ORGANIC LETTERS

2010
Vol. 12, No. 7
1448−1451

Gold(I)-Catalyzed Tandem Cyclization Approach to Tetracyclic Indolines

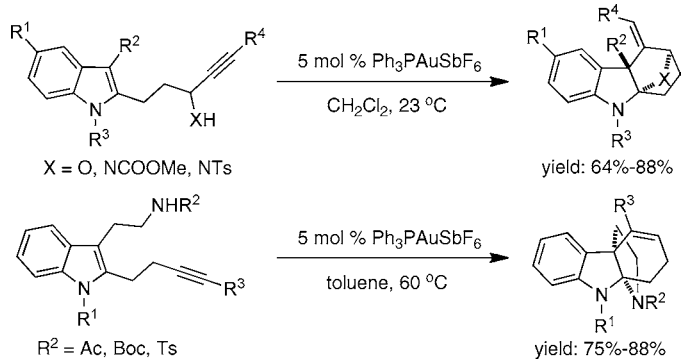
Yongxiang Liu, Wenqing Xu, and Xiang Wang*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309

xiang.wang@colorado.edu

Received January 21, 2010

ABSTRACT



Two highly stereoselective cationic gold(I)-catalyzed tandem cyclization reactions of alkynylindoles are described. These reactions demonstrated a novel and general strategy to rapidly construct highly functionalized polycyclic indolines. This approach was successfully employed for a formal synthesis of the akuammiline alkaloid minfiensine.

Indoline alkaloids are a class of molecules, many of which were discovered from natural sources that have been widely used in traditional medicine and have shown a variety of biological activities.[1] However, further biological studies of these molecules are often hampered by their limited supplies. Their diverse and complex architectures (see representative structures in Figure 1A) have attracted the attention of a number of synthetic research groups worldwide and have led to the development of many novel synthetic methods and strategies,[2,3] such as the Diels−Alder/amine cyclization approach,[3e] the Heck−iminium cyclization approach,[3b] and the tandem [4 + 2]/[3 + 2] cycloaddition approach.[3a] However, novel approaches are still urgently needed for the practical synthesis of bioactive indoline alkaloids.

Recent studies have shown that noble metals, such as gold and platinum, are excellent Lewis acids for the selective activation of unsaturated carbon−carbon bonds and are able to catalyze a large number of organic transformations with high efficiency at ambient conditions.[4] However, applications of these methods to the synthesis of complex natural products[5] have not reached their full potential.

(1) (a) Pearce, H. L. In *The Alkaloids*; Brossi, A., Suffness, M., Eds; Academic: San Diego, 1990; Vol. 37, p 145. (b) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 13, p 163. (c) Rocha, L. G.; Almeida, J. R. G. S.; Macêdo, R. O.; Barbosa-Filho, J. M. *Phytomedicine* **2005**, *12*, 514. (d) Gigant, B.; Wang, C.; Ravelli, R. B. G.; Roussi, F.; Steinmetz, M. O.; Curmi, P. A.; Sobel, A.; Knossowl, M. *Nature* **2005**, *435*, 519.

(2) For reviews, see: (a) Rahman, A.; Basha, A. *Indole Alkaloids* ; Taylor & Francis: Amsterdam, 1998; Vol. 2 pp 324. (b) Hudlický, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, 2007; p 759. (c) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2009**, *26*, 803, and previous articles in this series.

(3) For examples on recent syntheses of indole alkaloids, see: (a) Ishikawa, H.; Colby, D. A.; Boger, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 420. (b) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368. (c) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886. (d) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360. (e) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606.

10.1021/ol100153h
Published on Web 03/02/2010

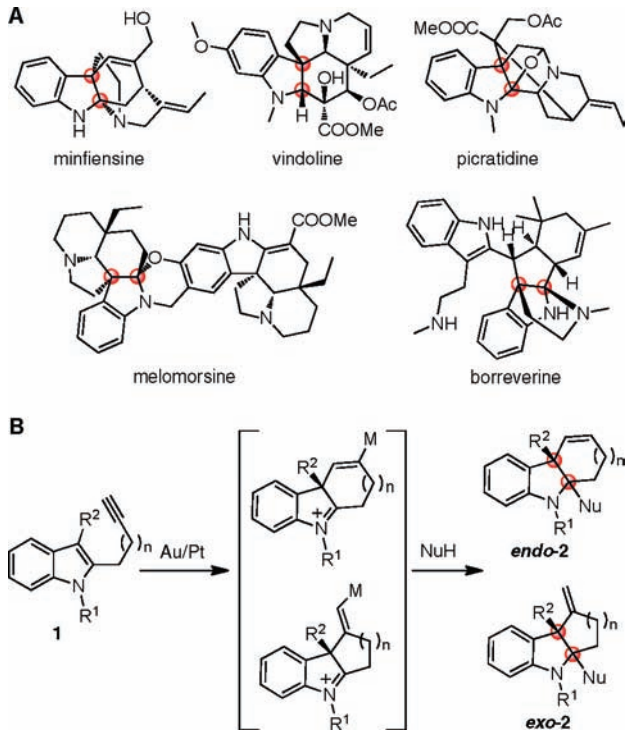
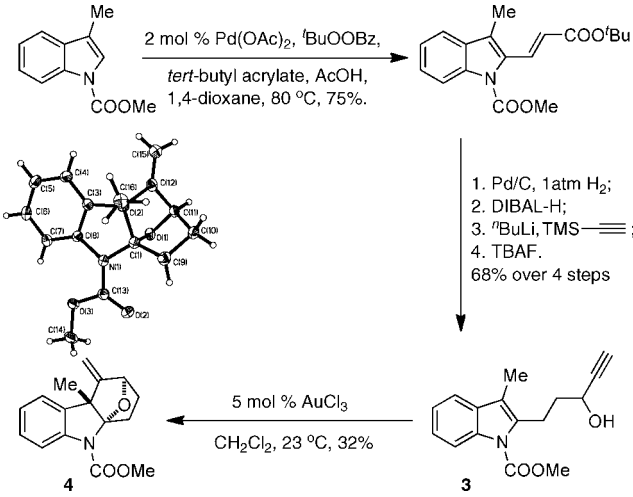


Figure 1. Representative indoline alkaloid natural products and our proposed approach.

We envisioned a novel and potentially general approach to polycyclic indolines by using noble metal catalysis as shown in Figure 1B.[6] This approach may rapidly construct polycyclic indolines bearing two quaternary stereocenters. A gold or platinum catalyst may selectively activate the terminal alkyne of alkynylindoles (e.g., **1**, Figure 1B) and promote either *endo*- or *exo*-cyclization. The resulting iminium ions should be susceptible to nucleophilic attack and provide highly functionalized indolines (e.g., *endo*- and *exo*-**2**, Figure 1B) after protonation of the vinylmetal species. Herein, we describe two stereoselective cationic gold(I)-catalyzed tandem cyclization reactions to construct highly functionalized tetracyclic indolines.

Scheme 1. First Attempt of Tandem Cyclization Using Alkynylindole **3**



We began our studies with an alkynylindole **3** (Scheme 1), which is easily synthesized in five steps from the protected indole.[7] Compound **3** also contains a secondary alcohol, which may serve as an internal nucleophile in a second cyclization step. We were pleased to find that when **3** was treated with 5 mol % of $AuCl_3$ in dichloromethane at room temperature, cyclized product **4** was obtained in 32% yield as a single regioisomer and diastereomer (Scheme 1). Its structure was assigned based on a series of 1D and 2D NMR studies and was further confirmed by X-ray crystallographic analysis (Scheme 1).[7] The substrate undergoes a 6-*exo*-*dig* cyclization upon activation by the catalyst, and the stereochemistry at the two quaternary centers is controlled solely by the stereochemistry of the secondary alcohol.

Next we surveyed several other catalysts (Table 1) to improve this tandem cyclization reaction. Platinum(II) chloride and triflic acid are also capable of promoting this reaction (Table 1, entries 2 and 3); however, significant decomposition of the substrate is also observed in these conditions. Attempts to use weaker acids such as $AgSbF_6$ and *p*-toluenesulfonic acid failed to provide any desired product (Table 1, entries 4 and 5). Ph_3PAuCl-promoted process requires higher temperature, longer reaction time, but provides slightly higher yield (Table 1, compare entries 1 and 6) of **4**. Good to high yields of the isolated products are obtained (67−83%; see Table 1, entries 7−9) by using

(4) For recent reviews on gold and/or platinum catalysis, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (g) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (i) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (j) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (k) Jiménez-Neŭñz, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (l) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (m) Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776. (n) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

(5) For recent applications of gold and/or platinum catalysis on target-oriented synthesis, see: (a) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239. (b) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (c) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279. (d) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760. (e) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629. (f) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (g) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485. (h) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780. (i) Kozak, J. A.; Dake, G. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 4221. (j) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315. (k) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650.

(6) For recent references on noble metal catalysis involving indoles, see: (a) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genét, J. P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (c) Wang, M. Z.; Wong, M. K.; Che, C. M. *Chem.—Eur. J.* **2008**, *14*, 8353. (d) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533.

(7) See the Supporting Information for details.

Table 1. Optimization of the Tandem Cyclization Conditions

entry	catalyst/additive[a]	time/temp (h/°C)	conversion[b] (%)	yield[c] (%)
1	$AuCl_3$	0.5/23	100	32
2	$PtCl_2$	12/80	50	14[d]
3	TfOH	12/23	70	35
4	$AgSbF_6$	12/23	0	0
5	TsOH	12/23	0	0
6	Ph_3PAuCl	12/80	80	55[e]
7	Ph_3PAuCl/ $AgBF_4$	1/23	100	78
8	Ph_3PAuCl/ AgOTf	1/23	100	67
9	Ph_3PAuCl/ $AgSbF_6$	1/23	100	83

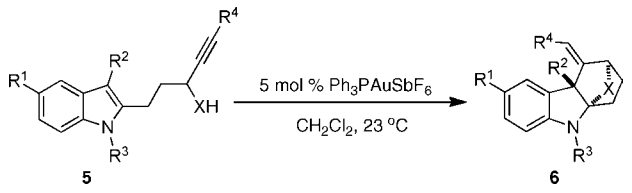
[a] 5 mol %. [b] Reaction conversions were based on the consumption of **3** calculated by the integration of ^1H NMR spectra. [c] Average isolated yield of at least two runs. [d] In toluene. [e] In acetonitrile.

cationic gold(I) species, and antimony hexafluoride was found to be the optimal counterion providing the product in 83% yield (Table 1, entry 9).

A variety of substrates were then screened using the optimized conditions, the reactions remained very good in all cases as shown in Table 2. No other regioisomers or diastereomers were identified from the reaction mixtures. Indoles possessing substitution at C3 and C5, including tryptamine derivatives (Table 2, entries 6 and 10), are generally well tolerated. The indole nitrogen requires an electron-withdrawing group, such as a methoxycarbonyl, a Boc, or a tosyl group, for the reaction to provide the desired products. The N^{in}-Me or N^{in}-H substrates failed to cyclize under the standard reaction conditions and provided a complex mixture of products at higher temperature. Phenyl-substituted alkynes (Table 2, entries 2, 3, 5, and 9) require longer reaction time and provide slightly lower yields of the desired products. The olefin geometry of the products was determined to be *E* by 1D NOE studies,[7] which is consistent with literature reports on several other gold-catalyzed cyclizations.[8] However, alkyl-substituted alkynes did not produce any desired cyclization product but afforded the corresponding enones instead.[9]

These tandem cyclization reactions are not limited to alcohol nucleophiles. Sulfonamides or carbamates also served as nucleophiles in the second cyclization reaction and afforded the desired tetracyclic indolines with good yields and selectivities (Table 2, entries 11−14). However, the acetamide substrates cyclized to form 5-methylene-4,5-dihydrooxazoles instead of the desired tetracyclic indolines.[7,10]

Table 2. Scope of Gold(I)-Catalyzed Tandem Cyclization Reaction

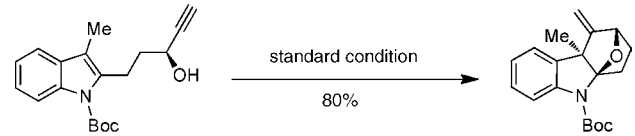


5 **6**

entry	**5**	R^1/ R^2/ R^3/ R^4	X	yield[a] (%)
1	**5a**	H/Et/COOMe/H	O	83
2	**5b**	H/Me/COOMe/Ph	O	65
3	**5c**	H/H/COOMe/Ph	O	67
4	**5d**	OMe/Et/COOMe/H	O	85
5	**5e**	OMe/Et/COOMe/Ph	O	75
6	**5f**	H/CH_2CH_2NPhth /Boc/H	O	84
7	**5g**	H/Me/Ts/H	O	85
8	**5h**	OMe/Et/Ts/H	O	88
9	**5i**	OMe/Et/Ts/Ph	O	64
10	**5j**	H/CH_2CH_2NPhth/Ts/H	O	82
11	**5k**	OMe/Et/COOMe/H	NCOOMe	78
12	**5l**	OMe/Et/COOMe/H	NTs	75
13	**5m**	OMe/Et/Ts/H	NCOOMe	79
14	**5n**	OMe/Et/COOMe/H	NNs	70

[a] Average isolated yield of at least two runs.

Scheme 2. Gold(I)-Catalyzed Tandem Cyclization Using Enantioenriched Substrate **5o**



5o 81% *ee* **6o** 81% *ee*

An enantioenriched substrate **5o** (81% ee) was also prepared and afforded the desired product **6o** in 81% ee under the standard conditions (Scheme 2).[7] This result proved

(8) (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (c) Harkat, H.; Weibel, J. M.; Pale, P. *Tetrahedron Lett.* **2007**, *48*, 1439. (d) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.

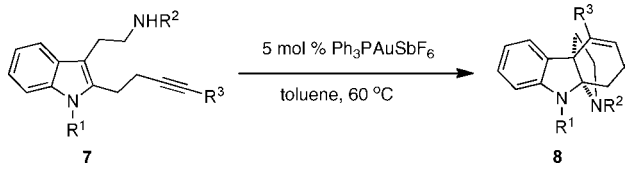
(9) (a) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *9*, 1867. (b) Ramóny, R. S.; Marionz, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767.

(10) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (b) Robles-Machín, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023. (c) Buzas, A.; Gagosz, F. *Synlett* **2006**, 2727. (d) Lee, E. S.; Yeom, H. S.; Hwang, J. H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503.

quantitative retention of chirality at the secondary propargyl alcohol, which should be useful for the synthesis of complex indoline alkaloids.

Having proved our hypothesis, we then examined a tandem cyclization approach on tryptamine derivatives **7** (Table 3), each of which contains a two-carbon linker between the indole and the alkyne. To our delight, the reaction proceeded smoothly using the same catalyst system in toluene at 60 °C and provided *6-endo-dig* cyclization products **8** cleanly.

Table 3. Scope of Gold(I)-Catalyzed Tandem Cyclization Studies for the Synthesis of Akuammilines



7 **8**

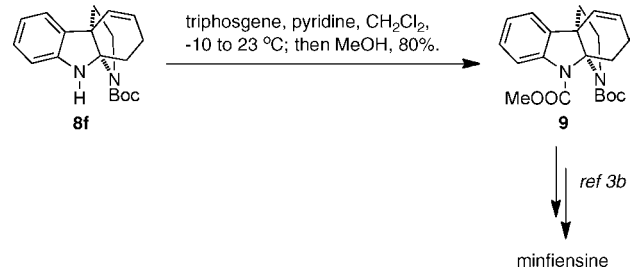
entry	**7**	R^1	R^2	R^3	**8**	yield[a] (%)
1	**7a**	Boc	Boc	H	**8a**	75
2	**7b**	Boc	Boc	Ph	**8b**	84
3	**7c**	Boc	Ts	H	**8c**	81
4	**7d**	Boc	Ns	H	**8d**	88
5	**7e**	Boc	Ac	H	**8e**	80
6	**7f**	H	Boc	H	**8f**	87
7	**7g**	H	Ac	H	**8g**	83
8	**7h**	Me	Ts	H	**8g**	86

[a] Average isolated yield of at least two runs.

For all substrates we tested (see Table 3), the reactions went to completion within 2 h and afforded the core structures of the akuammiline alkaloids[2a,c] in good yields (75−88%); no 5-*exo-dig* products were detected in all cases. In addition to carbamates and sulfonamides, secondary amides (Table 3, entries 5 and 7) also serve as nucleophile in the second cyclization step. Interestingly, the N^{in}-H and N^{in}-Me substrates also participate in this tandem cyclization reaction and provide tetracyclic indolines **8** cleanly (Table 3, entries 6−8).

The aniline of tetracyclic indoline **8f** was converted to a methyl carbamate when treated with triphosgene followed by quenching with anhydrous methanol (Scheme 3). The resulting compound (**9**) is a key intermediate in Overman's total synthesis of the akuammiline alkaloid natural product minfiensine (Figure 1A).[3b]

Scheme 3. Formal Synthesis of Minfiensine



In summary, we have developed a novel approach to the construction of tetracyclic indolines using stereoselective cationic gold(I)-catalyzed tandem cyclization reactions. This approach allows rapid assembly of two rings and two stereocenters including a quaternary carbon center in a single step with a wide substrate scope. These two tandem cyclization reactions have also shown excellent versatility regarding the functional groups involved. A formal synthesis of the akuammiline alkaloid natural product minfiensine is also described. Further mechanistic studies, evaluation of the biological activities of the synthesized unnatural indoline alkaloids, and applications of this approach to indoline alkaloid synthesis are in progress and will be reported in due course.

Acknowledgment. We are grateful to Dr. Richard Shoemaker (Department of Chemistry and Biochemistry, University of Colorado at Boulder) for NMR spectroscopic assistance and to Professors Tarek Sammakia and Andrew Phillips (Department of Chemistry and Biochemistry, University of Colorado at Boulder) for useful discussions. Financial support for this work was provided by the University of Colorado.

Supporting Information Available: Full experimental details, including the spectroscopic and analytical data of all new compounds and X-ray crystallographic data of compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100153H