Published in final edited form as:

Angew Chem Int Ed Engl. 2012 July 16; 51(29): 7301–7304. doi:10.1002/anie.201203303.

Access to Electron-Rich Arene-Fused Hexahydroquinolizinones via A Gold Catalysis-Triggered Cascade Process

Lianzhu Liu [Dr.] and Liming Zhang* [Prof. Dr.]

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California (USA)

Abstract

Golden Cascade? Using a tethered, electron-rich arene as the internal nucleophile, a gold catalyzed amide cyclization to an alkyne serves as the trigger of a cascade process that ends with a Ferrier rearrangement. Electron-rich arene-fused hexahydroquinolizin-2-ones are formed in good yields and can be converted into indole alkaloids in short orders.

Keywords

gold; cascade; alkaloid; indole; catalysis

Recently we have developed a two-step, one-pot synthesis of piperidine-4-ols.^[1] In this reaction, the protonated cyclic imidate intermediate **A**, prepared via a gold-catalyzed^[2] amide cyclization, is reduced by an external hydride (e.g., catecholborane), which triggers a key Ferrier rearrangement^[3] (Scheme 1A). We envision that a carbon nucleophile could replace the hydride in this chemistry; moreover, if such a nucleophile is attached to the amide nitrogen, no reagent addition during the reaction is needed. The reaction would constitute a gold catalysis-triggered 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 β -yohimbine.

We chose the tertiary formamide **1a** as the substrate as the formyl group would minimize steric hindrance for nucleophilic attack and the indole ring can behave as a good neutral carbon nucleophile. Importantly, the anticipated product **2a**, a tetracyclic piperidine-4-one, shares a common hexahydroindolo[2,3-*a*]quinolizine skeleton with various indole alkaloids including dihydrocorynantheol,^[4] yohimbine,^[5] and vincamine^[6] (Figure 1). Notably, the latter two are marketed medicines for peripheral vasodilation.^[7]

*Fax: (+1) 805-893-4120, zhang@chem.ucsb.edu, Homepage: <http://www.chem.ucsb.edu/~zhang/index.html>.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

The formamide **1a** was readily prepared from tryptamine via a straightforward two-step sequence: alkylation with but-3-yn-1-yltosylate and formylation with ethyl formate. When it was treated with IPrAuNTf_2 (5 mol %) at ambient temperature, no desired product **2a** could be detected (Table 1, entry 1). Instead, the tricyclic formamide **3**, formed due to a gold-catalyzed 8-*exo-dig* cyclization,^[8] was 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 h. The main side product was the corresponding methyl ketone **4**, formed due to gold-catalyzed alkyne hydration. To gain insight into the reaction mechanism, the reaction was run in CDCl_3 and monitored by $^1\text{H NMR}$. Surprisingly, the initial gold-promoted cyclization and subsequent protodeauration^[9] were facile and efficient even at 0 °C, and the formamide **1a** was converted to the 1,3-oxazin-3-iumintermediate **C** (see Table 1 footnote) in ~80% NMR yield after only 40 min. Since the Ferrier rearrangement is expected to be fast, this result suggested that the cyclization by **C** is very slow, which is unexpected.

To further improve the reaction, we subsequently screened other acids. As shown in Table 1, entries 3–5, trifluoroacetic acid (TFA) turned out to be the most effective, and the indole-fused hexahydroquinolizinone **2a** was formed in 82% yield (entry 4). Of the other gold catalysts examined, BrettPhosAuNTf_2 ^[10] provided a slightly better yield (entry 7), while AuCl_3 was barely competent (entry 8).

Using the optimized reaction conditions, the scope of this gold catalysis-triggered cascade reaction was explored. Different substituents on the indole benzenoid ring including an electron-donating 5-MeO (entry 1), electron-withdrawing 6-F (entry 2) and 5-Cl (entry 3), and a 5-Me (entry 4) were all allowed, and the reactions afforded the indole-fused hexahydroquinolizines all in good yields. The formamide **1f**, easily prepared from tryptophan ethyl ester, also reacted smoothly, and the tetracyclic keto ester product **2f** was formed in 79% yield, although the diastereoselectivity ($\alpha/\beta = 2/3$) was low (entry 5). The tolerance of substitution on the but-3-yn-1-yl group was then studied. With a phenyl group α to the nitrogen, the reaction occurred smoothly (entry 6). Notably, the reaction was highly diastereoselective, and the 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 isolated yield and equally excellent stereoselectivity (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 ($\alpha/\beta = 2.4/1$, entry 8). Owing to 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 (entry 9) and benzo[1,3]dioxole (entry 10) participated in the cascade, yielding the benzene-fused hexahydroquinolizin-2-ones in synthetically serviceable yields.

With this cascade chemistry showing a pretty general reaction scope, we then turned our attention to studying its utility in the synthesis of indole alkaloids featuring 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 been subjected to many elegant total synthesis throughout the years.^[11] As shown in Scheme 2, the ethyl formamide **6a** was easily prepared in 72% overall yield in two steps from tryptamine and 2-ethylbut-3-yn-1-yltosylate, which in turn was synthesized in 44% yield in two steps^[12] from cheap commercially available 1-pentyne. **6a** underwent the cascade reaction uneventfully, and the hexahydroindolo[2,3-*a*]quinolizinone **7a** was isolated in 87% yield, albeit as a mixture of diastereomers. The low diastereoselectivity, similar to what observed in the case of **2i**, however, posed no problem for the total synthesis. Hence, when **7a** was subjected to the HWE reaction, the enoate **8** was isolated as the only diastereomer in an excellent yield. Apparently, under the 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 double bond was highly stereoselective,^[13] and upon a subsequent DIBAL-H reduction dihydrocorynantheol was isolated as the only diastereomer in 80% yield. 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 need in the whole synthetic sequence!*

The same synthetic strategy can be employed en route to the formal synthesis of yohimbine^[5] and β -yohimbine. Hence, the hexahydroindolo[2,3-*a*]quinolizine **7b** with a 3-benzyloxyprop-1-yl group α 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 chemistry bore no consequence, and 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 via a chemoselective Dieckmann reaction^[14] and a subsequent Pt-catalyzed hydrogenation.^[15]

In summary, we have developed an efficient synthesis of electron-rich arene-fused hexahydroquinolizines. In this cascade reaction, an initial gold-catalyzed amide cyclization to a tethered C-C triple bond triggers subsequent Friedel-Crafts-type cyclization and 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*]quinolizine skeleton, which is the common core structure in various indole alkaloids. This new method permits the development of a succinct and stereoselective synthesis of dihydrocorynantheol and a formal synthesis of yohimbine and β -yohimbine.

Experimental Section

General procedure for the gold catalysis-triggered cascade reaction

A formamide, BrettPhosAuNTf₂ (0.05 equiv) and trifluoroacetic acid (2.0 eq.) 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 through silica gel flash chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank NIGMS (R01 GM084254) and UCSB for generous financial support, and Sigma-Aldrich for generous donation of BrettPhosAuNTf₂.

References

1. Cui L, Li C, Zhang L. *Angew. Chem., Int. Ed.* 2010; 49:9178.
2. For selected reviews, see: Fürstner A, Davies PW. *Angew. Chem., Int. Ed.* 2007; 46:3410. Hashmi ASK. *Chem. Rev.* 2007; 107:3180. [PubMed: 17580975] Arcadi A. *Chem. Rev.* 2008; 108:3266. [PubMed: 18651778] Jiménez-Núñez, Es; Echavarren, AM. *Chem. Rev.* 2008; 108:3326. [PubMed: 18636778] Li Z, Brouwer C, He C. *Chem. Rev.* 2008; 108:3239. [PubMed: 18613729] Patil NT,

- Yamamoto Y. *Chem. Rev.* 2008; 108:3395. [PubMed: 18611054] Abu Sohel SM, Liu R-S. *Chem. Soc. Rev.* 2009; 38:2269. [PubMed: 19623349] Wang S, Zhang G, Zhang L. *Synlett.* 2010:692. Zhong C, Shi X. *Eur. J. Org. Chem.* 2010:2999. Biannic B, Aponick A. *Eur. J. Org. Chem.* 2011; 2011:6605. Garayalde D, Nevado C. *Beilstein. J. Org. Chem.* 2011; 7:767. [PubMed: 21772928]
3. For other gold-catalyzed reactions involving a Ferrier rearrangement, see: Bae HJ, Jeong W, Lee JH, Rhee YH. *Chem. Eur. J.* 2011; 17:1433. [PubMed: 21268144] Sze EML, Rao W, Koh MJ, Chan PWH. *Chem. Eur. J.* 2011; 17:1437. [PubMed: 21268145]
4. Gilbert B, Antonaccio LD, Djerassi C. *J. Org. Chem.* 1962; 27:4702.
5. Haack E, Popelak A, Spingler H, Kaiser F. *Naturwiss.* 1954; 41:479.
6. Schlittler E, Furlenmeier A. *Helv. Chim. Acta.* 1953; 36:2017.
7. Cook P, James I. *New Eng. J. Med.* 1981; 305:1560. [PubMed: 7031468]
8. For precedents of such cyclizations, see: Ferrer C, Echavarren AM. *Angew. Chem., Int. Ed.* 2006; 45:1105. Ferrer C, Amijs CHM, Echavarren AM. *Chem. Eur. J.* 2007; 13:1358. [PubMed: 17206736]
9. a) Hashmi ASK, Weyrauch JP, Frey W, Bats JW. *Org. Lett.* 2004; 6:4391. [PubMed: 15524491] b) Weyrauch JP, Hashmi ASK, Schuster A, Hengst T, Schetter S, Littmann A, Rudolph M, Hamzic M, Visus J, Rominger F, Frey W, Bats JW. *Chem.--Eur. J.* 2010; 16:956. [PubMed: 19938017] c) Hashmi ASK, Schuster AM, Litters S, Rominger F, Pernpointner M. *Chem. Eur. J.* 2011; 17:5661. [PubMed: 21488108]
10. a) Fors BP, Watson DA, Biscoe MR, Buchwald SL. *J. Am. Chem. Soc.* 2008; 130:13552. [PubMed: 18798626] b) Ye L, He W, Zhang L. *Angew. Chem., Int. Ed.* 2011; 50:3236.
11. a) Kametani T, Kanaya N, Hino H, Huang S-P, Ihara M. *Heterocycles.* 1980; 14:1771. b) Ihara M, Taniguchi N, Fukumoto K, Kametani T. *J. Chem. Soc. Chem. Commun.* 1987:1438. c) Ihara M, Taniguchi N, Yasui K, Fukumoto K. *J. Chem. Soc., Perkin Trans.* 1990:2771. d) Beard RL, Meyers AI. *J. Org. Chem.* 1991; 56:2091. e) Ohba M, Ohashi T, Fujii T. *Heterocycles.* 1991; 32:319. f) Lounasmaa M, Jokela R, Tirkkonen B, Miettinen J, Halonen M. *Heterocycles.* 1992; 34:321. g) Diez A, Vila C, Sinibaldi ME, Troin Y, Rubiralta M. *Tetrahedron Lett.* 1993; 34:733. h) Deiters A, Martin SF. *Org. Lett.* 2002; 4:3243. [PubMed: 12227759] i) Tosaka A, Ito S, Miyazawa N, Shibuya M, Ogasawara K, Iwabuchi Y. *Heterocycles.* 2006; 70:153. j) Amat M, Gomez-Esque A, Escolano C, Santos MMM, Molins E, Bosch J. *J. Org. Chem.* 2009; 74:1205. [PubMed: 19072689] k) English BJ, Williams RM. *J. Org. Chem.* 2010; 75:7869. l) Sun X, Ma D. *Chem.--Asian J.* 2011; 6:2158. [PubMed: 21671404] m) Zhang W, Bah J, Wohlfarth A, Franzen J. *Chem.--Eur. J.* 2011; 17:13814. [PubMed: 22052788]
12. Khan GR, Pover KA, Scheinmann F. *J. Chem. Soc. Chem. Commun.* 1979:215.
13. a) Andrae S, Blasko G, Szantay C. *J. Prakt. Chem.* 1987; 329:374. b) Malhotra IP, Malhotra N. *J. Serb. Chem. Soc.* 1999; 64:155.
14. Szántay C, Honty K, Tóke L, Buzas A, Jacquet JP. 1971; 12:4871.
15. a) Szántay C, Honty K, Tóke L, Szabó L. *Chem. Ber.* 1976; 109:1737. b) Blaskó G, Knight H, Honty K, Szántay C. 1986; 1986:655.

dihydrocorynantheol

yohimbine (α-17-OH)
β-yohimbine (β-17-OH)

vincamine

Figure 1.
Selected alkaloids containing the indolo[2,3-*a*]quinolizine skeleton.

Scheme 1.

Design: a gold catalysis-triggered cascade en route to bicyclic piperidine-4-ones.

Scheme 2.

Stereoselective total synthesis of dihydrocorynantheol and formal synthesis of yohimbine and β-yohimbine. Reagents and conditions: i) K₂CO₃, CH₃CN, 85 °C, 36 h. ii) Ethyl formate, 80 °C, 8 h. iii) BrettPhosAuNTf₂ (5 mol %), TFA (2 equiv), CH₂Cl₂, rt, 24 h. iv) Methyl (dimethoxyphosphiny)acetate, NaH, benzene. v) Pd/C, H₂, MeOH, rt, 2 h; then DIBAL-H, CH₂Cl₂, 0 °C, 3 h. vi) methyl (dimethoxyphosphiny)acetate, NaH, benzene. vii) Pd(OH)₂/C, HCl, THF, 4 h; then SO₃-Py, Et₃N, DMSO, rt, 10 h. viii) KOH, I₂, MeOH, 0 °C, 4 h.

Table 1

Initial discovery and condition optimization.^[a]

entry	catalyst	acid additive (equiv)	yield (%) ^[b]
1	IPrAuNTf ₂	-	— ^[c]
2	IPrAuNTf ₂	MsOH (2)	56 ^[d]
3	IPrAuNTf ₂	TsOH (2)	64 ^[d]
4	IPrAuNTf ₂	TFA (2)	82 ^[d]
5	IPrAuNTf ₂	AcOH (2)	— ^[e]
6	Ph ₃ PAuNTf ₂	TFA (2)	83 ^[d]
7	BrettPhosAuNTf ₂	TFA (2)	89 ^[d] (87% ^[f])
8	AuCl ₃	TFA (2)	12 ^[d]

^[a] [1a] = 0.05 M.^[b] Estimated by ¹H NMR using diethyl phthalate as the internal reference.^[c] 12% of **3** formed after reaction for 6 h.^[d] **4** as the identifiable side product.^[e] Messy reaction.^[f] Isolated yield.

Table 2

The reaction scope.^[a]

entry	1	2	yield ^[b]
1			82%
2			84%
3			83%
4			82%
5			79% $\alpha/\beta = 2/3$
6			72%
7			72%
8			81% $\alpha/\beta = 2.4/1$
9			68%
10			61% ^[c]

^[a] [1] = 0.05 M.

[b] Isolated yield.

[c] TFA (5 equiv), 4 d.