ChemComm
Chemical Communications

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View Article Online
DOI: 10.1039/D0CC03285A

COMMUNICATION

Gold(I)-Catalyzed Tandem Cyclization of Cyclopropylidene-tethered Propargylic Alcohols: An Approach to Functionalized Naphtho[2,3-c]pyrans

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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An unprecedented gold(I)-catalyzed cyclization of cyclopropylidene-tethered propargylic alcohols via a *6-endo-dig* enyne cyclization followed by a ring-open of cyclopropane and nucleophilic closure reaction to construct naphtho[2,3-c]pyrans was developed. This transformation represents a highly efficient method for the synthesis of policyclic compounds in one-pot, and two new rings are formed in an atom economic manner.

Fused pyrans are important heterocycles,[1] of which naphtho[2,3-c]pyran moieties are important structural motifs embedded in numerous natural products showing a broad range of remarkable biological activities containing cytotoxicity, anti-inflammatory activity, antimalarial activity, antitubercular activity and Anti-HSV-1 activity (Figure 1).[2] However, the synthetic methods have been reported were limited, and most of which are only applied to furnish the products with a narrow scope of structural diversity.[3] Therefore, the development of new strategies to construct naphtho[2,3-c]pyrans is highly desirable.

Gold-catalyzed[4] tandem cyclizations of 1, *n*-enynes are useful strategies to construct various active heterocyclic systems,[5] and of which 1,*n*-enynol, bearing a hydroxyl group on the alkyne, has also been used to participate in different kinds of regioselective transformations. For examples, Bandini reported a stereoselective, intramolecular gold(I)-catalyzed dearomatization of indole derivative via *5-exo-dig* cyclization of enynol to access special polycyclic compounds. Maestri and co-workers developed a gold(I)-catalyzed cascade *6-endo-dig* bicyclization of 1,5-enynols for the construction of heterocycles with structural diversity (Scheme 1a).[6] Cyclopropylidene, as one kind of particular alkene, has been widely used in diversified organic transformations by Shi, and other groups.[7] We envisioned that the cyclopropylidene-tethered propargylic alcohols could be employed in a *6-exo-dig* enyne cyclization followed by a concerted ring-open of cyclopropane. As part of our ongoing work in the field of gold catalysis,[8] we reported herein a gold(I)-catalyzed tandem enyne cyclization/cyclopropane opening reactions from cyclopropylidene-tethered propargylic alcohols (Scheme 1b). Notably the reaction, if developed, would offer novel and rapid access to valuable fused naphtho[2,3-c]pyrans.

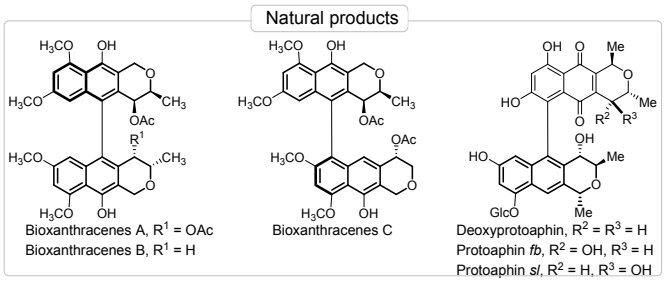
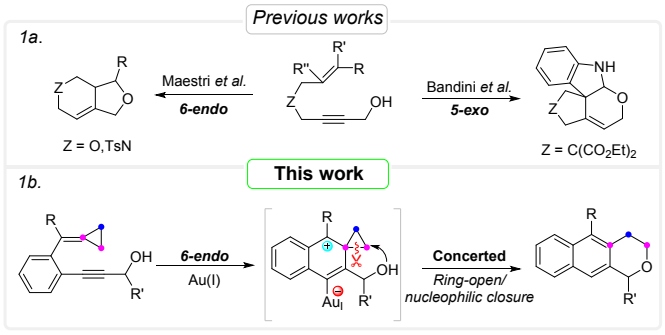


Figure 1. Representative natural products.



Scheme 1. Cascade reactions of enynols.

To test the feasibility of our hypothesis, an initial scouting reaction was conducted with cyclopropylidene-ynol **1a** in the presence of various gold catalysts (Table 1). The use of Au(III) catalyst did not promote the reaction efficiently, only leading to a collection of inseparable products (Table 1, entry 1). When $Ph_3PAuCl/AgNTf_2$ was used, the expected product did not obtain but the starting material remained intact (Table 1, entry 2). Moreover, the use of more electron-rich or electron-

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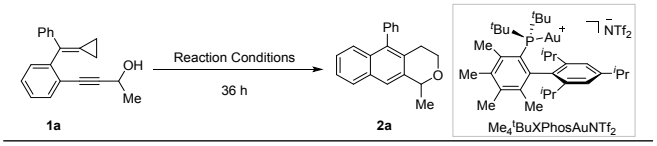
Electronic Supplementary Information (ESI) available: CCDC 1985419. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

deficient or bulky ligands such as BrettPhos, Phosphite, IPr and XPhos, all led to messy products (Table 1, entries 3 - 6). Gratifyingly, we were pleased to find that switching to the Au(I) complex $Me_4{}^tBuXPhosAuCl$ along with $AgNTf_2$ (halide scavenger) afforded the desired product **2a** in 44% yield (Table 1, entry 7). With this promising result, we proceeded further to achieve the optimal reaction conditions. The subsequent solvents screening results showed that the fluorobenzene was the optimal solvent (Table 1, entries 8 - 11). Increasing the reaction temperature to 85 °C led to the isolation of naphthopyran **2a** in 83% yield in 24 h. A brief screening of the Ag salts identified $AgNTf_2$ as the best halide scavenger.

Table 1 Optimization of Reaction Conditions[a]

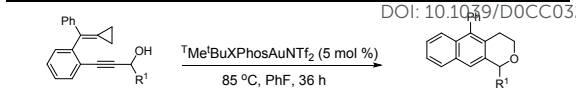


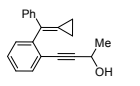
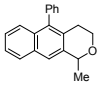
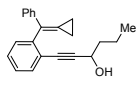
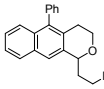
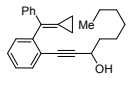
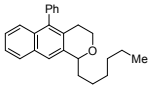
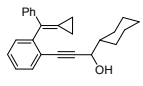
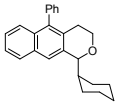
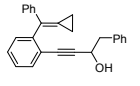
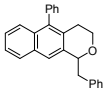
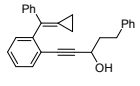
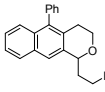
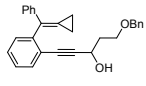
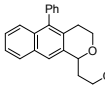
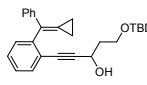
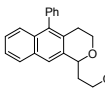
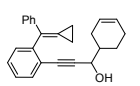
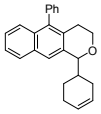
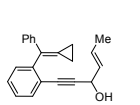
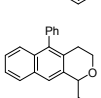
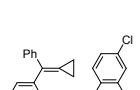
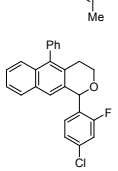
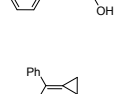
entry	Catalyst (5 mol %)	conditions	yield (%)[b]
1	$PicAuCl_2$	DCE, 75 °C	Messy
2	$Ph_3PAuCl/AgNTf_2$	DCE, 75 °C	N.R.
3	$(2,4\text{-}{}^tBu_2PhO)_3PAuCl/AgNTf_2$	DCE, 75 °C	Messy
4	$BrettPhosAuCl/AgNTf_2$	DCE, 75 °C	Messy
5	$IPrAuCl/AgNTf_2$	DCE, 75 °C	Messy
6	$XPhosAuCl/AgNTf_2$	DCE, 75 °C	Messy
7	$Me_4{}^tBuXPhosAuCl/AgNTf_2$	DCE, 75 °C	44
8	$Me_4{}^tBuXPhosAuNTf_2$	toluene, 75 °C	60
9	$Me_4{}^tBuXPhosAuNTf_2$	$PhCF_3$, 75 °C	55
10	$Me_4{}^tBuXPhosAuNTf_2$	PhCl, 75 °C	77
11	$Me_4{}^tBuXPhosAuNTf_2$	PhF, 75 °C	81
12[c]	$Me_4{}^tBuXPhosAuNTf_2$	PhF, 85 °C	83
13	$Me_4{}^tBuXPhosAuCl/ AgX$	PhF, 85 °C	<24

[a] Reaction conditions: All reactions were run in vials in the presence of **1a** (0.2 mmol); [**1a**] = 0.05 M. [b] Isolated yields. [c] Reaction time = 24 h. X^- = OTs^-, OTf^-, SbF_6^-.

With the optimized reaction conditions in hand, we subsequently investigated the substrate scope of this cascade cyclization (Table 2). As expected, the ynols comprising propyl, hexyl and cyclohexyl groups were suitable for this annulation, rendering 3,4-dihydro-*1H*-benzo[g]isochromenes **2b**-**2d** in high to excellent yields. Varying substituents of the ynol moieties to a benzyl or a phenethyl had no significant effects on the outcomes of the reaction and gave corresponding products **2e** and **2f** in 90% and 97% yields, respectively. Functional groups such as -OBn and -OTBDPS were also tolerated, delivering desired compounds **2g**-**2h** in excellent yields. Derivative of the ynol bearing 3-cyclohexenyl group participated in this tandem cyclization smoothly, and the desired product **2i** was obtained in 95% yield. The substrates equipped with π system in the α-position of –OH were also applicable in this reaction and the desired naphthopyrans **2j**-**2k** were isolated in 68% and 76% yields, respectively, albeit with higher reaction temperatures. Moreover, the primary alcohol **1l** also underwent the reaction smoothly, leading to the corresponding product **2l** in a good yield.

Table 2 Substrate Scope of Substituted Enynols[a]

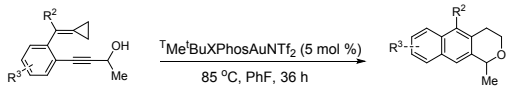


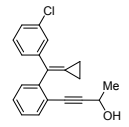
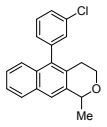
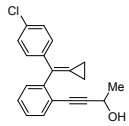
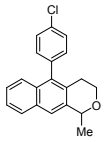
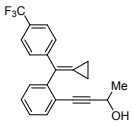
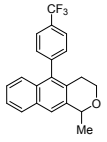
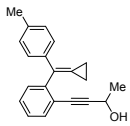
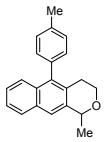
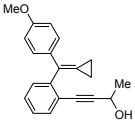
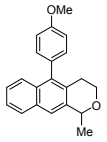
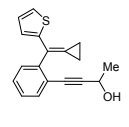
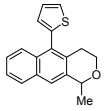
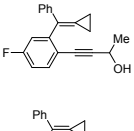
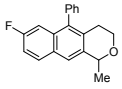
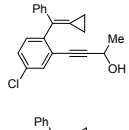
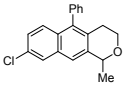
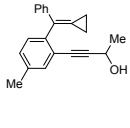
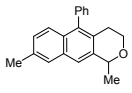
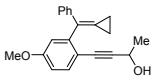
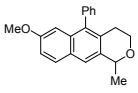
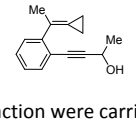
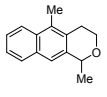
Entry	Substrate	1	Product	2	Yield (%)
1[b]		**1a**		**2a**	83
2		**1b**		**2b**	81
3		**1c**		**2c**	95
4		**1d**		**2d**	98
5		**1e**		**2e**	90
6		**1f**		**2f**	97
7		**1g**		**2g**	93
8		**1h**		**2h**	94
9		**1i**		**2i**	95
10[c]		**1j**		**2j**	68
11[c]		**1k**		**2k**	76
12[c]		**1l**		**2l**	77 (74)[d]

[a] All reactions were carried out in 4 mL PhF in the presence of **1** (0.2 mmol); isolated yields are reported. [b] Reactions time = 24 h. [c] Reactions carried out in 4 mL PhCl at 120 °C for 24 h. [d] The reaction was carried out at 1 gram scale.

Next, substrates bearing different functional groups on the aromatic rings were also investigated (Table 3). Notably, electron-donating and electron-withdrawing substituents on the phenyl ring of the cyclopropylidene moieties were readily accommodated, delivering the final products **2m**-**2q** in moderate to good yields.

Table 3. Substrate Scope of Aromatic Ethers[a]



Entry	Substrate	1	Product	2	Yield (%)
13		**1m**		**2m**	66
14		**1n**		**2n**	60
15		**1o**		**2o**	57
16		**1p**		**2p**	64
17		**1q**		**2q**	71
18		**1r**		**2r**	53
19		**1s**		**2s**	64
20		**1t**		**2t**	53
21		**1u**		**2u**	68
22		**1v**		**2v**	95
23		**1w**		**2w**	76

[a] All reaction were carried out in 4 mL PhF in the presence of **1** (0.2 mmol); isolated yields are reported.

Importantly, substrate derived from thiophene was also compatible with this annulation yielding naphthopyran derivative **2r** in a moderate yield. Varying the substituents on the phenyl ring of the phenylacetylene moieties resulted in considerable changes in the yields of the desired products, and the electronic factor played a major role in the reaction outcomes. Electron-deficient enynols (4-F and 3-Cl) underwent the reaction smoothly, providing the corresponding products **2s**-**2t** in moderate yields, while the electron -rich enynols (3-Me and 4-OMe) gave the final products **2u**-**2v** in higher yields. The structure of **2v** was established by X-ray crystallographic analysis (CCDC 1985419) and other naphthopyran derivatives were assigned by analogy.[9] Notably, aliphatic derived substrate **1w** successfully afforded the desired product **2w** in high yield.

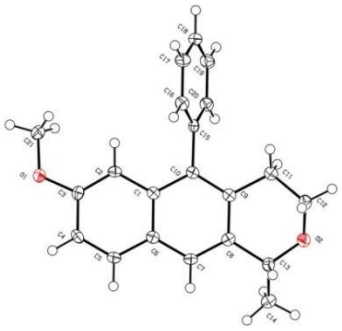
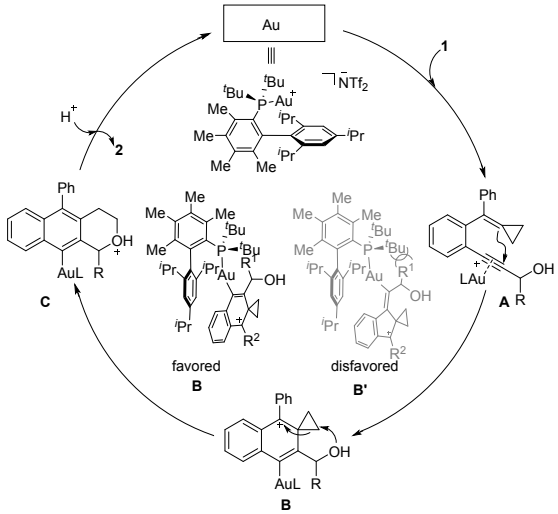


Figure 2. Solid-state molecular structure of **2v**

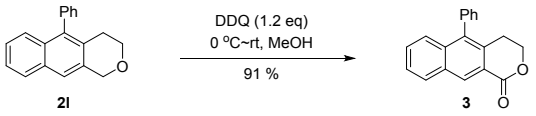
Interestingly, the *6-endo-dig* cyclization product **2** was obtained as the sole product while the the *5-exo-dig* cyclization product was not observed. This outcome led by the use of an electron-rich and sterically hindered ligand which would make the cationic intermediate less electropositive and then slowed the rate of deauration by proton. Moreover, the naphthalene would be preferred due to its aromatic and thermodynamically stable characters.[11]

On the basis of the above observations and control experiments (see ESI†), we propose the following plausible mechanisms for this transformation.[7d] Gold(I) first coordinates with the C-C triple bonds, a subsequent *6-endo-dig* cyclization to yield the carbon cationic intermediate **B**, which stabilized by aryl or aliphatic substituents is more favorable than intermediate **B'**.[10] Then the nucleophilic addition of the intramolecular hydroxyl leads to ring open of cyclopropane to form intermediate **C** in a concerted manner. Finally, protodeauration gives the desired product **2**.



Scheme 2. Proposed Reaction Mechanism.

To demonstrate the synthetic utility of the current method, the oxidation of product **2l** could afford the lactone **3** in a high yield (Scheme 3).



2l 3

Scheme 3. Oxidation of **2l**

In conclusion, we have established an unprecedented gold(I)-catalyzed cascade cyclization of enynols via a concerted ring-open of cyclopropane and nucleophilic closure to afford biologically important naphtho[2,3-c]pyran derivatives in a one-pot reaction. This reaction features high yields, broad substrate scope and easy operation. We anticipate that this approach would be valuable in both natural products synthesis and medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21702170), Natural Science Foundation of Shaanxi (2018JQ2072, 2019JQ647) and the Youth Training Program of Northwest A&F University (Nos. 2452016006, 2452017034).

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