Organic LETTERS

Gold(I)-Catalyzed Polycyclization of Linear Dienediynes to Seven-Membered Ring-Containing Polycycles via Tandem Cyclopropanation/Cope Rearrangement/C–H Activation

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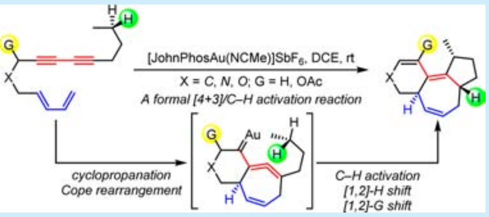
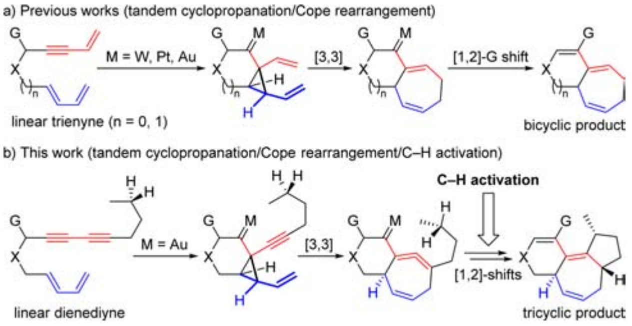
Supporting Information

ABSTRACT: A novel gold(I)-catalyzed polycyclization of easily prepared linear dienediynes has been developed for the construction of fused 5,7,6-tricyclic ring systems in one step with high diastereocontrol. The polycyclization, a formal [4 + 3]/C–H activation reaction, takes place through gold(I)-catalyzed intramolecular cyclopropanation of diene with diyne, Cope rearrangement of *cis*-alkenylalkynylcyclopropane, aliphatic C–H activation via a seven-membered-ring allene intermediate, and [1,2]-H and -G (H or OAc) shifts.



Seven-membered ring-containing polycycles are widely found in natural products and pharmaceuticals with impressive biological properties. Tremendous efforts have been devoted to the development of new methodologies and strategies to build the polycyclic skeletons of these natural products and their analogues with seven-membered rings.[1,2] One powerful and widely used reaction to synthesize seven-membered carbocycles is the Cope rearrangement of divinylcyclopropanes.[3−7] However, preparation of the substrates is usually not trivial. Recently, it was found that linear trienyne substrates can undergo tandem cyclopropanation/Cope rearrangement smoothly under the catalysis of transition metal complexes, such as $[W(CO)_5(L)]$,[4] $PtCl_2$,[5] and cationic gold complex,[6] to form seven-membered ring-containing bicyclic ring systems (Scheme 1a).[7] In principle, these methods could also be extended to synthesize polycyclic ring systems if the rest of the cyclic structures is preinstalled in the substrates. However, additional synthetic steps would be required in such an indirect approach. We envisioned that if one alkene moiety of the trienyne substrate is replaced by an alkynyl group, the resulting dienediyne substrate can also undergo the tandem cyclopropanation/Cope rearrangement,[8] generating a reactive bent allene intermediate,[9] which may initiate further transformations to incorporate additional ring junctions (Scheme 1b),[10] and consequently the synthetic efficiency toward seven-membered ring-containing polycycles would be greatly enhanced.

Scheme 1. Tandem Cyclopropanation/Cope Rearrangement for the Construction of Fused Ring Systems



Here we report our discovery of a novel gold(I)-catalyzed polycyclization of dienediynes, merged with an unprecedented site-specific aliphatic C–H activation process[10−12] via a seven-membered-ring allene intermediate, to give the fused 5,7,6-tricyclic skeleton of daphnane and tigliane diterpenes as the final product (Figure 1).

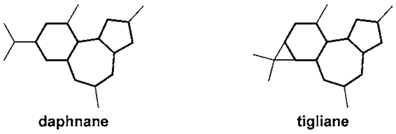


Figure 1. Structures of daphnane and tigliane diterpenes.

When we treated dienediyne **1a** under gold catalysis, we observed diastereoselective synthesis of tricyclic products **2a** and **3a** (Table 1). Compound **2a** was usually observed as the major product together with a trace amount of **3a** as the minor one. The relative configuration of **2a** was confirmed by X-ray crystallographic analysis. Further optimization of the reaction conditions revealed that the reaction was sensitive to water and basic counteranions. For instance, when the solvent was not sufficiently dry or when AgOTf was used, the percentage of **3a**

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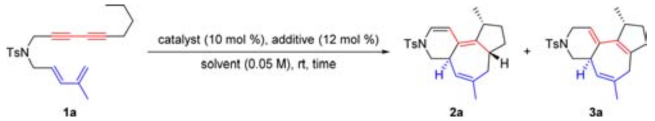
Table 1. Optimization Studies on the Gold(I)-Catalyzed Polycyclization[a]

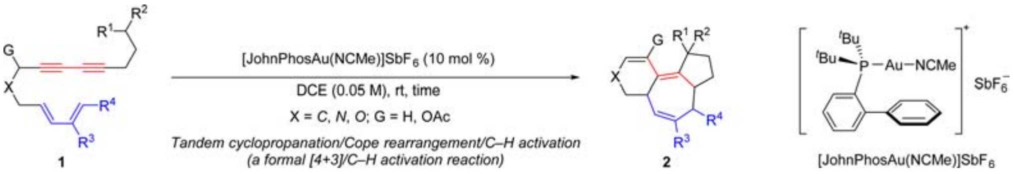


1a **2a** **3a**

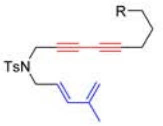
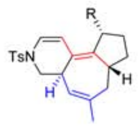
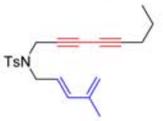
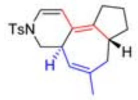
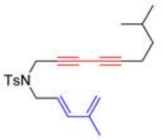
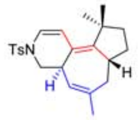
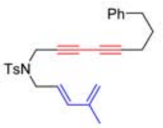
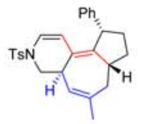
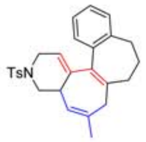
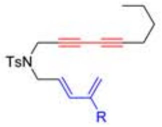
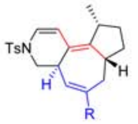
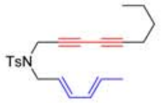
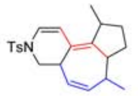
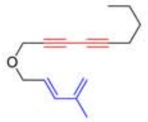
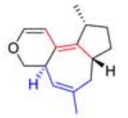
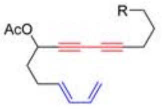
entry	catalyst	additive	solvent	time (h)	isolated yield of **2a**	isolated yield of **3a**
1	$(2,4\text{-}^t\text{Bu}_2\text{-C}_6\text{H}_3\text{O})_3\text{PAuCl}$	AgSbF_6	DCM	5.5	34%	18%
2	Ph_3PAuCl	AgSbF_6	DCM	14	19%	20%
3	IPrAuCl	AgSbF_6	DCM	6	30%	34%
4	BrettPhosAuCl	AgSbF_6	DCM	17	36%	trace
5	XPhosAuNTf_2	none	DCM	5	65%	trace
6	JohnPhosAuCl	AgSbF_6	DCM	2	72%	trace
7	JohnPhosAuCl	AgPF_6	DCM	2	64%	trace
8	JohnPhosAuCl	AgBF_4	DCM	2	77%	trace
9	JohnPhosAuCl	AgNTf_2	DCM	2	72%	trace
10	JohnPhosAuCl	AgOTf	DCM	2	trace	69%
11	$[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$	none	DCM	2	71%	trace
12	$[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$	none	CDCl_3	3	55%	trace
13	$[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$	none	DCE	2	79%	trace

[a] Reaction conditions: dienediyne **1a**, catalyst (10 mol %), and additive (12 mol %) in solvent (0.05 M) at rt.

Table 2. Reaction Scope[a]



1 **2**

entry	dienediyne **1**	product **2**	yield[b] (dr[c]), time
1	 **1a** (R = Me)	 **2a** (R = Me)	79% (15:1), 2 h
2	**1b** (R = $^n\text{C}_5\text{H}_{11}$)	**2b** (R = $^n\text{C}_5\text{H}_{11}$)	70% (>20:1), 2 h
3	**1c** (R = CH_2OTBS)	**2c** (R = CH_2OTBS)	47% (7:1), 4 h
4	 **1d**	 **2d**	24%[d] (>20:1), 24 h
5	 **1e**	 **2e**	56% (>20:1), 3 h
6	 **1f**	 30% **2f** (>20:1)	39% **4f**, 14 h
7	 **1g** (R = Bn)	 **2g** (R = Bn)	77% (12:1), 12 h
8[e]	**1h** (R = ^{i}Pr)	**2h** (R = ^{i}Pr)	94% (10:1), 6 h
9	**1i** (R = H)	**2i** (R = H)	87% (8:1), 11 h
10	 **1j**	 **2j**	67% (3:1), 10 min
11	 **1k**	 **2k**	74% (>20:1), 0.5 h
12[f]	 **1l** (R = Me)	 **2l** (R = Me)	66%[g], 4.5 h
13[f]	**1m** (R = Et)	**2m** (R = Et)	76%[h], 4 h

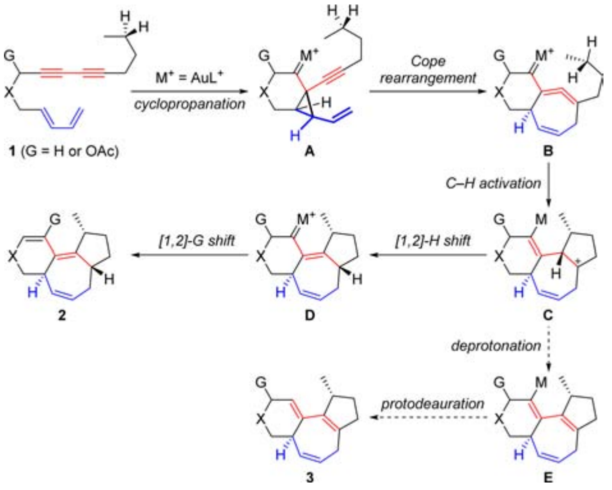
[a] Reaction conditions: dienediyne **1** and $[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$ (10 mol %) in DCE (0.05 M) at rt. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis after column chromatography. [d] Combined isolated yield of **2d** and an unidentified and inseparable byproduct (6:1[c]) based on recovered starting material. [e] $[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$ (11 mol %) was used. >20:1 dr and 78% isolated yield were obtained when DCM was used as solvent. [f] $[\text{JohnPhosAu(NCMe)}]\text{SbF}_6$ (20 mol %) and 4 Å MS were used. [g] Combined isolated yield of **2l** and two unidentified byproducts (20:2:1, determined by GC–MS). [h] Combined isolated yield of **2m** and three unidentified byproducts (27:2:2:1, determined by GC–MS).

increased (Table 1, entry 10). Furthermore, silver additives were found to promote the generation of **3a**. Therefore, we decided to use the cationic gold(I) complex [JohnPhosAu(NCMe)]SbF_6 as the catalyst without using silver additives (Table 1, entries 11−13). When DCE was used as solvent, we obtained product **2a** predominantly in a good yield under very mild conditions.

After obtaining the optimal reaction conditions, we began to investigate the scope of the polycyclization (Table 2). First, we synthesized dienediynes with various types of C(sp^3)−H bonds including primary, secondary, and tertiary C−H bonds on the γ position of the distal alkyne moiety (Table 2, entries 1−6). We found that the cyclization of **1a** gave **2a** in 79% isolated yield within 2 h. The side chain of the substrates can be elongated (Table 2, entry 2) or substituted (Table 2, entry 3), and the desired tricyclic products were formed in moderate yields in both cases. When substrate **1d** with primary C−H bonds was used, the reaction became much slower (Table 2, entry 4). In this case, we found that, even after 24 h, there was still a large amount of **1d** remaining intact in the reaction system. It was expected that tertiary C−H bond activation should be difficult due to steric hindrance. However, the reaction of **1e** took place very smoothly within 3 h with 56% isolated yield, generating **2e** with a newly formed all-carbon quaternary center (Table 2, entry 5). In general, seven-membered-ring allene insertion into a secondary C−H bond is most favored among primary, secondary, and tertiary C−H bonds because insertion into a secondary C−H bond can stabilize positive charge buildup[13] without being too sterically crowded, which is formally observed in the well-known Rh(II) carbene C−H insertion chemistry.[14] Our attempts to activate the benzylic C−H bond of **1f** resulted in the generation of **2f** and **4f** (Table 2, entry 6). **2f** was the desired benzylic C−H activation product, whereas **4f** was the Friedel−Crafts product with the formation of another seven-membered ring. Futhermore, we found that the methyl group in the diene part can be replaced by both benzyl and isopropyl groups (Table 2, entries 7 and 8). Monosubstituted diene **1i** can also give the polycyclization product in a good yield (Table 2, entry 9). We found that the reaction of substrate **1j**, which has a terminal substituent on the diene moiety, proceeded quite rapidly (Table 2, entry 10), possibly due to the electron richness of the methyl-terminated diene. Dienediyne **1k** with an oxygen tether also worked very well, giving the desired product **2k** in 74% isolated yield within 30 min (Table 2, entry 11). Unfortunately, dienediyne substrate tethered by a malonate motif [$C(CO_2Me)_2$] did not give the desired polycyclization product, and only the starting material was recovered. To our delight, when we introduced an acetoxy group at the proximal propargylic position of the substrates, the desired polycyclization occurred, giving the fused 5,7,6-tricyclic carbocycles in moderate yields, showing that our method can be used to synthesize the challenging tricyclo[$9.3.0.0^{2,7}$]tetradecane ring system in daphnane and tigliane diterpenes (Figure 1) with high efficiency (Table 2, entries 12 and 13). Unfortunately, the polycyclization of several other carbon-tethered substrates gave complex mixture,[15] and further screening of other catalytic systems to achieve the polycyclization of these carbon-tethered substrates will be the next goal of our research.

We proposed that the polycyclization, a formal [4 + 3]/C−H activation reaction, starts with the gold(I)-catalyzed intramolecular cyclopropanation of dienediyne **1** to a *cis*-alkenylalkynylcyclopropane **A**, which undergoes the Cope rearrangement to form a cyclic bent allene **B** (Scheme 2). Then C−H activation occurs,[10] leading to a carbocation **C**, which undergoes the subsequent [1,2]-H shift to form a gold carbenoid **D**. Finally, **D** undergoes another [1,2]-G (G = H or OAc) shift to form the tricyclic product **2** and regenerate the gold catalyst. Preliminary DFT studies supported this mechanism and further investigation is ongoing. For the formation of byproduct **3**, we hypothesized that carbocation **C** may also undergo deprotonation after the C−H activation step, leading to a vinyl−gold species **E**, which undergoes the subsequent protodeauration to form the tricyclic product **3** and release the gold catalyst. Water and triflate anion may promote the deprotonation of intermediate **C**, and consequently, more **3** would be generated.

Scheme 2. Proposed Mechanism



In summary, a mild and efficient gold(I)-catalyzed tandem cyclopropanation/Cope rearrangement/aliphatic C−H activation of dienediynes has been achieved to synthesize the fused 5,7,6-tricyclic ring system with good yields and high diastereocontrol. This reaction represents a new example for step-economical synthesis of complex molecules, and has its potential usage in target- and function-oriented syntheses.[16] The depicted polycyclization, a formal [4 + 3]/C−H activation, can be further developed to synthesize other complex and new skeletons by introducing various components in the substrates or in the reaction system. Further work to study the detailed reaction mechanism and explore the cyclic allene chemistry is underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(13) To further understand the substituent effect on the relative reactivity of different substrates, we synthesized two substrates with electron-withdrawing groups (Cl and CN) on the *γ* position of the distal alkyne moiety (see Supporting Information for details). Both of them gave complex mixtures under the standard conditions, which further supported that bent allene C−H insertion favors the sites where positive charge buildup can be stabilized.

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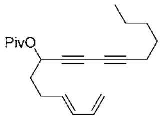

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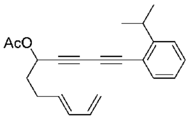

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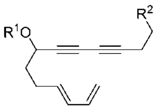

1p (R^1 = Ac, R^2 = ^{i}Pr)
1q (R^1 = Ac, R^2 = CH_2CH_2OTBS)
1r (R^1 = Me, R^2 = Et)

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