

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

Cuili Chen,[†] Yongzhen Zou,[†] Xianxiao Chen,[†] Xiaoxiang Zhang,[†] Weidong Rao,^{*,†} and Philip Wai Hong Chan^{*,‡,§}

[†]Jiangsu Key Laboratory of Biomass-based Green Fuels and Chemicals, College of Chemical Engineering, Nanjing Forestry University, Nanjing 210037, China

[‡]School of Chemistry, Monash University, Clayton, Victoria 3800, Australia

[§]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom

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 cathographic final and as a single radio and as a sin



carbocyclic family in good to excellent yields and as a single regio- and diastereomer.

• old-catalyzed cycloisomerization of 1,*n*-diynes has become ${f J}$ 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*-divne 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-divne and 1-ene-4,10-divne 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 regioand 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 Scheme 1. Gold-Catalyzed Reaction Pathways of 1,*n*-Diyne Esters"



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 $^{\circ}$ C for 24 h afforded the tetracycloundecene

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Table 1. Optimization of the Reaction Conditions⁴



^{*a*}All reactions were performed at the 0.2 mmol scale with catalyst/1a ratio = 1:20 in $(CH_2Cl)_2$ 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. ^{*c*}No reaction based on TLC analysis and ¹H NMR measurements of the crude mixture.

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 Ph₃PAuNTf₂ 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 $Rh(COD)_2BF_4$ and $Pd(PPh_3)_2Cl_2$ 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 welltolerated, 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



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.

sulfonamide (1e), acetyl (1f), aryl ether (1g,h), or malonate (1i,j) group at the R² 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-with-drawing (1m,o) substituent at the 4- or 3,5-positions of the phenyl group at the R³ 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 (1 α) group on the alkene bond gave the corresponding cyclic products $2x-\alpha$ in 62–85% yield. It was also pleasing to find the starting nitrobenzoates 1 β and 1 γ , 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 $1x-\gamma$. 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 K₂CO₃ in methanol at

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



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

A tentative mechanism for the present gold(I)-catalyzed 1ene-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-envne 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

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



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 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 1ene-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 ¹H and ¹³C NMR spectra for all starting materials and products (PDF) X-ray data for **2a** (CIF) X-ray data for **4d** (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: weidong@njfu.edu.cn.

*E-mail: phil.chan@monash.edu; p.w.h.chan@warwick.ac.uk.

Notes

The authors declare no competing financial interest.

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