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Gold(I)-Catalyzed Ring Expansion of Alkynylcyclopropyl Allyl Ethers to Construct Tetrasubstituted Methylenecyclobutanones: A Mechanistic Investigation about the Character of Catalytic Amount of Water

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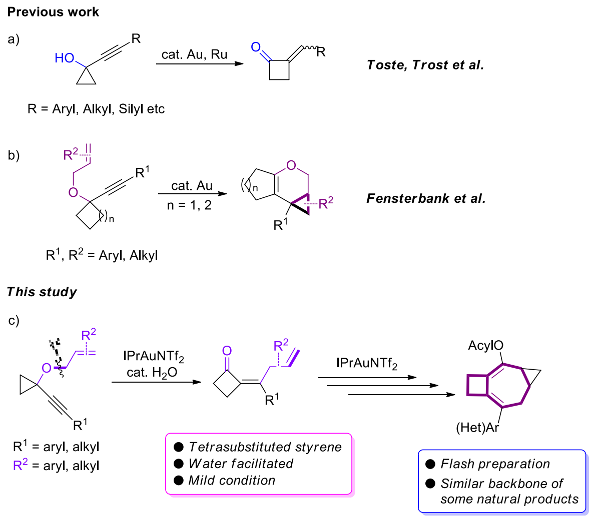
Abstract: A gold(I)-catalyzed ring expansion of alkynylcyclopropyl allyl ethers to produce tetrasubstituted methylenecyclobutanones in moderate to good yields has been disclosed in this paper. This reaction proceeded through an intramolecular [3,3]-sigmatropic rearrangement followed by [1,2]-allyl shift pathway in the presence of catalytic amount of water upon gold(I) catalysis. The intriguing reaction mechanism has been proposed on the basis of deuterium and ^{18}O-labeling experiments, Mass spectroscopic analysis, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic tracking and density functional theory (DFT) calculations. The further transformation of these methylenecyclobutanones into polycyclic skeleton has been realized by a practical three-step synthetic procedure. Several other transformations have been also indicated.

Keywords: gold-catalyzed; alkynylcyclopropyl allyl ethers; methylenecyclobutanones; water

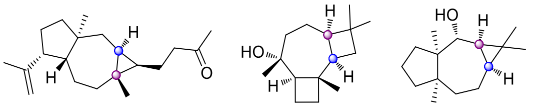
Introduction

Methylenecyclobutanones are ubiquitous functional building blocks that can be further transformed to various ring skeletons in organic synthesis.[1] However, the synthetic methods for the preparation of these compounds are underdeveloped along with limited substrate scope due to the existence of the strained four-membered-ring moiety.[2] Moreover, the present synthetic approaches are basically under very special or harsh reaction conditions to realize these four-membered carbocycles.[3] On the other hand, the cyclopropane could be easily prepared by many known synthetic methods, such as Simmons-Smith reaction,[4] Kulinkovich reaction or de Meijere-Kulinkovich reaction,[5] and others.[6] It is conceivable that a strain-driven ring expansion strategy[7] might be an alternatively efficient approach for construction of diversified cyclobutanone derivatives.[8]

During the last decade, gold catalysis has attracted considerable attention in organic synthesis due to its unique performance as Lewis acid catalyst, π–activator or carbenoid intermediate.[9] Particularly, the gold catalyst as the most soft Lewis acid performed very well in ring expansion reactions under mild conditions as compared with the other transition metal catalysts.[10] For example, in 2005 and 2008, Toste's and Trost's groups reported an intramolecular ring expansion of alkynylcyclopropanols to deliver methylenecyclobutanones in high yields in the presence of gold or ruthenium catalysts, respectively (Scheme 1a).[8b, e] Later in 2012, Fensterbank and co-workers discovered a gold-catalyzed cycloisomerization of *O*-tethered 1,6-enynes to produce natural-product-like macrocycles (Scheme 1b).[11] During our ongoing investigations on the chemical transformation of strained small rings,[12] we envisioned that introducing a highly strained cyclopropane ring into enyne's backbone might lead to an interesting ring expansion consequence to give functionalized four-membered-ring scaffolds. Inspired by this working hypothesis, various enynes bearing cyclopropane moiety were synthesized and we found that some of them exhibited unique chemical reactivities. Herein, we wish to disclose that a cyclopropane-tethered enyne could be rapidly transformed to the scarcely tetrasubstituted vinylcyclobutanone in assistance with catalytic amount of water upon gold catalysis (Scheme 1c). Furthermore, the obtained vinylcyclobutanone could be further transformed to [4.7.3] polycyclic compound by several steps. The framework of these polycyclic compounds is similar to those of natural products, such as *Dilospirane* B which possesses potential antibiotic activity, and *Koraiol* and (-)-*Neomeranol* B as well (Figure 1),[13] indicating the potential application of this methodology (Scheme 1c).



Scheme 1. Gold-catalyzed ring expansion reactions to construct methylenecyclobutanone derivatives



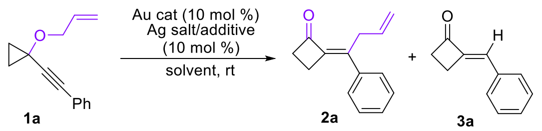
Dilospirane B *Koraiol* *(-)-Neomeranol B*

Figure 1. Structure of several polycyclic natural compounds

Results and Discussions

The examination of the reaction conditions was conducted by applying **1a** as a model substrate, and the results are summarized in Table 1. First, using AgNTf$_2$ as the silver salt, we examined the gold catalysts with different phosphine ligands such as PPh$_3$AuCl (10 mol %) and JohnPhosAuCl (10 mol %) in DCM, but we found that the reaction only afforded a complex mixture (Table 1, entries 1 and 2). However, when IPrAuCl (10 mol %), a NHC ligated (*N*-heterocyclic carbene-type ligand) gold complex, was used as the catalyst, the desired product **2a** was given in 60% yield within 60 h (Table 1, entry 3). Subsequently, the use of other silver salts or NaBArF as the additives was examined in order to accelerate the reaction rate. We found that adding AgOTf, AgSbF$_6$, AgBF$_4$ or NaBArF as the additive into this gold-catalyzed reaction system indeed could accelerate the reaction proceeding, giving **2a** in slightly improved yields within 12 h (Table 1, entries 4-7). However, their NMR spectra and TLC plates indicated that besides products **2a** and **3a**, the final reaction mixtures always contain some other impurities, perhaps due to the excessive activity of silver salt. Using prepared IPrAuNTf$_2$ as the catalyst delivered the desired product **2a** in 66% yield within 12 h, suggesting that the reaction could proceed more smoothly in the absence of silver salt (Table 1, entry 8). To our surprise, the yield of **2a** experienced an enhancement to 76% when we cut down the amount of gold catalyst to 5 mol % presumably due to that the use of less amount of gold catalyst could suppress the partial decomposition of the formed products **2a** and **3a**, leading to a cleaner reaction system (Table 1, entry 9). In addition, we discovered that the reaction rate was further accelerated when the wet solvent was employed. Enlightened by this phenomenon and our previous work, we assumed that extra H$_2$O might be able to facilitate this gold-catalyzed reaction.[14] Subsequently, 1.0 equiv of water was added and we found the reaction was indeed accelerated although **2a** was obtained in 62% yield within 6 hours (Table 1, entry 10). Then the solvent effect was investigated thoroughly with addition of 1.0 equiv of water, revealing that 1,2-dichloroethane (1,2-DCE) was the best one, affording **2a** in 66% yield within 6 hours (Table 1, entries 11-14). However, the fall in yield of **2a** indicated that redundantly external water might hedge the water effect in this reaction. Thus, we reduced the amount of H$_2$O to 0.5 equiv and found that the yield of **2a** was improved to 80% yield (78% isolated yield) within 6 h as the optimized result (Table 1, entry 15). The control experiment indicated that no reaction occurred in the absence of gold catalyst (Table 1, entry 16). It should be also mentioned that **3a** was detected as a by-product during these screening processes.

Table 1. Optimization of the reaction conditions for the transformation of **1a** to **2a**

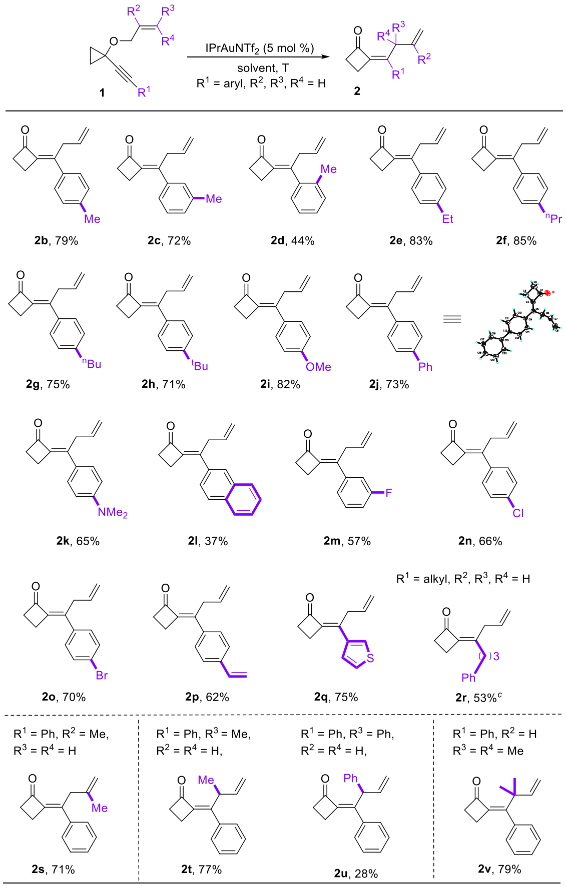


1a **2a** **3a**

entry	Au cat	[Ag] or additive	solvent	time (h)	yield/%^{b}	
					2a	**3a**
1	PPh$_3$AuCl	AgNTf$_2$	DCM	12	complex	/
2	JohnPhosAuCl	AgNTf$_2$	DCM	12	complex	/
3	IPrAuCl	AgNTf$_2$	DCM	60	60	12
4	IPrAuCl	AgOTf	DCM	12	48	16
5	IPrAuCl	AgSbF$_6$	DCM	12	65	18
6	IPrAuCl	AgBF$_4$	DCM	12	66	17
7	IPrAuCl	NaBArF	DCM	12	63	16
8	IPrAuNTf$_2$	/	DCM	12	66	13
9	IPrAuNTf$_2^c$	/	DCM	12	76	15
10	IPrAuNTf$_2^c$	1.0 equiv H$_2$O	DCM	6	62	13
11	IPrAuNTf$_2^c$	1.0 equiv H$_2$O	1,2-DCE	6	66	15
12	IPrAuNTf$_2^c$	1.0 equiv H$_2$O	1,2-DCE	12	trace	trace
13	IPrAuNTf$_2^c$	1.0 equiv H$_2$O	THF	12	complex	/
14	IPrAuNTf$_2^c$	1.0 equiv H$_2$O	toluene	12	trace	trace
15	***IPrAuNTf$_2^c$***	***0.5 equiv H$_2$O***	***1,2-DCE***	***6***	***80 (78)***	***14***
16	/	AgNTf$_2$, 0.5 equiv	1,2-DCE	12	N.A.	trace

^{a}The reaction scale is 0.1 mmol of **1a** in anhydrous solvent (0.1 M) at room temperature. ^{b}Yield was determined by ^{1}H-NMR yield using 1-bromo-4-methoxybenzene as an internal standard. ^{c}5 mol % of gold catalyst was used.

Having established the optimal reaction conditions, we decided to investigate the substrate scope and the results are summarized in Scheme 2. We firstly examined the reaction outcomes by using **1** with different electron-donating group (EDG) substituted aromatic rings as substrates. As can be seen from Scheme 2, for substrates **1b**-**1k**, most of the reactions proceeded smoothly in 1,2-DCE, furnishing the corresponding products **2b**-**2k** in 44-85% yields. Especially, the substrates bearing Et (**1e**), ^{n}Pr (**1f**) or OMe (**1i**) group afforded the desired products in good yields, ranging from 82% to 85%. However, changing the phenyl group to 2-naphthyl group, the desired product **2l** was obtained in 37%. When the phenyl group in substrates **1** was substituted by electron-withdrawing group (EWG) (**1m** to **1o**), the desired products **2m**-**2o** were given in relatively lower yields, perhaps due to the electronic effect. The reaction also performed very well when vinyl group was installed on the phenyl moiety, giving the corresponding product **2p** with the yield of 62%. Heteroaromatic group was also tolerated, furnishing the desired product **2q** in 75% yield. Substrate **1r** bearing an aliphatic alkyl group is also compatible, giving the desired product **2r** in 53% yield after prolonging the reaction time. In addition, this reaction also tolerated a wide variety of allyl derivatives, giving the desired products **2s**-**2v** with the yields ranging from 28% to 79%. The structure of **2j** has been unequivocally confirmed by X-ray diffraction. The corresponding ORTEP drawing is shown in Scheme 2.



[a]General condition: **1** (0.2 mmol), $IPrAuNTf_2$ (0.01 mmol), H_2O (0.1 mmol) in 1,2-DCE (0.1 M), at room temperature, 6 h. [b]All yields are the isolated yields. [c]The reaction time was 24 h.

Scheme 2. Substrate scope of alkynylcyclopropyl allyl ethers **1**.[a,b]

To clarify the reaction mechanism, several mechanistic investigations have been carried out as shown in Scheme 3. We firstly added 3Å molecular sieves into the reaction system to remove the ambient water from the reaction mixture and found that the reaction proceeding became sluggish, affording **2a** in 32% yield and 34% of **1a** was recovered (Scheme 3a). To figure out the exact role of water in this reaction, further analysis of this reaction with different amount of water was conducted, and the results illustrated that the H_2O participated in the catalytic process and accelerated the reaction proceeding, although variation on the concentration of extra water exhibited little correlation with the reaction velocity, which is nearly constant at the initial stage (Figure 2).

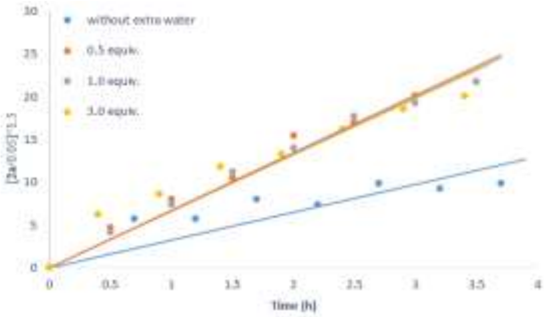
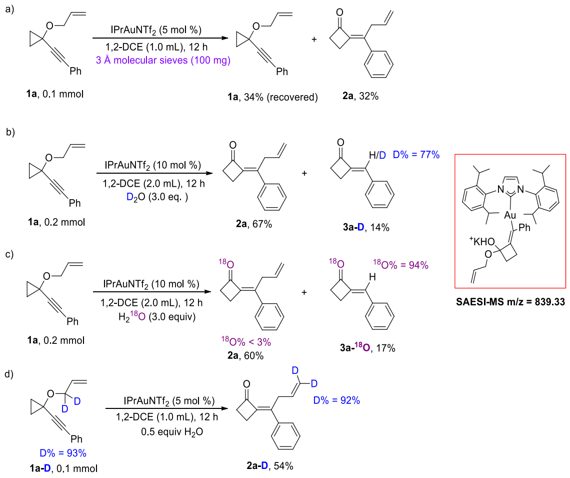


Figure 2. Analysis of the reaction rate with different amount of H_2O

Moreover, adding D_2O and $H_2{}^{18}O$ into the reaction mixture respectively, to our surprise, **3a** as a by-product was successfully labeled by both deuterium and ^{18}O atoms, but **2a** was formed without incorporation of deuterium and ^{18}O atoms (Schemes 3b and 3c). This intriguing result motivated us to do further investigation on H_2O effect in this reaction. On the basis of ^1H-NMR spectroscopic tracking experiment, the formation of allyl alcohol was identified in nearly 8% yield under the standard conditions along with the formation of **3a**. Furthermore, the ^{13}C-NMR spectroscopic tracking experiment disclosed a signal at $\delta = 98.3$ ppm, indicating the formation of ketal intermediate or its analogues (see Supporting Information for the details). We also found that this signal stayed throughout the reaction even after the reaction completed, suggesting that this species is quite stable and less reactive. Although we failed to isolate this species, the SAESI-MS analysis of the reaction mixture showed a possibly corresponding potassium ion peak (m/z = 839.33) (Schemes 3b, 3c). On the basis of these results, the existence of a hemiacetal species could be identified, which could be considered as a resting state in the catalytic cycle due to its relatively low reactivity. Finally, the use of deuterated **1a**-D (D content = 93%) produced **2a**-D in 54% yield along with 92% D content under the standard conditions, indicating a [3,3]-sigmatropic rearrangement process in the catalytic cycle (Scheme 3d).



Scheme 3. Mechanistic control experiments

We also embarked on a DFT study to gain insight into the reaction mechanism. All calculations have been performed at CPCM/M06/6-311+G(d,p)/SDD//B3LYP/6-31G(d)/SDD level with Gaussian 09 program.[15] The solvation Gibbs free energy profile in 1,2-DCE for the suggested reaction pathway is shown in Figure 3 (the ΔG_{298} (kcal/mol), see Supporting Information for the details). We investigated the reaction pathway starting from gold complex **A** shown in Figure 3. First, the cyclopropane moiety of the gold complex **A** undergoes a ring expansion process to give intermediate **B** *via* transition state TS_1 with an energy barrier of 20.8 kcal/mol. Then, the intermediate **B** could be resonanced to a gold carbenoid intermediate **C**. In addition, intermediate **C** will produce intermediate **D** through transition state TS_2 peaked at 22.8 kcal/mol, followed by the participation of ambient H_2O to afford intermediate **E**. Then, the intermediate **E** passes through transition state TS_3 with an energy barrier of 22.1 kcal/mol to furnish a key intermediate **F**. The intermediate **F** is hard to be located without extra water, and a possibly ion-dipole interaction between carbenium ion and H_2O (Distance between carbon and oxygen atom is 1.61Å) is shown in the 3D-geometric model of intermediate **F**. At last, the intermediate **F** undergoes the elimination of gold catalyst to give the final product, H_2O and AuL^+ through transition state TS_4 with 17.7 kcal/mol energy barrier. Moreover, the total ΔG_{298} in 1, 2-DCE of this reaction is -30.8 kcal/mol overall, indicating that this reaction is thermodynamically favorable and has a significant driving force to be transformed from the starting materials to the product.

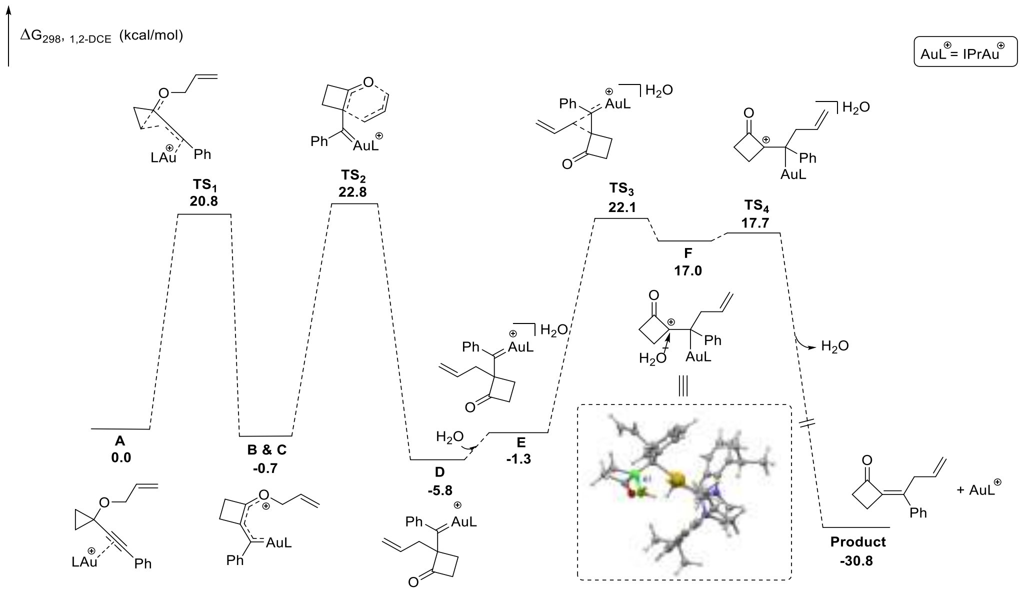
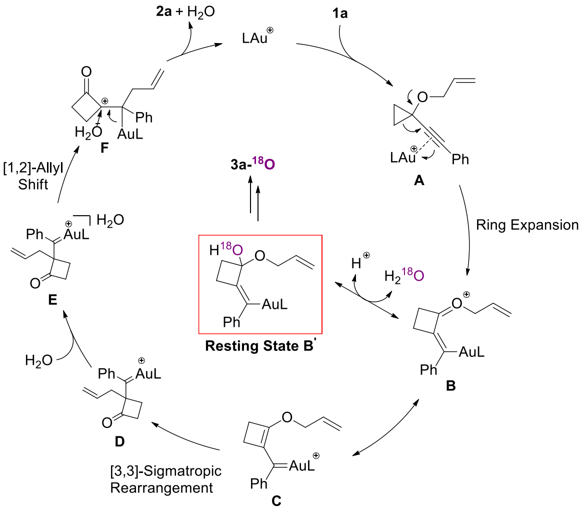


Figure 3. DFT calculation on reaction pathway (a relative Gibbs energy values in 1,2-dichloroethane solution are given in kcal/mol and selected bond distances in Å).

On the basis of these mechanistic studies and our previous work, a plausible mechanism is outlined in Scheme 4. As for substrate **1a**, the coordination with the employed gold catalyst gives intermediate **A**, followed by a ring expansion to furnish intermediate **B**. Then, the intermediate **B** can be transformed to its resonance form as the carbenoid intermediate **C**, which triggers a [3,3]-sigmatropic rearrangement to deliver the corresponding intermediate **D**. Subsequently, extra amount of water participates in the catalytic cycle, affording the hydrated intermediate **E**, which is supported by DFT calculation as shown in Figure 3. A [1,2]-allyl shift process[16] takes place to give intermediate **F**, in which the carbenium ion must be stabilized by H_2O. Finally, the regeneration of gold catalyst produces the desired product **2a** along with the release of water. During this catalytic cycle, the existence of a resting state **B'** (shown as an ^{18}O species), which has been proven by the mechanistic experiments, also contributes to the formation of side product **3a** through a deallyl alcohol step and a protodeauration process.



Scheme 4. A plausible reaction mechanism

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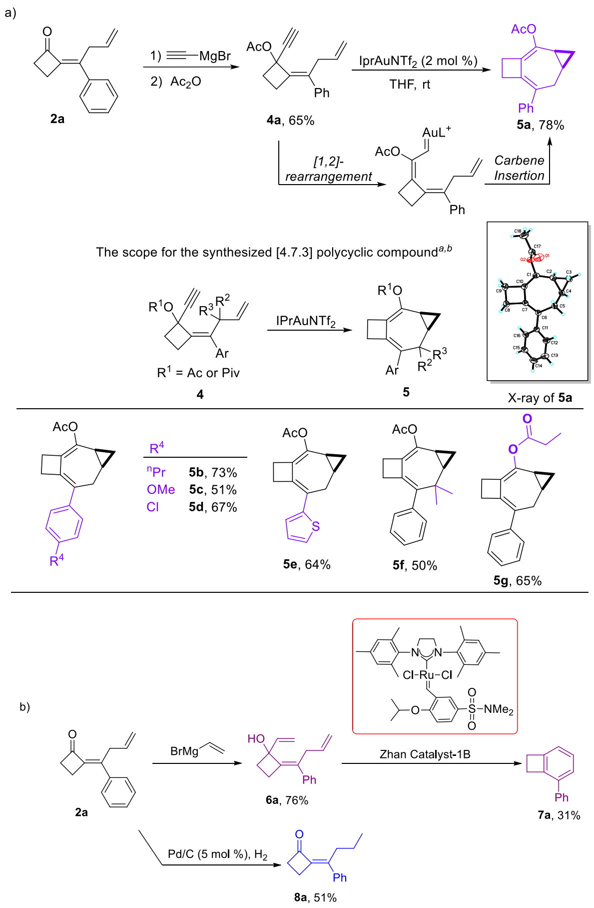
As the last part of this scenario, further derivatizations of the obtained vinylcyclobutanone were performed. Ketone **2a** can be transformed into polycyclic compound **5a** through a three-step synthetic sequence. As shown in Scheme 5a, addition of ethynyl Grignard reagent to **2a**, followed by esterification with Ac_2O, afforded the corresponding alkynylcyclobutyl acetate **4a** in 65% yield under mild conditions. Next, a gold-catalyzed 1,2-rearrangement gave a gold carbenoid intermediate, which underwent a carbene insertion process to afford **5a** bearing a polycyclic skeleton in 78% yield within 10 minutes (see Supporting Information for the condition screening).[17] The substrate scope has been examined and the results are shown in Scheme 5. All of the reactions proceeded smoothly, affording the desired products **5b-5g** in moderate to good yields. These synthesized polycyclic products have the similar framework as those of natural products shown in Figure 1. The structure of **5a** has been further confirmed by X-ray diffraction (Scheme 5a). More details about the corresponding ORTEP drawing and the CIF data are summarized in the Supporting Information. In addition, treating **2a** with vinylmagnesium bromide afforded **6a** in 76% yield, which could be further transformed to synthetically important benzocyclobutene **7a** in 31% yield through a subsequent RCM reaction procedure along with a dehydration pathway (Scheme 5b). Meanwhile, **2a** could be easily converted to **8a** in 51% yield through a Pd/C-catalyzed hydrogenation at room temperature (Scheme 5b).



aGeneral condition: **4** (0.2 mmol), IPrAuNTf$_2$ (2 mol %) in THF (0.1 M), at r.t., 10 min. bAll yields are the isolated yields.

Scheme 5. Further transformations of the synthesized tetrasubstituted methylenecyclobutanones

Conclusion

In summary, we have disclosed the first example of gold(I)-catalyzed ring expansion of alkynylcyclopropyl allyl ethers to construct tetrasubstituted methylenecyclobutanones in moderate to good yields under mild conditions. This reaction proceeded through a gold(I)-catalyzed intramolecular [3,3]-sigmatropic rearrangement followed by [1,2]-allyl shift process in the presence of catalytic amount of water. The intriguing reaction mechanism has been verified on the basis of a series of mechanistic studies and DFT calculation, demonstrating the intriguing character of catalytic amount of water in this gold-catalyzed transformation. These methylenecyclobutanones could be transformed to natural-product-like polycyclic skeletons through a practical three-step synthetic protocol. Further investigations on expanding the scope and applications of this method are undergoing in our laboratory.

Experimental Section

General procedure for the synthesis of tetrasubstituted methylenecyclobutanones

To a 25 mL oven-dried round-bottom flask were added IPrAuNTf$_2$ (8.6 mg, 0.01 mmol), H_2O (1.8 mg, 0.1 mmol) under argon atmosphere, and then ((1-(allyloxy)cyclopropyl)ethynyl)benzene (**1a**) (0.2 mmol) dissolved in 1,2-DCE (2.0 mL) was added dropwise through a syringe. The reaction mixture was stirred at room temperature for specific hours. After that, the reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography with petroleum ether-EtOAc (100:1) as an eluent to afford the desired product (*E*)-2-(1-phenylbut-3-en-1-ylidene)cyclobutan-1-one (**2a**).

Supporting Information Available

Detailed descriptions of experimental procedures and their spectroscopic data as well as the crystal structures are presented in the Supporting Information. CCDC 1843477 (**2j**) and CCDC 1851584 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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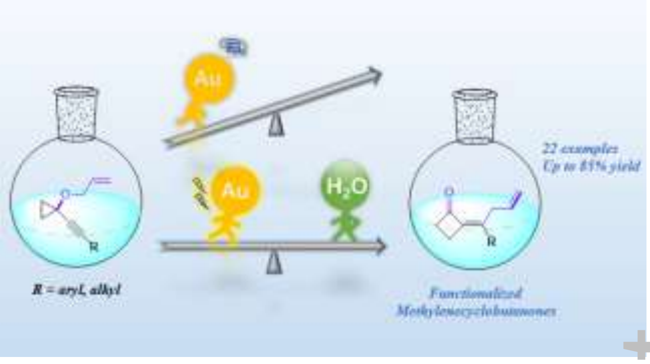

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