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FULL PAPER

Access to Indole-Fused Benzannulated Medium-Sized Rings through Gold(I)-Catalyzed Cascade Cyclization of Azido-Alkynes

Luca C. Greiner,[a] Shinsuke Inuki,[a] Norihito Arichi,[a] Shinya Oishi,[a] Suzuki Rikito,[a] Tomohiro Iwai,[b] Masaya Sawamura,[b] A. Stephen K. Hashmi,[c] Hiroaki Ohno*[a]

Abstract: Because benzannulated and indole-fused medium-sized rings are found in many bioactive compounds, the combination of these fragments may lead to unexplored areas of biologically relevant and uncovered chemical space. Here we show that α-imino gold carbene chemistry can play an important role in solving the difficulty in the formation of medium-sized rings. Namely, phenylene-tethered azido-alkynes undergo arylative cyclization through the formation of a gold carbene intermediate to afford benzannulated indole-fused medium-sized tetracycles. The reactions allow a range of different aryl substitution patterns and efficient access to these otherwise difficult-to-obtain medium-sized rings. This study also demonstrates the feasibility of the semihollow-shaped C-dtbm ligand for the construction of a nine-membered ring.

Introduction

The indole group is among the top ten most occurring heterocycles in natural products and marketed drugs and is thus classified as a privileged structure in drug discovery with a wide spectrum of biological activities.[1] Especially, polycyclic indoles fused with a medium-sized ring are key structural motifs in pharmaceutically relevant compounds, such as the pharmaceutical iprindole,[2] the indole alkaloid velbanamine,[3] and the bis-indole alkaloid caulerpin (Figure 1a, blue).[4] Given the structures of nefopam and heliannuol A (Figure 1a, red), benzannulated medium-sized rings containing one or more heteroatom(s) can be considered potential drug-like structures (Figure 1b).[5] A natural product fragment-based approach, fusing both promising frameworks to the atypical molecular scaffold of indole-fused benzannulated medium-sized rings, could uncover diverse biological properties through covering biologically relevant uncharted chemical space that has not yet been explored by evolution (Figure 1b).[6]

Medium-sized rings (eight to eleven-membered) are classified as the most difficult rings to synthesize because of their relatively high magnitudes of transannular strain in association with disfavored entropic factors impeding access to the rigidified cyclic transition state.[7] Thus, it is difficult to efficiently construct a compound library containing various indole-fused medium-sized rings, including benzannulated ones. We expected that exploitation of highly reactive intermediates could play an important role in solving this challenging problem.

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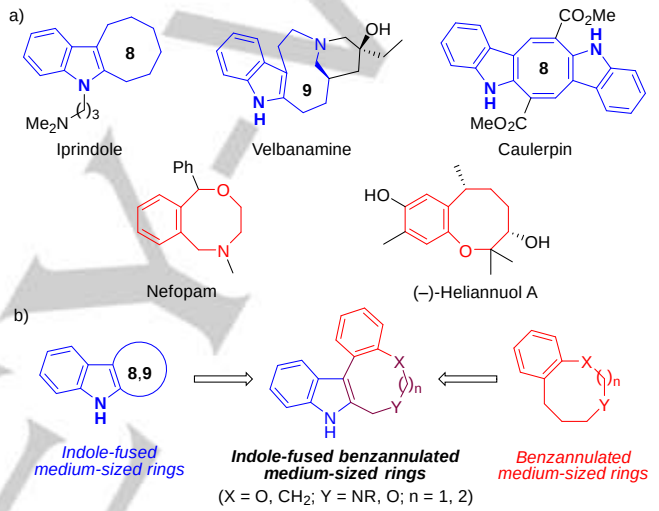

Figure 1: a) Representative structures of pharmaceuticals and natural products containing a fused indole and a medium-sized ring. b) Strategic fusion of the drug-like structures to afford indole-fused medium-sized rings.

α-Imino gold(I)-carbenes have manifested themselves as valuable key intermediates for the composition of pharmaceutical relevant aza-heterocycles.[8] Pioneering work in the gold(I)-catalyzed synthesis of substituted pyrroles involving α-imino gold(I)-carbenes can be attributed to Toste *et al.* using alkyl tethered alkynyl-azides as nitrene transfer agents.[9] By incorporating a phenylene tether, Gagosz and Zhang simultaneously demonstrated that benzannulated α-imino gold(I)-carbenes are feasible C3 umpolung indole equivalents, which can be trapped with nucleophiles, such as alcohols and arenes (Scheme 1a).[10] Zhang and Xu exemplified the cyclization of α-imino gold(I)-carbenes with a tethered aryl or alcohol moiety to generate benzannulated indole-fused oxepines (Scheme 1b).[10a,c] However, an eight-membered ring formation was not disclosed except for the isolated example using a highly-restrained azido-ynamide precursor reported by our group.[11] Those circumstances and outlooks motivated us to generate sp^3-enriched benzannulated medium-sized rings by using the α-imino gold(I)-carbene chemistry. Here we report the arylative cyclization of α-imino gold(I)-carbenes to obtain indole-fused benzannulated medium-sized rings as potential drug-like structures, employing azido-alkynes (Scheme 1c). The applicability of the semihollow-

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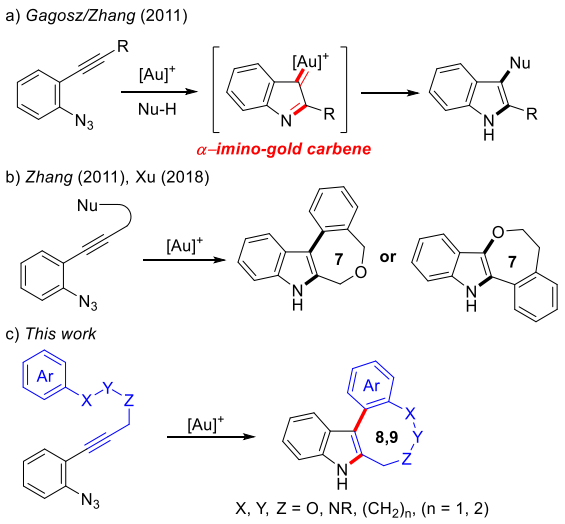
shaped C-dtbm ligand[12] on α-imino gold(I)-carbenes to generate an indole-fused nine-membered ring is also presented.



Scheme 1. Reported indole formation through gold carbenes and this work.

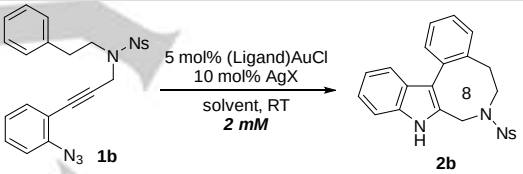
Results and Discussion

We prepared azido-alkynes **1** (see Supporting information) and investigated the eight-membered ring formation using a gold(I) catalyst. The initial approach to cyclize a tosylamide **1a** to eight-membered ring **2a** using $Ph_3PAuCl/AgSbF_6$ in CH_2Cl_2 (500 mM) solely resulted in polymerization with no traces of the desired product (Scheme 2). To our delight, the substitution of the Ts group of **1a** with the stronger electron-withdrawing Ns (*o*-nitrobenzenesulfonyl) group allowed us to obtain the corresponding eight-membered ring (azocine) **2b** in 22% yield. We assumed that the electron-withdrawing Ns group could positively influence the reactivity of the α-imino gold(I)-carbene in the electrophilic arylation for the azocine formation. However, the observation of significant amounts of black tar in these reactions could indicate that a polymerization process competes with the desired cyclization.

Scheme 2: Initial attempts of azocine formation.

To avoid potential intermolecular side reactions, we optimized the reaction conditions by diluting the substrate concentration to 2 mM (Table 1). Fortunately, we observed that the tar formation was suppressed, leading to a satisfactory 66% yield of **2b** (Table 1, entry 2). To investigate the counter anion effect[13a,b] on the reaction, the pre-catalyst Ph_3PAuCl was exposed to diverse chloride scavengers based on Ag(I)X (X = $^-$OTs, $^-PF_6$, $^-NTf_2$, or $^-SbF_6$, entries 2–5). Among these counter anions, the highest catalytic activity was found for $^-SbF_6$, which generates the cationic gold(I)-complex with the lowest dissociation energy, as illustrated by Hammond, Xu, Ujaque and Bandini *et al*.[13c-f] Next, we were interested in the ligand's influence on the eight-membered ring formation. An electron-deficient phosphine ligand such as $(p\text{-}CF_3C_6H_4)_3P$ resulted in reduced yield and catalytic activity (entry 6). While the use of Et_3P did not affect the yield significantly (entry 7) compared with Ph_3P, employment of tBu$_3$P led to an optimized yield of 76% (entry 8). Application of the NHC-based IPr ligand reduced the yield to 60% with an intermediate reaction time of 45 min (entry 9). From these results, tuning of the gold carbene character through variations of the ligands *trans*-influence and π-acidity is important, as reported by Zhang[10a] and Toste.[14a] An additional investigation using the bulky BrettPhos ligand resulted in rapid polymerization without detecting the desired product (entry 10). Consecutively, we attempted to pre-organize the cyclic transition state through the use of the semihollow-shaped C-dtbm ligand, designed by the Sawamura group.[12] Unfortunately, a sharp decrease in yield and inseparable unidentified side products were observed (entries 11 and 12). Finally, solvent screening demonstrated that non-coordinating CH_2Cl_2 is the most suitable solvent (entries 13–15). Interestingly, it was found that the presence of MS 4Å completely inhibited the reaction (entry 16), suggesting that MS 4Å may poison or neutralize the gold catalyst,[12b,15,16] or contaminating water may play a crucial role in this reaction.[16] After isolation of **2b**, the molecular structure was unambiguously confirmed by X-ray diffraction (Figure 2).[17]

Table 1. Optimization of the reaction conditions



Entry	Ligand[a]	X	t [h]	Solvent	Yield [%][b]
1	Ph_3P	SbF_6	0.5	CH_2Cl_2[c]	22
2	Ph_3P	SbF_6	0.5	CH_2Cl_2	66
3	Ph_3P	NTf_2	24	CH_2Cl_2	65
4	Ph_3P	PF_6	24	CH_2Cl_2	55
5	Ph_3P	OTs	24	CH_2Cl_2	–[d]
6	$(p\text{-}CF_3C_6H_4)_3P$	SbF_6	1.0	CH_2Cl_2	25
7	Et_3P	SbF_6	0.5	CH_2Cl_2	63
8	**tBu$_3$P**	**SbF_6**	**0.5**	**CH_2Cl_2**	**76 (71)**
9	IPr	SbF_6	0.75	CH_2Cl_2	60
10	BrettPhos	SbF_6	0.75	CH_2Cl_2	–[e]
11	C-dtbm	SbF_6	0.5	CH_2Cl_2	31
12	C-dtbm	NTf_2	1.0	CH_2Cl_2	37
13	tBu$_3$P	SbF_6	0.5	$MeNO_2$	–[e]
14	tBu$_3$P	SbF_6	12	THF	NR
15	tBu$_3$P	SbF_6	12	MeCN	NR
16[f]	tBu$_3$P	SbF_6	12	CH_2Cl_2	NR

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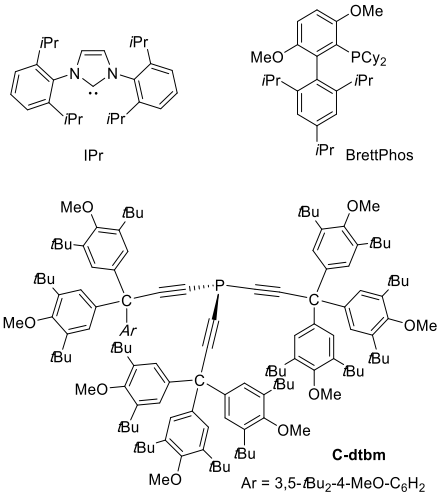


[a] The ligand structures are shown above. [b] Determined by ^{1}H-NMR analysis with TPM (triphenylmethane) as an internal standard. Yield in parenthesis is the isolated yield. [c] The reaction was conducted at 500 mM (Scheme 2). [d] An unidentified compound was formed. [e] Black tar formation was observed. [f] MS 4Å were added.

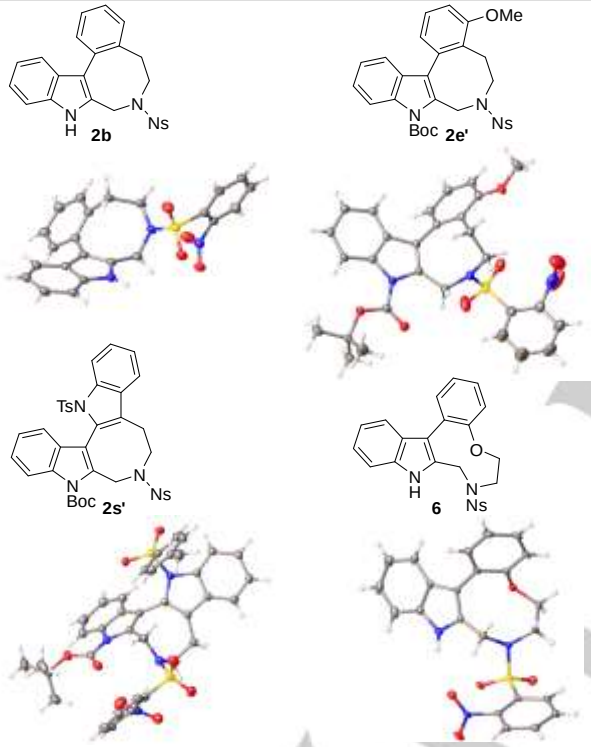
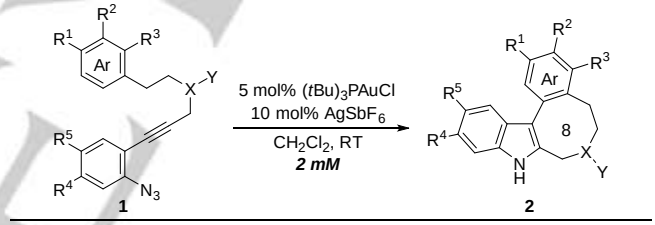


Figure 2. X-ray crystal structures of **2b**, **2e'** (Boc-**2e**), **2s'** (Boc-**2s**), and **6**.[17] For **2e'** and **6**, there are two crystallographically independent molecules in the single crystal lattices, one of which is shown for clarity.

With the optimized conditions in hand, we explored the scope of the eight-membered ring formation protocol (Table 2). First, the regioisomeric impact of various methoxyphenyl groups as the nucleophiles on the cyclization was examined. We were interested in understanding if placing the electron-donating methoxy group in a *meta*-position relative to the alkyl tether (**1c**, R^2 = OMe) could increase the nucleophilicity of the *ortho*-position and thereby enhance the rate of the direct eight-membered ring formation. Interestingly, we observed the opposite result to our expectation with a significantly decreased yield of **2c** and an increased reaction time, suggesting that an alternate reaction pathway could dominate the reaction outcome. According to the Brown's modification of the σ^+-values developed for aromatic electrophilic substitutions, we estimated that the methoxy substituent of **2c** could inductively deactivate the *ipso* position at the alkyl tether, and consequently lower the nucleophilicity of an *ipso* attack on the gold carbene.[18] For clarification, we activated the *ipso*-position with the *para*-substituted regioisomer **1d** (R^1 = OMe) and found a striking increase in reactivity (six-fold decrease in reaction time) as well as in yield (74%), suggesting that the *ipso*-position plays an essential role for the azocine formation. On the contrary, a sluggish cyclization of the *ortho*-substituted methoxyphenyl precursor **1e** (R^3 = OMe) was observed to produce **2e** (54%), probably because of steric effects as well as the decreased number of reaction sites. The molecular structure of the *N*-Boc derivative obtained from **2e** was confirmed through X-ray diffraction (Figure 2).[17] Our investigation of the methoxy derivatives was finalized with the employment of the veratrole tether (R^1 = R^2 = OMe, **2f**). To our surprise, the yield decreased significantly, and dilution to 0.1 mM was required to obtain the product in 59% yield, signaling an increased readiness of the substrate to undergo polymerization because of the high polarity difference of the reacting end groups. The order of the reactivity depending on the substituent R^1 (Me > Br > Cl) revealed that this cyclization is limited to slightly activated and neutral phenyl tethers (**2g–i**).

Table 2. Scope of the arylative cyclization to indole-fused heterocycles[a]



2b: R^1 = R^2 = R^3 = H 71% (0.5 h)
2c: R^2 = OMe, R^1 = R^3 = H 60%, 3/1[b] (40 min)
2d: R^1 = OMe, R^2 = R^3 = H 74% (1 mM, 5 min)
2e: R^3 = OMe, R^1 = R^2 = H 54%[c] (1 mM, 1 h)
2f: R^1 = R^2 = OMe, R^3 = H 59%[c] (0.1 mM)

2g: R^1 = Me 64% (0.5 h)
2h: R^1 = Br 19%[c] (1.5 h)[d]
2i: R^1 = Cl NR[e] (0.5 h)

2j: R^5 = CH_3 39% (1 mM, 1 h)
2k: R^5 = CF_3 75% (1 mM, 15 min)
2l: R^5 = Cl 58% (0.5 h)
2m: R^5 = NO_2 69% (0.1 mM)

2n: R^4 = CH_3 34%[c] (1 mM)
2o: R^4 = Cl NR[e] (0.5 h)

2a: Y = Ts 62% (1 mM, 6 h)
2p: Y = *p*-Ns 66% (0.5 h)

2q: 39% (1 mM, 1 h)

2r: R = Boc (–)[f]
2s: R = Ts 31%[c] (0.1 mM, 2 h)

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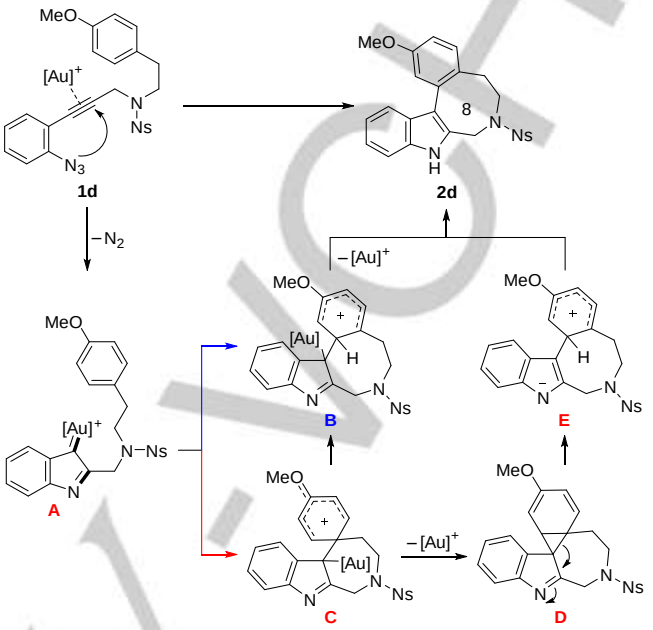
[a] Isolated yields are shown. [b] Combined isolated yield and regioisomeric ratio. [c] Characterized after *N*-Boc protection. [d] 22 mol% tBu$_3$PAuCl and 62 mol% AgSbF$_6$ were employed. [e] No reaction. [f] Black tar formation.

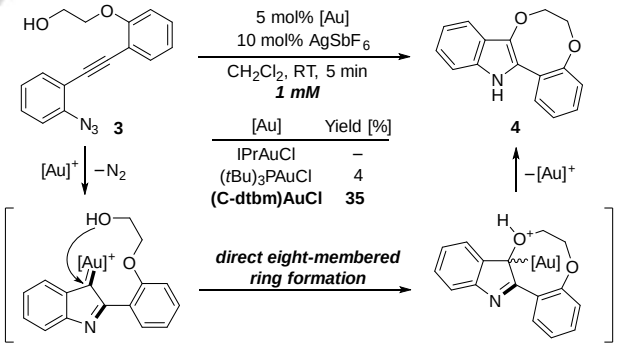
Next, we focused on the substituent effect of the aryl azide part. When a methyl group is appended to the *meta*-position of the alkynyl group, a marginal 2% yield of **2j** was obtained at 2 mM (data not shown). Decreasing the substrate concentration to 1 mM increased the yield of **2j** to 39%. We supposed that the methyl substituent contributes to the additional stabilization of the gold carbene and consequently decreases the required electrophilicity for the cyclization. A rationale for this result could also be found in the high nucleophilicity of the formed methyl-substituted indole that could instantaneously react with the highly electrophilic gold carbene.[19] In harmony with this notion, destabilization of the gold carbene through an electron-withdrawing CF_3 group significantly accelerated the cyclization to produce 75% of **2k**. In the case of a moderate electron-withdrawing halogen substituent with a competing positive mesomeric effect, such as chlorine, a moderate yield of **2l** (58%) was obtained. However, further increasing the electrophilicity of the gold(I)-carbene with a nitro group required even higher dilution conditions to give **2m** (69%). In close relationship to **2j**, the reaction of a methylated substrate resulted in a decreased yield of 34% (**2n**). In stark contrast to **2l**, cyclization to **2o** could not be initiated through the employment of the standard conditions, presumably because the resonance contribution of the chloride-lone pair deactivates the gold carbene species. A brief investigation of the sulfonyl protecting group revealed that its electron density influenced the rate of cyclization. When the electron-withdrawing force was reduced through the application of a Ts-protecting group, the substrate concentration had to be diluted to 1 mM to suppress polymerization, hence suggesting a more sluggish cyclization with a yield of 62% (**2a**). When *p*-Ns was used, no significant change in the reactivity compared with the model system was noticed (**2p**, 66%); thus, we concluded that spatial interaction of the nitro group is not significant to enhance the cyclization reaction. This reaction is also applicable to oxacycle formation (**2q**, 39%) by using an oxygen-tethered substrate.[7a] Finally, a nucleophilic *N*-Boc protected indole was employed as a cyclization precursor. Even when performing the reaction under 0.1 mM substrate concentrations, it allowed us to observe only a trace amount of the desired product **2r** in the crude NMR while the formation of black tar dominated. In contrast, decreasing the nucleophilicity of the indole through substitution of a Boc group with a Ts group turned out to be beneficial to produce the pharmaceutically promising bisindole-fused eight-membered ring **2s** at 0.1 mM substrate concentrations in 31% yield. Its structure was confirmed by X-ray analysis of the Boc-derivative **2s'** (Figure 2).[17]

A plausible reaction mechanism for the eight-membered ring formation is shown in Scheme 3. After the formation of α-imino gold carbene species **A**, arylation to form **B** and deauration and rearomatization would produce the azocine **2d**. Based on the above-mentioned results on the effect of the methoxy group, we propose that the cyclization proceeds via a low strain and low torsional entropy demanding spirocycle pathway. Accordingly, an *ipso* attack forms the spiro compound **C**, with a subsequent 1,2-ring-expansion[20a,b] via dienone-phenol rearrangement, as described by Marx,[20c] to **B** could result in the azocine **2d**. Alternately, the spirocyclic intermediate **C** could also undergo cyclopropanation, forming norcadiene derivative **D**,[20] which could facilitate ring-opening reaction forming **E**, which can then be converted to **2d** via rearomatization. At this stage, the involvement of a thermodynamically more challenging eight-membered ring formation to directly form **B** from **A** cannot be ruled out.



Scheme 3: Proposed mechanism of azocine formation

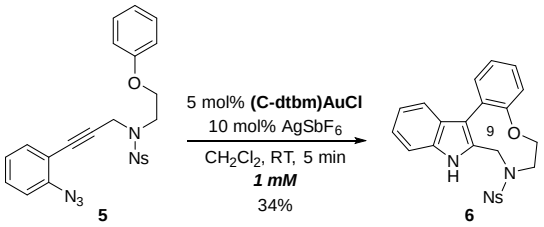
To test the efficiency of an unambiguously direct end-to-end cyclization to the eight-membered ring (dioxocine) **4**, glycol tethered azido-alkyne **3** was exposed to the gold(I)-catalyzed cyclization conditions (Scheme 4). It was demonstrated that compared with conventional ligands (IPr, tBu$_3$P) the semihollow-shaped C-dtbm was significantly superior for this cyclization and allowed the isolation of **4** in 35% yield. Considering that this reaction cannot proceed through the spirocyclic pathway (intermediate **C** in Scheme 3), this result clearly shows the difficulty of direct eight-membered ring formation.



Scheme 4: Construction of the indole-fused dioxocine through the employment of the semihollow-shaped C-dtbm ligand.

Finally, the construction of an indole-fused nine-membered ring (oxazonine) was investigated. Cyclization to nine-membered rings is generally considered to be significantly more challenging than the construction of eight-membered rings because the cyclization is afflicted with enhanced transannular strain and

rotational entropy. Unfortunately, the optimized condition for the eight-membered ring formation was ineffective, and the substrate was recovered completely. We once more attempted to utilize the C-dtbm ligand[12] and found that oxazonine **6** was isolated with 34% yield after full conversion (Scheme 5). The molecular structure was unambiguously confirmed through X-ray crystallographic analysis (Figure 2).[17] The isolation of **4** and **6** clearly demonstrate the feasibility of the semihollow-shaped C-dtbm ligand for direct end-to-end eight-membered ring formation and arylative nine-membered ring formation.



Scheme 5: Construction of the indole-fused oxazonine using the semihollow-shaped C-dtbm ligand.

Conclusion

In summary, we have shown that indole-fused benzannulated eight- and nine-membered rings can be obtained through gold-catalyzed cascade cyclizations of azido-alkynes, when arenes are used as internal nucleophiles for trapping the intermediary α-imino gold(I)-carbenes. Notably, the ease of ring closure was significantly affected by high dilution conditions, the polarization of the gold(I)-carbene, the arene moiety, and the *N*-protecting group.[22] Additionally, we found that the semihollow-shaped C-dtbm ligand is indispensable for the alkoxylative eight-membered- and arylative nine-membered ring formation. The developed method can enter biologically relevant chemical space and created a library of a promising class of indole- and bisindole-fused medium-sized rings, potentially useful for medicinal applications.

Acknowledgements

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Keywords: arylation • medium-sized rings • gold-catalysis • heterocycles • α-imino gold(I)-carbenes

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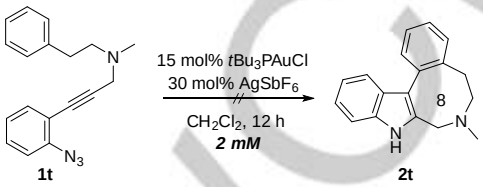
[22] It should be noted that the reaction of *N*-alkyl derivative **1t** resulted in polymerization without producing the desired product **2t**.



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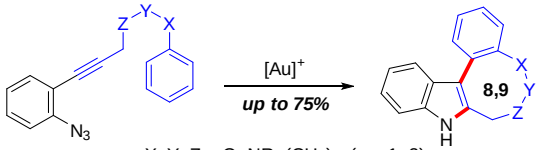

X, Y, Z = O, NR, $(CH_2)_n$, (n = 1, 2)

Starting from phenylene tethered azido-alkynes, pharmaceutically relevant indole-fused benzannulated eight-membered rings were constructed by exploiting α-imino gold(I)-carbenes as key intermediates for the gold(I)-catalyzed cascade reaction. The necessity of the C-dtbm ligand for the cyclization to a more challenging nine-membered ring is also demonstrated.