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Letter

Modular Synthesis of Polycyclic Alkaloid Scaffolds via an Enantioselective Dearomative Cascade

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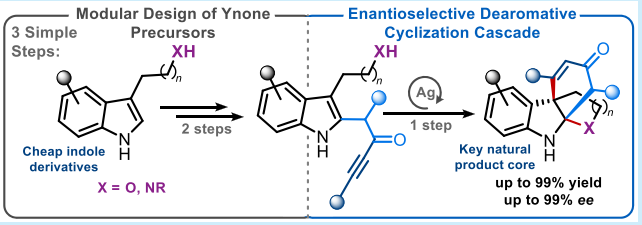
ABSTRACT: The polycyclic core of the akuammiline alkaloids can be synthesized from simple tryptamine and tryptophol derivatives via a Ag(I)-catalyzed enantioselective dearomative cyclization cascade sequence. The complex tetracyclic scaffolds are prepared via a rapid, versatile, three-step modular synthesis from simple commercially available indole derivatives in high yields and enantiomeric excess (up to 99% yield and >99% *ee*).



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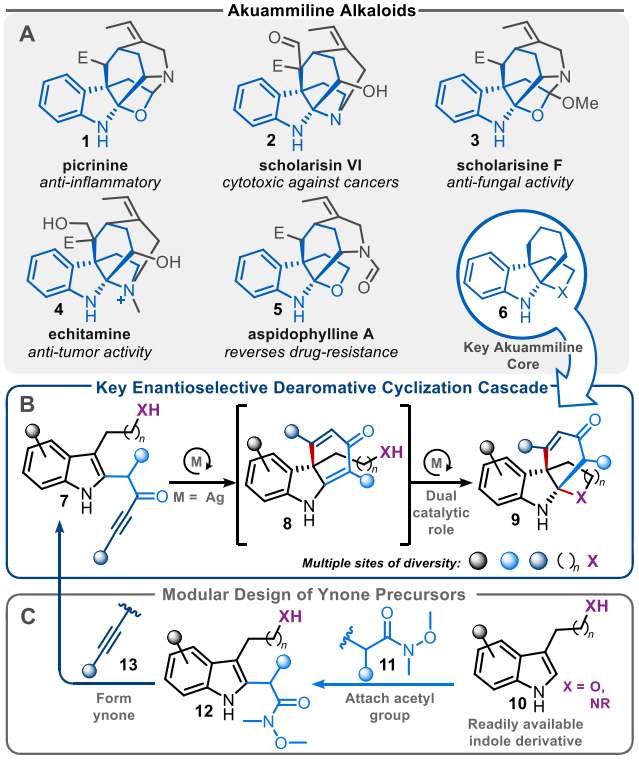
Complex polycyclic scaffolds are widely present in biologically important alkaloid natural products. The akuammiline alkaloids (see **1**−**5**, Scheme 1A) are prominent examples, with various members of this diverse family of bioactive compounds based on a common tetracyclic core **6**.[1]

Scheme 1. (A) Akuammiline Alkaloids 1−5 (E = CO_2Me); (B) Enantioselective Dearomative Cyclization Cascade; (C) Modular Preparation of Ynone Precursors



Accordingly, these alkaloids have attracted considerable attention from both synthetic and medicinal chemists; several innovative total syntheses have been accomplished,[2] although these methods often require multiple linear synthetic operations and are typically directed toward selected akuammiline synthetic targets. Alkaloids are unquestionably highly important in medicine, and strategies to access core alkaloid frameworks, via short and flexible synthetic sequences, are arguably of even greater value in medicinally oriented discovery, given their potential for the rapid assembly of diverse collections of complex, natural product-like scaffolds.[3]

The dearomatization of indoles through reactions with tethered ynones is well established,[4] with many of these methods generating quaternary centers and forming multiple stereoisomers. However, partly due to the linear nature of the alkyne unit, controlling the enantioselectivity of such dearomatization reactions is challenging. This is illustrated by the limited number of enantioselective dearomatization reactions of alkyne-tethered indoles reported in the literature.[5] Furthermore, to the best of our knowledge, examples of highly enantioselective (>80% *ee*) indole dearomatization reactions employing ynone-tethered precursors have not yet been reported.

In this manuscript, we report the successful realization of a Ag(I)-catalyzed enantioselective dearomatizing[6] cascade sequence for the rapid construction of the akuammiline alkaloid core scaffold **9** via ynone-tethered indoles **7** (Scheme 1B). Key to the success of this process was the selection of a chiral π-acid catalyst able to perform three roles in the proposed cascade: (1) activation of the ynone moiety tethered to the C2-

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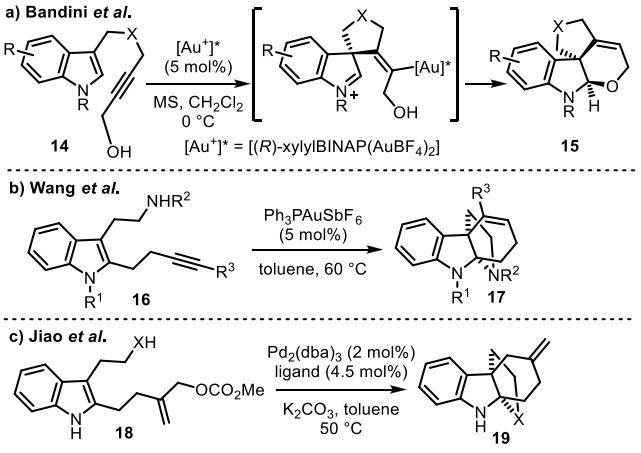
position of a tryptamine or tryptophol derivative to induce dearomatization of the indole core (7 → 8); (2) activation of the resulting dienone group in intermediate **8** to facilitate nucleophilic attack at the vinylogous amide junction; (3) effective control of enantioselectivity, with the planned transformation involving the formation of two stereogenic centers at separate points in the cascade.

To augment the synthetic utility of the cyclization cascade, a modular approach for the preparation of ynone precursors **7** has also been developed (Scheme 1C). This route starts from readily available tryptamine and tryptophol derivatives **10** and allows synthetically useful functionality from modules **11** and **13** to be easily installed at each stage of the synthesis. By combining the modular precursor synthesis with the key enantioselective dearomative cascade reaction, diverse complex tetracyclic akuammiline scaffolds **9** can be been prepared in three simple synthetic steps (**10** → **12** → **7** → **9**).

Methods for the dearomatization of indole derivatives using electrophilic reagents are well established,[4−7] and the idea to trap the resulting products (usually indolenines)[6i] with a tethered nucleophile is also known; for example, Bandini et al. demonstrated the power of this approach for the conversion of indole-tethered propargyl alcohols **14** into tetracyclic fused furoindolines **15** using a gold-catalyzed cyclization cascade (Scheme 2a).[6d] Indeed, a similar strategy has also been used

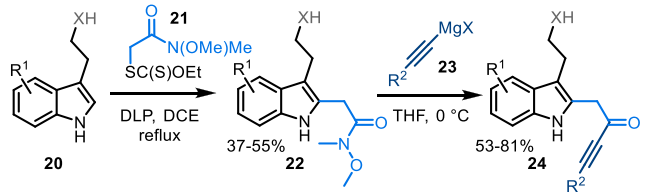
Scheme 2. Dearomatization/Indolenine Trapping Cascade Reactions of Indoles



for the assembly of tetracyclic alkaloid scaffolds **17** via alkyne activation,[8] exemplified by a gold(I)-catalyzed system reported by Wang et al. (Scheme 2b);[8a] the same group also demonstrated the value of this method in the formal synthesis of minfiensine and used it for the generation of medicinally relevant scaffolds.[9] Methods to prepare enantioenriched scaffolds in this way are less well established,[10] and are most commonly achieved via transition-metal catalyzed asymmetric allylation reactions,[10a] exemplified by Jiao's study summarized in Scheme 2c.[3d]

We reasoned that the improved reactivity profile typically offered by indole-tethered ynones in dearomative reactions (when compared with analogous alkynes lacking the carbonyl group) would aid the discovery of new asymmetric processes of this type, by allowing the use of milder reaction conditions.[4] The ynone carbonyl was also expected to facilitate substrate binding to the Lewis- or π-acid catalysts needed to impart asymmetric induction in the initial dearomative step. To test this idea, we started by devising a short and versatile method to construct the requisite ynone cyclization precursors **24** (Scheme 3). Thus, using a radical alkylation approach,

Scheme 3. Modular Preparation of Ynone Cyclization Precursors 24



tryptamine derivatives **20** were found to undergo efficient reaction with various xanthates **21** to directly install the required Weinreb amide functionality exclusively at the indole C2-position forming indoles **22**. Alkynyl Grignard reagents **23** were then used to promote formation of the ynone cyclization precursors **24**. This modular approach was used to prepare all starting materials featured in this manuscript, with full experimental details included in the Supporting Information (SI).

Attention was then focused toward optimizing the key enantioselective cyclization cascade, using phenyl-tethered ynone **24a** as a model substrate. A variety of racemic/achiral metal catalysts known to facilitate alkyne activation were first tested, including (Au-, Ag-, Cu-, and Pd-based catalyst systems; see SI for details), with several catalysts found to promote the desired transformation. Afterward, asymmetric investigations were pursued, which initially focused on Au- and Cu-based catalytic systems but following limited success (using Au-SEGPHOS and Cu-BOX catalysts, see SI), focus switched to the use of Ag(I) chiral phosphoric acid (CPA)[11−14] catalysts (Table 1). We first investigated the reaction with Ag(I) salts of commercially available CPAs **A** and **B** (Table 1, entries 1 and 2), with moderate conversion into **25a** and no/low enantioselectivity observed; significant silver plating was seen in each, which likely contributed to the poor performance of these catalysts. Pleasingly, 4 Å molecular sieves (which are often included as additives in related catalytic processes)[15] were effective at preventing visible silver plating and resulted in an increased yield (Table 1, entry 3). Reducing the temperature to 0 °C was shown to further increase enantioselectivity without affecting yield (entry 5). We then synthesized and tested a wide range of CPAs based on (*R*)-BINOL, (*S*)-H8-BINOL, and (*R*)-SPINOL backbones (for further optimization, see SI), and pleasingly (*R*)-SPINOL CPA-**H** bearing two 9-phenanthryl groups afforded the desired product **25a** as a single diastereoisomer in 99% yield and 97% *ee* (entry 12).[16] Reducing the catalyst loading (from 10 to 5 mol %, entry 13) was possible in comparable *ee*, but resulted in a significant drop in conversion; hence, 10 mol % was retained as the optimal catalyst loading.

Next, the scope of the enantioselective dearomative cyclization cascade was explored using (*R*)-SPINOL CPA-**H** (Scheme 4). The protecting group on the tryptamine tether was varied first, and three common *N*-protecting groups were well tolerated, furnishing products (**25a**−**25c**) in high yields and *ee*. A wide variety of functional groups were tolerated around the indole phenyl ring to give the desired polycyclic

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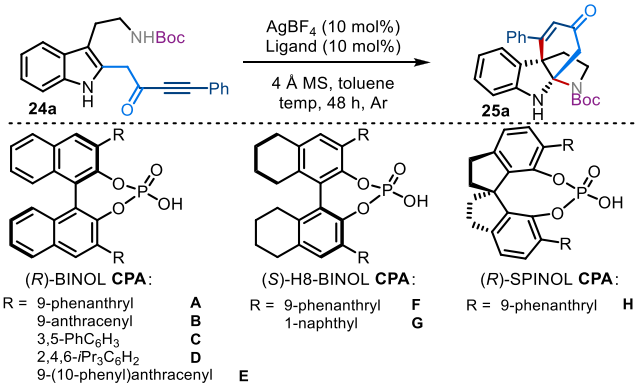
Table 1. Enantioselective Dearomative Cyclization Cascade Optimization

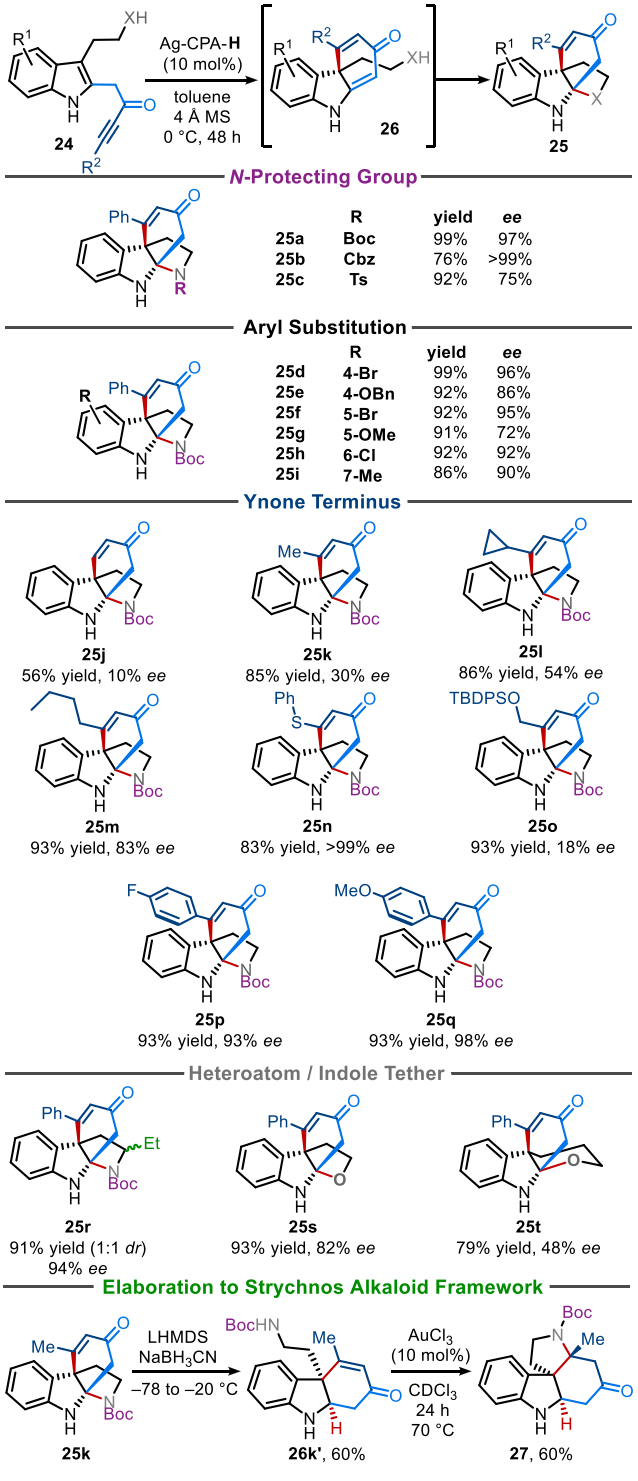


entry[a]	ligand	temp/°C	yield/%[b]	*ee*/%[c]
1[d]	**CPA-A**	RT	35	0
2[d]	**CPA-B**	RT	51	13
3	**CPA-B**	RT	76	11
4[e]	**CPA-B**	RT	0	–
5	**CPA-B**	0	76	25
6	**CPA-A**	0	30	0
7	**CPA-C**	0	0	–
8	**CPA-D**	0	73	0
9	**CPA-E**	0	89	86
10	**CPA-F**	0	60	14[f]
11	**CPA-G**	0	66	7[f]
12	**CPA-H**	0	99	97
13[g]	**CPA-H**	0	59	96

[a]Reactions were performed on 0.05 mmol scale in toluene (0.1 M) using 4 Å MS at 0 °C for 48 h. Ag-CPAs were formed by premixing CPAs with $AgBF_4$ for 30 min. [b]Yields based on trimethoxybenzene internal standard. [c]*Ee* values measured by HPLC using Chiralpak AD-H column, eluting with 20% IPA in hexane. Unless stated, the major enantiomer is the *S,R* isomer drawn. [d]4 Å MS not added. [e]$AgBF_4$ not added. [f]The opposite enantiomer to that drawn (i.e., *R,S*) was formed in excess. [g]5 mol % Ag-CPA loading.

products **25d**–**25i** in excellent yields and *ee*. Substituents at the ynone terminus were then investigated, with electron-withdrawing and electron-donating aryl groups each being tolerated, as are a range of alkyl groups, protected alcohol, and sulfide groups directly attached to the ynone terminus. Interestingly, the *ee* increased markedly across the series H → Me → cyclopropyl → *n*-butyl (**25j**–**25m**), indicating that steric bulk at this position enhances enantioselectivity. The placement of the steric bulk also appears to be important, as OTBDPS-substituted tetracycle **25o** was formed in 93% yield but in low *ee* of 18%; the bulky silyl group is presumably not oriented in a suitable conformation to promote effective asymmetric induction in this example. It was also possible to use oxygen trapping nucleophiles and vary the length of the trapping tether to generate the oxygen and six-membered analogues **25s** and **25t** in high yields. We did not anticipate the length of the trapping tether would play an important role in the enantioselective step of the reaction; however, increasing the tether by a single carbon atom (**25t**) led to a surprisingly large decrease in *ee*. Therefore, it seems that the tethered nucleophile may be involved in either promoting or disrupting asymmetric induction, leading to a diminished *ee* for some tether lengths. Sulfur and carbon nucleophiles were also tested in the dearomative cyclization cascade, but neither led to the

Scheme 4. Substrate Scope of Dearomative Cyclization Cascade and Elaboration to the Strychnos Alkaloid Framework



formation of the corresponding tetracyclic products.[17] The assigned absolute stereochemistry of these products is based on X-ray crystallographic data for compound **25d** (CCDC 1906384 (*S,R*-**25d**)), with the stereochemistry of the other products assigned through analogy.[16] Finally, prototypical product **25k** was converted into **27** (CCDC 1964308) via a simple two-step reductive ring-opening and Au(III)-catalyzed recyclization approach (**25k** → **26k'** → **27**), with this

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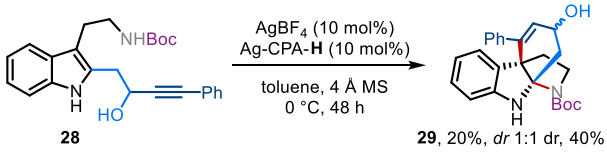
rearranged polycyclic scaffold widely found in various Strychnos alkaloid natural products.[18]

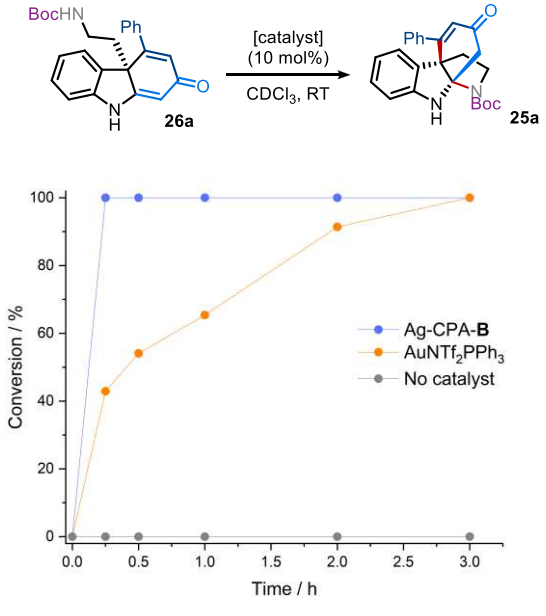
Notably, when the optimized conditions were tested on propargylic alcohol **28** (analogous to **24a** but lacking the carbonyl group), a significantly diminished yield and *ee* of polycycle **29** were observed (20% yield, 1:1 *dr* and 40% *ee*), attesting to the importance of the ynone moiety in achieving high conversion and *ee* (Scheme 5).

Scheme 5. Inferior Reactivity of Propargyl Alcohol 28, Demonstrating the Importance of the Ynone Moiety



To examine the roles of different catalytic species in the final trapping step, untrapped intermediate **26a** (itself formed from the ring opening of **25a** using LHMDS at −78 °C) was treated with catalytic amounts of Ag-CPA-**B** and $AuNTf_2PPh_3$ (Scheme 6). Complete cyclization into polycyclic scaffold

Scheme 6. Conversion of 28a into 25a with Ag(I), Au(I), and No Catalyst[a]

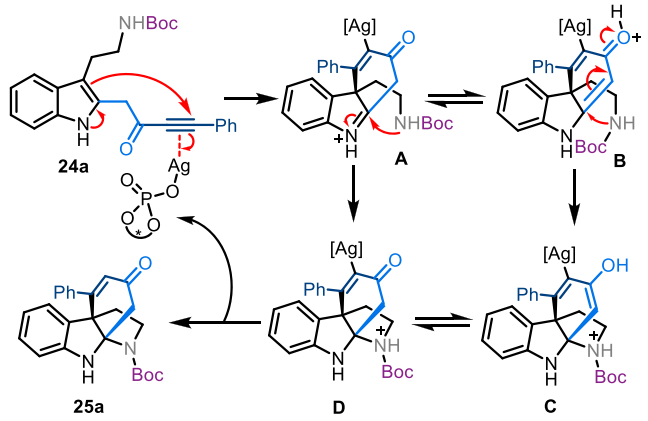


[a]Reactions were performed on 0.05 mmol scale in $CDCl_3$ that had been washed with K_2CO_3 before use. Ag-CPA-**B** was formed by premixing CPA-**B** with $AgBF_4$ for 30 min.

25a was observed in just 20 min at room temperature when using Ag-CPA-**B** (blue line, Scheme 6). In contrast, in a control reaction in which the Ag-CPA catalyst was omitted, no cyclization was observed after 3 h of stirring at room temperature, clearly showing the key role played by the catalyst in the second cyclization. Interestingly, the same reaction could also be catalyzed by $AuNTf_2PPh_3$, but a longer reaction time (3 h) was needed to ensure full conversion; Au(I) catalysts are often preferred to Ag(I) in related processes involving alkyne activation,[19] but were less effective in this study.[20]

A plausible mechanism for the overall transformation of **24a** into **25a** is presented in Scheme 7. First, dearomatization of

Scheme 7. Proposed Mechanism



indole **24a** is proposed (**24a** → **A**), facilitated by π-acid coordination of the Ag-CPA catalyst to the ynone alkyne moiety, with this being the stereochemistry defining step. Indolenine salt **A** could then be trapped by nucleophilic attack of the tethered nucleophile (in this example the Boc-protected amine, **A** → **D**) or tautomerize to **B** and cyclize via an alternative conjugate addition mode (**B** → **C**). Protodemetalation (e.g., **D** → **25a**) is also needed to complete the catalytic cycle, to form product **25a** and regenerate the silver catalyst, with this step being viable from any of the intermediates **A**–**D** (or their conjugate bases). The exact role played by the silver catalyst in facilitating the second cyclization step is not clear, but its involvement in this step is clearly demonstrated by the accelerated cyclization of intermediate **26a** (with both π-acids and Brønsted acids) summarized above in Scheme 6 and the associated text.

In summary, an efficient method for the preparation of the tetracyclic core of a diverse array of alkaloids has been developed, relying on a Ag(I)-catalyzed dearomative cascade sequence. The reactions are high yielding as well as broad in scope and proceed with high diastereoselectivity and enantioselectivity in most cases. The short and expedient nature of the modular route used to prepare the requisite starting materials should also increase the value of this method, which we anticipate being of value in alkaloid target syntheses, as well as in synthetic and medicinal chemistry projects focused on efficient complexity generation.[21]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00053.

Experimental procedures, spectroscopic data, additional optimization details (PDF)

Accession Codes

CCDC 1906384 and 1964308 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The

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Author Contributions

‡J.A.R.-A. and A.K.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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