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Gold- and Brønsted Acid-Catalyzed Cycloisomerization of 1,8-Diynyl Vinyl Acetates to Bicyclo[2.2.1]hept-2-en-7-ones

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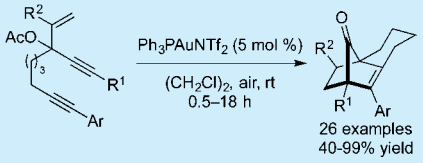
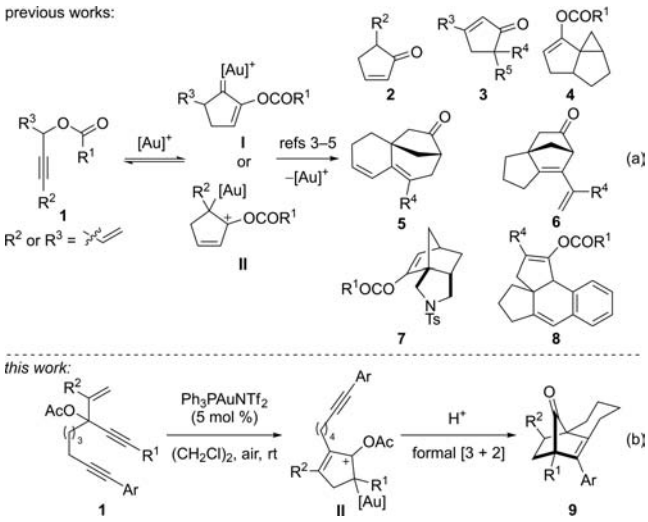
Supporting Information

ABSTRACT: A synthetic method for the efficient assembly of bicyclo[2.2.1]hept-2-en-7-ones that relies on gold(I)-catalyzed Rautenstrauch rearrangement followed by Brønsted acid-mediated formal [3 + 2]-cycloaddition/deacetylation of 1,8-diynyl vinyl acetates at room temperature under atmospheric conditions is described.



Functional group transformations catalyzed by a gold(I) or gold(III) complex have become one of the most powerful synthetic tools to rapidly assemble molecular complexity in a single step.[1−7] A recent illustrative example of this is the gold(I)-catalyzed 1,3-acyloxy migration/Nazarov cyclization and Rautenstrauch rearrangement of 1,3- and 1,4-enyne esters to a myriad of synthetically useful cyclopentyl derivatives **2**−**8** (Scheme 1a).[3−5,8] Included in this has been efforts by us and

Scheme 1. Gold(I)-Catalyzed Reactivities of 1,3- and 1,4-Enyne Esters



others to intercept the putative carbenoid (**I**) and cyclopentenium (**II**) complexes of the Group 11 metal by an appropriately placed functional group so as to access the bridged and fused carbo- and *N*-heterocyclic compounds **3**−**8** shown in Scheme 1a.[5] Building on these initial works, we were drawn to the potential reactivity of cyclopentadienylgold intermediates containing an alkyne motif generated from 1,8-diynyl vinyl acetates in the presence of a gold(I) complex (Scheme 1b). In doing so, we found the posited *in situ* generated 2-(hex-5-yn-1-yl)cyclopenta-1,3-diene adduct obtained in this manner to undergo a Brønsted acid-catalyzed formal [3 + 2]-cycloaddition/deacetylation pathway.[9,10] This provided the decalin ring system with an architecturally challenging bridged ketone scaffold that sits on one of the fused carbon centers and, more importantly, a motif that is present in a variety of natural products and active pharmaceutical ingredients (APIs).[7,11−14] To our knowledge, the skeletal rearrangement also represents the first example of such cyclopenta-1,3-diene intermediates generated *in situ* in this manner using gold catalysis to undergo a formal [3 + 2]-cycloaddition pathway. Herein, we describe the details of this chemistry that delivers an expedient and selective synthetic route to bicyclo[2.2.1]hept-2-en-7-ones in good to excellent yields under mild atmospheric conditions at room temperature.

We initiated our study by examining the gold(I)-mediated cycloisomerization of 1,8-diynyl vinyl acetate **1a** to establish the optimal reaction conditions (Table 1). This initially revealed subjecting the substrate to 5 mol % of gold(I) phosphine complex **A** in 1,2-dichloroethane at reflux temperature for 4 h gave **9a** in 67% yield (entry 1).[15] The structure of the decalin analogue was determined by NMR measurements and X-ray single crystal analysis.[16] Comparable or slightly lower product yields of 33−63% were obtained on repeating the reaction with the gold(I) phosphine complexes **B**−**D**, NHC−Au(I) (NHC = *N*-heterocyclic carbene) complex **E**, and $Ph_3PAuCl/AgSbF_6$ or $Ph_3PAuNTf_2$ in place of **A** as the catalyst (entries 3−6, 9 and 10). In contrast, the analogous reactions mediated by gold(I) phosphine complex **A** at room temperature, NHC−Au(I) complex **F**, or Ph_3PAuCl at reflux temperature led to either the

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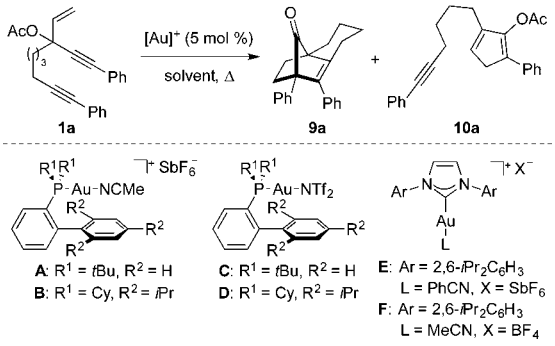
Table 1. Optimization of the Reaction Conditions[a]



entry	[Au]+	solvent	time	yield[b]
1	**A**	$(CH_2Cl)_2$	4	67
2[c]	**A**	$(CH_2Cl)_2$	2	*d*
3	**B**	$(CH_2Cl)_2$	4	63
4	**C**	$(CH_2Cl)_2$	4	33
5	**D**	$(CH_2Cl)_2$	4	46
6	**E**	$(CH_2Cl)_2$	2	58
7	**F**	$(CH_2Cl)_2$	16	*e*
8	Ph_3PAuCl	$(CH_2Cl)_2$	22	*e*
9	$Ph_3PAuCl/AgSbF_6$	$(CH_2Cl)_2$	4	67
10	$Ph_3PAuNTf_2$	$(CH_2Cl)_2$	0.5	51[f]
11[c,g]	**$Ph_3PAuNTf_2$**	**$(CH_2Cl)_2$**	**2**	**77**[f]
12[c,g]	PPh_3AuNTf_2	THF	18	6
13[c,g]	PPh_3AuNTf_2	MeCN	16	10
14[c,g]	PPh_3AuNTf_2	toluene	3	6
15[c,g]	PPh_3AuNTf_2	acetone	16	*e*

[a]All reactions were conducted using 0.15 mmol of **1a** and 5 mol % of gold(I) catalyst in 1.5 mL of solvent at reflux temperature. [b]Crude product yield estimated by ^1H NMR analysis with dibromomethane as the internal standard. [c]Reaction performed at room temperature. [d]Compound **10a** isolated as the only product in 84% yield. [e]Unknown byproducts detected by TLC analysis and ^1H NMR measurements of the crude reaction mixture. [f]Isolated product yield. [g]Reaction performed in nondistilled solvent under atmospheric conditions.

cyclopenta-1,3-diene **10a** in 84% yield or substrate decomposition (entries 2, 7, and 8). Our investigations subsequently found a product yield of 77% was achieved when $Ph_3PAuNTf_2$ was employed as the catalyst in nondistilled 1,2-dichloroethane at room temperature under atmospheric conditions (entry 11).[15] However, a survey of other nondistilled solvents such as toluene, acetone, THF, and acetonitrile instead of 1,2-dichloroethane under these latter reaction conditions was observed to result in significantly lower product yields of 6–10% or a mixture of unknown decomposition products (entries 12–15). On the basis of the above results, the reaction of **1a** in the presence of 5 mol % of $Ph_3PAuNTf_2$ as the catalyst in nondistilled 1,2-dichloroethane under atmospheric conditions at room temperature for 2 h was deemed to provide the optimum conditions.

We next turned our attention to evaluating the generality of the present procedure with a variety of substituted 1,8-diynyl vinyl acetates (Figure 1). Overall, the $Ph_3PAuNTf_2$-catalyzed reaction conditions were found to be broad, affording a series of decalin analogues containing a variety of substitution patterns in 40–99% yield from the corresponding substrates **1b–z**. Experiments with starting acetates containing other aryl (**1b–g**), 3-thiophenyl (**1h**), alkyl (**1i,j**), or cycloalkyl (**1k,l**) groups at the R^1 position were well tolerated. In these transformations, the corresponding bridged ketone products **9b–l** was obtained

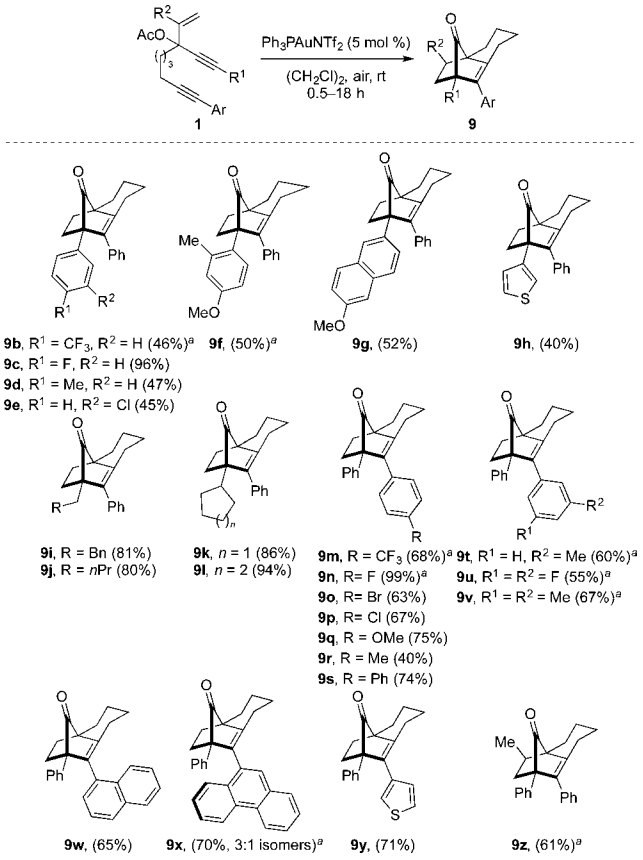


Figure 1. Cycloisomerization of **1b–z** catalyzed by $Ph_3PAuNTf_2$. All reactions were conducted at the 0.14–0.32 mmol scale with 5 mol % of $Ph_3PAuNTf_2$ in nondistilled 1,2-dichloroethane (0.1 M) at room temperature under atmospheric conditions for 0.5–18 h. Values in parentheses denote isolated product yields. [a]Reaction conducted with 5 mol % of Tf_2NH that was added after 0.5 h of the start time.

in 40–96% yield. 1,8-Diynyl vinyl acetates with electron-withdrawing (**1m–p,u**) or -donating (**1q–t,v**) substituents at various positions of the phenyl acetylene motif were demonstrated to give the corresponding carbocyclic compounds **9m–v** in 40–99% yield. The presence of a 1-naphthyl, 9-phenanthrenyl, or 3-thiophenyl moiety in place of the ethynylbenzene group, as in **1w–y**, was also found to have no effect on the outcome of the reaction. In our hands, the corresponding cycloadducts **9w–y** was afforded in 65–71% yield with **9x** being furnished in a 3:1 ratio of diastereomers. Likewise, the rearrangement of **1z** with a pendant isoprenyl group on the carbinol carbon center was shown to proceed well and provide **9z** in 61% yield. In this experiment and a number of examples depicted in Figure 1, the addition of 5 mol % of Tf_2NH was found to accelerate the transformation, reducing the reaction time from over 24 h to 0.5–1 h. More notably, the above gold(I)-mediated cycloisomerizations additionally illustrated that the ring-forming process occurs in a selective manner with the decalin derivative only being obtained. On the basis of NMR measurements of the crude reaction mixtures, the formation of other cyclization compounds such as that arising from a potentially competitive formal [4 + 2]-cycloaddition pathway was not observed.

While fortuitous, the isolation of **10a** under the gold(I) phosphine complex **A**-catalyzed conditions described in Table 1, entry 2, argues in favor for its proposed involvement put forward in Scheme 1b. This argument was further supported by

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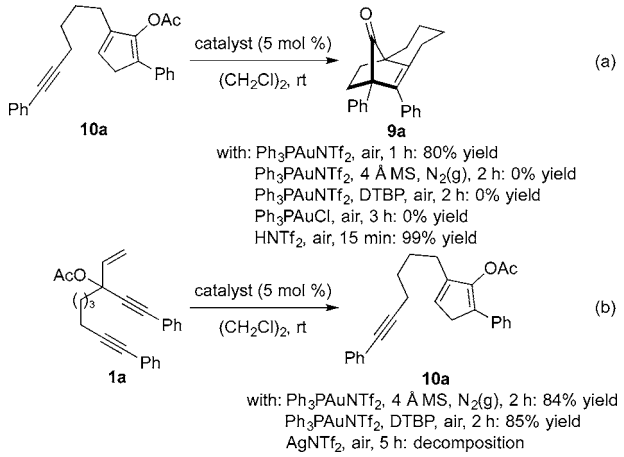
a control experiment showing the conversion of the cyclopenta-1,3-diene adduct to **9a** in 80% yield on resubjecting the monocyclic adduct to 5 mol % of $Ph_3PAuNTf_2$ under the reaction conditions shown in Scheme 2a.

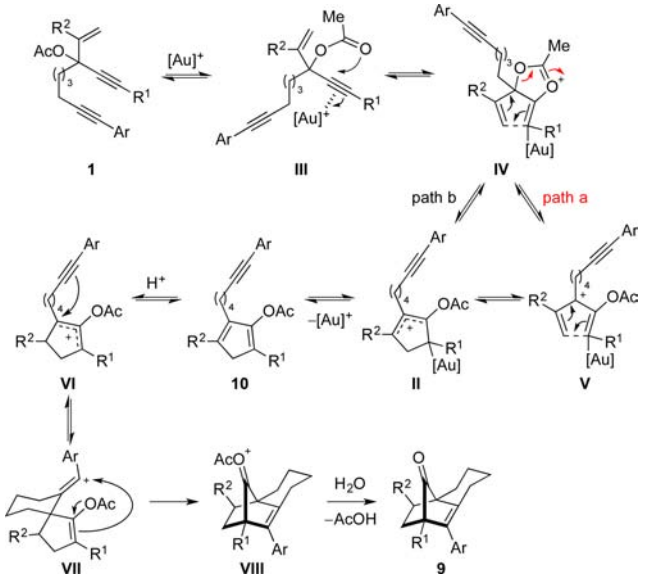
Scheme 2. Control Experiments with 1a and 10a



To gain better insight into the mechanism of the present procedure, we next performed the following control reactions (Scheme 2). In a first set of experiments, the introduction of either 50 mg of 4 Å molecular sieves (MS) or 10 mol % of 2,6-di-*tert*-butylpyridine (DTBP) to the $Ph_3PAuNTf_2$-catalyzed reaction of **1a** under the standard conditions was found to give **10a** as the only adduct in 84 and 85% yield, respectively (Scheme 2b).[15] However, the analogous $AgNTf_2$-catalyzed reaction with the 1,8-diynyl vinyl acetate was observed to lead to a mixture of byproducts that could not be identified by ^1H NMR measurements. Moreover, retreating the cyclopenta-1,3-diene to both the former two gold(I)-mediated reaction conditions led only to the recovery of the substrate (Scheme 2a). A similar outcome was found on subjecting **10a** to the standard conditions but with Ph_3PAuCl in place of $Ph_3PAuNTf_2$ as the catalyst. In contrast, treatment of the monocyclic compound to 5 mol % of Tf_2NH in 1,2-dichloroethane at room temperature for 15 min was found to give **9a** in near quantitative yield. Overall, these observations support the posited reaction pathway outlined in Scheme 1b involving Au(I)-catalyzed Rautenstrauch rearrangement of the substrate. This is then followed by Brønsted acid-mediated [3 + 2]-cycloaddition/deacetylation of the ensuing intermediate to give the product. This latter hypothesis would also be consistent with the observed decrease in reaction times in a number of substrates examined in Figure 1 on the addition of 5 mol % of Tf_2NH to the reaction mixture.

A tentative mechanism for the present Au(I)- and Brønsted acid-catalyzed cycloisomerization is presented in Scheme 3. This could involve activation of the C≡C bond of the 1,4-enyne motif in **1** by the Group 11 catalyst to give the gold-coordinated species **III**. As a consequence, this leads to [2,3]-sigmatropic rearrangement of the acetate group and formation of the putative vinyl gold species **V** via the 1,3-dioxin-1-ium intermediate **IV** (Scheme 3, path a).[6] Metallo-Nazarov cyclization of this newly formed organogold species followed by deauration of the resulting cyclopentenium complex **II** posited in Scheme 1 might then afford the cyclopenta-1,3-diene adduct **10**. A second possibility could be the unsaturated carbocyclic intermediate being directly formed from metallo-

Scheme 3. Proposed Mechanism for the Cycloisomerization of 1,8-Diynyl Vinyl Esters Catalyzed by $Ph_3PAuNTf_2$



Nazarov-type cyclization of **IV** as it is being assembled and deauration of **II** following path b in Scheme 3.[4c] Under the acidic reaction conditions, protonation of the five-membered ring adduct might furnish the cyclopent-3-en-1-ylium adduct **VI**.[17] This is the posited active species that undergoes the formal [3 + 2]-cycloaddition stepwise process involving addition of the remaining pendant alkyne moiety to the resonance-stabilized allylic carbocation motif in **VI** to give the spirocyclic species **VII**. Subsequent nucleophilic attack of the alkene bond to the vinyl carbocation center generated from this initial intramolecular cyclization step followed by hydrolysis of the ensuing oxonium species **VIII** would deliver the product **9**.

In summary, we have developed a gold(I)- and Brønsted acid-catalyzed cycloisomerization strategy for the construction of bicyclo[2.2.1]hept-2-en-7-ones from 1,8-diynyl vinyl esters. Achieved under mild conditions at room temperature for a wide variety of substrates, the synthetic method provides a facile and convenient tactic to put in place a bridging ketone motif onto the decalin ring system that would be challenging following conventional approaches. Efforts to develop an asymmetric version of this tandem process are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03049.

Detailed experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all starting materials and products (PDF)

Compound **9a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ ACKNOWLEDGMENTS

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