Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

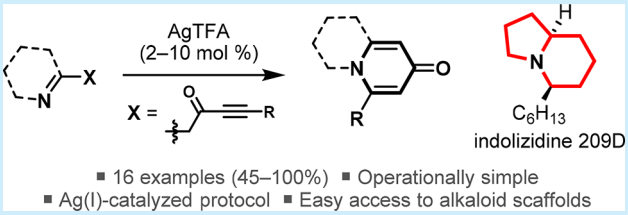
Ag(I)-Catalyzed Synthesis of Azabicyclic Alkaloid Frameworks from Ketimine-Tethered Ynones: Total Synthesis of Indolizidine 209D

Hon Eong Ho, Michael J. James, Peter O'Brien, Richard J. K. Taylor,* and William P. Unsworth*

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K.

Supporting Information

ABSTRACT: An efficient Ag(I)-catalyzed π-acid activation method for the cyclization of cyclic ketimine-tethered ynones is reported. Various nitrogen-containing scaffolds commonly found in bioactive alkaloids can be prepared in high yields, and the utility of the method is demonstrated by a formal synthesis of (±)-lasubine II and in a short total synthesis of (±)-indolizidine 209D.



Azabicycles are ubiquitous in bioactive alkaloids,[1] with exemplar compounds **1**−**6** representing a small fraction of the diverse structural classes found in Nature (Figure 1).[2]

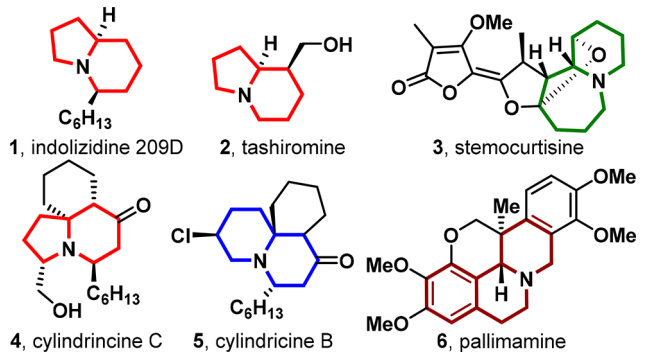
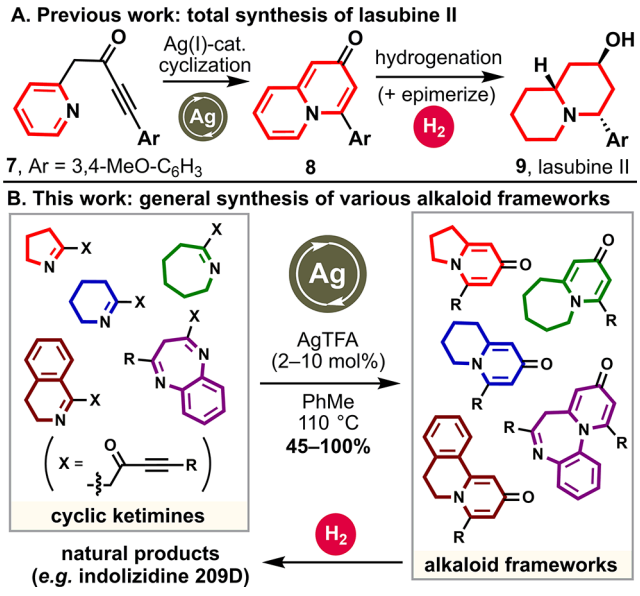


Figure 1. Alkaloid natural products containing fused azacycles.

Fused bicyclic indolizidines (e.g., **1** and **2**) and quinolizidines are particularly common motifs, although alkaloids based on other ring sizes (e.g., 6,7-bicylic systems such as **3**) and more complex polycyclic systems (e.g., **4**−**6**) are also known. The challenge of constructing such azacycles, allied to the fact that many exhibit broad biological activity, has propagated much research effort to develop efficient methods for their synthesis.[1]

We recently reported a new method for the preparation of 6,6-fused azacycles, exemplified in a five-step total synthesis of the quinolizidine alkaloid lasubine II (**9**) (Scheme 1A).[3] A key step in this dearomative synthesis[4] was the cyclization of pyridyl ynone **7** into quinolizinone **8** via π-acid activation[5] of the alkyne with catalytic Ag(I).[6] Following hydrogenation[7] and two further steps to epimerize the alcohol, a short, gram-scale synthesis of lasubine II (**9**) was completed in 36% overall yield.[8] This method was also shown to work well with other pyridyl ynones and represents an efficient method for the preparation of quinolizinones while also allowing entry into the quinolizidine framework following hydrogenation. In this paper, we describe the application of a similar strategy to

Scheme 1. Aza-ynone Cyclization Reactions



cyclic ketimines (Scheme 1B). While the cyclization of protected saturated amine nucleophiles onto tethered alkynes is reasonably well-established (via aza-Michael-type reactions or metal-catalyzed hydroamination),[9] to the best of our knowledge, there are no published examples of similar processes that proceed via cyclization through the sp^2-hybridized nitrogen of a cyclic ketimine precursor.[10]

There are several benefits of the approach outlined in Scheme 1B compared to our previous work on pyridyl systems: (1) a much wider array of azabicycles should be accessible, as we will not be limited to pyridyl starting materials; (2) the requisite starting materials can be easily prepared by exploiting the enamine character of ketimine precursors, without the need

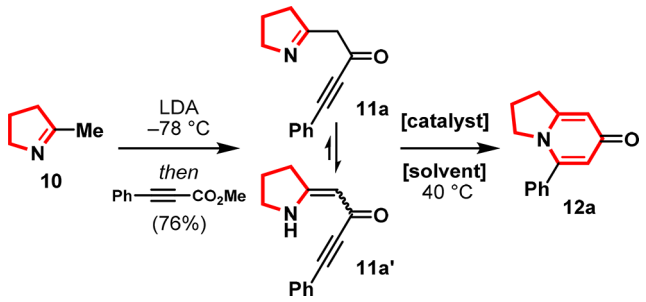
Received: January 22, 2018

DOI: 10.1021/acs.orglett.8b00225
Org. Lett. XXXX, XXX, XXX−XXX

to use protecting groups;[11] (3) the use of nonaromatic starting materials reduces the number of bonds requiring hydrogenation to prepare saturated alkaloid analogues. The realization of this Ag(I)-catalyzed cyclization approach is described herein, enabling a range of alkaloid frameworks to be prepared in high yields under operationally simple reaction conditions. The utility of the method in natural product synthesis is also demonstrated during a formal synthesis of (±)-lasubine II and in a short total synthesis of (±)-indolizidine 209D.

We started by examining the cyclization of pyrroline-tethered ynone **11a**, which is readily prepared from 2-methyl-1-pyrroline **10** and methyl phenylpropiolate (Table 1).[12] Thus, ynone **11a**

Table 1. Optimization of the Cyclization of 11a[a]



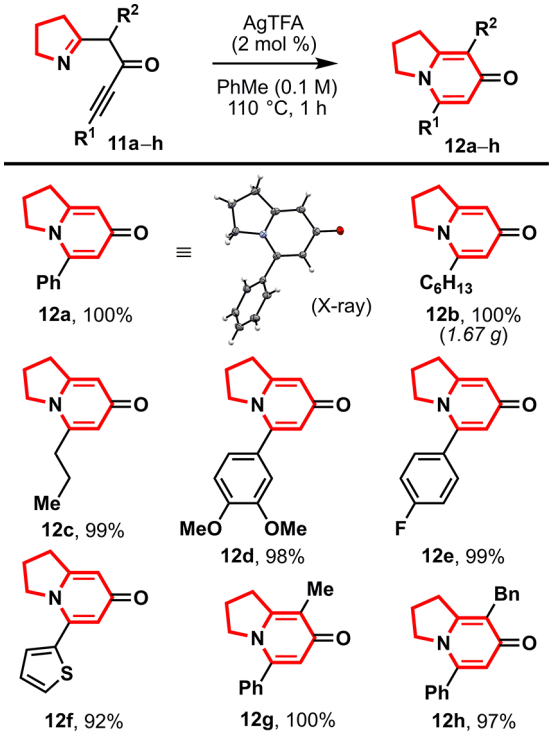
entry	catalyst (mol %)	solvent	time (h)	**12a**[b] (%)
1	$Cu(MeCN)_4PF_6$ (10)	CH_2Cl_2	18	0
2	$Cu(OTf)_2$ (10)	CH_2Cl_2	18	0
3	$Ph_3PAuNTf_2$ (10)	CH_2Cl_2	18	0
4	AgOTf (10)	CH_2Cl_2	18	36
5	$AgNTf_2$(10)	CH_2Cl_2	18	64
6	$AgNO_3$ (10)	CH_2Cl_2	18	100
7	AgTFA(10)	CH_2Cl_2	18	100
8	$AgNO_3$ (5)	CH_2Cl_2	21	>95
9	AgTFA (5)	CH_2Cl_2	21	100
10	AgTFA (5)	CH_2Cl_2	11	57
11	AgTFA (5)	PhMe	11	100
12[c]	AgTFA (5)	PhMe	1	100
13[c]	**AgTFA (2)**	**PhMe**	**1**	**100 (100)**
14[c]		PhMe	1	<5

[a]Reactions were performed using 0.2 mmol of **11a**, with the listed catalyst/loading and solvent, at 0.1 M at 40 °C, unless otherwise stated. [b]Yields determined using ^{1}H NMR spectroscopy of the unpurified reaction mixtures using 3,5-bis(trifluoromethyl)-bromobenzene as an internal standard. Isolated yield is shown in parentheses. [c]Reaction performed at 110 °C.

(which exists predominantly as its enamine tautomer **11a′** in solution in $CDCl_3$) was reacted with common Cu(I)-, Cu(II)-, Au(I)-, and Ag(I)-based catalysts (10 mol %) in DCM at 40 °C for 18 h (entries 1–7), with $AgNO_3$ and AgTFA (entries 6 and 7) being particularly effective at promoting the desired transformation into 4-pyridone **12a** (structure confirmed by X-ray crystallography). Further optimization showed that AgTFA was slightly more effective than $AgNO_3$, solvent screens revealed that the rate of reaction could be increased by performing the reaction in toluene, and the catalyst loading could be reduced to 2 mol % by raising reaction temperature to 110 °C, which also led to a reduced reaction time of 1 h (entry 12). Control experiments showed that only trace amounts of pyridone **12a** were formed under thermal conditions without a catalyst (entry 12).

With optimized conditions in hand, we next examined the scope of this reaction with other pyrroline-tethered ynones (Scheme 2). Pyrroline–ynones **11b–h** were prepared from

Scheme 2. Substrate Scope for Ag(I)-Catalyzed Cyclization of Pyrroline-Tethered Ynones

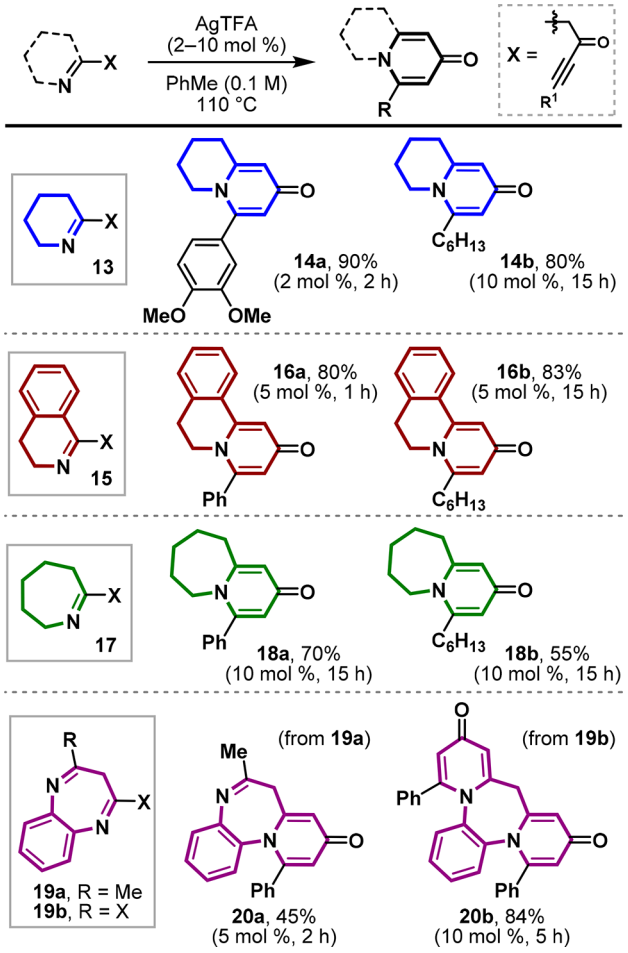


commercially available sources in good to excellent yield using methods similar to that used to prepare **11a** (see the Supporting Information); as before, these substrates exist largely in their enamine form in solution in $CDCl_3$. First, pyrrolines tethered to aliphatic ynone subunits were well tolerated under the standard conditions, affording products **12b** and **12c** in near-quantitative yields. The preparation of **12b** was also achieved on a 1.67 g scale with no appreciable drop in yield. Ynone substrates bearing functionalized phenyl groups were also well tolerated (**12d** and **12e**) as was a thiophene-substituted ynone (to form **12f**). Additional substituents on the ynone tether were also compatible with the standard method (**12g** and **12h**), with all of the examples proceeding in excellent to quantitative yield (92–100%). These results are especially pleasing given the abundance of the 5,6-framework in indolizidine alkaloids.[13]

The scope of the reaction with respect to the cyclic ketimine was then examined (Scheme 3). The methylated cyclic ketimines were prepared from the corresponding lactam precursors using a reported procedure[14] and then converted into the tethered ynones using the same method used to make **11a** (see the SI).[15] First, two dihydropiperidine ketimine derivatives of the form **13** were prepared and converted into cyclized products **14a** and **14b** using 2 and 10 mol % of AgTFA respectively; notably, compound **14a**, which is a key intermediate in our previous synthesis of lasubine II, was obtained in particularly high yield (90%).[3] Next, two partially unsaturated isoquinoline-tethered ynones of the form **15** were prepared, and each was converted into the corresponding 4-pyridone adducts in high yield, following treatment with 5 mol

DOI: 10.1021/acs.orglett.8b00225
Org. Lett. XXXX, XXX, XXX–XXX

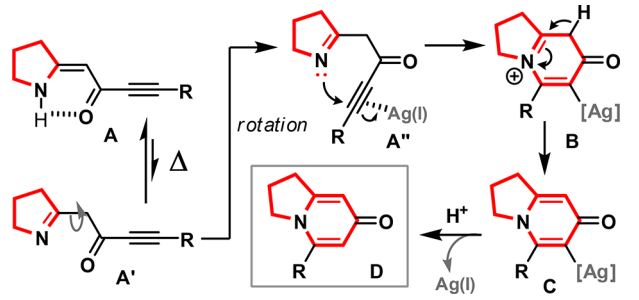
Scheme 3. Substrate Scope for Ag(I)-Catalyzed Cyclization of Ketimine-Tethered Ynones



% of AgTFA under the usual conditions. Simple 7-membered cyclic ketimine precursors (of the form **17**) were also well tolerated, furnishing products **18a,b** under similar conditions. We were also keen to demonstrate that the procedure is applicable to more complex systems with additional functionality that might improve the medicinal properties of the products. Thus, starting materials **19a** and **19b**, which were prepared from benzodiazepine precursors, were converted into the products **20a** and **20b**, respectively, and in the case of the latter, via a high-yielding double cyclization, from starting material **19b**. Many benzodiazepines are psychoactive and act as minor sedatives, and they have been used for the treatment of various neurological conditions including anxiety, insomnia, seizures, muscle spasms, and alcohol withdrawal.[16]

A proposed mechanism is outlined in Scheme 4. In all cases, the starting materials exist predominantly as enamine tautomers, which are likely stabilized by an intramolecular H-bond and present in the conformation depicted (**A**). Tautomerization (**A** → **A′**) followed by bond rotation (**A′** → **A″**) is proposed to generate an intermediate capable of undergoing cyclization via nucleophilic attack of the ketimine nitrogen lone-pair, induced by Ag(I)-mediated π-acid activation of the alkyne (**A″** → **B**). Subsequent deprotonation and protodemetalation would then generate the indolizinone product and release Ag(I) back into the catalytic cycle. Alternatively, intermediate **A″** might tautomerize back to the analogous *E*-enamine prior to cyclization to give **C**, although we

Scheme 4. Proposed Mechanism

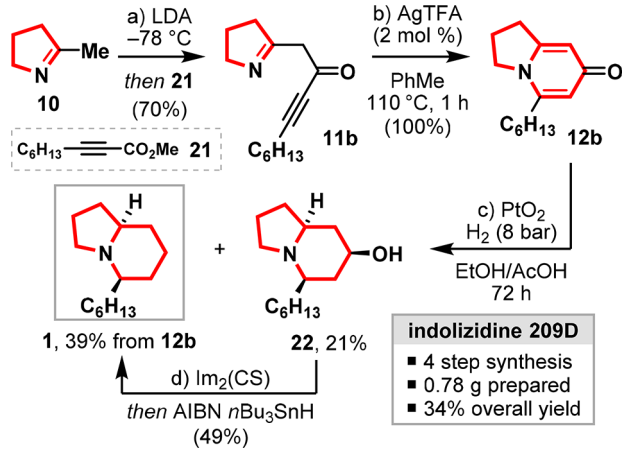


believe that this pathway is less likely in view of the expected low nucleophilicity of the nitrogen (a vinylogous amide) in this form.

Finally, the utility of the Ag(I)-catalyzed cyclization was demonstrated in a short total synthesis of indolizidine 209D, an alkaloid isolated from the skin secretions of the *Dendrobates* family of neotropical frogs, that is part of a family of alkaloids known to be effective noncompetitive inhibitors of the neuromuscular transmission receptor and nicotinic acetylcholine receptors.[17,18] Our synthesis began the with the acylation of 2-methyl-1-pyrroline **10** with ester **21** to provide **11b** in 70% yield. Then, AgTFA-catalyzed cyclization afforded the desired bicyclic product **12b** in quantitative yield as described above. This was followed by dearomative hydrogenation, using catalytic platinum(IV) oxide and hydrogen at 8 bar, which afforded a 1:2 mixture of hydroxylated product **22** and the fully saturated target molecule (±)-indolizidine 209D (**1**). The products were separable and isolated separately (with isolated yields of 21% for **22** and 39% for **1**), and each was formed as a single diastereoisomer, with the spectroscopic properties of the natural product **1** identical to those previously reported.[18] Furthermore, the yield of the natural product could be increased by subjecting partially reduced side product **22** to standard Barton–McCombie deoxygenation conditions,[18c] which furnished an additional quantity of (±)-indolizidine 209D **1** (when added to the original sample of **1**, an overall 49% yield for the conversion of **12b** into **1** was obtained). In total, 0.78 g of (±)-indolizidine 209D was prepared in four steps in 34% overall yield from ketimine **10** (Scheme 5).

In summary, we have developed an efficient and operationally simple Ag(I)-catalyzed cyclization of cyclic ketimine-

Scheme 5. Synthesis of (±)-Indolizidine 209D



DOI: 10.1021/acs.orglett.8b00225
Org. Lett. XXXX, XXX, XXX–XXX

tethered ynones to form partially saturated azabicycles containing 4-pyridones. The method is compatible with a range of cyclic ketimines, enabling the facile synthesis of several classes of azabicyclics. The prevalence of azabicycles in bioactive alkaloids augurs well for the use of this method in natural product synthesis and medicinal chemistry,[19] demonstrated in this work by a four-step total synthesis of (±)-indolizidine 209D. The method is also likely to be applicable to other more complex nitrogen-containing natural products; applications in target synthesis are ongoing in our laboratories, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00225.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1532716 contains 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

*E-mail: richard.taylor@york.ac.uk.
*E-mail: william.unsworth@york.ac.uk.

ORCID

Peter O'Brien: 0000-0002-9966-1962
William P. Unsworth: 0000-0002-9169-5156

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Engineering and Physical Sciences Research Council (EP/N035119/1, H.E.H.), the Leverhulme Trust (for an Early Career Fellowship, ECF-2015-13, W.P.U.) and the University of York (H.E.H., M.J.J., and W.P.U.) for financial support. We are also grateful to Dr. A. C. Whitwood and R. R. Bean for X-ray crystallography and to Dr. P. J. Rayner for assistance with the hydrogenation reactions (all University of York).

■ REFERENCES

(1) For the synthesis and biological activity of fused alkaloids, see the following books and reviews and the references cited therein: (a) Michael, J. P. In *The Alkaloids: Chemistry and Biology*; Academic Press: New York, 2001; Vol. *55*, pp 91−258. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (c) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556. (d) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. (e) Bhat, C.; Tilve, S. G. *RSC Adv.* **2014**, *4*, 5405. (f) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2017**, *34*, 62. (g) *The Alkaloids*; Knölker, H.-J., Ed.; Elsevier: Cambridge, MA, 2018; Vol. *79*.

(2) For background and the synthesis of compounds **1**−**6**, see: (a) Dau, X. D.; Willis, A. C.; Pyne, S. G. *Eur. J. Org. Chem.* **2015**, *2015*, 7282. (b) Brambilla, M.; Davies, S. G.; Fletcher, A. I.; Roberts, P. M.; Thomson, J. E.; Zimmer, D. *Tetrahedron* **2016**, *72*, 7417. (c) Lapointe, G.; Schenk, K.; Renaud, P. *Org. Lett.* **2011**, *13*, 4774. (d) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531. (e) Pilli, R. A.; Ferreira de Olivera, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117−127. (f) Pilli, R. A.; Rosso, G. B.; Ferreira de Olivera, M. C. *Nat. Prod. Rep.* **2010**, *27*, 1908. (g) Ronson, T. O.; Kitsiou, C.; Unsworth, W. P.; Taylor, R. J. K. *Tetrahedron* **2016**, *72*, 6099.

(3) James, M. J.; Grant, N. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2016**, *18*, 6256.

(4) For reviews on dearomatization reactions, see: (a) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (b) Roche, S. P.; Youte Tendoung, J.-J.; Treguier, B. *Tetrahedron* **2015**, *71*, 3549. (c) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. - Eur. J.* **2016**, *22*, 2856. (d) Liang, X.-W.; Zheng, C.; You, S.-L. *Chem. - Eur. J.* **2016**, *22*, 11918. (e) Wu, W.-T.; Zhang, L.; You, S.-L. *Chem. Soc. Rev.* **2016**, *45*, 1570.

(5) For the π-acid activation of alkynes, including pyridyl systems, see: (a) Johnson, D. G.; Lynam, J. M.; Mistry, N. S.; Slattery, J. M.; Thatcher, R. J.; Whitwood, A. C. *J. Am. Chem. Soc.* **2013**, *135*, 2222. (b) Halliday, C. J. V.; Lynam, J. M. *Dalton Trans.* **2016**, *45*, 12611.

(6) For previous work from our laboratories on dearomatizing spirocyclization reactions of aromatic ynones, see: (a) Unsworth, W. P.; Cuthbertson, J. D.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 3306. (b) James, M. J.; Cuthbertson, J. D.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem., Int. Ed.* **2015**, *54*, 7640. (c) James, M. J.; Clubley, R. E.; Palate, K. Y.; Procter, T. J.; Wyton, A. C.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2015**, *17*, 4372. (d) Liddon, J. T. R.; James, M. J.; Clarke, A. K.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Chem. - Eur. J.* **2016**, *22*, 8777. (e) Clarke, A. K.; James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 13798. (f) Liddon, J. T. R.; Clarke, A. K.; Taylor, R. J. K.; Unsworth, W. P. *Org. Lett.* **2016**, *18*, 6328. (g) Clarke, A. K.; Liddon, J. T. R.; Cuthbertson, J. D.; Taylor, R. J. K.; Unsworth, W. P. *Org. Biomol. Chem.* **2017**, *15*, 233.

(7) For related dearomative hydrogenation approaches, see: Yu, H.; Zhang, G.; Huang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 10912 and references cited therein.

(8) For selected previous syntheses of lasubine II, see: (a) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (b) Verkade, J. M. M.; van der Pijl, F.; Willems, M. M. J. H. P.; Quaedflieg, P. J. L. M.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2009**, *74*, 3207. (c) Chandrasekhar, S.; Murali, R. V. N. S.; Reddy, C. R. *Tetrahedron Lett.* **2009**, *50*, 5686. (d) Saha, N.; Biswas, T.; Chattopadhyay, S. K. *Org. Lett.* **2011**, *13*, 5128.

(9) For selected examples, see: (a) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702. (b) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793. (c) Pepe, A.; Pamment, M.; Georg, G. I.; Malhotra, S. V. *J. Org. Chem.* **2011**, *76*, 3527. (d) Gouault, N.; Le Roch, M.; Cheignon, A.; Uriac, P.; David, M. *Org. Lett.* **2011**, *13*, 4371. (e) Stevens, K.; Tyrrell, A. J.; Skerratt, S.; Robertson, J. *Org. Lett.* **2011**, *13*, 5964.

(10) For a discussion of the nucleophilicity of cyclic ketimines, see: (a) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 258. (b) Unsworth, W. P.; Taylor, R. J. K. *Synlett* **2016**, *27*, 2051.

(11) This contrasts to the majority of published amine cyclization methods (see refs 1 and 9) in which protecting groups are needed to attenuate the nucleophilicity of the amine.

(12) A modified protocol based on a literature method was used; see the SI and: Podoll, J. D.; Liu, L.; Chang, L.; Walls, S.; Wang, W.; Wang, X. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 15573.

(13) (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409. (b) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101. (c) Kim, G.; Jung, S.-D.; Kim, W.-J *Org. Lett.* **2001**, *3*, 2985. (d) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (e) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. (f) Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4617. (g) Kim, G.; Lee, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2073. (h) Corvo, M. C.; Pereira, M. M. C. *Tetrahedron Lett.* **2002**, *43*, 455. (i) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (j) Sun, Z.; Yu, S.;

DOI: 10.1021/acs.orglett.8b00225
Org. Lett. XXXX, XXX, XXX−XXX

Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (k) Cuthbertson, J. D.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 1490.
(14) Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.
(15) As for the pyrroline series, starting materials **13**, **15**, **17**, and **19** exist largely as their enamine tautomeric form in solution in $CDCl_3$. For simplicity, all substrates are drawn in their imine forms.
(16) For background on benzodiazepines, see: Rudolph, U.; Knoflach, F. *Nat. Rev. Drug Discovery* **2011**, *10*, 685 and references cited therein.
(17) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. *5*, Chapter 1. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1127.
(18) For additional background and selected previous syntheses of indolizidine 209D, see ref 13d and: (a) Kim, G.; Jung, S.-D.; Kim, W.-J. *Org. Lett.* **2001**, *3*, 2985. (b) Alegret, G.; Riera, A. *J. Org. Chem.* **2008**, *73*, 8661. (c) Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2379. (d) Chiou, H.-W.; Chen, H.-Y. *RSC Adv.* **2017**, *7*, 684 and references cited therein.
(19) For selected examples in which similar strategies have been used, see: (a) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. *ARKIVOC* **2004**, *8*, 52. (b) Natarajan, S. R.; Chen, M.-H.; Heller, S. T.; Tynebor, R. M.; Crawford, E. M.; Minxiang, C.; Kaizheng, H.; Dong, J.; Hu, B.; Hao, W.; Chen, S.-H. *Tetrahedron Lett.* **2006**, *47*, 5063. (c) Tynebor, R. M.; Chen, M. H.; Natarajan, S. R.; O'Neill, E. A.; Thompson, J. E.; Fitzgerald, C. E.; O'Keefe, S. J.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 411.

DOI: 10.1021/acs.orglett.8b00225
Org. Lett. XXXX, XXX, XXX−XXX