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Catalytic Dearomatization Approach to Quinolizidine Alkaloids: Five Step Total Synthesis of (±)-Lasubine II

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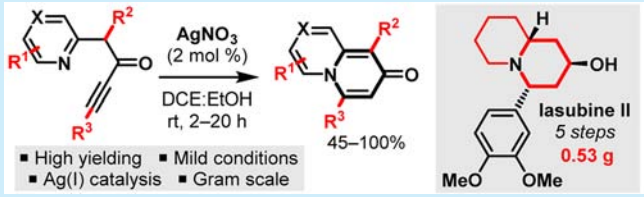
Supporting Information

ABSTRACT: A series of high-yielding silver(I)-catalyzed cyclization reactions of pyridine-, isoquinoline-, and pyrazine-ynones are described. The operationally simple and mild reaction conditions are a significant improvement over previously reported thermal cyclizations. The quinolizinone products were also used in a novel dearomatization strategy to prepare 0.53 g of the alkaloid lasubine II in five steps and 36% overall yield.



Pyridine and piperidine are the two most prevalent *N*-heterocycles used in medicinal chemistry, with a recent study showing their presence in 12% of all US FDA approved drugs.[1] New methods for the synthesis of these heterocycles and their derivatives, such as quinolizines/quinolizidines, are therefore of high value. The saturated quinolizidine framework is particularly notable for its presence in a number of bioactive natural products, such as **1**–**3** (Figure 1A),[2] which makes them highly attractive synthetic targets.

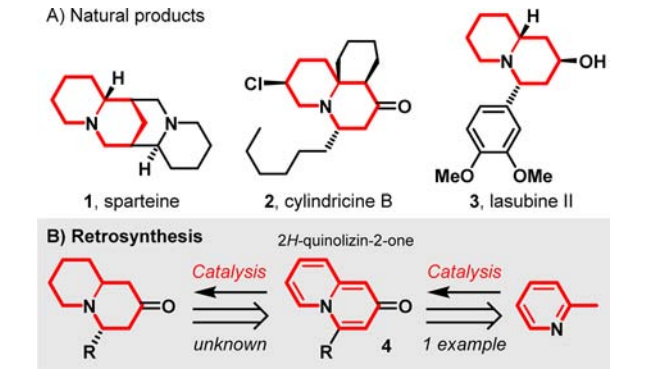
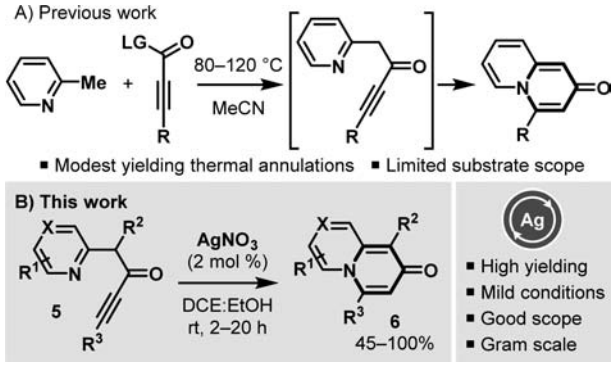


Figure 1. (A) Natural products containing the saturated quinolizidine framework; (B) proposed dearomative retrosynthesis.

An unexplored and expedient strategy by which to access these bicyclic frameworks is by the dearomatization of a 2*H*-quinolizin-2-one system **4** (Figure 1B). Dearomatization reactions are important transformations as they enable high value spiro-[3] or bridged-compounds[4] to be formed from inexpensive and readily available aromatic feedstocks.[5] However, current methods for the synthesis of 2*H*-quinolizin-2-ones are limited, relying primarily on harsh thermal conditions,[6] with catalytic examples being rare.[7] Seeking to address this limitation, an opportunity to build upon our recent work on the catalytic dearomatization/cyclization of aromatic alkynes was indentified.[8] This previous work is based on the activation of alkynes with π-acidic catalysts[9] to promote cyclization to generate spirocyclic/annulated products, and based on this, it was considered that pyridine-ynones would serve as useful precursors to 2*H*-quinolizin-2-ones. The viability of a related cyclization protocol had already been briefly demonstrated by both Katritzky and Natarajan (Scheme 1A);[6d,e] however, in this work the pyridine-ynone species is formed and cyclized in situ via the acylation of 2-picoline under relatively harsh, thermal conditions and the reported yields are modest. Herein, we describe a simple and scalable alternative approach, in which pyridine-, isoquinoline-, and pyrazine-ynones **5** can all be cyclized into annulated products **6** at room temperature using mild silver(I)-catalyzed conditions (Scheme 1B).

Scheme 1. Pyridine-ynone Cyclizations



Using this new method, a diverse array of quinolizinone products has been prepared in high yield, including reactions performed on gram scale. The methodology is likely to be of high value in natural product synthesis, and to demonstrate this,

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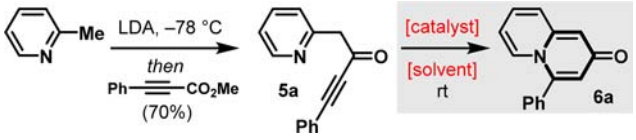
an efficient five-step synthesis of 0.53 g of the alkaloid lasubine II has also been developed, including a catalytic dearomatization of a quinolizinone product as a key step.

Our studies began with the preparation of pyridine-ynone **5a** via the deprotonation and acylation 2-picoline with methyl phenylpropiolate (Table 1). Ynone **5a** was then reacted with

Table 1. Optimization of the Pyridine-Ynone Cyclization



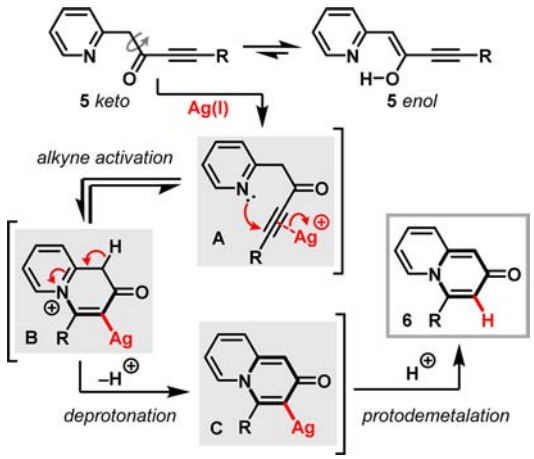
entry	[catalyst][a] (equiv)	[solvent]	time (h)	conv (%)[b]
1	$Cu(MeCN)_4PF_6$ (0.1)	CH_2Cl_2	16	0
2	$Cu(OTf)_2$ (0.1)	CH_2Cl_2	16	0
3	$Ph_3PAuNTf_2$ (0.1)	CH_2Cl_2	16	0
4	AgOTf (0.1)	CH_2Cl_2	16	>95
5	AgOTf (0.02)	CH_2Cl_2	2	90
6	$AgSbF_6$ (0.02)	CH_2Cl_2	2	25
7	$AgNO_3$ (0.02)	CH_2Cl_2	2	>95
8	$AgNO_3$ (0.01)	CH_2Cl_2	0.5	50

[a]Reactions performed with 0.2 mmol of **5a** and catalyst in the stated solvent (0.1 M) at rt. [b]Calculated by measuring the ratio of starting material to product in the ^1H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 5%.

four π-acidic catalysts in dichloromethane (Table 1, entries 1–4), of which only AgOTf was effective for the formation of quinolizinone **6a**. This prompted further scrutiny of other silver(I) catalysts, and of those tested, $AgNO_3$ provided the best reactivity (entries 7 and 8).

The silver(I) catalyst is proposed to catalyze this transformation as depicted in Scheme 2. The ynone starting

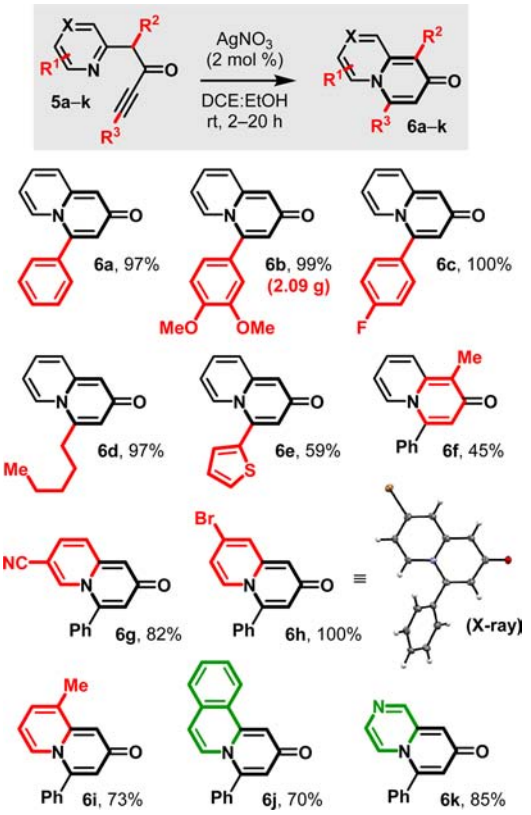
Scheme 2. Proposed Mechanism for the Silver(I)-Catalyzed Cyclization



material, which exists as an equilibrium of *keto–enol* tautomers (with the *enol* tautomer believed to be an unproductive resting state), is presumably activated by the π-acidic silver(I) catalyst (**A**), promoting nucleophilic attack from the pyridine lone pair to form pyridinium species **B** (which is likely a reversible process).[10] Deprotonation of the pyridinium species **B** at the acidic α-keto position then forms vinyl silver intermediate **C**; subsequent protodemetalation of this species then affords the final quinolizinone product **6** and regenerates the silver(I) catalyst.

The scope of this transformation was then examined, with minor modifications made to the conditions shown in Table 1. The solvent system was switched to a 1:1 mixture of ethanol/1,2-dichloroethane (see ref 12 for details) and 2 mol % of $AgNO_3$ was used as the catalyst in all of the examples for consistency (Scheme 3).

Scheme 3. Substrate Scope for the Silver(I)-Catalyzed Cyclization



First, the electronics of the aryl ynone subunit were varied to afford quinolizinones **6a–c** in quantitative/near-quantitative yield. Pleasingly, these reactions were equally effective on gram scale; for example, 2.09 g of quinolizinone **6b** were prepared in a single reaction in 99% yield. The aliphatic quinolizinone **6d** was also afforded in near-quantitative yield. Thiophene-substituted and methylated-quinolizinones **6e** and **6f** were also prepared, albeit in lower yield, which is believed to be a direct consequence of the instability of the ynone precursors (see Supporting Information for details). Substituents on the pyridine ring were also well tolerated, with quinolizinones **6g–i** bearing cyano, bromo, and methyl substituents, all being furnished in excellent to quantitative yield. The structure of the bromide **6h** was also confirmed by X-ray crystallography.[11] Finally, this methodology was also demonstrated on other heteroaromatic systems, to afford isoquinoline and pyrazine derived products **6j** and **6k** in excellent yield. The fully unsubstituted quinolizinone **6l** was also synthesized in excellent yield from TMS-ynone **5l** by using 20 mol % $AgNO_3$ and acetone to promote a one-pot desilylation–cyclization sequence (Scheme 4).[13,14] This reaction is particularly pleasing,

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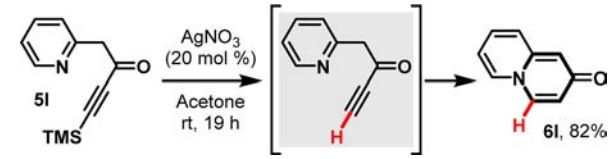
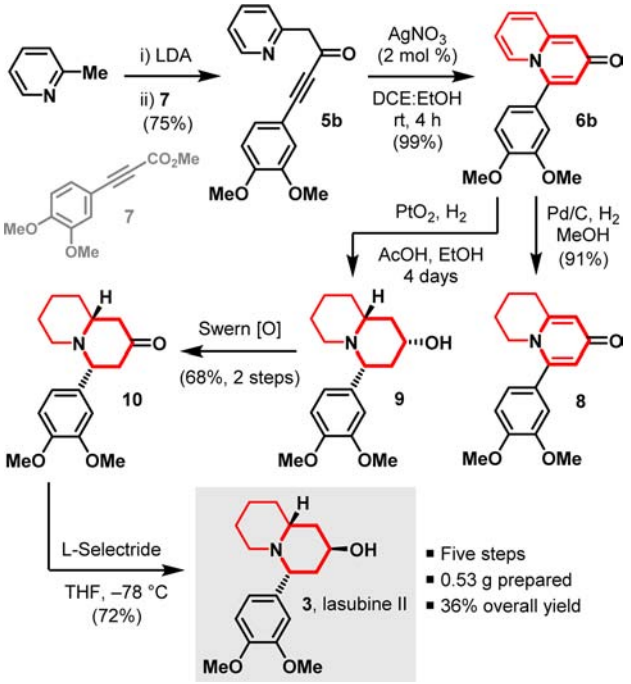
as the TMS ynone **5l** is completely unreactive under the previously reported thermal conditions.[6e]

Scheme 4. Tandem Ag(I)-Catalyzed Desilylation–Cyclization



The ease of formation of these quinolizinone products is likely to be of significant value in target synthesis projects, especially given the prevalence of saturated quinolizidine frameworks in Nature.[2] This was demonstrated in the five-step dearomative synthesis of (±)-lasubine II (Scheme 5).

Scheme 5. Five-Step Total Synthesis of (±)-Lasubine II



The synthesis began with the LDA-mediated deprotonation and acylation of 2-picoline with methyl ester **7**[15] to form ynone **5b** in good yield. Next, the silver(I)-catalyzed cyclization afforded the quinolizine **6b** in near-quantitative yield. Interestingly, the two ring systems of **6b** could then be selectively hydrogenated with either Pd/C or PtO_2 to form products **8** and **9** respectively.[16] The unpurified quinolizidine **9** was then oxidized under Swern conditions to form ketone **10** in excellent yield over the two-step sequence.[17] Finally, the known L-Selectride reduction of ketone **10** afforded 0.53 g of (±)-lasubine II **3** in 36% overall yield.[18,19]

In summary, we have developed a mild and operationally simple protocol for the high-yielding catalytic synthesis of quinolizinones. Furthermore, we demonstrated the synthetic utility of the products by preparing 0.53 g of (±)-lasubine II in just five steps and 36% overall yield from 2-picoline. The development of a protocol for the asymmetric hydrogenation of quinolizinones remains the focus of future work,[20] in hopes of enabling the enantioselective synthesis of lasubine II and other related alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03017.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(2) For reviews, see: (a) Grundon, M. F. *Nat. Prod. Rep.* **1985**, *2*, 235. (b) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (d) Veerasamy, N.; Carter, R. G. *Tetrahedron* **2016**, *72*, 4989.

(3) For recent examples of dearomatizing spirocyclization reactions, see: (a) Nandi, R. K.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Org. Lett.* **2016**, *18*, 1716. (b) Janssen-Müller, D.; Fleige, M.; Schlüns, D.; Wollenburg, M.; Daniliuc, C. G.; Neugebauer, J.; Glorius, F. *ACS Catal.* **2016**, *6*, 5735. (c) James, M. J.; O'Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 9671. (d) Wu, W.-T.; Xu, R.-Q.; Zhang, L.; You, S.-L. *Chem. Sci.* **2016**, *7*, 3427.

(4) For recent examples of dearomatization reactions in bridged- and fused-compound synthesis, see: (a) Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. *Nat. Chem.* **2015**, *7*, 842. (b) Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. *Nat. Chem.* **2016**, *8*, 922. (c) Liu, C.; Yi, J.-C.; Liang, X.-W.; Xu, R.-Q.; Dai, L.-X.; You, S.-L. *Chem. - Eur. J.* **2016**, *22*, 10813. (d) Xu, J.-H.; Zheng, S.-C.; Zhang, J.-W.; Liu, X.-Y.; Tan, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 11834.

(5) 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.; Tendoung, J.-J. Y.; 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.

(6) (a) Boekelheide, V.; Lodge, J. P. *J. Am. Chem. Soc.* **1951**, *73*, 3681. (b) Fozard, A.; Jones, G. *J. Chem. Soc.* **1964**, 2760. (c) Acheson, R. M.; Woollard, J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 446. (d) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. *ARKIVOC* **2004**, *viii*, 52. (e) 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.

DOI: 10.1021/acs.orglett.6b03017
Org. Lett. 2016, 18, 6256–6259

(7) To the best of our knowledge, only one example of a catalytic 2*H*-quinolizin-2-one synthesis has been reported; see: (a) Fan, X.; He, Y.; Zhang, X.; Wang, J. *Green Chem.* **2014**, *16*, 1393. For a relevant example of catalytic 4*H*-quinolizin-4-one synthesis, see: (b) Shinde, P. S.; Shaikh, A. C.; Patil, N. T. *Chem. Commun.* **2016**, *52*, 8152.
(8) (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.*, DOI: 10.1021/acs.orglett.6b03221.
(9) For useful insight into 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.
(10) For examples of similar mechanistic pathways, see: (a) Yang, Z.-P.; Wu, Q.-F.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6986. (b) Yang, Z.-P.; Wu, Q.-F.; Shao, W.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 15899.
(11) CCDC 1507022 (**6h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(12) For details of solvent screening studies see the Supporting Information. Note that whilst the reactions generally proceeded faster in pure ethanol, 1,2-dichloroethane was included as a cosolvent in the final optimized conditions to improve solubility across a wider range of substrates.
(13) For a review of $AgNO_3$-mediated desilylation reactions, see: Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199.
(14) Quinolizinone **6l** is also a potential precursor for the (±)-sparteine surrogate; see: Firth, J. D.; O'Brien, P.; Ferris, L. *Org. Biomol. Chem.* **2014**, *12*, 9357.
(15) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496.
(16) To the best of our knowledge, this is the first reported full hydrogenation of a 2*H*-quinolizin-2-one.
(17) For syntheses of related ketone systems, see: (a) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (b) Liu, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 7301.
(18) For syntheses of lasubine I/II via an L-Selectride reduction, see: (a) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807. (b) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. (c) Ukaji, Y.; Imai, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. (d) Back, T. G.; Hamilton, M. D. *Org. Lett.* **2002**, *4*, 1779. (e) Shan, Z.-H.; Liu, J.; Xu, L.-M.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2012**, *14*, 3712.
(19) For other recent 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.
(20) For a recent review on asymmetric hydrogenation, see: Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *ACS Catal.* **2016**, *6*, 5978.

DOI: 10.1021/acs.orglett.6b03017
Org. Lett. 2016, 18, 6256−6259