J|A|C|S COMMUNICATIONS

Published on Web 06/02/2006

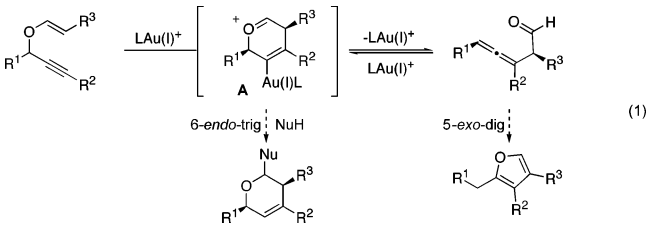
# Gold(I)-Catalyzed Synthesis of Dihydropyrans

Benjamin D. Sherry, Lisa Maus, Brian Ngo Laforteza, and F. Dean Toste*

*Center for New Directions in Organic Synthesis, Department of Chemistry, University of California, Berkeley, California 94720*

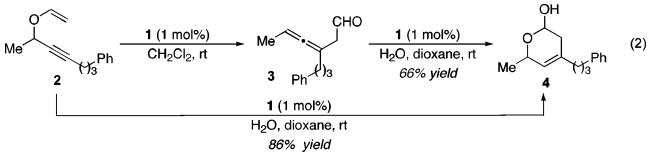
Received February 24, 2006; E-mail: fdtoste@uclink.berkeley.edu

The stereoselective preparation of pyran-containing molecules is a continuing challenge in organic synthesis.[1] Cascade sequences that afford the pyran framework from an acyclic precursor, with the concurrent installation of multiple stereocenters, offer a particularly attractive approach.[2,3] Our recent finding of a gold(I)-catalyzed propargyl Claisen rearrangement[4] prompted us to consider nucleophilic addition to the proposed oxocarbenium intermediate (**A**)[5] as a complimentary method for the stereoselective synthesis of dihydropyrans (eq 1). We anticipated that formation of the $\beta$-allenic aldehyde could be competitive with the trapping of **A**; however, **A** may be re-formed by subsequent 6-*endo*-trig heterocyclization of the aldehyde onto the allene. To execute this tandem propargyl Claisen rearrangement/heterocyclization, the Au(I) complex must catalyze two distinct reactions by sequential activation of an alkyne and an allene.[6,7]




(1)

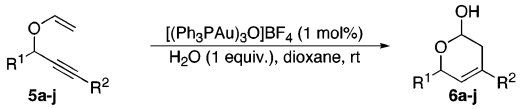
A fundamental obstacle to accessing pyrans by this approach is the tendency of allenes to undergo preferential 5-*exo*-dig cyclizations (eq 1).[7,8] Therefore, at the outset of this work, we sought to define a system wherein cyclization would occur with the opposite regiochemical outcome. Subjecting propargyl vinyl ether **2** to our previously reported conditions for the $[(Ph_3PAu)_3O]BF_4$ (**1**)-catalyzed propargyl Claisen rearrangement led to formation of expected allenic aldehyde **3**.[4a] Gratifyingly resubjecting **3** to the Au(I) catalyst, but in wet dioxane[9] rather than methylene chloride, led to formation of desired 2-hydroxy-3,6-dihydropyran **4**. Confident that heterocyclization could follow the desired 6-*endo*-trig pathway, the Claisen/heterocyclization cascade for the synthesis of pyrans directly from **2** was examined. To this end, reaction of propargyl vinyl ether with 1 mol % of Au(I) catalyst **1** in wet dioxane led to formation of desired pyran **4** in 86% yield.

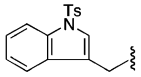



(2)

Having demonstrated the efficient generation of pyrans directly from an enol ether starting material, we set out to define the scope of this Au(I)-catalyzed reaction (Table 1). Substitution at the alkyne terminus was well tolerated, encompassing linear (entries 1, 2, and 6−10), branched (entry 5), and cyclic groups (entries 3 and 4). Additionally, primary tosylate (entry 1) and nitrile (entry 2) were compatible with the Au(I) catalyst. While terminal alkynes are viable substrates for the gold(I)-catalyzed Claisen rearrangement,[4a]

***Table 1.*** Au(I)-Catalyzed Pyran Synthesis

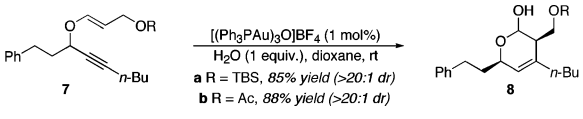



| entry | cmpd | $R^1$ | $R^2$ | yield[a] |
|---|---|---|---|---|
| 1 | **a** | $Ph(CH_2)_2$ | $(CH_2)_4OTs$ | 89% |
| 2 | **b** | $Ph(CH_2)_2$ | $(CH_2)_4CN$ | 88% |
| 3 | **c** | $Ph(CH_2)_2$ | *c*-$C_3H_5$ | 92% |
| 4 | **d** | $Ph(CH_2)_2$ | *c*-$C_6H_{11}$ | 80% |
| 5 | **e** | $Ph(CH_2)_2$ | *t*-Bu | 60% |
| 6 | **f** | *i*-Pr | $(CH_2)_3Ph$ | 90% |
| 7 | **g** | Bn | *n*-Bu | 95% |
| 8 | **h** | $TBSOCH_2$ | *n*-Bu | 77% |
| 9 | **i** | $(Me)_2CCH(CH_2)_2$ | *n*-Bu | 92% |
| 10 | **j** |  | *n*-Bu | 83% |

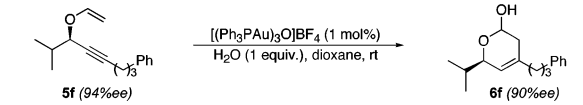
[a] Isolated as a 1−1.3:1 mixture of anomers after purification by column chromatography.

they failed to undergo the subsequent heterocyclization to deliver useful yields of the desired pyran product.[10] The propargyl position was also tolerant of substitution, including linear, branched, and oxygenated substituents (entries 6−8). Furthermore, an electron-rich alkene (entry 9) and *N*-tosyl indole (entry 10)-derived substrates showed high selectivity for the desired pyran formation.

We have previously demonstrated that the gold(I)-catalyzed propargyl Claisen rearrangement proceeds to afford allenes with excellent diastereocontrol and chirality transfer from the propargyl ether stereocenter. On the basis of these results, we hypothesized that the gold(I)-catalyzed reaction might provide a stereoselective synthesis of pyrans. Gratifyingly, (*E*)-1,2-disubstituted enol ethers rearranged stereoselectively to give 3,6-*syn*-substituted pyrans as a 4−6:1 mixture of anomers (eq 3).[11] Moreover, gold(I)-catalyzed rearrangement of enantioenriched ether **5f** affords pyran **6f** with only a minor decrease in the enantiomeric excess.[12]




(3)



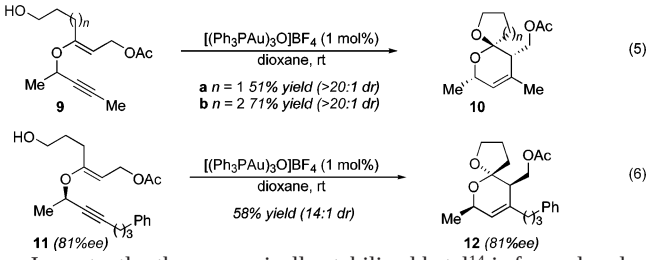

(4)

We envisioned that replacing water with a pendant alcohol as nucleophile might provide a stereoselective entry into spiroketals.[6h,13] To this end, 5,6- (**10a**) and 6,6-spiroketals (**10b**) were generated in good yield and with excellent diastereocontrol from the reaction of alcohols **9a**,**b** with 1 mol % of Au(I)−oxo catalyst **1**. Furthermore, treatment of enantiomerically enriched propargyl vinyl ether **11** led to the formation of spiroketal **12** with complete chirality transfer. Therefore from a linear precursor, in a single step, the

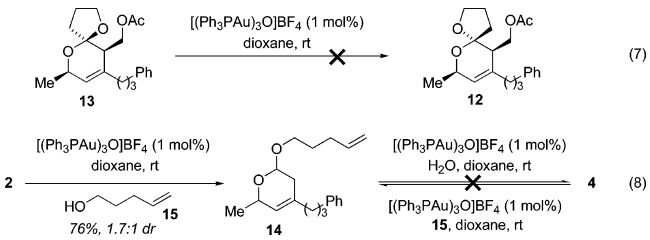


10.1021/ja061344d CCC: $33.50 

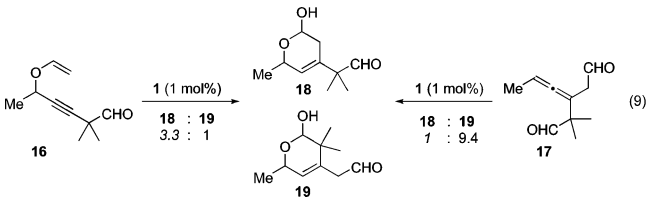
bicyclic spiroketal framework is established with complete stereocontrol over three centers and an alkene functional group in the product that could be engaged in post-cyclization diastereoselective transformations.




Importantly, the anomerically stabilized ketal[14] is formed under kinetic control, as indicated by the observation that resubjecting the minor diastereomer **13** to the reaction conditions did not result in isomerization to the major isomer **12**. Additionally, subjecting hemiacetal **4** or acetal **14** to the optimized reaction conditions in the presence of alcohol **15** or water, respectively, led to no equilibration of these two compounds (eq 8).




On the basis of these results, we envision two plausible pathways for this transformation. Both initiate by Au(I) coordination to the alkyne and addition of the pendant enol ether to afford cationic intermediate **A** (eq 1). In one case, intermolecular trapping of **A** by water or alcohol generates the pyran directly, after protonation of the vinyl gold intermediate. Alternatively, Grob-type fragmentation of **A** to an allenic aldehyde, followed by 6-*endo*-trig addition of the aldehyde, regenerates **A**, which can be trapped by water or alcohol.[15] To investigate this hypothesis, propargyl vinyl ether **16** bearing a pendant aldehyde was prepared. Subjecting **16** to the optimized reaction conditions led to a 3.3:1.0 mixture of **18**:**19**. Alternatively, when dialdehyde **17** was subjected to the Au(I) catalyst, a 1.0:9.4 mixture of **18**:**19** was obtained. Taken together, these results suggest a mechanism wherein fragmentation of **A** occurs at a rate slower than, but competitive with, direct nucleophilic trapping (eq 9).




In conclusion, we have developed a gold(I)-catalyzed method for the stereocontrolled synthesis of 2-hydroxy-3,6-dihydropyrans from propargyl vinyl ethers. This reaction is amenable to the synthesis of spirocyclic compounds from appropriately functionalized precursors. Efforts aimed at elucidating the mechanism of this transformation and applications of this methodology in natural product synthesis are ongoing and will be reported in due course.

**Acknowledgment.** We gratefully acknowledge the University of California, Berkeley, NIHGMS (R01 GM073932-01), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, Eli Lilly & Co., Pfizer, and AstraZeneca for financial support. B.D.S. thanks Eli Lilly & Co. for a graduate fellowship. L.M. thanks the German National Academic Foundation.

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

## References

(1) (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113.

(2) For recent examples of pyran synthesis using tandem reactions, see the following. Oxonia Cope−Prins: (a) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662. (b) Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939. Mukaiyama−Michael: (c) Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044. Alkyne−enone coupling/Michael addition: (d) Trost, B. M.; Yang, H.; Wuitschik, G. *Org. Lett.* **2005**, *7*, 4761. Cycloisomerization/hydroalkoxylation: (e) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949. Cyclization/addition: (f) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456. Mukaiyama aldol/Prins: (g) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420.

(3) For reviews concerning tandem reactions, see: (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York, 1992. (c) Hall, N. *Science* **1994**, *266*, 32. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(4) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (b) Grissom, J. W.; Kilingberg, D.; Huang, D.; Slattery, B. J. *J. Org. Chem.* **1997**, *62*, 603.

(5) For Au(III)-catalyzed generation and trapping of cationic intermediates, see: (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (b) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *125*, 10921. (c) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3862. (d) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091.

(6) For some recent examples of alkyne activation by Au(I) complexes, see: (a) Shi, X.; Gorin, D. J.; Toste F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (b) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (c) Nieto-Oberhuber, C.; López, S.; Munoz, M. P.; Cardenas, D. J.; Bunel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (e) Nevado, C.; Echavarren, A. M. *Chem.−Eur. J.* **2005**, *11*, 3155. (f) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (g) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (h) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem.* Soc. **2005**, *127*, 9976. (i) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (j) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (k) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (l) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112.

(7) For allene activation by Au(I), see: (a) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (c) Morita, N.; Krause, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1897. For allene activation by Au(III), see: (d) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (e) Hoffmann-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537. (f) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (g) Kang, J.-E.; Lee, E.-S.; Park, S. I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431. (h) Zhou, C.-Y.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 325. For reviews of additions to allenes, see: (i) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (j) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12.

(8) (a) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (b) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151.

(9) Reaction in $CH_2Cl_2$ gave only allenyl aldehyde **2** even the presence of water. THF and dioxane afforded the desired pyran in 14 and 4 h, respectively. Reactions in DME returned only starting material.

(10) Gold(I)-catalyzed reaction of a terminal alkyne (Table 1, **5** $R^1$ = Ph-$(CH_2)_2$, $R^2$ = H) afforded a 1:1.6:0.5 ratio of the desired dihydropyran: furan:[8a]an unidentified aldehyde.

(11) Relative stereochemistry was ascertained through nOe analysis; see Supporting Information for details.

(12) The enantiomeric excess of pyran **6f** was determined after in situ reduction to the corresponding allylic alcohol (see Supporting Information for details).

(13) (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (c) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. In *Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1992; Vol. 8, p 533. (d) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(14) (a) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. (b) Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75*, 6.

(15) An alternative mechanism in which gold(I) catalyzes the addition of the hemiacetal, not the aldehyde, to the allene is also possible. See: (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Nilsen, N. O.; Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand. B* **1987**, 459.

JA061344D