DOI: 10.1002/adsc.201401161

Gold(I)-Catalyzed Tandem Reaction of γ-Amino-Substituted Propargylic Esters to Pyrrolines and its Application in the Formal Synthesis of (±)-Aphanorphine

Zhengshen Wang,[a] Huaiji Zheng,[a] Juan Yang,[a] Xingang Xie,[a,*] and Xuegong She[a,b,*]

[a] State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China
E-mail: xiexg@lzu.edu.cn or shexg@lzu.edu.cn
[b] Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, People's Republic of China

Received: December 14, 2014; Revised: March 20, 2015; Published online: June 10, 2015

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201401161.

Abstract: An effective synthesis of structurally diverse pyrroline derivatives has been accomplished by a gold(I)-catalyzed tandem 1,3-acyloxy rearrangement/intramolecular azacylization reaction of γ-amino-substituted propargylic esters in good to excellent chemical yields (52–98%). The reaction proceeds under extremely mild conditions and has also demonstrated its potential in a concise formal synthesis of (±)-aphanorphine with a catalyst loading as low as 0.5 mol% to provide the key intermediate 5-(4-methoxybenzyl)-1-tosyl-2,5-dihydro-1*H*-pyrrol-3-yl pivalate on a gram scale.

Keywords: 1,3-acyloxy rearrangement; azacylization; gold(I)-catalyzed reaction; propargylic esters; pyrrolines

Introduction

Nitrogen-containing heterocycles, especially of the pyrroline and pyrrolidine types, are particularly ubiquitous and essential structural elements for pharmaceutical agents and biologically active natural alkaloids, such as preussin,[1] codonopsinine,[2] aphanorphine,[3] and pretomaymycin[4] (Figure 1). Consequently, the development of efficient methodologies for the synthesis of structurally diverse pyrrolines and pyrrolidines is of considerable importance. Various methods have been developed, especially those based on transition metal catalysis including Pd, Ru, Rh, Fe, Cu and so on.[5] At the end of the 20th century, Fukuda, Utimoto and Teles et al. reported that gold salts could efficiently catalyze the addition reactions of O- and N-nucleophiles to alkenes or alkynes due to their incredible and unique reactivity for the electrophilic activation of carbon-carbon multiple bonds.[6] Ever since, the applications of gold complexes as π-acid catalysts for organic transformations have increased dramatically.[7]

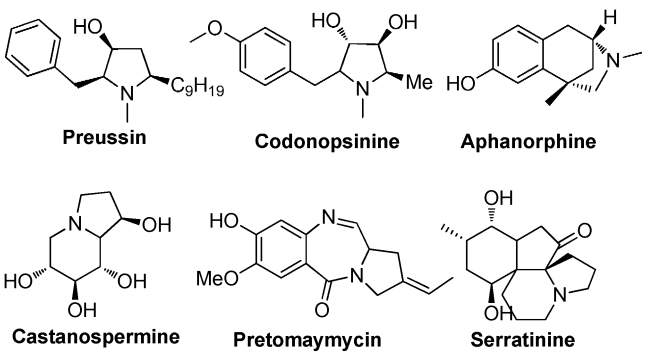
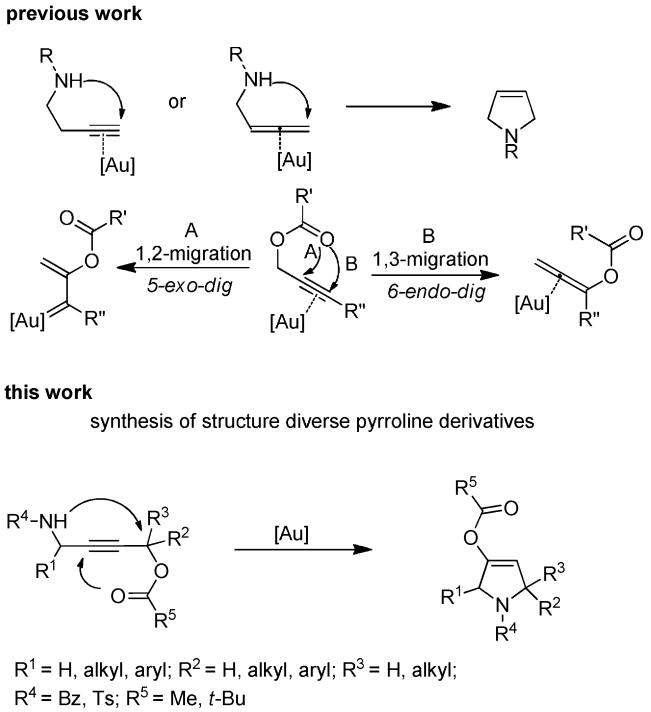


Figure 1. Natural products with a substituted pyrroline subunit.

As well, the metal, especially gold- and platinum-catalyzed isomerization of propargylic esters has become a powerful tool to obtain valuable functionalized synthons for organic chemistry. The isomerization of propargylic esters proceeds *via* two routes: 1,2-acyloxy migration and 1,3-acyloxy rearrangement, which differ mainly in the initial carbonyl group cyclization to the activated carbon-carbon triple bond in either the 5-*exo*-*dig* or 6-*endo*-*dig* model[8] (Scheme 1). Recently, the Diver group developed an elegant gold-promoted heterocyclization of internal alkynes for the generation of dehydropyrrolidines or dehydropiperidine. However, the ratio of the products



Scheme 1. Activation of the carbon-carbon multiple bond.

depends on the alkyne substrates.[9] To the best of our knowledge, a cascade transformation between the *in situ* formed metal-allene complex intermediates and an internal nucleophilic species would be synthetically valuable, as it would lead to an overall reductive substitution process of the starting propargylic esters. In this manuscript, we describe our efforts to expand the scope of this reaction *via* gold-catalyzed tandem 1,3-acyloxy rearrangement/intramolecular azacylization, which provides an efficient synthesis of 2,5-disubstituted pyrrolines from γ-amino-substituted propargylic esters. As well, its potential was also demonstrated in a concise formal synthesis of (±)-aphanorphine.

Results and Discussion

Initially, propargylic ester **1a** was selected as a model substrate to investigate this proposed tandem transformation. The isomerization of γ-amino-substituted propargylic ester **1a** was examined under a variety of conditions (Table 1). Pleasingly, the reaction proceeded smoothly in the presence of $AuCl_3{\cdot}2H_2O$ (10 mol%) in dichloromethane (DCM) at room temperature for 0.5 h, leading to **2a** in 61% yield (Table 1, entry 1), while $AuBr_3$ (10 mol%) or $AuPPh_3Cl$ (10 mol%) (entries 2 and 3) proved to be ineffective. To our delight, the yield was readily increased to 96% in the presence of 5 mol% $AuPPh_3Cl/AgSbF_6$ (entry 4). Likewise, employing gold(I) complexes with alternative counter ions such as $SO_3CF_3^-$ or BF_4^- could also provide the desired product with slightly lower yields (entries 5 and 6). Using $AuPPh_3Cl/AgSbF_6$ as the catalyst system, the reaction also proceeded well in tetrahydrofuran (THF) or 1,2-dichloroethane (DCE) as solvent (entries 7 and 8). When the reaction was carried out in CH_3NO_2, toluene, wet DCM or CH_3CN, no reaction was observed (entries 9–12). In addition to Au catalysts, $PtCl_2$ in toluene was also examined, which was ineffective for this transformation (entry 13).

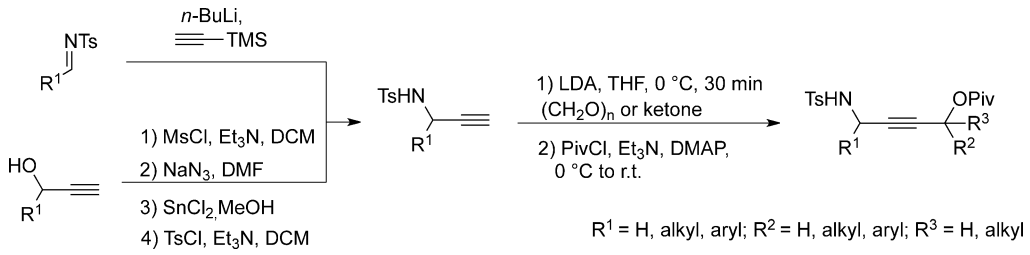
Having established the optimal reaction conditions, a series of bifunctional propargylic esters was then easily prepared in a modular way either from the corresponding imines in 3 steps or from the corresponding propargylic alcohols in 6 steps (Scheme 2). The details of their preparation and characterization data can be found in the Supporting Information.

Table 1. Optimization of the reaction conditions.[a]

1a **2a**

Entry	Catalyst	Solvent	Time	Yield[b]
1	$AuCl_3{\cdot}2H_2O$ (10 mol%)	DCM	0.5 h	61%
2	$AuBr_3$ (10 mol%)	DCM	12 h	trace[c]
3	$AuPPh_3Cl$ (10 mol%)	DCM	12 h	NR
4	**$AuPPh_3Cl/AgSbF_6$ (5 mol%)**	**DCM**	**0.5 h**	**96%**
5	$AuPPh_3Cl/AgOSO_2CF_3$ (5 mol%)	DCM	0.5 h	84%
6	$AuPPh_3Cl/AgBF_4$ (5 mol%)	DCM	0.5 h	83%
7	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	THF	5 h	58%
8	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	DCE[d]	0.5 h	91%
9	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	CH_3NO_2	12 h	NR
10	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	toluene	12 h	NR
11	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	wet DCM	12 h	NR
12	$AuPPh_3Cl/AgSbF_6$ (5 mol%)	CH_3CN	12 h	NR
13	$PtCl_2$ (10 mol%)	toluene	12 h	NR

[a] *Reaction conditions:* room temperature, freshly distilled solvent, in the air.
[b] Isolated yields.
[c] The remaining **1a** was recovered.
[d] DCE = 1,2-dichloroethane.
[e] Ts = *p*-methylbenzenesulfonyl, Piv = pivaloyl.

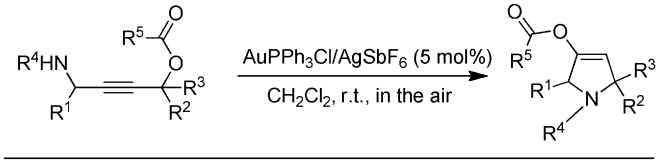


Scheme 2. Synthesis of the key substrate for the starting materials.

With the propargylic esters in hand, we then investigated the scope of this reaction. Firstly, the substrates **1b** and **1c** with the different *N*-protecting group or the ester group were treated with 5 mol% $AuPPh_3Cl/AgSbF_6$ at room temperature in dichloromethane and were also found to be suitable for this gold-catalyzed reaction, but needing much more time and the yields were slightly lower (Table 2, entries 1 and 2), which also demonstrated that the substrate with the *p*-methylbenzenesulfonyl group as the *N*-protecting group and pivaloyl as the ester was the most suitable one for this gold-catalyzed tandem reaction.

The generality of this gold-catalyzed cyclization reaction was then examined. As revealed in Table 2, the reaction of the γ-amino-substituted propargylic esters

Table 2. Gold(I)-catalyzed synthesis of substituted pyrolines.[a]



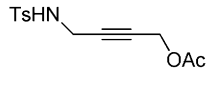
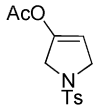
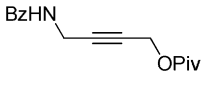
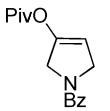
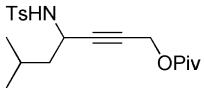
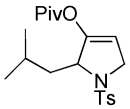
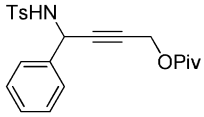
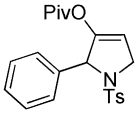
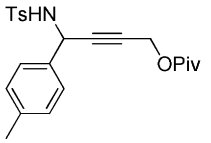
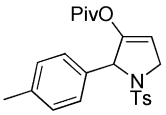
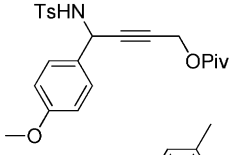
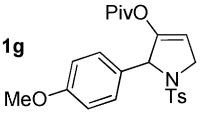
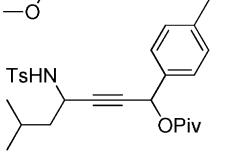
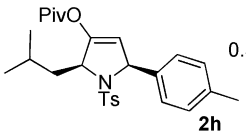
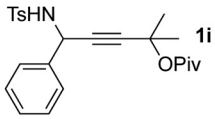
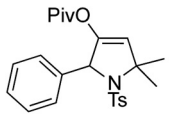
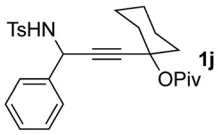
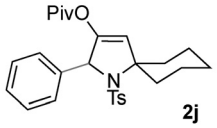
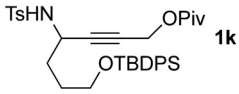
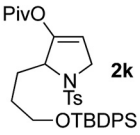
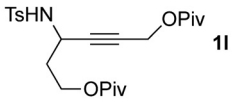
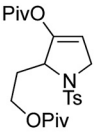
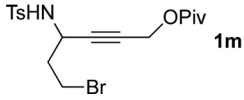
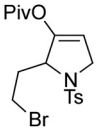
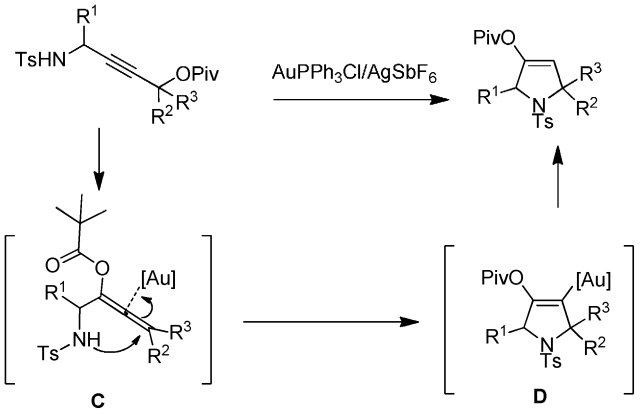
Entry	Substrate	Product	Time	Yeld[b]
1	 **1b**	 **2b**	1.5 h	52%
2	 **1c**	 **2c**	4 h	85%
3	 **1d**	 **2d**	0.5 h	97%
4	 **1e**	 **2e**	0.5h	80%
5	 **1f**	 **2f**	0.5 h	96%
6	 **1g**	 **2g**	8 h	78%
7	 **1h**	 **2h**	0.5 h	75%

Table 2. (Continued)

Entry	Substrate	Product	Time	Yeld[b]
8	 **1i**	 **2i**	0.5 h	80%
9	 **1j**	 **2j**	0.5 h	84%
10	 **1k**	 **2k**	0.5 h	98%
11	 **1l**	 **2l**	0.5 h	80%
12	 **1m**	 **2m**	0.5 h	85%

[a] *Reaction conditions:* catalyst (5 mol%), room temperature, dry dichloromethane, in the air.
[b] Yield of isolated product.
[c] Ts = *p*-methylbenzenesulfonyl, Bz = benzoyl, Piv = pivaloyl.

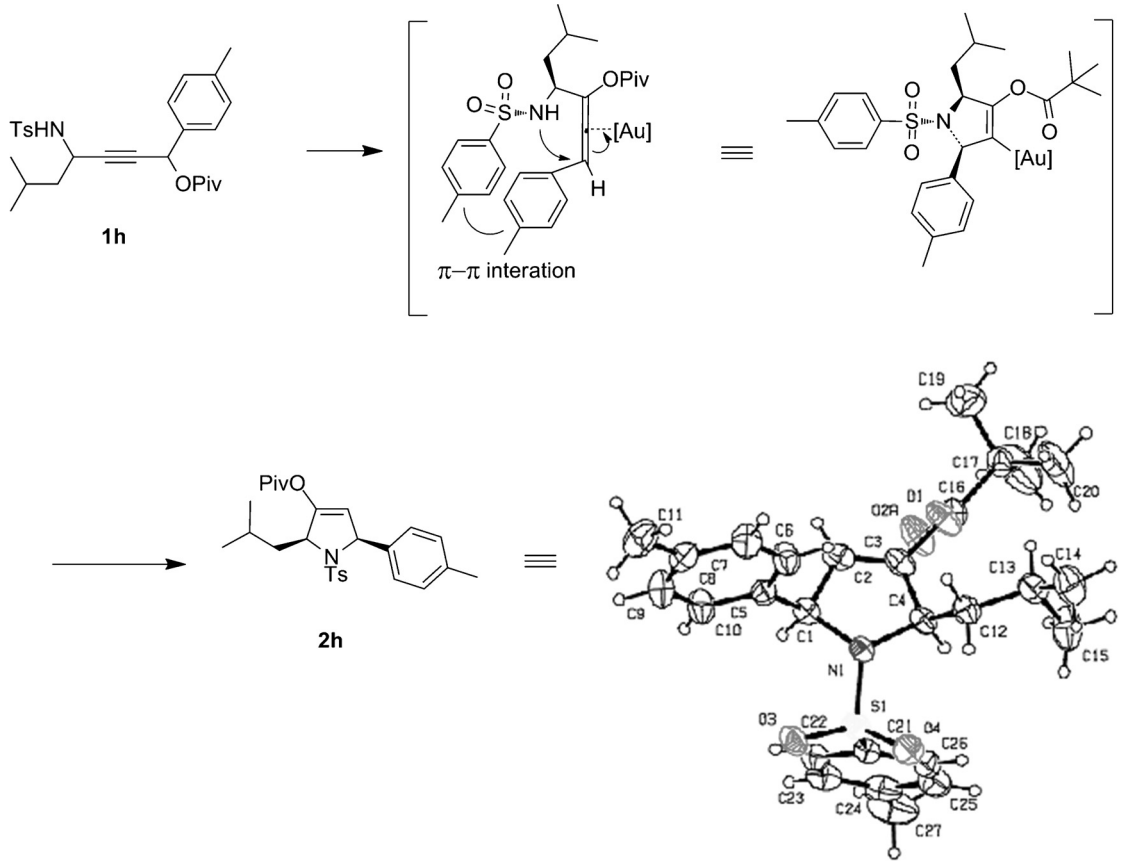
with another alkyl or aryl substituent at the γ-position proceeded in the presense of $AuPPh_3Cl$ (5 mol%) and $AgSbF_6$ (5 mol%) in dichloromethane (DCM) at room temperature for 0.5 h, leading to the corresponding pyrolines in good yields ranging from 78 to 98%. During these runs, the substrates with a strong electron-donating group (OMe) at the *para* position of the phenyl ring required a longer reaction time (Table 2, entry 6 *vs.* entries 4 and 5) probably due to electronic activation of the double bond of the allene which was not beneficial for the formation of pyrrolines.



Scheme 3. Proposed mechanism for gold-catalyzed pyrroline formation.

For substrates substituted in the α- or γ-position, the transformation was expected to be more favorable because of a Thorpe–Ingold effect.[10] To our delight, all the gold-catalyzed cyclization reactions led to the corresponding 2,5-disubstituted pyrrolines (entries 7–9) in 75–84% yield and the relative configuration of **2h** was confirmed by X-ray crystallographic analysis.[11] Especially, the cyclization of substrate **1j** provides a facile construction of the essential structural element, the azaspiro[4,5]decane ring system, which could be found in many kinds of natural alkaloids. Also, a γ-amino-substituted propargylic ester with a protected hydroxy group, **1k**, was tolerated under our reaction conditions and the corresponding pyrroline **2k** was obtained in high 98% yield, which could be further converted to the bicyclic amine and used for the synthesis of biologically active alkaloids, such as castanospermine[12] and serratinine[13] (Figure 1). The easily modifiable functional groups (Br and OPiv) on the alkyl chain are well-tolerated and the desired products **2l** and **2m** (entries 11 and 12) are obtained in attractive yields, demonstrating the mild nature of the catalytic conditions.

Our present understanding of the mechanism of this gold-catalyzed cycloisomerization reaction of γ-



Scheme 4. The favorable route for 2,5-disubstituted pyrrolines (**2h**).

amino-substituted propargylic esters is shown in Scheme 3.[14] Firstly, in the presence of $AgSbF_6$, gold(I) coordinated to the π-system of the alkyne and initiated the 3,3-rearrangement of the pivaloate group to form π-complex **C**. Subsequently, an intramolecular S_N2-type reaction occurred to give the cyclic vinylgold intermediate **D** which underwent an elimination reaction to produce the pyrroline product and regenerate the catalytic gold(I) species.[15] During this course, π-complex **C** was produced from isomerization of the alkyne, and the conformation of the allene intermediate **C** could be (*R*)- or (*S*)- which depended on the difference of its substituents.

The observed **2h** as the *cis*-product could be explained by an envelope-like transition state in which the *π*–*π* interaction between the aryl substituent and the *p*-methylbenzenesulfonyl group to lead the gold coordinated to the upside of the allene intermediate, and the aryl group's preference for the equatorial position rather than the axial one. Next, an intramolecular S_N2-type reaction takes place to produce the pyrroline as the *cis*-product. (Scheme 4**)**

In light of this novel gold-catalyzed cyclization, we became interested in exploring its application to synthesize structurally diverse natural alkaloids. (±)-Aphanorphine **(**Figure 1), an alkaloid with potential biological activity and a unique tricyclic 3-benzazepine framework which has attracted considerable attention and a number of syntheses have been reported,[16] was chosen as our target molecule.

Our synthesis commenced from the addition reaction of 4-methoxyphenylacetaldehyde **3** and Ts-protected propargylic amine **4**.[17] The obtained secondary alcohol was subsequently protected as pivolate **5**, and the overall yield of the two steps was 59%. As we expected, the gold-catalyzed tandem reaction of propargylic amine **5** proceeded smoothly in the presence of $AuPPh_3Cl$ and $AgSbF_6$ as the catalyst system in dichloromethane at ambient temperature to give pyrroline **6** in 95% yield. It was worthy to note here that this step could be executed on a gram-scale together with the catalyst loading being reduced to 0.5 mol%. Subsequently hydrolysis of the pivaloyl followed by a nucleophilic methylation produced the tertiary alcohol **7** in 77% yield. Then an $AlCl_3$-promoted intramolecular Friedel–Crafts alkylative cyclization of alcohol **7** was effected to furnish the desired tricyclic compound **8** as colorless needles,[18] for which the relative structure was confirmed by X-ray crystallographic analysis (Figure 2). The synthesis of (±)-aphanorphine could be accomplished from the tricyclic precursor **8** in three additional steps (desulfurization, *N*-methylation, and *O*-demethylation), which has been reported by Ogasawara and co-workers[19] (Scheme 5).

Conclusions

In conclusion, we have accomplished an effective synthesis of structurally diverse pyrroline derivatives *via* a novel gold(I)-catalyzed tandem 1,3-acyloxy rearrangement/intramolecular azacylization reaction of γ-amino-substituted propargylic esters. Our reaction proceeds under mild conditions, features low catalyst loading, short reaction time, and its potential in organic synthesis has also been demonstrated in the concise formal synthesis of (±)-aphanorphine. A further modification of this new tandem reaction and its

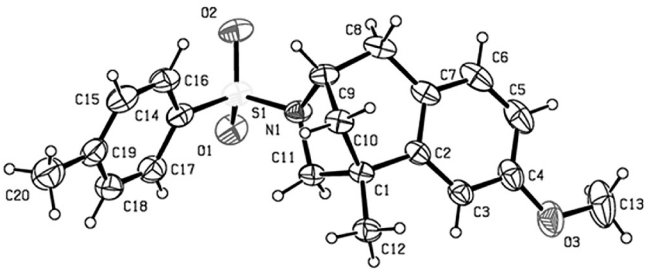
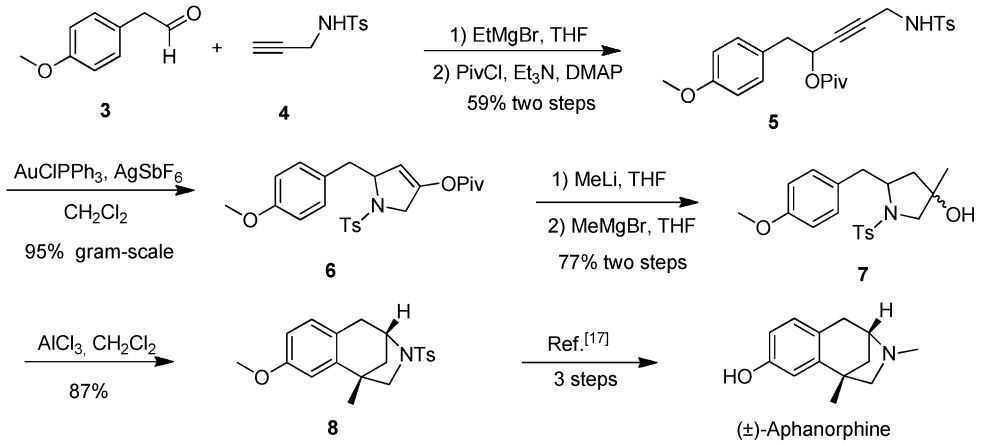


Figure 2. X-ray single crystal structure of compound **8**.



Scheme 5. Formal synthesis of (±)-aphanorphine.

applications to the syntheses of other bioactive natural products containing pyrroline motifs is currently underway in our lab and will be reported in due course.

Experimental Section

Typical Procedure for the Cyclization Reaction

To a solution of **1a** (156 mg, 0.48 mmol) and $AuClPPh_3$ (12 mg, 5 mol%) in DCM (10 mL), was added $AgSbF_6$ (8 mg, 5 mol%), the mixture was stirred at room temperature for 30 min until the starting material was completely consumed. The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petrol ether/ethyl acetate 3:1) gave **2a** as a white crystalline solid; yield: 150 mg (96%); mp 81–82 °C.

Acknowledgements

We are greatful for the financial support by the NSFC (21125207, 21372103, 21472079), SRFDP (20130211110018) and Program 111.

References

[1] a) A. N. Hulme, E. M. Rosser, *Org. Lett.* **2002**, *4*, 265–267; b) M. Overhand, S. M. Hecht, *J. Org. Chem.* **1994**, *59*, 4721–4722; c) W. Deng, L. E. Overman, *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250; d) P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489; e) C. S. Pak, G. H. Lee, *J. Org. Chem.* **1991**, *56*, 1128–1133.

[2] a) A. Toyao, O. Tamura, H. Takagi, H. Ishibashi, *Synlett* **2003**, 35–38; b) E. A. Severino, C. R. D. Correia, *Org. Lett.* **2000**, *2*, 3039–3042; c) H. Yoda, T. Nakajima, K. Takabe, *Tetrahedron Lett.* **1996**, *37*, 5531–5534; d) C. H. J. Wang, J. C. Calabrese, *J. Org. Chem.* **1991**, *56*, 4341–4343; e) H. Iida, N. Yamazaki, C. Kibayashi, *J. Org. Chem.* **1987**, *52*, 1956–1962.

[3] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, J. Clardy, *Tetrahedron Lett.* **1988**, *29*, 4381–4384.

[4] A. Lorente, D. Pla, L. M. Cañedo, F. Albericio, M. Álvarez, *J. Org. Chem.* **2010**, *75*, 8508–8515.

[5] Examples: a) E. Ingalls, P. A. Sibbald, W. Kaminsky, F. E. Michael, *J. Am. Chem. Soc.* **2013**, *135*, 8854–8856; b) G. Barker, J. L. McGrath, A. Klapars, D. Stead, G. Zhou, K. R. Campos, P. O'Brien, *J. Org. Chem.* **2011**, *76*, 5936–5953; c) F. A. Davis, H. Xu, Y. Z. Wu, J. Y. Zhang, *Org. Lett.* **2006**, *8*, 2273–2276; d) Q. Yang, H. Alper, W. Xiao, *Org. Lett.* **2007**, *9*, 769–771; e) C. Paderes, S. R. Chemler, *Org. Lett.* **2009**, *11*, 1915–1918; f) S. K. Kang, K. J. Kim, *Org. Lett.* **2001**, *3*, 511–514; g) R. K. Dieter, H. Yu, *Org. Lett.* **2001**, *3*, 3855–3858; h) N. T. Jui, J. A. O. Garber, F. G. Finelli, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403; i) B. M. Trost, A. B. Pinkerton, D. J. Kremzow, *J. Am. Chem. Soc.* **2000**, *122*, 12007–12008; j) N. R. Candeias, L. C. Branco, P. M. P. Gois, C. A. M. Afonso, A. F. Trindade, *Chem. Rev.* **2009**, *109*, 2703–2802.

[6] a) X. Z. Shu, X. Y. Liu, H. Q. Xiao, K. G. JI, L. N. Guo, C. Z. Qi, Y. M. Liang, *Adv. Synth. Catal.* **2007**, *349*, 2493–2498; b) B. Alcaide, P. Almendros, *Adv. Synth. Catal.* **2011**, *353*, 2561–2576; c) S. A. Kozmin, L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; d) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729–3731; e) Y. Fukuda, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013–2015; f) Y. Fukuda, K. Utimoto, *Synthesis* **1991**, 975–978; g) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475–1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418; h) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442; i) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239–3265; j) D. Eom, D. Kang, P. H. Lee, *J. Org. Chem.* **2010**, *75*, 7447–7450; k) K. H. Nguyen, S. Tomasi, M. L. Roch, L. Toupet, J. Renault, P. Uriac, N. Gouault, *J. Org. Chem.* **2013**, *78*, 7809–7815; l) A. S. K. Hashmi, T. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; m) A. S. K. Hashmi, L. Schwarz, J. Choi, T. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288.

[7] a) L. Z. Zhang, J. W. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; b) M. Bandini, *Chem. Soc. Rev.* **2011**, *40*, 1358–1367; c) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; d) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; e) T. C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910–1925; f) T. J. Brown, D. Weber, M. R. Gagné, R. S. Widenhoefer, *J. Am. Chem. Soc.* **2012**, *134*, 9134–9137; g) L. W. Ye, L. Cui, G. Z. Zhang, L. M. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259; h) A. K. Mourad, J. Leutzow, C. Czakelius, *Angew. Chem.* **2012**, *124*, 11311–11314; *Angew. Chem. Int. Ed.* **2012**, *51*, 11149–11152; i) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211; j) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084–3213; k) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485–4488; l) Y. Wang, K. Zheng, R. Hong, *J. Am. Chem. Soc.* **2012**, *134*, 4096–4099; m) M. Rudolph, A. S. K. Hashmi, *Chem. Soc. Rev.* **2012**, *41*, 2448–2462; n) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766–1775.

[8] a) H. Ito, A. Harada, H. Ohmiya, M. Sawamura, *Adv. Synth. Catal.* **2013**, *355*, 647–652; b) Z. Jin, R. S. Hidinger, B. Xu, G. B. Hammond, *J. Org. Chem.* **2012**, *77*, 7725–7729; c) H. J. Zheng, J. Y. Zheng, B. X. Yu, Q. Chen, X. L. Wang, Y. P. He, Z. Yang, X. G. She, *J. Am. Chem. Soc.* **2010**, *132*, 1788–1789; d) B. A. B. Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469; e) G. T. Li, G. Z. Zhang, L. M. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 3740–3741; f) D. Garayalde, E. Gomez-Bengoa, X. G. Huang, A. Goeke, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 4720–4730; g) W. D. Rao, D. Susanti, P. W. H. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 15248–15251; h) Y. Sawama, Y. Sawama, N. Krause, *Org. Lett.* **2009**, *11*, 5034–5037; i) M. Yu, G. T. Li, S. Z. Wang, L. M. Zhang, *Adv. Synth. Catal.* **2007**, *349*, 871–875; j) N. Marion, S. Díez-González, P. P. De Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729–3732; *Angew. Chem.*

Int. Ed. **2006**, *45*, 3647–3650; k) N. Marion, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 2806–2809; *Angew. Chem. Int. Ed.* **2007**, *46*, 2750–2752; l) S. Wang, G. Zhang, L. Zhang, *Synlett* **2010**, 692–706; m) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; n) L. Wang, H. Zhu, A. Wang, Y. Qiu, X. Liu, Y. Liang, *J. Org. Chem.* **2014**, *79*, 204–212; o) N. Sun, M. Chen, Y. Liu, *J. Org. Chem.* **2014**, *79*, 4055–4067; p) A. S. K. Hashmi, W. Yang, Y. Yu, M. M. Hansmann, M. Rudolph, F. Rominger, *Angew. Chem.* **2013**, *125*, 1368–1371; *Angew. Chem. Int. Ed.* **2013**, *52*, 1329–1332; q) T. Lauterbach, S. Gatzweiler, P. Nösel, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Adv. Synth. Catal.* **2013**, *355*, 2481–2487.

[9] J. M. French, S. T. Diver, *J. Org. Chem.* **2014**, *79*, 5569–5585.

[10] a) M. B. Schmid, K. Zeitler, R. M. Gschwind, *J. Am. Chem. Soc.* **2011**, *133*, 7065–7074; b) M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, L. J. Casely, M. S. Hill, P. A. Procopiou, *J. Am. Chem. Soc.* **2009**, *131*, 9670–9685.

[11] CCDC 912225 (**2h**) and CCDC 912766 (**8**) contain 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] L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold, J. Clardy, *Phytochemistry* **1981**, *20*, 811–814.

[13] H. Morita, J. Kobayashi, *J. Org. Chem.* **2002**, *67*, 5378–5381.

[14] A. S. K. Hashmi, K. Stephen, *Angew. Chem.* **2010**, *122*, 5360–5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241.

[15] a) L. P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643; b) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615; c) C. Shu, M. Q. Liu, Y. Z. Sun, L. W. Ye, *Org. Lett.* **2012**, *14*, 4958–4961; d) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266–3325; e) P. H. Y. Cheong, P. Morganelli, M. R. Luzung, K. N. Houk, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 4517–4526; f) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161; g) N. Morita, N. Krause, *Org. Lett.* **2004**, *6*, 4121–4123; h) C. Winter, N. Krause, *Chem. Rev.* **2011**, *111*, 1994–2009; i) A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem.* **2009**, *121*, 8396–8398; *Angew. Chem. Int. Ed.* **2009**, *48*, 8247–8249; j) A. S. K. Hashmi, T. D. Ramamurthi, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 971–975; k) A. S. K. Hashmi, *Gold Bull.* **2009**, *42*, 275–279.

[16] a) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268; b) A. N. Hulme, S. S. Henry, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 1265–1270; c) Y. Kita, J. Futamura, Y. Sawama, J. K. Ganesh, H. Fujioka, *J. Org. Chem.* **2003**, *68*, 5917–5924; d) J. Quirante, X. Vila, C. Escolano, J. Bonjoch, *J. Org. Chem.* **2002**, *67*, 2323–2328; e) A. B. Pulipaka, S. C. Bergmeier, *J. Org. Chem.* **2008**, *73*, 1462–1467; f) O. Tamura, T. Yanagimachi, T. Kobayashi, H. Ishibashi, *Org. Lett.* **2001**, *3*, 2427–2429; g) J. R. Fuchs, R. L. Funk, *Org. Lett.* **2001**, *3*, 3923–3925; h) D. N. Mai, B. R. Rosen, J. P. Wolfe, *Org. Lett.* **2011**, *13*, 2932–2935; i) S. J. Luo, C. F. Ye, Y. X. Ma, H. B. Zhai, *J. Org. Chem.* **2003**, *68*, 8268–8271; j) X. B. Yang, H. B. Zhai, Z. Li, *Org. Lett.* **2008**, *10*, 2457–2460; k) F. Foubelo, M. Medjahdi, J. C. González-Gómez, M. Yus, *Eur. J. Org. Chem.* **2011**, 2230–2234; l) R. S. Grainger, E. J. Welsh, *Angew. Chem.* **2007**, *119*, 5473–5476; *Angew. Chem. Int. Ed.* **2007**, *46*, 5377–5380.

[17] K. G. Ji, H. T. Zhu, F. Yang, X. Z. Shu, X. Y. Liu, A. Shaukat, Y. M. Liang, *Chem. Eur. J.* **2010**, *16*, 6151–6154.

[18] Z. Q. Ma, H. W. Hu, W. T. Xiong, H. B. Zhai, *Tetrahedron* **2007**, *63*, 7523–7531.

[19] M. Shimizu, T. Kamikubo, K. Ogasawara, *Heterocycles* **1997**, *46*, 21–26.

