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Communication

Stereospecific access to bridged [*n*.2.1] skeletons through gold-catalyzed tandem reaction of indolyl homopropargyl amides

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ABSTRACT

An efficient gold-catalyzed anti-Markovnikov cycloisomerization-initiated tandem reaction of Boc-protected indole tethered homopropargyl amides has been achieved. This method delivers a wide range of valuable bridged aza-[*n*.2.1] skeletons ($n = 3–7$) at room temperature with high diastereoselectivity and enantioselectivity by a chirality-transfer strategy. Moreover, the gold-catalyzed tandem reaction of homopropargyl alcohol is also achieved to produce the bridged oxa-[3.2.1] skeleton.

Since the last decade, gold-catalyzed nucleophilic addition reactions to alkynes have received tremendous interest and been widely used in the facile synthesis of an incredible variety of complex molecules, especially the valuable cyclic compounds [1]. Among these, the terminal alkynes can undergo various highly regioselective transformations catalyzed by gold, thus providing an efficient way for C—C, C—H and C—X bond formation. However, Markovnikov regioselectivity is normally observed in this kind of nucleophilic addition (Scheme 1a), and recent reports involving the anti-Markovnikov regioselectivity are mostly limited to reactions driven by aromatization [2a–c] and involving the gold vinylidene intermediate [2d,e]. Of note, the dominance of the LUMO coefficient on the internal carbon in the π-complexes of terminal alkynes and gold(I) complexes has been computed in detail, even involving a fully relativistic treatment [3]. Recently, our group has achieved a variety of gold-catalyzed anti-Markovnikov cycloisomerization-initiated cascade cyclizations by utilizing the steric strain in ring formation [4h], and this strategy has been applied to the synthesis of various *N*-heterocycles from readily available homopropargyl alcohols or amides [4]. Inspired by these results and our recent study on the copper-catalyzed tandem reaction of sulfonyl-protected indole tethered homopropargyl amides [4g], we envisioned that the gold anti-Markovnikov cycloisomerization might be realized by choosing the suitable protecting groups (Scheme 1b) [5]. However, it remains a highly challenging task because of the difficulty in preventing the competing Markovnikov cyclization [6] and achieving the desired cascade cyclization [7].

Herein, we disclose a gold-catalyzed anti-Markovnikov cycloisomerization-initiated tandem reaction by employing the Boc-protected indole tethered homopropargyl amides as substrates [8,9], enabling facile access to a wide range of valuable bridged aza-[*n*.2.1] skeletons ($n = 3–7$) at room temperature with high diastereoselectivity and enantioselectivity by a chirality-transfer strategy.

At the outset, Boc-protected indole tethered chiral homopropargyl amide **1a** was chosen as the model substrate (Table 1). To our delight, typical gold catalysts such as $Ph_3PAuNTf_2$ and $IPrAuNTf_2$ could indeed catalyze the cascade cyclization reaction to produce the desired aza-[3.2.1] skeleton **2a**, albeit along with the byproduct **2aa**, which was formed presumably through a direct gold-catalyzed Markovnikov cycloisomerization-initiated tandem reaction (entries 1 and 2; Supporting information for details). We

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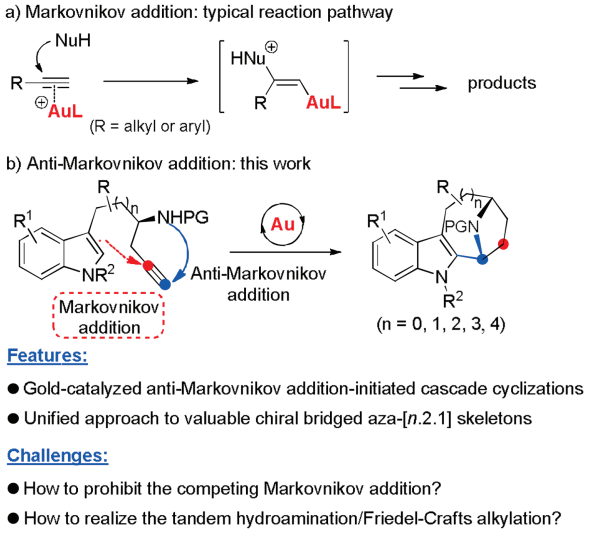
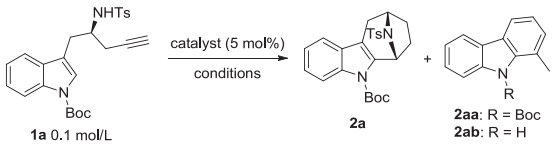


Scheme 1. Gold-catalyzed nucleophilic addition to terminal alkynes.

Table 1
Optimization of reaction conditions.

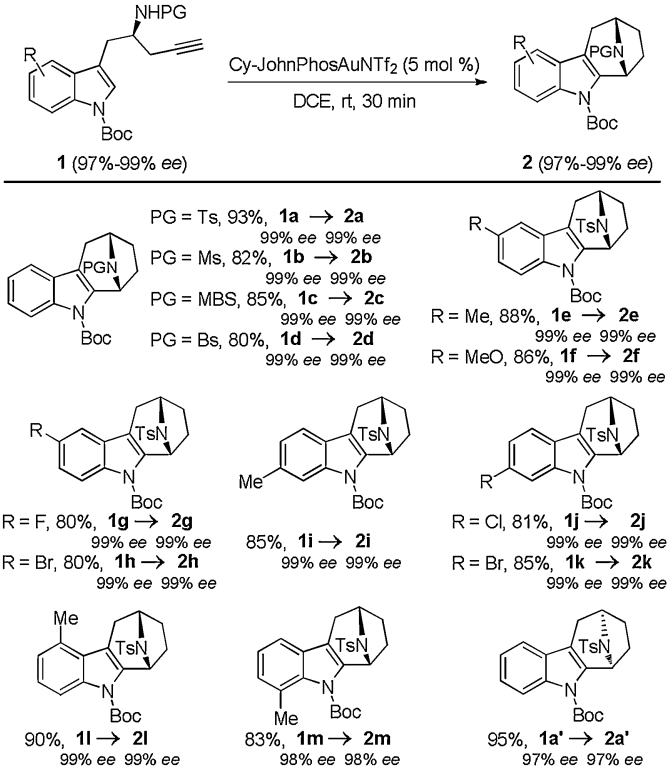


Entry	Catalyst	Reaction conditions	Yield (%)[a]	
			2a	2aa
1	$Ph_3PAuNTf_2$	DCE, r.t., 6 h	56	32
2	$IPrAuNTf_2$	DCE, r.t., 2 h	50	28
3	Cy-JohnPhosAuNTf$_2$	DCE, r.t., 30 min	96	<1
4	BrettPhosAuNTf$_2$	DCE, r.t., 2 h	90	<1
5	$PtCl_2$	DCE, 60 °C, 24 h	18	79
6[b]	$AgNTf_2$	DCE, 60 °C, 2 h	<1	64
7[b]	AgOTf	DCE, 60 °C, 2 h	<1	81
8[b]	CuOTf	DCE, 80 °C, 3 h	28	61
9[b]	TfOH	DCE, 60 °C, 5 h	<1	62
10[b]	MsOH	DCE, 60 °C, 5 h	<1	58
11	Cy-JohnPhosAuNTf$_2$	DCM, r.t., 30 min	95	<1

Ts: 4-toluenesulfonyl; Boc: *tert*-butyl carbonate.
[a] Measured by ^{1}H NMR using diethyl phthalate as internal standard.
[b] 20 mol% of catalyst was used. **2ab** was obtained instead of **2aa**.

then investigated other gold catalysts and were delighted to find that excellent yields were achieved by employing Cy-JohnPhos-AuNTf$_2$ and BrettPhosAuNTf$_2$ as catalysts (entries 3 and 4). Of note, by employing $PtCl_2$ as the catalyst, the occurrence of **2aa** could become dominant (entry 5). In contrast to the gold catalysts, other transition metal catalysts and Brønsted acids promoted selective formation of **2ab** (entries 6–10) [10]. Finally, it was found that the reaction proceeded equally well in DCM as the solvent (entry 11).

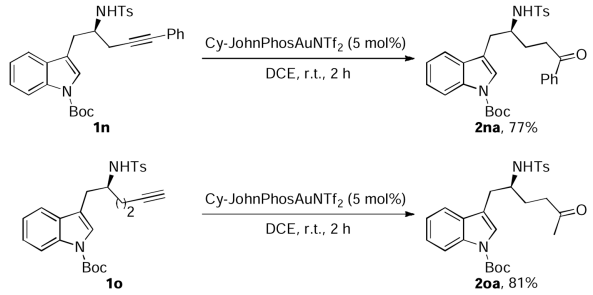
With the optimized reaction conditions in hand, the scope of this gold-catalyzed tandem reaction was explored, as shown in Scheme 2. Chiral Boc-protected indole tethered homopropargyl amides **1** were accessed with excellent enantiomeric excesses (97%–99% *ee*) from readily available indolyl aldehydes by Ellman's *tert*-butylsulfinamide chemistry (Supporting information for details). Different *N*-protecting groups were first screened, and it was found that the reaction occurred efficiently to afford the corresponding aza-[3.2.1] skeletons **2a**–**d** in 80%–93% yields (**2a**



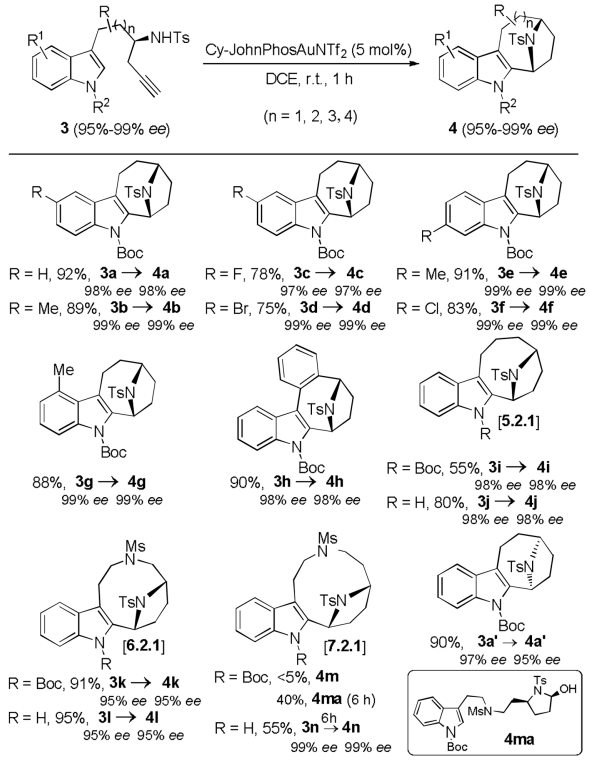
Scheme 2. Synthesis of bridged aza-[3.2.1] skeletons **2**. Reactions run in vials; [**1**] = 0.1 mol/L, isolated yields are reported.

was confirmed by X-ray diffraction analyses (CCDC No. 1554636)). Additionally, the reaction was also extended to amides bearing different substituents on the indole ring, leading to the desired products **2e**–**k** in high yields. Notably, the reaction could be even extended to sterically hindered indolyl substrates **1l** and **1m**, and the desired products **2l** and **2m** were formed in high yields. Our attempts to extend the reaction to internal alkyne **1n** and indolyl amide **1o** only resulted in the formation of the corresponding hydration products **2na** (77%) and **2oa** (81%), respectively (Scheme 3). Finally, the reaction also proceeded smoothly with (*S*)-(+)-*tert*-butylsulfinamide-derived **1a'**, delivering the desired **2a'** with the opposite enantioselectivity. Importantly, complete chirality transfer was observed in all cases.

Moreover, this gold-catalyzed tandem reaction was also extended to the efficient synthesis of other bridged aza-[*n*.2.1] skeletons (Scheme 4). Various chiral indolyl homopropargyl amides **3** were suitable substrates for this tandem cyclization to furnish the desired bridged aza-[*n*.2.1] skeletons **4** in mostly good to excellent yields. A variety of amides containing various



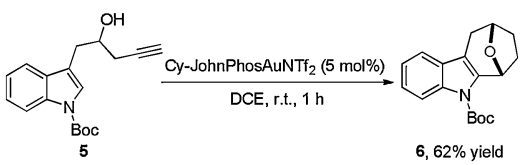
Scheme 3. Gold-catalyzed cascade cyclization of homopropargyl amides **1n** and **1o**.



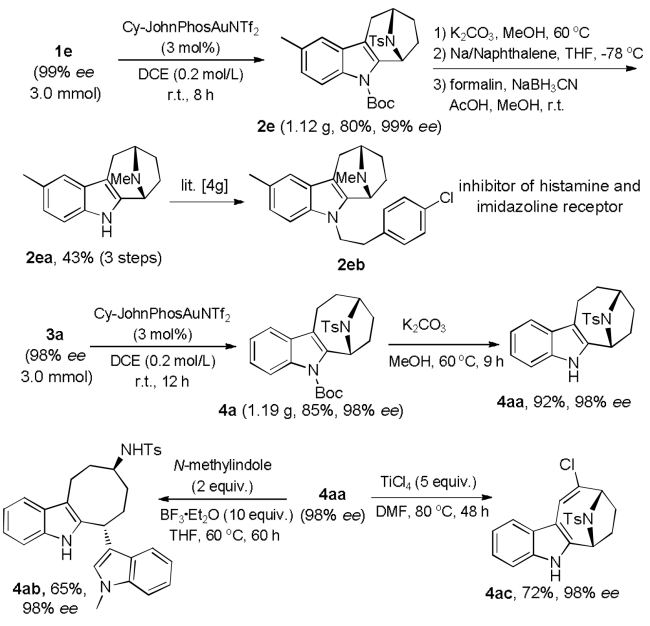
Scheme 4. Synthesis of bridged aza-[3.2.1] skeletons **4**. Reactions run in vials; [**3**] = 0.1 mol/L, isolated yields are reported.

substituents on the indole ring were readily tolerated, leading to the corresponding aza-[4.2.1] skeletons **4a**–**g** in good to excellent yields. In addition, the reaction worked satisfactorily with aryl-linked substrate **3h**, thus providing the desired **4h** in 90% yield. (*S*)-(+)-*tert*-Butylsulfinamide-derived **3a**′ were also compatible with this gold catalysis, and the desired **4a**′ with the opposite enantioselectivity was formed in 90% yield. Finally, it was found that this tandem reaction was viable for the construction of the aza-[*n*.2.1] skeletons **4i**–**n** (*n* = 5–7) in 55%–95% yields except for substrate **3m**, and significantly improved yields were achieved when unprotected indolyl homopropargyl amides were used (**4k** was confirmed by X-ray diffraction analyses (CCDC No. 1554638)). While five- and six-membered rings are formed in most gold-catalyzed intramolecular reactions, such medium-sized rings are very rare in gold catalysis [11,6b,6c]. Again, complete chirality transfer was observed in all cases.

Interestingly, we were delighted to find that this gold-catalyzed cascade cyclization could be further extended to the homopropargyl alcohol. As shown in Scheme 5, the tandem reaction of homopropargyl alcohol **5** under the gold-catalyzed standard conditions led to the bridged oxa-[3.2.1] skeleton **6** in 62% yield. Notably, the reaction failed to give even a trace of **6** under the previous copper catalysis [4g]. A likely reason is that the homopropargyl alcohol substrate, which is not as stable as the homopropargyl amide substrates, would undergo decomposition easily at high temperature (80 °C) required in the copper-catalyzed protocol.



Scheme 5. Gold-catalyzed cascade cyclization of homopropargyl alcohol **5**.

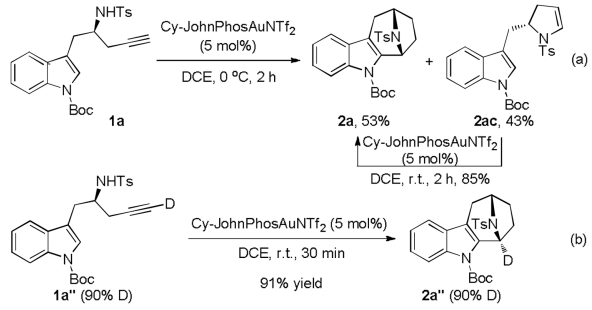


Scheme 6. Gram scale reaction and synthetic applications.

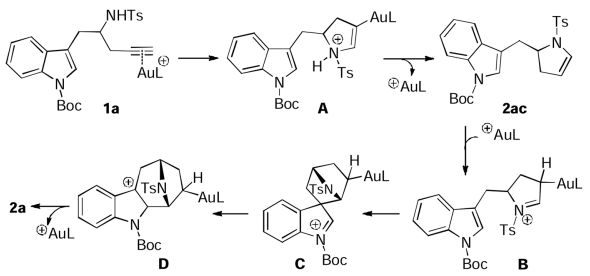
Further synthetic transformations of the above products were then explored (Scheme 6). The *N*–Ts group in **2e**, prepared on a gram scale in 80% yield, could be readily converted into the desired *N*–Me group, delivering **2ea** in 43% yield (3 steps), which underwent facile alkylation to eventually produce the bioactive **2eb** [4g]. In addition, deprotection of **4a** (gram scale: 85% yield) afforded **4aa**, which could be further transformed into the valuable indole-fused cyclooctane **4ab** [12] and chlorinated aza-[4.2.1] skeleton **4ac** (**4ac** was confirmed by X-ray diffraction analyses (CCDC No. 1566099)). Importantly, enantioselectivity was well maintained in all these cases.

To probe the reaction mechanism, we first tried to trap the likely reaction intermediate (Scheme 7a). To our delight, the indolyl dihydropyrrole **2ac** was isolated in 43% yield when the reaction ran at 0 °C. Moreover, **2ac** could be readily converted into the desired **2a** in the presence of gold catalyst while no **2a** was observed without gold catalyst. These results strongly support that **2ac** is the key intermediate for this tandem reaction [5], and gold catalyzes both the hydroamination and Friedel–Crafts alkylation process. In addition, a deuterium labeling study revealed that almost no deuterium loss was observed (Scheme 7b), thus ruling out the gold vinylidene intermediate pathway.

On the basis of the above experimental observations and previously published results [4], a rationale for the formation of the bridged heterocycle **2a** is shown in Scheme 8. The reaction starts with formation of the vinyl gold intermediate **A** by alkyne π coordination and concomitant 5-*endo-dig* cyclization.



Scheme 7. Control experiments.



Scheme 8. Plausible mechanism.

Intermediate **A** then undergo facile protodeauration, leading to indolyl dihydropyrrole **2ac**, which could be further converted into iminium species **B** catalyzed by gold. Subsequent Friedel−Crafts alkylation at C-3 of the indole followed by a 1,2-migration [6g], and aromatization/protodeauration process delivers the final product **2a** along with the regeneration of the gold catalyst.

In summary, we have developed a gold-catalyzed anti-Markovnikov cycloisomerization-initiated cascade cyclization of Boc-protected indole tethered homopropargyl amides, delivering a wide range of bridged aza-[*n*.2.1] skeletons at room temperature with high diastereoselectivity and enantioselectivity by a chirality-transfer strategy. Moreover, the gold-catalyzed tandem reaction of homopropargyl alcohol is also achieved to produce the bridged oxa-[3.2.1] skeleton. In addition, the mechanistic rationale for this cascade cyclization is well supported by a variety of control experiments, and thus the mechanism of this gold catalysis is distinctively different from the previous copper catalysis [4g].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.10.019.

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