TfOH-catalyzed tandem cyclopropane ring enlargement/C–C formation/etherification of alkynylcyclopropanes and 1,3-diketones to cyclobutane-fused dihydrofurans†

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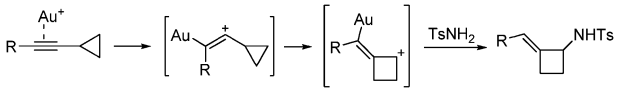
A new type of TfOH-catalyzed tandem cyclopropane ring enlargement/C–C formation/etherification reaction between alkynylcyclopropanes and 1,3-diketones to cyclobutane-fused dihydrofurans is described. The reaction tolerates a range of aryl and alkyl substituents with moderate to good yields.

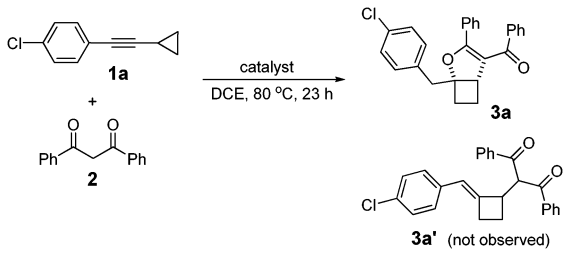
Reactions and methods to synthesize four-membered carbocycles, which are useful building blocks[1] in many bioactive natural products, are limited. Besides the various [2+2] cycloadditions (*via* photochemical methods,[2] transition metal catalysis,[3] or thermal conditions[4]), the ring expansion reaction of three-membered carbocycles is another efficient way to reach this target.[5] In recent years, the intramolecular ring expansions of alkynylcyclopropanols and alkynylcyclopropyl alkanols to useful cyclobutane derivatives, under the catalysis of transition metal complexes, were reported by several groups.[6] Based on the cation triggered/trapping strategy, we developed a new type of gold(I)-catalyzed ring expansion of alkynylcyclopropanes (without the hydroxyl group) to (*E*)-2-alkylidenecyclobutanamines by using sulfonamides as the trapping reagents.[7] In this transformation, a four-membered carbocycle as well as a new C–N bond were created in one pot (Scheme 1). This success encouraged us to find a suitable carbon nucleophile to trap the *in situ* generated cation, so that a C–C bond formation would be realized. If so, this strategy would provide a new approach to synthesize various cyclobutane derivatives and find applications in natural product synthesis and medicinal chemistry.

Enolates are widely used carbon nucleophiles. 1,3-Diketones can easily tautomerize to the corresponding enol forms,[8] which may be the appropriate nucleophiles in our design. We first used dibenzoylmethane **2** as the trapping reagent. Treatment of substrate **1a** and 1,3-diketone **2** under 10 mol% $(PPh_3)_3AuOTf$ produced an unexpected product **3a**, instead of the alkylidenecyclobutane derivative **3a′**, in 40% yield (entry 1, Table 1). Product **3a** contains a novel *cis*-fused bicyclic 4, 5-ring skeleton,[9] which is also viewed as a multifunctional dihydrofuran. By comparison between **3a** and **3a′**, we speculated that 1,3-diketone might act as a dinucleophile to react with the alkynylcyclopropane (Scheme 2). For this reaction, we proposed that, after the cation-triggered ring expansion of alkynylcyclopropane **A**, the enol form **C** of 1,3-diketone could trap the four-membered carbocyclic cation **B** to form the intermediate **D**. At this stage, the desired four-membered carbocycle and the C1–C2 bond were constructed. The newly formed alkylidenecyclobutane moiety, a class of strained alkenes, was prone to be activated by the cationic



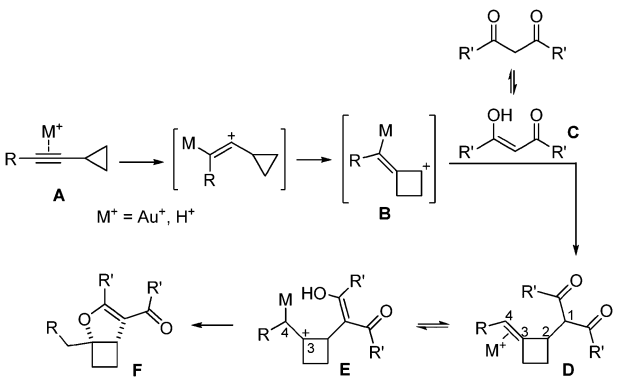
Scheme 1

Table 1 Catalyst screening[a]



Entry	Catalyst	Yield[b] (%)
1	10 mol% $AuPPh_3Cl$, 10 mol% AgOTf	40
2	10 mol% TfOH	75
3	10 mol% Tf_2NH	42
4	10 mol% CF_3COOH	NR[c]
5	10 mol% (+)-CSA	NR[c]
6	5 mol% TfOH	54
7	2 mol% TfOH	34

[a] Reaction condition: **1a** (0.5 mmol), **2** (0.55 mmol), solvent (5 mL). [b] Isolated yields. [c] NR = no reaction. (+)-CSA = (1*S*)-(+)-camphor-10-sulfonic acid.



Scheme 2

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catalyst. The positive charge preferred to locate at C3 rather than at C4 because a more stable tertiary carbocation was formed. Through tautomerization, the hydroxyl group in the intermediate **E** could nucleophilically attack C3, leading to the dihydrofuran structure **F** after the proton transfer.

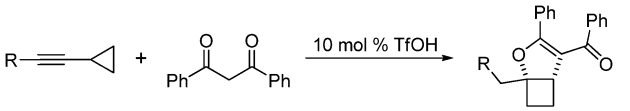
The discovery of the above reaction was very exciting to us, considering the fact that dihydrofuran is an important unit in chemical and biological research,[10,11] and the reactants used in the reaction are ubiquitous (many 1,3-diketones are commercially available) or can be easily prepared (**1a** from a Sonogashira reaction). Therefore, we screened reaction parameters to develop this tandem reaction into a practical approach for the synthesis of multifunctional dihydrofurans with very reasonable yields.

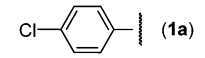
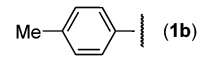
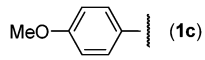
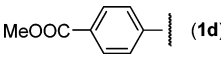
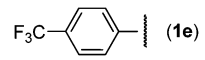
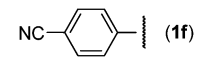
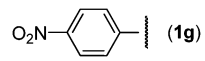
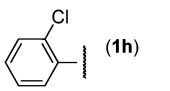
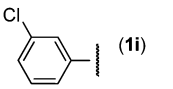
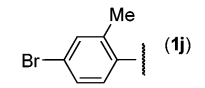
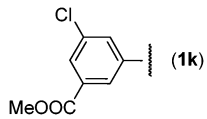
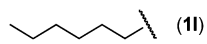
In our previous work, we found that the strong Brönsted acid, TfOH, can also catalyze the ring expansion of alkynylcyclopropanes.[12] Therefore, we tested the possibility and efficiency of TfOH as the catalyst for this reaction. To our delight, under 10 mol% TfOH, the reaction yield increased to 75% (entry 2, Table 1), suggesting that TfOH is more efficient than $(PPh_3)_3AuOTf$. Another strong Brönsted acid, Tf_2NH, turned out to be less efficient, as the reaction yield reduced to 42% (entry 3, Table 1). In contrast, weaker Brönsted acids, such as CF_3COOH and (+)-CSA, were not able to catalyze the desired tandem reaction (entries 4 and 5, Table 1). We further lowered the TfOH loading to 5 mol% and 2 mol%, respectively, and found that the reactions became slower (entries 6 and 7, Table 1). Based on these results shown in Table 1, together with the impetus to develop metal-free green chemistry, we chose 10 mol% TfOH as the best catalyst for the tandem reaction.

We further studied the scope of this tandem reaction. Similar to our previous work, we again found that the electron-donating aryl group in the substrate easily led to other side reactions. For example, when a *p*-tolyl group was introduced, the yield dropped to 40% (entry 2, Table 2). Substrate **1c**, containing a strong electron-donating *p*-methoxy group, decomposed under the TfOH catalysis and failed to furnish the desired product (entry 3, Table 2). However, electron-withdrawing groups were well compatible under the present tandem reaction conditions. Substituents such as ester, trifluoromethyl, cyano, and nitro groups in the substrates afforded the expected dihydrofurans in moderate to good yields (entries 4–7, Table 2). Besides *para*-substitution, *ortho*-, *meta*-, and even disubstituted phenyl alkynyl substrates could be well transformed into the expected products (entries 8–11, Table 2), suggesting that the steric effect on benzene ring did not affect the reactivity significantly. The alkyl-substituted substrate **1l** was found to undergo the tandem reaction in mild conditions, but the yield was only 19% (entry 12, Table 2).[13] In addition, the framework of the dihydrofurans was further confirmed by X-ray crystallographic analysis of **3g** (Fig. 1).†

Various 1,3-diketones and β-keto-esters were further investigated to know whether they were also good nucleophiles in the present tandem reaction. The 1,3-diketone **4** with a *para*-chloro group on its benzene ring was proved to be an efficient nucleophile in the tandem reaction with a good yield (entry 1, Table 3). When an electron-donating methoxy group was introduced, the reaction became slow. Raising the reaction temperature to 100 °C accelerated the consumption of substrate **1a** and the reaction maintained a good yield (entry 2, Table 3).

Table 2 Scope of alkynylcyclopropanes



Entry	R	Condition[a]	Time/h	Yield[b] (%)
1	 (**1a**)	A	23	75 (**3a**)
2	 (**1b**)	A	7	40 (**3b**)
3	 (**1c**)	A	7	ND[c,d] (**3c**)
4	 (**1d**)	A	20	76 (**3d**)
5	 (**1e**)	A	23	70 (**3e**)
6	 (**1f**)	B	7	32 (**3f**)
7	 (**1g**)	B	22	41 (**3g**)
8	 (**1h**)	B	21	61 (**3h**)
9	 (**1i**)	A	21	78 (**3i**)
10	 (**1j**)	B	19	63 (**3j**)
11	 (**1k**)	B	19	61 (**3k**)
12	 (**1l**)	C	22	19 (**3l**)

[a] Condition A: DCE as the solvent, heated at 80 °C. Condition B: TCE as the solvent, heated at 100 °C. Condition C: DCE as the solvent, heated at 40 °C. [b] Isolated yields. [c] ND = product not detected. [d] **1c** was totally consumed.

Acetylacetone **6**, an alkyl-substituted 1,3-diketone, was proved to be less active. The reaction proceeded under a high temperature (100 °C) and the yield was poor (entry 3, Table 3). For the cyclic 1,3-diketones, cyclohexane-1,3-dione **8** afforded the desired tricyclic product **3q** in a moderate yield

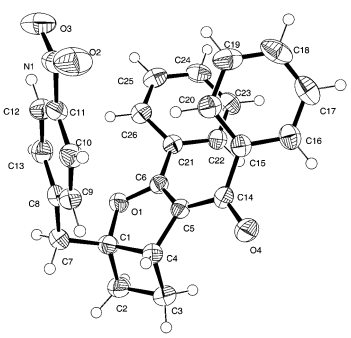
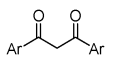
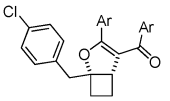
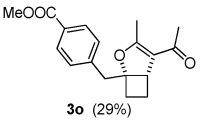
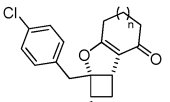
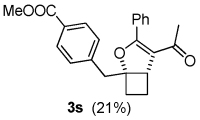
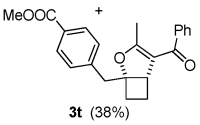
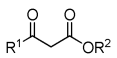
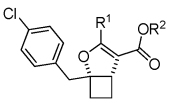


Fig. 1 X-Ray structure of product **3g**.

Table 3 Scope of nucleophiles

Entry	Substrate	Nucleophile	Condition[a]	Product (yield[b])
				
1	**1a**	Ar = *p*-ClC_6H_4	DCE, 80 °C, 20 h	**3m** (75%)
2	**1a**	Ar = *p*-$MeOC_6H_4$	TCE, 100 °C, 21 h	**3n** (72%)
3	**1d**	 **6**	TCE, 100 °C, 22 h	 **3o** (29%)
				
4	**1a**	*n* = 0 **7**	TCE, 120 °C, 25 h	**3p** (ND[c,d])
5	**1a**	*n* = 1 **8**	TCE, 120 °C, 22 h	**3q** (45%)
6	**1a**	*n* = 2 **9**	TCE, 100 °C, 14 h	**3r** (ND[c,d])
7	**1d**	 **10**	TCE, 100 °C, 19 h	 **3s** (21%) +  **3t** (38%)
				
8	**1a**	R^1 = Ph, R^2 = Et **11**	DCE, 80 °C, 15 h	**3u** (trace)
9	**1a**	R^1 = Me, R^2 = Me **12**	DCE, 80 °C, 15 h	**3v** (ND[c,d])

[a] 10 mol% TfOH as the catalyst. [b] Isolated yields. [c] ND = product not detected. [d] **1a** was totally consumed.

(entry 5, Table 3), despite the reaction required an even higher temperature (120 °C). Unfortunately, five- and seven-membered cyclic 1,3-diketones (**7** and **9**) failed to afford the products with the starting materials decomposed (entries 4 and 6, Table 3). For the unsymmetric 1,3-diketone **10**, the reaction produced two isomers in 59% yield, and the ratio of **3s** and **3t** was about 1 : 1.8 (entry 7, Table 3). These results suggest that the aryl-substituted 1,3-diketones are better nucleophiles than the alkyl-substituted 1,3-diketones. Unfortunately, neither the phenyl nor the methyl substituted β-keto-ester is the suitable nucleophile in this tandem reaction (entries 8 and 9, Table 3).

In summary, we have developed a new type of TfOH-catalyzed tandem cyclopropane ring enlargement/C–C formation/etherification reaction between alkynylcyclopropanes and 1,3-diketones to reach four-membered carbocycle-fused dihydrofurans that are architecturally interesting. A range of aryl and alkyl substituents are compatible in this tandem reaction.

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13 When 10 mol% Lewis acids, such as $Sc(OTf)_3$ and $In(OTf)_3$, were used as the catalysts, the reaction yields were 20% and 16%, respectively, showing that they were not superior to TfOH as the catalysts.

