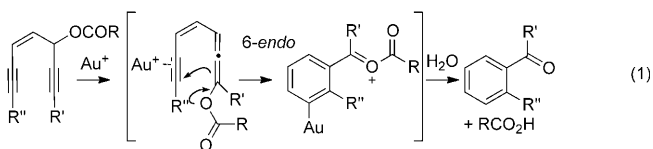


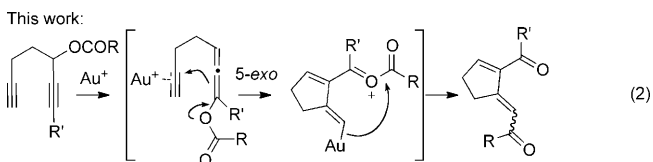
Gold-Catalyzed 1,3-Acyloxy Migration/5-*exo*-dig Cyclization/1,5-Acyl Migration of Diynyl Esters**

David Lebœuf, Antoine Simonneau, Corinne Aubert, Max Malacria,* Vincent Gandon,* and Louis Fensterbank*

Gold-catalyzed cycloisomerizations of unsaturated precursors have become a recognized tool for the rapid construction of complex molecules.^[1] While the skeletal reorganization of enyne systems has been the most intensively studied,^[1c] diynes have also proved to be valuable substrates for various gold-catalyzed transformations.^[2] Of particular interest, hydrative cyclizations of (*Z*)-hepta-4-ene-1,6-diyn-3-yl esters led to aromatic ketones after 1,3-sigmatropic acyloxy shift, 6-*endo*-dig cyclization, and acyl elimination [Eq. (1)].^[2c,d] If the



acylium ion could instead be trapped by the nucleophilic Au–C bond, a new kind of cycloisomerization product would ensue. Herein, we report our investigation on the gold-catalyzed transformation of hepta-1,6-diyn-3-yl esters. An efficient method for the preparation of δ -diketones based on an unprecedented Au-triggered 1,5-acyl shift has been devised [Eq. (2)].^[3]



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When acetate **1a**^[4] was submitted to [Ph₃PAuCl]/AgSbF₆ in dichloromethane at 0°C, a new product formed rapidly in nearly quantitative yield (Table 1, entry 1). While the pres-

Table 1: Optimization of the reaction conditions.

Entry	Cat. (loading)	Solvent	T [°C]	t [h]	Yield [%] ^[a]
1	[Ph ₃ PAuCl]/AgSbF ₆ (2 mol %/2 mol %)	CH ₂ Cl ₂	0	0.33	99
2	AgSbF ₆ (2 mol %)	CH ₂ Cl ₂	RT	24	— ^[b]
3	A (2 mol %)	CH ₂ Cl ₂	RT	0.66	98
4	Ph ₃ PAuNTf ₂ (2 mol %)	CH ₂ Cl ₂	RT	0.66	95
5	AuCl (2 mol %)	CH ₂ Cl ₂	RT	1	80
6	AuCl ₃ (2 mol %)	CH ₂ Cl ₂	RT	1	90
7	PtCl ₂ (5 mol %)	toluene	reflux	1	92
8	PtCl ₄ (2 mol %)	toluene	reflux	1	91

[a] Yield of isolated product. [b] Decomposition.

ence of two carbonyl functionalities was evident in the ¹³C NMR spectrum, the rest of the structure was assigned on the basis of 2D spectroscopic studies and NOE experiments. Diketone **2a** was isolated as a single diastereomer of *E* configuration relative to the exocyclic double bond. Whereas AgSbF₆ alone led to decomposition products (Table 1, entry 2), other salts of Au^I, Au^{III}, Pt^{II}, or Pt^{IV} provided **2a** in good to excellent yields (Table 1, entries 3–8). In our further investigation, we selected [Ph₃PAuCl]/AgSbF₆ and **A**^[5] as the best potential catalysts.

The scope of the reaction was studied next (Table 2). We first kept the basic framework of **1a** and checked the substitution at the propargyl acetate moiety (Table 2, substrates **1b–g**). No reaction occurred with R = H (**1b**) or TMS (**1c**).^[6] On the other hand, the desired products were formed diastereoselectively in excellent yields at 0°C in 30 min with [Ph₃PAuCl]/AgSbF₆ when alkyl groups were installed at the alkyne terminus (**1d–g**). The presence of an additional triple bond, although deactivated by a TMS group, was very well tolerated, and **2h** was isolated in 99% yield. Not only aryl and alkyl, but also vinyl groups could be placed at the triple bond, as shown by the formation of the interesting divinyl ketone framework of **2i**. Also of particular interest, the *p*-nitrobenzoate group was tolerated and **2j** obtained quantitatively. To rule out any possible influence of the ring size or of the dioxolane fragment, the cyclization was carried out with five-

Table 2: Gold-catalyzed 1,3-acyloxy migration/5-*exo*-dig cyclization/1,5-acyl migration of diynyl esters.^[a]

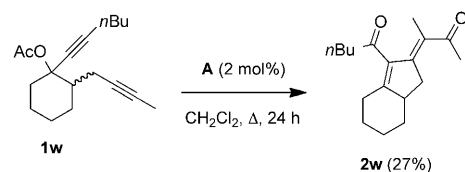
Substrate	Product	Substrate ^[b]	Product
1b R = H	- [c]	1k (<i>n</i> = 1) R = Ph	2k (80%) ^[d]
1c R = TMS	- [c]	1l (<i>n</i> = 1) R = <i>n</i> Bu	2l (73%) ^[d]
1d R = Me	2d (98%)	1m (<i>n</i> = 1) R = cyclopropyl	2m (98%) ^[d]
1e R = CH ₂ OTBDPS	2e (95%)	1n (<i>n</i> = 2) R = Ph	2n (75%) ^[e]
1f R = cyclopropyl	2f (90%)	1o (<i>n</i> = 3) R = Ph	2o (94%) ^[f]
1g R = <i>t</i> Bu	2g (97%)		
1h	2h (99%)	1p	2p (66%) ^[g]
1i	2i (70%)	1q	2q (80%) ^[f]
1j	2j (99%)	1r	2r (81%) ^[h]
1s R = <i>n</i> Bu	2s (64%) ^[g]	1t R = Ph	2t (98%) ^[g]
1u R = <i>t</i> Bu	2u (99%) ^[g]	1v R = cyclopropyl	2v (99%) ^[g]

[a] General reaction conditions: diynyl ester (0.025 M in CH₂Cl₂), [Ph₃PAuCl] (2 mol %), AgSbF₆ (2 mol %), 0 °C, 30 min (see the following for occasional modifications). [b] **1k–q** are mixtures of diastereomers. [c] No reaction. [d] Using **A** (2 mol %), 0 °C, 10 min. [e] Using **A** (2 mol %), 0 °C, 1 h. [f] Using **A** (2 mol %), RT, 1 h. [g] Using **A** (2 mol %), RT, 12 h. [h] RT, 12 h. TBDPS = *tert*-butyldiphenylsilyl.

six-, and seven-membered-ring substrates (substrates **1k–o**). Gratifyingly, all of them transformed into the expected products in good to high yields using catalyst **A**. To conclude our work on cyclic substrates, extension of the title reaction to acrylate **1p** was achieved, yielding **2p** in 66 % after 12 h at RT. We next turned our attention to acyclic compounds such as triyne **1q**, which pleasingly cyclized to give **2q** in 80 % yield. Because all the substrates tested so far were tertiary esters, we next engaged the simple secondary acetate **1r**, which eventually resulted in the formation of **2r** in 81 % yield. In the series of secondary acrylates, acyclic diynes **1s–v** also proved to be valuable substrates for the title reaction.

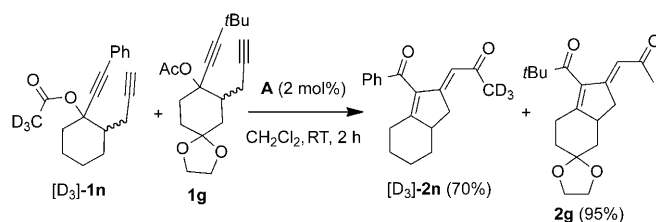
During this preliminary screening, the only limitation we found was related to the substitution at the triple bonds: when a disubstituted propargyl ester moiety is required, the second

triple bond must remain monosubstituted; otherwise complex mixtures are obtained from which the desired product can sometimes be isolated in poor yield (Scheme 1).



Scheme 1. Cyclization of a substrate bearing disubstituted triple bonds.

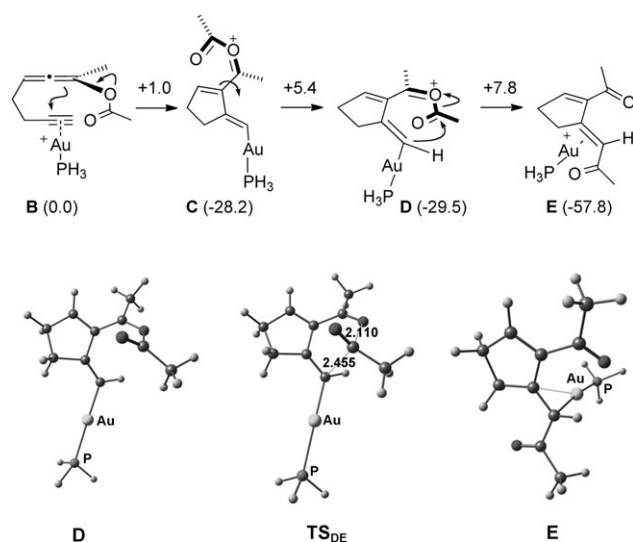
Because of the *E* configuration of the exocyclic double bond of all products, an intramolecular acyl shift may seem difficult. However, the reaction of the labeled compound [D₃]-**1n**, in the presence of **1g**, did not lead to any deuterium scrambling (Scheme 2).



Scheme 2. H/D crossover experiment.

To shed light on the stereoselectivity issue, we sought to validate our mechanistic assumptions by DFT computations. Since the rearrangement of propargyl acetates into allenyl acetates is a well-described process,^[7] we started our investigation directly from complex **B** (Scheme 3). From there, an outer-sphere 5-*exo*-dig cyclization could be modeled through a low-lying transition state at an enthalpic cost of 1 kcal mol^{−1}, and the resulting complex **C** is more stable than **B** by 28.2 kcal mol^{−1}.^[8] Rotation of the acyloxy group was necessary to reach the next reactive conformation **D**. This requires a low enthalpy of activation of only 5.4 kcal mol^{−1}. In **D**, the p orbitals at the terminal carbons of the π system are well oriented for an efficient overlap. 1,5-Acy migration to give the final product **E** can take place in a concerted fashion through **TS_{DE}**, which lies 7.8 kcal mol^{−1} higher in energy than **D**. This process is accompanied by the liberation of 28.3 kcal mol^{−1} of energy. Thus, these calculations show the feasibility of an intramolecular 1,5-acyl shift giving rise to a *E*-exocyclic double bond. The Au–C bond is cleaved by the acylium ion in a stereoselective fashion, the electrophile being delivered intramolecularly. The formation of the *Z* stereoisomer would require either an unfavorable inner-sphere 5-*exo*-dig cyclization or the isomerization of the vinylgold moiety in **C**, which is kinetically very difficult to achieve.^[9] The stereochemical outcome is therefore dictated by the cyclization step.^[10]

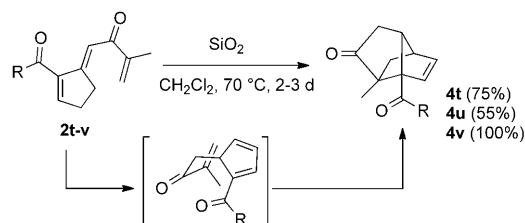
Because the triple bond of the putative 1,5-allenyl intermediate must be monosubstituted for the reaction to



Scheme 3. Mechanistic rationale supported by DFT computations (B3LYP/LANL2DZ(Au)/6-31G(d) (other elements); ΔH_{298} [kcal mol⁻¹]. Energy barrier heights to the transition states are written above the arrows. Selected bond lengths in Å.

proceed efficiently, one may wonder whether a dual activation of a terminal alkyne by two molecules of gold complex might be the operative mechanism.^[11] However, in the 1,5-allenynes series, it was shown that the cycloisomerization did not take place at all when the triple bond was disubstituted, which is not the case here (Scheme 1). Besides, it would be quite unlikely in this case to observe exclusive *E* stereochemistry of the double bond in the final products.

The reactivity of the product δ -diketones was briefly examined (Scheme 4). Compounds **2t–v** were heated in a sealed tube in the presence of 100 equiv of SiO₂, leading to the



Scheme 4. Acid-catalyzed rearrangement of diketones **2t–v**.

polycyclic products **4t–v** in up to 100% yield as single diastereomers.^[12] The structure of **4t** was ascertained by a X-ray diffraction analysis (see the Supporting Information).^[13] These compounds presumably arise from the acid-catalyzed migration of the exocyclic double bond to give the corresponding cyclopentadiene, which undergoes intramolecular [4+2] cycloaddition with the pendant double bond.^[14] This transformation is very promising because such products can be valuable intermediates en route to natural products.^[14b,15]

In conclusion, we have developed a new cycloisomerization protocol involving an unprecedented 1,5-sigmatropic acyl shift. We are now exploiting this unique cascade reaction for the synthesis of complex molecules.

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