Gold-catalyzed cycloisomerization of alk-4-yn-1-ones†

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Depending on the substitution pattern and the solvent, the gold-catalyzed cyclization of alk-4-yn-1-ones **1** affords different oxygen heterocycles under mild reaction conditions. Alkynones with one substituent at C-3 undergo a *5-exo-dig* cycloisomerization to substituted furans **2**, whereas a *6-endo-dig* cyclization to 4*H*-pyrans **3** is observed with substrates bearing two substituents at C-3. In alcoholic solvents, alkylidene/benzylidene-substituted tetrahydrofuranyl ethers **4** are formed in a tandem nucleophilic addition/cycloisomerization.

Introduction

The development of new methods for the synthesis of heterocycles is of particular interest in organic chemistry. Due to their atom efficiency, transition metal-catalyzed cycloisomerizations belong to the most powerful tools in organic synthesis. Whereas gold catalysis had received little attention in the past (mainly because gold was considered to be inert and expensive), the use of gold salts in homogeneous catalysis has attracted more and more interest in the last decade because of their ability to activate carbon-carbon multiple bonds.[1] Thus, a variety of nucleophiles can be added under extremely mild conditions to these activated multiple bonds.

Due to their unique electronic structure and reactivity,[2] alkynes are the substrates of choice in homogeneous gold catalysis.[1] They are much more reactive than the corresponding alkenes. In gold-catalyzed cycloisomerization reactions, various internal nucleophiles such as nitrogen,[3] oxygen,[4] and even sulfur[5] groups have been used for addition to the activated triple bond, thereby granting access to a high diversity of heterocyclic products. Of particular interest is the use of carbonyl groups since they can undergo tandem reactions, consisting of a nucleophilic addition to this function followed by cyclization. Various heterocycles have been synthesized using this approach in homogeneous gold catalysis.[6] Godet *et al.* recently reported a tandem acetalization/cycloisomerization of quinoline derivatives providing pyranoquinolines with a high conversion rate.[6a] 1-Alkynyl-1*H*-isochromenes were synthesized by Li and coworkers in an alkynylation-cyclization sequence of terminal alkynes with alkynylaryl aldehydes,[6b] whereas cyclization of 2-oxobut-3-ynoates with nucleophiles provides a general route to 3(2*H*)-furanones.[6c] Pyrroles can be obtained by cycloisomerization of imines formed *in situ* from alkynones.[6d]

Furans play a special role in the field of oxygen heterocycles. Because of their importance as intermediates in organic synthesis[7] and their occurrence in a variety of natural compounds[8] and important pharmaceuticals,[8,9] many methods for the synthesis of furans have been developed.[10] Whereas some examples for the cyclization of pentynones leading to furans under strong acidic[11] or basic[12] conditions were reported in literature, only a few examples of transition metal-catalyzed cycloisomerizations of alk-4-yn-1-ones to substituted furans are known. Besides Pd catalysis at elevated temperatures (>60 °C),[13] Nishizawa and coworkers reported a $Hg(OTf)_2$-catalyzed cycloisomerization of pentynones to methylfurans in benzene at room temperature.[14] Also gold-catalyzed cycloisomerizations of functionalized alkynes play an important role: (*Z*)-alk-2-en-4-yn-1-ols,[15] alka-2,3-dien-1-ones,[16] alk-3-yn-1-ones[17] and alkynyloxiranes[18] can be converted to substituted furans. Herein we report the results of our study on the gold-catalyzed cycloisomerization of alk-4-yn-1-ones **1** which, depending on the substitution pattern of the substrate and the reaction conditions, can afford furans **2**, 4*H*-pyrans **3**, or tetrahydrofuranyl ethers **4** (Scheme 1).

Results and discussion

The starting materials are readily available either by $FeCl_3$-catalyzed nucleophilic substitution of propargyl acetates with enoxysilanes[10a] or by reaction of an enolate with propargyl bromide.[6d] Different aryl groups were introduced into terminal alk-4-yn-1-ones by Sonogashira coupling.[19] Initial cycloisomerization experiments were performed with ketone **1a** as model substrate using different gold precatalysts (2 mol%) and catalytic

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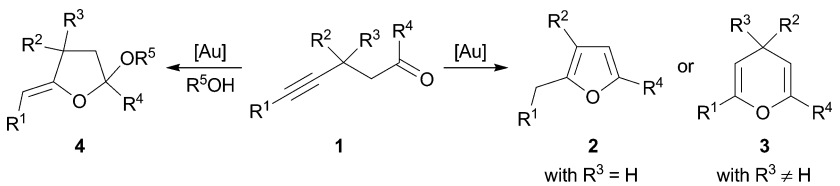
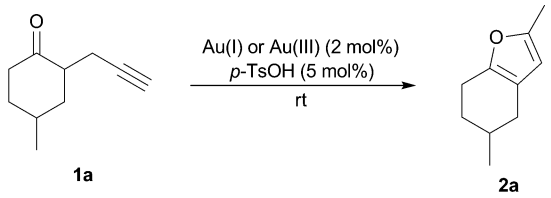


Scheme 1 Gold-catalyzed cycloisomerization of alk-4-yn-1-ones **1**.

Table 1 Optimization of reaction conditions for the gold-catalyzed cycloisomerization of alkynone **1a** to furan **2a**



1a **2a**

Entry	Solvent	Precatalyst	Additive	Time	Yield/%
1[a]	toluene	Ph_3PAuCl	AgOTf	1 h	80
2	toluene	Ph_3PAuCl	AgOTf	20 min	91
3	toluene	Ph_3PAuCl	$AgSbF_6$	20 min	85
4	toluene	Ph_3PAuCl	$AgBF_4$	20 min	57
5	toluene	$AuCl_3$	—	5 h	traces[b]
6	toluene	AuCl	—	5 h	traces[c]
7	toluene	$HAuCl_4$	—	3 h	63
8	toluene	$Au(OAc)_3$	—	4 h	35[d]
9	toluene	$AuBr_3$	—	3 h	57
10	toluene	—	AgOTf	5 h	—
11	toluene	—	—	5 h	—
12	CH_2Cl_2	Ph_3PAuCl	AgOTf	20 min	82
13	Et_2O	Ph_3PAuCl	AgOTf	20 min	70
14	THF	Ph_3PAuCl	AgOTf	3 h	47
15	MeCN	Ph_3PAuCl	AgOTf	3 h	44

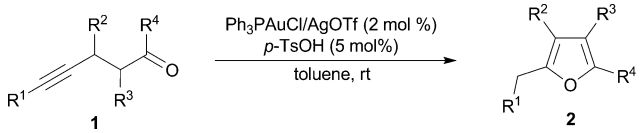
[a] In the absence of *p*-TsOH · H_2O. [b] 84% of starting material was reisolated. [c] 78% of starting material was reisolated. [d] 50% of starting material was reisolated.

amounts of *p*-TsOH · H_2O (5 mol%) in various solvents at room temperature (Table 1).

In contrast to the cyclization of alk-4-ynones with *p*-TsOH which requires refluxing in toluene,[10a] the furan **2a** was obtained with 80% yield at room temperature in the presence of just 2 mol% of the cationic gold precatalyst $Ph_3PAuOTf$ generated *in situ* from Ph_3PAuCl and AgOTf (entry 1). Combining gold and acid catalysis by addition of 5 mol% of *p*-TsOH · H_2O led to a slightly increased reaction rate and chemical yield (entry 2). In contrast to this, other cationic (entries 3, 4) or neutral gold precatalysts (entries 5–9) gave inferior results. AgOTf and *p*-TsOH · H_2O alone are inactive under the reaction conditions (entries 10, 11). Besides toluene, other weakly coordinating solvents (dichloromethane, diethyl ether; entries 12, 13) can be used as well, whereas low reaction rates and yields were observed in THF or acetonitrile (entries 14, 15).

Since the gold-catalyzed cycloisomerization of alk-4-yn-1-ones can be performed in the presence or absence of the Brønsted acid *p*-TsOH, both stable and acid-labile substrates can be converted to substituted furans under the appropriate reaction conditions. The generality of the method was proven by applying the optimized reaction conditions to various alk-4-yn-1-ones **1** (Table 2). Both

Table 2 Gold catalyzed cycloisomerization of alk-4-yn-1-ones **1** to substituted furans **2**[a]



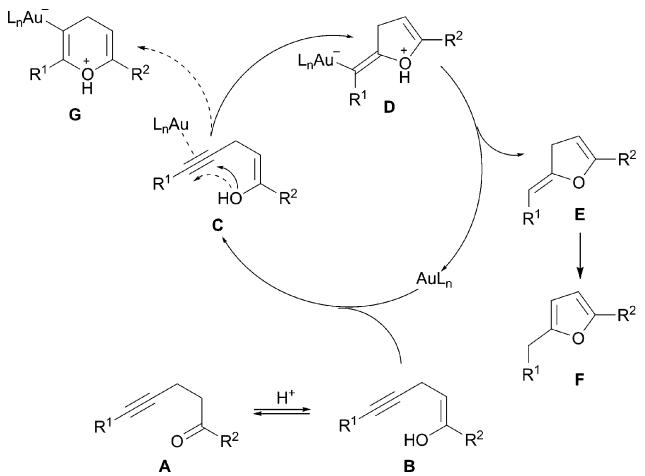
1 **2**

Entry	**1**	R^1	R^2	R^3	R^4	Time/min	**2** (Yield/%)
1	**1b**	H	H	H	Ph	20 (30)	**2b** 87 (82)
2	**1c**	H	H	H	4-$MeOC_6H_4$	20	**2c** 77
3	**1d**	H	H	*i*-Pr	*i*-Bu	120 (180)	**2d** 76 (74)
4	**1e**	H	H	$CH_2C{\equiv}CH$	4-$MeOC_6H_4$	60	**2e** 64
5	**1f**	4-BrC_6H_4	H	H	Ph	60	**2f** 84
6	**1g**	4-$MeO_2CC_6H_4$	H	H	4-$MeOC_6H_4$	45	**2g** 57
7	**1h**	4-BrC_6H_4	H	$CH_2CHMeCH_2CH_2$		45	**2h** 72
8	**1i**	4-BrC_6H_4	H	Me	Et	60	**2i** 81
9	**1j**	4-BrC_6H_4	H	*i*-Pr	*i*-Bu	300	**2j** 69
10	**1k**	4-$MeOC_6H_4$	H	Me	Et	60	**2k** 71
11	**1l**	Ph	Ph	H	Ph	30 (40)	**2l** 63 (67)
12	**1m**	Ph	Ph	Me	*i*-Pr	90	**2m** 75

[a] Reaction time and yield given in parentheses refer to cyclizations performed in the absence of *p*-TsOH · H_2O.

terminal (entries 1–4) and internal alkynes (entries 5–12) can be cyclized with similar efficiency to afford the furans **2** with 57–87% yield. The presence of sterically demanding groups (entries 3, 9, 12) led to slightly increased reaction times, but full conversion was reached within 1.5–5 h. The method also tolerates the presence of electron-rich (entries 2, 4, 6, 10) or electron-deficient aryl groups (entries 5–9), of additional triple bonds (entry 4) as well as ester groups (entries 6, 10). It should be noted that even the tetrasubstituted furan **2m** is accessible with good yield (75%) by our method. Performing the cycloisomerization in the absence of *p*-toluenesulfonic acid resulted in slightly slower reactions, but very similar yields (entries 1, 3, 11).

On the basis of the accelerating affect of the Brønsted acid *p*-TsOH, we propose the reaction mechanism shown in Scheme 2. The catalytic cycle is initiated by coordination of the gold catalyst to the triple bond of enol **B** to afford the π-complex **C** which is transformed into the zwitterionic intermediate **D** by *5-exo-dig* attack of the oxygen at the activated triple bond. Protodemetalation of **D** releases the gold catalyst into the catalytic cycle and affords the alkylidene derivative **E** which undergoes a rapid isomerization to the substituted furan **F**. The accelerating effect of the Brønsted acid *p*-TsOH may be twofold: it catalyzes the equilibrium between the starting alkynone **A** and its enol form **B**, and it might also be involved in the protodemetalation of intermediate **D**.



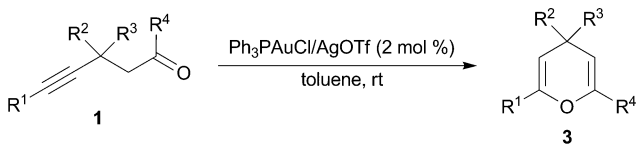
Scheme 2 Proposed mechanism for the gold-catalyzed cycloisomerization of alk-4-yn-1-ones to furans.

Interestingly, the formation of a six-membered ring **G** by *6-endo-dig* cyclization of intermediate **C** was not observed with the alk-4-yn-1-ones used so far. However, this pathway becomes accessible if the substrate bears two substituents at C-3 which prevent formation of a furan **2**. Treatment of the alkynones **1n–q** with 2 mol% of Ph_3PAuCl and AgOTf afforded the corresponding 4*H*-pyrans **3** with 53–67% yield after 20–45 min reaction time at room temperature (Table 3). With AgOTf alone, no conversion of substrate **1n** was observed (entry 1). The butyl-substituted alkynone **1q** (entry 4) was found to cyclize faster than the phenyl-substituted counterparts **1n–o** (entries 1–3) and gave the highest yield. In contrast to the formation of furans **2**, addition of *p*-TsOH · H_2O does not affect the rate of the *6-endo-dig* cyclization.

A third pathway for the gold-catalyzed cyclization of alk-4-yn-1-ones was opened by changing the solvent from toluene to an alcohol. This acts not only as solvent, but also as nucleophile and induces formation of alkylidene/benzylidene-substituted tetrahydrofuranyl ethers **4** instead of furans **2** or 4*H*-pyrans **3**. The scope of this tandem nucleophilic addition/cycloisomerization reaction is summarized in Table 4.

Whereas treatment of the terminal alkynone **1a** with 2 mol% of Ph_3PAuCl and AgOTf in methanol resulted in the formation of a complex product mixture, various alkynones **1l–t** with an internal triple bond and one (entries 1, 2) or two substituents at C-3 (entries 3–14) afforded the *5-exo-dig* cyclization products **4** with 53–87% yield. The substrate was consumed after 10–30 min at room temperature when primary alcohols were used while 60 min were required in the reaction of alkynone **1o** with isopropanol (entry 6). No conversion of ketone **1n** or **1r** was observed in the absence of Ph_3PAuCl (entries 3, 9). Similar to the other cyclization modes of alkynones **1**, the formation of the tetrahydrofuranyl ethers **4** is not affected by the substituent pattern. Besides various benzylidene-substituted tetrahydrofuranyl ethers, the alkylidene-substituted product **4qa** was obtained with 53% yield from alkynone **1q** and ethanol (entry 8). Even the cyclohexyl-substituted ketone **1n** furnished the corresponding spiro compounds **4na**/**4nb** with good yield (66/76%, entries 3, 4). In the case of substrates bearing two different substituents at C-3, the tandem nucleophilic addition/cycloisomerization leads to the formation of diastereomeric products; the diastereoselectivities are low and range from 55 : 45 to 80 : 20 (entries 1, 2, 5–8). All tetrahydrofuranyl ethers were formed as a single isomer with regard to the excocyclic double bond. The configuration of product **4oa** was determined with the aid of an NOE experiment; a strong

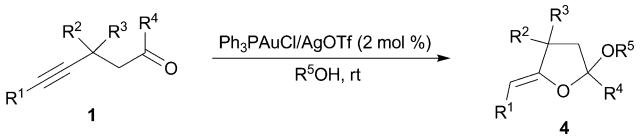
Table 3 Gold-catalyzed cycloisomerization of alk-4-yn-1-ones **1** to 4*H*-pyrans **3**



Entry	**1**	R^1	R^2	R^3	R^4	Time/min	**3** (Yield/%)
1	**1n**	Ph	$(CH_2)_5$		Ph	45	**3n** (53)[a]
2	**1o**	Ph	Ph	Me	Ph	40	**3o** (58)
3	**1p**	Ph	Ph	Me	Me	40	**3p** (64)
4	**1q**	*n*-Bu	Ph	Me	Ph	20	**3q** (67)

[a] No conversion in the absence of Ph_3PAuCl.

Table 4 Gold-catalyzed tandem nucleophilic addition/cycloisomerization alk-4-yn-1-ones **1** to tetrahydrofuranyl ethers **4**



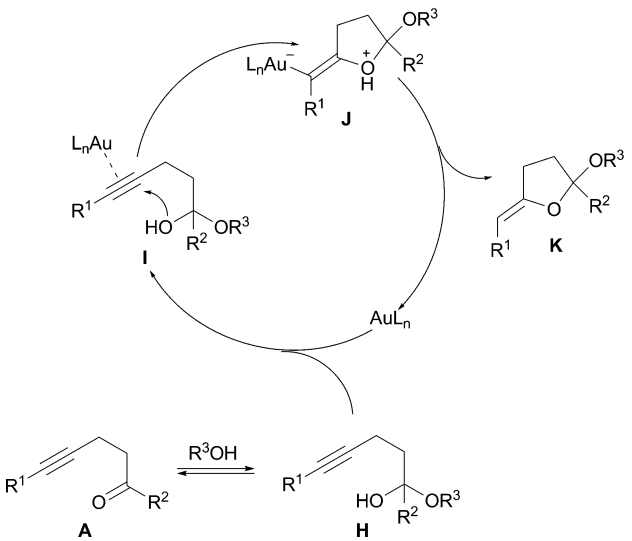
Entry	1	R^1	R^2	R^3	R^4	R^5	Time/min	4 (yield/%)
1	**1l**	Ph	Ph	H	Ph	Me	20	**4la** (75)[a]
2	**1l**	Ph	Ph	H	Ph	Et	40	**4lb** (67)[a]
3	**1n**	Ph	$(CH_2)_5$		Ph	Me	10	**4na** (76)[b]
4	**1n**	Ph	$(CH_2)_5$		Ph	Et	30	**4nb** (66)
5	**1o**	Ph	Ph	Me	Ph	Me	20	**4oa** (87)[c]
6	**1o**	Ph	Ph	Me	Ph	*i*-Pr	60	**4ob** (59)[c]
7	**1p**	Ph	Ph	Me	Me	Me	20	**4pa** (78)[d]
8	**1q**	*n*-Bu	Ph	Me	Ph	Et	30	**4qa** (53)[e]
9	**1r**	Ph	Me	Me	Ph	Me	10	**4ra** (62)[b]
10	**1r**	Ph	Me	Me	Ph	Et	30	**4rb** (64)
11	**1s**	Ph	Et	Et	Ph	Me	10	**4sa** (76)
12	**1s**	Ph	Et	Et	Ph	Et	20	**4sb** (75)
13	**1s**	Ph	Et	Et	Ph	*n*-Pr	20	**4sc** (70)
14	**1t**	4-$MeO_2CC_6H_4$	Me	Me	Ph	Me	20	**4ta** (59)

[a] *dr* = 80 : 20. [b] No conversion in the absence of Ph_3PAuCl. [c] *dr* = 57 : 43. [d] *dr* = 63 : 37. [e] *dr* = 55 : 45.

cross peak between the vinylidene proton and the methyl group at C-4 of the tetrahydrofuran ring proves the *Z*-configuration.

Interestingly, the addition of the Brønsted acid *p*-toluenesulfonic acid has a pronounced influence on the course of the gold-catalyzed cyclization of alk-4-yn-1-ones **1** in alcohols. Whereas treatment of alkynone **1l** with catalytic amounts of Ph_3PAuCl, AgOTf, and *p*-TsOH · H_2O in methanol or ethanol furnished the furan **2l** (67/71% yield) instead of the tetrahydrofuranyl ethers **4la**/**4lb**, the substrate **1o** with two substituents at C-3 gave a 1 : 3-mixture of the 4*H*-pyran **3o** and the ether **4oa**, accompanied by other non-identified products.

Similar to the tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohols to tetrahydrofuranyl ethers,[4e] the formation of the heterocycles **4** may be explained by a hydroalkoxylation of 2,3-dihydrofurans **E** (Scheme 2). However, it seems difficult to explain why no attack of the alcohol at the exocyclic double bond of intermediate **E** is observed. In order to account for this experimental finding, we assume that the reaction is initiated by a (gold-catalyzed?) formation of the hemiacetal **H** which then undergoes addition to the activated triple bond in intermediate **I** (Scheme 3). This leads to the zwitterionic species **J**, protodemetalation of which affords the tetrahydrofuranyl ether **K** with *Z*-configuration at the exocyclic double bond.



Scheme 3 Proposed mechanism for the gold-catalyzed tandem nucleophilic addition/cycloisomerization alk-4-yn-1-ones to tetrahydrofuranyl ethers.

Conclusions

In this paper, we describe three efficient pathways for the gold-catalyzed cycloisomerization of alk-4-yn-1-ones. Substrates **1a–m** with a terminal or internal triple bond undergo a *5-exo-dig* cycloisomerization to the corresponding multisubstituted furans **2** under very mild conditions by using the cationic gold complex $Ph_3PAuOTf$ in toluene. Addition of catalytic amounts of *p*-TsOH · H_2O accelerates the reaction, but is not mandatory. Various functional groups are tolerated in this transformation, which uses much milder and/or environmentally benign conditions than previous methods. A change in regioselectivity was observed with alkynones **1n–q** bearing two substituents at C-3 which furnish 4*H*-pyrans **3** by *6-endo-dig* cycloisomerization. Finally, both substrate types afford alkylidene/benzylidene-substituted tetrahydrofuranyl ethers **4** when the reaction was carried out in an alcoholic solvent. These transformations probably proceed *via* enols or hemiacetals which act as internal nucleophiles for the attack at the triple bond which is activated by the gold catalyst. Our results underline the power of gold catalysis for the synthesis of structurally diverse heterocycles.

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