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Gold-Catalyzed Tandem 1,3-Migration/Double Cyclopropanation of 1-Ene-4,*n*-diyne Esters to Tetracyclodecene and Tetracycloundecene Derivatives

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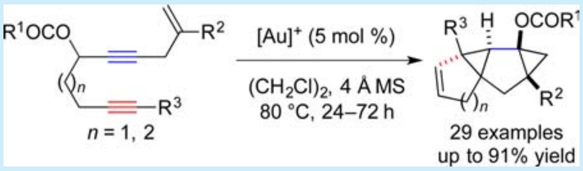
S *Supporting Information*

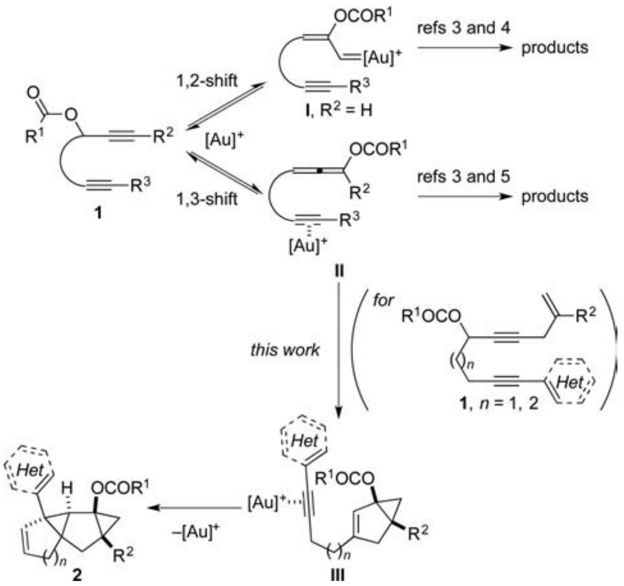
ABSTRACT: A synthetic method that relies on Au(I)-catalyzed tandem 1,3-acyloxy migration/double cyclopropanation of 1-ene-4,9-diyne and 1-ene-4,10-diyne esters to construct the respective architecturally challenging tetracyclodecene and tetracycloundecene derivatives is described. Achieved under mild reaction conditions, the transformation was shown to be robust with a wide variety of substitution patterns tolerated to give the two members of the carbocyclic family in good to excellent yields and as a single regio- and diastereomer.



Gold-catalyzed cycloisomerization of 1,*n*-diynes has become one of the most efficient and versatile synthetic strategies for the rapid construction of highly functionalized cyclic compounds in a single step.[1−7] Within the field, this has included examples that have exploited the propensity of 1,*n*-diyne esters to undergo 1,2- and 1,3-acyloxy migration and further reactivity to give a variety of synthetically valuable products, as shown in Scheme 1.[2−7] For example, we recently reported a synthetic route to tricyclic bridged hexenones and heptenones involving the gold(I)-catalyzed 1,3-acyloxy migration/metallo-Nazarov cyclization and respective formal [4 + 2]-cyclization and cyclopropanation/Cope rearrangement of 1,11-diene-3,9-diynye esters.[5b] As part of an ongoing program to develop this catalytic tactic for carbocyclic synthesis, we were drawn to the potential reactivity of 1-ene-4,9-diyne and 1-ene-4,10-diyne esters, the chemistry of which has so far remained unexplored.[6] We anticipated the gold-activated species **II** generated from Au(I)-catalyzed 1,3-acyloxy migration of the substrate would be susceptible to a pathway involving 1,4-enallene cycloisomerization followed by 1,2-hydride migration.[7] Subsequent 1,6-enyne rearrangement of the resulting putative bicyclo[3.1.0]hexenyl gold adduct **III** might then be expected to provide the respective tetracyclodecene and tetracycloundecene ring systems.[8,9] Herein, we describe the details of this chemistry that provides an expedient and chemoselective approach to these two potentially useful carbocycles possessing four quaternary carbon centers at the ring junctions in good to excellent yields and as single regio- and diastereomers.

To test the feasibility of our hypothesis, the 1-ene-4,10-diyne 4-nitrobenzoate **1a**, prepared from 5-hexynoic acid, was selected as the model substrate to establish the reaction conditions (Table 1).[10] This initially revealed that treatment of the starting material with 5 mol % of gold(I) phosphine catalyst **A** in 1,2-dichloroethane at 80 °C for 24 h afforded the tetracycloundecene

Scheme 1. Gold-Catalyzed Reaction Pathways of 1,*n*-Diyne Esters[a]



[a]Het = heteroaryl group.

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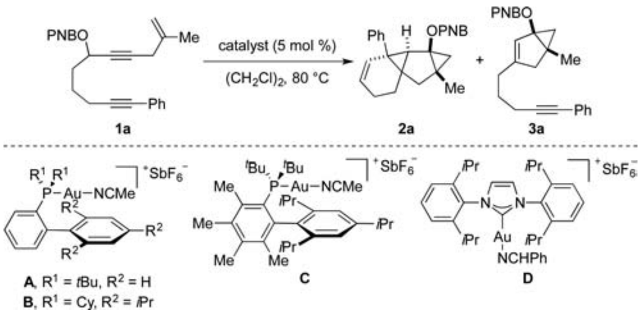
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	reaction time (h)	yield[b] (%)	
			2a	3a
1	**A**	24	83	
2[c]	**A**	24	91	
3[d]	**A**	24		96
4	**B**	30	73	
5	**C**	72	71	
6	**D**	24	68	
7	Ph$_3$PAuNTf$_2$	24	7	51
8	Rh(COD)$_2$BF$_4$	48	[e]	
9	Pd(PPh$_3$)$_2$Cl$_2$	48	[e]	

[a] All reactions were performed at the 0.2 mmol scale with catalyst/**1a** ratio = 1:20 in (CH$_2$Cl)$_2$ at 80 °C. [b] Isolated yield. [c] Reaction carried out in the presence of 4 Å MS (100 mg). [d] Reaction carried out at room temperature. [e] No reaction based on TLC analysis and ^{1}H NMR measurements of the crude mixture.

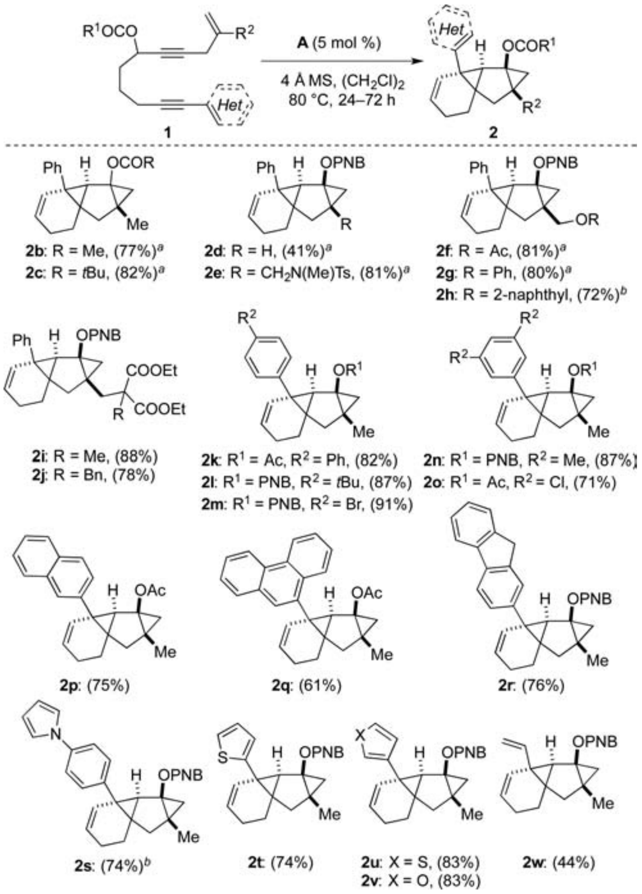


Figure 1. Gold(I)-catalyzed 1,3-migration/double cycloisomerization of 1-ene-4,10-diyne esters **1b–w**. All reactions were performed on a 0.2 mmol scale with a catalyst/**1** ratio = 1:20 and 4 Å MS (100 mg) at 80 °C for 24 h. Values in parentheses denote isolated product yields. Reaction time: (a) 48 h, (b) 72 h.

product **2a** as a single regio- and diastereomer in 83% yield (entry 1). The structure and relative stereochemistry of the tetracarbocycle was unambiguously ascertained by NMR measurements and X-ray single-crystal analysis.[11] The introduction of 4 Å molecular sieves (MS) to the reaction conditions was found to lead to an increase in product yield from 83 to 91% (entry 2). The analogous control reaction at room temperature, on the other hand, was found to give the bicyclo[3.1.0]hexene adduct **3a** in 96% yield (entry 3). In our hands, lower product yields of 68–73% along with increased reaction times were observed on repeating the reaction with the more sterically crowded Au(I) complexes **B** and **C** or the NHC–Au(I) (NHC = *N*-heterocyclic carbene) complex **D** in place of **A** as the catalyst (entries 4–6). However, the analogous control experiment with Ph$_3$PAuNTf$_2$ as the catalyst gave a mixture of **2a** and **3a** in yields of 7 and 51% (entry 7). No reaction was detected in control experiments with the metal complexes Rh(COD)$_2$BF$_4$ and Pd(PPh$_3$)$_2$Cl$_2$ as the catalyst (entries 8 and 9). On the basis of the above results, the cycloisomerization of **1a** in the presence of Au(I) complex **A** (5 mol %) as the catalyst in 1,2-dichloroethane at 80 °C for 24 h was deemed to provide the optimum reaction conditions.

With the optimal conditions in hand, we first strived to assess the generality of the procedure for a series of 1-ene-4,10-diyne esters, and the results are summarized in Figure 1. Overall, these reactions illustrated that the Au(I) complex **A**-catalyzed conditions were broad and afforded a diverse array of tetracycloundecenes containing a variety of substitution patterns in 41–91% yield from the corresponding substrates **1b–w**. Reactions of starting esters containing an Ac (**1b**) or Piv (**1c**) instead of a PNB migrating group were found to be well-tolerated, furnishing the corresponding tetracarbocycles **2b** and **2c** in 77 and 82% yield, respectively. Likewise, the cyclization of substrates bearing a monosubstituted allyl motif (**1d**) or a tertiary sulfonamide (**1e**), acetyl (**1f**), aryl ether (**1g,h**), or malonate (**1i,j**) group at the R^2 position were shown to proceed well, giving the corresponding dicyclopropanes **2d–j** in 41–88% yield. The presence of an electron-donating (**1k,l,n**) or electron-withdrawing (**1m,o**) substituent at the 4- or 3,5-positions of the phenyl group at the R^3 position of the substrate was also found to have no appreciable influence on the course of the reaction. In these experiments, the corresponding tetracyclic products **2k–o** were provided in yields of 71–91%. Similarly, starting materials with a pendant sterically demanding aryl group, as in **2p–r**, a heteroaryl (**1s–v**) motif at the same position, or a 1,3-enyne unit (**1w**) gave the corresponding carbocycles **2p–w** in 44–83% yield.

We next turned our attention to evaluating the scope of the Au(I) complex **A**-catalyzed procedure to assemble the tetracyclodecene ring system from 1-ene-4,9-diyne 4-nitrobenzoates (Figure 2). Under the optimized reaction conditions, this revealed experiments with substrates containing an isoprenyl motif (**1x**) or an acetyl (**1y**), phenyl ether (**1z**), or malonate (**1α**) group on the alkene bond gave the corresponding cyclic products **2x–α** in 62–85% yield. It was also pleasing to find the starting nitrobenzoates **1β** and **1γ**, containing a sterically bulky 2-9*H*-fluorenyl group, to proceed well upon application of the Au(I) complex **A**-mediated method and afforded the tetracyclodecene derivatives **2β** and **2γ** in yields of 77 and 64%.

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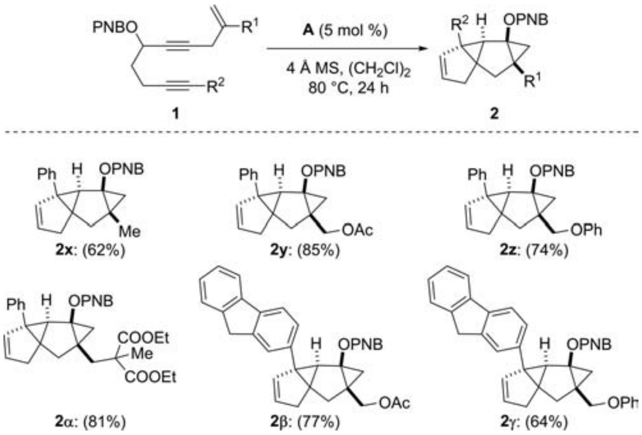
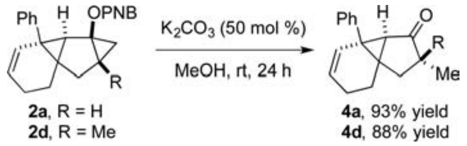


Figure 2. Gold(I)-catalyzed 1,3-migration/double cycloisomerization of 1-ene-4,9-diyne esters **1x**−**γ**. All reactions were performed on a 0.2 mmol scale with a catalyst/**1** ratio = 1:20 and 4 Å MS (100 mg) at 80 °C for 24 h. Values in parentheses denote isolated product yields.

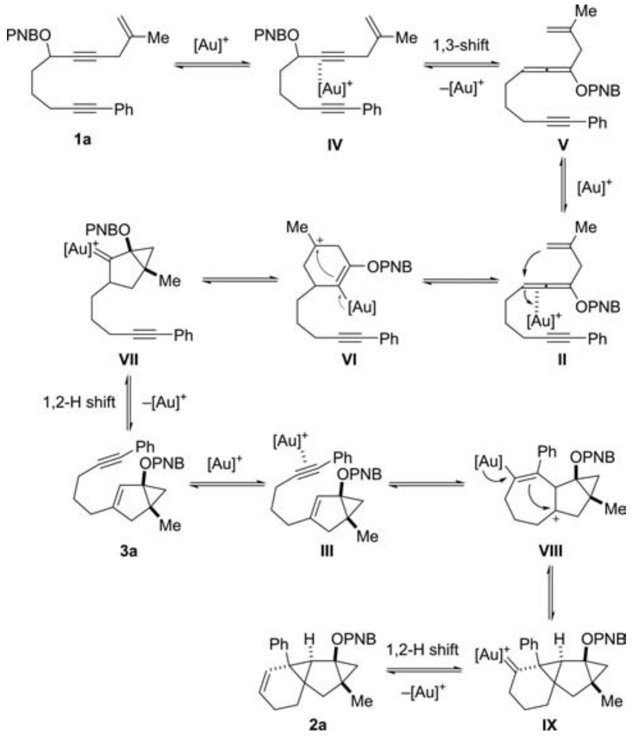
In this work, the conversion of two tetracycloundecene examples to their tricyclic ketone derivatives was also examined (Scheme 2). Subjecting compound **2a** to K_2CO_3 in methanol at room temperature was found to give the anticipated tricycloundecenone **4a** in 93% yield.[7b] Under similar reaction conditions, the based-mediated methanolysis of **2d** afforded **4d** in 88% yield, the structure of which was determined by both NMR measurements and X-ray crystallography.[11]

Scheme 2. Base-Mediated Methanolysis of 2a and 2d

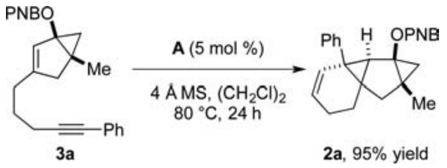


A tentative mechanism for the present gold(I)-catalyzed 1-ene-4,9-diyne and 1-ene-4,10-diyne ester cycloisomerization transformations is outlined in Scheme 3. With **1a** as a representative example, this might involve initial selective activation of the alkynyl ester moiety of the substrate by the gold(I) complex. This initiates 1,3-acyloxy migration of the resulting gold-coordinated species **IV** to produce the allenic ester **V**, which upon further activation by the metal catalyst gives the allenic gold species **II** that is susceptible to 1,4-enallene cycloisomerization. Subsequent 1,2-hydride migration of the resulting presumed gold carbenoid species **VII**, obtained via the cationic cyclohexenyl intermediate **VI**, followed by deauration would furnish the bicyclo[3.1.0]hexene **3a**.[7b] Further activation of the remaining pendant alkyne moiety in the newly formed cyclopropane adduct by the gold(I) complex would provide the gold-coordinated analogue **III** put forward in Scheme 1. This is the active species that undergoes the second cyclopropanation step involving cycloisomerization of the 1,6-enyne motif to give the putative gold carbenoid complex **IX** via the carbocationic cycloheptenyl species **VIII**.[8,9] Regeneration of the gold(I) catalyst and delivery of the tetracycloundecene product **2a** might then occur as **VIII** becomes susceptible to a 1,2-hydride shift and deauration. The proposed involvement of the bicyclo[3.1.0]hexene intermediate **2a** posited in Schemes 1 and 3 would be in good agreement with the isolation of the cyclopropane-fused five-membered ring adduct isolated in control experiments detailed in Table 1, entries 3 and 7. It is also further supported by our findings in a control reaction showing **2a** being furnished in 95% yield on treating **3a** with 5 mol % of gold(I) phosphine complex **A** as the catalyst and 4 Å MS in 1,2-dichloroethane at 80 °C for 24 h (Scheme 4).

Scheme 3. Tentative Mechanism for the Gold(I)-Catalyzed 1,3-Migration/Double Cycloisomerization of 1-Ene-4,10-diyne Esters



Scheme 4. Control Experiment with 3a



In summary, we have developed an approach to tetracyclodecene and tetracycloundecene derivatives with four quaternary carbon centers at the ring junctions from gold(I)-catalyzed tandem 1,3-acyloxy migration/double cyclopropanation of 1-ene-4,9-diyne and 1-ene-4,10-diyne esters. The utility of the present method to the two members of carbocyclic family was shown by the conversion of two examples to their ketone derivatives, which are also potentially useful building blocks in organic synthesis.[12] Efforts to explore the synthetic applications of the present reactions are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02404.

Detailed experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all starting materials and products (PDF)
X-ray data for **2a** (CIF)
X-ray data for **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1496251 (**2a**) and CCDC 1496253 (**4d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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