67 : 33
3	**3c**	OMe	H	H	20	>99 : 1
4	**3d**	Cl	H	H	55	45 : 55
5	**3e**	CF_3	H	H	53	43 : 57
6[d]	**3e**	CF_3	H	H	81	30 : 70
7	**3f**	NO_2	H	H	70	42 : 58
8	**3g**	H	NO_2	H	65	34 : 66
9[d]	**3g**	H	NO_2	H	15	1 : >99
10	**3h**	H	H	Me	65	18 : 82
11[d]	**3h**	H	H	Me	57	1 : >99
12[d]	**3i**	Cl	H	Me	80	1 : >99
13[d]	**3j**	CF_3	H	Me	76	1 : >99
14[e]	**3k**	H	NO_2	Me	66	1 : >99

[a] Unless otherwise stated, the reaction was conducted under the standard conditions: JohnPhosAu(MeCN)SbF$_6$ (5 mol %) and TCE (2 mM) at 90 °C for 0.5 h. [b] Combined isolated yield. [c] Ratio determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] JohnPhosAuCl/NaBARF (10 mol %) was employed and the reaction time was 4 h. [e] JohnPhosAuCl/NaBARF (10 mol %) was employed and the reaction time was 3 h. BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

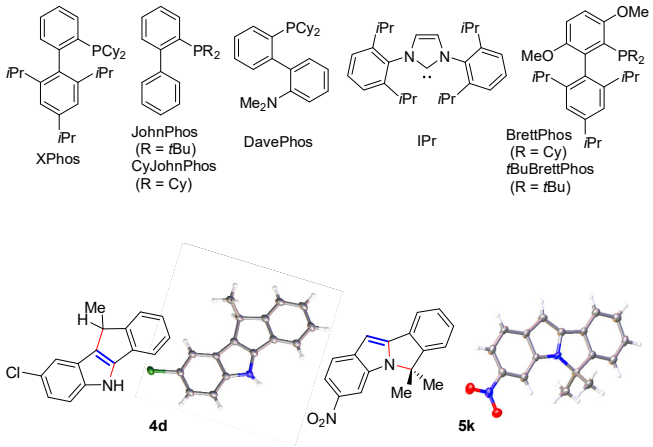
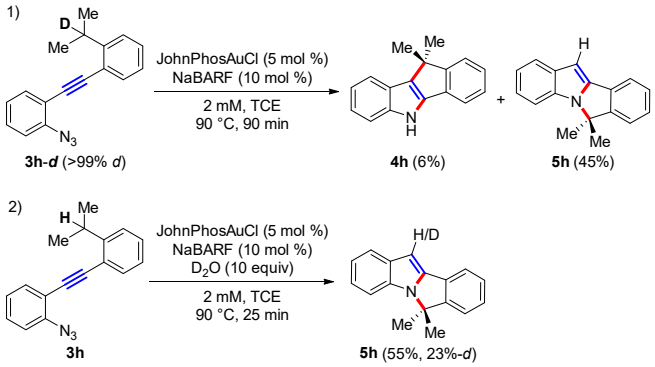


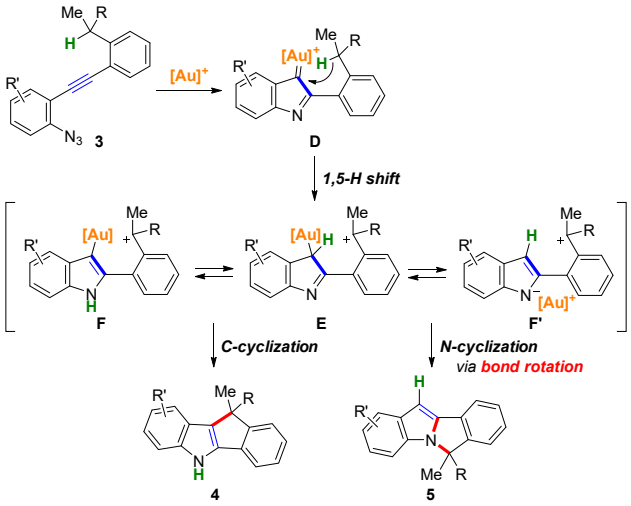
Figure 1. Solid-state structures of indeno[*b*]- and indeno[*a*]-fused indoles.

To gain insight into the benzylic C(sp^3)-H functionalization, an isotopic labeling experiment was carried out (Scheme 3). The gold(I)-catalyzed cascade cyclization of isotope-labeled **3h-*d*** (>99%-*d*) resulted in the complete loss of the deuterium labeling, affording **4h** (6%) and **5h** (45%) after a prolonged reaction time (90 min; Scheme 3, eq 1). This observation implies that a D/H exchange is involved in one of the elementary steps in the cascade sequence. Conducting the reaction of the non-labeled substrate **3h** in the presence of D_2O as a deuteron source gave **5h-*d*** in 55% yield with 23% deuterium incorporation (Scheme 3, eq 2), indicating that the H/D atom at the indole 3 position can be exchanged to D/H in the presence of D_2O, HDO, or H_2O in the reaction mixture.



Scheme 3. Isotopic labeling experiment.

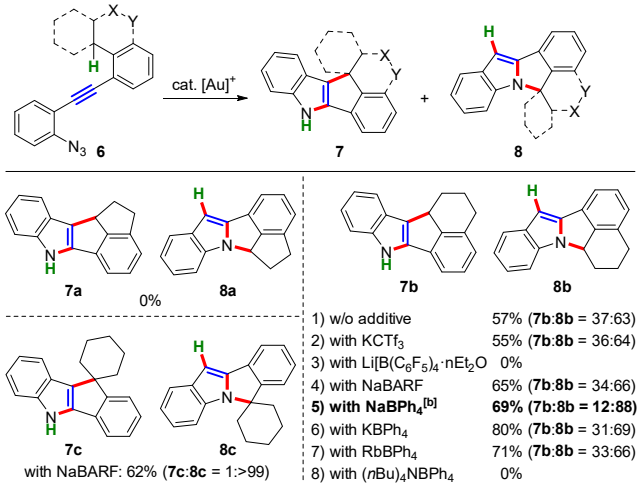
Based on these results, a proposed mechanism is outlined below (Scheme 4). When azido alkyne **3** is subjected to the gold catalyst, the α-imino gold carbene **D** is generated in an initial gold-catalyzed acetylenic Schmidt reaction. The following 1,5-hydride shift from the benzylic position on the gold carbene generates the corresponding carbocation **E**, which is in a state of equilibrium between the aromatized intermediates **F** and **F'**. Deaurative carbon-carbon bond formation affords the *C*-cyclization product **4**, whereas a bond rotation and C-N bond formation gives the *N*-cyclization product **5**.



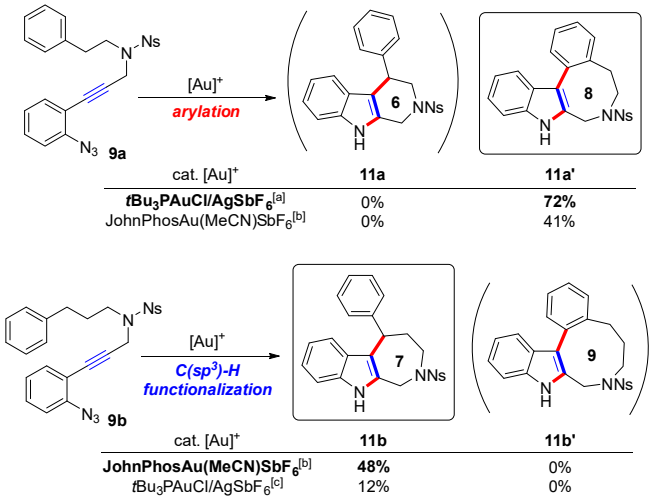
Scheme 4. Proposed mechanism of the product bifurcation based on the 1,5-hydride shift.

Considering the result of the isotope experiments in which the deuterium labeling at the benzylic position was completely lost, we assume that the interconversion between **E** and **F** would be significantly faster than the cyclization. If the C-N bond formation without forming **F** is sufficiently fast, the *N*-cyclization product **5** would carry a deuterium atom at the 3-position. The deuterated substrate **3h-*d*** produced a small amount of the *C*-cyclization product **4h** (6%), in striking contrast to the reaction of **3h**, which afforded exclusively the *N*-cyclization product **5h** (entry 11, Table 1). These results might suggest that the *N*-cyclization occurs preferentially through the aromatized intermediate **F**, the formation of which requires C-H/D bond cleavage. The higher *C*-cyclization selectivity of the ethylated substrate **3b** (R = H) over the isopropyl precursor **3h** (R = Me) can be explained by the relatively high reactivity of the carbocations **E** and **F**/**F'** derived from **3b**. This high reactivity facilitates the *C*-cyclization before the bond rotation. Similarly, the substituent effect on the aromatic ring, whereby the electron-withdrawing R' group increased the ratio of the *N*-cyclization product, can be understood by the decreased nucleophilicity of the indole moiety of the carbocations **E** and **F**/**F'**, providing sufficient opportunity for bond rotation. The counter-anion effect can be explained through the decreased coordination ability of BARF as compared with SbF_6, resulting in a favored intramolecular ionic interaction with the indole aza-anion, thus increasing the selectivity for *N*-cyclization.[66] At this stage, an alternate mechanism involving *C*-cyclization via insertion cannot be ruled out.[67-70]

Scheme 5. Synthesis of fused-ring derivatives.[a]



[a] Unless otherwise stated, the reaction was conducted under the standard conditions: JohnPhosAu(MeCN)SbF_6 (5 mol %) and TCE (2 mM) at 90 °C for 0.5 h. [b] $NaBPh_4$ (50 mol%) was employed. Tf = triflyl (CF_3SO_2).



Scheme 6. Selectivity study between arylation and C(sp^3)-H functionalization. Reaction conditions: [a] tBu$_3$PAuCl (5 mol %), $AgSbF_6$ (10 mol %), dichloromethane (2 mM), rt, 30 min. [b] JohnPhosAu(MeCN)SbF_6 (5 mol %), TCE (2 mM), 90 °C, 15 min. [c] tBu$_3$PAuCl (5 mol %), $AgSbF_6$ (10 mol %), dichloromethane (0.2 mM), rt, 3 h.

The benzylic methylene C-H bond of the carbocyclic substrate **6** was next investigated (Scheme 5). When using the indane derivative **6a**, polymerization was the sole reaction observed, and the desired products **7a** and **8a** were not detected. Considering the highly strained ring system of the tricyclic indene rings fused with a five-membered ring in **7a** and **8a**, we subsequently examined the reaction of the tetralin derivative **6b**. The desired formation of the indole-fused pentacycles **7b** and **8b** was successfully achieved via edge-fusion with a yield of 57% (**7b**:**8b** = 37:63). A brief survey of the reaction conditions has revealed that the use of $NaBPh_4$ significantly improved the selectivity towards *N*-cyclization (**7b**:**8b** = 12:88), whereas the addition of $KCTf_3$, $LiB(C_6F_5)_4$, NaBARF, $KBPh_4$, $RbBPh_4$, and $(n\text{Bu})_4NBPh_4$ was less effective.[71] The decomposition of tetraphenylborate could play an important role in this process,[72] but also a counter-cation effect is conceivable that would influence the ionic character of the indole scaffold.[73] The spiro-fused pentacycle **8c** was obtained exclusively in 62% yield by the reaction of **6c** employing NaBARF.

Finally, we intended to exploit the ring size of the products forming during the benzylic functionalization. When **9a** (six-membered ring precursor) was exposed to the gold(I)-catalyzed cyclization conditions, only the eight-membered ring arylation product **11a'** was obtained in 41–72% yield (Scheme 6). This arylation was favored over the six-membered-ring-forming benzylic C-H functionalization, presumably because of the seven-membered *ipso* cyclization pathway.[47] In contrast, the reaction of the methylene homolog **9b** with JohnPhosAu(MeCN)SbF_6 resulted in the seven-membered ring via distal benzylic functionalization to generate the indole-fused product **11b** in 48% yield, without producing the nine-membered ring arylation product **11b'**. Notably, no π-conjugation for a 1,7-H shift is present in the saturated propyl tether.[74] These observations suggest that the direct arylation towards a high-strain product such as the nine-membered ring is less favored compared to the *C*-cyclization via the benzylic C(sp^3)-H pathway.

In conclusion, we have demonstrated that indole-fused tetra- and pentacycles can be obtained through a gold-catalyzed C(sp^3)-H functionalization originating from azido alkynes. The reaction requires non-coordinating TCE and the cationic JohnPhosAu(MeCN)SbF_6 under dilute conditions. The investigation of the ethyl and isopropyl substrates demonstrated that two isomers can be formed via *C*-cyclization or *N*-cyclization. The selectivity can be controlled by tuning the electron density of the azido-substituted aryl moiety and the stability of the benzylic carbocation, in combination with adjusting the counter-anion effect.[75]

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Keywords: gold catalysis • hydride shift • carbenes • fused indoles • C-H bond functionalization

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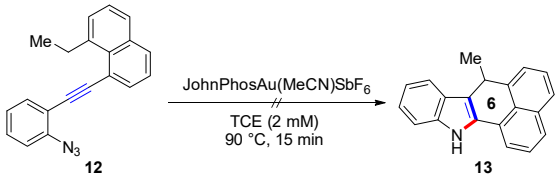
[74] A reliable study of the six-membered ring formation using the substrate without having the arylation site has not yet been conducted because of the difficulty in the preparation of the pure substrate: our general procedure for the five-membered ring precursors was not transferable to the six-membered ring precursor **12**. When subjecting the crude substrate to the optimized conditions, we observed black tar formation instead of the desired product **13** presumably due to the polymerization process.



12 **13**

[75] In the final stage just prior to submission of this paper, the related 1,6-hydride shift at the positions adjacent to nitrogen atoms was published as a preprint, which was recently published: D. F. León Rayo, A. Mansour, W. Wu, B. N. Bhawal, Fabien Gagosz, *Angew. Chem. Int. Ed.*, in press (DOI: 10.1002/anie.202212893).

Entry for the Table of Contents

The exposure of (alkylphenyl)ethynyl substituted phenyl azides to JohnPhosAu(I) catalysts leads to the divergent synthesis of indole-fused polycycles via *N*- or *C*-cyclization facilitated via benzyl to α-imino gold(I) carbene 1,5-hydride shift. The chemoselectivity depends on the counter-anion, the reactivity of the carbene, and the attached alkyl groups at the benzylic position.