DOI: 10.1002/adsc.200700319

Gold-Catalyzed Tandem Cycloisomerization of Alkynyloxiranes with Nucleophiles: An Efficient Approach to 2,5-Disubstituted Furans

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Received: June 29, 2007; Revised: August 6, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: An efficient approach to 2,5-disubstituted furans has been developed by utilizing gold-catalyzed sequential nucleophilic attack onto metal-complexed alkynes with complete regioselectivity. The reaction proceeds efficiently under mild conditions with commercially available catalysts to afford furans in moderate to excellent yields (up to 96%) with high diversity.

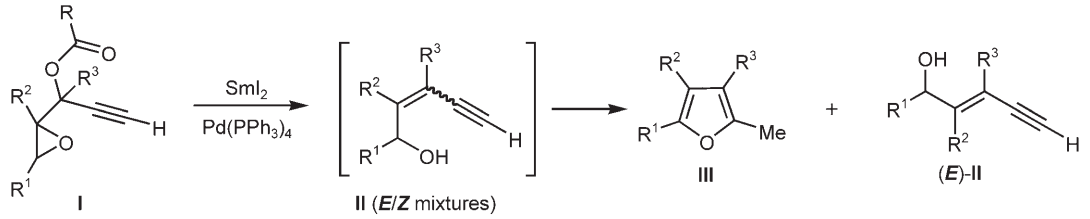
Keywords: alkynes; alkynyloxiranes; cycloisomerization; epoxides; furans; gold

Introduction

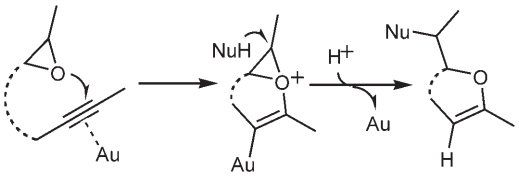
Furans are an important class of heterocyclic compounds which are extensively used as synthetic building blocks[1] and appear as a subunit in many natural products which exhibit interesting biological activities and substances of relevance for industry.[2] For this reason, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic chemists.[3]

Among many different approaches to furans, the isomerization of alkynyloxiranes to furans looks quite attractive. However traditional methods of these approaches have some limitations as follows: (i) The disadvantages of the Hg catalysis are obvious, which does not meet the contemporary requirement against hazardous reagents.[4] (ii) Strong base- or acid-promoted cyclizations are not suitable for the synthesis of base- or acid-sensitive furans.[5,6] (iii) Mo- and Ru-catalyzed isomerizations of alkynyloxiranes to furans are only suitable for terminal alkynes.[7] (iv) SmI_2/Pd(0 or II) systems need stoichiometric amounts of SmI_2 with a sequential procedure.[8] Furthermore, only the minor (*Z*)-isomers of intermediates **II** cyclize to the corresponding furans while the major (*E*)-isomers remain unchanged (Scheme 1).[8a]

Recently, gold salts have emerged as promising catalysts for C–O bond formation reactions through activation of alkynes toward nucleophilic attack.[9] Besides alcohols,[9l,m,q] carbonyl compounds,[9p,t] and carboxylic acids[9s], epoxides also act as good nucleophiles. However, only one example of this type of reaction has been reported.[9n] Consequently, the use of gold catalysis in the area of epoxides remains largely



Scheme 1.



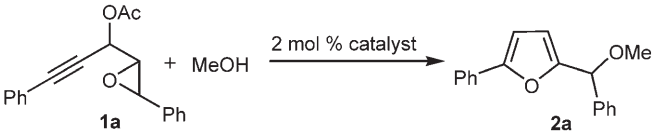
Scheme 2.

unexplored. Due to their unique structures, species formed from alkynes and epoxides might be further attacked by nucleophiles. This might provide an efficient approach to the formation of a C–O bond and a remote carbon-nucleophile bond in one pot (Scheme 2). Herein, we disclose the first results on the corresponding cycloisomerization of alkynyloxiranes with nucleophilies to afford 2,5-disubstituted furans by utilizing gold-catalyzed nucleophilic domino attack onto metal-complexed alkynes with complete regioselectivity. The alkynyloxiranes could be easily obtained by epoxidizing the corresponding 1-en-4-yn-3-ols following an acylation process.

Results and Discussion

We began our investigation with ester of 1-alkynyl-2,3-epoxy alcohol **1a**[10] (0.3 mmol) in methanol (1.0 mL) using a variety of transition metal complexes (2 mol%) (Table 1). In the presence of $Cu(OTf)_2$ or $AgSbF_6$, the formation of furan **2a** was not observed (entries 1 and 2). Treatment of alkynyloxirane **1a** with 2 mol% of $Pd(OAc)_2$ or $PtCl_2$ gave the desired furan **2a** in 13% and 11% yields, respectively. However the reaction did not proceed to completion even after 24 h at room temperature (entries 3 and 4). Among the gold catalysts used, Au(I) and Au(III) all afforded good yields of furan **2a** without any 1,3-migration product[11] (entries 5–11). $AuCl_3$ gave the best result (92%, 1.5 h). Addition of Ag(I) salts to the gold systems led to a dramatic decrease in the formation of **2a** (entries 6, 7 and 9). On the other hand, on increasing the temperature to 60 °C, a high yield of up to 92% was also obtained by $HAuCl_4{\cdot}4H_2O$ (entry 12). Considering the acidity of these catalyst systems,[12] protic acids such as TFA , chloroacetic acid have also been tested. However, the substrate underwent the deacylation process efficiently to afford the starting material, 1-alkynyl-2,3-epoxy alcohol, without any desired furan product (entries 14 and 15). Thus, the use of $AuCl_3$ (2 mol%) at room temperature (conditions A) or $HAuCl_4{\cdot}4H_2O$ (2 mol%) at 60 °C (conditions B) was found to be the most efficient and was used as the standard conditions.[13] In the absence of gold catalyst, no reaction took place. This result indicates that the gold catalyst is required for the reaction to proceed.

Table 1. Efficiency of transition-metal catalysts for the transformation of **1a** into **2a**.[a]

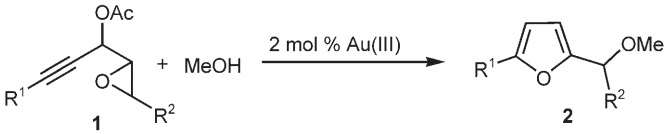


Entry	Catalyst	Temp. [°C]	Time [h]	Yield [%][b]
1	$Cu(OTf)_2$	r.t.[c]	1.0	0[d]
2	$AgSbF_6$	r.t.	24	0
3	$Pd(OAc)_2$	r.t.	24	13
4	$PtCl_2$	r.t.	24	11
5	AuCl	r.t.	1.5	74
6	2% $Au(PPh_3)Cl$/2% $AgBF_4$	r.t.	1.5	55
7	2% $Au(PPh_3)Cl$/2% $AgSbF_6$	r.t.	1.5	57
8	$AuCl_3$	r.t.	1.5	93
9	2% $AuCl_3$/6% $AgSbF_6$	r.t.	2	53
10	$Bu_4N[AuCl_4]$[14]	r.t.	24	69
11	$HAuCl_4{\cdot}4H_2O$	r.t.	20	74
12	$HAuCl_4{\cdot}4H_2O$	60	2	92
13	$HAuCl_4{\cdot}4H_2O$	80	2	86
14	10% TFA	r.t.	1.5	0
15	10% $ClCH_2CO_2H$	r.t.	1.5	0

[a] *Conditions:* 0.3 mmol of **1a** with 2 mol% of catalysts in methanol (1.0 mL).
[b] Isolated yield.
[c] 23–25 °C.
[d] No starting material of **1a** remained.

To examine the scope of this cyclization, we first investigated a range of esters of 1-alkynyl-2,3-epoxy alcohols with methanol, as depicted in Table 2. Both aromatic (entries 1–3) and aliphatic (entry 4) R^2 groups worked well. Electron-rich aryl groups showed better results than those with an electron-withdrawing group in this cyclization (entries 2 *vs.* 3). These results would be ascribed to the fact that an intermediate **C**, having an electron-donating group as the R^2 group, would be stabilized effectively (*vide infra*). Less hindered substrates like **1d** and **1e** gave the corresponding products in slightly lower yields (entries 4 and 5). Accordingly, steric hindrance did not appear to be a major problem. We have also investigated the reactions of alkynyloxiranes containing different R^1 groups at the end of the triple bond with methanol. The reactions of alkynes bearing an electron-withdrawing group or an electron-donating group with methanol all led to good yields of the desired products (entries 6–9). Alkynes with heteroaromatic groups such as 2-thienyl proceeded smoothly to afford the corresponding furan, e.g., **2j** in 80% yield (entry 10). Alkynyloxirane **1k** containing an *n*-pentyl group also afforded the desired furan **2k** in good yield (entry 11). Although $HAuCl_4{\cdot}4H_2O$ is a suitable catalyst for many reac-

Table 2. Au(III)-catalyzed synthesis of substituted furans **2** by cyclization of esters of 1-alkynyl-2,3-epoxy alcohols **1** with methanol.[a]



Entry	**1**[c]	R^1	R^2	Conditions	**2**	Yields [%][d]
1	**1a** (7:5)	Ph	Ph	A, 1.5 h; B, 2 h	**2a**	93; 92
2	**1b** (10:7)	Ph	*p*-CH_3-C_6H_4	A, 1 h	**2b**	83
3	**1c** (2:1)	Ph	*p*-Cl-C_6H_4	A, 2 h; B, 2 h	**2c**	67; 70
4	**1d** (2:1)	Ph	CH_3	B, 4 h	**2d**	62
5	**1e** (9:7)	Ph	H	A, 2 h; B, 2.5 h	**2e**	78; 75
6	**1f** (2:1)	*p*-Cl-C_6H_4	Ph	B, 4 h	**2f**	63
7	**1g** (2:1)	*m*-Cl-C_6H_4	Ph	B, 1 h	**2g**	72
8	**1h** (7:5)	*m*-CH_3-C_6H_4	Ph	B, 2 h	**2h**	74
9	**1i** (9:7)	*p*-CH_3O-C_6H_4	Ph	A, 1 h; B, 2 h	**2i**	96; 55
10	**1j** (2:1)	2-thienyl	Ph	A, 1 h	**2j**	80
11[b]	**1k** (5:3)	*n*-C_5H_{11}	H	A, 0.5 h	**2k**	57

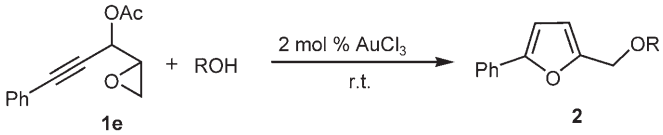
[a] Unless noted, all reactions were carried out using **1** (0.3 mmol) with 2 mol% of catalysts in MeOH (1.0 mL). Conditions A: $AuCl_3$ at room temperature. Conditions B: $HAuCl_4 \cdot 4H_2O$ at 60 °C.
[b] Reaction run with 5 mol% catalyst loading.
[c] *syn*/*anti* mixtures of the substrate were used; *syn*:*anti* ratio determined by ^1H NMR.
[d] Isolated yield.

tions, $AuCl_3$ acts as a more active catalyst in some cases. For example, the cyclization of **1i** afforded prouct **2i** in 96% yield by $AuCl_3$ catalyst (entry 9). However, only a moderate yield of **2i** was obtained when $HAuCl_4 \cdot 4H_2O$ was used (entry 9).

Then we investigated the scope of nucleophiles in this cyclization (Table 3). It was found that, in addition to methanol, a variety of alcohols could be used as effective nucleophiles for this reaction. Treatment of **1e** with ethanol resulted in the formation of **2l** with an ethoxy group in 70% yield (entry 2). When isopropyl alcohol was employed, the corresponding furan **2m** was formed smoothly in 62% yield (entry 3). The use of sterically more hindered alcohols such as *t*-BuOH also proceeded to afford the cyclized product **2n** in 60% yield (entry 4). In addition, allylic alcohol and benzylic alcohol were also readily reacted (entries 5 and 6).

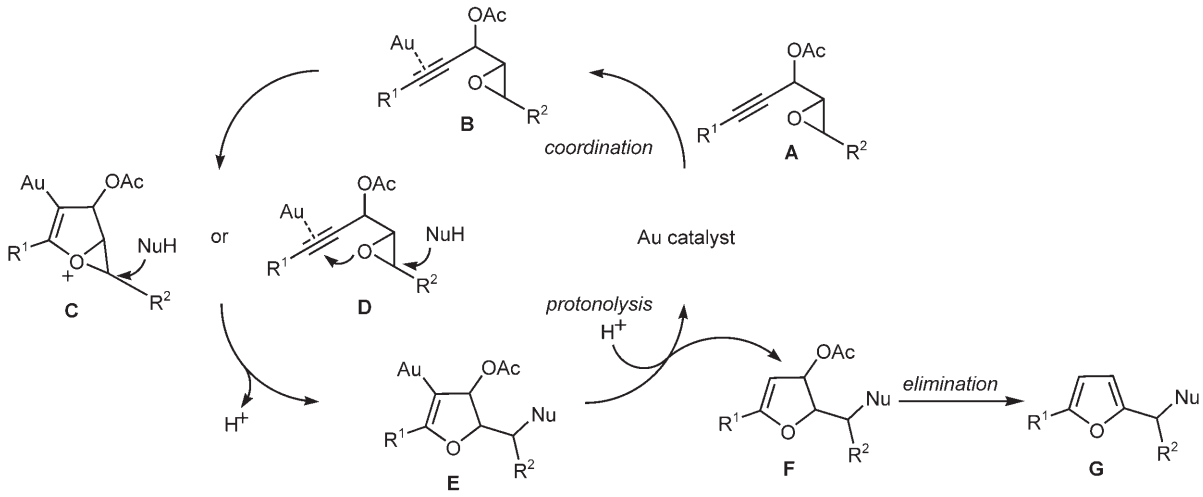
On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 3, which may involve the following steps. (i) Coordination of the alkynyl moiety of **A** to Au catalyst gives the complex **B**. (ii) The subsequent domino nucleophilic attack/*anti-endo-dig* cyclization affords organogold intermediate **E**. (iii) Protonation of **E** yields 2,3-dihydrofuran **F** and regenerates the catalyst Au. (iv) **F** undergoes direct reductive elimination of acetic acid, presumably *via* the corresponding oxonium ion, to afford the 2,5-disubstituted furan **G**.[15] Alternatively, the reaction may involve an oxonium ion **C**,[16] which is formed by the nucleophilic attack of epoxide oxygen to the gold-coordinated alkynes.[17] The oxonium ion **C** undergoes the subsequent reaction with alcohols followed by protonation to regenerate the Au catalyst and produce 2,3-dihydrofuran **F**.

Table 3. Synthesis of 2,5-disubstituted furans **2** using different nucleophiles.[a]



Entry[b]	ROH	Time	**2**	Yields (%)[c]
1	MeOH	2 h	**2e**	(78)[d]
2	EtOH	6 h	**2l**	(70)
3	*i*-PrOH	6 h	**2m**	(62)
4	*t*-BuOH	6 h	**2n**	(60)
5		6 h	**2o**	(60)
6		6 h	**2p**	(61)

[a] Unless noted, all reactions were carried out using **1e** (0.3 mmol) with 2 mol% of $AuCl_3$ in alcohols (1.0 mL) at room temperature (conditions A).
[b] *syn*/*anti* mixtures of **1e** were used in the reaction.
[c] Isolated yield.
[d] 75% yield of **2e** was isolated when the reaction was proceeded under 2 mol% of $HAuCl_4 \cdot 4H_2O$ at 60 °C for 2.5 h.



Scheme 3. Proposed reaction mechanism for Au-catalyzed cyclization.

Conclusions

In summary, a novel catalytic approach to 2,5-disubstituted furans has been developed through the cyclization of esters of 1-alkynyl-2,3-epoxy alcohols with various nucleophiles in moderate to excellent yields under gold catalysts. The reaction proceeds efficiently under mild conditions with commercially available catalysts without any additive. Further studies on the mechanism and the scope of this reaction are in progress in our laboratory.

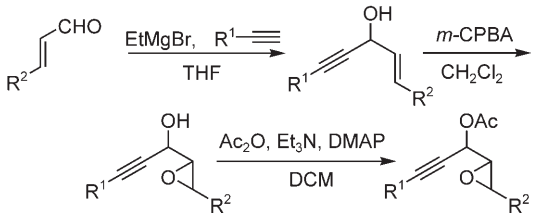
Experimental Section

General Remarks

Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded on 300 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 75 MHz in $CDCl_3$. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All compounds were further characterized by elemental analysis; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting Information. Room temperature is 23–25 °C. Commercially available reagents and solvents were used without further purification. THF was distilled immediately before use from Na/benzophenone.

Representative Procedure for the Synthesis of Alkynyloxiranes 1a–1d, 1f, 1i

To a stirred solution of the appropriate terminal alkyne (1.2 equivs.) in THF (1.0 M) was added ethylmagnesium bromide (1.0 M in THF, 1.1 equivs.) at room temperature. The resulting solution was stirred for 1 h at 50 °C. Then α,β-unsaturated aldehyde (1.0 equiv.) in THF (0.35 M) was added slowly by syringe to the resulting solution at room temperature and stirred for 3 h. The reaction mixture was quenched



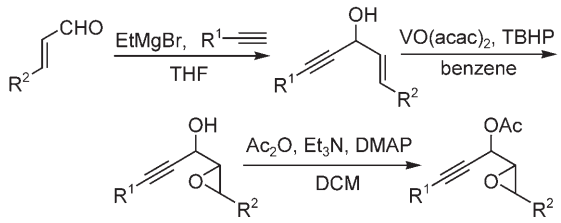
by addition of saturated aqueous ammonium chloride (40 mL) and extracted with ethyl ether (2×40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash column chromatography to obtain the pure propargylic alcohol in quantitative yield.

The propargylic alcohol in dichloromethane (0.35 M) was cooled to 0 °C. To this cooled solution was added *m*-CPBA (1.2 equivs., 77 % w/v in water) and the mixture was stirred for 10 h at room temperature, then the mixture was poured into a mixture of saturated aqueous solutions of $NaHSO_3$ and $NaHCO_3$ (40 mL, 1:1). The aqueous layer was extracted with ethyl ether (2×30 mL). The combined organic layer was dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash column chromatography on silica gel to obtain the 1-alkynyl-2,3-epoxy alcohol as a mixture of diastereoisomers.

To a mixture of the epoxy alcohol in dichloromethane (0.35 M) was added triethylamine (3 equivs.), acetic anhydride (1.2 equivs.), and DMAP (10 mol %) under a nitrogen atmosphere at room temperature. The resultant mixture was stirred for 3 h then washed with water, brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The concentrate was purified by flash column chromatography to obtain the desired esters of 1-alkynyl-2,3-epoxy alcohols as a mixture of diastereoisomers.

Representative Procedure for the Synthesis of Alkynyloxiranes 1e, 1k

The propargylic alcohol was prepared according to the above method. The propargylic alcohol in benzene (0.2 M)

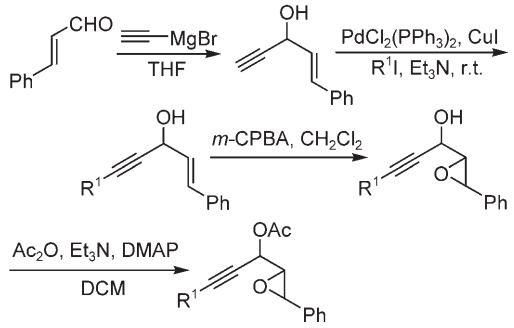


was added $VO(acac)_2$ (10 mol%) at room temperature. After stirring for 5 mim, a solution of *t*-BuOOH (2 equivs., 70% w/v in water) was added and the mixture allowed to refux for 3 h. The reaction mixture was cooled to 0 °C and an aqueous solution of saturated $Na_2S_2O_3$ was added (10 mL). The mixture was stirred for 20 min at room temperature and then extracted with ether (2×40 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield the crude product, which was purified by flash column chromatography to obtain the pure epoxy alcohol as a mixture of diastereoisomers.

Acylation were performed as described in the above procedure.

Representative Procedure for the Synthesis of Alkynyloxiranes 1g, 1h, 1j

To a stirred solution of ethynylmagnesium bromide (3 equivs., 0.35 M in THF) was added cinnamaldehyde



(20 mmol, 0.35 M in THF) at room temperature and stirred for 3 h. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride (60 mL) and extracted with ethyl ether (2×80 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by flash column chromatography to obtain 1-phenylpent-1-en-4-yn-3-ol; yield: 2.37 g (15.0 mmol, 75%).

To a solution of 1-phenylpent-1-en-4-yn-3-ol (1.2 equivs.) and R^1I (1 equiv.) in Et_3N was added $PdCl_2(PPh_3)_2$ (3 mol%). The mixture was stirred for 5 min and CuI (6 mol%) was added. The resulting mixture was then stirred under an argon atmosphere at room temperature for 12 h. The ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding propargylic alcohol.

Epoxidation and acylation were performed as described in the representative procedure.

General Procedure for the Cycloisomerization of Esters of 1-Alkynyl-2,3-epoxy Alcohols to Substituted Furans

Method A: To a solution of esters of 1-alkynyl-2,3-epoxy alcohols **1** (0.30 mmol) in alcohols (1.0 mL) was added 1.81 mg (0.006 mmol, 2 mol%) of $AuCl_3$ under air at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was diluted with ethyl ether (40 mL), washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding furans.

Method B: To a solution of esters of 1-alkynyl-2,3-epoxy alcohols **1** (0.30 mmol) in alcohols (1.0 mL) was added 2.47 mg (0.006 mmol, 2 mol%) of $HAuCl_4{\cdot}4H_2O$ under air at 60 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and diluted with ethyl ether (40 mL). The mixture was washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding furans.

Supporting Information Available

Characterization data for the compounds prepared and copies of ^1H and ^{13}C NMR spectra for **2a–f** are given in the Supporting Information file.

Acknowledgements

We thank the NSF (NSF-20621091, NSF-20672049) and the "Hundred Scientist Program" from the Chinese Academy of Sciences for financial support.

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