Au salts have been shown as exceptional catalysts to activate alkenes, alkenes, and allenes toward nucleophilic attacks. A variety of structural motifs have been efficiently accessed under exceedingly mild reaction conditions.

Cyclopentenones are key intermediates in organic synthesis. Among a variety of approaches for their preparation, the Nazarov reaction is arguably one of the most versatile and efficient methods. However, most synthetically viable applications of the Nazarov reaction have to include structural elements to control the double bond position in the enone product. Furthermore, the divinyl ketone starting materials or equivalents are commonly prepared convergently from substrates containing a double bond or its surrogate, which limits the substrate scope and hence the utility of this reaction.

Herein, we report a Au(I)-catalyzed highly efficient synthesis of cyclopentenones from readily available enynyl esters via tandem 3,3-rearrangement and the Nazarov reaction. In this reaction, AuCl(PPh3)/AgSbF6 plays dual roles of activating both alkynes and enones, and enynyl alcohols can be prepared in a modular manner which could undergo the Nazarov reaction and lead to cyclopentenones. Since enynyl alcohols can be prepared in a modular manner either from aldehyde/enyne or from aldehyde/acylene/alkenyl halide, this could constitute either a $[1+4]$ or a $[1+2+2]$ approach toward versatile 2-cyclopentenone derivatives with high efficiency and flexibility.

We began by treating enynyl acetate 1 with 1 mol % of AuCl(PPh3)/AgSbF6 in anhydrous CH2Cl2. 1 was completely consumed in 0.5 h, and gratifyingly, the desired cyclopentenone 3 was formed in 8% yield along with unhydrolyzed cyclopentadienylacacetate 2 ($65\%$ yield; Table 1, entry 1). When wet CH2Cl2 was used as reaction solvent, the yield of 3 was increased dramatically to 92%, while a small amount of 2 was observed by 1H NMR during most of the reaction period (Table 1, entry 2). No double bond isomer of 3 was observed. It is noteworthy that C-3 of cyclopentenone 3 was derived from the carbonyl group of hexanal, and the other ring carbons were from the enyne moiety of 2-methylbut-1-en-3-yne. The effectiveness of AuCl(PPh3)/AgSbF6 was evident, as other catalysts were either less efficient (e.g., AuCl3 and PtCl2; Table 1, entries 3–5) or incompetent (e.g., AgSbF6 and TfOH; Table 1, entries 6 and 7).

With these results in hand, we set out to examine the scope of this reaction. As shown in Table 2, enynyl acetates derived from $\alpha$-branched aldehydes (i.e., compounds 4 and 6) underwent smooth reaction, and the corresponding cyclopentenones were isolated in excellent yields (entries 1 and 2), indicating steric tolerance at the propargylic position. While the parent vinyl derivative 8 reacted readily to give 3-pentyl-2-cyclopenten-1-one (9) in good yield (entry 3), various substituents on the C–C double bond were allowed. For example, treatment of enynyl acetates containing cyclopentene (entry 4), cyclohexene (entry 5), and cycloheptene (entry 6) moieties with 1 mol % of AuCl(PPh3)/AgSbF6 led to bicyclic cyclopentenones in fairly good to excellent yields. The relatively low yield of cis-5,5-fused enone 11 was likely due to ring strain. In addition, phenyl substitution at the double bond (entry 7) was tolerated, although a higher catalyst loading (5 mol %) was necessary; cyclopentenone 17 was isolated in 74% yield. Surprisingly, partial desilylation occurred during the cyclization of TIPS-protected acetate 18. As a result, hydroxyl enone 19 was isolated in 81% yield after treating the resulting reaction mixture with TFA. Less clean reactions were observed when the hydroxyl group was protected by either a TBS or a THP group.

Remarkably, treatment of enynyl acetate 20 derived from benzaldehyde with AuCl(PPh3)/AgSbF6 (5 mol %) resulted in the formation of cyclopentadienyl acacetate 21 in 91% yield even in wet CH2Cl2 (eq 1). Hydrolysis of 21 in the presence of HNTf2 (1 mol %) gave enone 22 in excellent yield. Similarly, acetate 23 with a $\nu$-CF3-substituted phenyl group underwent smooth cyclization, and enone 24 was isolated in 96% overall yield after hydrolysis.

**Table 1.** Screen of Reaction Conditions for Cyclopentenone Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1% AuCl(PPh3)/AgSbF6</td>
<td>dry CH2Cl2, rt</td>
<td>0.5</td>
<td>&gt;99</td>
<td>65b 8c</td>
</tr>
<tr>
<td>2</td>
<td>1% AuCl(PPh3)/AgSbF6</td>
<td>wet CH2Cl2, rt</td>
<td>0.5</td>
<td>&gt;99 &lt;1</td>
<td>92c</td>
</tr>
<tr>
<td>3</td>
<td>5% AuCl3</td>
<td>dry CHCl2, rt</td>
<td>0.5</td>
<td>48</td>
<td>31 &lt;1</td>
</tr>
<tr>
<td>4</td>
<td>5% AuCl3</td>
<td>wet CHCl2, rt</td>
<td>0.5</td>
<td>96</td>
<td>5 &lt;1</td>
</tr>
<tr>
<td>5</td>
<td>5% PtCl2</td>
<td>dry toluene, 80°C</td>
<td>4</td>
<td>4</td>
<td>32 &lt;1</td>
</tr>
<tr>
<td>6</td>
<td>5% AgSbF6</td>
<td>wet CHCl2, rt</td>
<td>0.5</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7</td>
<td>5% TfOH</td>
<td>dry CH2Cl2, rt</td>
<td>0.5</td>
<td>62d</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* Estimated by 1H NMR using diethyl phthalate as internal standard.
* Isolated yield. c Due to adventitious water. d Decomposed amount.
The mechanism of this remarkable reaction is hypothesized in Scheme 2. Pentadienyl cation D is generated via cationic Au(I)-catalyzed tandem 3,3-rearrangement of enynyl acetate C and activation of the in situ generated allenyl cation. Subsequent electrocyclic ring closure of D forms Au-containing cyclopentenyl cation E, which should be in resonance with Au carbeneoid species F. While cyclopentadienyl acetate H can be formed from E/F via either regioselective 1,2-hydride shift followed by the collapse of cation G or E1-type elimination assisted by H2O and protonation of alkenylgold intermediate I, interestingly, both pathways seem operative as partial deuterium incorporation at the cyclopentenone 2 position of 3 was observed when CH2Cl2 saturated with D2O was used.\(^{10}\) Remarkably, Au(I) seems to assist highly selective formation of H in both pathways. It is striking that cations D, E, and G do not undergo hydrolysis to any significant extent, presumably due to rapid ensuing transformations. When R in H is an alkyl group, hydrolysis of the enol acetate moiety occurs, and cyclopentenone J is formed as final product. The catalyst for hydrolysis of H is proposed to be H2O+SbF6–, instead of [Au(PPh3)3]SbF6–, based on the following observations: (1) AuCl(PPh3)3/SbF6 (up to 5 mol %) hydrolyzed 2 in wet CD2Cl2 very slowly; (2) AuCl(PPh3)3/SbF6 (1 mol %) hydrolyzed 2 quickly (in less than 30 min) when 2 was mixed with 1 equiv of enynyl acetate I; (3) when a mixture of 1 and 2 was treated with the Au(I) catalyst, the consumption of 1 could be stopped halfway by the addition of BuSMe2;\(^{11}\) while 2 was continuously hydrolyzed; (4) HOAc did not efficiently promote the hydrolysis; however, 2 was completely converted into enone 3 in 10 min with 1 mol % of HNTf2. Presumably a small amount of H2O+SbF6– was generated during the reaction of [Au(PPh3)3]SbF6– with 1. In the cases of aryl compounds 20 and 23, either H2O+SbF6– was not generated or it was consumed via the formation of a stable benzyl-type cation.

In conclusion, we have developed a highly efficient method for the synthesis of versatile cyclopentenones from enynyl acetates via tandem Au(I)-catalyzed 3,3-rearrangement and the Nazarov reaction. Significant substrate flexibility and excellent control of the double bond position in the cyclopentenone ring render this an attractive method for cyclopentenone synthesis.

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Supporting Information Available: Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References


(8) Compound 2 was not very stable on silica gel column. However, quick flash column allowed its isolation and characterization.

(9) Generated by shaking distilled CH2Cl2 with deionized water in a separatory funnel.

(10) This experiment was suggested by one reviewer. The incorporation of deuterium was estimated to be 24% by 1H NMR and 13C NMR.

(11) BuSMe2 was used to poison the cationic Au(I) catalyst, while it is not basic enough to neutralize the acid generated during the reaction.