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Gold(I)-Catalyzed Oxidative Cascade Cyclization of 1,4-Diyn-3-ones for the Construction of Tropone-Fused Furan Scaffolds

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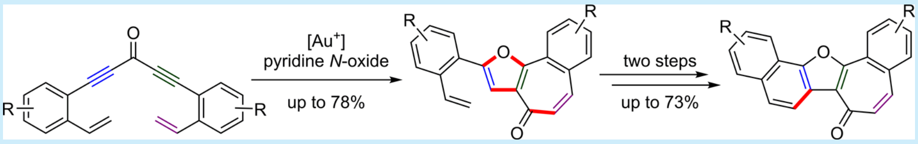
Supporting Information



ABSTRACT: Gold(I)-catalyzed cascade cyclization of 1,4-diyn-3-ones with a pyridine *N*-oxide enabled direct construction of a benzo[6,7]cyclohepta[1,2-*b*]furan scaffold with the formation of four bonds. This reaction would proceed through oxidative cyclization, alkynyl migration, and 5-*endo-dig* type cyclization. Synthesis of benzotropone-fused naphtho[1,2-*b*]furans through a two-step sequence, including epoxidation and In(OTf)$_3$-catalyzed intramolecular carbon−carbon bond formation, is also presented.

Cascade reactions are a powerful method for increasing molecular complexity in a single operation from readily available starting materials.[1] In particular, gold-catalyzed cascade reactions of 1,*n*-diynes are useful strategies for the synthesis of various carbocycles and heterocycles.[2] Highly reactive intermediates are generated in these reactions, which facilitate further transformations, such as cyclopropanation, ring expansion, nucleophilic addition, C−H bond insertion, and cycloaddition, to give polycyclic products. It has been well established that gold-catalyzed oxidation of alkynes with a pyridine oxide derivative forms a highly electrophilic α-oxo gold carbenoid species, avoiding the use of potentially explosive diazo compounds.[3] The generated α-oxo gold carbenoids undergo a variety of transformations to produce various types of cyclic products. For example, in 2011, Liu's group reported an intramolecular cyclopropanation of 1,5-enynes for the synthesis of cyclopropane-fused indanone derivatives[4] (Scheme 1A). Hashmi et al. developed a gold-catalyzed furan formation reaction using 1,4-diyn-3-ol or 3-amine derivatives, which proceeds through formation of α-oxo gold carbenoid and 1,2-alkynyl migration (Scheme 1B).[5] Zhang's group reported cyclopentanone formation using C−H insertion as the termination step, through oxidation of ynone-type substrates (Scheme 1C).[6] In this reaction, the two acyl groups are assumed to provide steric hindrance to suppress intermolecular side reactions of the highly electrophilic gold carbenoid species.

Herein, we report an oxidative cascade cyclization of 1,4-diyn-3-ones bearing alkene moieties **1** to produce benzotropone-fused furan derivatives **3** (Scheme 1D). Our initial expectation was that a gold catalyst would activate 1,4-diyn-3-ones **1** in the presence of a pyridine *N*-oxide to form β-diketone-α-gold carbenoid intermediate **A**, which would undergo cyclopropanation to give intermediate **B** bearing an ynone moiety. Subsequent activation of the other alkyne by the same gold catalyst would facilitate 6-*endo-dig* cyclization by the carbonyl group with ring expansion to give benzo[*h*]chromene **2**. Unexpectedly, we found that the major product was benzo[6,7]cyclohepta[1,2-*b*]furan **3**, although formation of the chromene **2** was also observed depending on the reaction conditions. In this contribution, our efforts to examine this novel cyclization and its application to highly fused naphthofuran derivatives are presented.

At the outset, we chose the diynone **1a** bearing two alkene moieties as the substrate to avoid any regioselectivity issues between the two alkynes (Table 1). The reaction of **1a** with 3,5-dichloropyridine *N*-oxide in the presence of 5 mol % of BrettPhosAuNTf$_2$ gave the expected benzo[*h*]chromene **2a** in 15% yield (entry 1). Use of JohnPhosAuNTf$_2$ or PPh$_3$AuNTf$_2$ as the catalyst gave the tropone-fused furan, benzo[6,7]-cyclohepta[1,2-*b*]furan derivative **3a**, along with **2a** (entries 2, 3). The structures of **2a** (CCDC 1827398) and **3a** (CCDC 1827399) were confirmed by X-ray crystallography (Figure 1). When using IPrAuNTf$_2$ as the catalyst, the tropone-fused furan **3a** was formed in 28% yield without formation of benzo[*h*]-chromene **2a** (entry 4). A possible explanation for the observed ligand effects would be that the electronically poor nature of the IPr gold complex might be inappropriate for activation of the triple bond of ynone **B** to facilitate the cyclization to **2** (Scheme 1). Further screening of the reaction conditions to obtain **3a** as the major product was conducted, and to our delight, the addition of 10 equiv of hexafluoropropan-2-ol (HFIP) gave **3a** in 42% yield (entry 5). Gevorgyan's group recently reported that 1,4-diyn-3-ones can undergo a 1,3-transposition to produce 2,4-diyn-1-ones (isomerization from skipped diynes to conjugated ones) in the presence of gold catalysts.[7] To accelerate the desired

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Scheme 1. Previous Work and Concept of This Work

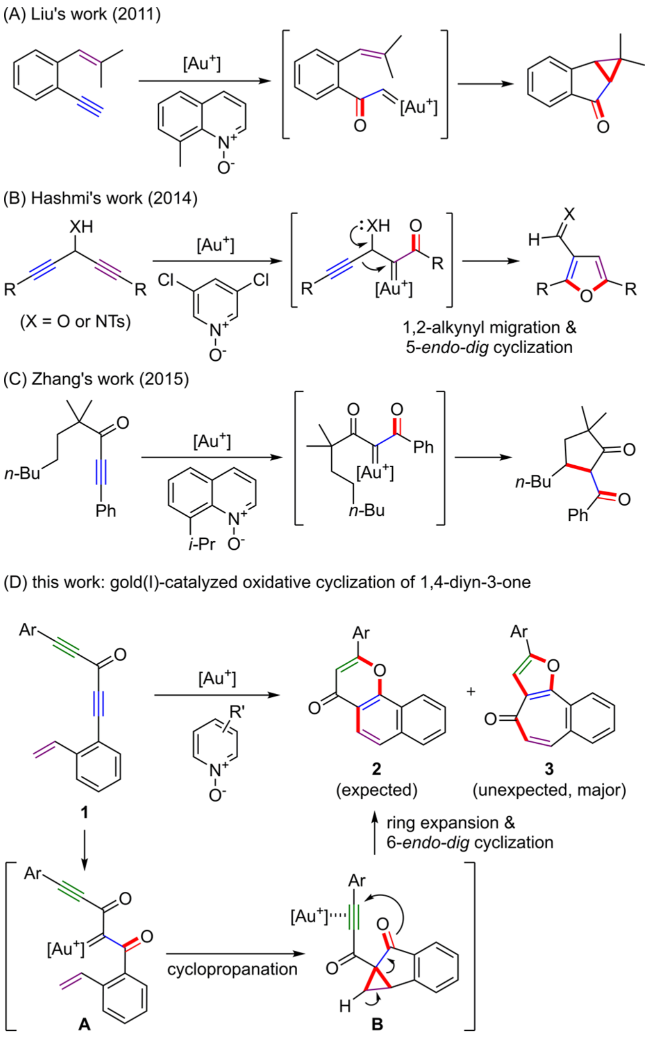
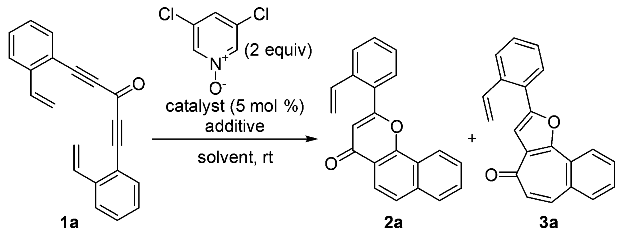
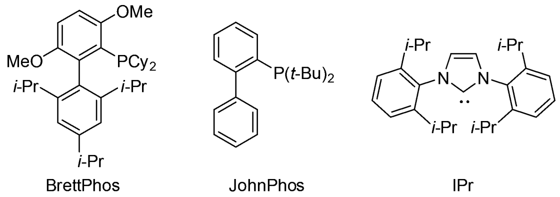


Table 1. Optimization of the Reaction Conditions



entry	catalyst	additive (equiv)	solvent (M)	yield (%)[a]	
				2a	3a
1	BrettPhosAuNTf$_2$	–	DCE (0.05)	15	–[b]
2	JohnPhosAuNTf$_2$	–	DCE (0.05)	10[c]	17[c]
3	PPh$_3$AuNTf$_2$	–	DCE (0.05)	trace	trace
4	IPrAuNTf$_2$	–	DCE (0.05)	–	28
5	IPrAuNTf$_2$	HFIP[d] (10)	DCE (0.05)	–	42
6	**IPrAuNTf$_2$**	**HFIP (10)**	**DCE (0.1)**	–	77
7	IPrAuNTf$_2$	HFIP (10)	DCE (0.2)	–	63
8	IPrAuNTf$_2$	HFIP (10)	toluene (0.1)	–	31
9	IPrAuNTf$_2$	HFIP (10)	EtOH (0.1)	–	–
10	IPrAuNTf$_2$	–	HFIP (0.1)	–	38

[a] Isolated yields. [b] Not detected. [c] Determined by ^{1}H NMR analysis and combined yield of **2a** and **3a**. [d] HFIP = hexafluoropropan-2-ol.



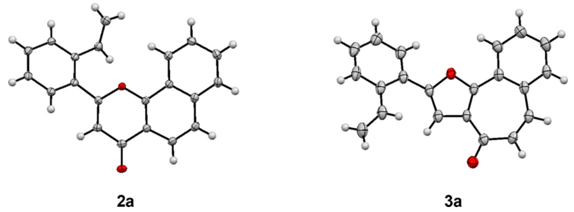


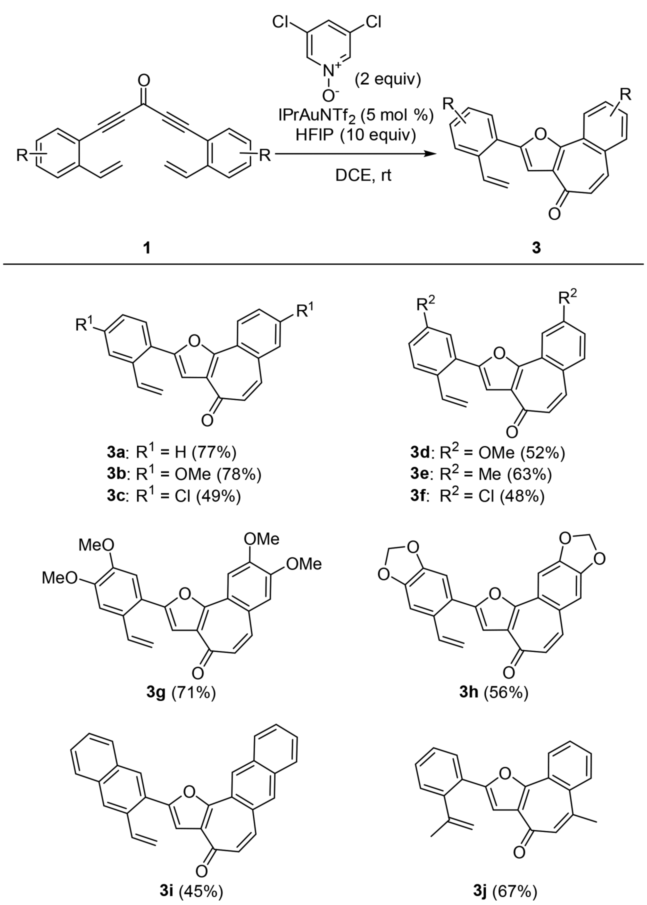
Figure 1. X-ray structures of **2a** and **3a**.

intermolecular reaction with the pyridine *N*-oxide over other reactions, including the intramolecular 1,3-transposition, we next focused our attention on the influence of the substrate concentrations. Indeed, more concentrated conditions (0.1 M **1a**) led to a significant improvement in the yield of tropone **3a** (77%, entry 6), while further concentration was ineffective (0.2 M **1a**; 63%, entry 7). Finally, several other solvents were tested in the reaction, including toluene, EtOH, and HFIP (entries 8–10); however, all these solvents resulted in a decreased yield of **3a** or inhibited the reaction (EtOH, entry 9).

With the optimized conditions in hand (Table 1, entry 6), we investigated the scope of the reaction using a variety of substrates (Scheme 2). 1,4-Diyn-3-one **1b**, bearing electron-donating methoxy groups at the 4-position of the both phenyl groups, smoothly underwent the desired reaction to afford the corresponding tropone-fused furan **3b** in 78% yield. Halogen substituents at the 4-position were also tolerated in this reaction to provide **3c**, although the yield was relatively low (49%). The substituents at the 5-position (*meta*-position to alkyne) slightly decreased the yields of the furan **3**. For example, 1,4-diyn-3-ones **1d** and **1e** with electron-donating methoxy or methyl groups gave **3d** and **3e** in 52% and 63% yields, whereas the 5-chlorinated substrate **1f** showed a similar reactivity to the 4-chlorinated one to afford **3f** in 48% yield. Diynone **1g** with 3,4-dimethoxyphenyl groups showed good reactivity, resulting in a 71% isolated yield of **3g**. Introduction of fused benzene rings into the substrate afforded the corresponding tetracyclic fused tropone derivatives **3h** and **3i** in moderate yields (56% and 45%, respectively). Finally, 1,4-diyn-3-one **1j** bearing isopropenyl groups at the 2-position (instead of vinyl groups) was tested, and methylated tropone derivative **3j** was obtained in good yield (67%).

Our mechanistic proposal for the cascade reactions is depicted in Scheme 3. As reported by Zhang and co-workers,[6] β-diketone-α-gold carbenoid species **A** would be generated as the key reactive intermediate by gold-promoted oxidation of the ynone. There are then two possible mechanisms: through formation of a cyclopropane intermediate **B** (path a) or via benzyl cation intermediate **E** (path b). In path a, after cyclopropanation of the gold carbenoid with the vinyl group to give **B**, ring expansion to cationic cyclobutane intermediate **C** would facilitate a 1,2-alkynyl shift[5,8] to generate intermediate **D**. The reaction is terminated by gold-catalyzed intramolecular 5-*endo-dig* cyclization to the other alkyne moiety, with ring expansion and subsequent protodeauration to produce the

Scheme 2. Substrate Scope[a]



[a] Isolated yields.

tropone-fused furan **3**. In path b, the styrene moiety acts as a nucleophile to attack the carbonyl group of ynone **A** to give the benzyl cation intermediate **E**. Subsequently, a 1,2-alkynyl shift onto the gold carbenoid species[5] would form a diketone intermediate **F**. Finally, 5-*endo-dig* cyclization followed by protodeauration gives the same fused furan **3** as path a. Since both pathways sufficiently rationalize the observed results, further experimental and theoretical studies are necessary for complete elucidation of the reaction mechanism.

We next focused on the application of the resulting furan derivatives to the synthesis of highly fused compounds. We expected that the remaining vinyl group in **3** could be efficiently used for the construction of an additional benzene ring. This strategy would lead to the construction of a fused naphthofuran motif, which is found not only in biologically active natural and synthetic products (Figure 2)[9] but also in fluorescent markers[10] and electronic devices.[11] Considering that Lewis acid catalyzed cyclization of ethylene oxide is one of the most efficient ways to synthesize fused aromatic molecules,[12] we prepared epoxide **4a** by treatment of **3a** with oxone in the presence of $NaHCO_3$ in a mixture of CH_2Cl_2/acetone/H_2O (Scheme 4).

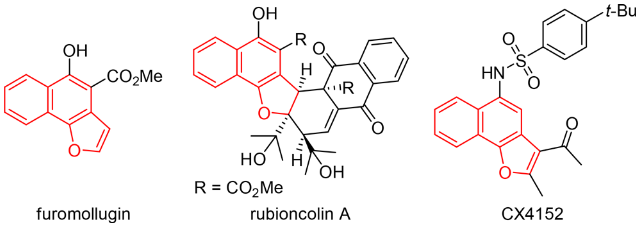
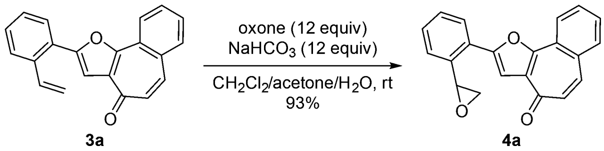
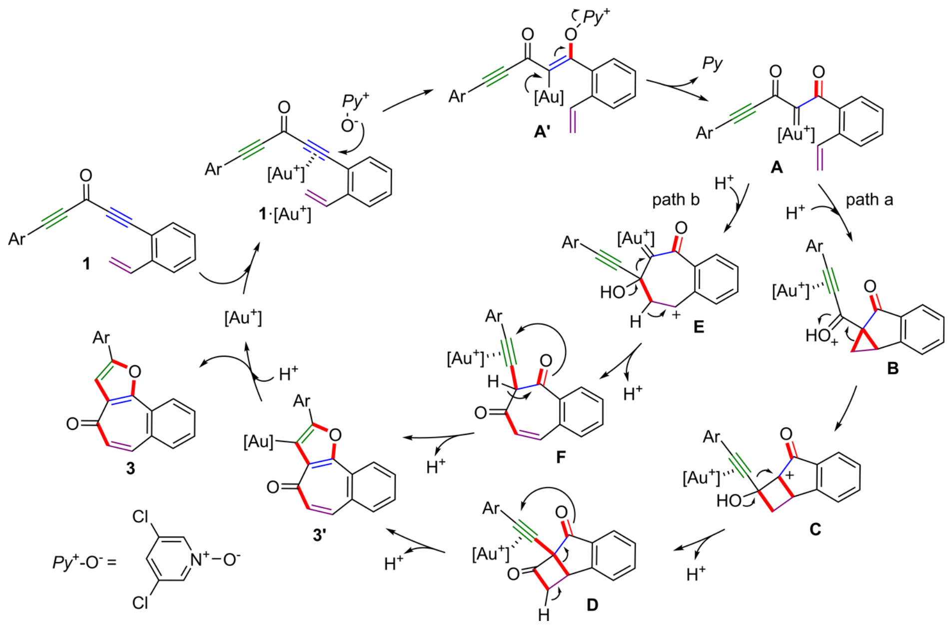


Figure 2. Natural products and a bioactive compound bearing a naphthofuran moiety.

Scheme 4. Epoxidation of 3a

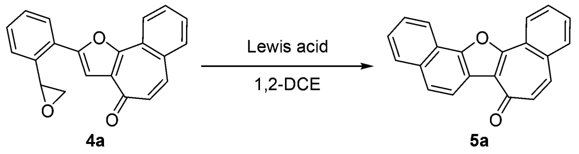


Scheme 3. Proposed Reaction Mechanisms



We then examined the cyclization of the epoxide **4a** with a Lewis acid (Table 2), which would facilitate the benzene ring construction by the sequence of the ring opening of the epoxide, the 1,2-hydride shift to form aldehyde, and an intramolecular electrophilic aromatic substitution followed by dehydration.[12b] Fortunately, treatment of the epoxide **4a** with 2 equiv of $ZnCl_2$ in 1,2-DCE gave the desired highly fused naphthofuran **5a** (CCDC 1827401), although in low yield (20%, entry 1). After screening various Lewis acids (entries 2–5), we found that the use of $In(OTf)_3$ led to an increase in the yield of **5a** (68%, entry 5). A catalytic reaction using 20 mol % $In(OTf)_3$ at an elevated temperature (80 °C) also produced **5a** in 68% yield within 3 h (entry 7). To our delight, crude epoxide **4a** (after simple workup) can be similarly used for the Lewis acid catalyzed cyclization, thus affording **5a** in 64% yield in two steps from fused furan **3a**.

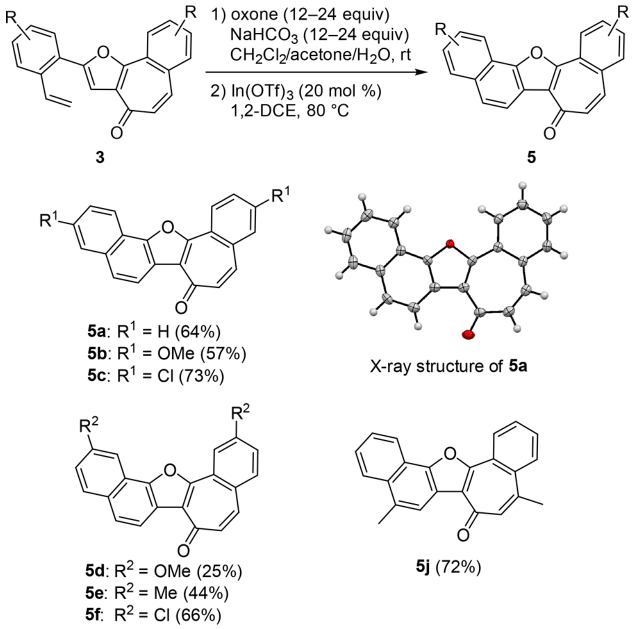
Table 2. Optimization of the Reaction Conditions for the Lewis Acid Mediated Cyclization



entry	Lewis acid (equiv)	temp (°C)	time (h)	yield (%)[a]
1	$ZnCl_2$ (2)	50	6	20
2	$FeCl_3$ (2)	50	6	38
3	$InCl_3$ (2)	50	6	56
4	$InBr_3$ (2)	50	4	61
5	$In(OTf)_3$ (2)	50	4	68
6	$In(OTf)_3$ (0.2)	50	8	54
7[b]	**$In(OTf)_3$ (0.2)**	**80**	**3**	**68**

[a] Isolated yields. [b] The reaction was conducted under Ar.

Scheme 5. Substrate Scope[a]



[a] Isolated yields.

Substrate scope for the cyclization over two steps is shown in Scheme 5. Fused furan **3b** bearing methoxy groups at the R^1 positions resulted in the desired product **5b** in 57% yield. Similarly, chlorinated substrate **3c** provided naphthofuran **5c** in a higher yield (73% over two steps). Methoxy or methyl substitution at the R^2 position led to a decrease in the yields of the corresponding naphthofurans **5d** and **5e** (25% and 44%, respectively). These results can be attributed to the cation stabilizing ability of the electron-donating groups at the *para*-position, which may decrease the reactivity of the 1,2-hydride shift. As expected, furan **3f** bearing an electron-withdrawing chlorine group gave the corresponding naphthofuran **5f** in good yield (66%). Finally, we tested the reaction of fused furan **3j** with an isopropenyl group and obtained a dimethylated product **5j** in 72% yield over two steps.[13]

In summary, we have developed a novel gold-catalyzed cascade reaction of 1,4-diyn-3-ones in the presence of a pyridine *N*-oxide. The reaction proceeds through several steps, including gold carbenoid formation and 1,2-alkynyl migration. This approach enabled the direct construction of a benzo[6,7]cyclohepta[1,2-*b*]furan scaffold with the formation of four bonds in a single operation. Furthermore, a two-step conversion of the resulting furans gave highly fused naphthofuran derivatives. We are currently working on the reaction mechanisms and application studies of this novel methodology.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01524.

Experimental procedures, characterization data for all new compounds (PDF)

Accession Codes

CCDC 1827398–1827399 and 1827401 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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