Synthetic Methods

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Gold-Catalyzed Oxidative Ring Expansions and Ring Cleavages of Alkynylcyclopropanes by Intermolecular Reactions Oxidized by Diphenylsulfoxide**

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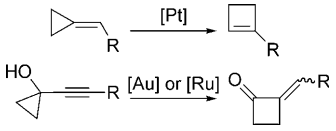
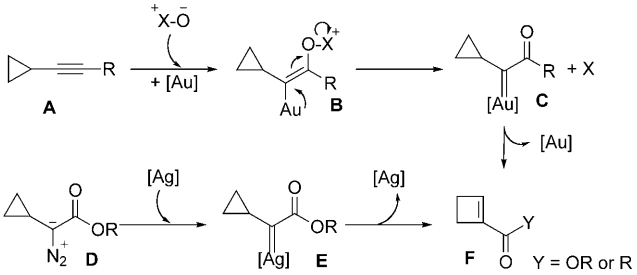
Cyclobutane derivatives are important structural units in many natural products,[1,2] but efficient methods for their synthesis are few compared to those for the preparation of other carbocyclic systems.[3,4] An advance in the synthesis of cyclobutane derivatives involves metal-catalyzed ring-expansions of cyclopropane derivatives, including alkylidenecyclopropanes,[5] allenylcyclopropanols[6] or alkynylcyclopropanols,[7] with selected examples depicted in Scheme 1. Such



Scheme 1. Metal-catalyzed ring-expansions of certain cyclopropane derivatives.

reported reactions should be classified as isomerization reactions, without introduction of a new functionality.[8] Herein, we report a gold-catalyzed oxidative ring-expansion of alkynylcyclopropanes **A** via hypothetic carbenoids **C** (Scheme 2); this approach introduces a new ketone functionality in a regioselective manner using an external oxygen donor such as X^+-O^-. Related to this work is a report by Tang and co-workers[9] on the synthesis of cyclobutenyl esters **F** via silver(I)-catalyzed decomposition of diazocarbonyl precursors **D** (Scheme 2). Our new method is advantageous because substrate preparation is much easier for alkynylcyclopropane derivatives **A** than for cyclopropyl diazocarbonyl species **D**. Besides ring-expansions, we have also developed an oxidative ring-cleavage of cyclopropylalkynes using Ph_2SO.

The generation of hypothetic gold α-carbonylcarbenoids from tethered sulfur, amine, imine, and pyridine oxides was reported by the research groups of Toste, Zhang, and Shin,

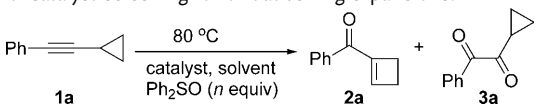


Scheme 2. Approach for ring-expansions of certain cyclopropane derivatives.

respectively.[10–12] These oxidation reactions were performed exclusively with cationic gold catalysts $[PR_3AuCl]/AgX$. Despite their elegant work, these oxygen donors were commonly used to generate gold α-carbonylcarbenoids[12] by intramolecular activation of alkynes.[13,14] An intermolecular process is likely perturbed by secondary oxidation of α-carbonylcarbenoid intermediates with these oxides.[7b,15]

In Table 1, we selected Ph_2SO as the oxygen donor because amine oxide, pyridine oxide,[16] and imine oxide were inactive for the oxidation of alkynylcyclopropane **1a** when using $[PPh_3Au]SbF_6$. With this sulfoxide (1.0 equiv) and $[PPh_3Au]SbF_6$ (5 mol%) in hot 1,2-dichloroethane (DCE,

Table 1: Catalyst screening for oxidative ring-expansions.[a]



Entry	Catalyst (5 mol%)	Ph_2SO [equiv]	Solvent	t [h]	Products (yield [%])[b]		
					1a	2a	3a
1	$[PPh_3AuCl]/AgSbF_6$	1	DCE	24	35	40	20
2	$[IPrAuCl]/AgSbF_6$	1	DCE	24	50	19	29
3	$[LAuCl]/AgSbF_6$	1	DCE	24	48	42	–
4	$[LAuCl]/AgNTf_2$	1	DCE	24	43	52	–
5	$[LAuCl]/AgNTf_2$	3	DCE	24	23	70	–
6	$[LAuCl]/AgNTf_2$	5	DCE	24	–	83	–
7	$AgNTf_2$	5	DCE	24	96	–	–
8	$[LAuCl]/AgNTf_2$	5	$MeNO_2$	12	–	90	–
9	$[LAuCl]/AgNTf_2$	5	1,4-dioxane	12	–	62	–
10	$[LAuCl]/AgNTf_2$	5	MeCN	12	98	–	–
11	TfOH	5	DCE	24	94	–	–

[a] Reaction conditions: [substrate] = 0.1 M, 100 °C, $MeNO_2$. [b] Yield of isolated product after separation by column chromatography on silica gel. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, L = P(*t*Bu)$_2$(*o*-biphenyl), Tf = trifluoromethanesulfonyl.

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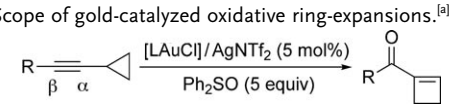
80 °C, 24 h) we observed an oxidation of species **1a** to give the desired cyclobutenyl ketone **2a** (40 %), diketone **3a** (20 %), and starting material **1a** (35 %; Table 1, entry 1). Poor activity and chemoselectivity were also observed for [IPrAuCl]/$AgSbF_6$ under the same reaction conditions (Table 1, entry 2). Although [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/$AgSbF_6$ showed an improved selectivity toward the desired **2a** (48 %) with negligible formation of diketone **3a**, the extent of conversion was moderate (52 %; Table 1, entry 3). We selected $AgNTf_2$ to generate [P(*t*Bu)$_2$(*o*-biphenyl)Au]NTf_2 which improved the yield (52 %) of desired **2a** (Table 1, entry 4). Enhanced yields were obtained with three- and fivefold excess of Ph_2SO and afforded **2a** in 70 % and 83 % yields, respectively (Table 1, entries 5 and 6). We speculate that Ph_2SO tends to stabilize the Au^I complex from decomposition to Au^0. $AgNTf_2$ alone failed to catalyze the reaction at all (Table 1, entry 7). When we examined the solvent effects (Table 1, entries 8–10), we found that nitromethane gave the best yield of **2a** (90 %) over a moderate period (12 h) at 80 °C. Brønsted acid TfOH was inactive as a catalysis in this reaction (Table 1, entry 11).

Table 2 includes various alkynylcyclopropane derivatives **1b**–**1q** bearing either an aryl or an amino group to ensure that attack of Ph_2SO occurs only at the C_β carbon atom. Under optimized conditions, the gold-catalyzed ring-expansions occurred smoothly, without formation of diketone by-products. Entries 1–6 of Table 2 show the effects of *para*-substituted phenyl substituents; we obtained excellent yields (92–95 %) of resulting cyclobutenyl ketones **2b**–**2c** bearing electron-donating groups such as methyl and methoxy. Notably, the catalytic reactions maintained satisfactory efficiency with substrates **1d**–**1g** containing electron-withdrawing groups including fluoro, chloro, bromo, and ethoxycarbonyl; the corresponding products **2d**–**2g** were obtained in 61–86 % yields after longer reaction times. Such oxidative ring-expansions worked well with phenylalkynylcyclopropanes **1h**–**1m** bearing altered *meta*-substituents comprising methoxy, fluoro, chloro, 2,4-dimethoxy, 2,3-methylenedioxy, and 2-naphthyl groups; their resulting products **2h**–**2m** were obtained in 72–95 % yields (Table 2, entries 7–12). This gold catalysis is particularly suitable for aminoalkynylcyclopropanes **1n**–**1q**; the reactions were completed within 2–5 hours, and gave desired cyclobutenyl amides in 91–95 % yields (Table 2, entries 13–16).

Table 3 shows the applicability of this catalysis to substituted cyclopropylalkynes **4a** and **4b**, which delivered cyclobutenyl ketones **6a** and **6b** in 71 and 76 % yields, respectively. Substrate **4c** underwent smooth reaction with PhArSO (1.0 equiv, Ar = 2-MeC_6H_4) and gave the desired ketone **6c** in 84 % yield. In the case of substituted cyclopropylalkynes **4d** and **4e**, the desired products **6d** and **6e** were obtained in 56 and 61 % yields, respectively. These reaction outcomes resulted from a selective migration of the more substituted C–C cyclopropyl bond.

For curiosity, we extended the use of this catalysis to other arylalkyne derivatives **5a**,**b**; these oxidation reactions proceeded smoothly using Ph_2SO (1.2 equiv), but gave compounds **7a**,**b** arising from addition of Ph_2S to the alkynyl carbon atom adjacent to the aryl group. Similar results were reported by Ujaque, Asensio, and co-workers,[10e] who proposed a [3,3]-sigmatropic rearrangement rather than carbenoid intermediates to give these addition products. Accordingly, we performed crossover experiments (Scheme 3), which clearly indicate that external sulfides are not the reaction sources for compounds **7c** and **7c′**, thus excluding the intermediacy of α-carbonylcarbeniods **C** that were hypothesized in Scheme 2.

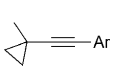
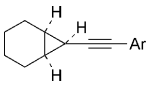
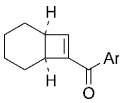
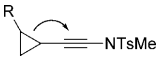
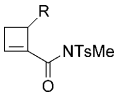
Table 2: Scope of gold-catalyzed oxidative ring-expansions.[a]



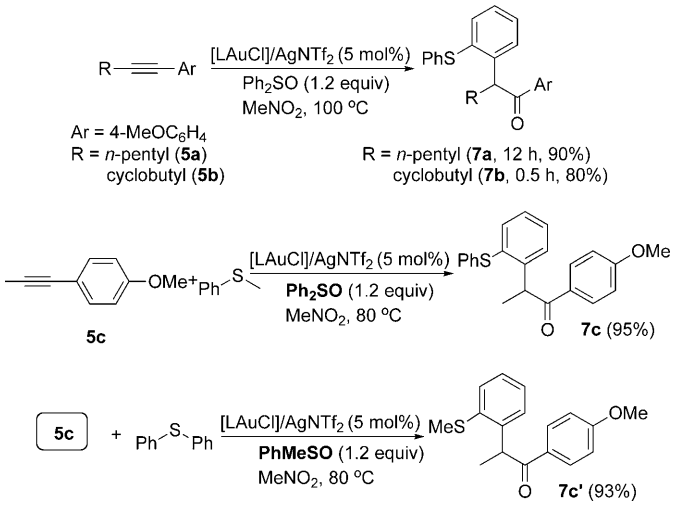
Entry	Substrate	*t* [h]	Product (yield [%])[b]
1	R = 4-MeC_6H_4 (**1b**)	10	**2b** (92)
2	R = 4-MeOC_6H_4 (**1c**)	8	**2c** (95)
3	R = 4-FC_6H_4 (**1d**)	15	**2d** (86)
4	R = 4-ClC_6H_4 (**1e**)	24	**2e** (77)
5	R = 4-BrC_6H_4 (**1f**)	20	**2f** (69)
6	R = 4-$MeO_2CC_6H_4$ (**1g**)	24	**2g** (61)
7	R = 3-MeOC_6H_4 (**1h**)	8	**2h** (85)
8	R = 3-FC_6H_4 (**1i**)	12	**2i** (72)
9	R = 3-ClC_6H_4 (**1j**)	15	**2j** (72)
10	R = 3,5-$(MeO)_2C_6H_3$ (**1k**)	12	**2k** (72)
11	R = 3,4-$(OCH_2O)C_6H_3$ (**1l**)	8	**2l** (95)
12	R = 2-naphthyl (**1m**)	12	**2m** (92)
13	R = TsNMe (**1n**)	5	**2n** (94)
14	R = TsN(*n*Pr) (**1o**)	2	**2o** (91)
15	R = MsNMe (**1p**)	5	**2p** (95)
16	R = MsNBn (**1q**)	5	**2q** (93)

[a] Reaction conditions: [substrate] = 0.1 M, 100 °C, $MeNO_2$. [b] Yield of isolated product after separation by column chromatography on silica gel. Bn = benzyl, L = P(*t*Bu)$_2$(*o*-biphenyl).

Table 3: Gold catalyzed ring-expansion of substituted cyclopropylalkynes.

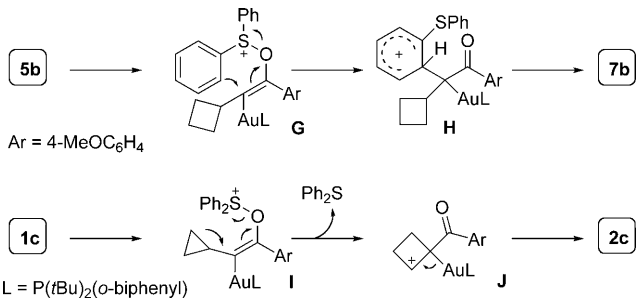
Entry	Cyclopropane	Conditions[a]	Product (yield [%])[b]
			
1	Ar = 4-MeOC_6H_4 (**4a**)	$MeNO_2$, 8 h	**6a** (71)
2	Ar = 3,4-$(MeO)_2C_6H_3$ (**4b**)	$MeNO_2$, 8 h	**6b** (76)
			
3	Ar = 4-MeOC_6H_4 (**4c**)	$MeNO_2$, 5 h	**6c** (84)[c]
			
4	R = $C_6H_4CH_2$ (**4d**)[d]	$MeNO_2$/DCE[e]	**6d** (56)
5	R = *n*-C_6H_{13} (**4e**)[d]	$MeNO_2$, 7 h	**6e** (61)

[a] Reaction conditions: [LAuCl]/$AgNTf_2$ (5 mol %; L = P(*t*Bu)$_2$(*o*-biphenyl)), [substrate] = 0.1 M, Ph_2SO (5 equiv), 100 °C, $MeNO_2$. [b] Yield of isolated product after separation by column chromatography on silica gel. [c] PhArSO (1.0 equiv, Ar = 2-MeC_6H_4) was used. [d] 1:1 mixture of diastereomers. [e] Solvent ratio of 1:1, 24 hours.



Scheme 3. Crossover experiments.

For the Ph_2SO-oxidation of cyclobutylalkyne species **5c** (Scheme 4), we speculate that initial intermediate **G** proceeds through a reported [3,3]-sigmatropic rearrangement; this mechanism was supported by computational results.[10e] We

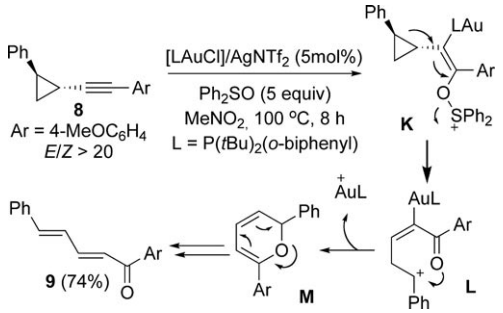


Scheme 4. Mechanism for Ph_2SO-oxidation of cyclopropylalkyne and cyclobutylalkyne.

did not observe this rearrangement for tested cyclopropylalkyne substrates including **1c**; we hypothesize that the absence of rearrangement is attributed to a competitive 1,2-cyclopropyl expansion that facilitates cleavage of the O–S^+ bond to generate cyclobutyl cationic intermediate **J** and the observed product **2c**.

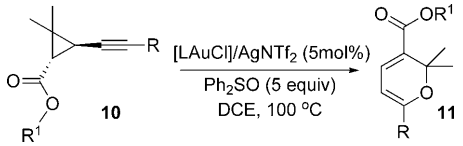
Cyclopropane compounds are prone to ring-cleavage when the donor and acceptor groups are present as vicinal substituents at the cyclopropane ring.[16] As shown in Scheme 5, we observed a new catalysis involving the oxidative ring-cleavage of cyclopropylalkynes **8** using Ph_2SO and the gold catalyst that gave 2,4-dien-1-one **9** in 74% yield. We envisage that this ring-cleavage follows a typical push-pull model,[16] as exemplified by species **K**, giving benzyl cation **L** with an *E* configuration that ultimately gave **9** through a *retro*-6π electrocyclization of 2*H*-pyran species **M**.

Table 4 depicts the use of this oxidative cleavage reaction for an efficient synthesis of 2*H*-pyrans; we were pleased to find that the same gold catalysis on the functionalized cyclopropylalkynes **10a**–**10g** gave the desired 2*H*-pyrans



Scheme 5. Oxidative ring-cleavage of cyclopropylalkynes **8**.

Table 4: Oxidative cleavage reaction for an efficient synthesis of 2*H*-pyran.[a]



Entry	Cyclopropane	R	R^1	*t* [h]	Product (yield [%])[b]
1	**10a**	C_6H_5	Me	32 (48)[c]	**11a** (55, 19[d])
2	**10b**	4-MeC_6H_4	Me	40	**11b** (72)
3	**10c**	4-$tBuC_6H_4$	Me	40	**11c** (62)
4	**10d**	4-$MeOC_6H_4$	Et	40	**11d** (70)
5	**10e**	3,4-$(MeO)_2C_6H_3$	Me	30	**11e** (65)
6	**10f**	3,5-$(MeO)_2C_6H_3$	Me	30	**11f** (60)
7	**10g**	4-FC_6H_4	Et	35	**11g** (65)

[a] Reaction conditions: [LAuCl]/$AgNTf_2$ (5 mol%; L = IPr), [substrate] = 0.1 M. [b] Yield of isolated product after separation by column chromatography on silica gel. [c] This is the reaction time when L = P(*t*Bu)$_2$(*o*-biphenyl). [d] This is the yield when L = P(*t*Bu)$_2$(*o*-biphenyl).

11a–**11g** in up to 72% yield, without a *retro*-6π ring-opening. For cyclopropylalkyne **10a**, [IPrAuCl]/$AgNTf_2$ gave 2*H*-pyran **11a** in a better yield (55%; Table 4, entry 1) than that obtained when [P(*t*Bu)$_2$(*o*-biphenyl)AuCl]/$AgNTf_2$ was used (19%; Table 1, entry 2). Such syntheses of 2*H*-pyran are suitable for substrates **10b**–**10f** bearing electron-donating groups including methyl, *tert*-butyl, and methoxy at the various positions on the phenyl ring, and gave the resulting products **11b**–**11g** in 60–72% yields (Table 4, entries 2–6). The fluoro analogue **10g** gave the desired product **11g** in 65% yield (Table 4, entry 7).

In summary, we have reported a novel gold-catalyzed oxidative ring-expansion of unactivated cyclopropylalkynes using Ph_2SO as an oxidant. This catalysis enables the generation of a ketone group at the alkynyl carbon atom in a regioselective manner, accompanied by expansion of a cyclopropyl ring. Crossover experiments exclude the participation of gold α-carbonylcarbenoid intermediates. For substrates bearing an electron-donor group at the cyclopropane ring, our preliminary results reveal a distinct cyclopropane cleavage arising from the Ph_2SO oxidation of the alkyne functionality. Such a ring-cleavage is further applicable to the synthesis of 2*H*-pyrans, further manifesting the use of this method.

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