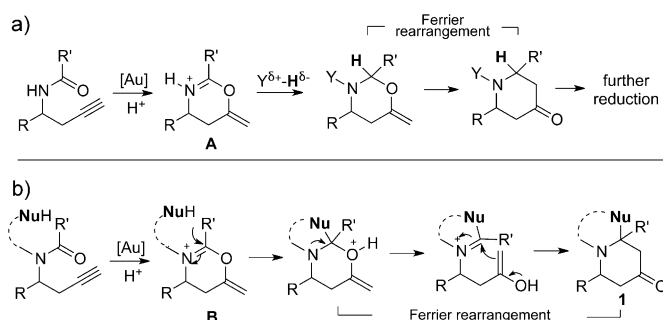


# N-Heterocycles

## Access to Electron-Rich Arene-Fused Hexahydroquinolizinones through a Gold-Catalysis-Initiated Cascade Process\*\*

Lianzhu Liu and Liming Zhang\*

We have recently developed a two-step, one-pot synthesis of piperidine-4-ols.<sup>[1]</sup> In this reaction, the protonated cyclic imidate intermediate **A**, which is prepared by a gold-catalyzed<sup>[2]</sup> amide cyclization, is reduced by an external hydride (e.g., catecholborane), which initiates a key Ferrier rearrangement<sup>[3]</sup> (Scheme 1a). We envisioned that a carbon

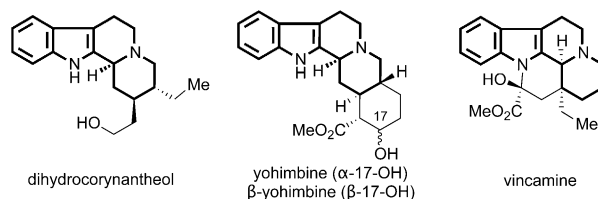


**Scheme 1.** A gold-catalysis-initiated cascade process toward bicyclic piperidine-4-ones.

nucleophile could replace the hydride in this chemistry; moreover, if such a nucleophile is attached to the amide nitrogen atom, addition of reagent in the course of the reaction is not needed. The reaction would constitute a gold-catalysis-initiated cascade process and might provide an efficient access to bicyclic piperidin-4-ones (e.g., **1**, Scheme 1b). Herein, we disclose our implementation of this strategy, which leads to an expedient synthesis of electron-rich arene-fused hexahydroquinolizinones; its synthetic utility is illustrated by a succinct and stereoselective synthesis of dihydrocorynantheol without the use of any protecting group, and a formal synthesis of yohimbine and  $\beta$ -yohimbine.

We chose tertiary formamide **1a** as substrate, as the formyl group would minimize steric hindrance for nucleophilic attack and the indole ring can act as a good neutral carbon nucleophile. Importantly, the anticipated product **2a**, a tetracyclic piperidine-4-one, shares a common hexahydro-

indolo[2,3-*a*]quinolizine skeleton with various indole alkaloids, including dihydrocorynantheol,<sup>[4]</sup> yohimbine,<sup>[5]</sup> and vincamine<sup>[6]</sup> (Scheme 2). Notably, the latter two are marketed drugs for peripheral vasodilation.<sup>[7]</sup>



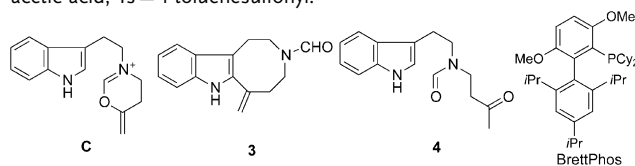
**Scheme 2.** Selected alkaloids containing the indolo[2,3-*a*]quinolizine skeleton.

The formamide **1a** was readily prepared from tryptamine through a straightforward two-step sequence: alkylation with but-3-yn-1-yl tosylate and formylation with ethyl formate. When **1a** was treated with  $\text{IPrAuNTf}_2$  (5 mol %) at ambient temperature, desired product **2a** could not be detected (Table 1, entry 1). Instead, tricyclic formamide **3**, which was formed by a gold-catalyzed 8-*exo-dig* cyclization,<sup>[8]</sup> was

**Table 1:** Initial discovery and condition optimization.<sup>[a]</sup>

Entry	Catalyst	Acid additive (equiv)	Yield [%] <sup>[b]</sup>
1	$\text{IPrAuNTf}_2$	–	— <sup>[c]</sup>
2	$\text{IPrAuNTf}_2$	MsOH (2)	56 <sup>[d]</sup>
3	$\text{IPrAuNTf}_2$	TsOH (2)	64 <sup>[d]</sup>
4	$\text{IPrAuNTf}_2$	TFA (2)	82 <sup>[d]</sup>
5	$\text{IPrAuNTf}_2$	AcOH (2)	— <sup>[e]</sup>
6	$\text{Ph}_3\text{PAuNTf}_2$	TFA (2)	83 <sup>[d]</sup>
7	$\text{BrettPhosAuNTf}_2$	TFA (2)	89 <sup>[d]</sup> (87) <sup>[f]</sup>
8	$\text{AuCl}_3$	TFA (2)	12 <sup>[d]</sup>

[a] [**1a**] = 0.05 M. [b] Yield estimated by  $^1\text{H}$  NMR spectroscopy with diethyl phthalate as internal standard. [c] 12% of **3** formed after reaction for 6 h. [d] **4** is the identifiable side product. [e] Reaction resulted in a complex mixture of products. [f] Yield of isolated product. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Cy = cyclohexyl, Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.



[\*] Dr. L. Liu, Prof. Dr. L. Zhang  
Department of Chemistry and Biochemistry, University of California  
Santa Barbara, CA (USA)  
E-mail: zhang@chem.ucsb.edu  
Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>

[\*\*] The authors thank NIGMS (R01 GM084254) and UCSB for generous financial support, and Sigma-Aldrich for generous donation of  $\text{BrettPhosAuNTf}_2$ .

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201203303>.

detected in a small amount. To our delight, when MsOH (2 equiv) was added, the desired product **2a** was formed in 56% yield after 24 hours. The main side product was the corresponding methyl ketone **4**, formed by gold-catalyzed alkyne hydration. To gain insight into the reaction mechanism, the reaction was run in CDCl<sub>3</sub> and monitored by <sup>1</sup>H NMR spectroscopy. Surprisingly, the initial gold-promoted cyclization and subsequent protodeauration<sup>[9]</sup> were facile and efficient, even at 0 °C, and the formamide **1a** was converted to the 1,3-oxazin-3-ium intermediate **C** (see Table 1, footnote) in approximately 80% NMR yield after only 40 minutes. Because the Ferrier rearrangement is supposed to be fast, this result suggested that the cyclization of **C** is very slow, which is unexpected.

To further improve the reaction, we subsequently screened other acid additives (Table 1, entries 3–5). Trifluoroacetic acid (TFA) turned out to be the most effective additive, and the indole-fused hexahydroquinolizinone **2a** was formed in 82% yield (Table 1, entry 4). Among the other examined gold catalysts, BrettPhosAuNTf<sub>2</sub><sup>[10]</sup> provided a slightly better yield (Table 1, entry 7), while use of AuCl<sub>3</sub> resulted in a very low yield (entry 8).

With the optimized reaction conditions in hand, the scope of this gold-catalysis-initiated cascade reaction was explored. Different substituents on the indole benzenoid ring, including an electron-donating 5-MeO (Table 2, entry 1), electron-withdrawing 6-F (entry 2) and 5-Cl (entry 3), and a 5-Me (entry 4), were tolerated, and the reactions afforded indole-fused hexahydroquinolizinones in good yields. The formamide **1f**, which was easily prepared from tryptophan ethyl ester, also reacted smoothly, and the tetracyclic keto ester product **2f** was formed in 79% yield, although the diastereoselectivity was low ( $\alpha/\beta = 2/3$ ; Table 2, entry 5). The tolerance of the reaction toward substituents on the but-3-yn-1-yl group was then studied. The reaction occurred smoothly with a phenyl group in  $\alpha$  position to the nitrogen atom (Table 2, entry 6). Notably, the reaction was highly diastereoselective, and product **2g**, with the phenyl group *cis* to the indole ring, was isolated as the only diastereoisomer in 72% yield. When a 4-benzyloxybut-1-yl group replaced the phenyl group, the reaction proceeded with the same yield of isolated product and equally excellent stereoselectivity (Table 2, entry 7). A cyclohexyl group at the propargylic position posed no problem, and the cyclized product was isolated in 81% yield, albeit with a low diastereoselectivity ( $\alpha/\beta = 2.4/1$ ; Table 2, entry 8). Because of the general interest in indole alkaloids, all the examples thus far used indole rings as the tethered nucleophiles. This, however, is not a limitation to the chemistry. For example, electron-rich benzene rings, such as methoxybenzene (Table 2, entry 9) and benzo[1,3]dioxole (entry 10), participated in the cascade, giving the benzene-fused hexahydroquinolizin-2-ones in synthetically useful yields.

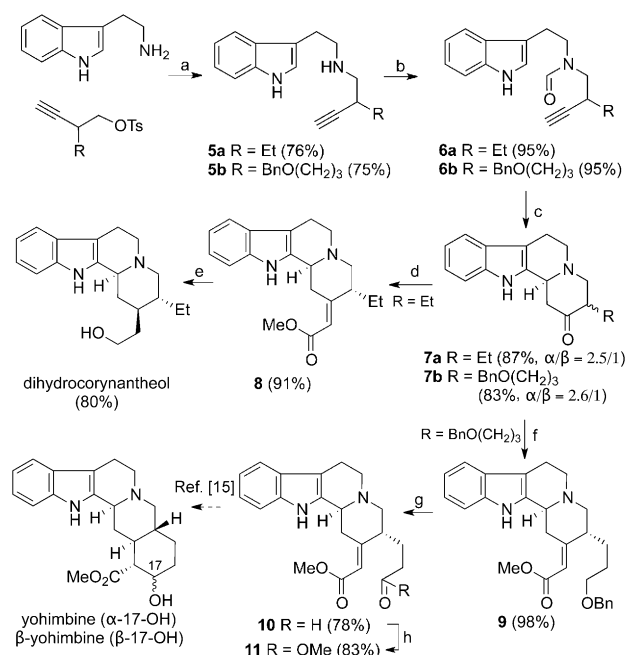
With the relatively general reaction scope of this cascade approach in hand, we turned our attention to the investigation of its utility in the synthesis of indole alkaloids that feature the hexahydroindolo[2,3-*a*]quinolizine skeleton. We first chose dihydrocorynantheol, which was first isolated from the bark of the Amazonian tree *A. marcgravianum* Woodson and has

**Table 2:** The reaction scope.<sup>[a]</sup>

Entry	1	2	Yield [%] <sup>[b]</sup>
1			82
2			84
3			83
4			82
5			79
6			72
7			72
8			81
9			68
10			61 <sup>[c]</sup>

[a] [1] = 0.05 M. [b] Yield of isolated product. [c] TFA (5 equiv), 4 days. DIBAL-H = diisobutylaluminum hydride, DMSO = dimethylsulfoxide, Py = pyridine.

been synthesized through many elegant total synthesis approaches.<sup>[11]</sup> The ethyl formamide substrate **6a** was easily prepared in 72% overall yield in two steps from tryptamine and 2-ethylbut-3-yn-1-yl tosylate (Scheme 3), which in turn was synthesized in 44% yield in two steps<sup>[12]</sup> from cheap commercially available 1-pentyne. Compound **6a** underwent the cascade reaction smoothly, and the hexahydroindolo[2,3-*a*]quinolizinone **7a** was isolated in 87% yield, albeit as



**Scheme 3.** Stereoselective total synthesis of dihydrocorynantheol, and formal synthesis of yohimbine and β-yohimbine. Reagents and conditions: a) K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, 85 °C, 36 h; b) ethyl formate, 80 °C, 8 h; c) BrettPhosAuNTf<sub>2</sub> (5 mol %), TFA (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT, 24 h; d) methyl(dimethoxyphosphinyl)acetate, NaH, benzene; e) Pd/C, H<sub>2</sub>, MeOH, RT, 2 h; then DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 3 h; f) methyl(dimethoxyphosphinyl)acetate, NaH, benzene; g) Pd(OH)<sub>2</sub>/C, HCl, THF, 4 h; then SO<sub>3</sub>-Py, Et<sub>3</sub>N, DMSO, RT, 10 h; h) KOH, I<sub>2</sub>, MeOH, 0 °C, 4 h.

a mixture of diastereomers. The low diastereoselectivity, which is similar to what observed in the case of **2i**, however, posed no problem for the total synthesis. Hence, when **7a** was subjected to the Horner–Wadsworth–Emmons (HWE) reaction, the enoate **8** was isolated as the only diastereomer in an excellent yield. Apparently, under basic reaction conditions, the axial ethyl group in the β isomer of **7a** was epimerized to the more stable equatorial position, either before or after the HWE reaction. Pd/C-catalyzed hydrogenation of the exocyclic C=C bond was highly stereoselective,<sup>[13]</sup> and dihydrocorynantheol was isolated as the only diastereomer in 80 % yield upon subsequent DIBAL-H reduction. This total synthesis constitutes a short, six-step sequence from tryptamine, and the overall yield from 1-pentyne in eight steps is 20 %. Notably, no protecting group is needed in the whole synthetic sequence!

The same synthetic strategy can be employed in the formal synthesis of yohimbine<sup>[5]</sup> and β-yohimbine. The hexahydroindolo[2,3-*a*]quinolizone **7b** with a 3-benzyloxyprop-1-yl group in α position to the carbonyl group was readily accessed in a similarly efficient manner (59 % overall yield in three steps from tryptamine and the corresponding tosylate). Again, the low diastereoselectivity in the cascade process had no consequence, because both diastereomers of **7b** were converted into the desired enoate product **9** with the side chain occupying the more stable equatorial position. Hydrogenative debenzoylation and consecutive oxidations afforded the diester **11**, which has been previously converted to

a separable mixture of yohimbine and β-yohimbine through a chemoselective Dieckmann reaction<sup>[14]</sup> and a subsequent Pt-catalyzed hydrogenation.<sup>[15]</sup>

In summary, we have developed an efficient synthesis of electron-rich arene-fused hexahydroquinolizones. In this cascade reaction, a gold-catalyzed amide cyclization to a tethered C=C bond initiates a subsequent Friedel–Crafts-type cyclization followed by a Ferrier rearrangement. When an indole ring is employed as the tethered nucleophile, this reaction provides a rapid access to the hexahydroindolo[2,3-*a*]quinolizone skeleton, which is the common core structure in various indole alkaloids. This new method enables a succinct and stereoselective synthesis of dihydrocorynantheol and a formal synthesis of yohimbine and β-yohimbine.

## Experimental Section

General procedure for the gold catalysis-initiated cascade reaction: A formamide, BrettPhosAuNTf<sub>2</sub> (0.05 equiv), and trifluoroacetic acid (2.0 equiv) were dissolved in anhydrous methylene chloride (0.1 M) in a flame-dried vial. The mixture was stirred at RT typically for 24 h. Ammonium hydroxide (≈14.8 N, the same volume as methylene chloride) was added to quench the reaction. The organic phase was separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried with anhydrous sodium sulfate. After filtration and concentration, the resulting residue was purified by flash chromatography on silica gel (eluent: ethyl acetate/MeOH/NH<sub>4</sub>OH = 10:1:0.1).

Received: April 30, 2012

Published online: June 12, 2012

**Keywords:** alkaloids · cascade reactions · catalysis · gold · indoles

- [1] L. Cui, C. Li, L. Zhang, *Angew. Chem.* **2010**, *122*, 9364; *Angew. Chem. Int. Ed.* **2010**, *49*, 9178.
- [2] For selected reviews, see: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; b) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; c) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; d) E. s. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326; e) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; f) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; g) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269; h) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692; i) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999; j) B. Biannic, A. Aponick, *Eur. J. Org. Chem.* **2011**, 6605; k) D. Garayalde, C. Nevado, *Beilstein J. Org. Chem.* **2011**, *7*, 767.
- [3] For other gold-catalyzed reactions involving a Ferrier rearrangement, see: a) H. J. Bae, W. Jeong, J. H. Lee, Y. H. Rhee, *Chem. Eur. J.* **2011**, *17*, 1433; b) E. M. L. Sze, W. Rao, M. J. Koh, P. W. H. Chan, *Chem. Eur. J.* **2011**, *17*, 1437.
- [4] B. Gilbert, L. D. Antonaccio, C. Djerassi, *J. Org. Chem.* **1962**, *27*, 4702.
- [5] E. Haack, A. Popelak, H. Spingler, F. Kaiser, *Naturwissenschaften* **1954**, *41*, 479.
- [6] E. Schlittler, A. Furlenmeier, *Helv. Chim. Acta* **1953**, *36*, 2017.
- [7] P. Cook, I. James, *N. Engl. J. Med.* **1981**, *305*, 1560.
- [8] For precedents of such cyclizations, see: a) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105; b) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358.

- [9] a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391; b) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956; c) A. S. K. Hashmi, A. M. Schuster, S. Litters, F. Rominger, M. Pernpointner, *Chem. Eur. J.* **2011**, *17*, 5661.
- [10] a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552; b) L. Ye, W. He, L. Zhang, *Angew. Chem.* **2011**, *123*, 3294; *Angew. Chem. Int. Ed.* **2011**, *50*, 3236.
- [11] a) T. Kametani, N. Kanaya, H. Hino, S.-P. Huang, M. Ihara, *Heterocycles* **1980**, *14*, 1771; b) M. Ihara, N. Taniguchi, K. Fukumoto, T. Kametani, *J. Chem. Soc. Chem. Commun.* **1987**, 1438; c) M. Ihara, N. Taniguchi, K. Yasui, K. Fukumoto, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2771; d) R. L. Beard, A. I. Meyers, *J. Org. Chem.* **1991**, *56*, 2091; e) M. Ohba, T. Ohashi, T. Fujii, *Heterocycles* **1991**, *32*, 319; f) M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, M. Halonen, *Heterocycles* **1992**, *34*, 321; g) A. Diez, C. Vila, M. E. Sinibaldi, Y. Troin, M. Rubiralta, *Tetrahedron Lett.* **1993**, *34*, 733; h) A. Deiters, S. F. Martin, *Org. Lett.* **2002**, *4*, 3243; i) A. Tosaka, S. Ito, N. Miyazawa, M. Shibuya, K. Ogasawara, Y. Iwabuchi, *Heterocycles* **2006**, *70*, 153; j) M. Amat, A. Gomez-Esque, C. Escolano, M. M. M. Santos, E. Molins, J. Bosch, *J. Org. Chem.* **2009**, *74*, 1205; k) B. J. English, R. M. Williams, *J. Org. Chem.* **2010**, *75*, 7869; l) X. Sun, D. Ma, *Chem. Asian J.* **2011**, *6*, 2158; m) W. Zhang, J. Bah, A. Wohlfarth, J. Franzen, *Chem. Eur. J.* **2011**, *17*, 13814.
- [12] G. R. Khan, K. A. Pover, F. Scheinmann, *J. Chem. Soc. Chem. Commun.* **1979**, 215.
- [13] a) S. Andreae, G. Blasko, C. Szantay, *J. Prakt. Chem.* **1987**, 329, 374; b) I. P. Malhotra, N. Malhotra, *J. Serb. Chem. Soc.* **1999**, *64*, 155.
- [14] C. Szántay, K. Honty, L. Töke, A. Buzas, J. P. Jacquet, *Tetrahedron Lett.* **1971**, *12*, 4871.
- [15] a) C. Szántay, K. Honty, L. Töke, L. Szabó, *Chem. Ber.* **1976**, *109*, 1737; b) G. Blaskó, H. Knight, K. Honty, C. Szántay, *Liebigs Ann. Chem.* **1986**, 655.