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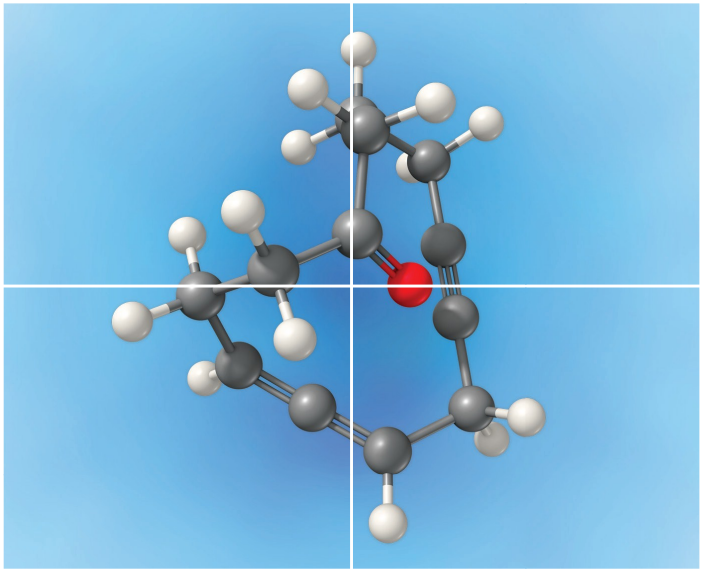

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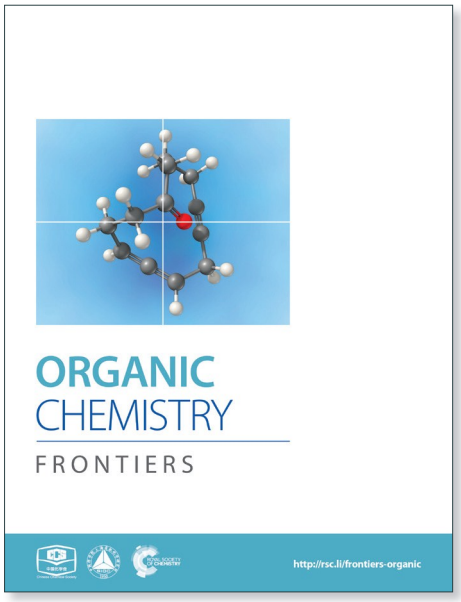

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Journal Name

ARTICLE

Gold-Catalyzed Tandem Synthesis of Bioactive Spiro-dipyrroloquinolines and Its Application in the One-step Synthesis of Incargranine B Aglycone and Seneciobipyrrolidine (I)†

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The Au-catalyzed tandem process of aminoalkynes was explored, providing simple and efficient access to richly functionalized dipyrroloquinoline frameworks with good to excellent yields. The reaction exhibits great efficiency and high atom economy in multiple-bond formation for constructing bioactive azaspiro polycylic molecules with densely multiple stereogenic centers including quaternary carbons, and shows a broad substrate scope and synthetically important functional group tolerance, which has been illustrated in the first one-step synthesis of incargranine B aglycone and seneciobipyrrolidine (I).

Polycylic azaheterocycles are a component omnipresent in a wide range of naturally occurring and biologically active molecules.[1] In particular, spiroheterocycles with multiple stereogenic centers are key subunits found in a large number of natural alkaloids like cylindricine A, ansalactam A, haplophytine and grandilodine A with a great diversity of important biological properties (Figure 1).[2] Despite the significant efforts in the development of efficient strategies for the synthesis of spiroheterocyclic alkaloids, the one-step and stereocontrolled construction of these molecular scaffolds with high atom economy, preferably by using simple catalytic systems starting from readily available acyclic starting materials, has been much less explored and remains a very important and formidable synthetic challenge because of structural complexity/diversity.

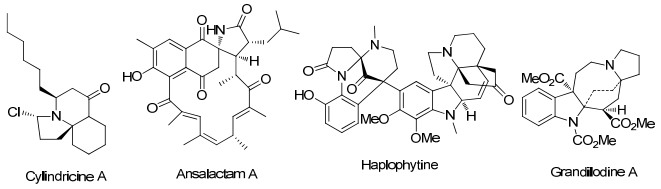

Figure 1. Natural Products and Pharmaceuticals Containing an Azaspiro Moiety.

We and Xu have independently reported the synthesis of substituted azaheterocycles via transition-metal-catalyzed tandem cyclization of aminoalkynes with some electrophiles or nucleophiles (Scheme 1a).[3,4] In these previously reported reactions,[3,4] the transformation might be realized using aminoalkynes for the generation of activated enamine intermediate through metal-catalyzed hydroamination to spur further transformations. On the other hand, the aza-Diels-Alder reaction of 2-azadienes and electron-rich olefins to access azaheterocycles represents one of the most important developments in modern synthetic chemistry and has a broad range of applications in the synthesis of natural products and bioactive compounds,[5,6] owing to their bond-forming efficiency, atom economy, excellent stereoselectivity, product structural diversity/complexity. We wondered if the synthetic potential of the aminoalkyne reactivity as enamine precursors in the presence of transition-metal-catalysis could be further harnessed to simultaneously serve as both dienophile and 2-azadiene through aza-Diels-Alder reaction to directly access different types of polycyclic azaheterocycles (Scheme 1b). Interestingly, this proposed reaction would overcome one of the main limitations of the aza-Diels-Alder reaction involving the extremely instable enamine/iminium ion reagents.[7] In this scenario, several major challenges had to be overcome to accomplish the desired reaction. First, the difficulty in controlling both regioselectivity and diastereoselectivity owing to concomitant generation of two or three stereocenters with such strategy has to be substantially overcome. The other is that the rapid enamine/iminium equilibrium may lead to a number of reaction pathways and combination cascades such as aldol, Mannich and Claisen to give a mixture of products. Herein, we present the gold-catalyzed[8] one-pot tandem reaction for the efficient formation of multiple bonds, and thus

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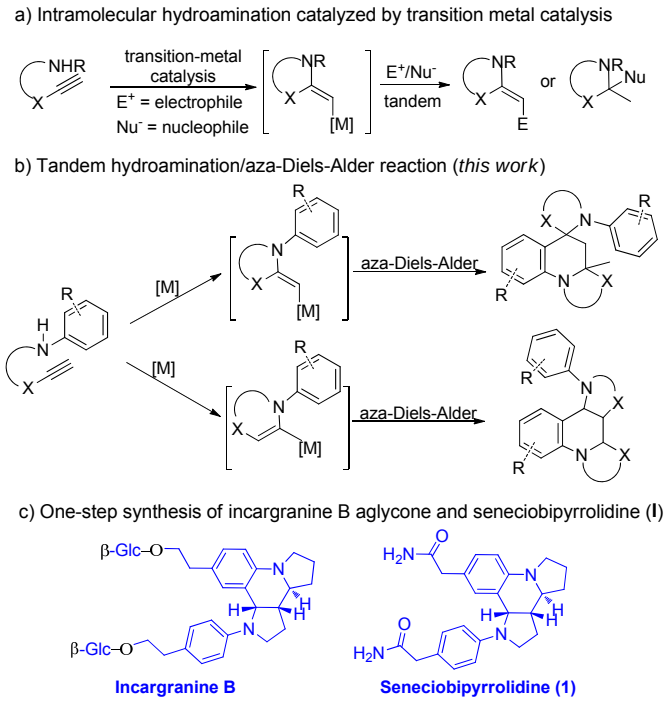
†Electronic Supplementary Information (ESI) available: Text gives the experimental procedures, ^{1}H and ^{13}C NMR spectrum, mechanism studies and biological assay. See DOI: 10.1039/x0xx00000x

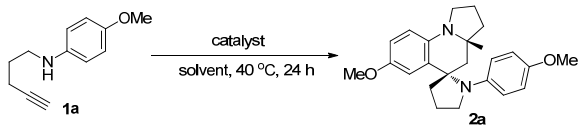


Scheme 1. A Tandem Synthesis of Complex Bioactive Polycyclic Azaheterocycles.

provide facile access to richly functionalized spiro-dipyrroloquinoline frameworks bearing two quaternary stereogenic centers with potential anticancer activity (Scheme 1b). Significantly, this highly convenient and economical methodology was successfully applied to the first one-step synthesis of incargranine B aglycone and (±)-seneciobipyrrolidine (**I**) in good yield on a gram-scale (Scheme 1c).

Our investigation started with the use of 1,4-aminoalkyne **1a** as the model substrate for identifying a suitable catalytic system, based on our previous reports that such substrate can easily undergo hydroamination under transition-metal-catalysis to give enamine/iminium ion intermediates.[3,4] Thus, we initially examined the reaction of **1a** in the presence of 5 mol% of $PPh_3AuCl/AgSbF_6$ (mol ratio = 1:1) in ethanol (EtOH) at 40 °C for 24 h. To our delight, the desired product **2a** could be obtained with an excellent all-*trans* diastereoselectivity, albeit with only 10% yield, demonstrating that gold catalyst can selectively catalyse such tandem reaction (Table 1, entry 1). To improve the product yield, a panel of gold(I) complexes with different ancillary ligands were screened for the activity and diastereo-induction in the tandem reaction. However, using gold complexes bearing different auxiliary ligands including NHC,[9] $(t\text{Bu})_2(o\text{-diphenyl})\text{P}$[10] resulted in the formation of product **2a** in only moderate yield (entries 2 and 3). Next, we screened various coinage metal salts like $AgSbF_6$, AuCl and $KAuCl_4$ for this tandem reaction, and found that $KAuCl_4$ was most beneficial for the reaction to exclusively provide the desired product **2a** in 71% yield as a single diastereoisomer and with up to almost complete chemoselectivity (entries 4-6). Further screening of solvents showed that protic solvent EtOH gave the best result, while aprotic solvents toluene, THF and

Table 1. Optimization of reaction conditions.[a]



1a 2a

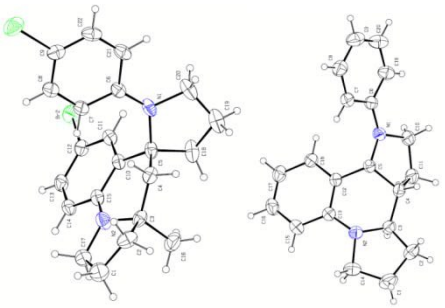
Entry	Catalyst	Solvent	Additive	Yield [%][b]
1	$PPh_3AuCl/AgSbF_6$	EtOH	4 Å MS	10
2	$Au(L)Cl^{[c]}/AgSbF_6$	EtOH	4 Å MS	48
3	$(NHC)AuCl^{[d]}/AgSbF_6$	EtOH	4 Å MS	26
4	$AgSbF_6$	EtOH	4 Å MS	12
5	AuCl	EtOH	4 Å MS	9
6	$KAuCl_4$	EtOH	4 Å MS	71
7	$KAuCl_4$	DCE	4 Å MS	11
8	$KAuCl_4$	toluene	4 Å MS	8
9	$KAuCl_4$	THF	4 Å MS	9
10	$KAuCl_4$	dioxane	4 Å MS	6
11	$KAuCl_4$	EtOH	5 Å MS	50
12	$KAuCl_4$	EtOH	\	64

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (5 mol%), solvent (1 mL), at 40 °C under argon for 24 h. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as internal standard. [c] Au(L)Cl = $(t\text{Bu})_2(o\text{-diphenyl})$PAuCl. [d] NHC = N,N'-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene.

dioxane gave low product yields (entries 6-10). We then investigated the effect of additives and found that the use of 5Å MS or the absence of MS gave the desired product in relatively lower yield as compared with the use of 4 Å MS (entries 11 and 12).

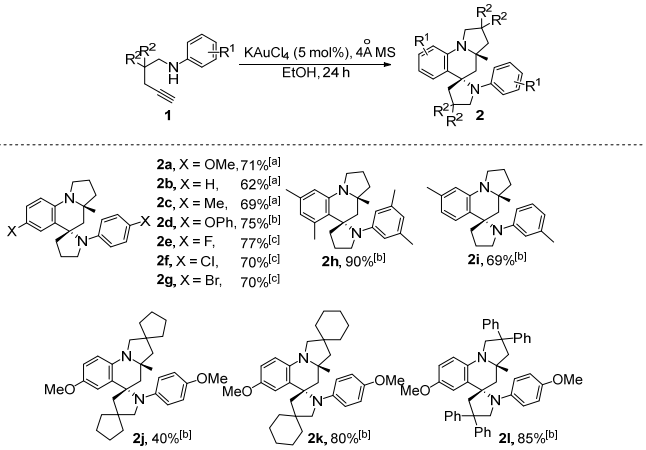
With this set of optimized reaction conditions, the scope of this gold(III)-catalyzed tandem reaction is demonstrated with a variety of differently substituted 1,4-aminoalkynes. Gratifyingly, good to excellent yields for the tandem reaction were generally obtained for most of the substrates under the mild reaction conditions. As can be seen in Scheme 2, the reaction provided the azaspiro polycycles **2** in 62-77% yields regardless of the substrates **1** with either electron-donating substituents, such as OMe (**1a**), Me (**1c**), and OPh (**1d**), or synthetically attractive electron-withdrawing groups, such as F (**1e**), Cl (**1f**), Br (**1g**) at the *para* position of the benzene group. Notably, F, Cl and Br substituents can be tolerated in this reaction, thereby, facilitating further modifications at halogenated positions (**2e**-**2g**). 3,5-Dimethyl-*N*-(pent-4-yn-1-yl)aniline (**1h**) bearing dimethyl groups gave the corresponding product **2h** in 90% yield as well. Interestingly, when 3-methyl-*N*-(pent-4-yn-1-yl)aniline (**1i**) was used in the reaction, the 6-position C-H bond with less steric hindrance was selectively activated to afford the corresponding product **2i** in 69% yield as a single diastereoisomer, with no 2-position C-H bond activated product **2i'**, thus exhibiting not only excellent diastereoselectivity but also excellent regioselectivity for such tandem reaction. Notably, the 1,4-aminoalkynes with R^2 being phenyl, cyclohexyl or cyclopentyl group underwent this Au(III)-catalyzed tandem cyclization to furnish spirocyclic products **2j**-**2l** in 40-85% yields with the rapidly concomitant installation of three or two new spiro rings. The relative configuration of **2g** was determined by X-ray crystallographic analysis (Figure

2a).[11] The relative configuration of all other products was determined with reference to **2g**.



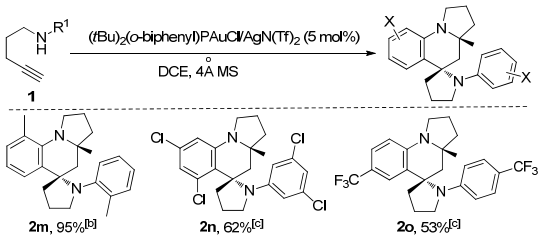
(a) (b)

Figure 2. X-ray structures of **2g** and **4'**.



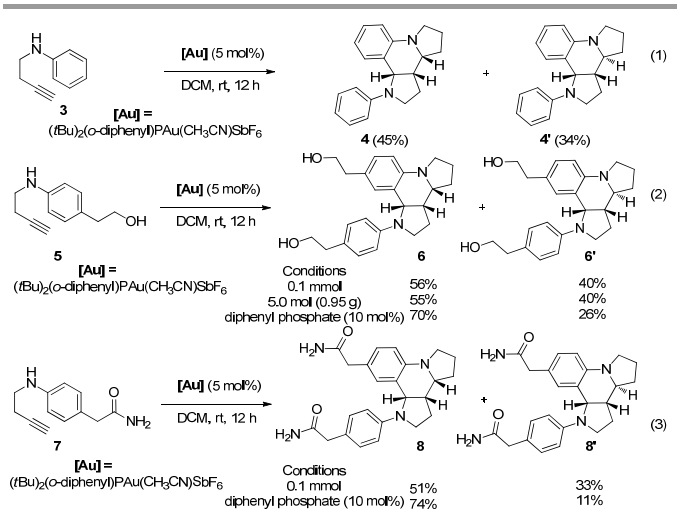
Scheme 2. KAuCl4-Catalyzed Synthesis of Azaspiro Polycycles. Reaction conditions: 1 (1.0 mmol), KAuCl4 (5 mol%), 4 Å MS (100 mg), EtOH (1 mL) for 24 h. [a] at 40 °C. [b] at rt. [c] at 60 °C.

When 1,4-aminoalkynes with *ortho*-substituent (e.g., 2-Me) or strong electron-withdrawing substituents (e.g., 3,5-dichloro) were used, unfortunately, the reaction did not give the corresponding azaspiro polycycles under the conditions described above, and this could be attributed to the weak activation of $KAuCl_4$ catalyst for the subsequent aza-Diels-Alder reaction of the sterically more congested or electron-poor 2-azadiene intermediate.[8b] To further expand the scope of such useful tandem reaction, we tested the use of the more reactive Au(I) cation derived from the reaction of (*t*Bu)$_2$(*o*-diphenyl)PAuCl[10] with an equimolar amount of $AgN(Tf)_2$ as the catalyst. After a carefully survey of the reaction conditions, we were pleased to find that the corresponding products **2m**-**2o** were afforded in 53-95% yields, when 1,4-aminoalkynes **1m**-**1o** bearing *ortho*-substituent (e.g., 2-Me) and strong electron-withdrawing substituents (e.g., 3,5-dichloro, 4-CF_3) were treated in the presence of 5 mol% of (*t*-Bu)$_2$(*o*-biphenyl)PAuCl/$AgN(Tf)_2$ (mol ratio = 1:1) with 4 Å MS in DCE (Scheme 3).



Scheme 3. Au(I)-Catalyzed Synthesis of Azaspiro Polycycles. Reaction conditions: 1 (1.0 mmol), (tBu)2(o-diphenyl)PAuCl/AgN(Tf)2 (5 mol%), 4 Å MS (100 mg), DCE (1 mL). [b] at rt for 11 h. [c] at 75 °C for 48 h.

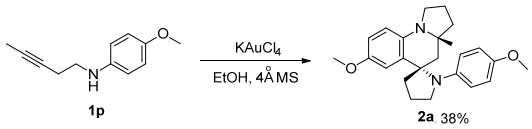
The azaspiro polycyclic molecules easily constructed from the current reaction from simple starting materials have the similar core structure with a wide variety of biologically active natural products (Figure 1).[2] The structure resemblance encouraged us to evaluate the biological activity of our products. Our preliminary studies revealed that **2j** exhibited significantly high cytotoxicities against the A549 (human lung carcinoma) cell line (IC_{50} = 5.37 μM) and MGC80-3 (human gastric adenocarcinoma) cell line (IC_{50} = 10.76 μM), suggesting a potential application of this class of complex polycyclic azaheterocylic molecules in anti-cancer studies.



Scheme 4. One-step synthesis of Incargranine B aglycone and (±)-Seneciobipyrrolidene (**I**).

The current protocol was also applied to achieve the one-step synthesis of two alkaloids encompassing dipyrroloquinoline[12] ring framework. To achieve such dipyrroloquinoline ring framework, we selected 1,3-aminoalkyne **3** as the model substrate and were delighted to find that the tricyclic azaheterocyles **4** and **4'** as a mixture of two diastereomers (45:34 d.r.) was obtained in 79% yield with the use of (*t*Bu)$_2$(*o*-diphenyl)PAu(CH_3CN)SbF_6 (5 mol%) as a catalyst in DCM at room temperature (Scheme 4, eq 1). It should be noted that only two diastereoisomers of these products with three stereocenters were selectively obtained favoring 2,3-*cis*-substituted diastereoselectivity and easily separated by simple flash chromatography. The relative configurations of **4a'** were determined by X-ray crystallographic analysis (Figure 2b).[11] It is well-known that

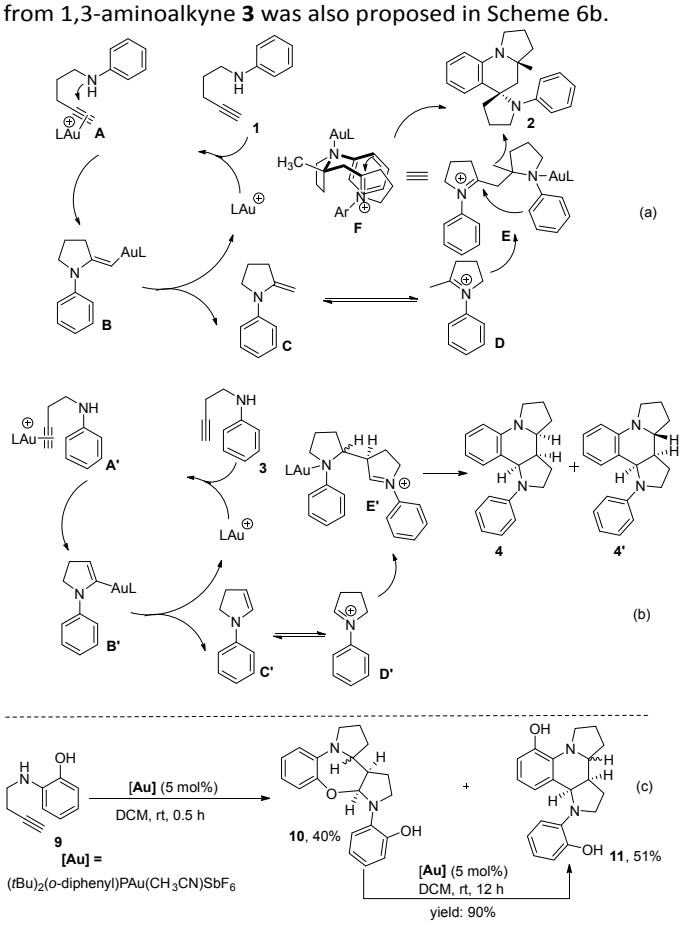
incargranine B was isolated from *Incarvillea mairei* var. *grandiflora* in 2010 by Zhang and co-workers,[13a] yet only one total synthesis of this molecule requiring six steps with only 50% combined yield in the key step has been recently reported by Lawrence and co-workers.[13b] For the purpose of accessing incargranine B aglycone **6** and **6'**, we conducted the reaction of **5** under the standard conditions, and observed that the desired product was afforded in almost quantitative yield as a 56:40 mixture of diastereomers (Scheme 4, eq 2). This protocol could be scaled up to gram-scale for the synthesis of incargranine B aglycone without decrease of product yield. It should be noted that the use of the combination of Au(I) catalyst and diphenyl phosphate as the catalyst resulted in improving the diastereoselectivity to 70:26 (**6**:**6'**). Most importantly, seneciobipyrrolidine (**I**) was more recently isolated from Senecio scandens Buch.-Ham ex D. Don by Tan and co-workers, the latter is an plant used in folk medicine for the treatment of inflammation and bacterial infection in China.[14] To synthesize (±)-seneciobipyrrolidine (**I**) at the first time, we carried out the tandem reaction of **7** with 5 mol% of Au(I) catalyst alone, or the combination of Au(I) catalyst and diphenyl phosphate, respectively. To our delight, the desired products **8** and **8'** was afforded in 84% and 85% yield as a 51:33 and 74:11 mixture of diastereomers; the analytical data were in agreement with those reported for natural seneciobipyrrolidine (**I**) (Scheme 4, eq 3).[14]



Scheme 5. $KAuCl_4$-Catalyzed Synthesis of Azaspiro Polycycles. Reaction conditions: **1p** (1.0 mmol), $KAuCl_4$ (5 mol%), 4 Å MS (100 mg), EtOH (1 mL) for 24 h at 40°C.

Furthermore, we examined 1,3-aminoalkyne bearing internal alkyne (4-methoxy-N-(pent-3-yn-1-yl)aniline **1p**) as reaction substrate using $KAuCl_4$ as catalyst, to be of interest, the reaction gave compound **2a** with good diastereoselectivity, albeit with moderate yield (38%). This could be attributed to the lower reaction activity of internal alkyne (Scheme 5).

On the basis of the established reactivity of gold-alkyne complexes toward nucleophiles,[3,8,15] a reaction mechanism for the Au-catalyzed tandem reaction of aminoalkynes is proposed (Scheme 6a and 6b). Take 1,4-aminoalkyne **1** as example, coordination of the triple bond of **1** to gold catalyst[16] and subsequent nucleophilic attack of nitrogen atom to the gold-coordinated alkyne **A** afford the gold-enamine intermediate **B** that is protonated to give enamine intermediate **C**. Once enamine **C** is formed, the second catalytic cycle "Povarov reaction" likely proceeds in a stepwise manner[17] initiated by the Mannich reaction rather than via a concerted aza-Diels-Alder mechanism due to the polarized nature of the enamine double bond under the current reaction system. This hypothesis is supported by the finding that the seven-membered ring product **10** was obtained in 40% yield via the intramolecular trap of the iminium intermediate generated after the Mannich reaction by the hydroxyl nucleophile when 1,3-aminoalkyne **9** bearing *ortho*-hydroxyl group was treated with a catalytic amount of (tBu)$_2$(o-diphenyl)PAu(CH_3CN)SbF_6 for 0.5 h under otherwise identical conditions. In addition, compound **10** was completely transformed to the final product **11** in the presence of gold(I) catalyst (Scheme 6c). These results provided direct evidence of a stepwise mechanism of our catalytic Povarov-type reaction. Thus, the enamine intermediate **C** approaches the corresponding iminium ion species **D** tautomerized from **C** via a Mannich reaction to afford intermediate **E**. A final intramolecular aza-Friedel-Crafts reaction activated with excellent stereoselectivity control via a favorable chairlike six-membered transition state **F**, in which the methyl group is placed in a pseudoequatorial position and the situation of the nitrogen atom of the iminium ion in a pseudoaxial position favored by anomeric effect,[6] followed by rearomatization and protodemetallation leads to final product **2**. As a net result, two new C–C bonds and two C–N bonds are stereoselectively generated from this tandem annulation, as well as three new rings containing one spiro ring. On the other hand, the formation of dipyrroloquinoline ring framework **4** from 1,3-aminoalkyne **3** was also proposed in Scheme 6b.



Scheme 6. Proposed Mechanism and control experiment.

Conclusion

In summary, a catalytic transformation has been achieved on the basis of an intramolecular hydroamination and aza-Diels–Alder tandem process of aminoalkynes with high regio- and diastereoselectivity and up to almost complete

chemoselectivity in a broad spectrum of substrates. The developed gold-catalyzed tandem catalytic methodology showed great efficiency in multiple-bond formation and establishing spiro-dipyrroloquinolines with densely multiple stereogenic centers including quaternary carbons in a stereocontrolled fashion, and therefore provides a convenient one-step access to complex azaheterocylic molecules of medicinal interest. This methodology allowed the first one-step synthesis of incargranine B aglycone and (±)-seneciobipyrrolidine (**I**) in good yield which represents the first application of the gold-catalyzed tandem methodology toward the highly efficient one-step synthesis of natural products. Further studies, including an asymmetric variant of this transformation and its synthetic application to chiral incargranine B and seneciobipyrrolidine (**I**) are currently underway in our laboratory.

Acknowledgements

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Notes and references

1 For selected recent examples, see: a) D. L. Boger, C. W. Boyce, R. M. Garbaccio, J. A. Goldberg, *Chem. Rev.* 1997, **97**, 787. b) S. M. Weinreb, *Chem. Rev.* 2006, **106**, 2531.

2 a) E. F. Rogers, H. R. Snyder, R. F. Fischer, *J. Am. Chem. Soc.* 1952, **74**, 1987; b) P. Yates, F. N. MacLachlan, I. D. Rae, M. Rosenberger, A. G. Szabo, C. R. Willis, M. P. Cava, M. Behforouz, M. V. Lakshmikantham, W. Zeiger, *J. Am. Chem. Soc.* 1973, **95**, 7842; c) A. J. Blackman, C. Li, *Tetrahedron* 1993, **49**, 8645; d) C. Boonlarppradab, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* 2008, **10**, 5505; e) M. C. Wilson, S.-J. Nam, T. A. M. Gulder, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* 2011, **133**, 1971; f) C. Dufour, J. Wink, M. Kurz, H. Kogler, H. Olivan, S. Sablé, W. Heyse, M. Gerlitz, L. Toti, A. Nuber, A. Rey, C. Couturier, A. Bauer, M. Brönstrup, *Chem. Eur. J.* 2012, **18**, 16123.

3 a) X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* 2008, **47**, 3805; b) X.-Y. Liu, C.-M. Che, *Angew. Chem. Int. Ed.* 2009, **48**, 2367.

4 a) J. Han, B. Xu, G. B. Hammond, *J. Am. Chem. Soc.* 2010, **132**, 916; b) J. Han, B. Xu, G. B. Hammond, *Org. Lett.* 2011, **13**, 3450.

5 For selected recent reviews on the aza Diels-Alder reaction, see: a) P. Buonora, J.-C. Olsen, T. Oh, *Tetrahedron* 2001, **57**, 6099; b) V. V. Kouznetsov, *Tetrahedron* 2009, **65**, 2721; c) P. R. Girling, T. Kiyoi, A. Whiting, *Org. Biomol. Chem.* 2011, **9**, 3105; d) X. Jiang, R. Wang, *Chem. Rev.* 2013, **113**, 5515; e) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* 2013, **42**, 902.

6 For some selected elegant examples on the transition-metal-catalyzed tandem aza Diels-Alder reaction, see: a) J. Barluenga, A. Mendoza, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* 2008, **47**, 7044; b) J. Barluenga, A. Mendoza, F.Rodríguez, F. J. Fañanás, *Chem. Eur. J.* 2008, **14**, 10892; c) J. Barluenga, A. Braham, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed.* 2009, **48**, 1644.

7 Aza Diels-Alder reaction reactions of preformed enamines as the dienophiles in the literature are restricted to relative stable enamines, see: Nomura, Y.; Kimura, M.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* 1978, 268.

8 For selected reviews on gold-catalyzed reactions, see: a) D. J. Gorin, F. D. Toste, *Nature* 2007, **446**, 395; b) A. S. K. Hashmi, *Chem. Rev.* 2007, **107**, 3180; c) Z. Li, C. Brouwer, C. He, *Chem. Rev.* 2008, **108**, 3239; d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* 2008, **108**, 3326; e) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* 2008, **108**, 3351; f) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* 2009, **38**, 2269; g) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* 2010, **49**, 5232.

9 For recent reviews on catalytic applications of NHC-Au complexes, see: a) N. Marion, S. P. Nolan, *Chem. Soc. Rev.* 2008, **37**, 1776; b) S. P. Nolan, *Acc. Chem. Res.* 2011, **44**, 91.

10 C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* 2005, **127**, 6178.

11 CCDC 1013665 (**2g**) and 1013666 (**4'**) 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 For selected examples for the synthesis of dipyrroloquinoline ring framework, see: a) G. H. Kerr, O. Meth-Cohen, E. B. Mullock, H. Suschitzky, *J. Chem. Soc.,Perkin Trans. 1* 1974, **14**, 1614; b) B. B. Snider, Y. Ahn, B. M. Foxman, *Tetrahedron Lett.* 1999, **40**, 3339; c) D. W. Ma, C. F. Xia, J. Q. Jiang, J. H. Zhang, *Org. Lett.* 2001, **3**, 2189; d) D. W. Ma, C. F. Xia, J. Q. Jiang, J. H. Zhang, W. J. Tang, *J. Org. Chem.* 2003, **68**, 442; e) M. Buswell, I. Fleming, *Chem. Commun.* 2003, 202; f) M. Buswell, I. Fleming, U. Ghosh, S. Mack, M. Russella, B. P. Clarkb, *Org. Biomo. Chem.* 2004, **2**, 3006; g) S. Fustero, P. Bello, J. Miro, M. Sanchez-Rosello, M. A. Maestro, J. Gonzalez, C. D. Pozo, *Chem. Commun.* 2013, **49**, 1336; h) M. Chang, S. Abbas, S. Daniel, *Org. Lett.* 2014, **16**, 2756.

13 a) Y.-H. Shen, Y.-Q. Su, J.-M. Tian, S. Lin, H.-L. Li, J. Tang, W.-D. Zhang, *Helv. Chim. Acta* 2010, **93**, 2393; b) P. D. Brown, A. C. Willis, M. S. Sherburn, A. L. Lawrence, *Angew. Chem. Int. Ed.* 2013, **52**, 13273.

14 D. Tan, G. Chou, Z. Wang, *Chem. Nat. Compd.* 2014, **50**, 329.

15 a) N. D. Shapiro, F. D. Toste, *Proc. Natl. Acad. Sci. U. S. A.* 2008, **105**, 2779; b) R. L. LaLonde, J. W. E. Brenzovich, D. Benitez, E. Tkatchouk, K. Kelley, III. W. A. Goddard, F. D. Toste, *Chem. Sci.* 2010, **1**, 226.

16 For selected reviews, see: a) C. Bruneau, *Angew. Chem. Int. Ed.* 2005, **44**, 2328; b) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* 2006, **348**, 2271; c) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* 2008, **47**, 4268.

17 For selected examples, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* 2004, **43**, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* 2004, **126**, 5356; c) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem. Int. Ed.* 2006, **45**, 2254; d) M. Terada, K. Machioka, K. Sorimachi, *J. Am. Chem. Soc.* 2007, **129**, 10336; e) M. Terada, K. Soga, N. Momiyama, *Angew. Chem. Int. Ed.* 2008, **47**, 4122; f) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *Angew. Chem. Int. Ed.* 2009, **48**, 6717; g) C. Luo, Y. Huang, *J. Am. Chem. Soc.* 2013, **135**, 8193.