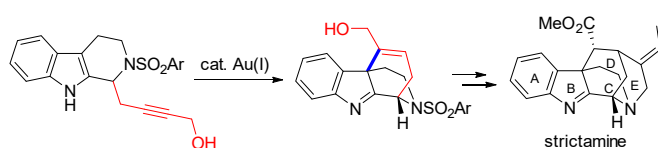


Title	Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization
Author(s)	Nishiyama, Daisuke; Ohara, Ayako; Chiba, Hiroaki; Kumagai, Hiroshi; Oishi, Shinya; Fujii, Nobutaka; Ohno, Hiroaki
Citation	Organic Letters (2016), 18(7): 1670-1673
Issue Date	2016-4
URL	http://hdl.handle.net/2433/241632
Right	This document is the Accepted Manuscript version of a Published Work that appeared in final form in 'Organic Letters', copyright © American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://doi.org/10.1021/acs.orglett.6b00536 .; The full-text file will be made open to the public on 24 March 2017 in accordance with publisher's 'Terms and Conditions for Self-Archiving'.; This is not the published version. Please cite only the published version. この論文は出版社版ではありません。引用の際には出版社版をご確認ご利用ください。
Type	Journal Article
Textversion	author

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

Daisuke Nishiyama, Ayako Ohara, Hiroaki Chiba,[†] Hiroshi Kumagai, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan



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 (\pm)-strictamine.

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

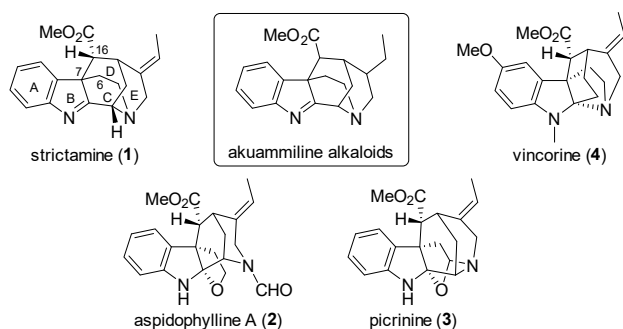
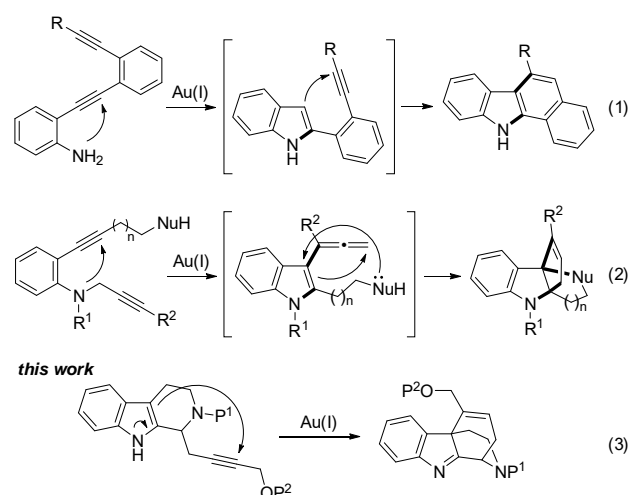


Figure 1. Structure of akummline alkaloids.

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 (\pm)-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

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

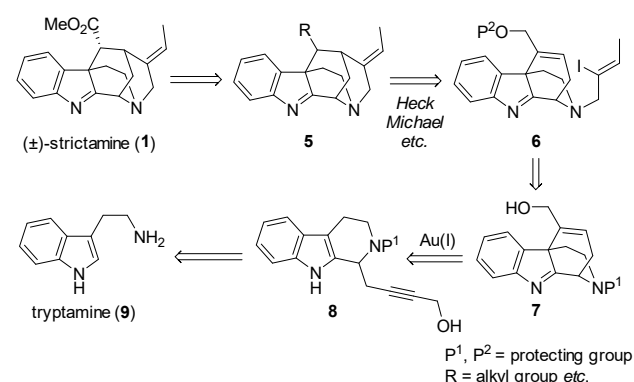


Our group is engaged in developing gold-catalyzed cascade cyclizations of alkynes for construction of indole-derived polycyclic heterocycles.⁸ For example, we have developed a fused carbazole synthesis based on the intramolecular cascade cyclization reaction of aniline bearing a diyne moiety (Scheme 1, eq 1).^{8a-c} This reaction proceeds through 5-*endo-dig* hydroami-

nation 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} 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 akuamline 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 Garg⁴ and Zhu⁵ prompted us to report our study on the formal total synthesis of (\pm)-strictamine by gold-catalyzed cyclization.

Our retrosynthetic analysis of strictamine (**1**) is outlined in Scheme 2. Strictamine can be obtained from **6** by construction of the E-ring using a reductive Heck-type reaction¹⁰ 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**).

Scheme 2. Retrosynthetic Analysis of Strictamine (**1**)



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 , 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 (entry 1). Improvement in yield was observed by use of IPrAuCl (cat. **17**)¹³ and

$\text{JohnPhosAu}(\text{MeCN})\text{SbF}_6$ (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).

Scheme 3. Synthesis of the Cyclization Precursors

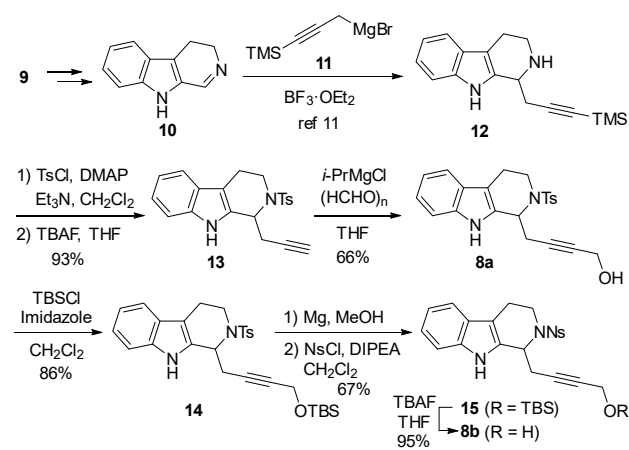
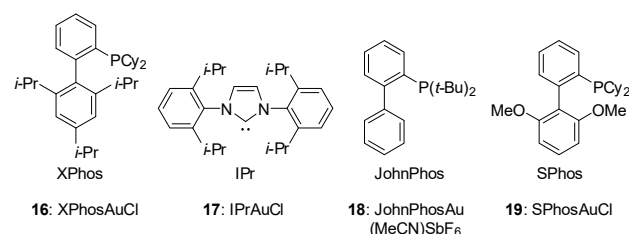


Table 1. Optimization of Reaction Conditions

8a ($P = \text{Ts}$) / **8b** ($P = \text{Ns}$) $\xrightarrow[\text{solvent, 60 } ^\circ\text{C}]{\text{catalyst (10 mol \%)}}$ (\pm)-**7a** ($P = \text{Ts}$) / (\pm)-**7b** ($P = \text{Ns}$)

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

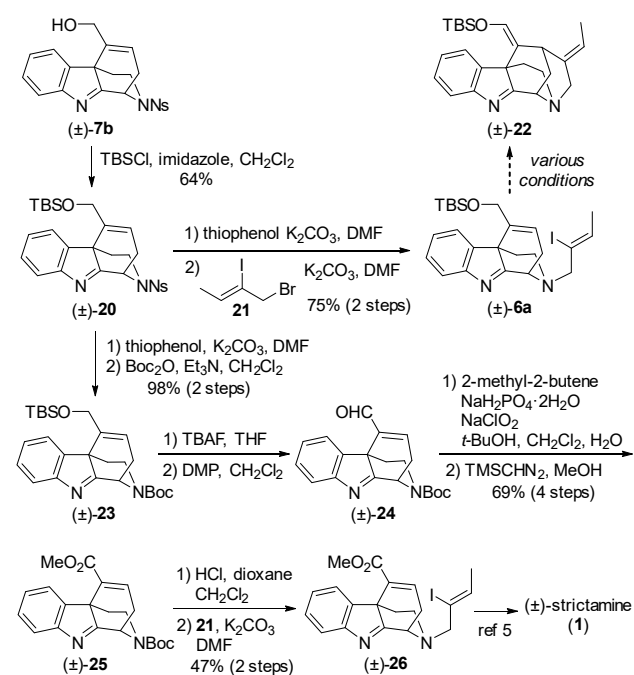
^aDCE = 1,2-dichloroethane. ^bIsolated yield.



The formal total synthesis of (\pm)-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, PPh₃, *n*-Bu₄NCl, and K₂CO₃ 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 group¹⁷ 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

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.xxxxxxx.

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

AUTHOR INFORMATION

Corresponding Author

* E-mail: nfuji@pharm.kyoto-u.ac.jp (N. Fujii).

* E-mail: hohno@pharm.kyoto-u.ac.jp (H. Ohno).

Present Addresses

†Department of Chemistry, Graduate School of Science, Tohoku University, 6-3 Aramaki-Aza Aoba, Aoba-ku, Sendai 980-8578, Japan.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for the Encouragement of Young Scientists (A) (H.O.) and Scientific Research (B) (H.O.) and the Platform for Drug Design, Discovery, and Development from the MEXT, Japan. H.C. is grateful for Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

REFERENCES

- (a) Bhattacharya, S. K.; Dutta, S. C.; Ray, A. B.; Guha, S. R. *Indian J. Exp. Biol.* **1979**, *17*, 598. For reviews: (b) Eckermann, R.; Gaich, T. *Synthesis* **2013**, *45*, 2813. (c) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 400.
- (2) Schnones, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Am. Chem. Soc.* **1966**, *31*, 1642.
- (3) (a) Dolby, L. J.; Esfandiari, A. *J. Org. Chem.* **1972**, *37*, 43. (b) Dolby, L. J.; Nelson, S. J. *J. Org. Chem.* **1973**, *38*, 2882. (c) Bannasar M.-L.; Zulaica, E.; López, M.; Bosch, J. *Tetrahedron Lett.* **1988**, *29*, 2361. (d) Koike, T.; Takayama, H.; Sakai, S.-I. *Chem. Pharm. Bull.* **1991**, *39*, 1677. (e) Bannasar, M.-L.; Zulaica, E.; Ramirez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239. (f) Edwankar, R. V.; Edwankar, C. R.; Namjoshi, O. A.; Deschamps, J. R.; Cook, J. M. *J. Nat. Prod.* **2012**, *75*, 181. (g) Komatsu, Y.; Yoshida, K.; Ueda, H.; Tokuyama, H. *Tetrahedron Lett.* **2013**, *54*, 377. (h) Ren, W.; Tappin, N.; Wang, Q.; Zhu, J. *Synlett* **2013**, *24*, 1941. (i) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.-I.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 906.
- (4) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc.* **2016**, *138*, 1162.
- (5) Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 3500.
- (6) (a) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 4504. (b) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. *J. Org. Chem.* **2015**, *80*, 8954.
- (7) Strictamine was accessed from picrinine in a five step sequence: Banerji, J.; Chakrabarti, R. *Indian J. Chem., Sect. B* **1984**, *23B*, 453.
- (8) (a) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368. (b) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212. (c) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068. (d) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 7862. For our related reactions based on gold-catalyzed indole formation, see: (e) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138. (f) Matsuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Eur. J.* **2015**, *21*, 1463. (g) Naoe, S.; Saito, T.; Uchiyama, M.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2015**, *17*, 1774. (h) Taguchi, M.; Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2015**, *17*, 6250.
- (9) (a) Xu, W.; Wang, W.; Wang, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9546. For a related reaction, see: (b) Zhang, L.; Wang, Y.; Yao, Z.-J.; Wang, S.; Yu, Z.-X. *J. Am. Chem. Soc.* **2015**, *137*, 13290.
- (10) (a) Teng, M.; Zi, W.; Ma, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 1814. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.
- (11) Kolundžić, F.; Murali, A.; Pérez-Galán, P.; Bauer, J. O.; Strohmman, C.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8122.

(12) Partyka, D. V.; Robilotto, T. J.; Zeller, M.; Hunter, A. D.; Gray, T. G. *Organometallics* **2008**, *27*, 28.

(13) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448.

(14) Mudd, R. J.; Young, P. C.; Jordan-Hore, J. A.; Rosair, G. M.; Lee, A. *J. Org. Chem.* **2012**, *77*, 7633.

(15) Hashmi, A. S. K.; Graf, K.; Ackermann, M.; Rominger, F. *Chem-CatChem* **2013**, *5*, 1200.

(16) Yin, W.; Kabir, S.; Wang, Z.; Rallapalli, S. K.; Ma, J.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3339.

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

