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Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization

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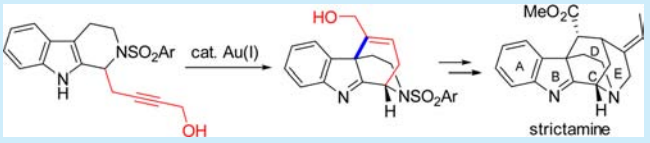
Supporting Information

ABSTRACT: A gold-catalyzed cyclization of 1-propargyl-1,2,3,4-tetrahydro-β-carboline led to formation the D-ring of strictamine. Functional group modifications of the resulting tetracyclic indolenine led to the formal total synthesis of (±)-strictamine.



Akuammiline alkaloids (Figure 1) are monoterpene indole alkaloids bearing a cage-like structure and a broad range

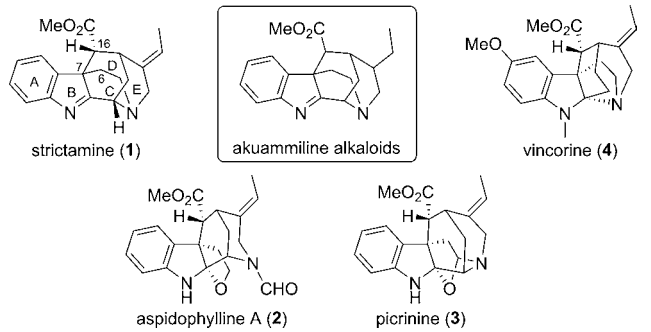


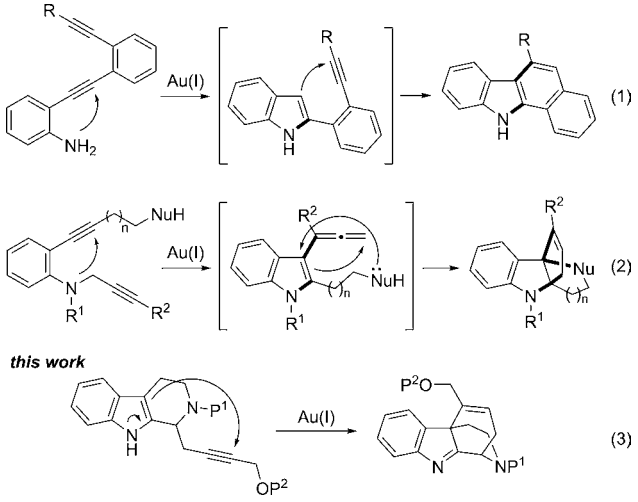
Figure 1. Structure of akuammiline alkaloids.

of biological activities, including anticancer, antibacterial, anti-inflammatory, and antimalarial inhibitory activities.[1] Strictamine (**1**) was first isolated by Ganguli et al. in 1966 from *Rhazya stricta*, used as a folk medicine in India,[2] and was seen as a pharmaceutical resource due to its potent inhibition of monoamine oxidase(s).[1a] The unique pentacyclic cage-like structure of strictamine has attracted the attention of many synthetic chemists, and much effort has been expended seeking a total synthesis;[3] however, its total synthesis has not been disclosed until quite recently.[4,5] This is mainly due to the difficulty of forming the C7−C16 bond for construction of the central D-ring and the construction of the E-ring, which induces a disfavored boat−boat conformation of C/E rings.

In 2014, Garg et al. reported the total synthesis of picrinine (**3**),[6] which also constitutes a formal synthesis of strictamine (**1**).[7] Quite recently, the same group completed an asymmetric total synthesis of strictamine (**1**) based on the gold-catalyzed cyclization of an enantioenriched silyl dienol ether to form the D−E-ring system and late-stage construction of the indolenine and C-rings.[4] Almost at the same time, Zhu and co-workers achieved total synthesis of (±)-strictamine, which relies on an early-stage creation of the C7 quaternary carbon, successive construction of the D-, C-, and indolenine rings, and the arduous construction of the E-ring as the final ring closure.[5]

Our group is engaged in developing gold-catalyzed cascade cyclizations of alkynes for construction of indole-derived polycyclic heterocycles.[8] For example, we have developed a fused carbazole synthesis based on the intramolecular cascade cyclization reaction of aniline bearing a diyne moiety (Scheme 1, eq 1).[8a−c] This reaction proceeds through 5-*endo*-*dig* hydroamination to form an indole ring, followed by 6-*endo*-*dig* hydroarylation from the C3 position of the indole ring. More recently, we reported construction of a tetracyclic indoline ring through formation of a 3-allenylindole intermediate by migration of a propargyl group on the nitrogen atom of an aniline, followed by second and third cyclizations (eq 2).[8d]

Scheme 1. Our Concept for Construction of the D-Ring of Strictamine Based on Gold(I)-Catalyzed Cyclization



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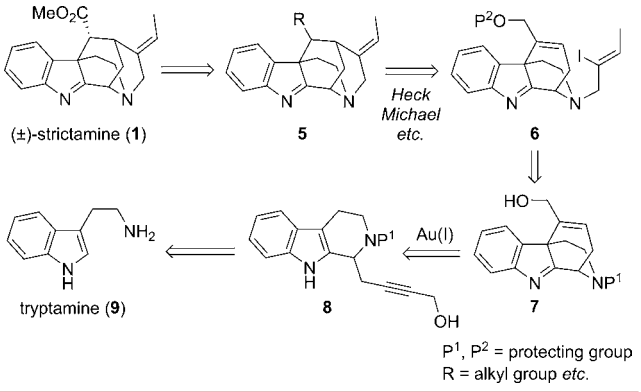
In these reactions, gold catalysts efficiently promote nucleophilic attack of the indole ring on a carbon−carbon multiple bond to facilitate the second ring closure. On the basis of this chemistry, we expected that gold-catalyzed cyclization at the indole C3 position of 1-propargyl-1,2,3,4-tetrahydro-β-carboline (THBC) derivatives would allow efficient construction of the D-ring of akuammiline alkaloids including strictamine (**1**) (eq 3). It should be noted that a related approach based on a gold-catalyzed 6-*exo*-*dig* cyclization of 1-homopropargyl-THBC was recently reported by Wang et al.[9] This reaction requires N-silylation for selective cyclization at the C3 position of indole. This contribution and the recent achievements by Garg[4] and Zhu[5] prompted us to report our study on the formal total synthesis of (±)-strictamine by gold-catalyzed cyclization.

Our retrosynthetic analysis of strictamine (**1**) is outlined in Scheme 2. Strictamine can be obtained from **6** by construction

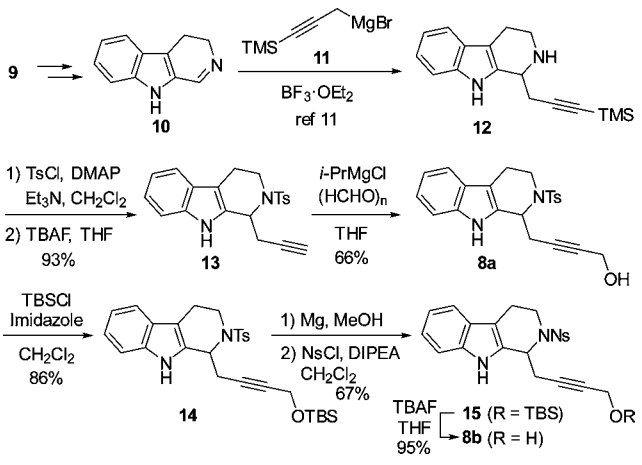
Scheme 2. Retrosynthetic Analysis of Strictamine (1)



of the E-ring using a reductive Heck-type reaction[10] according to Zhu's protocol,[5] in addition to formation of the methyl ester moiety. The iodobutenyl group of **6** can be easily introduced to the nitrogen atom of **7**, which is the expected product of the aforementioned gold-catalyzed cyclization reaction. The cyclization precursor, 1-propargyl-THBC derivative **8**, will be readily prepared from tryptamine (**9**).

Synthesis of the cyclization precursor of type **8** is shown in Scheme 3. Following the procedure documented in the literature,[11] the known 1-propargyl-THBC derivative **12** was prepared from tryptamine (**9**) via formylation with HCO_2Et,

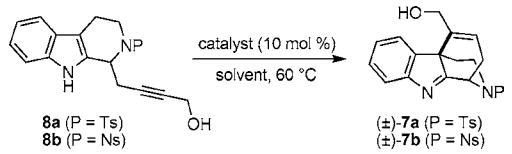
Scheme 3. Synthesis of the Cyclization Precursors



cyclization with $POCl_3$, and addition of Grignard reagent **11**. Tosylation and desilylation of **12** afforded propargyl-THBC derivative **13**. Hydroxymethylation of the terminal alkyne of **13** and protecting group modifications afforded cyclization precursors **8a** and **8b**, bearing a tosyl or nosyl protecting group, respectively.

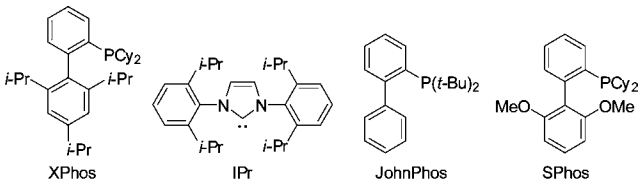
We then investigated the gold-catalyzed cyclization of propargyl THBC derivatives. Fortunately, treatment of the tosylamide **8a**, having an unprotected hydroxymethyl group with XPhosAuCl (cat. **16**)[12] possessing a bulky electron-donating ligand in the presence of $AgNTf_2$ in 1,2-dichloroethane (DCE), gave the desired compound **7a** in 20% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions



entry	substrate	catalyst	solvent	time (h)	yield (%)[b]
1	**8a**	cat. **16**/$AgNTf_2$	DCE[a]	24	20
2	**8a**	cat. **17**/$AgNTf_2$	DCE[a]	18	33
3	**8a**	cat. **18**	DCE[a]	10	35
4	**8a**	cat. **18**	THF	20	52
5	**8a**	cat. **18**	EtOH	4	50
6	**8a**	cat. **19**/$AgNTf_2$	EtOH	5	69
7	**8b**	cat. **19**/$AgNTf_2$	EtOH	14	76

[a]DCE = 1,2-dichloroethane. [b]Isolated yield.



16: XPhosAuCl **17**: IPrAuCl **18**: JohnPhosAu(MeCN)SbF6 **19**: SPhosAuCl

Improvement in yield was observed by use of IPrAuCl (cat. **17**)[13] and JohnPhosAu(MeCN)SbF_6 (cat. **18**)[14] (33−35%, entries 2 and 3). Screening of the reaction solvents revealed that THF (52%, entry 4) and EtOH (50%, entry 5) are more suitable for the reaction. Among the catalysts examined, a combination of SPhosAuCl (cat. **19**)[15] and $AgNTf_2$ showed the most efficient activity (69%, entry 6). Use of the nosylamide **8b** as the substrate slightly improved the yield to 76% (entry 7).

The formal total synthesis of (±)-strictamine is shown in Scheme 4. An iodobutenyl group was introduced using **21**[16] after protection of the terminal hydroxyl group and removal of the Ns group to give substrate **6a** for the Heck-type reaction. Unfortunately, all our attempts at construction of the E-ring using **6a** have been unsuccessful. For example, treatment of **6a** with $Pd(OAc)_2$, PPh_3, *n*-Bu_4NCl, and K_2CO_3 in DMF gave a complex mixture of unidentified products without promoting the desired cyclization. Thus, we decided to prepare the enoate-type cyclization precursor **26**.[5] Conversion of the N-protecting group[17] of **20** from Ns to Boc to give **23**, removal of the silyl group, two-step oxidation of the primary alcohol, and esterification of the resulting carboxylic acid gave the enoate **25**. Finally, removal of the Boc group and iodobutenylation of the amino group led to the desired enoate **26**, which is Zhu's strictamine precursor.[5] The spectral data of **26** were in good agreement with those reported.[5]

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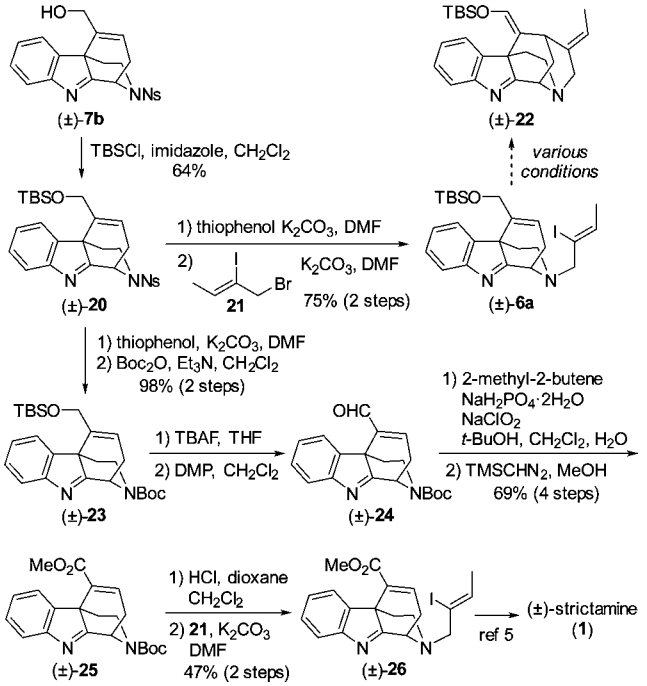
Scheme 4. Formal Total Synthesis of (±)-Strictamine



In summary, we succeeded in the formal total synthesis of (±)-strictamine, an akuammiline alkaloid possessing a cage-like structure. Starting from tryptamine, tetracyclic indolenines bearing the A–D-ring system were synthesized based on gold-catalyzed cyclization of 1-propargyl-1,2,3,4-tetrahydro-β-carboline derivatives. Further studies on asymmetric total synthesis of strictamine including optimization of protecting group strategy are now under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00536.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Conversion of the nitrogen protecting groups (Ts, Ns, and Boc) was necessary because (1) hydroxymethylation of Ns derivative with HCHO was less efficient than that of the Ts derivative **13**, (2) deprotection of Ns group was unsuccessful after construction of the enoate moiety, and (3) as our first choice, the replacement of Ns group in **20** with Boc group was safer than direct replacement with an iodobutenyl group, considering the later oxidative treatment. For optimization of our synthesis, a Boc-based synthesis or conversion of **6a** to **26** should be examined. Fortunately, our preliminary investigation has revealed that the gold-catalyzed cyclization of *N*-Boc

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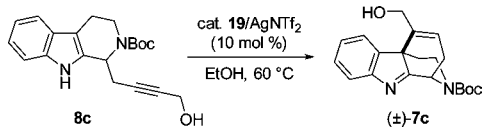
substrate **8c** (for Boc-based synthesis) gave the desired product in 41% yield (not optimized, see graphic).



8c (±)-**7c**

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