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Au(I)-Catalyzed Rearrangement Reaction of Propargylic Aziridine: Synthesis of Trisubstituted and Cycloalkene-Fused Pyrroles

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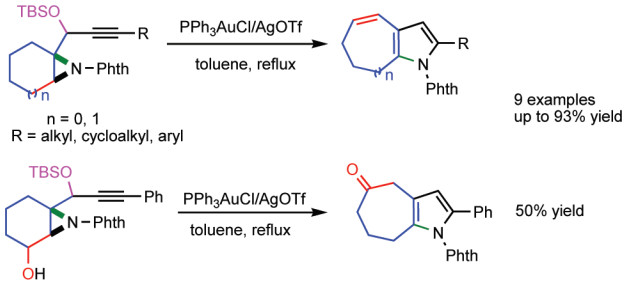
ABSTRACT



A rearrangement reaction of propargylic aziridine, catalyzed by $PPh_3AuCl/AgOTf$, forming trisubstituted and cycloalkene-fused pyrroles is described which involves an unusual tandem cyclization/ring-opening/Wagner−Meerwein process. The unique structures of the products demonstrated its potential applications for synthesizing structurally diverse alkaloids.

Pyrroles are ubiquitous structural units that extensively exist in numerous pharmaceuticals and natural products.[1] As more and more pyrrole derivatives are identified that possess significant biological activity,[2] the development of highly efficient methodology for synthesizing structurally diverse pyrroles has attracted the attention of chemists.[1,3] Although various methods, especially those based on transition-metal catalysis, are available,[4] efficient construction of cycloalkene-fused pyrroles has been rarely achieved, and even fewer of these have been derived through the annulation of a multifunctionalized aziridine with a C−C triple bond.[5] Recently, our independent research efforts in gold catalysis as well as aziridine chemistry have made some interesting contributions to synthetic methodology.[6] One example involves the construction of a quaternary carbon-containing aminoalkyne

(1) (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264.

(2) (a) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357. (b) Perrin, D.; van Hille, B.; Barret, J.-M.; Kruczynski, A.; Etievant, C.; Inbert, T.; Hill, B. T. *Biochem. Pharmacol.* **2000**, *59*, 807.

(3) (a) Ferreira, V. F.; De Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411. (b) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I. *Chem. Rev.* **2004**, *104*, 2481. (c) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043.

(4) For selected examples, see: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (c) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (d) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (e) Lu, Y.; Fu, X.; Chen, H.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 129. (f) Merkul, E.; Boersch, C.; Frank, W.; Müller, T. J. J. *Org. Lett.* **2009**, *11*, 2269. (g) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664.

(5) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293.

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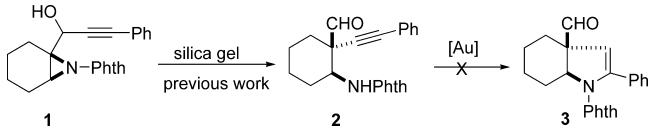
2, a versatile Mannich base, from propargylic aziridine **1** as presented in Scheme 1. This result led us to envision that

Scheme 1. Previous Work



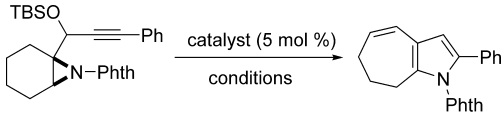
treatment of propargylic aziridine **1** with a suitable gold catalyst would permit a tandem semipinacol rearrangement and a 5-*endo-dig* cyclization[7] to produce the 2,3-dihydropyrrole **3** in one pot.[8]

Our preliminary treatment of **1** with 10 mol % of $PPh_3AuCl/AgOTf$ in CH_2Cl_2, however, did not provide the expected dihydropyrrole **3** but, not surprisingly, a semipinacol rearrangement product **2**. Further tests using several gold and silver complexes in different solvents still failed to produce **3**. To our delight, when the substrate **4** (Table 1) with a hydroxyl group protected by TBSCl was subjected to treatment using the above catalysts in toluene at reflux temperature, a light yellow solid was obtained, which was identified as *N*-phthaloylcycloheptene-2,3-fused-5-phenylpyrrole **5**.[9] This transformation was important as it involved a unique sequential N-addition to a C−C triple bond, ring-opening of an aziridine, and a Wagner−Meerwein-type C-to-C rearrangement[10] and also efficiently constructed the 3-vinyl-2,3,5-trisubstituted pyrrole. To the best of our knowledge, this type of reaction has not been reported. Herein we present our experimental results in detail.

Given the information above, **4** was selected as a model substrate to pursue optimization of reaction conditions using different gold/silver complexes and solvents (Table 1). Gratifyingly, under promotion of 5 mol % of $PPh_3AuCl/AgOTf$ at reflux temperature in toluene, the reaction of **4** gave rise to the desired product **5** in 63% yield (entry 1). When the reaction was performed in dry toluene, a lower yield of **5** was obtained (entry 2). Changing the PPh_3AuCl catalyst with AuCl slightly decreased the yield (entry 3). No desired product was obtained when the PPh_3AuCl catalyst was replaced with $AuCl_3$ (entry 4). No reaction was observed if the reaction was run at room temperature (entry 5) or with sole AuCl or PPh_3AuCl catalysts (entries 6 and 7). Also, no expected product was obtained when AgOTf was solely used (entry 8). Control experiments to examine the simple Brønsted acid catalysis with 5 mol % of TfOH (entry 9) were also performed that indicated no desired product could be obtained.[11]

With the optimal conditions (Table 1, entry 1) in hand, the scope of this rearrangement reaction was further investigated. Initially, we inspected the substitution effect of R at the triple bond terminal. The results obtained (Table 2) indicated that this reaction was tolerant of both electron-rich and electron-poor aryl groups (entries 1−3) as well as the acyclic and cyclic alkyl groups (entries 4 and 5), and the corresponding products **7a**−**e** could be obtained in moderate to high yields. Analogously, heteroaryl and fused aryl substitutions for R were also compatible with this reaction (entries 6 and 7). Successively, the size of carbocycle fused to the aziridine was investigated, and the result revealed that reactions of five-membered ring substrates (entries 8 and 9) proceeded much faster than those of the six-membered ring substrates, possibly because the formation of six-

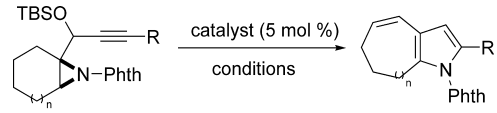
Table 1. Optimization of Au-Catalyzed Reaction Conditions of **4**[a]



entry	catalyst	conditions	yield[b] (%)
1	**$PPh_3AuCl/AgOTf$**	**toluene, 110 °C, 4 h**	**63**
2	$PPh_3AuCl/AgOTf$	dry toluene, 110 °C, 3.5 h	55
3	AuCl/AgOTf	toluene, 110 °C, 2 h	50
4	$AuCl_3$/AgOTf	toluene, 110 °C, 3 h	0
5	$PPh_3AuCl/AgOTf$	toluene, rt, 24 h	0
6	AuCl	toluene, 110 °C, 24 h	0
7	PPh_3AuCl	toluene, 110 °C, 24 h	0
8	AgOTf	toluene, 110 °C, 2 h	0
9	TfOH	toluene, rt, 5 min	0

[a] Reaction conditions: The propargylic aziridine 4 (0.5 M in toluene) was treated with 5 mol % of catalysts. [b] Isolated yield.

Table 2. Au-Catalyzed Reactions of Ring-Fused Propargylic Aziridines[a]



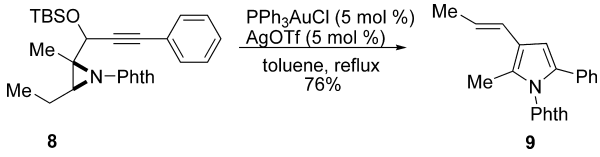
entry	n	R[b]	product	time (h)	yield[c] (%)
1	1	Ph	**7a**	4.0	63
2	1	4-$MeOC_6H_4$	**7b**	2.5	65
3	1	4-$F_3CC_6H_4$	**7c**	4.0	76
4	1	*n*-pentyl	**7d**	3.0	76
5	1	cyclopropyl	**7e**	4.0	90
6	1	3-thiophenyl	**7f**	1.0	93
7	1	2-naphthyl	**7g**	3.0	88
8	0	Ph	**7h**	0.1	60
9	0	4-$MeOC_6H_4$	**7i**	0.1	55

[a] The reaction was performed on a 0.5 mmol scale in 10 mL of toluene with 5 mol % of PPh_3AuCl and 5 mol % of AgOTf at reflux temperature. [b] For a diastereomeric ratio of the substrates, see the Supporting Information. [c] Isolated yield.

(6) (a) Zhang, E.; Tu, Y.-Q.; Fan, C.-A.; Zhao, X.; Jiang, Y.-J.; Zhang, S.-Y. *Org. Lett.* **2008**, *10*, 4943. (b) Zhang, Y.-Q.; Chen, Z.-H.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Wang, A.-X.; Yuan, D.-Y. *Chem. Commun.* **2009**, 2706.

membered rings in **7h** and **7i** via ring expansion was more favorable than the seven-membered rings in **7a**−**g**. Additionally, when an acyclic propargylic aziridine substrate **8** was subjected to the reaction under the general conditions, a 2,3,5-trisubstituted pyrrole **9** was also smoothly obtained in 76% yield (Scheme 2).[12,13] Finally, to further explore the structural

Scheme 2. Screening of Acyclic Substrate

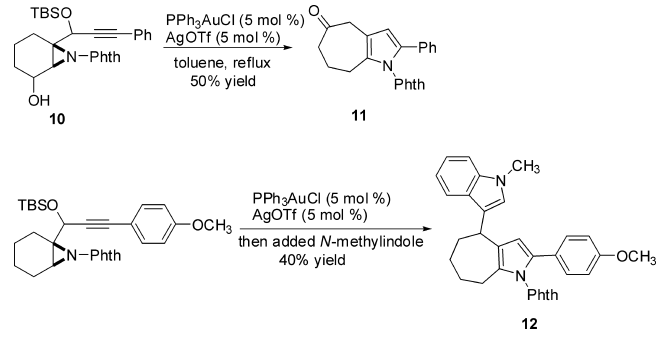


8 **9**

diversity of pyrroles that could be synthesized using our methodology, a reaction with the hydroxycyclohexane-fused aziridine **10** and a two-component reaction of the substrate of entry 2 in Table 2 with *N*-methylindole were conducted separately, and the expected ketone carbonyl **11**[14] and α-indolyl-substituted products **12** were successfully obtained, respectively (Scheme 3).

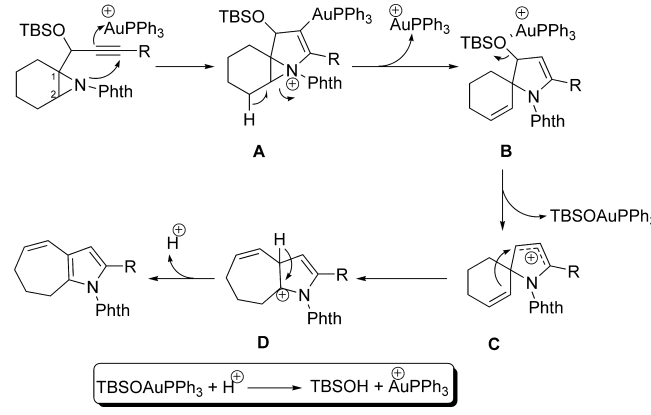
On the basis of these results and literature reports,[5,15] a plausible mechanism for the reaction is outlined (Scheme 4). It commences with a 5-*endo-dig* cyclization of the N-atom of the aziridine with the Au(I)-activated C−C triple bond, forming an ammonium cation intermediate **A**. Unlike our previous work where **A** underwent an aziridine ring-opening between the N atom and the quaternary C1, instead **A** would undergo a ring-opening between the N atom and the C2, which would be followed by elimination of a β-proton to give a spirocycle intermediate **B** and regenerate the catalytic gold species. Successively, a Au(I)-catalyzed ionization of spirocycle **B** would lead to the formation of an allylic cation **C**, which could undergo a Wagner−Meerwein rearrangement/ring expansion leading to a 1,2-fused bicycle **D**.

Scheme 3. Further Examples



10 **11** **12**

Scheme 4. Proposed Mechanism of the Au(I)-Catalyzed Reaction of Propargylic Aziridine



Subsequent elimination of a proton from **D** would afford the final product.[16]

In summary, we have disclosed a Au(I)-catalyzed rearrangement of propargylic aziridine. This reaction is suggested to involve an unusual tandem cyclization/ring-opening/Wagner−Meerwein rearrangement sequence, and it provides a useful entry into cycloalkene-fused and trisubstituted pyrroles. Further studies on the detailed mechanism and its application to alkaloid synthesis will be reported in due course.

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Supporting Information Available: General experimental procedures, characterization data for all products, and X-ray crystallographic data for compounds **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) For recent examples, see: (a) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2009**, *11*, 473. (b) Wender, P. A.; Strand, D. *J. Am. Chem. Soc.* **2009**, *131*, 7528.

(8) For selected reviews on Au catalysis, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Yamamoto, Y.; Patil, N. T. *Chem. Rev.* **2008**, *108*, 3395. (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(9) For similar substrates, see: (a) Motamed, M.; Bunnelle, E. M.; Singaram, S. W.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2167. (b) Schomaker, J. M.; Geiser, A. R.; Huang, R.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 3794.

(10) For selected reviews, see: (a) Pocker, Y. In *Molecular Rearrangements*; De Mayo, P., Ed.; Wiley-VCH: New York, 1963; Vol. 1, p 1. (b) Hanson, J. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 705. (c) Saunders, M.; Jimenez-Vazquez, H. A. *Chem. Rev.* **1991**, *91*, 1625.

(11) For an entire examination of catalysts, see the Supporting Information.

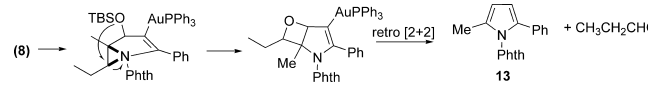
(12) We also obtained 2-methyl-5-phenyl-*N*-phthalimidepyrrole **13** in 19% yield.

(13) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

(14) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609.

(15) Lin, C.-C.; Teng, T.-M.; Tsai, C.-C.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16417.

(16) Formation of the product **13** is proposed to follow the mechanism shown here.



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