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Au-Catalyzed Pentannulation Reaction of Propargylic Esters Occurring at C(sp^3)−H Site

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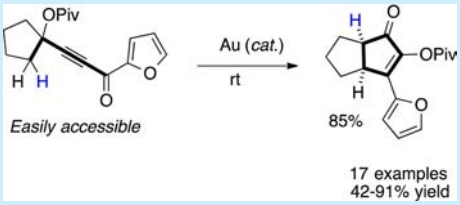
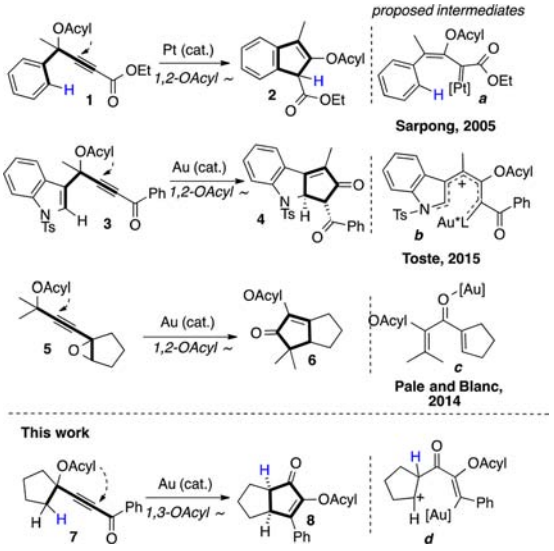
Supporting Information

ABSTRACT: A gold-catalyzed cascade cyclization reaction of easily accessible propargylic esters to cyclopentenones has been developed. This transformation features an unprecedented pentannulation reaction of propargylic esters which occurs at an unactivated C(sp^3)−H site to efficiently produce functionalized mono-, bis-, and tricyclic cyclopentenones.

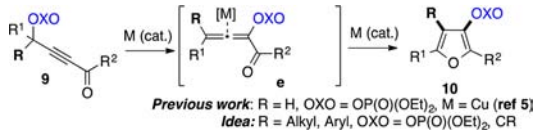


Readily available propargylic esters are versatile substrates for transition-metal-catalyzed transformations into a wide array of valuable acyclic, cyclic, and heterocyclic motifs.[1] Mechanistically diverse π-acidic metal-catalyzed pentannulation reactions of these substrates, possessing carbonyl or epoxide functionalities at the alkyne moiety, highlight their rich reactivities (Scheme 1).[2] Thus, Sarpong and co-workers reported that Pt-catalyzed Rautenstrauch rearrangement of propargylic ester **1** generates the metal carbene **a**, which upon insertion into the C(sp^2)−H bond produces cyclopentene **2**.[2a] On the other hand, the Toste group showed that Au-catalyzed 1,2-acyloxy migration of substrate **3** produces nonclassical cationic intermediate **b**, in which the generated cation is stabilized by the indole moiety. A ligand-controlled enantioselective imino-Nazarov cyclization of the latter produces the cyclopentenone-fused indoline **4**.[2b] In addition, Pale and Blanc et al. have recently reported that alkynyl epoxide **5** in the presence of a Au catalyst generates dienone **c** via a 1,2-acyloxy migration/oxygen delivery from an epoxide moiety, which upon Nazarov cyclization delivers the cyclopentenone **6**.[2c] All of the above transformations involve initial 1,2-acyloxy migration and furnish the pentannulated products either by cyclization at the C(sp^2)−H site (**a**) or via Nazarov annulation (**b** and **c**). Herein, we wish to report a new mode of pentannulation reaction of propargylic ester **7** in the presence of a gold catalyst,[3] where a cascade sequence of reactions involving a 1,3-acyloxy migration generates intermediate **d**, which upon cyclization produces fused pivalated cyclopentenone **8**. This transformation features an unprecedented involvement of an unactivated C(sp^3)−H site[4] in the pentannulation reaction of propargylic esters.

Scheme 1. Reactivity of Propargylic Esters in Pentannulation Reaction



Scheme 2. Initial Reaction Design for the Synthesis of Fully Substituted Heterocycles



Scheme 3. Summary of Reaction Optimization

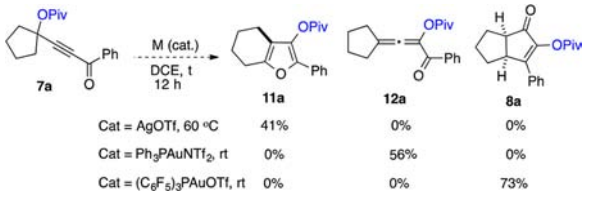


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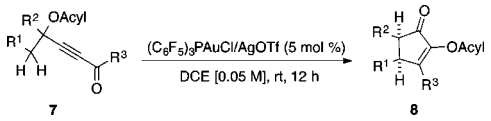
Table 1. Substrate Scope in Pentannulation Reaction of Propargylic Esters



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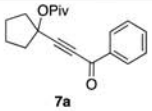
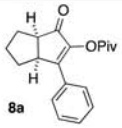
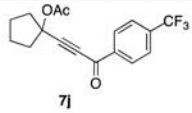
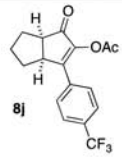
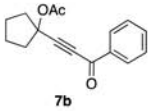
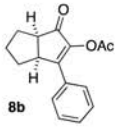
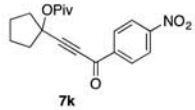
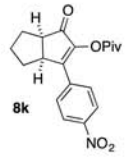
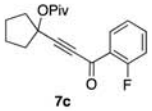
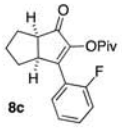
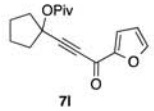
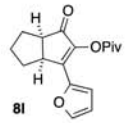
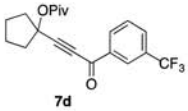
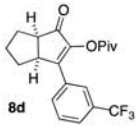
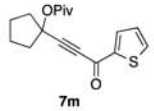
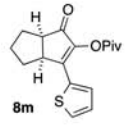
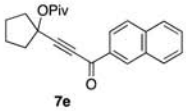
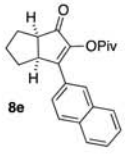
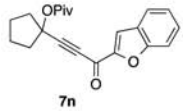
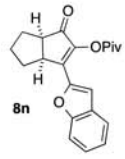
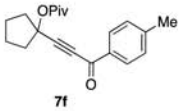
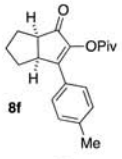
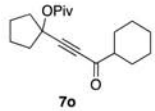
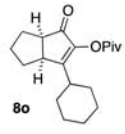
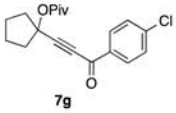
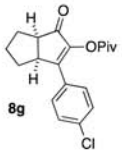
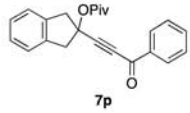
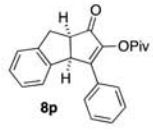
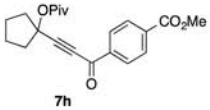
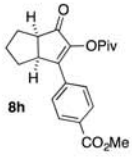
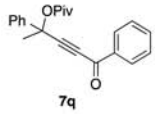
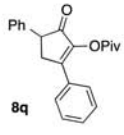
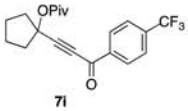
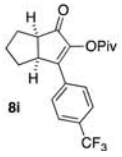
1	 7a	 8a	73	10	 7j	 8j	81
2	 7b	 8b	71	11	 7k	 8k	67
3	 7c	 8c	54	12	 7l	 8l	85
4	 7d	 8d	49	13	 7m	 8m	62
5	 7e	 8e	61	14	 7n	 8n	71
6	 7f	 8f	50	15	 7o	 8o	42
7	 7g	 8g	68	16	 7p	 8p	55
8	 7h	 8h	65	17	 7q	 8q	51[b]
9	 7i	 8i	91				

[a]Isolated yields. [b]The reaction was performed at −20 °C.

We have previously shown that the tertiary propargylic phosphates **9** (R = H) possessing a ketone moiety, in the presence of a copper catalyst, undergoes a facile migratory cycloizomerization reaction via the allene **e** to produce functionalized furan **10** (Scheme 2).[5] We hypothesized that by using the quaternary propargylic system **9** (R= alkyl, Ar), the transition-metal-catalyzed double migratory process[6] with the intermediacy of the tetrasubstituted allene **e** would be feasible[7] to produce the fully substituted furan **10**. To this end, the reactions of propargylic ester **7a**, possessing a five-membered ring toward the fused furan **11a** (via a 1,3-pivaloxy migration/ring expansion) was examined (Scheme 3).[8] Also in the presence of a silver

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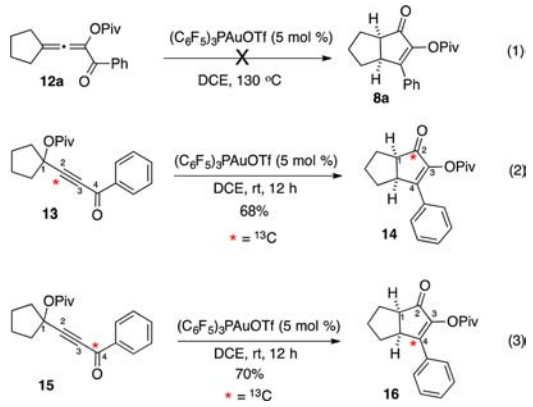
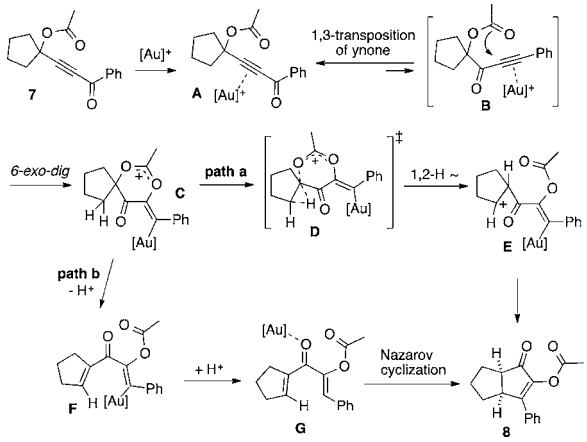
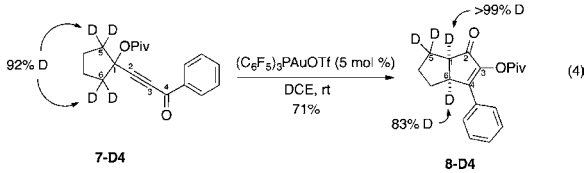
Scheme 4. Mechanistic Studies



Scheme 5. Proposed Mechanism



Scheme 6. Deuterium-Labeling Experiment



catalyst this transformation occurs to produce expected fused furan **11a**; the conditions for more efficient and general transformation have not been identified yet.[8] It was found that in the presence of a cationic gold catalyst the 1,3-pivaloxy migration[6b] occurred to give the expected allene **12a** in 56% yield, which, however, did not further cyclize into **11a** even under elevated temperatures.[8] Surprisingly, employing the $(C_6F_5)_3AuCl/AgOTf$ catalyst system[9] produced the fused cyclopentenone **8a**[10] in 73% isolated yield!

Inspired by the unexpected reactivity of propargylic esters and by the importance of the obtained products,[11] we explored the scope of this cascade pentannulation transformation (Table 1). Thus, both substrates **7a** and **7b** possessing pivaloxy and acetoxy migrating groups reacted smoothly under the reaction conditions to produce fused cyclopentenones **8a** and **8b** in good yields (entries 1, 2). *Ortho*-fluorinated phenyl-substituted cyclopentenone **8c** was obtained in 54% yield (entry 3). Pentannulation reactions of substrates **7d** and **7e**, possessing *meta*-trifluoromethyl phenyl and 2-naphthyl groups, occurred uneventfully affording products **8d** and **8e** in reasonable yields (entries 4, 5). It was found that propargylic esters **7f–k**, containing various groups at the *para* position of the phenyl moiety, are competent reactants in this cyclization. Thus, substrates **7f** and **7g**, possessing methyl and chlorine groups, worked well to give rise to **8f** and **8g** in 50% and 68% yields, respectively (entries 6, 7). Likewise, propargylic esters **7h–k**, possessing electron-deficient substituents, allowed for the efficient synthesis of fused cyclopentenones **8h–k** (entries 8–11). Notably, propargylic pivalate derivatives of various heterocycles, including furan **7l**, thiophene **7m**, and benzofuran **7n** cyclized in good to excellent yields (entries 12–14). Cyclohexyl-containing substrate **7o** underwent this cascade reaction to produce alkylated cyclopentenone **8o** in a modest yield (entry 15). The benzannulated substrate **7p** cyclized into the tricyclic cyclopentenone **8p**. We wondered whether the observed cascade pentannulation reaction is specific to cyclopentane-containing substrates or is more general.[12] To this end, we examined a potential cyclization of the acyclic substrate **7q** (analogue of **1**), which upon Pt-catalysis is known to cyclize at the $C(sp^2)$–H site to produce **2** (Scheme 1, eq 1).[2b] Remarkably, pentannulation reaction of **7q** at a lower temperature led to the exclusive cyclization at the $C(sp^3)$–H bond to produce the monocyclic cyclopentenone **8q**.

After establishing the scope of this gold-catalyzed pentannulation reaction, we performed some preliminary mechanistic studies (Scheme 4). First, subjecting the allenyl ketone **12a** to the reaction conditions did not lead to the cyclized product **8a** even under forcing conditions (eq 1). This observation rules out possible involvement of allene intermedite **12a** in this reaction. Next, to determine whether this cascade reaction involves a skeletal rearrangement, which is common for the gold-catalyzed reactions,[13] we performed the ^{13}C-labeling studies. Thus, subjecting the substrate **13**, labeled at the C2 of the alkyne moiety, to the reaction conditions afforded cyclopentenone **14** with the labeled carbon atom at the ketone moiety (eq 2). In addition, pentannulation reaction of **15**, possessing the labeled carbon at the carbonyl group of alkynyl ketone, produced **16** with the ^{13}C-labeled carbon residing at the olefinic C4 position (eq 3). Hence, these observations imply that this migratory cyclization reaction does not involve a skeletal rearrangement of the ynone moiety but involves a 1,3-acyloxy migration/1,3-oxygen transfer/cyclization cascade.

Based on the above observations, we propose the following plausible mechanism for this novel cascade transformation (Scheme 5). First, the π-philic gold catalyst activates the alkyne moiety of **7** to form **A**, thus triggering equilibrium to produce the 1,3-transposed[14] isomer **B**.[15] The following 6-*exo*-*dig* cyclization of the latter would occur by attacking the nucleophilic oxygen of the ester group at the activated alkyne moiety to produce **C**.[1] According to **path a**, a 1,2-H in **C** via the transition state **D** gives enone **E**, which further cyclizes to the fused cyclopentenone **8** upon nucleophilic attack of the vinyl gold species at the cationic center. Alternatively, the proton loss α to the spiro-center of **C** would occur to open the ring and form diene **F** (**path b**). Protiodemetalation of the latter would generate the activated dienone **G**, which upon Nazarov cyclization[16] would produce **8**.

To distinguish between the two possible pathways (**a** or **b**), we performed a deuterium-labeling study (Scheme 6).[17] Hence, the propargylic ester **7-D4** with 92% deuterium enrichment at the α-carbons (C5 and C6) was subjected to the reaction conditions. As a result, the pentannulated product **8-D4** was obtained with >99% enrichment at C1, whereas the C6 position contained 83% of deuterium. This observation strongly supports **path a** involving a clean 1,2-deuterium shift[18] over **path b**, which

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presumes a deuterium loss from a deuterated analog of intermediate **C** and thus scrambling of the deuterium label at C1 (Scheme 5).[19]

In summary, a new gold-catalyzed cascade reaction of propargylic esters possessing a ketone moiety to cyclopentenones has been developed. This method allowed for efficient synthesis of various mono-, bis-, and tricyclic cyclopentenones possessing alkyl, aryl, and heterocyclic substituents. ^{13}C- and deuterium-labeling studies suggested that this transformation proceeds via a cascade of 1,3-transposition of alkynyl ketone/1,3-acyloxy migration/pentannulation cyclization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01983.

Experimental procedures, compound characterization data, and crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

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