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Gold(I)-Catalyzed Tandem Rearrangement–Nucleophilic Substitution of α-Acetoxy Alkynyl Oxiranes or Aziridines: Efficient Approach to Furans and Pyrroles

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Keywords: Gold / Cyclization / Homogeneous catalysis / Oxygen heterocycles / Nitrogen heterocycles

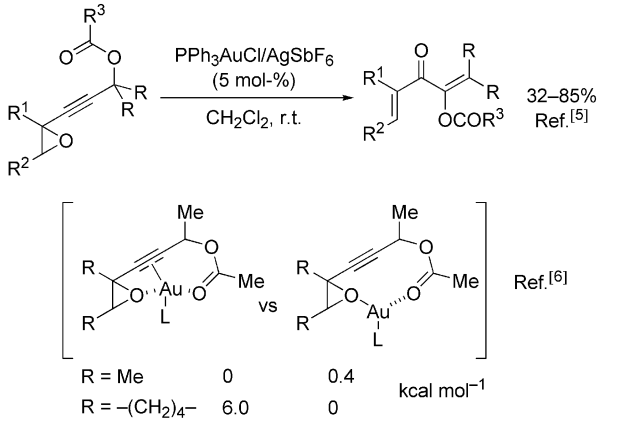
Highly substituted furans and pyrroles were efficiently formed by a new gold(I)-catalyzed tandem rearrangement–nucleophilic substitution of acetoxylated alkynyl oxiranes and aziridines in the presence of various nucleophiles.

Introduction

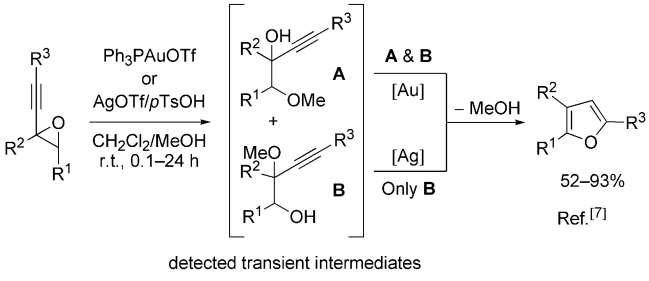
Gold catalysis[1] has revamped the chemistry of propargyl derivatives and especially that of propargyl esters.[2] Gold coordination to the alkyne moiety of such compounds usually induces rearrangements through internal 1,2- or 1,3-nucleophilic addition of the ester carbonyl group to the Au-activated alkyne. Although gold salts have the reputation of being alkeno- and alkynophilic,[1,3] recent evidence showed that oxophilicity could also play a key role in Au-catalyzed reactions of alkynyl derivatives containing heteroatoms.[4] This duality was also highlighted by our own work on the rearrangement of acyloxylated alkynyloxiranes into divinyl ketones catalyzed by a gold(I) complex (Scheme 1).[5] Moreover, recent theoretical mechanistic studies of this reaction revealed only a slight stability difference between π– and σ–Au complexes of such substrates (Scheme 1). These calculations also showed that both activations, that is, alkynophilicity and Lewis acid character of gold, could be operative in this rearrangement.[6]

In parallel, we recently found that alkynyloxiranes could also be rearranged into furans in the presence of an external nucleophile and catalytic amounts of silver or gold salts. This process occurred by nucleophile opening of the epoxide ring followed by a cyclization–elimination process (Scheme 2).[7]

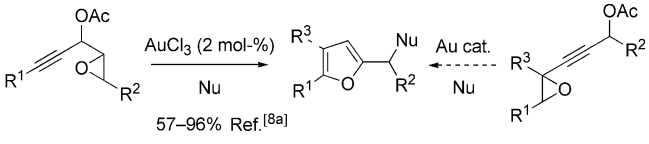
On the basis of our previous reports, we thought that 2,3,5-trisubstituted furans could also be produced from α-acyloxylated α′-alkynyloxiranes and external nucleophiles by gold catalysis through oxophilic and/or alkynophilic ac-



Scheme 1. Gold(I)-catalyzed rearrangement of acyloxylated alkynyl oxiranes in divinyl ketones.



Scheme 2. Coinage metal-catalyzed transformation of alkynyl oxiranes into furans.



Scheme 3. Nucleophile-mediated furan formation in gold catalysis.

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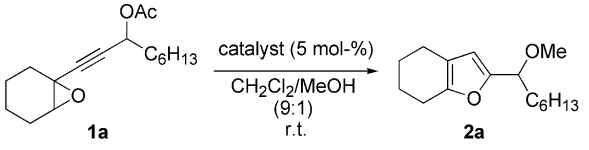
tivation. Such a route would be a convenient alternative to the rearrangement of α-acyloxylated β′-alkynyloxiranes described by Liang[8] (Scheme 3).

Results and Discussion

In the present study, we report that gold(I) catalyzes an efficient tandem rearrangement–nucleophilic substitution[9] of α-acetoxyalkynyl oxiranes mediated by various nucleophiles to afford furans. We also extended this chemistry to the corresponding aziridines, which gave pyrroles.

In order to establish the most appropriate reaction conditions, we subjected readily available (3-acetoxyprop-1-ynyl)-oxirane[5] **1a** to a series of gold catalysts in the presence of methanol in dichloromethane (Table 1). Treating **1a** with 5 mol-% of gold(I) chloride slowly provided the expected furan **2a** bearing a methoxy group, although in only 45% yield due to some decomposition (Table 1, Entry 1). $AuCl_3$ significantly improved the rate of the reaction, as **2a** was obtained in only 1 h in 76% yield (Table 1, Entry 2). Using the more cationic gold complex $Ph_3PAuSbF_6$ formed in situ, **2a** was formed in a fast and very clean reaction in excellent isolated yield (Table 1, Entry 3). Other counteranions did not improve this transformation (Table 1, Entries 4 and 5). Control experiments revealed that silver hexafluoroantimonate also catalyzed the same reaction but to a lesser extent[7b] (Table 1, Entry 6) and that triphenylphosphanylgold chloride alone was totally ineffective (Table 1, Entry 7).

Table 1. Screening of catalysts for the transformation of acetoxylated alkynyloxiranes **1a**.



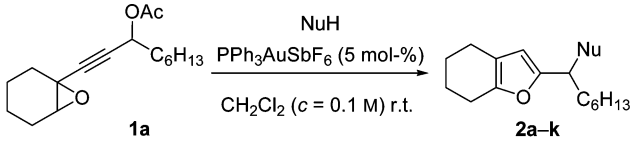
1a **2a**

Entry	Catalyst	Time [h]	Yield [%][a]
1	AuCl	15	45[b]
2	$AuCl_3$	1	76
3	$PPh_3AuCl/AgSbF_6$	0.25	95
4	$PPh_3AuCl/AgNTf_2$	0.5	74
5	$PPh_3AuCl/AgOTf$	0.25	85
6	$AgSbF_6$	20	50[c]
7	PPh_3AuCl	20	–[d]

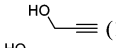
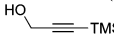
[a] Yield of isolated pure product. [b] Degradation of the starting material occurred. [c] 35% of the starting material was recovered. [d] No conversion.

Various representative nucleophiles, such as alcohols, thiols, and amines were then engaged in the transformation of **1a** (Table 2). In each case, we adjusted the amount of nucleophile used. For methanol, 2 equivalents was enough, although the efficiency of the reaction was slightly affected, but 5 equivalents gave the same yield than an excess of methanol (Table 2, Entries 1 and 2 vs. Table 1, Entry 3). Screening more hindered alcohols showed that 10 equivalents of nucleophile were necessary to keep high yields. Under these conditions, ethanol, butyl alcohol, and 2-propanol gave furans **2b**–**d** in 86, 83, and 82% yield, respectively (Table 2, Entries 3–5). In the presence of *tert*-butyl alcohol, the rapid formation of furan **2e** was detected but degradation occurred, which led to polar products (Table 2, Entry 6). Ten equivalents of allyl alcohol was required to obtain a reasonable yield of furan **2f** (Table 2, Entry 7). In contrast, treatment of **1a** with benzyl alcohol resulted in the formation of benzyloxy furan **2g** in high yield (Table 2, Entry 8). With the perspective to induce the formation of highly substituted phenols through a cascade reaction, similar to the report of Hashmi,[10] we tried to introduce a propargyl moiety adjacent to the furan. Epoxyalkyne **1a** was thus submitted to the reaction conditions in the presence of propargyl alcohol. Unfortunately, mostly degradation products were observed (Table 2, Entry 9). Nevertheless, with protected 3-trimethylsilylprop-2-yn-1-ol, furan **2i** was obtained in 41% yield (Table 2, Entry 10). Interestingly, ethanethiol and benzyl thiol proved fully compatible with the gold catalyst, despite their coordination ability. They acted as alcohols, leading to the corresponding thio-substituted furans **2j**,**k** in good yields (Table 2, Entries 11 and 12). In contrast, amines failed as nucleophiles, and starting materials were mostly recovered, probably due to their strong coordination to gold (Table 2, Entries 13 and 14).

Table 2. Scope of the nucleophiles used in the gold(I)-catalyzed rearrangement of **1a** into furans.



1a **2a–k**

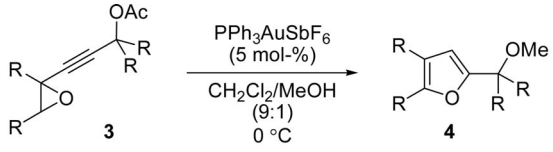
Entry	Nucleophile (equiv.)	Furan	Time [h]	Yield [%][a]
1	MeOH (2)	**2a**	0.5	82
2	MeOH (5)	**2a**	0.25	95
3	EtOH (10)	**2b**	1	86
4	BuOH (10)	**2c**	0.25	83
5	*i*PrOH (10)	**2d**	0.25	82
6	*t*BuOH (10)	**2e**	1	–[b]
7	allyl alcohol (10)	**2f**	0.5	59
8	benzyl alcohol (10)	**2g**	0.5	94
9	 (10)	**2h**	1	–[b]
10	 (10)	**2i**	0.5	41
11	EtSH (10)	**2j**	0.5	79
12	benzyl thiol (10)	**2k**	1	73[c]
13	benzyl amine (5)	**2l**	16	–[b]
14	$PhSO_2NH_2$ (5)	**2m**	16	–[d]

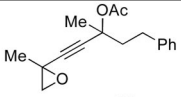
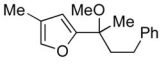
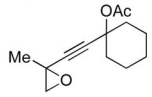
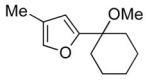
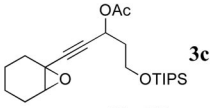
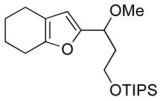
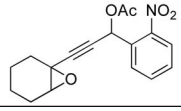
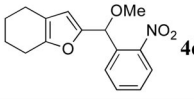
[a] Yield of isolated pure product. [b] Degradation occurred leading to unidentified byproducts. [c] Calculated yield on a nonseparable mixture of **2k** and benzyl thiol. [d] No conversion.

With these results in hand, we examined the scope of this gold(I)-catalyzed tandem rearrangement–nucleophilic substitution on various alkynyloxiranes (Table 3). Compounds **3a**,**b** were previously rearranged into divinyl ketones in the presence of $Ph_3PAuSbF_6$,[5] but addition of a nucleophile

led to completely different issues. Indeed, in the presence of methanol, α-methoxyfurans **4a**,**b** were rapidly obtained in high yields of 85 and 92%, respectively (Table 3, Entries 1 and 2) and it is noteworthy that no trace of other products could be detected. Similarly, alkynyloxirane **3c** generated α-methoxyfuran **4c** in good yield (Table 3, Entry 3). Even substrate **3d** bearing an *o*-nitrophenyl group attached to the propargylic position provided methoxyfuran **4d**, although in modest yield and with a longer reaction time (Table 3, Entry 4).

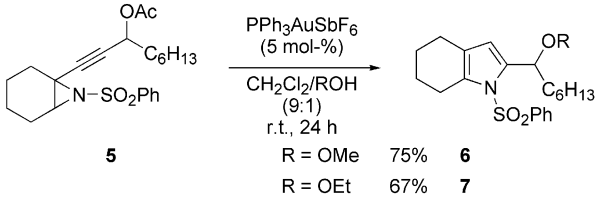
Table 3. Scope of the gold(I)-catalyzed tandem rearrangement–nucleophilic substitution of alkynyloxiranes to furans in the presence of methanol.



Entry	Alkynyloxirane		Time [h]	Furan		Yield [%][a]
1		**3a**	0.75		**4a**	85
2		**3b**	0.75		**4b**	92
3		**3c**	1		**4c**	74
4		**3d**	3		**4d**	59

[a] Yield of isolated pure product.

We then sought to extend the tandem reaction to analogous aziridine compounds that would give highly substituted pyrroles.[11] As expected, acyloxylated alkynylaziridine **5**, synthesized in 41% yield from the corresponding enyne by using the procedure of Andersson,[12] was efficiently converted into pyrroles **6** (75%) and **7** (67%) in the presence of methanol or ethanol, respectively (Scheme 4).



Scheme 4. Gold(I)-catalyzed rearrangement of alkynylaziridines into pyrroles in the presence of alcohols.

Conclusions

In conclusion, we have reported a novel Au-catalyzed cascade reaction of acetoxylated alkynyloxiranes and -aziridines. This cascade allows various highly substituted furans and pyrroles carrying different alkoxy or alkylthio groups at the α-position to be produced. Several mechanistic pathways can be considered such as 1,2-acyl migration concomitant with oxirane opening, followed by nucleophilic substitution, cyclization, and elimination (Scheme 5). Further studies, including calculations and detailed investigations into the mechanism of this reaction, are in progress in our laboratory.

Experimental Section

General Procedure for Preparation of α-Substituted Furans or Pyrroles: Alkynyloxirane or alkynylaziridine (0.2 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 (9:1, 1 mL) or in CH_2Cl_2 (1 mL) containing the corresponding nucleophile (5 or 10 equiv.) 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.

Supporting Information (see footnote on the first page of this article): Selected experimental procedures and spectroscopic data.

Acknowledgments

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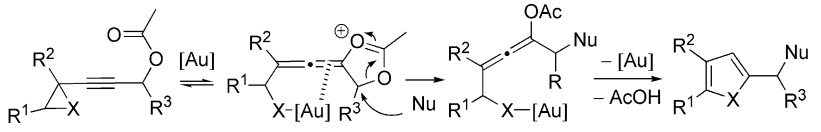

Scheme 5. Proposed mechanistic pathway.

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