

This is a repository copy of *Modular Synthesis of Polycyclic Alkaloid Scaffolds via an Enantioselective Dearomative Cascade*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/155905/>

Version: Published Version

Article:

Rossi-Ashton, James A, Clarke, Aimee K, Taylor, Richard J K orcid.org/0000-0002-5880-2490 et al. (1 more author) (2020) Modular Synthesis of Polycyclic Alkaloid Scaffolds via an Enantioselective Dearomative Cascade. *Organic Letters*. 1175–1181. ISSN: 1523-7052

<https://doi.org/10.1021/acs.orglett.0c00053>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

Modular Synthesis of Polycyclic Alkaloid Scaffolds via an Enantioselective Dearomative Cascade

James A. Rossi-Ashton,[‡] Aimee K. Clarke,[‡] Richard J. K. Taylor,^{*} and William P. Unsworth^{*}



Cite This: <https://dx.doi.org/10.1021/acs.orglett.0c00053>



Read Online

ACCESS |



Metrics & More

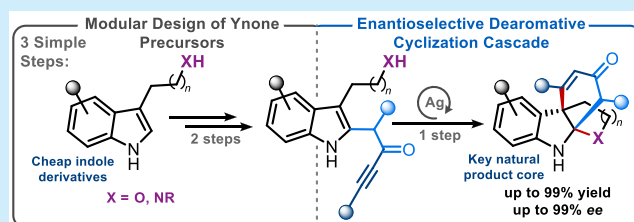


Article Recommendations



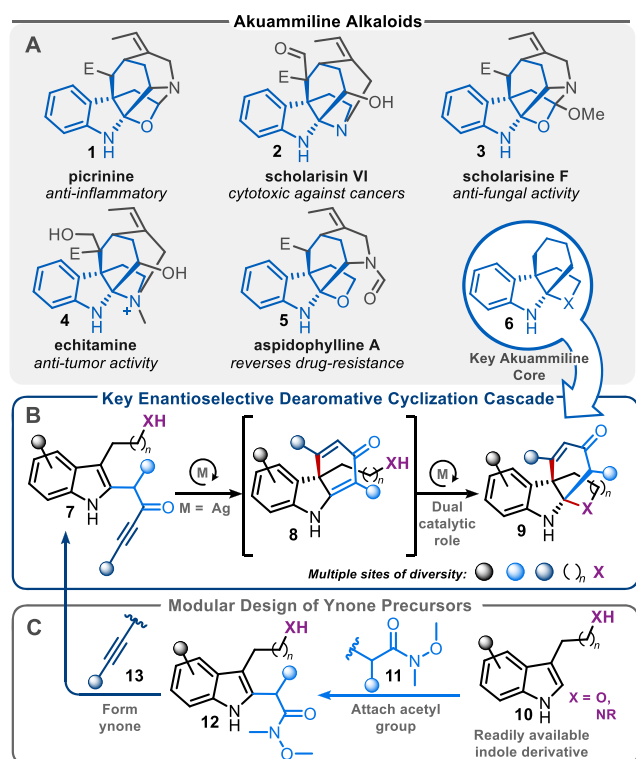
Supporting Information

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).



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.¹

Scheme 1. (A) Akuammiline Alkaloids 1–5 (E = CO₂Me); (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 medically 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 dearomatizing⁶ 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-

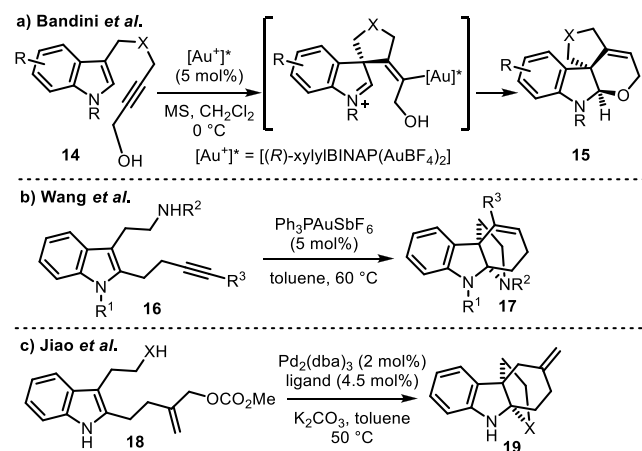
Received: January 6, 2020

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 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

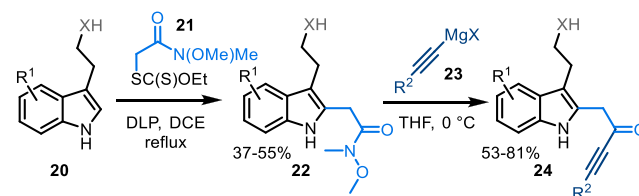


for the assembly of tetracyclic alkaloid scaffolds 17 via alkyne activation,⁸ exemplified by a gold(I)-catalyzed system reported by Wang et al. (Scheme 2b);^{8a} the same group also demonstrated the value of this method in the formal synthesis of minfiensine and used it for the generation of medicinally 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

Table 1. Enantioselective Dearomative Cyclization Cascade Optimization

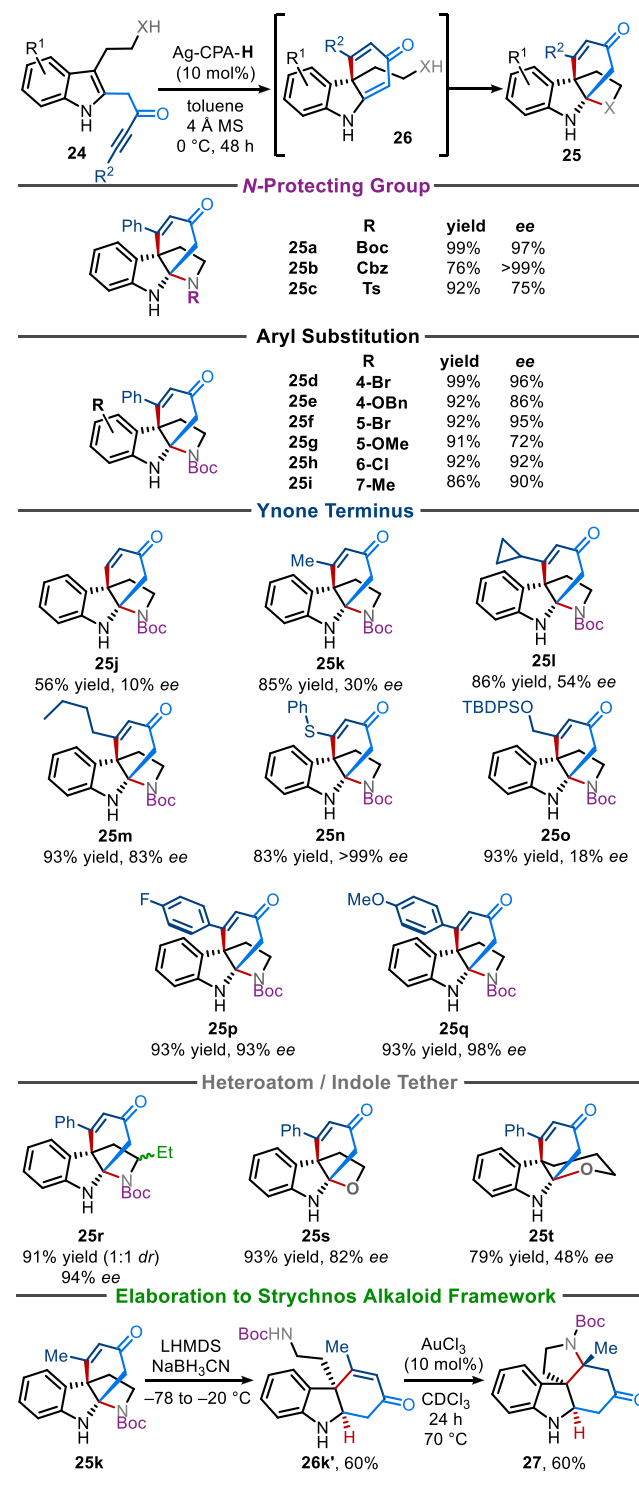
(R)-BINOL CPA: R = 9-phenanthryl (A), 9-anthracenyl (B), 3,5-PhC₆H₃ (C), 2,4,6-*i*-Pr₃C₆H₂ (D), 9-(10-phenyl)anthracenyl (E)
 (S)-H8-BINOL CPA: R = 9-phenanthryl (F), 1-naphthyl (G)
 (R)-SPINOL CPA: R = 9-phenanthryl (H)

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

^aReactions 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 AgBF₄ for 30 min. ^bYields based on trimethoxybenzene internal standard. ^cEe 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. ^d4 Å MS not added. ^eAgBF₄ not added. ^fThe opposite enantiomer to that drawn (i.e., *R,S*) was formed in excess. ^g5 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

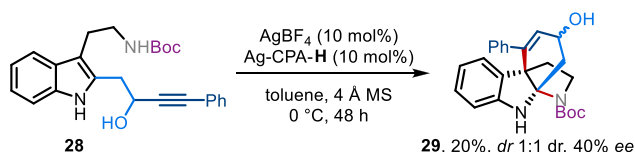


formation of the corresponding tetracyclic products.¹⁷ The assigned absolute stereochemistry of these products is based on X-ray crystallographic data for compound **25d** (CCDC 1906384 (*S,R*-**25d**)), with the stereochemistry of the other products assigned through analogy.¹⁶ Finally, prototypical 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

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

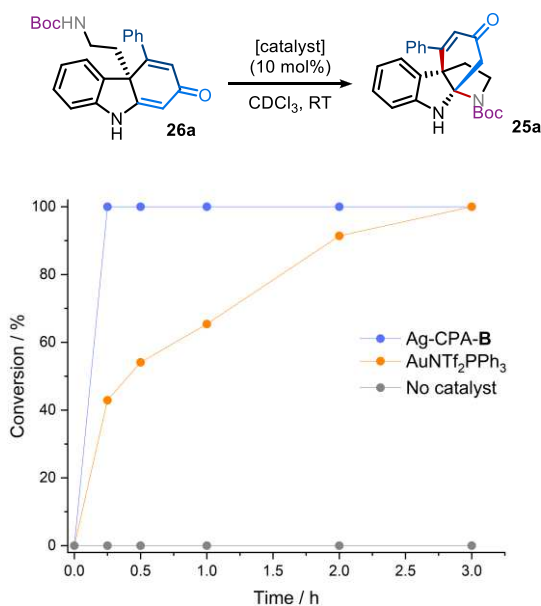
Notably, when the optimized conditions were tested on propargylic alcohol **28** (analogous to **24a** but lacking the carbonyl group), a significantly diminished yield and *ee* of polycycle **29** were observed (20% yield, 1:1 *dr* and 40% *ee*), attesting to the importance of the ynone moiety in achieving 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 $\text{AuNTf}_2\text{PPh}_3$ (Scheme 6). Complete cyclization into polycyclic scaffold

Scheme 6. Conversion of **26a into **25a** with Ag(I) , Au(I) , and No Catalyst^a**



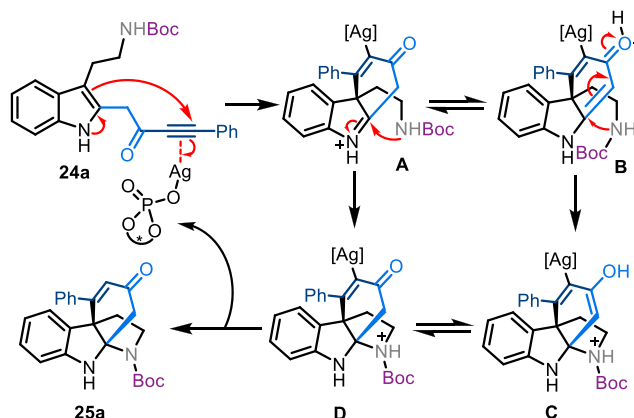
^aReactions were performed on 0.05 mmol scale in CDCl_3 that had been washed with K_2CO_3 before use. Ag-CPA-B was formed by premixing CPA-B with AgBF_4 for 30 min.

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 $\text{AuNTf}_2\text{PPh}_3$, 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** \rightarrow **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** \rightarrow **D**) or tautomerize to **B** and cyclize via an alternative conjugate addition mode (**B** \rightarrow **C**). Protodemetalation (e.g., **D** \rightarrow **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

Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

Richard J. K. Taylor – University of York, York, U.K.;

Email: richard.taylor@york.ac.uk

William P. Unsworth – University of York, York, U.K.;

orcid.org/0000-0002-9169-5156;

Email: william.unsworth@york.ac.uk

Other Authors

James A. Rossi-Ashton – University of York, York, U.K.

Aimee K. Clarke – University of York, York, U.K.

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acs.orglett.0c00053>

Author Contributions

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

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to thank the EPSRC (A.K.C. EP/R013748/1), the University of York (J.A.R.-A., W.P.U.), and the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-013, W.P.U.) for financial support. We also grateful for the provision of an Eleanor Dodson Fellowship (to W.P.U.) by the Department of Chemistry, University of York and to Dr. Adrian C. Whitwood (University of York) for X-ray crystallography.

REFERENCES

- (1) For reviews/book chapters, see: (a) Smith, J. M.; Moreno, J.; Boal, B. W.; Garg, N. K. Cascade Reactions: A Driving Force in Akuammiline Alkaloid Total Synthesis. *Angew. Chem., Int. Ed.* **2015**, *54*, 400–412. (b) Adams, G. L.; Smith, A. B., III *The Alkaloids: Chemistry and Biology*, Vol. 76; Knölker, H.-J., Ed.; Academic Press: New York, 2016; pp 171–257.
- (2) (a) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. Total Synthesis of the Akuammiline Alkaloid (±)-Vincorine. *J. Am. Chem. Soc.* **2009**, *131*, 6013–6020. (b) Ren, W.; Wang, Q.; Zhu, Z. Total Synthesis of (±)-Aspidophylline A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1818–1821. (c) Li, Y.; Zhu, S.; Li, J.; Li, A. Asymmetric Total Syntheses of Aspidodasycarpine, Lonicerine, and the Proposed Structure of Lanciferine. *J. Am. Chem. Soc.* **2016**, *138*, 3982–3985. (d) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. Enantioselective Total Syntheses of Akuammiline Alkaloids (+)-Strictamine, (–)-2(S)-Cathafoline, and (–)-Aspidophylline A. *J. Am. Chem. Soc.* **2016**, *138*, 1162–1165. (e) Du, K.; Yang, H.; Guo, P.; Feng, L.; Xu, G.; Zhuo, Q.; Chung, L. W.; Tang, W. Efficient syntheses of (–)-crinine and (–)-aspidospermidine, and the formal synthesis of (–)-minfiensine by enantioselective intramolecular dearomative cyclization. *Chem. Sci.* **2017**, *8*, 6247–6256. (f) Zhang, B.; Wang, X.; Cheng, C.; Sun, D.; Li, C. Total Synthesis of (±)-Corymine. *Angew. Chem., Int. Ed.* **2017**, *56*, 7484–7487. (g) Picazo, E.; Morrill, L. A.; Susick, R. B.; Moreno, J.; Smith, J. M.; Garg, N. K. Enantioselective Total Syntheses of Methanoquinolizidine-Containing Akuammiline Alkaloids and Related Studies. *J. Am. Chem. Soc.* **2018**, *140*, 6483–6492. (h) Zhang, X.; Kakde, B. N.; Guo, R.; Yadav, S.; Gu, Y.; Li, A. Total Syntheses of Echitamine, Akuammiline, Rhazicine, and Pseudoakuammigine. *Angew. Chem., Int. Ed.* **2019**, *58*, 6053–6058. (i) Li, W.; Chen, Z.; Yu, D.; Peng, X.; Wen, G.; Wang, S.; Xue, F.; Liu, X.-Y.; Qin, Y. Asymmetric Total Syntheses of the Akuammiline Alkaloids (–)-Strictamine and (–)-Rhazinoline. *Angew. Chem., Int. Ed.* **2019**, *58*, 6059–6063.
- (3) For general information on sp³-rich natural product frameworks in drug discovery, see: (a) Foley, D. J.; Craven, P. G. E.; Collins, P. M.; Doveston, R. G.; Aimon, A.; Talon, R.; Churcher, I.; von Delft, F.; Marsden, S. P.; Nelson, A. Synthesis and Demonstration of the Biological Relevance of sp³-rich Scaffolds Distantly Related to Natural Product Frameworks. *Chem. - Eur. J.* **2017**, *23*, 15227–15232. For examples of general stereoselective methods to access indole alkaloids, see: (b) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. A Novel and General Synthetic Pathway to Strychnos Indole Alkaloids: Total Syntheses of (–)-Tubifoline, (–)-Dehydrotubifoline, and (–)-Strychnine Using Palladium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807. (c) Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. Total Synthesis of (–)- and ent-(+)-Vindoline and Related Alkaloids. *J. Am. Chem. Soc.* **2006**, *128*, 10596–10612. (d) Zhang, Z.-X.; Chen, S.-C.; Jiao, L. Total Synthesis of (+)-Minfiensine: Construction of the Tetracyclic Core Structure by an Asymmetric Cascade Cyclization. *Angew. Chem., Int. Ed.* **2016**, *55*, 8090–8094. (e) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. Collective synthesis of natural products by means of organocascade catalysis. *Nature* **2011**, *475*, 183–188. (f) Jarret, M.; Tap, A.; Kouklovsky, C.; Poupon, E.; Evanno, E.; Vincent, G. Bioinspired Oxidative Cyclization of the Geissoschizine Skeleton for the Total Synthesis of (–)-17-nor-Excelsinidine. *Angew. Chem., Int. Ed.* **2018**, *57*, 12294–12298.
- (4) For examples of indole dearomatization using ynones, see: (a) Benito, D.; Carbery, D. R.; Heffernan, S. J.; Mahon, M. F.; Queru, M. E.; Silvanus, A. C.; Tellam, J. P.; Andrews, B. I.; Hennessy, A. J. Double Gold-Catalysed Annulation of Indoles by Enynones. *Adv. Synth. Catal.* **2013**, *355*, 1149. (b) Clarke, A. K.; James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Silica-Supported Silver Nitrate as a Highly Active Dearomatizing Spirocyclization Catalyst: Synergistic Alkyne Activation by Silver Nanoparticles and Silica. *Angew. Chem., Int. Ed.* **2016**, *55*, 13798–13802. (c) Liddon, J. T. R.; James, M. J.; Clarke, A. K.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones. *Chem. - Eur. J.* **2016**, *22*, 8777–8780. (d) Liddon, J. T. R.; Clarke, A. K.; Taylor, R. J. K.; Unsworth, W. P. Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives. *Org. Lett.* **2016**, *18*, 6328–6331. (e) Fedoseev, P.; Van der Eycken, E. V. Temperature switchable Brønsted acid-promoted selective syntheses of spiro-indolenines and quinolines. *Chem. Commun.* **2017**, *53*, 7732–7735. (f) Gan, P.; Pitzén, J.; Qu, P.; Snyder, S. A. Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by aza-Prins and Metal-Mediated Cyclizations. *J. Am. Chem. Soc.* **2018**, *140*, 919–925. (g) Ho, H. E.; Stephens, T. C.; Payne, T. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Merging π -Acid and Pd Catalysis: Dearomatizing Spirocyclization/Cross-Coupling Cascade Reactions of Alkyne-Tethered Aromatics. *ACS Catal.* **2019**, *9*, 504–510. For related examples based on other electron-deficient alkynes, see: (h) Schröder, F.; Sharma, U.; Mertens, M.; Devred, F.; Debecker, D.; Luque, R.; Van der Eycken, E. V. Silver-Nanoparticle-Catalyzed Dearomatization of Indoles toward 3-Spiroindolenines via a 5-exo-dig Spirocyclization. *ACS Catal.* **2016**, *6*, 8156–8161. (i) He, Y.; Li, Z.; Robeyns, K.; Van Meervelt, L.; Van der Eycken, E. V. A Gold-Catalyzed Domino Cyclization Enabling Rapid Construction of Diverse Polyheterocyclic Frameworks. *Angew. Chem., Int. Ed.* **2018**, *57*, 272–276.
- (5) For asymmetric dearomatization reactions of alkyne-tethered indoles, see: (a) Corkey, B. K.; Heller, S. T.; Wang, Y.-M.; Toste, F. D. Enantioselective cyclization of enamide-ynes and application to the synthesis of the kopsifoline core. *Tetrahedron* **2013**, *69*, 5640–5646. (b) James, M. J.; Cuthbertson, J. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones: Direct Access to Spirocyclic Scaffolds. *Angew. Chem., Int. Ed.* **2015**, *54*, 7640–7643. (c) Zhu, Y.; He, W.; Wang, W.;

Pitsch, C. E.; Wang, X.; Wang, X. Enantioselective Tandem Cyclization of Alkyne-Tethered Indoles Using Cooperative Silver-(I)/Chiral Phosphoric Acid Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 12206–12209. For dearomatization reactions of indoles involving alkynes delivered intermolecularly in Diels–Alder type processes, see: (d) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. Nine-Step Enantioselective Total Synthesis of (+)-Minfiensine. *J. Am. Chem. Soc.* **2009**, *131*, 13606–13607. (e) Laforteza, B. N.; Pickworth, M.; MacMillan, D. W. C. Enantioselective Total Synthesis of (–)-Minovincine in Nine Chemical Steps: An Approach to Ketone Activation in Cascade Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 11269–11272.

(6) For indole dearomatization, including asymmetric examples, see: (a) You, S.-L. *Asymmetric Dearomatization Reactions*; Wiley-VCH: Weinheim, 2016. (b) Roche, S. P.; Porco, J. A., Jr. Dearomatization Strategies in the Synthesis of Complex Natural Products. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093. (c) Zhuo, C.-X.; Zhang, W.; You, S.-L. Catalytic Asymmetric Dearomatization Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662–12686. (d) Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. Enantioselective Gold-Catalyzed Synthesis of Polycyclic Indolines. *Org. Lett.* **2012**, *14*, 1350–1353. (e) Zhuo, C.-X.; Zheng, C.; You, S.-L. Transition-Metal-Catalyzed Asymmetric Allylic Dearomatization Reactions. *Acc. Chem. Res.* **2014**, *47*, 2558–2573. (f) Ding, Q.; Zhou, X.; Fan, R. Recent advances in dearomatization of heteroaromatic compounds. *Org. Biomol. Chem.* **2014**, *12*, 4807–4815. (g) Wu, W.-T.; Zhang, L.; You, S.-L. Catalytic asymmetric dearomatization (CADA) reactions of phenol and aniline derivatives. *Chem. Soc. Rev.* **2016**, *45*, 1570–1580. (h) Zheng, C.; You, S.-L. Catalytic Asymmetric Dearomatization by Transition-Metal Catalysis: A Method for Transformations of Aromatic Compounds. *Chem.* **2016**, *1*, 830–857. For a review, see: (i) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. Synthesis of Spirocyclic Indolenines. *Chem. - Eur. J.* **2016**, *22*, 2856–2881.

(7) For examples of dearomatizing indole and trapping the resulting indolenine with tethered nucleophiles, see refs 6d, 6i, and: (a) Cera, G.; Crispino, P.; Monari, M.; Bandini, M. Stereoselective synthesis of tetracyclic indolines viagold-catalyzed cascade cyclization reactions. *Chem. Commun.* **2011**, *47*, 7803–7805. (b) Noey, E. L.; Wang, X.; Houk, K. N. Selective Gold(I)-Catalyzed Formation of Tetracyclic Indolines: A Single Transition Structure and Bifurcations Lead to Multiple Products. *J. Org. Chem.* **2011**, *76*, 3477–3483. (c) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. A copper-catalyzed arylation of tryptamines for the direct synthesis of aryl pyrroloindolines. *Chem. Sci.* **2012**, *3*, 3170–3174. (d) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Van Meervelt, L. V.; Van der Eycken, E. V. A Diversity-Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization. *Angew. Chem., Int. Ed.* **2012**, *51*, 9572–9575. (e) Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. Post-Ugi gold-catalyzed diastereoselective domino cyclization for the synthesis of diversely substituted spiroindolines. *Beilstein J. Org. Chem.* **2013**, *9*, 2097–2102.

(8) (a) Liu, Y.; Xu, W.; Wang, X. Gold(I)-Catalyzed Tandem Cyclization Approach to Tetracyclic Indolines. *Org. Lett.* **2010**, *12*, 1448–1451. For other methods accessing similar polycyclic scaffolds, see: (b) Nishiyama, D.; Ohara, A.; Chiba, H.; Kumagai, H.; Oishi, S.; Fujii, N.; Ohno, H. Formal Total Synthesis of (±)-Strictamine Based on a Gold-Catalyzed Cyclization. *Org. Lett.* **2016**, *18*, 1670–1673. (c) Smith, M. W.; Zhou, Z.; Gao, A. X.; Shimbayashi, T.; Snyder, S. A. A 7-Step Formal Asymmetric Total Synthesis of Strictamine via an Asymmetric Propargylation and metal-Mediated Cyclization. *Org. Lett.* **2017**, *19*, 1004–1007.

(9) (a) Podoll, J. D.; Liu, Y.; Chang, L.; Walls, S.; Wang, W.; Wang, X. Bio-inspired synthesis yields a tricyclic indoline that selectively resensitizes methicillin-resistant *Staphylococcus aureus* (MRSA) to β -lactam antibiotics. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 15573–15578. (b) Barbour, P. M.; Podoll, J. D.; Marholz, L. J.; Wang, X. Discovery and initial structure-activity relationships of N-benzyl tricyclic indolines as antibacterials for methicillin-resistant Staph-

yllococcus aureus. *Bioorg. Med. Chem. Lett.* **2014**, *24*, S602–S605. (c) Chang, L.; Podoll, J. D.; Wang, W.; Walls, S.; O'Rourke, C. P.; Wang, X. Structure-Activity Relationship Studies of the Tricyclic Indoline Resistance-Modifying Agent. *J. Med. Chem.* **2014**, *57*, 3803–3817. (d) Zhu, Y.; Cleaver, L.; Wang, W.; Podoll, J. D.; Walls, S.; Jolly, A.; Wang, X. Tetracyclic indolines as a novel class of β -lactam-selective resistance-modifying agent for MRSA. *Eur. J. Med. Chem.* **2017**, *125*, 130–142. (e) He, W.; Griffiths, B. M.; Wang, W.; Wang, X. Diastereoselective synthesis and biological evaluation of enantiomerically pure tricyclic indolines. *Org. Biomol. Chem.* **2017**, *15*, 4241–4245.

(10) See refs 5c–e and: (a) Zi, W.; Xie, W.; Ma, D. Total Synthesis of Akumamine Alkaloid (–)-Vincorine via Intramolecular Oxidative Coupling. *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129. (b) Jiang, S.-Z.; Zeng, X.-Y.; Liang, X.; Lei, T.; Wei, K.; Yang, Y.-R. Iridium-Catalyzed Enantioselective Indole Cyclization: Application to the Total Synthesis and Absolute Stereochemical Assignment of (–)-Aspidophylline A. *Angew. Chem., Int. Ed.* **2016**, *55*, 4044–4048. For a review on asymmetric allylic substitution reactions, see: (c) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855–1969.

(11) For rare examples of asymmetric Ag-CPA catalyzed reaction of alkynes, see ref 5b and: (a) Zhang, Q.-W.; Xiang, K.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, X.-M.; Zhao, Y.-M.; Zhang, T.-C. Formal Synthesis of (–)-Cephalotaxine Based on a Tandem Hydroamination/Semipinacol Rearrangement Reaction. *Chem. - Asian J.* **2012**, *7*, 894–898. (b) Zhang, H.; Zhu, L.; Wang, S.; Yao, Z.-J. Asymmetric Annulation of 3-Alkynylacrylaldehydes with Styrene-Type Olefins by Synergetic Relay Catalysis from AgOAc and Chiral Phosphoric Acid. *J. Org. Chem.* **2014**, *79*, 7063–7074. (c) Terada, M.; Li, F.; Toda, Y. Chiral Silver Phosphate Catalyzed Transformation of ortho-Alkynylaryl Ketones into 1H-Isochromene Derivatives through an Intramolecular-Cyclization/Enantioselective-Reduction Sequence. *Angew. Chem., Int. Ed.* **2014**, *53*, 235–239.

(12) For general information on asymmetric metal-CPA catalysis, see: Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047–9153.

(13) For a review on enantioselective silver-catalyzed transformations, see: Pellissier, H. Enantioselective Silver-Catalyzed Transformations. *Chem. Rev.* **2016**, *116*, 14868–14917.

(14) For silver-catalyzed alkyne activation, see: Fang, G.; Bi, X. Silver-catalyzed reactions of alkynes: recent advances. *Chem. Soc. Rev.* **2015**, *44*, 8124–8173.

(15) Mikami, K.; Terada, M.; Nakai, T. Asymmetric glyoxylate-ene reaction catalyzed by chiral titanium complexes: a practical access to α -hydroxy esters in high enantiomeric purities. *J. Am. Chem. Soc.* **1989**, *111*, 1940–1941 and references therein.

(16) The absolute stereochemistry of 25a was assigned by analogy to compound 25d, for which X-ray crystallographic data were obtained for an enantiopure crystalline sample.

(17) When performing this reaction in the presence of a sulfur nucleophile no reaction was observed. Ynone precursors bearing a carbon-based pronucleophile (a malonate system) underwent initial cyclization and dearomatization to afford the corresponding dienone product, but the carbon pronucleophile did not undergo nucleophilic attack to furnish the desired tetracyclic product.

(18) See refs 3b and c above and also: (a) Wang, Z.; Chen, L.; Yao, Y.; Liu, Z.; Gao, J.-M.; She, X.; Zheng, H. Dearomatization of Indole via Intramolecular [3 + 2] Cycloaddition: Access to the Pentacyclic Skeleton of Strychnos Alkaloids. *Org. Lett.* **2018**, *20*, 4439–4443. (b) He, W.; Hu, J.; Wang, P.; Chen, L.; Ji, K.; Yang, S.; Li, Y.; Xie, Z.; Xie, W. Highly Enantioselective Tandem Michael Addition of Tryptamine-Derived Oxindoles to Alkynones: Concise Synthesis of Strychnos Alkaloids. *Angew. Chem., Int. Ed.* **2018**, *57*, 3806–3809. (c) Saya, J. M.; Ruijter, E.; Orru, R. V. A. Total Synthesis of

Aspidosperma and *Strychnos* Alkaloids through Indole Dearomatization. *Chem. - Eur. J.* **2019**, *25*, 8916–8935.

(19) (a) Fürstner, A. Gold and platinum catalysis—a convenient tool for generating molecular complexity. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (b) Jiménez-Núñez, E.; Echavarren, A. M. Gold-Catalyzed Cycloisomerizations of Enynes: A Mechanistic Perspective. *Chem. Rev.* **2008**, *108*, 3326–3350. (c) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028–9072.

(20) The cyclization of **26a** into **25a** was also performed in the presence of AgBF₄ and CPA-B to probe their individual roles. After 20 min of stirring at rt, complete conversion into **25a** was observed when using AgBF₄ and after 3 h of stirring at rt cyclized product **25a** was formed in 30% yield when using CPA-B. These yields were determined by ¹H NMR spectroscopy using a trimethoxybenzene internal standard.

(21) Morgentin, R.; Dow, M.; Aimon, A.; Karageorgis, G.; Kalliokoski, T.; Roche, D.; Marsden, S.; Nelson, A. Translation of innovative chemistry into screening libraries: an exemplar partnership from the European Lead Factory. *Drug Discovery Today* **2018**, *23*, 1578–1583.