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Gold-catalyzed ring-expansion through acyl migration to afford furan-fused polycyclic compounds

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Changyuan Zhang,[a] Huanfeng Jiang,[a] and Shifa Zhu*[a,b]

A gold-catalyzed ring-expansion reaction of alkynones to access furan-fused polycyclic compounds is reported. Mechanistic studies revealed that the reaction might occur through a tandem of 1,2-acyl migration/Friedel-Crafts reaction.

Ring-expansion reactions represent powerful synthetic strategies for the construction complex cyclic compounds in organic synthesis,[1] which has attracted much attention from synthetic organic chemists. It is particularly useful in the synthesis of entropically unfavorable medium-sized rings (seven- and eight-membered).[2,3]

Furan-fused cycloalkanone system is the core framework of many important natural products and pharmaceutically active substances[4,5], such as radermachol[5a], bhimamycin B[5b], halenaquinone[5c] and viridin[5c] (Fig. 1). Among them, radermachol is a folk medicine, which contains a unique cycloheptanone-fused furan framework.[6a]

Traditionally, furan-fused polycyclic compounds were constructed through stepwise or skeleton rearrangement.[6,7] These methods generally suffered from low step-economy or low selectivity.[6,7] Development of new methods for the efficient synthesis of furan-fused polycyclic compounds would be of great importance. As part of our continuing efforts to develop high efficient tandem reactions based on enynal/enynone chemistry,[8] we envisioned that furan-fused cycloalkanone system, the core structure of radermachol and bhimamycin B, might be rapidly accessed through a ring expansion process from alkynone **1** (Scheme 1, path a). However, two different products **2** and **3** may compete with each other in this transition-metal catalytic process. The formation of **2** is proposed to be initiated by the attack of the exocyclic carbonyl group to the activated alkyne, and it involves an intramolecular acyl migration through

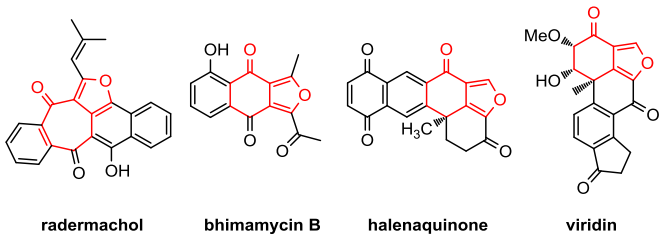
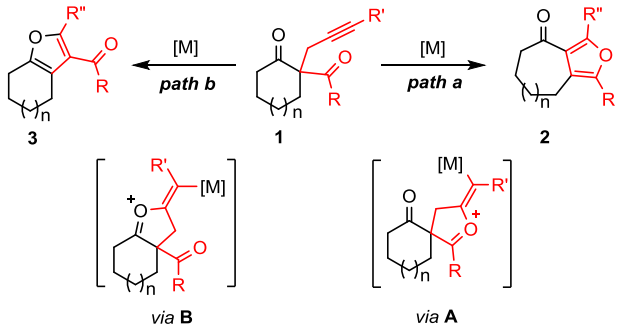


Fig. 1 Bioactive or natural compounds bearing cycloalkanones with furan ring compounds

the intermediate **A**. While the formation of **3** is initiated by the attack of the endocyclic carbonyl group and the reaction proceeds through the intermediate **B** (path b). Therefore, how to selectively produce the desired ring expansion product **2** would be a challenge.

To meet the challenge, benzofused alkynone **1a** was initially designed as the model substrate for the reaction condition screening to selectively produce the ring-expanded product **2a**. Over the last decade, cationic Au(I) complexes have proven to be the excellent Lewis acid catalysts to the alkyne.[9] Therefore, varieties of cationic Au(I) complexes were then applied as the potential catalysts for the transformation (Table 1). The reaction was initially conducted in DCE at 60 °C with PPh_3AuCl (5 mol %) and AgOTf (5 mol %) as catalyst.



Scheme 1 The strategy of ring-expansion reaction by 1,2-acyl migration

[a]Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, 510640, P. R. China. E-mail: zhusf@scut.edu.cn
[b]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China.

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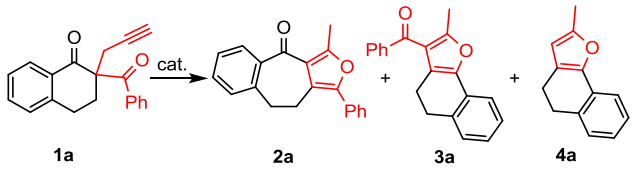
Table 1 Optimization of the reaction conditions[a]

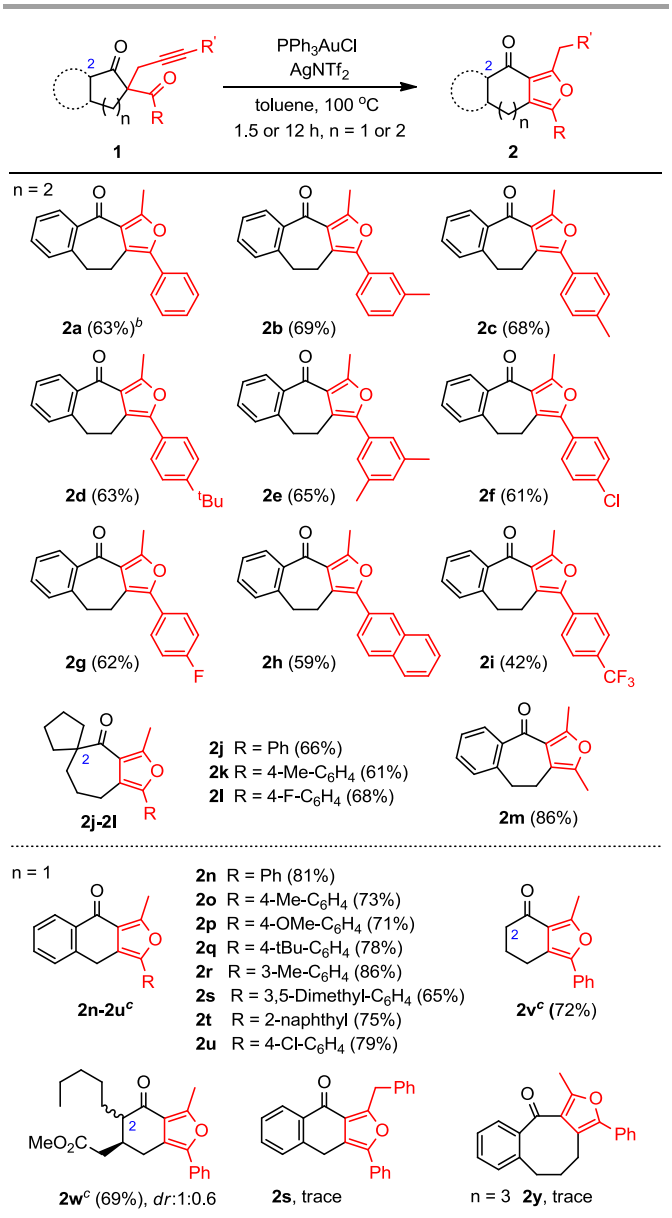


Entry	cat. (5 mol %)	T (°C)	yield (%)[b] 2a	3a	4a
1	$PPh_3AuCl/AgOTf$	60	18	27	49
2	$PPh_3AuCl/AgSbF_6$	60	trace	trace	89
3	$PPh_3AuCl/AgBF_4$	60	30	trace	57
4	$PPh_3AuCl/AgNTf_2$	60	35	trace	62
5	SIPr-AuCl/$AgNTf_2$	60	19	12	60
6	IMes-AuCl/$AgNTf_2$	60	29	17	47
7	$PPh_3AuCl/AgNTf_2$	80	32	trace	61
8	$PPh_3AuCl/AgNTf_2$	100	49	trace	44
9	$PPh_3AuCl/AgNTf_2$	120	43	trace	49
10[c]	**$PPh_3AuCl/AgNTf_2$**	**100**	**66**	**trace**	**18**
11[d,g]	$PPh_3AuCl/AgNTf_2$	100	13	trace	63
12[e,g]	$PPh_3AuCl/AgNTf_2$	100	14	17	37
13[f,g]	$PPh_3AuCl/AgNTf_2$	100	-	-	-

[a]Unless otherwise noted, the reaction was performed with **1a** (0.25 mmol) in DCE (2.5 mL), 1.5 h, under N_2. [b]Determined by ^1H NMR using CH_3NO_2 as internal standard. [c]PhMe as solvent. [d]CH_3NO_2 as solvent and DCE as internal standard. [e]THF as solvent. [f]CH_3CN as solvent. [g]24 hours.

As expected, the desired exocyclic carbonyl group-triggered product **2a** and the undesired endocyclic carbonyl group-triggered product **3a** could be detected in 18% and 27% yields, respectively (Table 1, entry 1). Furthermore, another major product **4a** was obtained in 49% yield, which should come from the deacylation through the C-C bond cleavage of intermediate **B** (Scheme 1).[7b] Interestingly, when $AgSbF_6$ was utilized as halide scavenger, product **4a** could be formed exclusively in 89% yield (entry 2). By changing the silver salts to $AgBF_4$ and $AgNTf_2$, the yields of ring-expanded product **2a** could be improved to 30% and 35% respectively (entries 3-4). When Ph_3PAuCl was changed to NHC-AuCl, it did not improve the yield of **2a** as well (entries 5-6). The yield of **2a** was enhanced to 49% when the reaction temperature was increased to 100 °C with $PPh_3AuCl/AgNTf_2$ as catalyst (entry 8). Lower or higher temperature gave inferior results (entries 7-9). Solvent screening (entries 10–13) indicated that toluene was the best solvent for this reaction, giving the product yield of **2a** in 66% (entry 10). The product structure of cycloheptanone-fused furan **2a** was further confirmed by X-ray diffraction analysis (see ESI†).

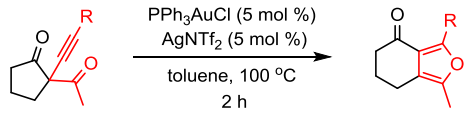
Under the optimized reaction condition (Table 1, entry 10), the substrates scope were then explored (Scheme 2). When different alkynones **1** with cyclohexanone moiety were used as the substrates, the desired ring-expanded products, cycloheptanone-fused furan **2a-2m**, could be obtained in 42-86% yields. For example, benzocyclohexanone alkynones with both electron-rich and -deficient aryl group could be efficiently transferred to the cycloheptanone-fused furan **2a-2i**. It seems that the benzocyclohexanone alkynone substrates with an electron-rich aryl group (**2b-2e**) functioned better than those with electron-poor aryl group (**2i**). Furthermore, the alkynones with a spiro-cyclopentane at 2-position of cyclohexanone could be transferred to the desired cycloheptanone-fused furans as well (**2j-2l**, 61-68%). Moreover, when the exocyclic acetyl group was used instead, the reaction proceeded even more efficiently (**2m**, 86%). However, the alkynones with a simple cyclohexanone ring (without substituents at 2-position) cannot be converted into the desired products. In most cases (Scheme 2), the side product **4** was formed only in trace amount, with the yield typically being less than 10%.



Scheme 2 The ring-expansion reaction of alkynones **1**.[a] [a]The reaction conditions: **1** (0.25 mmol), PPh_3AuCl (5 mol %) and $AgNTf_2$ (5 mol %) in toluene (2.5 mL) at 100 °C under N_2 for 1.5 h. [b]Isolated product. [c]The reaction conditions: **1** (0.25 mmol), PPh_3AuCl (10 mol %) and $AgNTf_2$ (10 mol %) in toluene (2.5 mL) at 100 °C under N_2 for 12 h.

In addition to alkynones **1** containing cyclohexanone structure, the alkynones **1** with cyclopentanone and cycloheptanone rings were investigated as well, aiming at different size of cycloalkanone-fused furans. As shown in Scheme 2, the alkynones **1** with cyclopentanone ring were better substrates than those with cycloheptanone rings, and the desired cyclohexanone-fused furans **2n-2w** were produced in 65-86% yields. Either alkynones with benzofused cyclopentanones or simple cyclopentanones (with or without substituents at 2-position) could be transferred to the desired cyclohexanone-fused furan products in good yields. It seems that the steric hindrance or electronic properties of the substrates have little effects on the product yield. The structure of cyclohexanone-fused furan products were also confirmed by the X-ray diffraction analysis of compound **2t** (see ESI†). Trying to extend this reaction to the alkynones with internal alkyne (**2s**) or alkynones with cycloheptanone failed (**2y**).

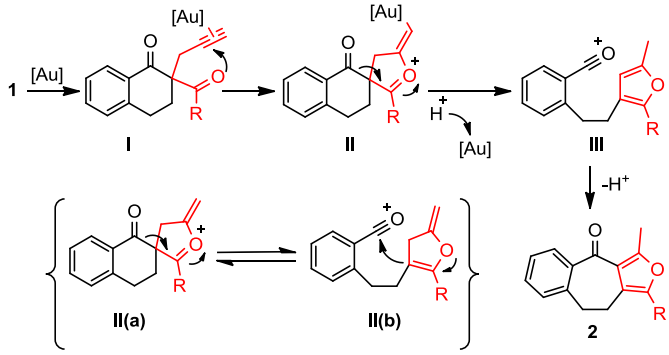
Although the alkynone with an internal propargyl group was not a suitable substrate for this ring-expansion reaction (Scheme 2, **2s**), the alkynones with internal ethynyl group were good substrates (Scheme 3). For example, under the same reaction conditions, alkynones **1z-1ad** could be converted into the corresponding cyclohexanone-fused furans **2z-2ad** in 54-88% yields, no deacylation side products 4 were detected for this reaction. The structure of dihydroisobenzofuranone **2aa** was also confirmed by X-ray diffraction analysis (see ESI†).



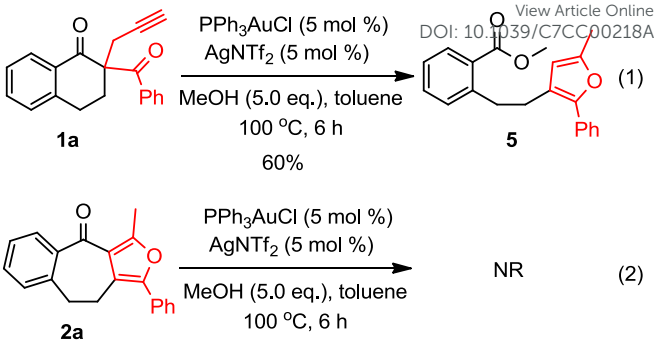
1z, R = Ph
1aa, R = 4-Me-C_6H_4
1ab, R = 3-Me-C_6H_4
1ac, R = 4-Cl-C_6H_4
1ad, R = 4-F-C_6H_4

2z, R = Ph (65%)
2aa, R = 4-Me-C_6H_4 (62%)
2ab, R = 3-Me-C_6H_4 (54%)
2ac, R = 4-Cl-C_6H_4 (77%)
2ad, R = 4-F-C_6H_4 (88%)

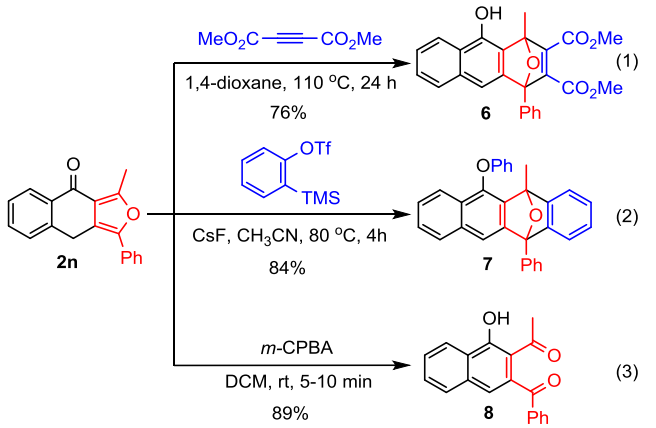
Scheme 3 The ring-expansion reaction of α-alkynyl diones **1**.[a] [a]The reaction was conducted in toluene at 100 °C for 2 h using 5 mol % PPh_3AuCl and 5 mol % $AgNTf_2$ under N_2, alkynones **1** (0.25 mmol), toluene (2.5 mL). Compounds **1z-ad** were prepared in situ and used immediately (see supporting information).



Scheme 4 The proposed reaction mechanism



Scheme 5 Control experiments



Scheme 6 Transformations for **2n** Reaction conditions: (1) **2n** (0.25 mmol), DMAD (3 equiv), 1,4-dioxane (1 mL); (2) **2n** (0.25 mmol), aryne (2.5 equiv), CsF (4 equiv), CH_3CN (1 mL); (3) **2n** (0.25 mmol), *m*-CPBA (2.5 equiv), DCM (1 mL). *m*-CPBA = 3-Chloroperbenzoic acid, Tf = Trifluoromethanesulfonyl, TMS = Trimethylsilyl.

The reaction mechanism was proposed in Scheme 4. The triple bond of alkyone **1** was initially activated by the gold salt to form oxonium intermediate **II**,[10a] which was followed by protodeauration [**II**→**II(a)**], ring-fragmentation [**II(a)**→**II(b)**], and aromatization [**II(b)**→**III**] to give the key intermediate, acyl cation **III**.[10b] The acyl cation **III** then underwent Friedel-Crafts reaction to give ring-expansion products **2**.

To further verify our proposed mechanism, two control experiments were then designed. As shown in Scheme 5, five equivalents of methanol was employed to trap the proposed acyl cation intermediate **III** as shown in Scheme 4. As expected, the desired product methyl 2-alkylbenzoat **5** could be successfully obtained in 60% yield (Scheme 5, eq. 1). Furthermore, cycloheptanone-fused furan **2a** remained unchanged when it was subjected to the standard reaction conditions in the presence of methanol (5.0 eq.), which rules out the alcoholysis of **2a** to ester **5** (Scheme 5, eq. 2).

With the ring-expansion products **2** in hand, several chemical transformations were then carried out to show the potential applications of these molecules (Scheme 6). Taking **2n** as an example, the furan moiety could be regarded as diene to react with the dienophiles, such as DMAD and benzyne, through a [4+2] cycloaddition. The desired cycloadducts **6** and **7** could be obtained in good yields. In this reaction process, the

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benzocyclohexanone moiety of **2n** aromatized to naphthanol. When benzyne was used as the dienophile, the hydroxyl group of naphthanol could react with the second benzyne to afford diaryl ether **7**. Furthermore, the furan ring could also be oxidized into the diketone **8** in 89% yield with *m*-CPBA as oxidant. An aromatization process of the cyclohexanone moiety occurred as well.

In conclusion, we have reported a gold-catalyzed ring-expansion through acyl migration to afford furan-fused polycyclic compounds. The reaction was proposed through consecutive process of ring-fragmentation, protodeauration, aromatization, and Friedel-Crafts reaction. The acylcation species was regarded as the key intermediate for this reaction. This ring-expansion strategy holds the advantages of mild reaction condition and good selectivity, which makes this system very appealing for organic chemists to synthesize different furan-fused polycyclic compounds.

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