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Gold(I)-Catalyzed Synthesis of γ-Hydroxyketones from 5-Allyloxy-1-ynes

Jae Youp Cheong, Donghong Im, Miryeong Lee, Wontaeck Lim, and Young Ho Rhee*

Department of Chemistry, Pohang University of Science and Technology, San-31 Hyojadong, Pohang 790-784, Korea

yhrhee@postech.ac.kr

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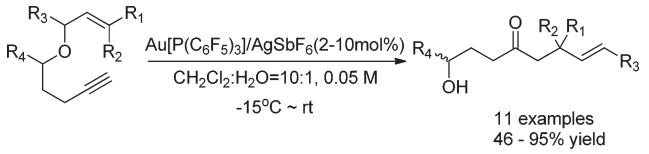
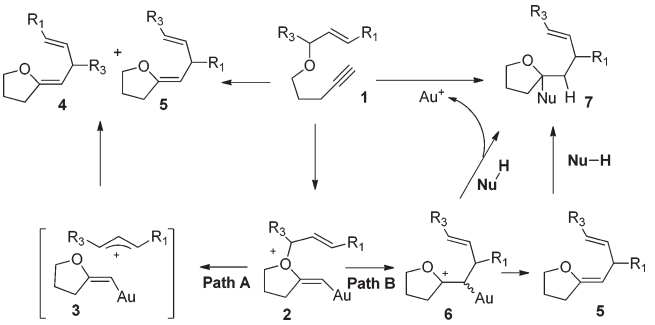


The Au(I)-catalyzed reactions of 5-allyloxy-1-ynes gave various γ-hydroxyketones, via a hydration-terminated domino sequence involving sigmatropic allyl migration as the key event. Moreover, the scope of the sigmatropic allyl transfer was systematically determined.

Domino processes where multiple events are combined in a single transformation have been considered an excellent way to introduce molecular complexity into organic structures with high chemical efficiency.[1] Metal-catalyzed domino reactions initiated by the addition of an X−R bond (X = heteroatom, R = alkyl group) to alkynes offer the unique possibility of installing various substitution patterns in heterocyclic compounds, via the subsequent rearrangement of alkyl groups. Although this sequence has been employed mostly in the carboalkoxylation of phenolic or benzylic ethers,[2] more challenging 5-alkoxy-1-ynes have rarely been employed as a viable substrate.[3] The reaction of 5-allyloxy-1-ynes **1** is particularly interesting because two different types of products can be formed depending upon the mechanism of the reaction (Scheme 1). If the C−O bond scission of the initial alkoxycyclization intermediate **2** is fast, the allylic cation may be formed. The subsequent recombination would generate a mixture of the formal [1,3]-product **4** and [3,3]-product **5** (path A). Alternatively, sigmatropic rearrangement is feasible from the intermediate **2** (path B), which will produce oxocarbenium ion intermediate **6** via concerted migration of the allylic moiety. Although the former pathway has been reported by Fürstner employing Pt catalysts,[2b,c] the latter pathway remains unknown, to our best knowledge.[4] Moreover, development of the Claisen-mediated domino pathways shown in path B would be highly useful from a synthetic viewpoint, because the sigmatropic rearrangement generates a structurally unique skeleton in a highly controlled manner. Although formation of the formal [3,3]-product **5** via demetalation is a plausible process, the proposed domino sequence can be combined with external nucleophiles to provide alternative structure **7**, with or without the involvement of cycloisomerization product **5** as an intermediate.

SCHEME 1. Mechanistic Consideration for the Gold(I)-Catalyzed Synthesis of γ-Hydroxyketones from 5-Allyloxy-1-yne



Because of the importance of the tetrahydrofuran frameworks in various natural products, we originally focused on the formation of **5** via Claisen-mediated pathway. On the basis of our recent study on the gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes,[3b,5] we envisioned that highly electrophilic cationic gold(I) complexes would facilitate this unprecedented tandem alkoxycyclization−sigmatropic process.

A preliminary study using prenyl ether **8** showed an unexpected result. Although the reaction was quickly completed when complex **11a** was employed in combination with $AgSbF_6$ (5 mol %),[6,7] the cycloisomerization product **9** could not be obtained. Instead, we were able to identify a significant amount

(1) For a review on the domino reactions, see: Parsons, P. J.; Penkett, C. S.; Shell, A. *J. Chem. Rev.* **1996**, *96*, 195.

(2) For some recent examples for transition metal-catalyzed carboalkoxylation generating benzylic or phenyl ethers, see: (a) Dube, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (b) Fürstner, A.; Daives, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (c) Fürstner, A; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (d) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473.

(3) (a) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 309. (b) Bae, H. J.; Baskar, B.; An, S. E.; Cheong, J. Y.; Thangadurai, D. T.; Hwang, I.-C.; Rhee, Y. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2263.

(4) For the related study involving aza-Claisen rearrangement, see: Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

(5) For reviews on the gold- and platinum-catalyzed reactions, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *26*, 2. (b) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (d) Hashimi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (e) Jiménez-Núñez, E.; Echavarren, M. *Chem. Commun.* **2007**, 333. (f) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (g) Hashimi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (h) Li, Z.; Brower, C.; He, C. *Chem. Rev.* **2008**, *107*, 3180. (i) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3266. (j) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

(6) For the preparation of complex **11a**, see: Shin, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 1925.

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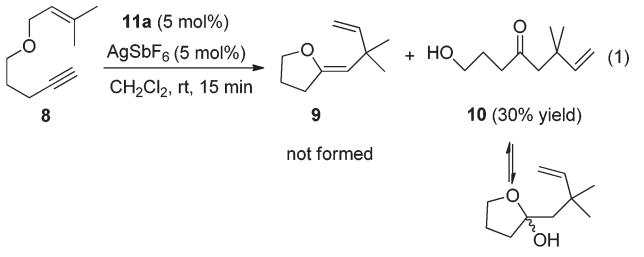
of γ-hydroxyketone **10** (~30% yield) after carefull analysis of spectral data.



Au[P(C6F5)3]Cl — **11a**

Au[P(C6H5)3]Cl — **11b**

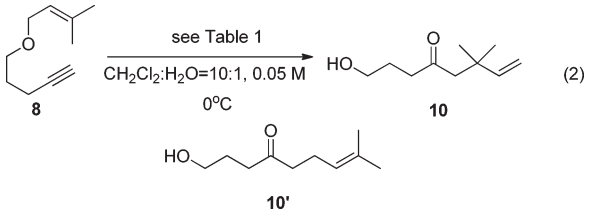
Au[t-Bu2P(o-biphenyl)]Cl — **11c**

We initially rationalized that **10** is formed by the hydration of the cycloisomerization product **9**. However, using anhydrous conditions failed to give **9**, although formation of **10** could be minimized.[8] This result strongly suggests that **10** may be formed via direct hydration of the oxacarbenium ion intermediate (**6** in Scheme 1), rather than the hydration of the cycloisomerization product **9**.

Based on this preliminary study, we turned our attention to the synthesis of γ-hydroxyketone **10** employing a hydration-terminated tandem sequence. A marked increase of the yield occurred simply by adding exogenous water to the reaction mixture (entry 1, Table 1). Use of an electrophilic catalyst **11a** was necessary, because employing less electrophilic gold catalysts **11b** and **11c** significantly dropped the conversion (entries 2 and 3). Reducing the catalyst loading of **11a** to 2 mol % still maintained the catalytic activity with a slight increase in the yield of **10** (entry 4). A significant counteranion effect was also noted. For example, using AgOTf showed significant catalytic activity (entry 5), while employing $AgBF_4$ slowed the reaction (entry 6). Notably, the formal [1,3] product **10′** was not observed even in trace amounts in these optimization studies.[9,10]

Using the optimized conditions shown in entries 1 and 4 of Table 1, various 5-allyloxy-1-ynes were converted into the corresponding γ-hydroxyketones. As can be seen in Table 2, the substitution pattern of the allylic ether moiety had a crucial effect on the rate and yield of the reaction. For example, the reaction of crotyl ether **12** was significantly slower than that of the prenyl ether **8** (entry 1). In this case, higher catalyst loading (5 mol %) was required to give the desired product **13** in 90% yield. On the other hand, the reaction of geranyl ether **14** was completed within 2 min even at −15 °C, when 5 mol % catalyst was used (entry 2). A similar reactivity pattern was seen with substrates

TABLE 1. Optimization of the Reaction Conditions



entry	catalyst (mol %)	time	conversion (%)	yield (%)[a]
1	**11a** (5)/ $AgSbF_6$ (5)	2 min	100	95 (91[b])
2	**11b** (5)/ $AgSbF_6$ (5)	5 h	trace	ND[d]
3	**11c** (5)/ $AgSbF_6$ (5)	5 h	trace	ND[d]
4	**11a** (2)/ $AgSbF_6$ (2)	30 min	100	98 (95[b])
5	**11a** (5)/ AgOTf (5)	5 min	100	90
6	**11a** (5)/ $AgBF_4$ (5)	5 h	30[c]	ND[d]

[a]NMR yield of compound **10** determined by using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield of compound **10**. [c]Determined by the analysis of the ^1H NMR of the crude reaction mixture. [d]Not determined.

bearing an additional alkyl group at the bis-homopropargylic position (entries 3−5). Thus, allyl ether **16** was only slowly converted into the product **17** in moderate 46% yield (entry 3); however, the crotyl ether **18** (entry 4) and the prenyl ether **20** (entry 5) significantly improved the yield of the reaction.[11] As is the case for the substrate **8**, [1,3]-products analogous to **10′** were not observed. This result clearly shows that the sigmatropic pathway is indeed dominating for the substrates possessing no alkyl substituents at the allylic position. It should be emphasized that the sigmatopic rearrangement shown here is unique in that increasing the steric congestion does not slow the reaction.[12−14]

We then investigated the substrate possessing an alkyl substituent at the allylic position (entries 6−10). On the basis of the reactivity pattern of the previous examples, we anticipated that these substrates should be effective toward the gold(I)-catalyzed tandem sequence. Indeed, substrate **22** produced the formal [3,3]-product **23** in reasonable 77% yield with no indication of the formation of the [1,3]-product (entry 6).[15] Increasing the alkyl substitution at the terminal position of the olefin moiety again facilitated the reaction (entry 6 vs entries 7 and 8). Although the example shown in entries 7 and 8 appears to significantly extend the scope of the Claisen-mediated pathway, the cationic pathway cannot be completely excluded because an identical structure would arise by two mechanisms (path A vs path B in Scheme 1). Thus, we tested **28** to rigorously examine the mechanistic issue described in Scheme 1 (entry 9). Unlike the previous examples, the gold(I)-catalyzed reaction of this compound gave a chromatographically inseparable mixture (~25:1 ratio)

(7) For selected examples where the complex **11a** is used, see: (a) Baskar, B.; Bae, H. J.; An, S. E.; Cheong, J. Y.; Rhee, Y. H.; Duschek, A.; Kirsch, S. F.; et al. *Org. Lett.* **2008**, *10*, 2605. (b) An, S. E.; Jeong, J.; Baskar, B.; Lee, J.; Seo, J.; Rhee, Y. H. *Chem.—Eur. J.* **2009**, *15*, 11837. (c) Kim, C.; Bae, H. J.; Lee, J. H.; Kim, H.; Sampath, V.; Rhee, Y. H. *J. Am. Chem. Soc.* **2009**, *131*, 14660. (d) Kang, J.-E.; Shin, S. *Synlett* **2006**, 717. (e) Gung, B. W.; Craft, D. T.; Bailey, L. N.; Kirschbaum, K. *Chem.—Eur. J.* **2010**, *16*, 639. (f) Kim, C.; Lim, W.; Rhee, Y. H. *Bull. Korean Chem. Soc.* **2010**, *31*, 1465. (g) Lee, P. H.; Kim, S.; Park, A.; Chary, B. C.; Kim, S. *Angew. Chem., Int. Ed.* **2010**, *122*, 1. (h) Nieto-Oberhuber, C.; Munoz, M. P.; Lopez, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gomez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677.

(8) In this case, an extensive amount of polymeric compounds was obtained.

(9) Within the detection limit of ^1H NMR analysis.

(10) (a) Using Pt complexes ($PtCl_2$ and $PtCl_4$) showed no conversion. (b) Employing $AgSbF_6$ also showed no conversion.

(11) All the γ-hydroxyketones obtained from studies exist as an open form except for compound **17**, which exists as an ca. 10:1 mixture of the open and cyclized form in $CDCl_3$ solution.

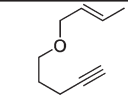
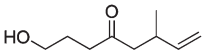
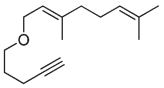
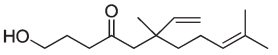
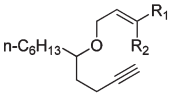
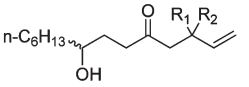
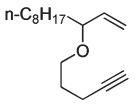
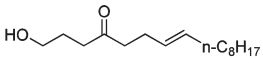
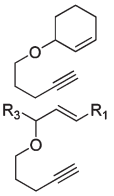
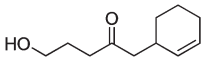
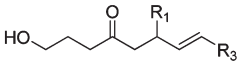
(12) For a review on the Claisen rearrangement, see: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(13) The sigmatropic nature of the allyl shift was further supported by a crossover experiment using a mixture of **14** and **20**, which provides only **15** and **21** without the apparent formation of the crossover products.

(14) A similar structural effect was reported for the aza-Claisen rearrangement, see ref 4.

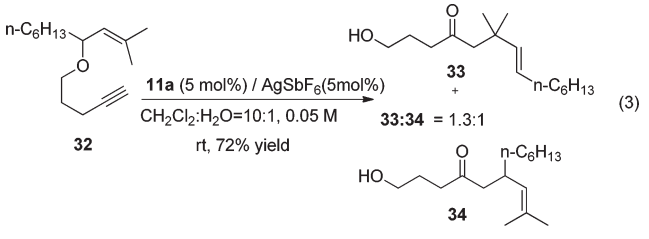
(15) Exclusive formation of the *trans* isomer **23** strongly suggests involvement of the chairlike transition state in the sigmatropic rearrangement. For a related issue in the thermal Claisen rearrangement, see : Nguyen, N. N. M.; Leclere, M.; Stogaitis, N.; Fallis, A. G. *Org. Lett.* **2010**, *12*, 168.

TABLE 2. Scope of the Gold(I)-Catalyzed Formation of γ-Hydroxyketones

entry	Substrate		catalyst (mol%)	time	temp	Product		Isolated yield
1		**12**[a]	5	90 min	rt		**13**	90%
2		**14**	5	2 min	-15°C		**15**	75%
								
3	R_1 = H, R_2 = H	**16**	10	5 h	rt		**17**	46%
4	R_1 = CH_3, R_2 = H	**18**[a]	2	3 h	0°C		**19**	83% [b]
5	R_1 = CH_3, R_2 = CH_3	**20**	2	10 min	0°C		**21**	89%
6		**22**	5	20 min	rt		**23**	77%
7		**24**	5	10 min	0°C		**25**	93%
								
8	R_1 = CH_3, R_3 = CH_3	**26**	5	2 min	0°C		**27**	85%
9	R_1 = n-C_6H_{13}, R_3 = CH_3	**28**	2	10 min	0°C		**29**	85%[c]
10	R_1 = CH_3, R_3 = n-C_6H_{13}	**30**	2	10 min	0°C		**31**	83%[c]

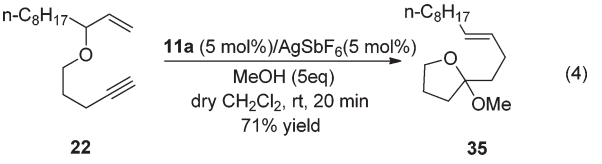
[a]Mixture of olefin isomers was used (E:Z = 5:1). [b]The product was obtained as a diastereomeric mixture (1:1). [c]The product was obtained as an inseparable mixture with a small amount of the isomeric [1,3]-product.

of [3,3]- and [1,3]-product (compound **29** and **31**) in 85% yield (entry 9). Substrate **30**, in which the R_1 and R_3 groups are interchanged from **28**, showed a similar pattern in erms of both yield and the product. Thus, a mixture of the [3,3]-product **31** and the [1,3]-product **29** (ca. 25:1 ratio) was obtained in 83% yield. This result indeed shows that increasing the alkyl substitution promotes the cationic mechanism (path A in Scheme 1). As depicted in eq 3, the effect of alkyl substitution promoting the cationic mechanism is more clearly seen with the substrate **32**. In this case, a nearly equimolar mixture of the [3,3]-product **33** and [1,3]-product **34** was obtained in 72% overall yield.[16]



(3)

Finally, it should be noted that another external nucleophile also can be easily incorporated with the domino alkoxycyclization-Claisen sequence. Thus, 2-alkoxytetrahydrofuan **35** could be obtained in 71% yield by the gold(I)-catalyzed reaction of substrate **22** in the presence of methanol (eq 4).



(4)

In summary, we discovered gold(I)-catalyzed access to synthetically useful γ-hydroxyketones from 5-allyloxy-1-ynes via a hydration-terminated domino sequence. Notably, this study systematically determines the scope of the Claisen pathway in allyl migration. Extrapolation of this tandem sequence to other catalytic cycles, as well as the application to the synthesis of bioactive natural products synthesis, is currently under investigation.

Experimental Section

General Procedure for the Gold(I)-Catalyzed Reaction. To a solution of $AgSbF_6$ (2.5 mg, 0.0073 mmol) in dry CH_2Cl_2 (1 mL)

(16) In contrast to the primary allylic ether **8**, isomeric tertiary allylic ether generated from isoprenol showed no reactivity. Presumably, the initial cyclization is significantly slow because of the steric effect of the alkyl groups.

was added a solution of **11a** (5.6 mg, 0.0073 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred for 10 min. The resulting solution was filtered though a pad of Celite and concentrated. The residue was dried over high vacuum for 2 h and then cooled to 0 °C. To this residue was added the solution of **8** (56 mg, 0.37 mmol) in CH_2Cl_2:H_2O = 10:1 (7.4 mL, precooled to 0 °C). The resulting green solution was stirred for 30 min. Triethylamine (1 mL) was added and the solution was stirred for 5 min. The resulting solution was filtered through a pad of silica and concentrated. The crude oil was purified by flash chromatography on silica gel (eluted with hexane:ethyl acetate = 70:30) to give the compound **10** as a colorless oil (60 mg, 0.35 mmol, 95% yield). R_f 0.08 (hexane:ethyl acetate = 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.77 (quint, J = 6.3 Hz, 2H), 2.03 (br s, 1H), 2.42 (s, 2H), 3.60 (t, J = 6.1 Hz, 2H), 4.90−4.96 (m, 2H), 5.89 (dd, J = 17.6 Hz, J = 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 27.2, 36.6, 41.8, 54.5, 62.4, 111.1, 147.3, 210.8; IR (cm^{-1}) ν 3397, 2966, 1640, 1456, 1371; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170. 1308.

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Supporting Information Available: Experimental procedures for catalytic formation of **10**, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.