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Copper-Catalyzed Cascade Cyclization of Indolyl Homopropargyl Amides: Stereospecific Construction of Bridged Aza-[*n*.2.1] Skeletons

*Tong-De Tan, Xin-Qi Zhu, Hao-Zhen Bu, Guocheng Deng, Yang-Bo Chen, Rai-Shung Liu, Long-Wu Ye**

***Abstract**: Catalytic cycloisomerization-initiated cascade cyclizations of terminal alkynes have received tremendous interest, and been widely used in the facile synthesis of a diverse array of valuable complex heterocycles. However, these tandem reactions have been mostly limited to noble-metal catalysis, and initiated via an exo-cyclization pathway. Reported herein is an unprecedented copper-catalyzed endo-cyclization-initiated tandem reaction of indolyl homopropargyl amides, where copper catalyzes both the hydroamination and Friedel−Crafts alkylation process. This method allows the practical and atom-economical synthesis of valuable bridged aza-[n.2.1] skeletons (n = 3–6) with wide substrate scope, and excellent diastereoselectivity and enantioselectivity by a chirality-transfer strategy. Moreover, the mechanistic rationale for this novel cascade cyclization is also strongly supported by control experiments, which is distinctively different from the related gold catalysis.*

The tropane (8-azabicyclo[3.2.1]octane) skeleton defines the core structure of more than 600 alkaloids with multiple bioactivities.[1] Among these, the indole-based tropanes are particularly important structural motifs that have been found in a wide range of biologically significant molecules (Figure 1).[2] However, these bridged scaffolds are regarded as difficult structures to access as the bridge segments make the molecules structurally less flexible

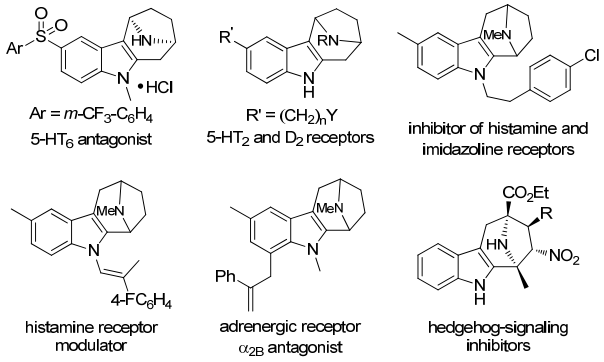
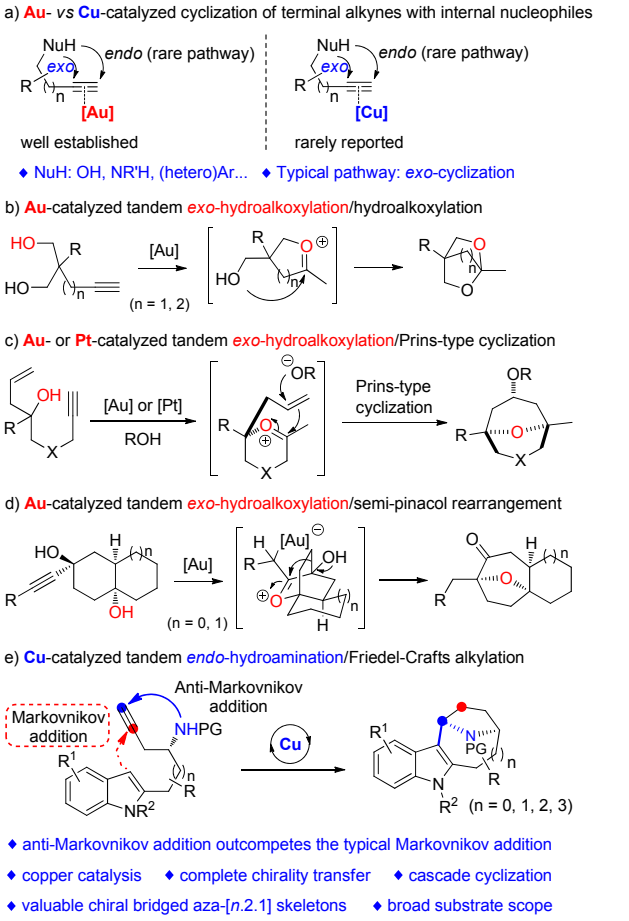


Figure 1. Indole-based tropanes in bioactive molecules.

compared to their homologous counterparts, and only very limited methods have been developed thus far.[2,3] In particular, there is a lack of efficient synthetic methods for their enantioselective synthesis.[2b,3e,3f]

Due to the unique π-acidic property of Au(I) catalyst, gold-catalyzed cyclization reaction of terminal alkynes with internal nucleophiles, typically via an *exo* cyclization, has received tremendous interest since the last decade (Scheme 1a), and been widely used in the facile synthesis of an incredible variety of the valuable cyclic compounds.[4,5] Meanwhile, copper-catalyzed such a cyclization has been far less vigorously investigated,[6] and the internal nucleophiles here are limited to the more nucleophilic electron-rich amines, thus severely limiting their further synthetic applications as the *N*-protecting groups of the formed products are difficult to be removed.



Scheme 1. Transition-metal-catalyzed cycloisomerization-initiated tandem reactions for the synthesis of bridged scaffolds.

The search for new avenues to molecular complexity from simple starting materials has been one of the major objectives of organic chemists in the past decades. In this context, tandem reactions have emerged as powerful tools to accomplish this goal

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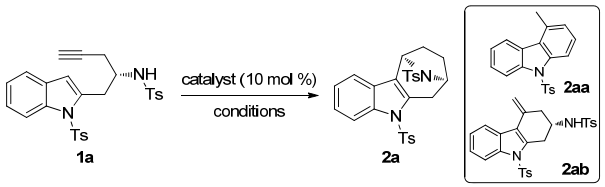
as it offers the opportunity of building up architecturally complex molecules in rapid, efficient, and economical ways.[7] Following this concept, transition-metal-catalyzed alkyne hydroalkoxylation and hydroamination initiated cascade cyclizations have been well documented to be a powerful method to synthesize a variety of structurally complex heterocycles,[4] especially the valuable bridged heterocycles.[8-11] For example, Michelet and Genêt in 2005 reported a gold-catalyzed tandem *exo*-hydroalkoxylation/hydroalkoxylation of bis-homopropargylic diols, allowing the facile formation of functionalized strained bicyclic ketals (Scheme 1b).[8a] A related platinum-catalyzed tandem cycloisomerization of alkyne-diols was subsequently disclosed by Ley et al. for the synthesis of [3.2.1]bicyclic acetals, and notable is that *endo*-hydroalkoxylation was observed in case of internal akynes.[8b] In 2006, Barluenga and co-workers reported an outstanding protocol for the gold- or platinum-catalyzed tandem *exo*-hydroalkoxylation/Prins-type cyclization, leading to a variety of 9-oxabicyclo[3.3.1]nonanes (Scheme 1c).[9a,9b] On the basis of this work, the relevant tandem *exo*-hydroalkoxylation /hydroarylation was further developed by the same group.[9c,9d] Such a hydroalkoxylation/Prins-type cyclization has also been aptly exploited by Liu and Wang.[10] In 2015, Yang and co-workers demonstrated an elegant approach for the efficient synthesis of oxabicyclo[3.2.1]octanes via gold-catalyzed *exo*-hydroalkoxylation/semi-pinacol rearrangement (Scheme 1d).[11] Despite these remarkable achievements, these intramolecular tandem reactions have so far been limited to the noble-metal catalysts (Au and Pt), and initiated via an *exo*-cyclization pathway in terms of terminal alkynes.

By utilizing the steric strain in ring formation to achieve anti-Markovnikov regioselectivity, our group has developed several gold-catalyzed 5-*endo*-*dig* hydroamination-initiated tandem reactions, affording valuable five-membered *N*-heterocycles.[12] Inspired by these results, we envisioned that the synthesis of indole-based tropanes might be achieved via such an anti-Markovnikov hydroamination-initiated cascade cyclization of indolyl homopropargyl amides (Scheme 1e).[13] However, achieving this cascade reaction is highly challenging: (1) how to prevent the competing *exo* cyclization of the terminal alkyne partner by the highly nucleophilic indole moiety via a typical Markovnikov addition;[5] and (2) how to achieve the desired cascade cyclization but not stopping at the dihydropyrrole intermediate.[14] Herein, we describe the realization of unprecedented copper-catalyzed cascade cyclization of indolyl homopropargyl amides,[15] allowing the practical and atom-economical synthesis of a diverse array of valuable bridged aza-[*n*.2.1] skeletons (*n* = 3–6) with excellent diastereoselectivity and enantioselectivity by a chirality-transfer strategy. Furthermore, a mechanistic rationale for this serial cascade cyclization is strongly supported by a variety of control experiments, and importantly, its mechanism is distinctively different from the related gold catalysis.

At the outset, indole-tethered chiral homopropargyl amide **1a** was chosen as the model substrate.[16] As outlined in Table 1,[17] 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** but in low yields (<25%). In these cases, **2aa** or **2ab** was formed as the main product presumably through a direct gold-catalyzed Markovnikov cycloisomerization-initiated tandem reaction (Table 1, entries 1–4).[17] We then investigated platinum and silver catalysts (Table 1, entries 5–7) and were delighted to find that 58% yield of **2a** was achieved in the presence of AgOTf (Table 1, entry 7).[17,18] Gratifyingly, subsequent studies revealed that copper catalysts could catalyze the cascade cyclization smoothly (Table 1, entries 8–11), and **2a** was fromed in 85% yield by employing CuOTf as the catalyst (Table 1, entry 9).[19] Interestingly, Brønsted acids promoted selective formation of **2aa** (Table 1, entries 12–13). Further screening of solvents such as toluene and chlorobenzene led to a slightly decreased yield (Table 1, entries 14–15). Finally, it should be mentioned that the reaction of unprotected and methyl-protected indolyl homopropargyl amides in the presence of CuOTf only led to the formation of the corresponding carbazoles as main products.[17] Thus, both the metal catalyst and protecting group of the substrate are the key to achieve the desired cascade cyclization.

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Reaction conditions	Yield [%][b] 2a	2aa	2ab
1[c]	$Ph_3PAuNTf_2$	DCE, RT, 2 h	11	80	<1
2[c]	$IPrAuNTf_2$	DCE, RT, 2 h	14	<1	80
3[c]	Cy-JohnPhosAuNTf$_2$	DCE, RT, 2 h	20	76	<1
4[c]	BrettPhosAuNTf$_2$	DCE, RT, 2 h	24	<1	51
5[c]	$PtCl_2$	DCE, 60 °C, 9 h	14	73	<1
6	$AgBF_4$	DCE, 60 °C, 6 h	50	36	<1
7	AgOTf	DCE, 60 °C, 2 h	58	21	<1
8	$Cu(OTf)_2$	DCE, 80 °C, 10 h	72	19	<1
9	**CuOTf**	**DCE, 80 °C, 5 h**	**85**	**<5**	**<1**
10	$Cu(CH_3CN)_4BF_4$	DCE, 80 °C, 20 h	75	13	<1
11	$Cu(CH_3CN)_4PF_6$	DCE, 80 °C, 30 h	74	15	<1
12[d]	TfOH	DCE, 80 °C, 10 h	<1	50	<1
13[d]	MsOH	DCE, 80 °C, 24 h	<1	55	<1
14	CuOTf	toluene, 80 °C, 5 h	84	6	<1
15	CuOTf	PhCl, 80 °C, 5 h	83	6	<1

[a] Reaction conditions: **1a** (0.05 mmol), catalyst (10 mol %) in solvent (0.5 mL) at rt−80 °C in vials. [b] Measured by ^{1}H NMR using diethyl phthalate as internal standard. [c] 5 mol % of catalyst was used. [d] 20 mol % of catalyst was used.

According to Ellman's chemistry (Figure 2),[12] chiral indolyl homopropargyl amides **1** were easily prepared with excellent enantiomeric excesses (98−99% ee) by starting from readily available indolyl aldehydes and (*R*)-(+)-*tert*-butylsulfinamide. With the optimal reaction conditions (Table 1, entry 9) and chiral indolyl homopropargyl amides **1** in hand, the scope of this cascade cyclization was explored (Table 2). Initial investigation of *N*-protecting groups of amide moiety demonstrated that the reaction proceeded smoothly with different sulfonyl groups to furnish the desired aza-[3.2.1] skeletons **2a**–**d** in 68−84% yields (Table 2, entries 1–4), and the Ts-protected homopropargyl amide **1a** gave the best result (Table 2, entry 1). Gratifyingly, the use of substrate containing Bs protecting group of indole moiety gave a significantly improved yield (Table 2, entry 5). In addition, amides containing different substituents on the indole ring also underwent smooth cascade cyclization, producing the corresponding **2f**–**n** in good to excellent yields (Table 2, entries 6–14), Finally, it was found that the reaction also occurred well with (*S*)-(+)-*tert*-butylsulfinamide-derived **1e′**, and thus the other enatiomer **2e′** was specifically produced (Table 2, entry 15). Importantly, the

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chirality of **1** can be completely transferred to the chiral indole-fused tropanes and excellent diastereoselectivity (d.r. > 50:1) can be achieved in all cases. The molecular structure of **2h** was further confirmed by X-ray diffraction (Figure 3).[20]

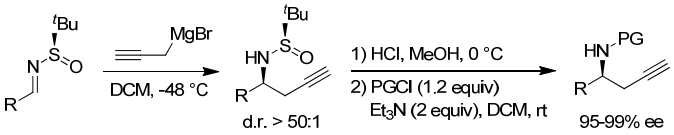


Figure 2. Synthesis of chiral homopropargyl amides using Ellman's chemistry.

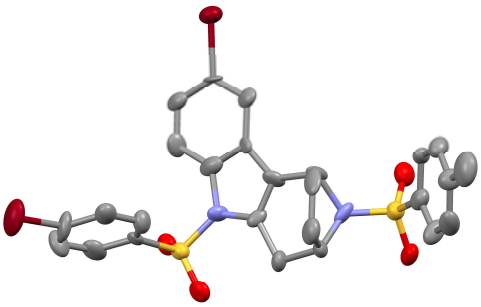
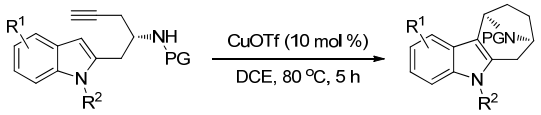
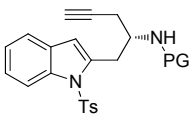
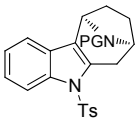
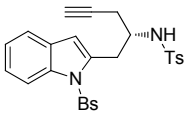
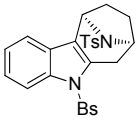
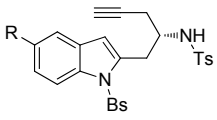
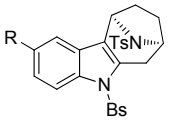
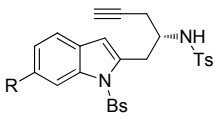
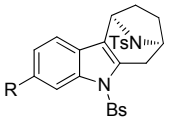
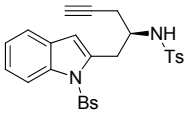
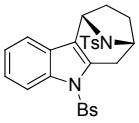


Figure 3. Structure of compound **2h** in its crystal.

Table 2. Construction of bridged aza-[3.2.1] skeletons **2**.[a]



1 (98-99% ee) **2** (98-99% ee)

Entry	Substrate	Product	Yield (%)
			
1	**1a**, PG = Ts, 99% ee	**2a**, PG = Ts, 99% ee	84
2	**1b**, PG = Ms, 99% ee	**2b**, PG = Ms, 99% ee	68
3	**1c**, PG = Bs, 99% ee	**2c**, PG = Bs, 99% ee	73
4	**1d**, PG = MBS, 99% ee	**2d**, PG = MBS, 99% ee	77
			
5	**1e**, 99% ee	**2e**, 99% ee	96
			
6[b]	**1f**, R = F, 99% ee	**2f**, R = F, 99% ee	81
7[b]	**1g**, R = Cl, 99% ee	**2g**, R = Cl, 99% ee	86
8[b]	**1h**, R = Br, 99% ee	**2h**, R = Br, 99% ee	89
9[b]	**1i**, R = CN, 99% ee	**2i**, R = CN, 99% ee	75
10	**1j**, R = OMe, 99% ee	**2j**, R = OMe, 99% ee	78
			
11[b]	**1k**, R = Cl, 99% ee	**2k**, R = Cl, 99% ee	75
12[b]	**1l**, R = Br, 99% ee	**2l**, R = Br, 99% ee	70
13[b]	**1m**, R = CO_2Me, 98% ee	**2m**, R = CO_2Me, 98% ee	78
14	**1n**, R = Me, 99% ee	**2n**, R = Me, 99% ee	87
			
15	**1e'**, 98% ee	**2e'**, 98% ee	94

[a] Reaction conditions: **1** (0.2 mmol), CuOTf (0.02 mmol), DCE (2 mL), 80 °C, 5 h, in vials; yields are those for the isolated products; ees are determined by HPLC analysis. [b] Reaction time: 10 h.

Besides the formation of bridged aza-[3.2.1] skeletons, this copper-catalyzed cascade cyclization was also viable for the construction of other valuable bridged aza-[*n*.2.1] skeletons. As shown in Table 3, the reaction proceeded efficiently with a variety of chiral indolyl homopropargyl amides **3**, also prepared with excellent ees (98−99% ee) by Ellman's *tert*-butylsulfinimine chemistry, affording the corresponding functionalized bridged aza-[*n*.2.1] skeletons **4** in mostly excellent yields with complete chirality transfer. It was found that amides containing various substituents on the indole ring were suitable substrates for this reaction to furnish the desired aza-[4.2.1] skeletons **4a**–**f** in 81–93% yields (Table 3, entries 1–6). Of note, (*S*)-(+)-*tert*-butylsulfinamide-derived **3a′** also underwent smooth cyclization to produce the desired **4a′** in 89% yield and the reaction was stereospecific (Table 3, entry 7). Moreover, this cascade cyclization could also be extended to the preparation of the aza-[*n*.2.1] skeletons **4g**–**i** (*n* = 5,6) in high yields (Table 3, entries 8–10). Thus, this protocol provides an efficient and practical route for the construction of the indole-fused medium-sized ring compounds with excellent diastereoselectivity (d.r. > 50:1) and enantioselectivity.

Interestingly, this cascade cyclization was also extended to 3-substituted indole-tethered homopropargyl amides **5**, and the desired aza-[3.2.1] skeletons **6a**–**h** were formed in generally good yields, as summarized in Table 4. Notably, the reaction could be extended to sterically hindered indolyl amide **5h**, and the desired **6h** was formed in 76% yield (Table 4, entry 8). In addition, (*S*)-(+)-*tert*-butylsulfinamide-derived **5a′** could also undergo smooth cyclization to deliver **6a′** and the reaction was stereospecific (Table 4, entry 9). Furthermore, this protocol was also used in the synthesis of aza-[4.2.1] skeleton **6i** in 78% yield (Table 4, entry 10). Importantly, complete chirality transfer and excellent diastereoselectivity (d.r. > 50:1) were achieved in all cases. The molecular structure of **6e** was further confirmed by X-ray diffraction (Figure 4).[20]

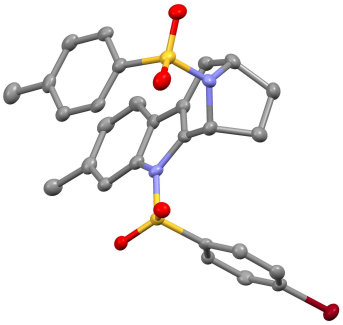


Figure 4. Structure of compound **6e** in its crystal.

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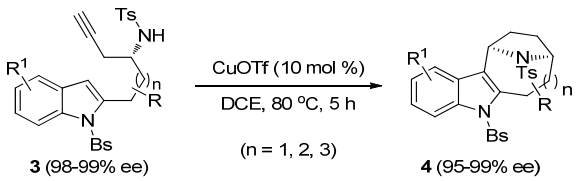
Table 3. Construction of bridged aza-[*n*.2.1] skeletons **4**.[a]

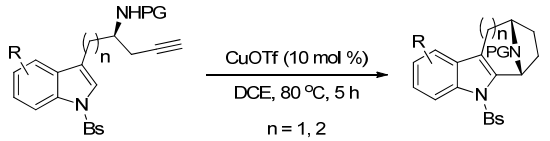


3 (98-99% ee) **4** (95-99% ee)

Entry	Substrate	Product	Yield (%)
1	**3a**, 99% ee	**4a**, 99% ee	93
2[b]	**3b**, R = Cl, 98% ee	**4b**, R = Cl, 98% ee	90
3[b]	**3c**, R = Br, 98% ee	**4c**, R = Br, 98% ee	85
4	**3d**, R = Me, 98% ee	**4d**, R = Me, 98% ee	91
5[b]	**3e**, R = CO_2Me, 99% ee	**4e**, R = CO_2Me, 99% ee	81
6	**3f**, R = Me, 98% ee	**4f**, R = Me, 98% ee	87
7	**3a'**, 99% ee	**4a'**, 99% ee	89
8	**3g**, 98% ee	**4g**, 98% ee	91
9	**3h**, 95% ee	**4h**, 95% ee	81
10	**3i**, 99% ee	**4i**, 99% ee	82

[a] Reaction conditions: **3** (0.2 mmol), CuOTf (0.02 mmol), DCE (2 mL), 80 °C, 5 h, in vials; yields are those for the isolated products; ees are determined by HPLC analysis. [b] Reaction time: 10 h.

Table 4. Construction of bridged aza-[*n*.2.1] skeletons **6**.[a]



5 (97-99% ee) **6** (97-99% ee)

Entry	Substrate	Product	Yield (%)
1	**5a**, PG = Ts, 99% ee	**6a**, PG = Ts, 99% ee	83
2	**5b**, PG = Ms, 99% ee	**6b**, PG = Ms, 99% ee	67
3	**5c**, R = Cl, 98% ee	**6c**, R = Cl, 98% ee	83
4	**5d**, R = Br, 98% ee	**6d**, R = Br, 98% ee	75
5	**5e**, R = Me, 98% ee	**6e**, R = Me, 98% ee	85
6	**5f**, R = OMe, 98% ee	**6f**, R = OMe, 98% ee	80
7	**5g**, 99% ee	**6g**, 98% ee	81
8	**5h**, 98% ee	**6h**, 98% ee	76
9	**5a'**, 97% ee	**6a'**, 97% ee	82
10	**5i**, 98% ee	**6i**, 98% ee	78

[a] Reaction conditions: **5** (0.2 mmol), CuOTf (0.02 mmol), DCE (2 mL), 80 °C, 5 h, in vials; yields are those for the isolated products; ees are determined by HPLC analysis.

In addition, other heterocycle-tethered homopropargyl amides **7a**-**c**, and even alkoxy arene-substituted amide **7d** were suitable substrates for such a copper-catalyzed cascade cyclization, delivering the desired aza-[3.2.1] skeletons **8a**–**d** in 56–86% yields [Eq. (1-3)]. It is notable that these heterocycle-based and aryl-based tropanes[3] can be found in various bioactive molecules, and their enantioselective synthesis often exhibits low efficiency.[2c] Interestingly, the cascade cyclization of indolyl alkyne **7e** under this copper catalysis could also produce the corresponding aza-[3.2.1] skeleton **8e** in 91% yield [Eq. (4)] via a presumable 5-*exo*-*dig* cyclization/Friedel−Crafts alkylation.[17] Moreover, this copper catalysis was also extended to the methyl- and ethyl-substituted internal alkynes **7f** and **7g**, and the desired

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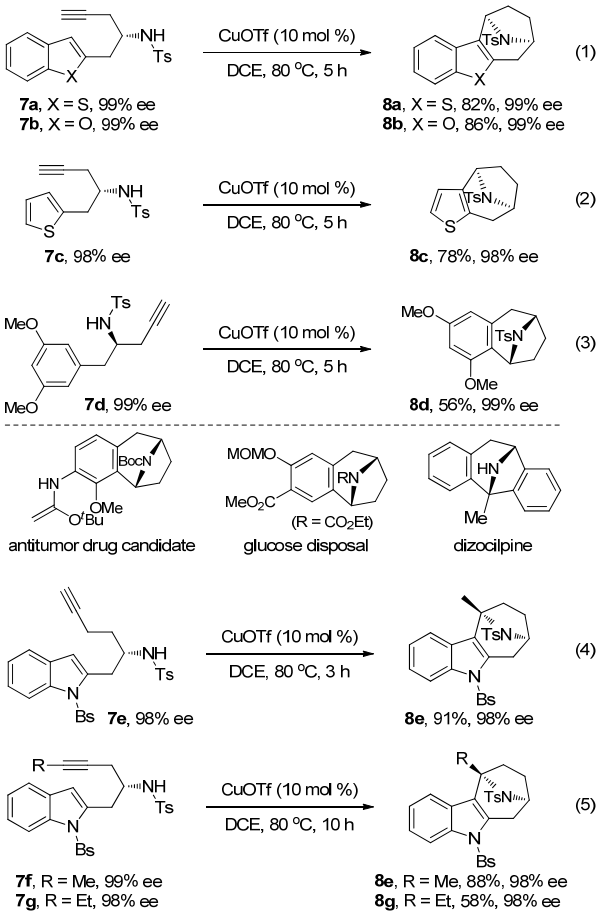
products **8e** and **8g** could be obtained in 88% and 58% yields, respectively [Eq. (5)].[21] Again, complete chirality transfer and excellent diastereoselectivity (d.r. > 50:1) were achieved in all these cases.



Further transformations of the as-synthesized bridged aza-[*n*.2.1] skeletons were also explored (Scheme 2). For example, the formal synthesis of a reported 5-HT_6 antagonist[2c] was achieved in 62% yield (2 steps) starting from the corresponding bridged heterocycle **2h** by a facile deprotection of both sulfonyl groups and selective Boc protection of nitrogen on the bridgehead. In addition, the *N*–Bs group in **4a**, which could be prepared on a gram scale in 89% yield, was easily converted into the corresponding *N*–Me group, affording the desired **4aa** in 72% yield (2 steps). **4aa** could undergo facile ring-opening by Et_3SiH and 2-methylfuran to deliver the valuable indole-fused cyclooctane **4ab** and **4ac**, respectively.[22] Moreover, **4aa** could also be selectively transformed into aza-[4.2.1] skeleton **4ad** and chlorinated aza-[4.2.1] skeleton **4ae** in 81% and 88% yield, respectively.[23,24] The molecular structure of **4ad** was further confirmed by X-ray diffraction (Figure 5).[20] Finally, it was found that **6g** could undergo deprotection of both sulfonyl groups,

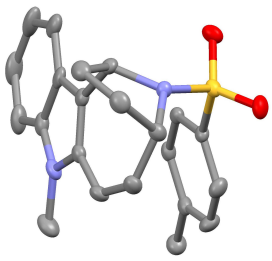
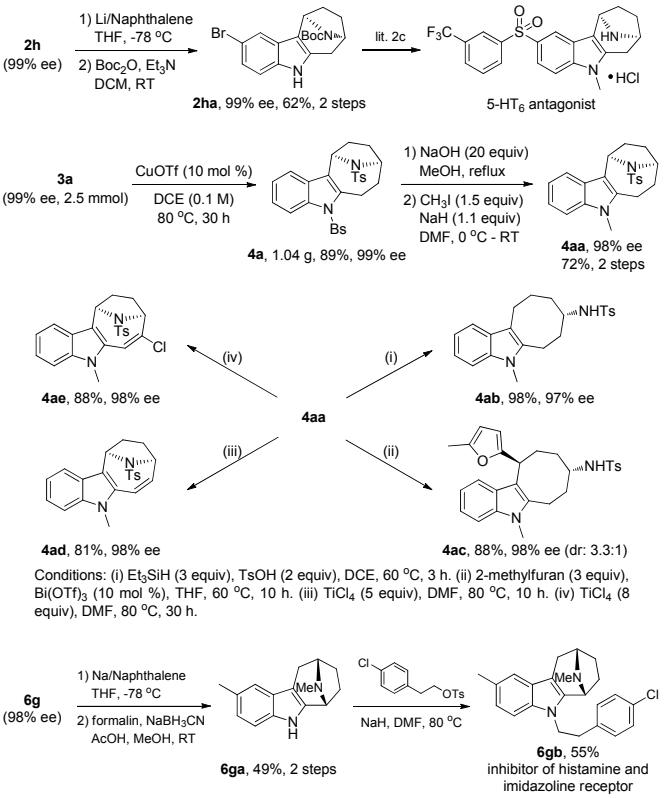


Figure 5. Structure of compound **4ad** in its crystal.



Scheme 2. Gram scale reaction and synthetic applications.

selective methyl protection, and subsequent alkylation to produce **6gb**, a known inhibitor of histamine and imidazoline receptor.[2a] Importantly, enantioselectivity was well maintained in all cases, and excellent diastereoselectivity (d.r. > 50:1) was achieved except for the case of the formation of **4ac**.

To probe the reaction mechanism, we first performed deuterium labelling studies [Eq. (6)]. It was found that no deuterium was incorporated into the product **2e** in the presence of CuOTf as catalyst and H_2O (5 equiv) as additive when starting from the deuterium-labelled substrate **1e** (88% D). However, almost no deuterium loss was observed if employing BrettPhosAuNTf$_2$ as catalyst. Similarly, 63% deuterium incorporation at C10 position was observed by using CuOTf as catalyst and D_2O (5 equiv) as additive. These results indicate that the copper acetylide complex is presumably involved in such a copper catalysis while the reaction is initiated through the direct π activation of the alkyne in case of gold catalysis.[12] In addition, we indeed detected the formation of the indolyl dihydropyrrole **2ea** by monitoring the cascade cyclization of **1e** using NMR spectroscopy under standard reaction conditions, but attempts to isolate **2ea** in the Cu-catalyzed reaction system failed. To our delight, the cyclization of **1e** catalyzed by Ag_2CO_3 (20 mol %) at 80 °C could only led to the formation of **2ea** in 68% yield, and almost no bridged heterocycle **2e** was obtained.[17] As shown in Eq. (7), we further found that **2ea** could be readily converted into the desired **2e** in the presence of copper or proton acid catalyst while low efficiency was observed without catalyst. These results strongly support the notion that **2ea** is the key intermediate for this cascade cyclization and copper catalyzes both an initial hydroamination step and a subsequent Friedel-Crafts-type alkylation step. Considering that the Csp^3-Cu bond is very difficult to be protonated, proton generated from the reaction of copper catalyst with trace water in the reaction system, that is the hidden Brønsted acid,[25] is probably the real species promoting this Friedel-Crafts alkylation process.

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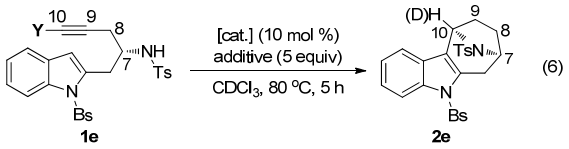
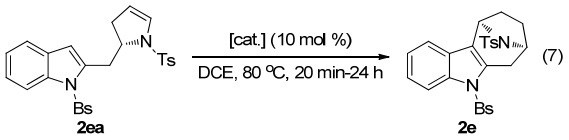
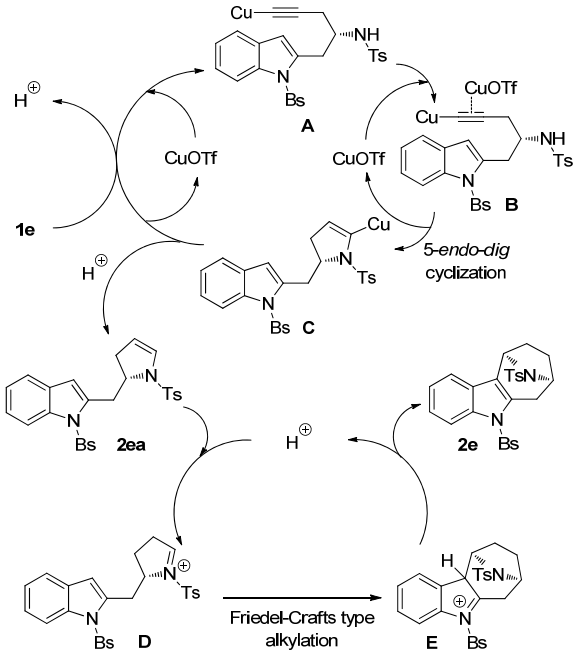


Y	catalyst	additive	yield	C-10 of **2e**
D (88%)	CuOTf	H_2O	94%	<1% D
D (88%)	BrettPhosAuNTf$_2$	H_2O	52%	83% D
H	CuOTf	D_2O	93%	63% D



without catalyst: 40% (24 h), 20% of **2ea** was recovered
CuOTf: 97% (3 h), <1% of **2ea** was recovered
HOTf: 92% (20 min), <1% of **2ea** was recovered

Based on the above experimental observations and our previous results,[12] a rationale for the formation of the bridged heterocycle **2e** is provided in Scheme 3. The reaction starts with formation of the copper acetylide complex **A**, which distinguishes this process from the related gold-catalyzed cyclization reactions,[12,9a,9b] where the Lewis acid-type activation of the starting alkyne is presumably involved. Intermediate **A** then undergoes 5-*endo-dig* cyclization to afford the vinyl copper intermediate **C**,[6a,26] probably involving the formation of σ,π-bis(copper) acetylides **B** by the assistance of another CuOTf serving as π acid.[27] Subsequent protodemetallation leads to indolyl dihydropyrrole **2ea**, which could be finally converted into the corresponding product **2e** through a Lewis acid or proton[8b] catalyzed Friedel-Crafts alkylation. In the cases where 3-substituted indole-tethered homopropargyl amides **5** are employed, the described sequence presumably involves the cyclization onto C3 position of indole moiety followed by subsequent 1,2-migration.[5i] Finally, it is noted that the stereospecificity of the reaction might be attributed to the fact that the Friedel-Crafts type reaction operating is geometrically forced to proceed with a chirality transfer, and the nature of the bicyclic motifs obtained also accounts for the chiral induction.



Scheme 3. Proposed mechanistic pathway.

In summary, we have developed an unprecedented copper-catalyzed anti-Markovnikov cycloisomerization-initiated tandem reaction of readily available indolyl homopropargyl amides, where the cheap and environmentally friendly copper catalyzes both the hydroamination and Friedel−Crafts alkylation process. The protocol allows the practical and atom-economical synthesis of valuable bridged aza-[*n*.2.1] skeletons (*n* = 3–6) with wide substrate scope, and excellent diastereoselectivity (d.r. > 50/1) and enantioselectivity (95-99% ee) by a chirality-transfer strategy. In addition, the synthetic usefulness of the bridged heterocycles is demonstrated through the synthesis of an inhibitor of histamine and imidazoline receptor and a key intermediate of a reported 5-HT_6 antagonist. Moreover, mechanistic studies revealed that the copper acetylide complex is presumably involved in this copper-catalyzed cascade cyclization, which is distinctively different from the related gold catalysis. The development of novel non-noble metal-catalyzed cascade cyclization reactions of alkynes for heterocycle synthesis and mechanistic investigations are the subjects of ongoing research in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: heterocycles · cyclizations · stereoselectivity · copper catalysis · tandem reaction

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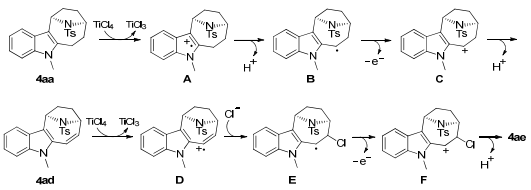

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Cyclizations

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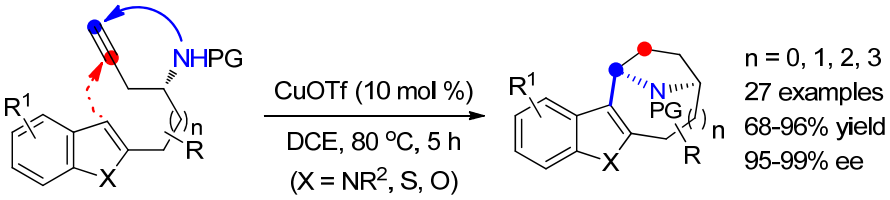
Copper-catalyzed Cascade Cyclization of Indolyl Homopropargyl Amides: Stereospecific Construction of Bridged Aza-[*n*.2.1] Skeletons



- ♦ anti-Markovnikov addition outcompetes the typical Markovnikov addition
- ♦ copper catalysis ♦ complete chirality transfer ♦ cascade cyclization
- ♦ valuable chiral bridged aza-[*n*.2.1] skeletons ♦ broad substrate scope

An unprecedented copper-catalyzed *endo*-cyclization-initiated tandem reaction of indolyl homopropargyl amides is achieved, where copper catalyzes both the hydroamination and Friedel−Crafts alkylation process. This method allows the practical and atom-economical synthesis of valuable bridged aza-[*n*.2.1] skeletons (*n* = 3–6) with wide substrate scope, and excellent diastereoselectivity and enantioselectivity by a chirality-transfer strategy.