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# Au-Catalyzed Cyclization of Monopropargylic Triols: An Expedient Synthesis of Monounsaturated Spiroketals

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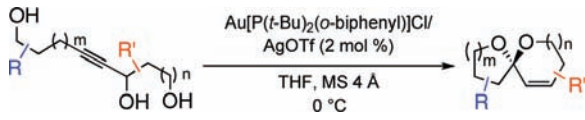
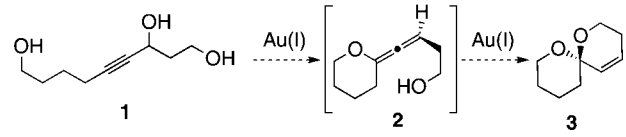
## ABSTRACT




**The gold-catalyzed cyclization of monopropargylic triols to form olefin-containing spiroketals is reported. The reactions are rapid and high yielding when 2 mol % of the catalyst generated in situ from Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl and AgOTf is employed in THF at 0 °C. A range of differentially substituted triols leading to substituted 5- and 6-membered ring spiroketals were prepared and function well in the reaction.**

Spiroketals are a common motif found in many structurally interesting and biologically significant natural products.[1] In addition to the fully saturated analogues, a number of families of natural products with olefin-containing spiroketals have been reported. Select examples include okadaic acid,[2] avermectin,[3] aigialospirol,[4] and the spirastrellolides.[5] These monounsaturated spiroketals with the general structure **3** have classically been prepared by the dehydration of α,β-unsaturated keto diols or *cis*-olefin-containing hemiacetals with a pendant-free alcohol.[1,6] As part of our program aimed at devising new gold-catalyzed dehydrative transformations of unsaturated alcohols, we began to explore the formation of monounsaturated spiroketals **3** from monopropargylic triols **1**.

Homogeneous catalysis using gold salts has emerged as a powerful new area in organic synthesis, with many interesting and useful new transformations appearing at an extremely rapid pace.[7] Based on our recent work involving the dehydrative cyclization of allylic diols,[8] we hypothesized that cyclic alkoxyallenes such as **2**[9] could be formed from **1** and, by the action of the same gold catalyst, cyclize to form the desired monounsaturated spiroketals **3**.




(1) For reviews on spiroketals, see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (d) Jacobs, M. F.; Kitching, W. B. *Curr. Org. Chem.* **1998**, *2*, 395. (e) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (f) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406.

(2) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469.

(3) Miller, T. W.; Chaiet, L.; Cole, D. J.; Cole, L. J.; Flor, J. E.; Goegelman, R. T.; Gullo, V. P.; Joshua, H.; Kempf, A. J.; Krellwitz, R. L.; Monaghan, R. L.; Ormond, R. E.; Wilson, K. E.; Albers-Schonberg, n/a.; Putter, I. *Antimicrob. Agents Chemother.* **1979**, *15*, 368.

(4) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457.

(5) Warabi, K.; Williams, D. E.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 508.

(6) For leading references on additional methods, see: (a) Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. (b) Wincott, F. E.; Danishefsky, S. J.; Schulte, G. *Tetrahedron Lett.* **1987**, *28*, 4951. (c) Whitby, R.; Kocienski, P. *Tetrahedron Lett.* **1987**, *28*, 3619. (d) Whitby, R.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1987**, 906. (e) Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125. (f) Tu, Y.-Q.; Bryiel, K. A.; Kennard, C. H. L.; Kitching, W. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1309. (g) Figueroa, R.; Hsung, R. P.; Guevarra, C. G. *Org. Lett.* **2007**, *9*, 4857.

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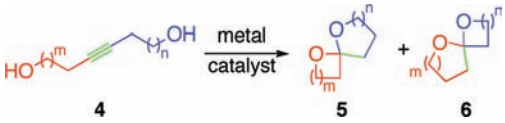
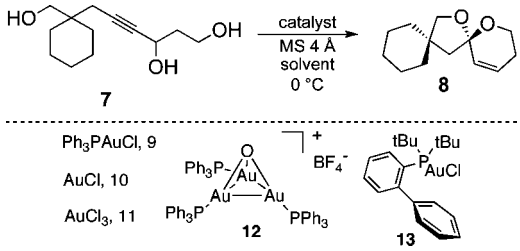
Previous reports of transition-metal-catalyzed spiroketalization of alkynyl diols to form saturated spiroketals indicate that ring size preference can be a challenging issue, forming mixtures of **5** and **6** from **4**.[10] Our route was particularly attractive because the olefin would be precisely placed according to the general scheme, leaving no ambiguity in the sizes of the rings formed, and the substrates would be easily prepared using numerous approaches. If successful, this method would provide rapid access to the desired compounds and open a new Au-catalyzed reaction pathway of propargyl alcohols.




**4** **5** **6**

To explore the feasibility of this idea, the triol **7** was prepared and treated with the cationic gold(I) catalyst system generated from 5 mol % of $Ph_3PAuCl$/AgOTf in $CH_2Cl_2$ at 0 °C (Table 1, entry 1). Gratifyingly, the desired spiroketal

**Table 1.** Optimization Studies




**7** **8** **12** **13**

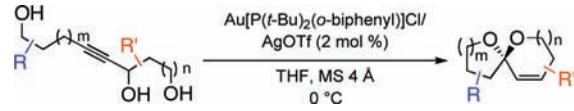
| entry | catalyst | additive | loading[a] (mol %) | solvent | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | **9** | AgOTf | 5 | $CH_2Cl_2$ | 6 | 59 |
| 2 | **9** | AgOTf | 5 | THF | 1.5 | 85 |
| 3[b] | **9** | AgOTf | 1 | THF | 24 | 60 |
| 4 | **10** | | 2 | THF | 0.5 | 51 |
| 5 | **11** | | 2 | THF | 0.5 | 77 |
| 6 | **12** | | 2 | THF | 24 | 26 |
| 7 | **13** | AgOTf | 5 | THF | 1.75 | 91 |
| 8 | **13** | AgOTf | 2 | THF | 1.75 | 88 |
| 9[c] | **13** | AgOTf | 2 | THF | 30 | 81 |
| 10 | **13** | | 2 | THF | 48 | 0 |
| 11 | | AgOTf | 2 | THF | 48 | 0 |
| 12[d] | | TfOH | 2 | THF | 48 | 0 |

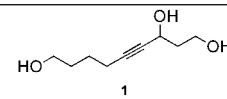
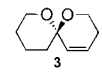
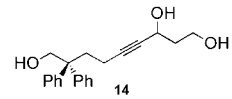
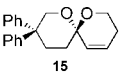
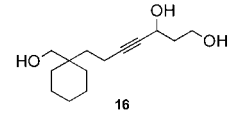
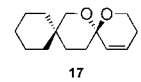
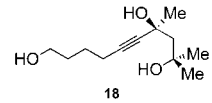
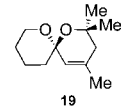
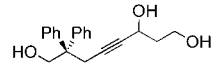
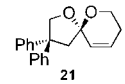
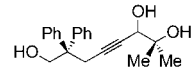
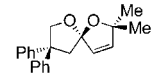
[a] Loading of both catalyst and additive (1:1). [b] 29% of triol **7** was recovered. [c] Molecular sieves omitted. [d] 70% of triol **7** was recovered.

**8** was obtained in 59% yield after 6 h. Using THF as solvent, the yield increased to 85% and the reaction time decreased to 1.5 h (entry 2), but the catalyst loading could not be reduced (entry 3). Although gold salts **9**−**13** all catalyzed the reaction, from the results it was clear that **13** was superior giving the highest yield in the shortest time. Additionally, the loading could be lowered to 2 mol % with minimal effect on the yield (entry 8). Control experiments demonstrated that molecular sieves and AgOTf were necessary (entries 9 and 10) and provided evidence that the cationic gold(I) complex, not AgOTf or TfOH alone, was the catalytically active species (entries 11 and 12).

With the optimal conditions established, the substrate scope was then examined (Table 2). The 1,7-dioxaspiro[5.5]-

**Table 2.** Reaction Scope




| entry | substrate[a] | product | time (min) | yield (%) |
|---|---|---|---|---|
| 1 |  **1** |  **3** | 60 | 81 |
| 2 |  **14** |  **15** | 25 | 81 |
| 3 |  **16** |  **17** | 40 | 83 |
| 4 |  **18** |  **19** | 80 | 80 |
| 5[b] |  **20** |  **21** | 35 | 99 |
| 6[c,d] |  **22** |  **23** | 60 | 75 |

[a] All triols were used in racemic form. [b] Reaction temperature = 23 °C. [c] 5 mol % of catalyst. [d] Reaction temperature = 45 °C.

undec-4-ene ring system is likely the most important olefin-containing spiroketal for natural product synthesis. Using these conditions, **3** and substituted derivatives **15** and **17** were smoothly formed in greater than 80% yield (Table 2, entries 1−3). As would be needed for okadaic acid, a trisubstituted alkene was easily prepared (entry 4), and the other combinations of 5- and 6-membered ring spiroketals **21** and **23** also proved to be readily available (entries 5 and 6).

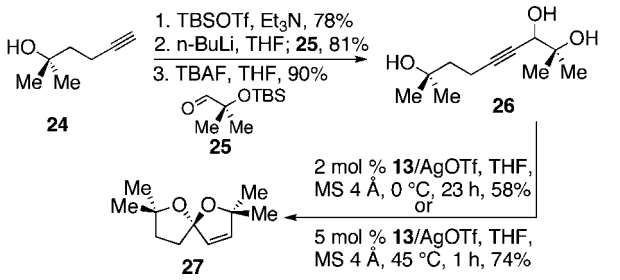
Since more highly substituted substrates would likely react at different rates, it was important to further explore the sterics in more demanding substrates. The cyclization of two

(7) For recent reviews, see: (a) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (b) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3366. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(8) (a) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (b) Aponick, A.; Biannic, B. *Synthesis* **2008**, *20*, 3356.

tertiary alcohols may be predicted to be difficult based on the proximity of steric bulk to the nucleophilic oxygens. To test this substitution pattern and demonstrate the utility of the method we sought to prepare the natural hop oil extract **27** (Scheme 1).[11]

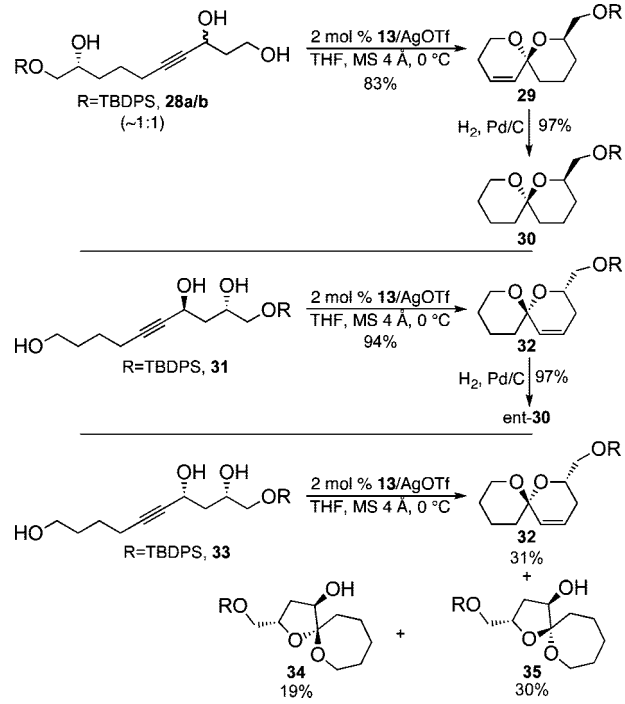
**Scheme 1.** Synthesis of the Natural Hop Extract **27**




A family of naturally occurring 1,6-dioxaspiro[4.4]-nonanes, non-3-enes (such as **27**), and nona-3,8-dienes have been reported.[6f] Spiroketal **27** was originally identified after extraction from a Japanese hop oil in 1967[11a] and later from pilsner beer.[11b] Our synthesis begins from **24** (Scheme 1), prepared by reaction of excess methylmagnesium bromide with the corresponding ethyl ester.[12] Protection of the tertiary alcohol as its silyl ether followed by deprotonation of the alkyne and addition to the aldehyde **25**[13] then provided the cyclization precursor **26** after deprotection. As was anticipated, the Au-catalyzed spiroketalization of **26** was more difficult than less sterically hindered substrates. Using the standard conditions, the reaction took 23 h and afforded **27** in 58% yield. Fortunately, the rate and yield were improved by using 5% catalyst loading at 45 °C to give the simple natural product in 74% yield demonstrating that highly substituted spiroketals are readily prepared by this method.

It was also of interest to determine to what extent the propargylic alcohol stereochemistry might influence the reaction of substrates bearing an additional stereogenic center. To this end, **28** was prepared from TBDPS-protected (*S*)-glycidol as an approximately 1:1 mixture of diastereomers as determined by HPLC (Scheme 2).[14] When this mixture was exposed to the standard reaction conditions, **29** was formed in 83% yield. The relative configuration of the spiroketal was determined by hydrogenation of the double bond and comparison to the previously reported data for **30**.[15] Since both diastereomers **28a/b** give the same product, with this substrate the relative configuration of the propargyl alcohol apparently has no influence on the course of the reaction.[16]

**Scheme 2.** Chirality in the Au-Catalyzed Spiroketalizations




Additionally, the triols **31** and **33** were prepared from malic acid[17] and tested in the reaction (Scheme 2). Exposure of **31** to the standard conditions smoothly provided the expected product **32** in 94% yield. The *syn*-diastereomer **33** showed similar reactivity but unexpectedly gave **34** and **35** in addition to the desired spiroketal **32**. Although it was unclear why the selectivity was affected by this change in substitution, we hypothesized that the order of the cyclization events may have significant influence on the outcome of the reaction.

Based on our previous work,[8] we initially envisioned that this transformation would involve an allene intermediate

(9) In a series of seminal reports, Kociensky has previously reported the preparation, isolation, and cyclization of allenol ethers, which are described as labile compounds. For leading references, see refs 6c and 6d.

(10) For leading references on transition-metal-catalyzed spiroketalization, see: (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (c) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279. (d) Dieguez-Vazquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 209.

(11) (a) Naya, Y.; Kotake, M. *Tetrahedron Lett.* **1967**, *8*, 1715. (b) Tressl, R.; Friese, L.; Fendesack, F.; Koppler, H. *J. Agric. Food Chem.* **1978**, *26*, 1422.

(12) Amos, R. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1978**, *33*, 555.

(13) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837.

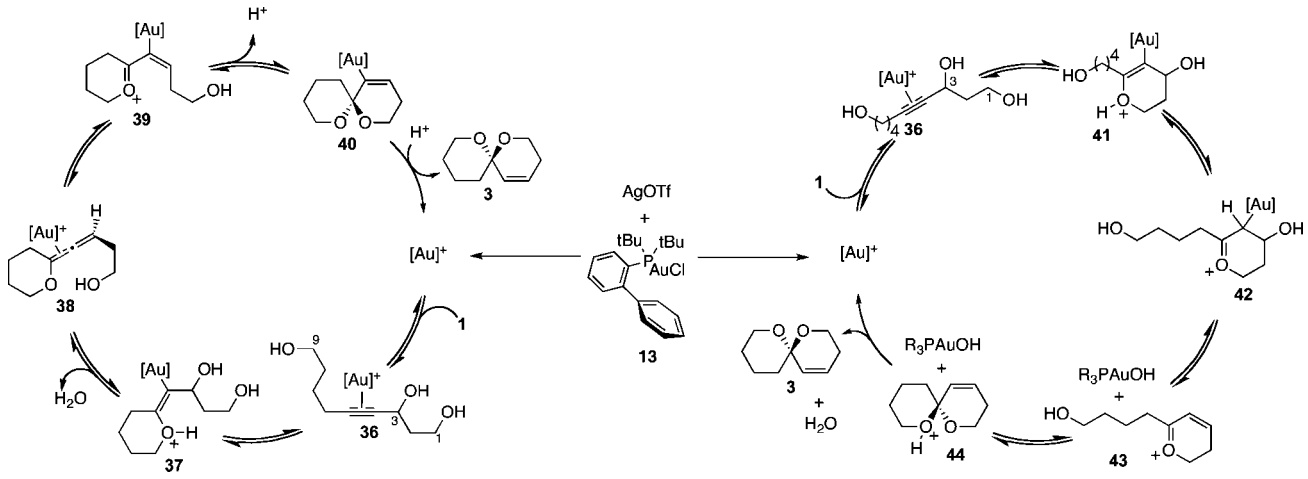
(14) Diastereomers **28a/b** are indistinguishable by both $^{1}$H and $^{13}$C NMR. Proof of this was obtained by Mitsunobu reaction and deprotection. A mixture of the starting material and product were indistinguishable. HPLC analysis, while not completely resolved, showed two peaks in ~1:1 ratio. See the Supporting Information for full details.

(15) Conway, J. C.; Quayle, P.; Regan, A. C.; Urch, C. J. *Tetrahedron* **2005**, *61*, 11910.

(16) To rule out any discrepancies in the event that the material was not an exact 1:1 mixture, the reaction was performed on substrate obtained after Mitsunobu inversion of the propargylic alcohol and identical results were obtained.

(17) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1147.

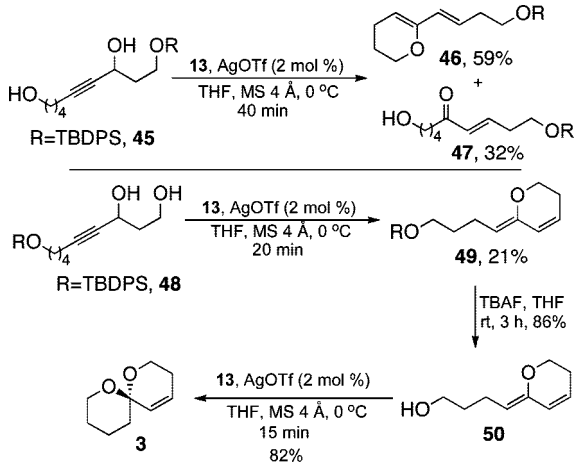
**Scheme 3.** Catalytic Cycle




(e.g., **2**), but cyclization of either of the terminal alcohols may be possible. A probable catalytic cycle is illustrated in Scheme 3. For the reaction to proceed through an allene intermediate, **36** is formed by complexation with the cationic gold complex generated from **13** and AgOTf. Nucleophilic addition of the pendent C9 hydroxyl group and loss of water then gives **39** after electrophilic addition of the catalyst via the Au-complexed allenol **38**.[18] The free C1 hydroxyl group subsequently adds to the oxocarbenium to provide **40** and the product **3** after protiodeauration. If the C1 alcohol preferentially cyclizes, intermediate **41** would be produced. Proton transfer would then give $\beta$-hydroxy Au complex **42** which may first eliminate to form **43** and cyclize to **44** or alternatively first cyclize then eliminate, also forming **44** and **3** after deprotonation.

To gain insight on the feasibility of cyclizing the terminal alcohols, the C1 and C9 monoprotected diols **45** and **48** were prepared and exposed to the reaction conditions (Scheme 4).

**Scheme 4.** Control Experiments




Cyclization of **45** provided **46** and the Meyer Schuster rearrangement[18] product **47** in a combined 91% yield. These products likely arise by further reaction of an intermediate such as **38** when the C1 alcohol is not available. Additionally, treatment of **48** under the reaction conditions yielded **49**,[19] albeit in 21% yield. Deprotection and re-exposure of the product to the reaction conditions gave the expected spiroketal **3**. These data suggest that it is possible for both pathways to be operative in the reaction. Spiroketals **34** and **35** may be the result of a competive 5-exo cyclization when the C1 alcohol cyclizes first, although this can be completely supressed by using the *anti*-diol **31** to obtain the same product.

In conclusion, a new mode of reactivity of propargyl alcohols has been reported that enables a facile preparation of highly useful monounsaturated spiroketals from propargylic triols by action of the cationic gold(I) complex generated from Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl and AgOTf. The reactions are rapid and generally high yielding, providing a concise synthesis of useful building blocks in short order. Further studies on the reaction mechanism and use of the method in natural product synthesis are underway and will be reported in due course.

**Acknowledgment.** We gratefully acknowledge the University of Florida, the Herman Frasch Foundation (647-HF07), and the donors of the Petroleum Research Fund (47539-G1) for their generous support of our programs.

**Supporting Information Available:** Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802491M

(18) A gold-complexed ketene acetal was recently proposed as an intermediate in the Au-catalyzed Meyer Schuster rearrangement. See: (a) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949. (b) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.

(19) The enol ether olefin geometry is assumed based on the trans hydroalkoxylation mechanism typically presented for Au-catalyzed reactions. A single olefin isomer was obtained.