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# Gold(I)-Catalyzed Synthesis of Highly Substituted Furans

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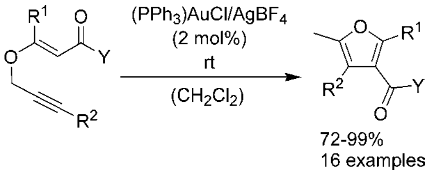
## ABSTRACT



**Cationic triphenylphosphinegold(I) complexes are excellent catalysts for a cascade reaction of propargyl-Claisen rearrangement and heterocyclization to synthesize tri- and tetrasubstituted furans. Starting from easily accessed propargyl vinyl ethers, the furans are obtained in 72–99% yield.**

Highly substituted furans play an important role as structural elements of many natural and pharmaceutically important substances (e.g., ranitidine or zantac).[1] Moreover, they are useful intermediates in synthetic organic chemistry.[2] Among the many different approaches to multiply substituted furans,[3,4] cycloisomerizations of alkynyl ketones catalyzed by transition metals are particularly attractive.[5] An alternative strategy involves allenyl ketones as starting materials for furan synthesis mostly using Rh(I), Ag(I), Au(III),[5c] and Pd(0/II) compounds as transition-metal catalysts for 5-*endo-trig* cyclizations.[6] Transition-metal-catalyzed cyclization has been typically used to prepare di- and trisubstituted furans, while tetrasubstituted furans are not readily accessed.[3d,6a,7]

Herein, we report a flexible synthetic approach to tri- and tetrasubstituted furans via a gold(I)-catalyzed cascade reaction of a formal [3,3]-sigmatropic rearrangement and a heterocyclization. Importantly, readily obtained acceptor substituted propargyl vinyl ethers are used as starting materials for this protocol.

To obtain highly substituted furans **3** from allenylcarbonyl compounds of type **2**, we planned a transition-metal-catalyzed 5-*exo-dig* cyclization (Scheme 1). A catalytic version of a propargyl-Claisen rearrangement[8] of propargyl vinyl ethers **1** should give access to the required allenylcarbonyl compounds **2**. We assumed that coordination of

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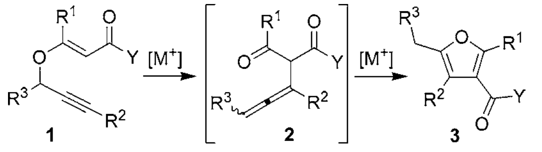
**Scheme 1.** Synthesis of Furan **3** from Propargyl Vinyl Ether **1**



transition metals to $\pi$-bonds[9] would allow for a catalyzed process related to the thermal rearrangement[10] through alkyne activation. In the ideal case, the catalyst system used for rearrangement should also promote the cycloisomerization to the furan in a cascade reaction that proceeds at ambient temperature and under neutral conditions.

On the basis of these considerations, we initially examined the conversion of proparyl vinyl ether **1a** ($R^1 = Me$, $R^2 = Me$, $R^3 = H$, $Y = OEt$) to furan **3a** (Table 1). The desired transformation was examined using a variety of transition-metal complexes in $CH_2Cl_2$ at room temperature. In the presence of CuI or $PdCl_2(MeCN)_2$, the formation of furan **3a** was not observed under these conditions (Table 1, entries 1−2). Treatment of proparyl vinyl ether **1a** with 2 mol % of $PtCl_2$[11] gave the desired tetrasubstituted furan **3a** in 52% yield, but the reaction did not proceed to completion even after 24 h at room temperature (Table 1, entry 3); in the absence of a transition-metal salt, furan formation did not take place. With 10 mol % of $AgBF_4$ as a catalyst, the starting alkyne **1a** was rapidly consumed, but capillary gas chromatography did not indicate traces of furan **3a** to be formed after 24 h (Table 1, entry 4).[12] Indeed, the starting material was completely and cleanly converted into an isomeric mixture of allene **2a** after 6 h. Among the gold catalysts[13,14] used (Table 1, nos. 5−7), only $AuCl_3$ gave furan **3a** (7% yield) with concomitant generation of allene **2a** (47% yield).[15] While $(PPh_3)AuCl$ was unreactive, changing of the counterion to hexafluoroantimonate by addition of $AgSbF_6$ led to a clean and rapid formation of furan **3a** in 83% yield. By far, the best catalyst system was a combination of $(PPh_3)AuCl$ and $AgBF_4$, which provided furan **3a** in 97% yield after 40 min [2 mol % $(PPh_3)AuCl/AgBF_4$, 23 °C, 40 min, $CH_2Cl_2$ (0.2 M)]. Activation of $(PPh_3)AuCl$ with other silver salts such as AgOTf was less effective (Table 1, nos. 8−10).[16] Solvent had a marked influence on catalytic efficiency. Reactions of propargyl vinyl ether **1a** in the presence of 2 mol % $(PPh_3)AuCl/AgBF_4$ at room temperature followed the order $CH_2Cl_2$ (97%, 40 min) ≈ $C_6H_6$ (95%, 40 min) > $C_6H_{12}$ (99%, 48 h) > MeCN (30%, 48 h) > THF (3%, 28 h).

**Table 1.** Efficiency of Transition-Metal Catalysts for the Transformation of **1a** into **3a**[a]

| entry | catalyst (mol %) | time | yield of **3a**[b] (%) |
|---|---|---|---|
| 1 | CuI (5) | 24 h | 0 |
| 2 | $PdCl_2(MeCN)_2$ (5) | 24 h | 0[c] |
| 3 | $PtCl_2$ (2) | 24 h | 52 |
| 4 | $AgBF_4$ (10) | 24 h | 0[d] |
| 5 | $K[AuCl_4]$ (5) | 24 h | 0 |
| 6 | $AuCl_3$ (2) | 24 h | 7[e] |
| 7 | $(PPh_3)AuCl$ (2) | 24 h | 0 |
| 8 | $(PPh_3)AuCl$ (2)/$AgBF_4$ (2) | 40 min | 97 |
| 9 | $(PPh_3)AuCl$ (2)/$AgSbF_6$ (2) | 40 min | 83 |
| 10 | $(PPh_3)AuCl$ (2)/AgOTf (2) | 40 min | 60 |

[a] Conditions: 0.2 mmol of **1a**, 23 °C, $CH_2Cl_2$ (0.2 M). [b] Yield of pure **3a** after column chromatography. [c] No starting material **1a** remained. [d] Complete conversion after 6 h under formation of allene **2a**. [e] Formation of allene **2a** with in 47% yield.

The scope of the triphenylphosphinegold(I)-catalyzed conversion of propargyl vinyl ethers to a variety of substituted furans is summarized in Table 2. With optimized reaction conditions[17] in hand, tetrasubstituted furans **3** were formed in high yields with $R^1$ being alkyl and phenyl substituents (Table 2, entries 1−3). Moreover, the corresponding trisubstituted furan **3d** ($R^1 = H$) was easily obtained in 75% yield (Table 2, entry 4). The acceptor substituents

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(11) Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023−5026.

(12) Other silver salts such as AgOTf, AgOAc, and $AgNO_3$ catalyzed the formation of allene **2a** less effectively. Generation of furan **3a** was not catalyzed.

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(15) Addition of $AgBF_4$ (6 mol %) or AgOTf (6 mol %) to $AuCl_3$ (2 mol %) did not lead to an increase in the formation of furan **3a**.

(16) Addition of AgOAc or $AgCOOCF_3$ to $(PPh_3)AuCl$ did not give a catalytically active gold(I) species.

(17) **General Procedure.** Synthesis of **3k**: $(PPh_3)AuCl$ (2 mol %, 2.3 mg) and $AgBF_4$ (2 mol %, 1.0 mg) were added subsequently to a solution of **1k** (70 mg, 0.26 mmol) in $CH_2Cl_2$ (1.3 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature. The dark reaction mixture was stirred at room temperature for 3 h (until TLC analysis indicated complete conversion). The mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel ($P/Et_2O = 90/10$) gave furan **3k** as a colorless oil (69 mg, 0.25 mmol, 99%). $R_f = 0.39$ (P/EA = 80/20). $^1H$ NMR (360 MHz, $CDCl_3$): $\delta = 1.03$ (t, $J = 7.2$ Hz, 3 H), 2.17 (s, 3 H), 2.55 (s, 3 H), 3.77 (s, 3 H), 4.06 (q, $J = 7.2$ Hz, 2 H), 6.89 (d, $J = 8.2$, 0.8 Hz, 1 H), 6.96 (dt, $J = 0.8$, 7.5 Hz, 1 H), 7.13 (dd, $J = 7.5$, 1.8 Hz, 1 H), 7.28 (dt, $J = 8.2$, 1.8 Hz, 1 H). $^{13}C$ NMR (90.6 MHz, $CDCl_3$): $\delta = 11.8$, 13.8, 13.9, 55.3, 59.5, 110.3, 114.5, 117.3, 120.1, 122.5, 128.5, 131.1, 147.1, 156.6, 157.4, 164.5. MS (70 eV): *m/z* 274 (100) $[M^+]$, 213 (92), 43 (68). HRMS: calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1206.

**Table 2.** Gold(I)-Catalyzed Formation of **3** from **1**[a]

|  | **1** |  |  |  |  | time | yield **3**[b] |
|---|---|---|---|---|---|---|---|
| entry | $R^1$ | Y | $R^2$ | $R^3$ | isomer | (h) | (%) |
| 1 | Me | OEt | Me | H | **a** | 4 | 95 |
| 2 | *n*Pent | OMe | Me | H | **b** | 15 | 97 |
| 3 | Ph | OEt | Me | H | **c** | 2 | 90 |
| 4[c] | H | OEt | Me | H | **d** | 4 | 75 |
| 5 | Ph | Ph | Me | H | **e** | 8 | 72 |
| 6 | Me | OEt | H | H | **f** | 12 | 82 |
| 7 | *n*Pent | OMe | H | H | **g** | 12 | 77 |
| 8 | Me | OEt | Ph | H | **h** | 2 | 87 |
| 9 | Ph | OEt | Ph | H | **i** | 4 | 90 |
| 10[c] | H | OEt | Ph | H | **j** | 4 | 84 |
| 11 | Me | OEt | 2-MeO-phenyl | H | **k** | 3 | 99 |
| 12 | Ph | OEt | 3-thienyl | H | **l** | 4 | 89 |
| 13[c] | Ph | OEt | 2-pyridyl | H | **m** | 48 | 82 |
| 14 | Ph | OEt | $CH_2$*c*-$C_6H_{11}$ | H | **n** | 5 | 73 |
| 15[d] | Ph | OEt | $CH_2CH_2OTBS$ | H | **o** | 3 | 72 |
| 16[d] | Me | OEt | TBS | H | **p** | 4 | 83 |
| 17[e] | Ph | OEt | Me | Me | **q** | 24 | 45 |

[a] Conditions: 0.2 mmol **1**, 2 mol % of [$(PPh_3)AuCl/AgBF_4$], 23 °C, $CH_2Cl_2$ (0.2 M). [b] Yield of pure product after column chromatography. [c] Solvent = benzene. [d] TBS = *tert*-butyldimethylsilyl. [e] 38 °C.

in the 3-position do not necessarily have to be esters (Y = OMe or OEt). The reaction of *E*-olefin **1e** with Y = Ph also took place in good yield (Table 2, entry 5). Reactions of terminal alkynes **1f,g** with $R^2$ = H provided the corresponding trisubstituted furans **3f,g** in 77−82% yield (Table 2, entries 6 and 7). A broad variety of propargyl vinyl ethers **1** with different substituents $R^2$ at the alkyne terminus was effectively converted into the substituted furans (Table 2, entries 8−16). Notably, the reaction of aromatic and heteroaromatic substrates was as clean as the reaction of the sterically demanding substrate **1n** ($R^2 = CH_2$-*c*-$C_6H_{11}$). The presence of heteroatom substituents in the propargyl vinyl ether was well tolerated. Propargyl vinyl ether **1o** containing a silyl ether gave furan **3o** in 72% yield,[18] as did substrates containing esters, ethers, and silanes. Although substrate **1q** derived from a secondary propargyl alcohol reacted to furan **3q** ($R^3$ = Me) in 45% yield, flexibility at this position remains limited. Preliminary experiments indicated that heterocyclization with $R^3 \neq$ H was slow under the influence of [$(PPh_3)AuCl/AgBF_4$] as catalyst system.

Several additional observations merit note. To our surprise, the conversion of propargyl vinyl ethers **1d** and **1j** ($R^1$ = H) in dichloromethane as a solvent led to a mixture of unidentified decomposition products. Nevertheless, performing the reaction in benzene allowed for the clean formation of the desired furans **3d** and **3j**.[19] The reactions reported in Table 2 were remarkably clean, taking place without the formation of significant amounts of any byproducts. It was not necessary to take special precautions to exclude air and moisture from the reaction mixture.[20,21] Reaction of the *Z*-stereoisomer of propargyl vinyl ether **1b** was marginally slower compared to the analogous *E*-isomer and led to the formation of furan **3b** in 92% yield. It was also possible to conduct the triphenylphosphinegold(I)-catalyzed furan formation with a mixture of *E*/*Z*-stereoisomers. For example, the *E*/*Z*-mixture of substrate **1e** was transferred into furan **3e** (70% yield).

The use of propargyl vinyl ethers as starting materials is particularly convenient as these intermediates can easily be prepared in high yields. Propargyl vinyl ethers **1a−q** were obtained from the corresponding proparyl alcohols and 2-propynoic acid derivatives in the presence of catalytic amounts of trimethylphosphine[22] in high yields (61−98%).[23]

A plausible mechanism for the furan formation reported herein is based on a cyclization-induced rearrangement (CIR) mechanism.[8a,24] A 6-*endo-dig* addition of the enol ether onto a gold(I)−alkyne complex leads to the formation of a six-membered intermediate, which collapses into the $\beta$-allenic ketone (or its tautomeric enol forms).[25,26] Gold(I)-catalyzed 5-*exo-dig* cyclization finally delivers furan **3**. We assume that cationic triphenylphosphinegold(I) is the catalytically active species in both steps of the reaction cascade. Indeed, we cannot rule out that silver(I) catalyzes the rearrangement step with the heterocyclization being catalyzed by gold(I).

In summary, a convenient and flexible method for the synthesis of tri- and tetrasubstituted furans is described. The reaction is accomplished at room temperature using low catalyst loadings, and allows for the introduction of highly functional groups by a novel cascade reaction. The starting propargyl vinyl ethers are easily accessible. Further studies, including detailed investigations into mechanism and catalytic active species, and applications in total synthesis, are currently underway in our labaratories.

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**Supporting Information Available:** Representative experimental procedures, copies of $^1H$ NMR spectra of **3a−q**, and $^{13}C$ NMR spectra of **3a−q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] With reaction times >3 h, decomposition of product **3n** was observed.

[19] The origin of this effect remains unclear.

[20] Dichloromethane was purchased from Fluka and contained less than 0.005% of water.

[21] In the presence of higher amounts of water (10% v/v), furan formation was not observed.

[22] Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241−244.

[23] Propargyl vinyl ethers **1b** and **1e** were obtained as a mixture of *E*- and *Z*-isomers. The *Z*-isomers of **1b** and **1e** were isolated in 15% and 38% yield, respectively.

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[25] Allene **2a** was isolated as a mixture of isomers and was not converted into furan **3a** by addition of $AgBF_4$ or $(PPh_3)AuCl$. Addition of 2 mol % of [$(PPh_3)AuCl/AgBF_4$] led to a quantitative furan formation.

[26] Allene **2a** was detected as intermediary occurring species in the catalyzed transformation **1a** → **3a** by capillary gas chromatography.