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A 7-Step Formal Asymmetric Total Synthesis of Strictamine via an Asymmetric Propargylation and Metal-Mediated Cyclization

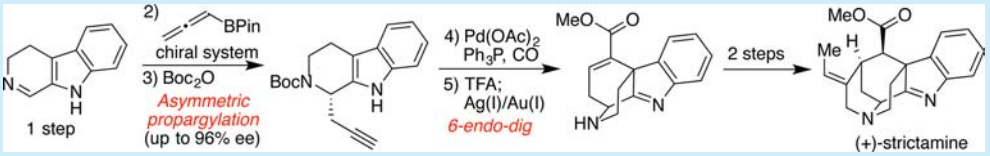
Myles W. Smith,[||,†,‡] Zhiyao Zhou,[||,§] Alison X. Gao,[||,‡] Takuya Shimbayashi,[§] and Scott A. Snyder*[,†,‡,§]

[†]Columbia University, Dept. of Chemistry, 3000 Broadway, New York, New York 10027, United States

[‡]The Scripps Research Institute, Dept. of Chemistry, 130 Scripps Way, Jupiter, Florida 33458, United States

[§]University of Chicago, Dept. of Chemistry, 5735 S. Ellis Avenue, Chicago, Illinois 60637, United States

Supporting Information



ABSTRACT: Herein is shown how a novel catalytic asymmetric propargylation of 3,4-dihydro-β-carboline, followed by a designed Au(I)/Ag(I)-mediated 6-*endo*-dig cyclization, can directly deliver the indolenine-fused methanoquinolizidine core of the akuammiline alkaloid strictamine in its native oxidation state, ultimately achieving a 7-step formal asymmetric total synthesis. Also demonstrated are how the cyclization products can rearrange into vincorine-type skeletons and a further use for the developed propargylation with the first catalytic asymmetric total synthesis of decarbomethoxydihydrogambirtannine.

The akuammilines are a structurally unique collection of bioactive natural products that fuse an array of rings into compact, cage-like frameworks containing multiple, contiguous stereogenic centers (such as **1**−**7**, Scheme 1).[1] Some of its members have been known for over 125 years,[2] and several have shown promising biological activity.[3] Given such a profile, it is unsurprising that numerous endeavors have sought to access them over the past 4 decades;[4] despite much effort, however, it is only within recent years that laboratory chemical synthesis has overcome their challenges, with successful total syntheses of scholarisine A (**1**),[5] aspidophylline A (**2**),[6] picrinine (**3**),[7] vincorine (**4**),[8] aspidodasycarpine (**5**),[9] and others[10] having been reported; one is from our group.[5c]

As an outgrowth of that study, we became interested in the unique connectivities of strictalamine (**6a**), rhazinoline (**6b**), and strictamine (**7**).[11] The latter of these has been known since 1966 following its isolation from *Rhazya stricta*,[11a] with subsequent X-ray crystallographic analysis establishing its characteristic methanoquinolizidine ring framework (highlighted in red), one shared by its differentially oxidized cousins.[11b,c] Within the past year, the first successful routes to this subgroup of the akuammilines have been reported. The inaugural report was an asymmetric preparation of (+)-strictamine (**7**) in 24 steps by the Garg group, employing their versatile Fisher indolization methodology.[12a] The Zhu group[12b] then reported a more expeditious, but racemic, 14-step preparation of **7** by way of **8**, using an alkylation and subsequent Ni(0)-mediated bond formation to complete the strained core, noting that the final C−C bond formation was low yielding. More recently, a team led by Fujii and Ohno[12c] developed an alternate synthesis of **8** (18 steps; 20 steps formally to **7**) which utilized a unique Au(I)/Ag(I)-mediated 6-*endo*-dig cyclization of **10** to construct the main elements of the core as expressed in **11**; while highly elegant, several synthetic operations were necessary both to prepare the starting alkyne and to elaborate its product to **8**. Finally, the Gaich group recently completed a formal total synthesis of strictamine by intersecting the penultimate intermediate from the Zhu synthesis (35 steps formally to **7**).[12d] Herein, we present a strategy, long under development,[13] which contains elements of both the Zhu and Fujii/Ohno routes. Critically, by developing a novel catalytic asymmetric propargylation of 3,4-dihydro-β-carboline (**9**) and effecting the key alkyne-based cyclization reaction without protecting groups and at proper oxidation state, enantioenriched strictamine (**7**) can be accessed in only 7 steps. We also illustrate the value of the asymmetric propargylation by synthesizing another alkaloid in enantioenriched form.

Our original retrosynthetic analysis for strictamine (**7**), shown in Scheme 1 with key results documented in a doctoral thesis,[13] was predicated on the same type of late stage *N*-alkylation and C−C bond formation to complete the target as used in the Zhu synthesis,[12b,4l,14] projecting multiple options for that final ring closure. And, similar to the Fujii/Ohno strategy,[12c] we wished to utilize a 6-*endo*-dig closure of a pendant alkyne, added onto **9**[15] through a propargylation reaction, to forge the core of **12**. Our key goals to translate this plan into a short and efficient synthesis were (1) to develop an asymmetric version of that propargylation, a reaction known in some contexts with aldehydes, ketones, and specific *N*-protected imines, but rarely with imines of this type;[16] and (2) to identify appropriate conditions to promote the desired

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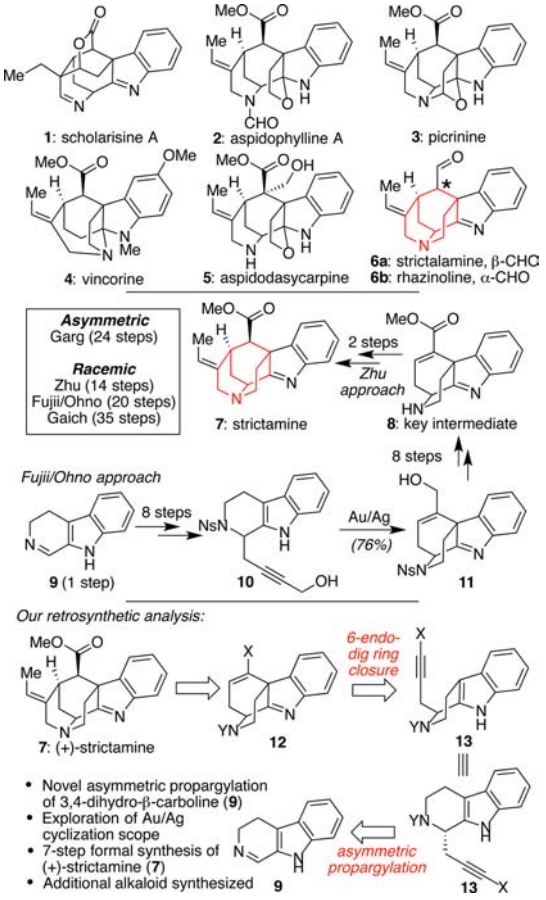
Scheme 1. Structures of Selected Akuammiline Alkaloids (1−6), Recent Syntheses of Strictamine (7), and a Retrosynthetic Analysis Based on Developing Two Key Reactions



6-*endo*-dig closure using functionality at the native oxidation state of the target.

Figure 1 provides a short summary of the extensive efforts undertaken to effect an asymmetric propargylation of **9**. While the racemic version of the reaction was readily achieved (allenylboronic acid pinacol ester, THF, 23 °C, 8 h), it proved difficult to identify systems, including those deployed for related asymmetric allylations, which could achieve chiral control. For instance, efforts using stoichiometric chiral reagents such as **15** and **16**,[17] selected for their allylation success and for being privileged chiral scaffolds, afforded **14** (following *in situ* methyl carbamate protection) with virtually no ee. Similarly, several chiral transition metal complexes or Brønsted acids, such as **17**−**19**, effective for the asymmetric propargylations of aldehydes, afforded improved product yields but only relatively modest enantioinduction (18−32% ee).[18,19] Our first significant hit came when we utilized CuCl and (*R*)-DTBM-SEGPHOS (**20**)[20] in a process which afforded **14** in modest yield (61%), but reasonable enantioselectivity (67% ee). Subsequent optimization (see SI for details) afforded reproducible results on 0.2 mmol scale where, with 12 mol % of ligand, 10 mol % of CuCl, and 40 mol % of *t*-BuONa solution, a 61% yield and 96% ee could be achieved for **14**. Pleasingly, even lower levels of chiral ligand, CuCl, and base could also be employed, with only modest loss of chiral induction (65% yield and 90% ee) on a similar scale.[21] Further scale-up under these conditions proved possible, with some erosion in enantioselection observed; recrystallization of **14** can, however, give enhanced optical purity, affording in one run using material of 75% ee a final product with 97% ee in 55% yield.

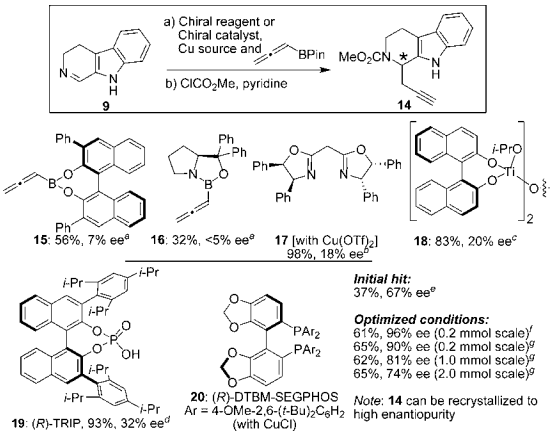
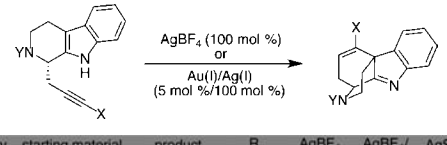
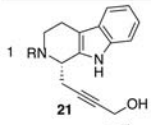
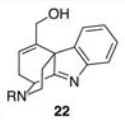
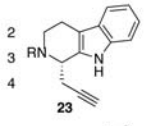
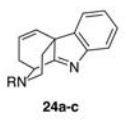
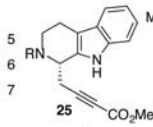
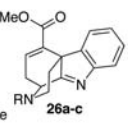
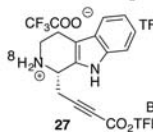
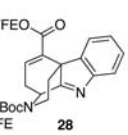


Figure 1. Development of an asymmetric propargylation of **9**. [a] Toluene, 0.05 M, −78 → −30 °C. [b] 12 mol % ligand, 10 mol % $Cu(OTf)_2$, CH_2Cl_2, 0.1 M, −78 → −30 °C. [c] 10 mol % complex, CH_2Cl_2, 0.1 M, −78 → −30 °C. [d] 10 mol % ligand, toluene/THF (20/1), 0.05 M, −30 °C. [e] 24 mol % ligand, 20 mol % CuCl, solid *t*-BuONa (80 mol %), MeOH (2 equiv), THF/toluene (2/1), 0.05 M, −78 → −30 °C. [f] 12 mol % ligand, 10 mol % CuCl, *t*-BuONa solution (40 mol %), MeOH (2 equiv), THF/toluene (2/1), 0.07 M, −78 → −30 °C. [g] 6 mol % ligand, 5 mol % CuCl, *t*-BuONa solution (12 mol %), MeOH (2 equiv), THF, 0.2 M, −78 → −30 °C.

Table 1. Exploring the Key 6-*endo*-dig Cyclization Varying the Protecting Group and Alkyne Substituent[a]



entry	starting material	product	R	$AgBF_4$ yield (%)	$AgBF_4$/Ph_3PAuCl yield (%)	$AgSbF_6$/Ph_3PAuCl yield (%)
1	 21	 22	Alloc	52	16	53
2	 23	 24a-c	CO_2Me	56	57	72
3			Ns	66	56	73
4			Alloc	50	71	94
5	 25	 26a-c	CO_2Me	15	45	59
6			Ns	37	50	56
7			Alloc	62	12	64
8	 27	 28	n.a.	n.r.[b]	24[b]	23[b]

[a]Reactions conducted at 0.1 mmol scale in $ClCH_2CH_2Cl$. $AgBF_4$ conditions: $AgBF_4$ (1.0 equiv), 23 °C, 24 h. $AgBF_4/Ph_3PAuCl$ conditions: Ph_3PAuCl (5 mol %), $AgBF_4$ (1.0 equiv), 23 °C, 24 h. $AgSbF_6/Ph_3PAuCl$ conditions: Ph_3PAuCl (5 mol %), $AgSbF_6$ (1.0 equiv), 23 °C, 24 h. [b]Performed at 50 °C, MsOH (2.0 equiv) added, using 10% Au with a terminating one-pot Boc protection.

Our efforts to effect the key 6-*endo*-dig cyclization on a range of free indoles,[22a] bearing various alkyne (X) and *N*-substituents (Y), are shown in Table 1. Conveniently, a panel of such substrates could be accessed in 3 to 6 steps (see the Supporting Information (SI) for details, all performed with racemic compound). Initial investigations (see SI) revealed three systems based on Ag or Au/

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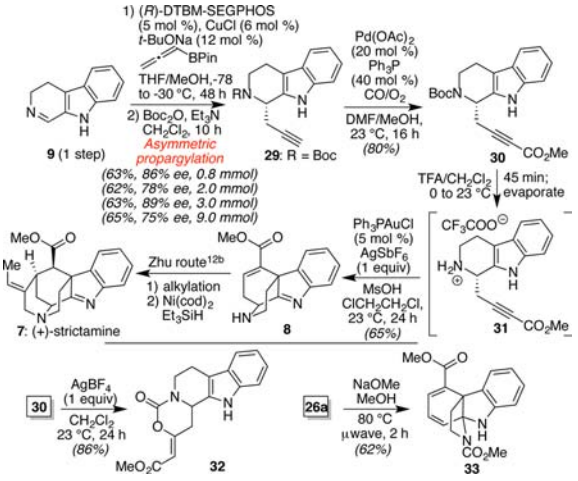
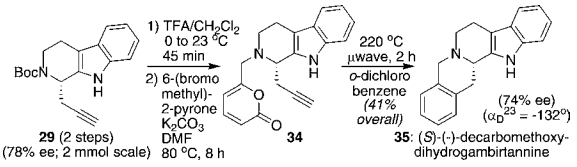
Scheme 2. A 7-Step Asymmetric Synthesis of Strictamine (7)



Scheme 3. Enantioselective Synthesis of Alkaloid 35



Ag salts worth further exploration. Starting with *N*-Alloc protected propargyl alcohol **21**, a compound similar to that used by Fujii and Ohno,[12c] cyclization proceeded at 23 °C in 1,2-dichloroethane using either stoichiometric $AgBF_4$ or a silver salt ($AgBF_4$ or $AgSbF_6$) with catalytic Ph_3PAuCl (here in a maximum of 53% yield). These conditions are distinct from those of Fujii and Ohno.[12c] The same conditions worked with terminal alkynes bearing a range of nitrogen protection (entries 2−4), with products typically obtained in yields superior to the original propargyl alcohol. Critically, electron-deficient ynoate esters were also competent (entries 5−7) despite their lower π-basicity and innate polarity favoring 5-*exo*-dig products.[23]

Globally, optimal yields were obtained using catalytic Ph_3PAuCl with stoichiometric $AgSbF_6$, with the addition of Au(I) generally affording improved yields in most cases relative to stoichiometric $AgBF_4$ alone.[24] In addition, given the observation that stoichiometric amounts of Ag(I) were needed to effect complete starting material consumption, the Lewis basic functionality present within general structures **12** and **13** (cf. Scheme 1), as a carbamate, sulfonamide, and/or imine, might deactivate the catalyst, with excess Ag(I) serving as a sacrificial species to allow for catalyst turnover. Given this analysis, we anticipated that an ammonium salt (generated by the *in situ* deprotection of the Boc-protected precursor of **27** with TFA) should be competent by providing transient protection of the basic amine in **12**/**13**. As an initial lead, such a compound bearing an even more electron-withdrawing ester (i.e., a 2,2,2-trifluoroethyl ester, **27**) could be cyclized in 23% yield (entry 8); key, here, was the addition of MsOH, an additive noted as being critical in similar indole cyclizations.[22c,25]

Given these results, we anticipated that a concise synthesis of compound **8** (cf. Scheme 1),[12b,c] was possible. Starting from **9**[15] (prepared in 1 step, see SI, Scheme 2), the use of our asymmetric allenylboronate-mediated propargylation, followed by Boc protection, provided **29** reproducibly in 63% yield and 86% ee (0.8 mmol scale; its absolute configuration was determined later, *vide infra*). Unfortunately, with this alternate mode of protection, recrystallization to enhance optical purity did not prove possible, and, as an initial effort at scale-up on 2.0 mmol scale showed a slight reduction in ee (as observed with **14**), we utilized the 86% ee material for the remaining sequence. Thus, this new intermediate was then converted into methyl ester **30** in 80% yield through a Pd-catalyzed oxidative carbonylation.[26] The stage was now set for the key 6-*endo*-dig cyclization. In the event, treatment of **30** with TFA and CH_2Cl_2 (1:9) effected its conversion into ammonium salt **31**; following solvent evaporation and resuspension in 1,2-dichloroethane, exposure to stoichiometric $AgSbF_6$, catalytic Ph_3PAuCl, and stoichiometric MsOH afforded **8** in 65% yield. Its spectral properties matched those reported by Zhu,[12b] thus completing a 5-step synthesis of this compound and a formal 7-step total synthesis of enantioenriched (+)-strictamine (**7**).[27] Significantly, the first 3 reactions were effective on gram scale in our scouting with racemic material, with the final step working well when conducted with 0.5 g of **30**; in the racemic route, Boc-protection can also be done *in situ* to afford a 4-step synthesis of (±)-**8**. Of note, the asymmetric propargylation step is more scaleable than our initial 2.0 mmol experiment indicated; efforts post-synthesis at 3.0 and 9.0 mmol using a new batch of allenylboronate show that the process succeeds without substantial ee erosion. Finally, use of the original Boc-protected material (i.e., **30**) in the 6-*endo*-dig cyclization afforded carbamate **32** in 86% yield in which the Boc group attacked the ynoate ester, indicating the value of the ammonium salt. In addition, some 6-*endo*-dig cyclized products, when subjected to base, rearrange into vincorine-type frameworks (**26a** → **33**, 62% yield).

Finally, to highlight the ability of the developed asymmetric propargylation to synthesize indole alkaloids beyond the akuammilines, we pursued an asymmetric total synthesis of decarbomethoxydihydrogambirtannine (**35**, Scheme 3).[28] Those efforts began by Boc-deprotection and *N*-alkylation of **29** (using material with 78% ee; 2.0 mmol scale) to afford pyrone **34**, poised for a thermally promoted intramolecular Diels−Alder/retro-[4+2] reaction sequence which afforded **35** in 41% overall yield with minimal loss of chiral integrity. Of note, although this target (i.e., **35**) has been prepared 10 times previously,[29,30] this novel approach constitutes the first catalytic asymmetric solution, with the recorded optical rotation establishing the absolute stereochemistry of the product formed in the asymmetric propargylation.

In conclusion, we developed an asymmetric propargylation of 3,4-dihydro-β-carboline and a suite of Au(I)/Ag(I)-based 6-*endo*-dig cyclizations that can afford the core frameworks of the akuammiline alkaloids in various oxidation states. Surprisingly, the latter transformation works even for electron-deficient alkynes and "protecting-group-free" materials, thus affording the means to formally access (+)-strictamine (**7**) in 7 steps. Finally, the developed asymmetric imine propargylation provides access to other alkaloids as highlighted by an effective synthesis of decarbomethoxydihydrogambirtannine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03839.

Full experimental details, copies of spectral data, and HPLC traces (PDF)

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AUTHOR INFORMATION

Corresponding Author

*E-mail: sasnyder@uchicago.edu.

ORCID

Myles W. Smith: 0000-0002-0231-0059
Scott A. Snyder: 0000-0003-3594-8769

Author Contributions

‖M.W.S., Z.Z., and A.X.G. contributed equally.

Notes

The authors declare no competing financial interest.

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