ORGANIC LETTERS

2006
Vol. 8, No. 9
1957−1959

# Gold(I)-Catalyzed Stereoselective Formation of Functionalized 2,5-Dihydrofurans

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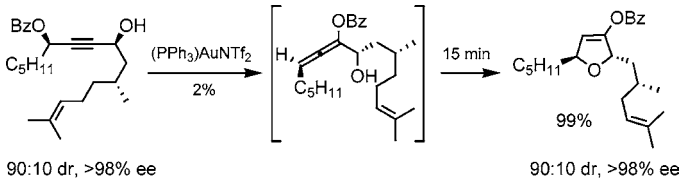
**Received March 20, 2006**

## ABSTRACT

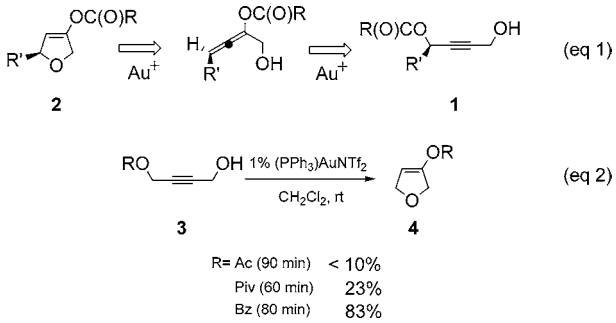



**A study concerning the gold(I)-catalyzed rearrangement of butynediol monobenzoates into functionalized 2,5-dihydrofurans is described. The mild reaction conditions employed allow the efficient and rapid stereoselective synthesis of a variety of 2,5-dihydrofurans via a sequence of two gold(I)-catalyzed isomerization steps.**

2,5-Dihydrofurans and their derivatives are structural motifs that are frequent in a wide variety of natural products exhibiting interesting biological activity.[1] As a consequence, the development of practical synthetic routes to access such structures is of major interest.

In this respect, Krause and co-workers have recently reported that gold(III) chloride efficiently catalyzed the cyclization of allenols to polysubstituted 2,5-dihydrofurans.[2] Since it has been recently shown that gold(I) complexes catalyzed the rearrangement of propargylic esters into allenes,[3] we surmised that a suitable propargylic ester **1** might be a valuable precursor for the synthesis of 2,5-dihydrofuran **2** through a gold-catalyzed sequence of allene formation and cycloisomerization (Scheme 1, eq 1).[4,5] This approach would be especially advantageous because the corresponding chiral substrates are easily accessible, allowing perhaps an enantioselective synthesis of 2,5-dihydrofurans.

**Scheme 1.** Synthetic Approach to Functionalized 2,5-Dihydrofurans




Compounds of type **3** were first chosen as model substrates to validate this approach (Scheme 1, eq 2). Among the esters tested, the benzoate derivative was the best precursor. It was rearranged in the presence of 1% of $(Ph_3P)AuNTf_2$ in dichloromethane to afford the desired 2,5-dihydrofuran **4** in 83% yield.[6] In contrast, the acetate and pivalate gave very poor results.

(1) For selected reviews, see the following. Polyether antibiotics: Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2474. Marine polyethers: Fernandez, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *23*, 26−78. Marine natural products: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *17*, 235−246.

(2) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537−2538. See also: Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121−4123.

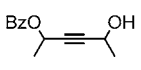
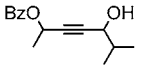
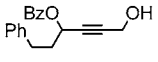
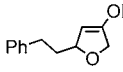
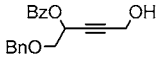
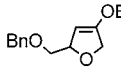
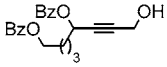
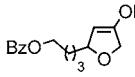
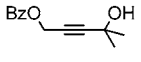
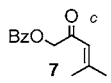
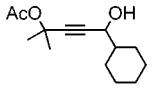
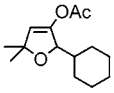
(3) (a) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805. (c) Ag catalysis: Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280−2282.

10.1021/ol0606839 CCC: $33.50 
**Published on Web 03/30/2006**

The reaction proved to be quite general and various substituted butynediol monobenzoates **5a**−**g** reacted using 2% of $(Ph_3P)AuNTf_2$ as the catalyst to furnish the corresponding 2,5-dihydrofurans **6a**−**g** in generally high yields (69−99%) (Table 1).[7] The presence of extra protected alcohols was tolerated. The time required to reach completion was in most cases shorter than 1 h. Mono- (entry 6), di- (entries 1−5), and trisubstituted (entry 7) propargylic esters reacted with the same efficiency, and no noticeable difference in reactivity was observed when primary or secondary alcohols were used. The moderate yield obtained in the case of substrate **5f** was due to the competitive formation of enone **7** arising from a gold(I)-catalyzed Rupe-type reaction.[8]

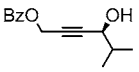
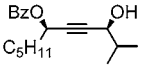
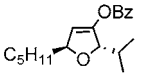
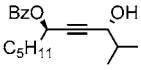
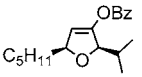
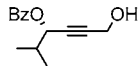
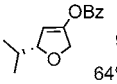
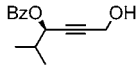
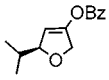
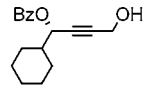
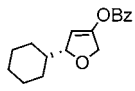
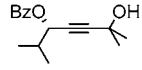
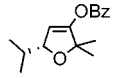
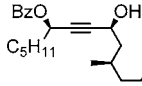
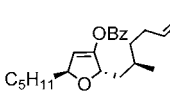
Various enantioenriched butynediol monobenzoates **8a**−**h** were next synthesized according to the procedure[9] developed by Carreira and co-workers and subjected to the gold(I)-catalyzed rearrangement using the same experimental conditions. As attested by the results compiled in Table 2, these were also converted into the corresponding 2,5-dihydrofurans **9a**−**h** in high yields (83−99%). Furthermore, enantioenriched alcohol **8a** furnished compound **9a** without loss of

**Table 1.** Au(I)-Catalyzed Synthesis of 2,5-Dihydrofurans **6a**−**g**[a]

| entry | substrate | | product | | time | yield[b] |
|---|---|---|---|---|---|---|
| 1 |  | **5a** |  | **6a** | 15 min | 95% |
| 2 |  | **5b** |  | **6b** | 20 min | 92% |
| 3 |  | **5c** |  | **6c** | 5 min | 95% |
| 4 |  | **5d** |  | **6d** | 20 min | 99% |
| 5 |  | **5e** |  | **6e** | 10 min | 99% |
| 6 |  | **5f** |   | **6f** **7**[c] | 60 min | 69% |
| 7 |  | **5g** |  | **6g** | 5 min | 82% |

[a] Reaction conditions: 0.5 M substrate in $CH_2Cl_2$, 2% of $(Ph_3P)AuNTf_2$, rt. [b] Isolated yields. [c] 23% of enone **7** were also isolated.

**Table 2.** Au(I)-Catalyzed Stereoselective Synthesis of 2,5-Dihydrofurans **9a**−**h**[a]

| entry | substrate | | product | | time | yield[b] |
|---|---|---|---|---|---|---|
| 1 |  | **8a** 87% ee |  | **9a** 86% ee | 3 h | 83% |
| 2 |  | **8b** 93:7 dr > 98% ee |  | **9b** 93:7 dr > 98% ee | 40 min | 97% |
| 3 |  | **8c** 94:6 dr > 98% ee |  | **9c** 92:8 dr > 98% ee | 35 min | 99% |
| 4 |  | **8d** 94% ee |  | **9d** 64% ee | 10 min | 99% |
| 5 |  | **8e** 96% ee |  | **9e** | | |
| | a- 2% $(Ph_3P)AuNTf_2$, rt | | | | 64% ee | 15 min 99% |
| | b- 2% $[(pCF_3Ph)_3P]AuNTf_2$, rt | | | | 66% ee | 15 min 99% |
| | c- 2% $(Ad_2nBuP)AuNTf_2$, rt | | | | 74% ee | 20 min 99% |
| | d- 2% $(Ph_3P)AuNTf_2$, 0°C | | | | 84% ee | 65 min 99% |
| | e- 2% $(Ad_2nBuP)AuNTf_2$, 0°C | | | | 90% ee | 120 min 99% |
| 6 |  | **8f** 94% ee |  | **9f** | | |
| | a- 2% $(Ph_3P)AuNTf_2$, rt | | | | 42% ee | 10 min 89% |
| | b- 2% $(Ad_2nBuP)AuNTf_2$, 0°C | | | | 77% ee | 145 min 91% |
| 7 |  | **8g** 81% ee |  | **9g** 80% ee | 50 min | 95% |
| 8 |  | **8h** 90:10 dr, >98% ee |  | **9h** 90:10 dr, >98% ee | 15 min | 99% |

[a] Reaction conditions: 0.5 M substrate in $CH_2Cl_2$, 2% of $(Ph_3P)AuNTf_2$, rt. [b] Isolated yields, dr and ee determined by chiral HPLC.

(4) A similar Ag(I)-catalyzed transformation of propargyl esters to dihydrofurans has been previously reported: (a) Shigemasa, Y.; Yasui, M.; Ohrai, S.-I.; Sasaki, M.; Sashiwa, H.; Saimoto, H. *J. Org. Chem.* **1991**, *56*, 910−912. (b) Saimoto, H.; Yasui, M.; Ohrai, S.-I.; Oikawa, H.; Yohoyama, K.; Shigemasa, Y. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 279−284. However, this transformation required 10% of $AgBF_4$ in refluxing benzene and furnished the dihydrofurans in moderate yields (~60%). Moreover, the cyclization was limited to the use of tertiary alcohols.

(5) For a recent review on gold catalysis, see: Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65. Selection of recent developments in gold catalysis: (a) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976−9977. (b) Asao, N.; Sato, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682−3685. (c) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391−4394. (d) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978−15979. (e) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260−11261. (f) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178−6179. (g) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963. (h) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803. (i) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105−1109. (j) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003. (k) Sromek, A. W.; Rubina, M. A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500−10501.

(6) For the synthesis and use of this stable Au(I) catalyst, see: Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.

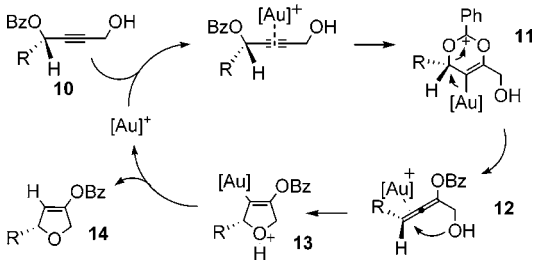
optical purity. The rearrangement of substrate **8b** possessing two asymmetric centers also took place witht a complete transfer of chirality and furnished *trans*-2,5-disubstituted dihydrofuran **9b** in 97% yield.[10] The parent diastereoisomer **8c** reacted equally well to give the *cis*-isomer **9c** in 99% yield. Under the same reaction conditions, primary alcohols **8d** and **8e** led, respectively, to enantiomers **9d** and **9e**, but with partial loss of optical purity (entries 4 and 5a).

This effect was much more pronounced when the reaction was performed on substrate **8f** bearing a bulkier cyclohexyl group (entry 6a). This racemization might be due to a competition between a possible gold(I)-catalyzed isomerization of the intermediate allene[5d] and the nucleophilic attack of the alcohol onto the gold-activated allene. The untoward erosion of optical purity could be largely eliminated by a proper choice of experimental conditions and the gold catalyst (entries 5b−e). Thus, conducting the cycloisomerization of **8e** at 0 °C with 2% of $(Ad_2n\text{-}BuP)AuNTf_2$[6] gave rise to **9e** in nearly quantitative yield and 90% ee.[11] Interestingly, tertiary alcohol **8g** smoothly rearranged under the general conditions furnishing 2,5-dihydrofuran **9g** in 95% yield with a complete transfer of chirality. This reactivity might be due to a Thorpe−Ingold effect approaching the nucleophilic alcohol closer to the gold(I)-activated allene.

To further explore the potential of this process, the reaction of functionalized alkyne **8h** bearing three asymmetric centers was examined. The transformation was exceptionally efficient and gave the corresponding *trans*-2,5-disubstituted dihydrofuran **9h** in 99% yield and complete transfer of the stereochemical information.[10]

To account for these observations, a mechanistic manifold for the formation of the 2,5-dihydrofurans is proposed in Scheme 2. Gold(I) activation of the triple bond in alkyne **10**

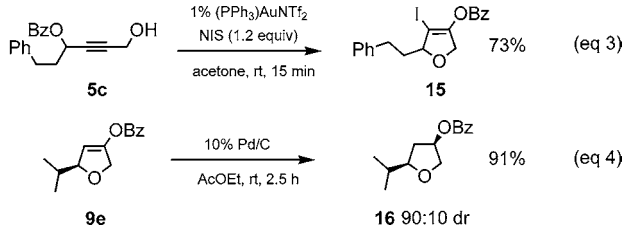
**Scheme 2.** Proposed Mechanism for the Formation of 2,5-Dihydrofurans




promotes the nucleophilic attack of the benzoate moiety and the subsequent formation of the stabilized cationic species **11**. Fragmentation of the allylic C−O bond in **11** can lead to the 1,3-shift of the benzoate group and the subsequent stereoselective formation of the intermediate allene **12**, after catalyst regeneration.[3,5d] A further gold(I) activation of the allene promotes the nucleophilic attack of the alcohol causing the stereoselective formation of the vinyl-gold species **13**.[2,3,5k] This latter is finally protonated to furnish 2,5-dihydrofuran **14**. This mechanism may account for the regioselective 1,3-shift of the benzoate moiety and for the inversion of configuration at the carbon center initially bearing this benzoate group. A gold(I) isomerization of the intermediate allene **12**, prior to the attack of the alcohol, may be responsible for the partial loss of the stereochemical information.[5d] This route seems to be effective in the case of unsubstituted free propargylic alcohols cyclizing onto sterically hindered carbon centers (Table 2, entries 4−6).

To further highlight the potential of this new process, we attempted to trap the intermediate vinyl-gold species **13** by a source of electrophilic iodine prior to protonation. To this end, alkyne **5c** was treated with 1% of $(Ph_3P)AuNTf_2$ and a slight excess of NIS in acetone (Scheme 3, eq 3).[12] We were

**Scheme 3**




pleased to observe the formation of vinyliodide **15**, which was isolated in 73% yield.

In addition, the functionalized 2,5-dihydrofurans can lend themselves to a number of useful transformations. For example, hydrogenation of compound **9e** with 10% of Pd/C in EtOAc resulted in the diastereoselective formation of tetrahydrofuran **16** in 91% yield (Scheme 3, eq 4).

In summary, we have shown that phosphine gold(I) complexes efficiently catalyze the stereoselective formation of various functionalized 2,5-dihydrofurans from readily available butynediol monobenzoates. A mechanism involving two gold(I)-catalyzed isomerization steps accounts for the observed regio- and stereoselectivities. Further studies related to this new gold(I)-catalyzed process as well as its application to the synthesis of natural products are underway.

**Acknowledgment.** We thank Prof. S. Z. Zard, Dr. B. Quiclet-Sire, and Dr. I. Hanna for helpful discussions, J-P. Pulicani for HPLC analyses, and Rhodia Chimie Fine for a donation of $HNTf_2$.

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

OL0606839

(7) Isomerization of **5g** into **6g** was performed from the acetate derivative for convenience reasons since the corresponding 3-acetoxy-3-methylbut-1-yne was commercially available.

(8) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180−14181.

(9) See, for instance: (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605−2606. (b) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017−3020. (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688.

(10) Structure and stereochemistry determined by full NMR analysis.

(11) $(Ad_2n\text{-}BuP)AuNTf_2$ is a less electrophilic catalyst than $(Ph_3P)AuNTf_2$. Its use might slow the isomerization of the intermediate allene without disfavoring the cyclization.

(12) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515−518.