

Gold(I)-Catalyzed Cascade Cyclization Reaction: Highly Regio- and Diastereoselective Intermolecular Addition of Water and Alcohols to Epoxy Alkynes

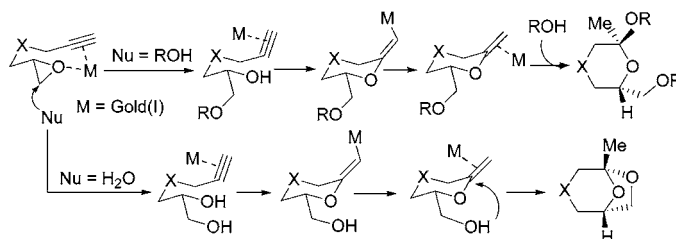
Lun-Zhi Dai, Ming-Juan Qi, Yong-Ling Shi, Xu-Guang Liu, and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, China 200032

mshi@mail.sioc.ac.cn

Received June 8, 2007

ABSTRACT



We have developed a novel access to ketal skeletons through a highly regio- and diastereoselective intermolecular addition of water and alcohols to alkynyl epoxides catalyzed by gold(I). This procedure involves a domino three-membered ring-opening, 6-*exo*-cycloisomerization, and subsequent intra- or intermolecular nucleophilic addition to a double-bond sequence.

Cyclizations of epoxy alkynes have provided rapid access to complex structures in an easy one-pot process in which a wide range of metal salts can be used, either in a stoichiometric or a catalytic manner. For example, Marson reported an efficient $\text{Sn}(\text{OTf})_2$ - or SnBr_4 -induced alkyne–epoxy alcohol cyclization leading to a seven-membered carbocyclic ring; however, the reaction generally requires an excess amount of metal reagents.^{1a} Gansauer found that a catalytic amount of $\text{Ti}(\text{III})$ complexes sufficed to implement radical epoxide–alkyne cyclization in the presence of excess Mn powder.^{1b} In addition, McDonald described a $\text{W}(\text{CO})_6$ -catalyzed cyclization of α -ethynyl epoxides to give furans.^{1c} The first intermolecular alkyne–epoxide coupling was

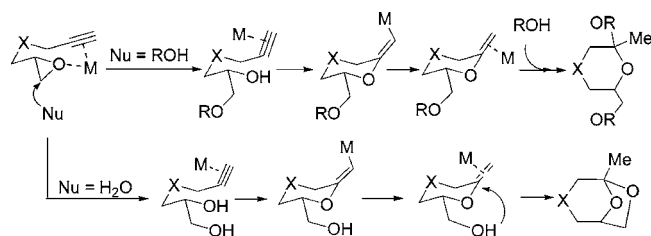
recently reported by Jamison with the use of $\text{Ni}(\text{O})\text{--PBu}_3$ catalyst.^{1d} Later on, Liu achieved a cascade alkyne–epoxide cyclization of (*o*-ethynyl)phenyl epoxides catalyzed by Ru complexes.^{1e} Recently, a AuCl_3 -catalyzed isomerization of alkynyl epoxides to furans under mild conditions was reported by Hashmi.² In the context of our ongoing efforts to develop cascade reactions,³ we envisaged that the alkynyl epoxides in the presence of various nucleophiles might undergo a domino pathway consisting of three-membered ring-opening, 6-*exo*-cycloisomerization, and subsequent nucleophilic addition to a double bond to give ketal skeletons (Scheme 1).

According to this mode, several problems should be taken into consideration. (i) Choose a proper catalyst M to activate the alkynyl group and the epoxy group as well as the subsequently formed double bond. For example, previous

(1) (a) Marson, C. M.; Khan, A.; McGregor, J.; Grinter, T. J. *Tetrahedron Lett.* **1995**, 36, 7145. (b) Gansauer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, 120, 12849. (c) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, 116, 9363. (d) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, 125, 8076. (e) Madhushaw, R. J.; Lin, M.-Y.; Sohel, S. M. A.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, 126, 6895.

(2) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, 346, 432.

(3) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, 8, 4043.

Scheme 1. Projected Domino Reaction

reports have shown that gold salts are a kind of powerful soft Lewis acid and can readily activate alkynes, allenes, and olefins toward attacks by a variety of nucleophiles.^{4,5} Moreover, we have found that gold(I) can also be an efficient catalyst for the rearrangement of oxirane. (ii) The rearrangement of epoxy group should be suppressed. As we know, the rearrangement of epoxides with a Lewis acid is a common method in organic synthesis and has been broadly studied.⁶ (iii) Once the catalyst M coordinates to the triple bond and the epoxy group, the nucleophile should be used to attack the epoxy group.^{6a}

To probe the feasibility of this strategy, we initially focused on the addition of water to the *N*-tethered alkynyl epoxide compound **1a** in the presence of various Lewis acids to examine the formation of the fused bicyclic ketal **2a** (see the Supporting Information). The reaction, which was carried out in 1,2-dichloroethane (DCE) using (Ph₃P)AuCl/AgSbF₆ as catalysts, gave the best result, and the desired product **2a** was obtained in 68% yield. The structure of compound **2a** was confirmed by X-ray diffraction study (see the Supporting Information). Under the optimized conditions, the scope of this domino approach from alkynyl epoxides to fused bicyclic ketals was summarized in Table 1. Subjection of *N*-tethered alkynyl epoxides **1b** and **1c** to the general protocol afforded the expected fused bicyclic compounds **2b** and **2c** in moderate yields respectively, indicating that the substituents on the aryl ring did not have significant effect to this transformation (Table 1, entries 2 and 3). The presence of

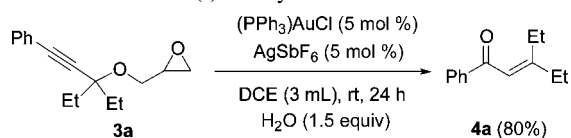
Table 1. Scope of Gold(I)-Catalyzed Addition of Water to Alkynyl Epoxides^a

entry	substrate	product ^b
1	1a : R ¹ = H, X = <i>p</i> -MeC ₆ H ₄ SO ₂ N	2a (68%)
2	1b : R ¹ = H, X = <i>o</i> -NO ₂ C ₆ H ₄ SO ₂ N	2b (56%)
3	1c : R ¹ = H, X = <i>p</i> -BrC ₆ H ₄ SO ₂ N	2c (63%)
4	1d : R ¹ = Me, X = <i>p</i> -MeC ₆ H ₄ SO ₂ N	2d (38%)
5	1e : R ¹ = CO ₂ Et, X = <i>p</i> -MeC ₆ H ₄ SO ₂ N	2e (70%)
6	1f : R ¹ = SiMe ₃ , X = <i>p</i> -MeC ₆ H ₄ SO ₂ N	2a (50%)

^a Reactions were conducted with 0.30 mmol of substrate and 0.45 mmol of water catalyzed by 5 mol % of (Ph₃P)AuCl/AgSbF₆ in 3 mL of DCE at room temperature for 48–72 h. ^b All of the yields given in parentheses are isolated yields.

an electron-withdrawing substituent on the alkyne appeared to be more beneficial than the presence of an electron-donating substituent (Table 1, entries 4 and 5). However, the reaction could not tolerate the TMS group on the alkyne in the substrate **1f** (Table 1, entry 6).

By investigating the scope of the reaction, we surprisingly found that the use of *O*-tethered alkynyl epoxide **3a** led to α,β -unsaturated carbonyl compound **4a** in 80% yield instead of fused bicyclic ketal (Scheme 2).

Scheme 2. Gold(I)-Catalyzed Addition of Water to **3a**

We further tested the cascade reaction of epoxy alkyne **1a** with methanol in DCE in the presence of 5 mol % of (Ph₃P)AuCl/AgSbF₆, but the results were not satisfactory. Gratifyingly, we discovered that treatment of **1a** with 5 mol % of (Ph₃P)AuCl/AgSbF₆ and 10 mol % of *p*-TsOH in 3.0 mL of methanol at room temperature afforded cleanly 2,6-trans-substituted morpholine **6a** in 75% yield with high diastereoselectivity (see the Supporting Information).

Having demonstrated the efficient reaction between epoxy alkyne and alcohol, we set out to explore the scope of this cascade addition (Table 2). The corresponding 2,6-trans-substituted morpholines **6b–d** were obtained in 44–70% yields by using (PPh₃)AuCl/AgSbF₆/*p*-TsOH in ethanol, prop-2-en-1-ol, or propan-2-ol (Table 2, entries 2–4). Aryl groups with substituents, including *o*-NO₂, *p*-Br, were allowed, and the corresponding morpholines **6e,f** (Table 2, entries 5 and 6) and **6g** (Table 2, entry 7) were obtained in moderate yields without the formation of by products. 1',2'-Disubstituted epoxide bearing a phenyl group was compatible with this transformation, affording the corresponding product

(4) For selected recent reviews on gold-catalyzed reactions, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (e) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (f) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (g) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (h) Nicolas, M.; Steven, P. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (i) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (j) Fürster, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (k) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

(5) For selected recent examples, see: (a) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744. (b) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596. (c) Guan, B.; Xing, D.; Cai, G.; Wan, X.; Yu, N.; Fang, Z.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 18004. (d) Han, X.; Widenhofer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (e) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (f) Genin, E.; Toullec, P. Y.; Antonietti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (g) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (h) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332.

(6) For reviews on the Lewis acid mediated rearrangement of epoxides, see: (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Rickborn, B. In *Comprehensive Organic Synthesis, Carbon–Carbon Bond Formation*; Pattenden, G., Ed.; Pergamon: Oxford, 1991; Vol. 3, Chapter 3.3, p 733.

Table 2. Scope of Gold- and Acid-Catalyzed Diastereospecific Addition of Alcohols to Alkynyl Epoxides^{a,b}

entry	substrate	product
1		
1		6a (R ³ = Me, 75%)
2		6b (R ³ = Et, 70%)
3		6c (R ³ = -CH ₂ CH = CH ₂ , 68%)
4 ^c		6d (R ³ = ⁱ Pr, 44%)
5		6e (R ³ = -CH ₂ CH = CH ₂ , 75%)
6		6f (R ³ = Et, 80%)
7		6g (71%)
8		6h (72%)
9		6i (65%)

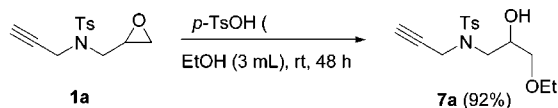
^a Reactions were conducted with 0.30 mmol of substrate catalyzed by 5 mol % of (Ph₃P)AuCl/AgSbF₆ and 10 mol % of *p*-TsOH in 3 mL of alcohol at room temperature for 6–24 h. ^b All of the yields given in parentheses are isolated yields. ^c The reaction was carried out at 45 °C, and 50% of starting material was recovered.

6h in 72% yield under identical conditions (Table 2, entry 8). The epoxy alkyne with a substituent on the end of alkynyl group gave 65% yield of morpholine product **6i** (Table 2, entry 9). The structures of **6a–i** were assigned by NMR spectroscopic analysis and by the X-ray diffraction determination of **6g** (see the Supporting Information).

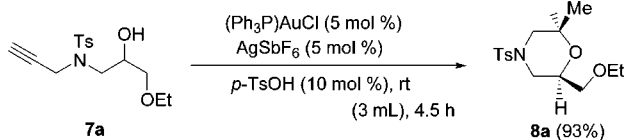
Remarkably, the foregoing experiment showed that the reaction of **1a** with ethanol using 10 mol % of *p*-TsOH in

Scheme 3. Stepwise Synthesis of **8a** from **1a**

Step 1. *p*-TsOH Catalyzed Regioselective Oxirane-Opening of the Epoxy Alkyne **1a** at Room Temperature.



Step 2. Gold and Acid-Catalyzed Addition of Prop-2-en-1-ol to **7a** at Room Temperature.



the absence of (Ph₃P)AuCl/AgSbF₆ only resulted in the formation of oxirane-opened product **7a** in 92% yield. Then, treatment of **7a** in prop-2-en-1-ol under these optimized conditions afforded morpholine **8a** in 93% yield (Scheme 3).

To gain some mechanistic insight into the function of *p*-TsOH in this reaction, a control experiment was carried out. We treated **7a** with (Ph₃P)AuCl/AgSbF₆ in prop-2-en-1-ol for 4.5 h in the absence of *p*-TsOH and found that the reaction proceeded smoothly to give **8a** in 76% yield, which was lower than that of the reaction in the presence of *p*-TsOH (Scheme 4). Therefore, according to the results shown in

Scheme 4. Gold-Catalyzed Addition of Prop-2-en-1-ol to **7a** at Room Temperature

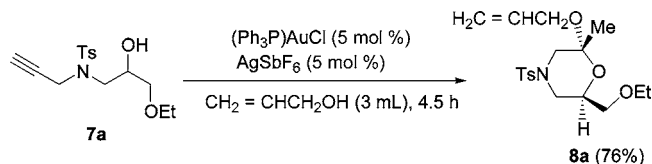
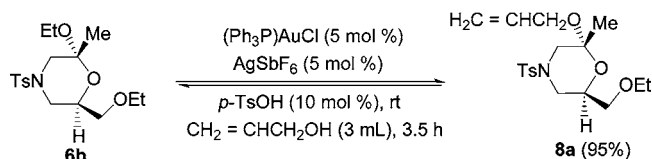


Table 2 and Schemes 3 and 4, we believed that *p*-TsOH was beneficial to both ring-opening of oxirane and hydroalkoxylation of double bond.⁷

Additionally, subjecting ketal **6b** to the reaction conditions in prop-2-en-1-ol resulted in ketal exchange to give ketal **8a** in 95% yield (Scheme 5).

Scheme 5. Gold and *p*-TsOH-Catalyzed Ketal Exchange



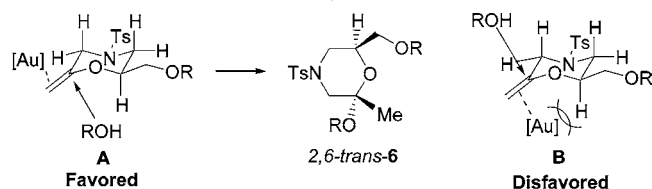
Possible reasons for this highly diastereoselective formation of 2,6-trans-substituted morpholines are shown in Scheme 6. Taking the reaction of epoxyalkyne **1a** with alcohol as an example, the pivotal intermediate of substituted 2-methylenemorpholine was formed through a three-membered ring-opening⁸ and 6-exo-cycloisomerization⁹ sequence. If gold(I) was an effective catalyst in this transformation,

(7) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489.

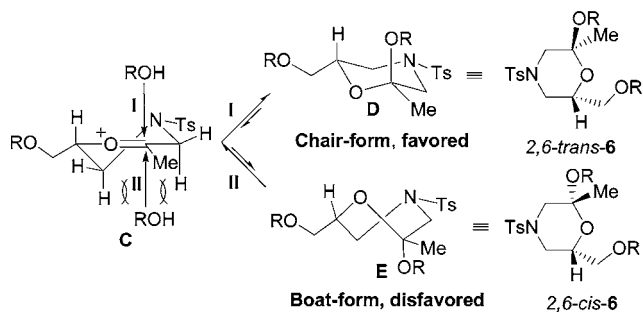
(8) A direct nucleophilic addition of an aryl-Au to epoxide has been reported by He. In this work, we believe that gold(I) works just as a Lewis acid to activate epoxides; see: Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964.

(9) (a) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553. (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (c) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *45*, 5350. (d) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (e) Gorin, D. J.; Davis, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (f) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. (g) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.

Scheme 6. Proposed Reasons for Diastereospecific Attacks of the Double Bond by Various Alcohols



p-TsOH as an effective catalyst for this transformation:



the following intermolecular nucleophilic addition of the double bond¹⁰ of 2-methylene morpholine by another molecule of alcohol was believed to proceed through a chairlike transition state. The cationic gold complex coordinated to the double bond from the less steric orientation forming transition state **A** (transition state **B** is disfavored), and the remaining alcohol attacked the double bond from the opposite direction to give 2,6-trans-substituted morpholine.¹¹ If *p*-TsOH was an effective catalyst,⁷ the success of this highly diastereoselective transformation relied on both stereoelectronic and steric control. Considering the half-chair conformation **C** resulting from protonation of 2-methylenemorpholine, energetically favorable perpendicular attack by alcohol could occur from either of two directions, for example, path **I** or path **II**. Path **I** attack would lead to chair conformation **D** having the new group axial to the ring. Path **II** attack would adopt a twist-boat conformation **E** which could undergo conformational change to give 2,6-cis-substituted morpholine. Because the chairlike transition state had lower energy than the twist-boat alternative, the path **I**

should be a favorable path in this reaction.¹² Based on the result shown in Scheme 5, the formed 2,6-cis-substituted morpholine would be transformed to the energetically favorable 2,6-trans-substituted morpholine through ketal exchange. Moreover, path **II** was less favorable because of the existence of double diaxial interactions.

In summary, we have developed a novel access to ketal skeletons¹³ that are found in a number of biologically active natural products through highly regio- and diastereoselective intermolecular addition of water and alcohols to alkynyl epoxides catalyzed by gold(I). This procedure involves a domino three-membered ring-opening, 6-*exo*-cycloisomerization, and subsequent intra- or intermolecular nucleophilic addition to a double-bond sequence.¹⁴ Additionally, the high regio- and diastereoselectivities and mildness of these reaction conditions should make this reaction a valuable tool for synthesis of 2,6-trans-substituted morpholines.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20472096, 203900502, and 20672127).

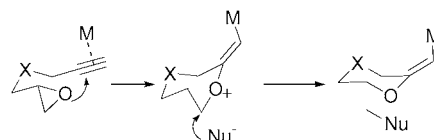
Supporting Information Available: Spectroscopic data of all new compounds, detailed descriptions of experimental procedures, and X-ray data for compounds **2a** (CCDC no. 633797) and **6g** (CCDC n. 645277). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0713640

(12) (a) Corey, E. J.; Sreen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269. (b) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935. (c) Huff, B. J. L.; Tuller, F. N.; Cane, D. J. *J. Org. Chem.* **1969**, *34*, 3070.

(13) (a) Kiyato, H. *Marine Natural Products*; Topics in Heterocyclic Chemistry, No. 5; Springer: Berlin, 2006; p 65. (b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. (c) Milroy, L.-G.; Zinzalla, G.; Prencipe, G.; Michel, P.; Ley, S. V.; Gunaratnam, M.; Beltran, M.; Neidle, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2493. A similar transformation has been reported by Genêt; see: (d) Antonietti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976.

(14) An alternative mechanism shown below is also resonable; see: (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (b) Zhang, J.; Schmalz, H. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962.



(10) (a) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (b) Yao, X.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884. (c) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673. (d) Lin, C.-C.; Teng, T.-M.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2007**, *129*, 3798. (11) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.