Silver-catalyzed intramolecular oxycyclization of alkynes to bridged bicyclic ketals†

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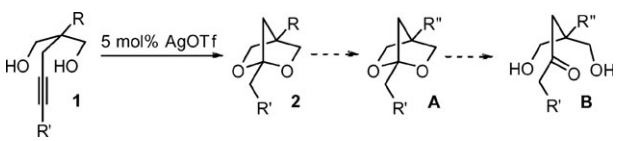
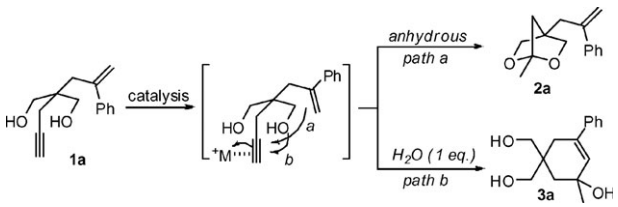
We have discovered a new and highly convenient Ag-catalyzed intramolecular oxycyclization of alkynes, leading to bridged bicyclic ketals as four carbon synthetic building blocks.

We have been interested in the oxycyclizations of 1,*n*-alkynols for the synthesis of epoxy-bridged tetrahydropyran skeletons, which are present in a wide range of natural products, including (+)-*exo*-brevicomin, (−)-frontalin, (+)-dedemniserinolipid B, (+)-xanthane epoxide and phyllaemblic acid.[1] We envisaged that bis-homopropargylic diols or their corresponding malonic acids might play a role in which they can serve as four carbon building blocks, with one remaining R group that can be manipulated into other valuable synthetic building blocks (Scheme 1).

Oxycyclizations of 1,*n*-alkynol, 1,*n*-alkenol and the corresponding carboxylic acids have been conducted efficiently by Pd,[2] W,[3] Ru,[4] Rh,[4] Ir,[5] Hg,[4c,6] Ag[4c,7] and Au[8] catalysts. In particular, gold cations are known to activate the terminal alkynes over the internal alkynes, leaving other labile functional groups such as alkenes, esters and hydroxyl groups intact. Genêt and co-workers have reported a very mild gold-catalyzed cyclization of bis-homopropargylic diols to the corresponding bicyclic ketals regioselectively.[8a,b] In spite of such tremendous developments in the oxycyclizations of alkynols, a closer look reveals some limitations in applying these methods for the preparation of labile bicyclic ketals such as **2a**. During our preparation of bicyclic ketal **2a**, we found an extremely simple, environmentally benign and practically cheap method for the oxycyclization of bis-homopropargylic diols or their corresponding acids by employing silver triflate (AgOTf) as a catalyst (Scheme 2). Herein we report our preliminary results. Silver compounds are also known to activate alkynes, *via* π-complexation, to nucleophilic addition and to serve as cocatalysts to activate other transition metals



Scheme 1



Scheme 2

in organic chemistry.[8] As cocatalysts, silver compounds generally react with transition metal halides to generate catalytically more active cationic species; often they are critical for successful organic transformations. The addition of nucleophiles to alkynes or allenes,[9] the hydrosilylation of aldehydes,[10] asymmetric aldol reactions,[11] the asymmetric α-functionalization of ketone enolates,[12] asymmetric cycloadditions to heterocycles,[13] coupling reactions,[14] three-component coupling of aldehyde–alkyne–amines to propargyl amines[15] and cyclizations[16] have been reported in silver-catalyzed organic synthesis.

Our study was initiated with substrate **1a** (Scheme 2), which was prepared by the double alkylation of malonate, followed by LAH reduction. The results are summarized in Table 1

The oxycyclization was initially conducted under Genêt's conditions: 5 mol% of AuCl and $AuCl_3$ in methanol. The reaction was complete within 10 min, but, after flash chromatography, yielded the corresponding product **2a** in about 35 and 45% yields, respectively (Table 1, entries 1 and 2), along with unknown by-products, presumably due to the labile double bond. When this reaction was conducted in deuterated methanol, formation of the desired ketal, **2a**, was detected as the major product. The same reaction in acetonitrile did not proceed at all (Table 1, entry 3). We also changed the reaction solvent to 1,2-dichloroethane (EDC) and employed silver triflate as a cocatalyst. Surprisingly, substrate **1a** was completely consumed in the presence of a catalytic amount of gold(III) or gold(I) compounds within 0.2 h; flash chromatography afforded the carbocycle **3a** in moderate yields along with a small amount of ketal **2a** (Table 1, entries 4–7). Knowing the importance of solvent effects and the incorporation of one equivalent of water, we were able to find the best solvent system. With EDC containing one equivalent of water, cyclization to **3a** took place exclusively (Table 1, entry 8).[17] These results might be understood by considering that the highly Lewis acidic gold cations catalyzed the carbocyclization rather than that oxycyclization of **1a**, presumably by reducing the

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† Electronic supplementary information (ESI) available: Characterization of new compounds **2a–d**, **2f–i**, **3a**, **4b** and **5b**. See DOI: 10.1039/b702704d.

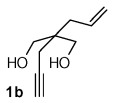
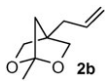
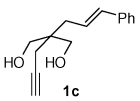
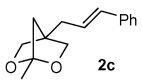
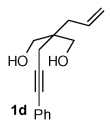
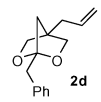
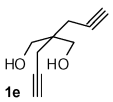
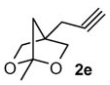
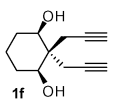
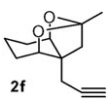
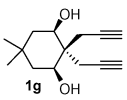
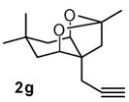
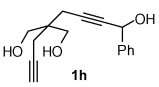
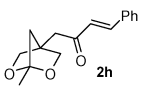
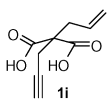
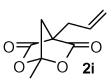
Table 1 Cyclizations of **1a** under various conditions

Entry	Catalyst	Solvent	Temperature	Time/h	Product	Yield (%)
1	AuCl	MeOH	rt	0.2	**2a**	35
2	$AuCl_3$	MeOH	rt	0.2	**2a**	45
3	AuCl	CH_3CN	rt	2.0	nr	nr
4	$AuBr_3$/AgOTf	EDC	rt	0.2	**3a**	65
5	$AuCl_3$/AgOTf	EDC	rt	0.2	**3a**	58
6	$AuCl(PPh_3)$/AgOTf	EDC	rt	0.2	**3a**	60
7	AuCl/AgOTf	EDC	rt	0.2	**3a**	66
8	$AuCl(PPh_3)$/AgOTf	EDC (aq.)	rt	0.2	**3a**	87
9	AgOTf	Toluene	rt	1.0	**2a**	85
10	AgOTf	Dioxane	rt	1.0	**2a**	80

nucleophilicity of their hydroxyl groups to **3a**. We realized that the oxycyclization of **1a** must be accomplished under less acidic and milder conditions due to the labile double bond. In fact, we found that ketal formation could be achieved in dry toluene or dry dioxane by employing silver triflate (5 mol%) with a slightly longer reaction time (Table 1, entries 9–10). This might imply that gold cations could activate the triple bond too much, but that silver cations themselves were enough to catalyze ketal formation. We do not know the exact role of silver cation, but speculate that it might activate the triple bond as a Lewis acid. Having this result, we extended the scope of the method to a series of substrates (Table 2).‡

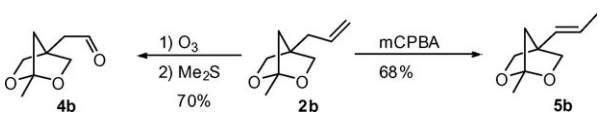
As expected, substrates **1b** and **1c** afforded the corresponding ketals **2b** and **2c** in good yields. Internal triple bonds are less prone to being activated by alkynophilic metal cations. Substrate **1d**, having such an internal triple bond, however, was cyclized in good yield. Substrate **1e** possesses two labile triple bonds; each hydroxyl group could react with each triple bond to give a mixture of unknown products, along with **2e** in low yield. This was solved in cyclohexane-anchored substrates **1f** and **1g**. 2,2-Bispropargyl-1,3-cyclohexanediols **1f** and **1g** were expected to cyclize with only the *cis*-oriented triple bond, leaving the other one intact. Thus, 1,3-cyclohexadiones were doubly propargylated and reduced with sodium borohydride to give diols **1f** and **1g** as the major products. Ag-catalyzed cyclization of both **1f** and **1g** afforded the corresponding **2f** and **2g** compounds in 75 and 82% yields, respectively. Further extension of this method to substrate **1h**, having a propargyl group and a triple bond, resulted in the cyclization with isomerization of its side propargylic alcohol to the corresponding enone in good yield. Extension to the corresponding carboxylic acid **1i** was also successful by heating and using longer reaction times to give the **2i**. We have shown here a successful reaction with a series of substrates to synthesize ketals and related compounds. Note that substrates **1b–i** did not undergo carbocyclization to the product, as did **2a**, which might require a stable carbocationic intermediate during such a carbocyclization. While a mechanistic interpretation was not carried out, the results shown here might be enough to have a valuable synthetic applicability for serving as a building block to more complex molecules. With product **2b**, we have carried out two more classical reactions: ozonolysis and Pd-catalyzed

Table 2 AgOTf-catalyzed oxycyclizations of bis-homopropargylic diols or their corresponding acids in toluene

Entry	Substrate	Product	Temperature/°C	Time/h	Yield (%)
1			25	1.0	76
2			25	1.0	88
3			25	1.0	80
4			25	1.0	10
5			25	1.0	75
6			25	1.0	82
7			25	1.0	68
8			70	2.0	70

isomerization. Both reactions proceeded well to give the corresponding products **4b** and **5b** in good yields (Scheme 3).

In conclusion, we have found that silver triflate itself catalyzes the oxycyclization of structurally diverse homopropargylic diols and related compounds, leading to bicyclic ketals bearing a functionalizable side chain.



Scheme 3

Experimental

The cyclization of **1a** is a typical example. To a mixture of silver triflate (6.5 mg, 5 mol%) in toluene (0.5 mL) was added a solution of bis-homopropagylic diol **1a** (98.7 mg, 0.49 mmol) in toluene (0.5 mL) at 0 °C under an argon atmosphere. The resulting mixture was stirred for 1.0 h at room temperature. Upon completion of the reaction, the solvent was removed under vacuum and the crude product was subjected to flash column chromatography (EtOAc : *n*-hexane = 1 : 10) to afford the pure product **2a** (84.0 mg, 85%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5 H), 5.28 (d, J = 1.2 Hz, 1 H), 5.07 (d, J = 1.2 Hz, 1 H), 3.65–3.58 (m, 4 H), 2.84 (s, 1 H), 1.51 (s, 2 H) and 1.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.29, 141.31, 128.48, 127.86, 126.15, 115.74, 108.32, 76.41, 48.73, 45.03, 34.80 and 17.87; IR (NaCl/cm^{-1}): 1621, 1482 and 1396; HRMS: Calc. for $C_{15}H_{18}NaO_2$ 253.1204, found 253.1207.

Acknowledgements

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‡ Products **2a–d**, **2f–i**, **3a**, **4b**, and **5b** were fully characterized by ^{1}H, ^{13}C, FT-IR and HRMS.

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