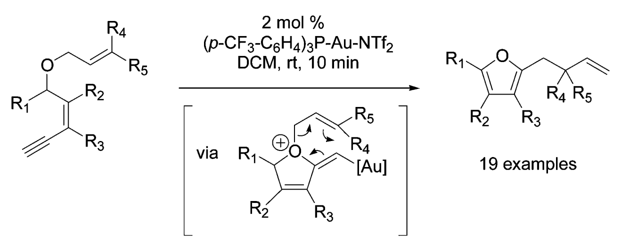
Synthesis of Functionalized Furans via Gold(I)-Catalyzed Claisen-Type Rearrangement

Florin M. Istrate and Fabien L. Gagosz*

Laboratoire de Synthèse Organique, UMR 7652/Ecole Polytechnique, Ecole Polytechnique, 91128 Palaiseau, France

gagosz@dcso.polytechnique.fr

Received October 22, 2007

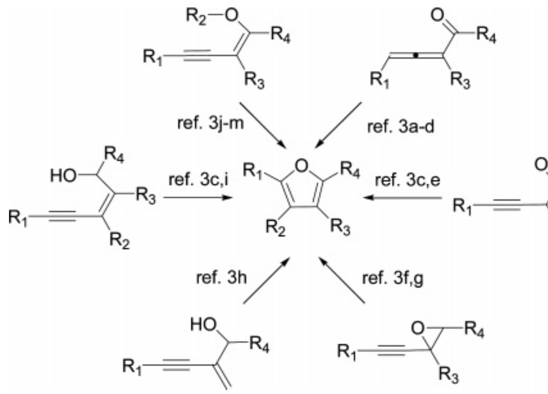


Gold(I)-catalyzed cyclization of pentenynyl allyl ethers allows the rapid construction of functionalized furans. The concerted oxy-Claisen-type mechanism induces a complete selectivity of the process and allows the easy formation of quaternary centers.

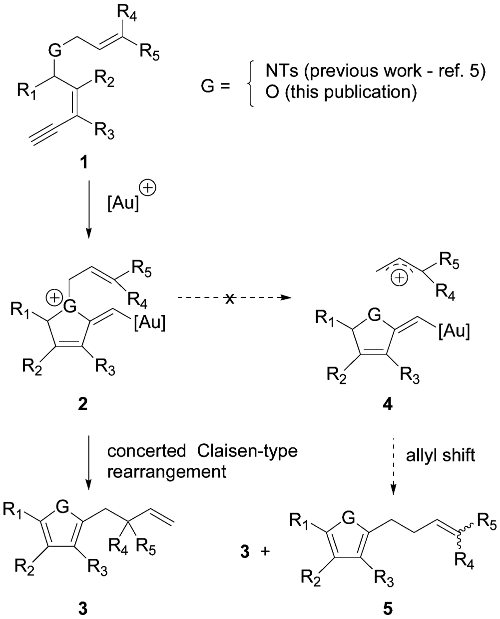
The synthesis of furans has attracted tremendous interest for well over a century,[1] reflecting both the importance of these heterocycles in natural and synthetic substances[2] and the requirement for more selective and versatile approaches for their synthesis. In particular, the development of routes that allow the facile assembly of substituted furans under mild conditions from simple readily available starting materials remains an important objective.

Classical approaches to substituted furans have involved the cyclocondensation of dicarbonyl compounds or equivalents, or the substitution of an existing furan ring.[1] More recently, alternative strategies have explored the cycloisomerization of alkyne- and allene-containing compounds, usually in the presence of a number of transition metals, including Cu, Ag, Pt, Pd, and Au (Scheme 1).[1,3]

SCHEME 1. Cycloisomerization Methods for the Synthesis of Substituted Furans from Allene- or Alkyne-Containing Substrates



SCHEME 2. Our Synthetic Approach to Functionalized Furans



However, there are some limitations, including ease of access to substrates that contain sensitive functional groups and the difficulty preparing 3-substituted furans by the direct cycloisomerization of allenes.[3d] Alkynes are typically considered to be more attractive starting materials than allenes, and recently, some ingenious methods to effect heterocyclization have been reported.[4]

On the basis of our previous work on the synthesis of functionalized pyrroles via a gold(I)-catalyzed aza-Claisen-type

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[1] For reviews of furan synthesis, see: (a) König, B. *Hetarenes and Related Ring Systems: Fully Unsaturated Small-Ring Heterocycles and Monocyclic Five-Membered Hetarenes with One Heteroatom. Methoden Org. Chem.*, 4th ed.; Houben-Weyl: 2001; Vol. 9, pp 183−286. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (c) Krasnoslobodskaya, L. D.; Goldfarb, Y. L. *Russ. Chem. Rev.* **1969**, *38*, 389.

[2] (a) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Oxford, 1997; Vol. 2, pp 395−436. (b) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, pp 657−712.

[3] For selected examples of cycloisomerization approaches to substituted furans, see: (a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581. (c) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (d) Ma, S. M.; Zhang, J. L.; Lu, L. H. *Chem.—Eur. J.* **2003**, *9*, 2447. (e) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (f) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432. (g) Miller, D. *J. Chem. Soc. C* **1969**, 12. (h) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (i) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089. (j) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (k) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (l) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (m) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760.

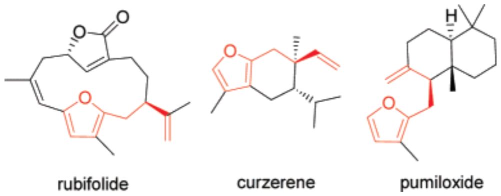
[4] (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (b) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

10.1021/jo7022685 CCC: $40.75

rearrangement,[5] we surmised that the synthesis of substituted furans might be possible via an analogous transformation.

In contrast with what was previously observed by Fürstner et al. for the rearrangement of allyl pentynyl ethers,[6] the results obtained in this previous study strongly suggest that no allyl cation is formed during the reaction. All the results seem to indicate a more concerted mechanism and tend to exclude the possibility of a simple N to C allyl shift (Scheme 2). Therefore, proving that an analogous transformation takes place via a similar pathway with oxygen—instead of nitrogen—derivatives will further confirm our initial mechanistic proposal and will broaden the scope of this new Claisen-type metal-catalyzed rearrangement.

From a synthetic point of view, this reaction can be particularly useful for the preparation of substituted 2-butenyl furans. Such a motif can be found in a wide variety of biologically active compounds, such as rubifolide,[7] curzerene,[8] or pumiloxide.[9] This approach is interesting for several reasons: (a) generally, cycloisomerization methods for the synthesis of substituted furans from allene- or alkyne-containing substrates only allows the formation of a new C−O bond, while by this method, new C−C and C−O bonds are formed in just one step; (b) the reaction allows the easy formation of quaternary centers or the introduction of other various substitutions in the side chain; (c) usually, the reaction conditions involved in gold-catalyzed reactions are extremely mild, hence the tolerance to a wide variety of substitutions; (d) the corresponding pentenynyl allyl ether derivatives are easily accessible via various methods.



We decided to employ the same reaction conditions as those used in our previous work for the cyclization of tosylamine derivatives and use the air-stable crystalline $(p\text{-}CF_3-C_6H_4)_3P-Au\text{-}NTf_2$ catalyst.[10] A large variety of substrates were synthesized and reacted under these conditions (Table 1). We were delighted to observe the rapid formation (usually less than 10 min) of the expected furans.

The allyl (**6a**), crotyl (**6b**), prenyl (**6c**), and geranyl (**6d**) derivatives of the primary alcohol readily isomerized in the presence of the gold catalyst. The isolation of the obtained furans **7a−d**, however, proved to be quite challenging due to their volatility. These reactions were therefore performed in CD_2Cl_2 in the presence of 1,3,5-trimethoxybenzene as internal reference, and the yields were assessed by NMR spectroscopy (75−92%).

All of the examples compiled in the entries 2−19 are in agreement with the postulated oxy-Claisen-type rearrangement since the exclusive formation of branched products (**3**) is observed. Indeed, no linear product (**5**) resulting from an O to C shift of the allylic moiety could be observed whatever the substrate used.[11]

Compounds **6b** and **6e**, although obtained as a mixture of *Z*/*E* isomers, afforded thus a unique product **7b** and **7e**, respectively, while compounds **6g**,**h**,**q**,**s**, possessing an exocyclic allyl, gave the corresponding spiro compounds **7g**,**h**,**q**,**s** (yields between 36% and quant.).

It is also worth mentioning that increasing the substitution at the terminal allylic moieties of the starting ethers (monosubstitution in the case of **6b**, disubstitution for **6c−s**) makes no noticeable difference in terms of reaction's conversion rate or yield, even though the steric hindrance of the postulated oxy-Claisen intermediate increases. This behavior strongly contrasts with the generally less efficient Claisen-type reactions of similarly substituted substrates and consequently allows the *easy creation of a new quaternary center* for the disubstituted substrates **6c−s**.

Interestingly, substrates **6h−m** derived from the corresponding secondary alcohols also rearrange easily to afford the expected 2-substituted furans (yields between 77% and quant.). A large variety of substitutions are tolerated: primary, secondary, or tertiary alkyls and even vinyl or phenyl groups.[12] The increased steric hindrance around the oxygen does not affect the cyclization step (nucleophilic attack of the oxygen on the activated triple bond). Compound **7l** easily polymerizes and therefore was isolated only in a poor yield (17%).

The substrate scope was then demonstrated by replacing the vinylic methyl with larger substituents (such as a phenyl group or a long alkyl chain) in the substrates **6n−q**. These substrates reacted in high yields (80−90%), showing that furans substituted at the 3 position with larger substituents (**7n−q**) can also be easily obtained. However, ethers **6r**,**s** (substituted simultaneously with two large groups) do not convert completely into the corresponding furans **7r**,**s** (probably due to an unfavorable conformation of the transition state).

To account for these observations, a mechanistic manifold for the formations of furans was proposed in Scheme 3. The results shown in entries 2−19 (Table 1) serve as a mechanistic probe, indicating that the key step of this transformation may therefore be seen as a gold-catalyzed oxy-Claisen-type reaction.

The following reaction pathway is therefore envisaged: gold(I) activation of the triple bond in substrate **9** promotes the nucleophilic addition of the oxygen and leads to the formation of the cationic vinyl gold intermediate **10**. A subsequent oxy-Claisen-type rearrangement furnishes intermediate **11**.[13] A proton loss from one of these two intermediates allows the aromatization of the system and the formation of a new gold intermediate **14**. This latter is subsequently protodemetalated to finally give furan **15**.

In summary, we have developed a new gold(I)-catalyzed formation of functionalized furans, which is characterized by

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(5) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, *16*, 3181.

(6) (a) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785.

(7) Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332.

(8) Saeed, M. A.; Sabir, A. W. *Fitoterapia* **2004**, 75, 1, 81.

(9) Tatsimo, S. J. N.; Tane, P.; Srinivas, P. V.; Sondengam, B. L.; Melissa, J.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M.; Khan, I. A. *Planta Med.* **2005**, *71*, 1145.

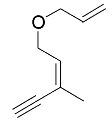
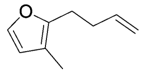
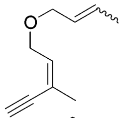
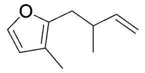
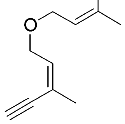
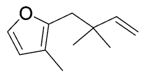
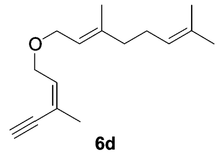
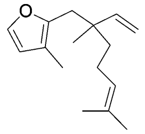
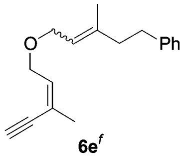
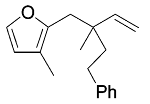
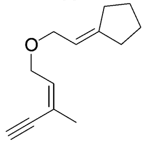
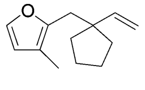
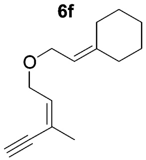
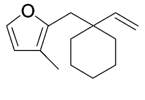
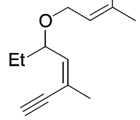
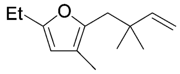
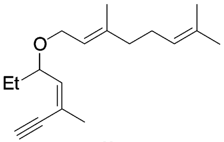
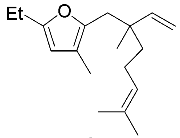
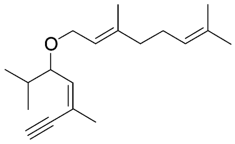
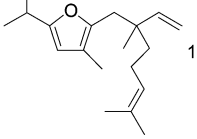
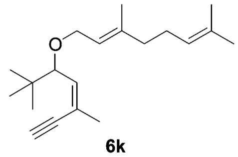
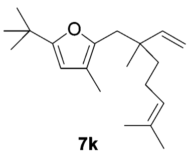
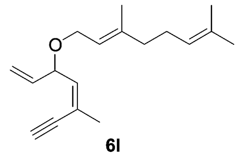
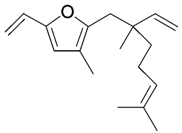
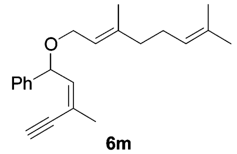
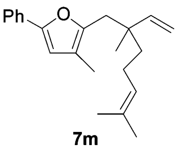
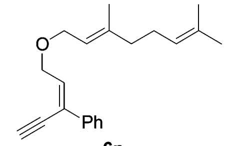
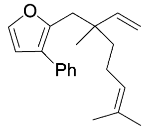
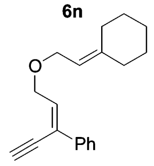
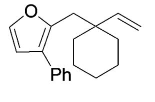
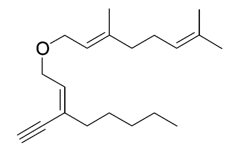
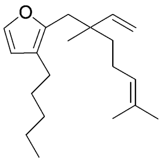
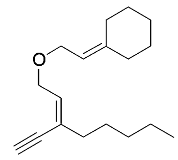
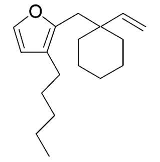
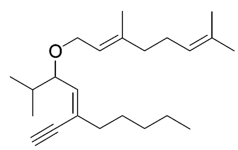
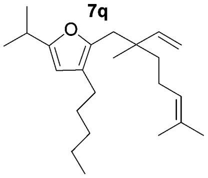
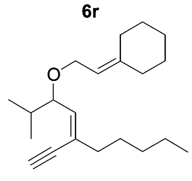
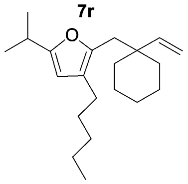
(10) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.

(11) Within the limits of detection by ^{1}H NMR of the crude mixture.

(12) In our previous study dealing with the formation of pyrroles (ref 5), substrates containing a disubstituted alkyne moiety did not cyclize. We therefore did not attempt to rearrange analogous substrates in the present study.

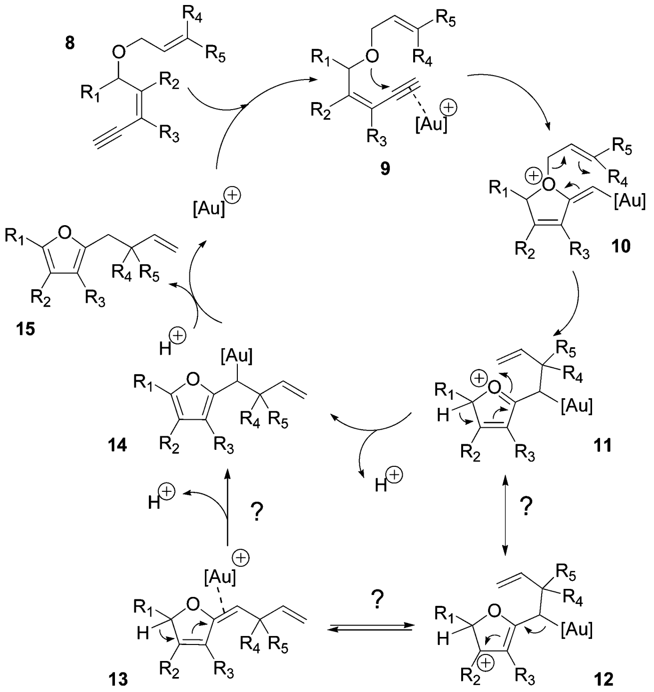
(13) Another possible, although less likely, pathway to obtain intermediate **14** is via the intermediate **13**, which is presumably in equilibrium with intermediate **11**.

TABLE 1. Scope of Au(I)-Catalyzed Synthesis of Furans[a]

entry	substrate	product	conversion[b]	yield[c]
1	 **6a**	 **7a**	100%	18% (75%[d])
2	 **6b**[e]	 **7b**	100%	39% (86%[d])
3	 **6c**	 **7c**	100%	59% (82%[d])
4	 **6d**	 **7d**	100%	81% (92%[d])
5	 **6e**[f]	 **7e**	100%	66%
6	 **6f**	 **7f**	100%	71%
7	 **6g**	 **7g**	100%	63%
8	 **6h**	 **7h**	100%	quant.
9	 **6i**	 **7i**	100%	quant.
10	 **6j**	 **7j**	100%	78%
11	 **6k**	 **7k**	100%	78%
12	 **6l**	 **7l**	100%	17%
13	 **6m**	 **7m**	100%	77%
14	 **6n**	 **7n**	100%	80%
15	 **6o**	 **7o**	100%	90%
16	 **6p**	 **7p**	100%	82%
17	 **6q**	 **7q**	100%	86%
18	 **6r**	 **7r**	>84%[g]	73%
19	 **6s**	 **7s**	>62%[g]	36%

[a] Reaction conditions: 0.1 M of substrate in DCM with 2 mol % of (p-CF_3−C_6H_4)$_3$P−Au-NTf_2 at rt for 10 min. [b] Conversion of the substrate determined by ^{1}H NMR of the crude mixture. [c] Isolated yields. [d] Yields determined by ^{1}H NMR of the crude mixture (with 1,3,5-trimethoxybenzene as internal reference). [e] *Z*/*E* ratio ~ 1/3. [f] *Z*/*E* ratio ~ 1/2.57. [g] Reaction time: 40 min.

SCHEME 3. Proposed Mechanism



its efficiency, the mild conditions employed, and the easy formation of quaternary centers. The complete selectivity observed in the structure of the final product is in agreement with the postulated oxy-Claisen-type rearrangement. Further studies related to the development of an asymmetric version of this new gold(I)-catalyzed process and its application to the synthesis of natural products are underway.

Experimental Section

General Procedure for the Catalysis Reactions: To a solution of the substrate (0.25 mmol, 1 equiv) in CH_2Cl_2 (0.1 M) was added (p-$CF_3-C_6H_4)_3P-Au-NTf_2$ (4.7 mg, 0.02 equiv). The mixture was stirred at rt and monitored periodically by TLC. Upon completion, the mixture was evaporated, loaded onto a silica gel column, and chromatographed with petroleum ether to give the furan. Synthesis of furan **7d**: 81%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $J = 1.8$ Hz, 1H), 6.18 (d, $J = 1.7$ Hz, 1H), 5.84 (dd, $J = 10.8$, 17.5 Hz, 1H), 5.10 (hept, $J = 1.4$, 7.1 Hz, 1H), 5.01 (dd, $J = 1.3$, 10.8 Hz, 1H), 4.93 (dd, $J = 1.3$, 17.5 Hz, 1H), 2.57 (s, 2H), 1.96 (s, 3H), 1.93 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.36 (m, 2H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 146.5, 139.9, 131.0, 124.9, 115.8, 112.5, 111.6, 41.4, 40.3, 37.5, 25.6, 23.0, 22.6, 17.5, 10.4; IR (CCl_4) 2965, 2924, 2868, 1636, 1511, 1452, 1376, 1149, 1069, 1002; MS (CI+, NH_3) m/z 233 (MH^+), 216, 183; HRMS (EI+) m/z calcd for $C_{16}H_{24}O$ 232.1827, found 232.1835.

Procedure for Catalysis Reactions in Deuterated Solvent with Internal Reference: To a solution of the substrate (0.1 mmol, 1 equiv) in CD_2Cl_2 (0.1 M) were added (p-$CF_3-C_6H_4)_3P-Au-NTf_2$ (1.9 mg, 0.02 equiv) and 1,3,5-trimethoxybenzene (17 mg, 1 equiv). The mixture was stirred at rt and monitored periodically by NMR. The yield of the desired product was also assessed by NMR.

Acknowledgment. We thank Prof. S. Z. Zard (CNRS/Ecole Polytechnique) and A. K. Buzas for helpful discussions, and Rhodia Chimie Fine for a gift 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.

JO7022685