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Acid-Catalyzed Skeletal Rearrangement of Epoxy Alkynes: A Fast Access to Highly Functionalized Allenes

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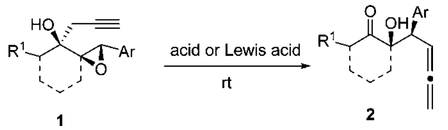
ABSTRACT

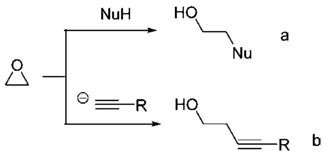


The acid-catalyzed reaction of epoxy alkyne involves an epoxide ring-opening attacked by π-alkyne, leading to a semipinacol-type rearrangement. In this process, a type of carbon−carbon 3,3-migration of the alkyne system has been discovered, which is promoted both by epoxide inducing and hydroxide promoting. This transformation enables the fast synthesis of allenes in mild conditions.

Epoxides, strained three-membered ring heterocycles, are among the most versatile intermediates in organic chemistry.[1] A number of important advances have been achieved in the chemistry of epoxides over the last years.[2] Actually, the epoxide-opening reaction is one of the most important procedures in giving potential intermediates for the synthesis of oxygen-containing natural products and biologically active compounds. In particular, epoxides can be subjected to a wide variety by inducing a hydrogen, alkyl, or aryl group to migrate between adjacent carbons. This skeletal rearrangement induced by epoxide has been thoroughly studied and plays a very important role in organic synthesis.[3]

As is known, nucleophilic substitution opening of the epoxide ring at a saturated carbon is representative of a reaction of fundamental importance in organic synthesis (Scheme 1, **a**). A wide range of applicable nucleophiles, involving group participation by heteroatoms and aryl groups, has been well-established for epoxide ring-opening.[4] Alkyne is also a reasonable nucleophile. However, addition products are formed exclusively when terminal alkynes are previously activated (Scheme 1, **b**),[5] or the epoxides will attack the

Scheme 1. Nucleophiles-Promoted Epoxide Opening Reactions



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[1] (a) Asahara, H.; Kubo, E.; Togaya, K.; Koizumi, T.; Mochizuki, E.; Oshima, T. *Org. Lett.* **2007**, *9*, 3421. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (c) Blay, G.; Cardona, L.; Collado, A. M.; Garca, B.; Pedro, J. R. *J. Org. Chem.* **2006**, *71*, 4929. (d) Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709. (e) Nakatani, M.; Nakamura, M.; Suzuki, A.; Inoue, M.; Katoh, T. *Org. Lett.* **2002**, *4*, 4483.

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[3] (a) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (b) Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, *63*, 8212. (c) Chang, C.-L.; Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2004**, *69*, 2793.

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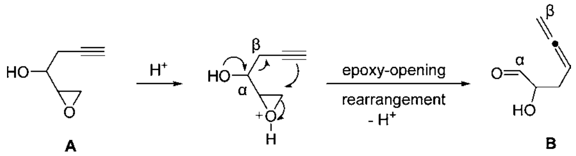
alkynes.[6] This limitation greatly restricts the application of epoxy alkyne, which is an important substance and also an interesting topic in organic synthesis.[7] In continuation of our interest in the development of new methodologies for α-hydroxy epoxide ring-opening,[8] we found the first member of this family that deviates from this requirement, wherein the π-system of one molecule (alkyne) combines with a functional group and has no multiple bonds (epoxide), affording synthetically useful allenes (Scheme 2).[9,10] To the best of our knowledge, there are only a few successful examples of this system.[11] Herein, we report a novel catalytic method for synthesis of allenes via acid-catalyzed skeletal rearrangement of epoxy alkynes. The π-system of the alkyne attacking at the epoxide ring acted as the key step.

Scheme 2



Initially, we started our investigation by using epoxy alkyne **1a** (0.3 mmol), treated with TsOH (5 mol %) in CH_3CN (2 mL) at room temperature. To our delight, the expected allene **2a** (Figure 1)[12] was obtained in 79% yield in 20 min (Table 1, entry 1). Then the catalysis conditions were optimized by changing the catalysts and solvents, as shown in Table 1.[13] Protic acids, including CF_3CO_2H and CH_3SO_3H, also catalyzed this reaction, and the desired product **2a** was obtained in 76% and 77% yields, respectively (entries 2 and 3). When the amount of TsOH was increased to 10 mol %, a satisfying yield of 87% was obtained in 10 min (entry 4). However, when a change was made to other solvents for this reaction, no superior results were obtained (entries 5−7). Lewis acids, such as $AlCl_3$, $AuCl_3$, $FeCl_3$, $BF_3{\cdot}OEt_2$, and $TiCl_4$, were also investigated, and we were pleased to find that similar results were obtained with lower catalyst loading (entries 8−12). Thus the use of TsOH (10 mol %) in CH_3CN (conditions A) and $AlCl_3$ (5 mol %) in CH_2Cl_2 (conditions B) at room temperature were both used as the standard conditions.

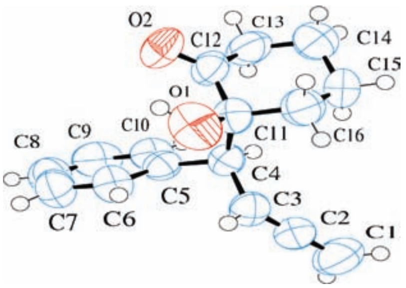
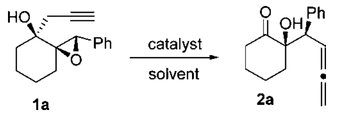


Figure 1. The X-ray structure of **2a**.

Table 1. Optimization of Reaction Conditions[a]



1a **2a**

entry	catalyst (mol %)	solvent	temp, °C	time, min	yield,[b] %
1	TsOH (5)	CH_3CN	rt	20	79
2	CF_3CO_2H (5)	CH_3CN	rt	20	76
3	CH_3SO_3H (5)	CH_3CN	rt	10	77
4	TsOH (10)	CH_3CN	rt	10	87
5	TsOH (10)	CH_2Cl_2	rt	15	77
6	TsOH (10)	toluene	rt	15	81
7	TsOH (10)	THF	rt	15	83
8	$AlCl_3$ (5)	CH_2Cl_2	rt	10	73
9	$FeCl_3$ (5)	CH_2Cl_2	rt	10	71
10	$AuCl_3$ (5)	CH_2Cl_2	rt	10	67
11	$BF_3{\cdot}OEt_2$ (5)	CH_2Cl_2	rt	30	67
12	$TiCl_4$ (5)	CH_2Cl_2	−78	60	66

[a] Reactions were conducted with 0.3 mmol of **1a**, in 2 mL of solvent. [b] Isolated yield.

With the optimal conditions in hand, we investigated more examples. The results are summarized in Table 2. In conditions A, the analogous substrates **1b** and **1c** were prepared and also successfully converted to the corresponding products **2b** and **2c** in 51% and 89% yields, respectively (entries 2 and 3). Successively, the more complex cyclic substrates **1e−g** demonstrated the efficiency of this rearrangement and gave the synthetically valuable allenes **2e−g** in 66−92% yields (entries 5−7). Experiments with acyclic substrates **1h−n**[14] were also examined, and the corresponding products **2h−n** were obtained in 41−65% yields (entries

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(5) (a) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495. (b) Kim, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 67.

(6) (a) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745. (b) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059. (c) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191.

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(8) (a) Shu, X.-Z.; Liu, X.-Y.; Ji, K.-G.; Xiao, H.-Q.; Liang, Y.-M. *Chem.—Eur. J.* **2008**, *14*, 5282. (b) Ji, K.-G.; Shen, Y.-W.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 1275. (c) Ji, K.-G.; Shu, X.-Z.; Chen, J.; Zhao, S.-C.; Zheng, Z.-J.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2009**, *7*, 2501.

(9) (a) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466. (b) Baner, K. *Liebigs Ann.* **l997**, 2005.

(10) (a) *Allenes in Organic Synthesis*; Schuster, H. F., Coppola, G. M., Eds.; John Wiley & Sons: New York, 1984. (b) *The Chemistry of Ketenes, Allenes, and Related Compounds, Part 1*; Patai, S., Ed.; John Wiley & Sons: New York, 1980. (c) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

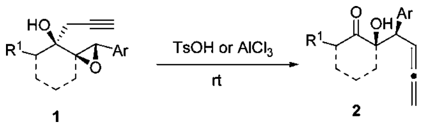
(11) Madhushaw, R. J.; Li, C.-L.; Shen, K.-H.; Hu, C.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2001**, *123*, 7427.

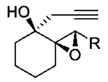
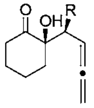
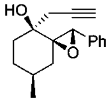
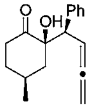
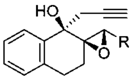
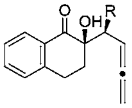
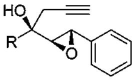
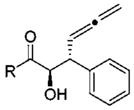
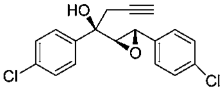
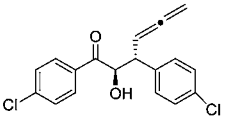
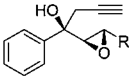
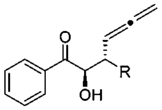
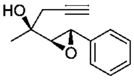
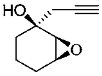
(12) The molecular structure of the corresponding product **2a** was determined by X-ray crystallography (Figure 1). Crystallographic data have been described in the Supporting Information.

(13) For detailed optimization of reaction conditions, see the Supporting Information.

(14) *Syn*/*anti* mixtures of the substrates were used and the ratio was determined by ^1H NMR spectroscopic analysis. For a full explanation and definition of the terms *syn* and *anti* as used herein see: Marson, C. M.; Benzies, D. W. M.; Hobson, A. D. *Tetrahedron* **1991**, *47*, 5491.

Table 2. Transformation of Epoxy Alkynes to Allenes



entry	substrate	R		*syn/anti* [a]	product		conditions A [b]	conditions B [c]
1		C_6H_5	**(1a)**			**(2a)**	20 min, 84% [d]	10 min,68%
2		*p*-$CH_3C_6H_4$	**(1b)**			**(2b)**	3 h, 51%	1.5 h, 42%
3		*p*-ClC_6H_4	**(1c)**			**(2c)**	5 min, 89%	3 min, 85%
4			**(1d)**			**(2d)**	6 h, 60%	2.5 h, 54%
5		C_6H_5	**(1e)**			**(2e)**	10 min, 85%	5 min, 79%
6		*p*- $CH_3C_6H_4$	**(1f)**			**(2f)**	4 h, 66%	1 h, 64%
7		*p*- ClC_6H_4	**(1g)**			**(2g)**	5 min, 92%	3 min, 89%
8		C_6H_5	**(1h)**	10:7		**(2h)**	0.5 h, 66%	
9		*p*-BrC_6H_4	**(1i)**	3:1		**(2i)**	2 h, 43%	
10			**(1j)**	10:7		**(2j)**	1 h, 56%	
11		*p*-ClC_6H_4	**(1k)**	5:1		**(2k)**	0.5 h, 65%	
12		*m*-ClC_6H_4	**(1l)**	2:1		**(2l)**	0.5 h, 58%	
13		*o*-ClC_6H_4	**(1m)**	5:4		**(2m)**	0.5 h, 59%	
14		*m*-$MeOC_6H_4$	**(1n)**	10:7		**(2n)**	1 h, 41%	
15			**(1o)**	5:4			24 h, No product.	
16			**(1p)**				24 h, No product.	

[a] *Syn*/*anti* mixtures of the substrates were used and the ratio was determined by ^1H NMR spectroscopic analysis. [b] Reactions were conducted with 0.3 mmol of **1**, 10 mol % of TsOH in 2 mL of CH_3CN at room temperature. [c] Reactions were conducted with 0.3 mmol of **1**, 5 mol % of $AlCl_3$ in 2 mL of CH_2Cl_2 at room temperature. [d] Isolated yield.

8−14). This transformation followed the same rules under conditions B; however, lower yields were always obtained (entries 1−7).

As seen, various aryl groups R^2 on the epoxy ring were tolerated (entries 1−3). An electron-withdrawing aryl group gave a better result relative to the electron-rich substituent (entries 2 vs. 3 and 6 vs. 7). This might be explained by assuming that an electron-withdrawing group increased the electrophilicity of the intermediate oxonium ions (Scheme 5, **C** and **D**), thus making the alkyne attack a favored process. Substitution on the ring was also tolerated (entry 4). Better results were always obtained when conjugated systems were applied (entries 5−7), whereas acyclic substrates always afforded lower yields of desired products (entries 8−14); this might be due to steric configuration, and *syn*-diastereoisomer favored allene formation (Scheme 5, **E** vs. **F**). Substrates **1o** and **1p** with aliphatic R^1 and R^2 groups afforded no allene product (entries 15 and 16).

An epoxy alkyne with a five-membered ring was investigated under conditions A. However, no desired product was obtained. When Lewis acid was induced, a mixture (10:7) of **2r** and **3r** was isolated in 60% yield under conditions B (Scheme 3).[15] The reason for the formation of **3r** was that the chloride ion attacked epoxide leading to the epoxide ring-opening instead of alkyne. Epoxy alkyne **1s** also afforded the same result (Scheme 3). The same phenomenon was not observed by TLC with other substrates, and it might be caused by the ring strain.

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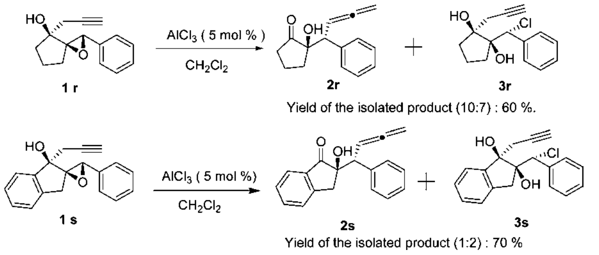
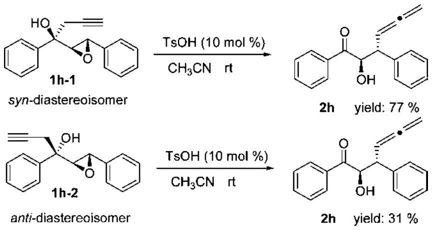
(15) The structure of **3r** was confirmed by X-ray crystallographic analyses, the X-ray structure of **3r** and crystallographic data are described in the Supporting Information. **2r** was confirmed by analysis of ^1H NMR spectroscopy of the mixture and **3r**. The proportion of **2r** and **3r** was confirmed by analysis of ^1H NMR spectroscopy.

Scheme 3. Reactions of **1r** and **1s**



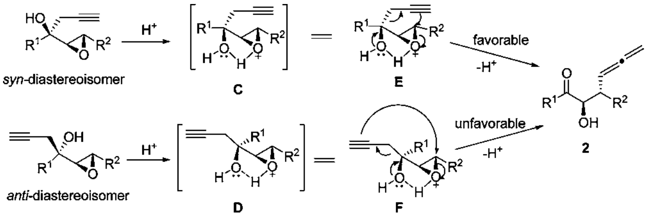
To uncover the stereoselectivity of this transformation, we investigated the reaction of *syn*-isomer **1h-1** and *anti*-isomer **1h-2** under conditions A, respectively (Scheme 4). Only one relative configuration allene product **2h** was obtained determined by NMR. The *syn*-diastereoisomer **1h-1** afforded a better yield (77%) compared to the *anti*-diastereoisomer **1h-2** (31%). These experimental results were consistent with our proposed mechanism.

Scheme 4



With the above experimental results in hand, a possible sequential mechanism of this rearrangement reaction is proposed, as depicted in Scheme 5. Activated by protic acid or Lewis acid, the five-membered-ring intermediates **C** and **D** might be formed. Under the dual role of promoting by hydroxy group and inducing of the activated epoxide ring, a carbon—carbon 3,3-migration leads to the formation of final keto-hydroxyl-allene product **2**. Although the two isomers gave the same product, the stereoselectivity of this transformation was observed based on results in Table 1 and Scheme 4. This observation was also reasoned in Scheme 5. For intermediate **F** from the *anti*-isomer, due to configurational orientation of the alkyne away from the epoxide, its attacking on the carbon of the epoxide ring is hindered, whereas this attacking process is favored for intermediate **E** (Scheme 5, **E** vs. **F**).

Scheme 5. Proposed Mechanism



In conclusion, we developed a new acid-promoted epoxide ring-opening with an alkynyl group. In this reaction, π-alkyne rearranged allene through a carbon—carbon 3,3-migration acted as a nucleophilic reagent. Therefore, a convenient and efficient method for constructing varieties of ready terminal allenes was achieved. We envisioned that this keto-hydroxyl-allene product could be applied to the synthesis of some natural products when proper substrates and catalysts were used.[16] Further investigations on this acid-catalyzed skeletal rearrangement and the application of these keto-hydroxyl-allene products are ongoing.

Acknowledgment. We thank the NSF (NSF-20621091, NSF-20732002) for financial support.

Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and CIF files for **2a** and **3r**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9014199

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[16] (a) Ma, S.-M. *Chem. Rev.* **2005**, *105*, 2829. (b) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257. (c) Widenhoefer, R. S. *Chem.—Eur. J.* **2008**, *14.*, 5382.