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Mechanistic Studies and Improvement of Coinage Metal-Catalyzed Transformation of Alkynyloxiranes to Furans: An Alcohol Addition−Cyclization−Elimination Cascade

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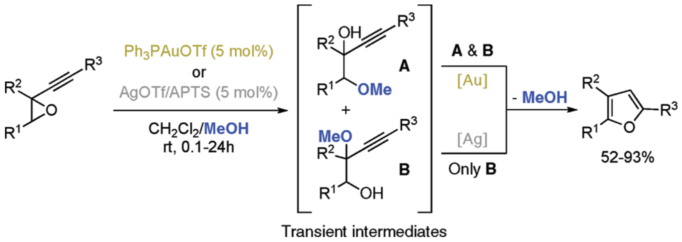

In the presence of alcohol Ag or Au salts or complexes catalyze the conversion of alkynyloxiranes to substituted furans. Both catalysts are effective, and a large furan diversity can be obtained in high yield with one or the other catalyst. Mechanistic studies revealed that a cascade pathway and not the sometimes reported direct intramolecular nucleophilic addition of oxirane oxygen atom to intermediate acetylene−metal π-complex occurs. Under the defined conditions, the intermediate formation of epoxide opening products has been identified. Depending on the catalyst, one or both of the latter cyclized to dihydrofurans, and further elimination of the alcohol led to the corresponding furans. These results highlight the duality between oxophilicity and alkynophilicity of Ag or Au salts.

Introduction

In the past few years, silver and more certainly gold salts and complexes have gained increasing interest from the synthetic organic chemist community. Acting as mild catalysts, they offer a wide variety of new and mild conditions for known reactions as well as new methods in organic synthesis.[1,2]

Most of these new methodologies were based on the alkeno- and alkynophilicity of silver or gold ions,[3] especially for the cyclization of allenyl, alkenyl, or alkynyl alcohols or acids. However, silver and gold ions are Lewis acids and calculations revealed that they also exhibit mild oxophilicity.[4] This property of Ag or Au species has so far been less investigated and applied than alkynophilicity. Nevertheless, a few publications highlight the dual role of late transition metals such as Au or Pd as catalysts.[5]

Reasoning that alkynyloxiranes would be ideal substrates for studying such dual behavior with Ag or Au species, we already studied the transformation of acyloxylated alkynyloxiranes in divinyl ketones through a gold(I)-catalyzed

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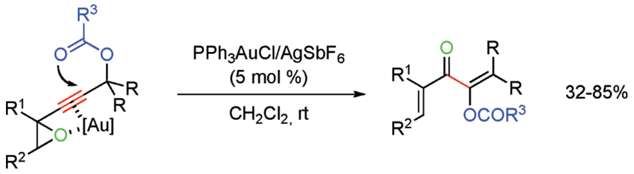
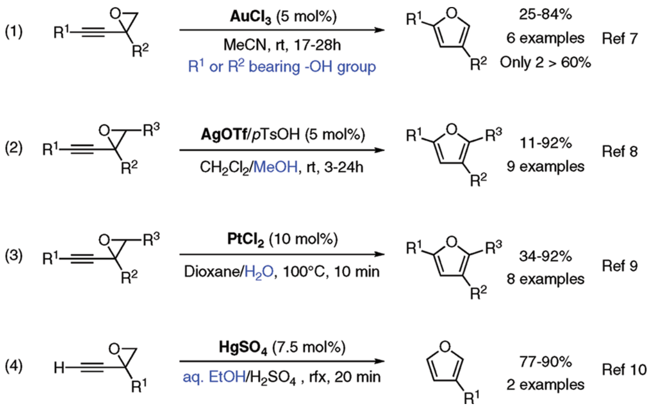
SCHEME 1. Gold(I)-Catalyzed Cascade Initiated by Intramolecular Nucleophilic Addition



SCHEME 2. Late Transition-Metal-Catalyzed Formation of Substituted Furans from Alkynyloxiranes



rearrangement (Scheme 1).[6] In the latter reaction, the acyloxy group served as the internal nucleophile. It is noteworthy that no trace of side reaction and especially no furan product were observed during these reactions even if gold salts are known to catalyze the formation of furans from alkynyloxiranes (Scheme 2, eq 1).[7] Based on this observation, we focused our attention on the mechanism of this furan formation and we very recently showed that silver salts were able to promote such reaction in the presence of an external nucleophile (Scheme 2, eq 2).[8] In parallel, platinum chloride also proved to be an efficient catalyst for this so-called rearrangement (Scheme 2, eq 3).[9] It is worth noting that such a reaction has already been mentioned decades ago with mercury salts as catalysts (Scheme 2, eq 4).[10]

Particularly noteworthy are the reaction conditions in this series. The mercury and platinum versions required ethanol and water, respectively. The role of the latter could not be ascribed. Although not pointed out by the authors, the Au-catalyzed version seemed efficient only when the starting material carried a free hydroxyl group. These observations suggested a key role of water or alcohol on the rate and efficiency of the reaction and led us to investigate an Ag-[8] and an Au-catalyzed versions in the presence of external hydroxy nucleophiles as well as to investigate the mechanism of these Ag and Au-catalyzed reactions. Hydroxy nucleophiles were expected to add to alkynyloxirane through S_N2 or S_N2' pathways, leading to alkynyl alkoxyalcohols or alkoxyallenyl alcohols, which could then be cyclized (Scheme 3, route b).

In the present contribution, we report a comparison of Ag and Au salts or complexes as catalysts for the formation of furans from alkynyloxiranes in the presence of alcohol. We also provided evidence revealing that such reactions did not proceed through the usually proposed intramolecular nucleophilic addition of the oxirane oxygen atom on an intermediate acetylene−metal π-complex[7,9] (Scheme 3, route a) but through a cascade of events promoted by external hydroxy nucleophiles, including adventitious water or alcohol (Scheme 3, route b). These silver- and gold-catalyzed reactions offered a very convergent and mild method for the preparation of highly substituted furans from simple and easily available alkynyloxiranes in the presence of methanol. The silver- and especially the gold-catalyzed transformations described herein clearly improved the few other known methods (see Scheme 2). These reactions also complemented the known late-transition-metal-catalyzed furan formations from allene or alkyne derivatives.[11-14]

Results and Discussion

The role of silver or gold species in the reaction of alkynyloxiranes with alcohols was first examined with the readily available 1-(hex-1-ynyl)-1,2-epoxycyclohexane[15] **1a** as starting material and methanol as external nucleophile.[8] Except for comparison experiments, dichloromethane was used as solvent, due to its low coordinative ability, allowing us to enhance the Lewis acid character of silver or gold ions.

Silver-Catalyzed Reaction. In this solvent at room temperature and with silver triflate as catalyst, **1a** was converted to the corresponding furan **2a**, although no external

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SCHEME 3. Possible Mechanisms of the Transition-Metal-Catalyzed Formation of Substituted Furans from Alkynyloxiranes

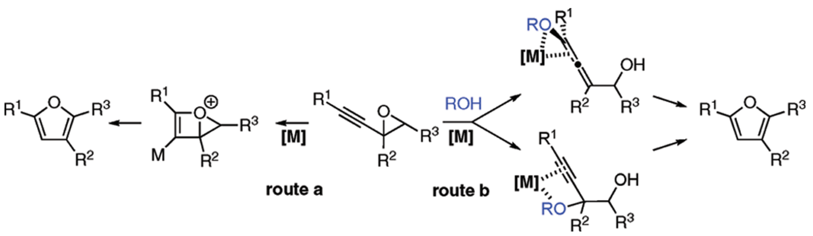
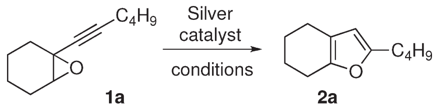


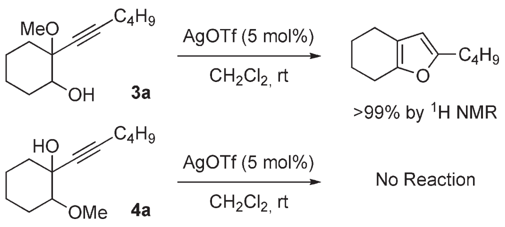
TABLE 1. Screening of Reaction Conditions for the Silver-Catalyzed Transformation of Alkynyloxirane 1a in the Presence of Methanol



entry	catalyst (mol %)	conditions[a]	time (h)	yield of **2a**[b] (%)	**3a**/**4a**[c]
1	AgOTf (5)	CH_2Cl_2 (dry), rt	24	30	
2	AgOTf (5)	CH_2Cl_2/MeOH (9/1), rt	24	73	80/20
3	$AgSbF_6$ (5)	CH_2Cl_2/MeOH (9/1), rt	24	55	74/26
4	$AgNTf_2$ (5)	CH_2Cl_2/MeOH (9/1), rt	24	41	64/36
5	AgOTf/*p*TsOH (5/5)	CH_2Cl_2/MeOH (9/1), rt,	24	**80**	88/12

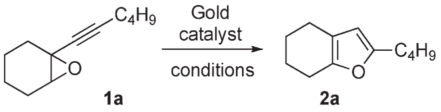
[a] Reactions run under argon, $C = 0.1$ mol/L. [b] Yields of **2a** were calculated from ^{1}H NMR integration relative to hexamethylbenzene as internal standard. [c] Ratio of transient intermediates **3a** and **4a** determined by ^{1}H NMR after 10 min (their presence could already be detected by TLC just after catalyst addition).

SCHEME 4. Reactivity of Compound 3a and 4a in the Presence of AgOTf



nucleophile was a priori present. However, this reaction proceeded in low yield and at a slow rate (Table 1, entry 1). Control experiments revealed that adventitious water either in the solvent or more importantly in the salt was able to catalyze the reaction, leading to variable yields. As expected, the same reaction performed in the presence of methanol as nucleophile provided the furan **2a** in good yield (entry 2). Under the same conditions, silver hexafluoroantimonate as well as silver triflimide induced the same transformation but at a lower rate and some degradation occurred; the product was thus only obtained in modest yields (entries 3 and 4). Monitoring of the later reactions allowed detecting the very fast transient formation of two intermediates, while none of them could be seen in the control experiment without methanol (Table 1, right column, entries 2−5 vs 1). As expected (cf. Scheme 3), these intermediates corresponded to **1a** opening products. However, independent synthesis and comparison with these authentic samples revealed that these intermediates corresponded to the two possible alcohols **3a** and **4a** resulting from methanol S_N2 reaction. The major intermediate **3a** corresponded to epoxide opening at the propargylic position, as shown by a $^3J_{H-OH}$ coupling (4 Hz) as well as its by characteristic chair coupling pattern and especially the shift of two equatorial protons (a broad doublet of triplet centered at 2.08 ppm and a complex broad doublet centered at 1.85 ppm).

TABLE 2. Screening of Reaction Conditions for the Gold-Catalyzed Transformation of Alkynyloxirane 1a in the Presence of Methanol



entry	catalyst (mol %)	conditions[a]	time (h)	yield[b] (%)
1	$AuCl_3$ (5)	CH_3CN (dry), rt	1	31[c]
2	$AuCl_3$ (5)	CH_2Cl_2 (dry), rt	1	36
3	$AuCl_3$ (5)	CH_2Cl_2/MeOH (9/1), rt	24	10
4	AuCl (5)	CH_2Cl_2 (dry), rt	24	12
5	AuCl (5)	CH_2Cl_2/MeOH (9/1), rt	24	11
6	$Ph_3PAuOTf$ (5)	CH_2Cl_2 (dry), rt	1	51
7	$Ph_3PAuOTf$ (5)	CH_2Cl_2/MeOH (9/1), rt	**0.1**	**90**
8	$Ph_3PAuSbF_6$ (5)	CH_2Cl_2/MeOH (9/1), rt	0.1	84
9	$Ph_3PAuNTf_2$ (5)	CH_2Cl_2/MeOH (9/1), rt	1	70

[a] Reactions run under argon, $C = 0.1$ mol/L. [b] Yields of **2a** were calculated from ^{1}H NMR integration relative to hexamethylbenzene as internal standard. [c] Cycloisomerization conditions; see ref 7

Interestingly, both regioisomers behave in a very different way in the presence of silver catalyst. The alcohol resulting from opening at the propargylic position **3a** quantitatively yielded the furan **2a**, while its isomer **4a** remained untouched in separate experiments (Scheme 4). With these results in hand and since the regioselectivity of the in situ oxirane opening seemed to vary with the catalyst nature (entry 4 vs 3 vs 2), we tried to favor the formation of the reactive intermediate **3a**, and the best condition we found was to

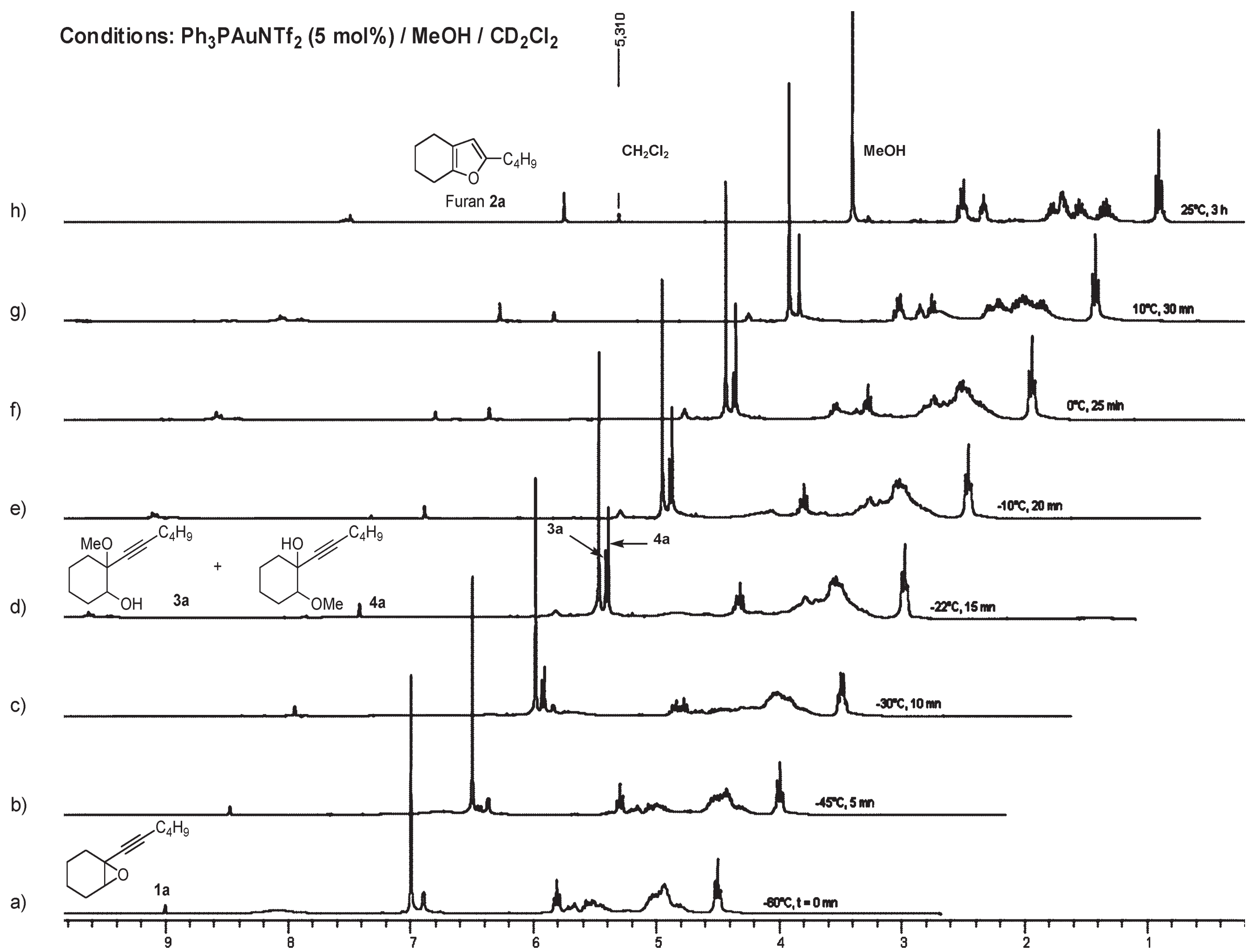


FIGURE 1. ^{1}H NMR spectra of the transient intermediates **3a** and **4a** in gold-catalyzed formation of furan (the ppm scale was calibrated on residual CH_2Cl_2 of the (h) spectrum).

add catalytic amount of *p*-toluenesulfonic acid together with silver triflate. Under these conditions, a high yield of furan was achieved (entry 5).[16]

Gold-Catalyzed Reaction. The gold species was similarly screened in the same transformation (Table 2). Gold trichloride in acetonitrile has been mentioned as catalyst for the cycloisomerization of some alkynyloxiranes to furans.[7] However, under these conditions, the yield of **2a** obtained from **1a** was low, and **1a** mostly gave unidentified polymeric materials. Replacing acetonitrile by dichloromethane did not significantly improve the reaction yield (entry 1 vs 2). In the presence of methanol, the reaction was surprisingly even less effective and mostly gave degradation products (entry 3). Similar results were obtained with gold(I) chloride in the presence or absence of methanol (entries 4−5). In contrast, gold(I) complexes were better catalysts (entries 6−9), especially in the presence of methanol (entry 6 vs 7).[17] The best results were achieved with triphenylphosphinogold triflate (entry 7). Less coordinating counterions proved less effective (entries 8−9 vs 7).

With gold(I) complexes as catalysts (entries 7−9), the reaction was much faster than with silver catalysts (5 min vs 24 h; see Table 1 vs Table 2). No intermediate could be detected during these fast reactions under the conditions set up above. However, running the reaction in a NMR tube at −60 °C in the presence of $Ph_3PAuNTf_2$ and monitoring the evolution of the starting material **1a** upon warming to room temperature revealed again the formation of the two intermediates **3a** and **4a**, even at low temperature (Figure 1; see the Supporting Information for ^{1}H NMR spectra of **3a** and **4a** in CD_2Cl_2 + MeOH). Both appeared at −45 °C, but **3a** already started evolving to the furan **2a** at −30 °C (lines b and c, respectively). Upon warming, **3a** gradually disappeared and at 10 °C, only **4a** was left (line g). However, and in sharp contrast with the Ag-catalyzed version, **4a** was also converted to furan at 25 °C (line h).

Mechanisms. These results showed that in both Ag- and Au(I)-catalyzed furan formation from alkynyloxiranes **1**, the same intermediates **3** and **4** resulting from oxirane opening by methanol were produced (Scheme 5). However, in the gold(I)-catalyzed version, both intermediates could be converted to furan, although at different rates, while in the Ag-catalyzed version, only one of the intermediates, i.e., **3**, could evolve further (see Scheme 4). Furthermore, NMR

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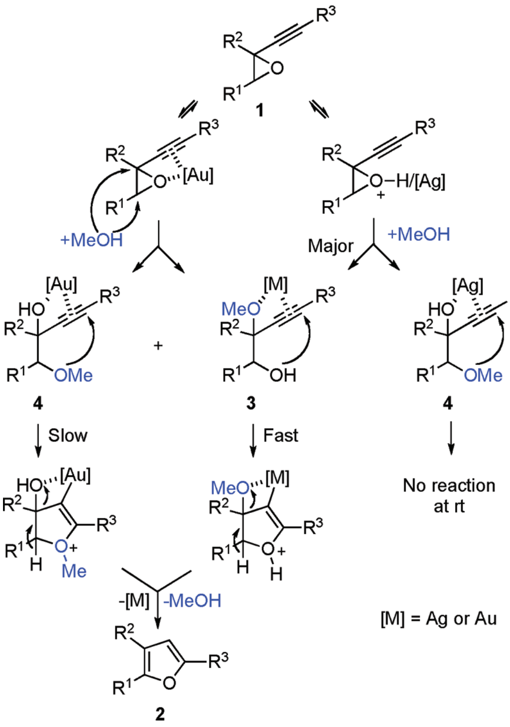
[16] A control experiment showed that *p*-TsOH is not able to allow cyclization of both alcohol **3a** and **4a**.[8]

[17] The reported yield (Table 2, entry 6) is dependent on the quality of CH_2Cl_2 and AgOTf used.

SCHEME 5. **Mechanism of Au- or Ag-Catalyzed Furan Formation by Alcohol Addition–Cyclization–Elimination**



monitoring (Figure 1, lines b, c) suggested that Au(I) was able to promote oxirane opening at *both* positions leading to almost equivalent amount of intermediates **3** and **4**, while Ag was mostly responsible for opening at the propargylic position of **1** (Table 1). These observations are in full agreement with the higher Lewis acidity of gold compared to silver and clearly exemplified this Lewis acid character.[3,4] Such oxirane-opening is also consistent with the recent view of gold as cationic intermediates promoter.[18]

In sharp contrast with silver, gold(I) was also clearly able to promote the cyclization of both intermediates, but for one of them, i.e., the homopropargylic alcohol **3**, the reaction was fast and even proceeded at low temperature, while it was slow and only proceeded at room temperature for the other regioisomer **4**. Such behavior differences could be rationalized by the demetalation step (Scheme 5, bottom part). For **3**, deauration could easily be achieved by proton loss, while for **4**, a methyl group must be removed, probably through nucleophilic displacement by either the water released upon elimination or excess of methanol (Scheme 5, left side). The latter process was clearly less easy than the former, accounting for the different evolution observed by NMR. Similar reasons could also contribute to the lack of reactivity of **4** in the presence of Ag, reinforcing its lower Lewis acid character (Scheme 5, right side).

One of the late steps of this cascade, i.e., elimination, could be assisted by electrophilic interaction with silver or gold. With gold, both intermediates exhibited either the hydroxy or methoxy groups adjacent to gold, and thus the Lewis acid character of gold could facilitate the elimination of these groups.[10] With silver, only the intermediate with the alkoxy group adjacent to the metal was formed and could also evolve by Lewis acid promoted elimination (Scheme 5, bottom part).[19] Nevertheless, protonation by the catalytic amounts of *p*-toluenesulfonic acid could not be excluded in this case.

It is worth noting that other hydroxy nucleophiles, such as water or ethanol, 2-propanol, could also be used in this cascade reaction. A slight decrease in isolated yields was nevertheless observed with larger alcohols.

These mechanistic studies allowed us to understand the role of water or alcohol, either added in purpose or adventitiously, in the known related reactions (see Scheme 2). In the Pt- and Hg-catalyzed reaction, water or ethanol was required as well as high temperatures, and under these conditions, they most probably induced oxirane opening. The formed intermediates probably evolved as described above for the Ag- and Au-catalyzed reactions. On the other hand, the $AuCl_3$-catalyzed reaction required substrate carrying free hydroxyl group. This alcohol most probably acted as water, methanol, or ethanol and induced the same cascade of events.

Scope. With these results in hands, we then explored the scope of this silver- or gold(I)-catalyzed furan formation. Various alkynyloxiranes were prepared by epoxidation of the corresponding enynes with *m*-chloroperbenzoic acid.[20] Non-commercially available enynes were obtained by Sonogashira-type[21] coupling reaction or by Carlson's[15] procedure (see the Supporting Information). The overall yields of this two- to three-step sequence were routinely higher than 30%.

For comparison purposes, each alkynyloxirane was submitted both to AgOTf and to *p*-TsOH and to $Ph_3PAuOTf$ as catalyst in the CH_2Cl_2/MeOH mixture at room temperature (Table 3).

In order to examine the role of alkyne substituents in these rearrangements, we compared a series of epoxycyclohexanes carrying a hexynyl, a phenylethynyl, or just an ethynyl chain (entries 1–3). As mentioned above, 1,2-epoxy-1-hexynylcyclohexane **1a** gave the corresponding 2-hexynyltetrahydrobenzofuran **2a** in high yields under both conditions (entry 1). However, 1,2-epoxy-1-phenylethynylcyclohexane **1b** gave low yield of product with Ag as catalyst due to degradation but high yield with Au as catalyst (entry 2). The simplest ethynyl derivative **1c** only led to decomposition products in the presence of AgOTf/*p*-TsOH, probably due to the formation of alkynyl silver under these conditions,[22] while Au catalyst gave the expected tetrahydrobenzofuran **2c** in high yield (entry 3).

The size of the ring joined to the epoxide was also examined, expecting that with a strained system the cascade reaction would be easier. Surprisingly, the five-membered derivative **1d** mostly gave degradation products with both

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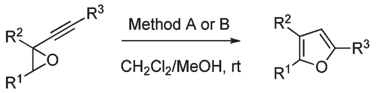
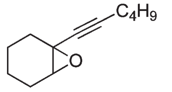
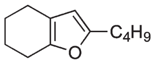
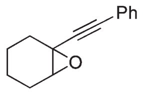
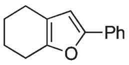
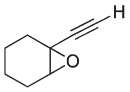
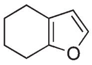
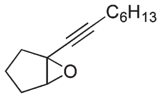
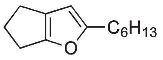
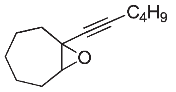
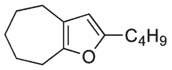
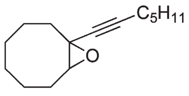
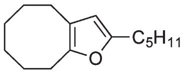
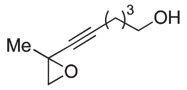
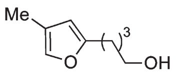
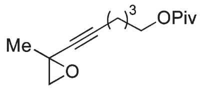
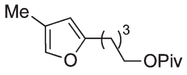
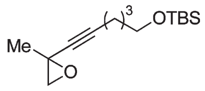
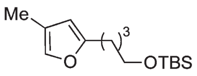
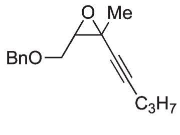
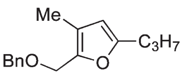
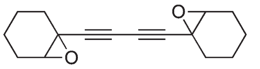
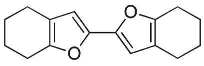
TABLE 3. Scope of Silver(I) or Gold(I)Catalyzed Furan Formations



entry	alkynyloxiranes		furans		A[a]		B[b]	
					yields (%)[c]	time (h)	yields (%)[c]	time (h)
1		**1a**		**2a**	80	24	85	0.1
2		**1b**		**2b**	11[e]	24	87[f]	1
3		**1c**		**2c**	-[e]	24	82	30
4		**1d**		**2d**	-[e]	24	20[d,e]	10
5		**1e**		**2e**	72	3	70	0.25
6		**1f**		**2f**	92	3	93	0.25
7		**1g**		**2g**	52	2	69[f]	0.25
8		**1h**		**2h**	81	16	75[f]	0.25
9		**1i**		**2i**	84	16	79[f]	0.25
10		**1j**		**2j**	-[e]	24	80[f]	0.25
11		**1k**		**2k**	-[e]	24	72	24

[a] Method A: AgOTf/*p*TsOH (5 mol%); [b] Method B: $Ph_3PAuOTf$ (5 mol%); [c] Isolated yields; [d] Yields calculated by ^1H NMR of the crude mixture; [e] Degradation occurred giving unidentified polymeric materials; [f] Reaction run at 0 °C.

catalysts, and only the gold-catalyzed reaction allowed us to detect some of the expected furan (entry 4). The seven membered derivative **1e** gave the same results under both conditions, but the furan formation was slightly less effective than with the six-membered epoxyalkyne **1a** (entry 5 vs 1). The reverse trend was observed with the eight membered derivative **1f**, which gave the corresponding furan in excellent yield with both catalysts (entry 6 vs 1).

Although they could compete as nucleophiles, free alcohols without protecting group were tolerated in these

Ag- and Au-catalyzed reactions (entry 7). As expected from our mechanistic studies, the Au-catalyzed version was so efficient that the reaction was best performed at 0 °C. Protection as ester or silyl ether proved nevertheless more efficient, the corresponding furans being isolated with higher yields (entries 8−9 vs 7). In these cases, the Ag catalyst was slightly more effective than the Au catalyst. The latter results contrasted with all other examples, for which gold catalysis proved to be milder than silver catalysis and gave better yields (column B vs A). This was clearly evidenced with the reaction of **1b−d** but also with the reaction of the benzyl protected epoxyalkyne **1j**, since in this case, the Ag catalyst led to decomposition while the Au catalyst allowed to isolate the expected furan in high yields (entry 10). The latter example showed that benzyl ether as protecting group was also well tolerated. The mildness and high efficiency of the Au-catalyzed rearrangement was highlighted with the reaction of a diepoxydiyne **1k** which could be cyclized twice under the Au catalysis conditions but not at all under the Ag catalysis conditions (entry 11).

Conclusion

In conclusion, we have found that alkynyloxiranes isomerized to highly substituted furans in a cascade reaction promoted by alcohols and catalyzed by Ag or Au catalysts. Mechanistic investigations revealed that such reactions proceed through a cascade of events: epoxide opening by the added alcohol, cyclization of the intermediates and elimination of alcohol. These observations also highlighted the dual role of silver or gold species in organic reactions.

Experimental Section

General Procedure for Silver(I)- or Gold(I)-Catalyzed Formation of Furans from Alkynyloxiranes. Method A (Silver Catalysis). To a solution of alkynyloxirane (1 mmol) in CH_2Cl_2/MeOH (5 mL, 9/1 v/v) were added successively *p*-toluenesulfonic acid (APTS, 0.05 mmol) and AgOTf (0.05 mmol) at room temperature. The reaction was monitored by thin-layer chromatography until completion. The reaction mixture was filtered throughout a pad of silica gel with CH_2Cl_2. Solvents were removed in vacuo, and the crude residue was purified by flash chromatography.

Method B (Gold Catalysis). Alkynyloxirane (1 mmol in 1 mL of CH_2Cl_2) was added to a stirred solution of premixed Ph_3PAuCl (0.05 mmol) and AgOTf (0.05 mmol) in CH_2Cl_2/MeOH (5 mL, 9/1 v/v) at 0 °C or room temperature. The reaction was monitored by thin-layer chromatography until completion. The reaction mixture was filtered throughout a pad of silica gel with CH_2Cl_2. Solvents were removed in vacuo, and the crude residue was purified by flash chromatography.

2-Butyl-4,5,6,7-tetrahydrobenzofuran (2a). Following method B, alkynyloxirane **1a** (200 mg, 1.12 mmol) gave **2a** (170 mg, 85%) as a colorless oil: $R_f = 0.64$ (cyclohexane/EtOAc 20%); IR (neat) ν_{max} 2935, 2870, 1738, 1674, 1520, 1446, 1379, 1220, 1165, 1120, 1095, 982 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.3$ Hz, 3 H), 1.39 (sext, 7.4 Hz, 2 H), 1.58 (quint, $J = 5.7$ Hz, 2 H), 1.66−1.75 (m, 2 H), 1.78−1.85 (m, 2 H), 2.37−2.40 (m, 2 H), 2.54−2.60 (m, 4 H), 5.79 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.1, 22.3, 23.1, 23.2, 23.3, 27.8, 30.4, 105.4, 117.1, 148.6, 154.2; MS (ESI) *m*/*z* 357 (100, $2M^{\bullet +} + 2H$), 179 (95, $M^{\bullet +} + H$); HR-MS 179.1438 ($C_{12}H_{18}O + H$ calcd 179.1430).

Following method A, alkynyloxirane **1a** (100 mg, 0.56 mmol) gave **2a** (80 mg, 80%).

2-(Benzyloxymethyl)-3-methyl-5-propylfuran (2j). Following method B, alkynyloxirane **1j** (75 mg, 0.3 mmol) gave **2j** (60 mg, 80%) as a colorless oil: $R_f = 0.58$ (cyclohexane/EtOAc 5%); IR (neat) ν_{max} 2963, 2932, 3874, 1725, 1682, 1496, 1453, 1377, 1314, 1270, 1176, 1095, 1069, 1026, 934 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 0.82 (t, $J = 7.4$ Hz, 3 H), 1.55 (sext, 7.5 Hz, 2 H), 1.85 (s, 3 H), 2.43 (t, $J = 7.8$ Hz, 2 H), 4.36 (s, 2 H), 4.41 (s, 2 H), 5.72 (s, 1 H), 7.05−7.16 (m, 3 H), 7.30 (d, $J = 6.7$ Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 9.9, 13.8, 21.6, 30.3, 62.2, 71.5, 108.7, 119.7, 127.5, 127.8, 128.4, 139.2, 146.3, 155.6; MS (ESI) *m*/*z* 283 (100, $M^{\bullet +} + K$), 267 (43, $M^{\bullet +} + Na$); HR-MS 283.1068 ($C_{16}H_{20}O_2 + K$ calcd 283.1095).

Acknowledgment. We gratefully acknowledge the CNRS and the French Ministry of Research for financial support. K.T. thanks the Friedrich-Alexander-Universität Erlagen-Nürnberg and ULP for their exchange program and support.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.