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Efficient Synthesis of Cyclopentenones from Enynyl Acetates via Tandem Au(I)-Catalyzed 3,3-Rearrangement and the Nazarov Reaction

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Au salts have been shown as exceptional catalysts[1] to activate alkynes,[2] alkenes,[3] and allenes[4] 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[5] 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.[6] 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(PPh$_3$)/AgSbF$_6$ plays dual roles of activating both alkynes and allenes. Moreover, this reaction allows significant substrate flexibility and has excellent control of the cyclopentenone double bond position.

Previously, I reported that cationic Au(I) complexes can not only catalyze 3,3-rearrangement of propargylic esters but also activate the resulting allenylic esters in situ for subsequent [2 + 2] cyclization via oxonium intermediate **A** (Scheme 1).[7] We envisage that when R^1 is an alkenyl group, **A** becomes pentadienylic cation **B**, 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/acetylene/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(PPh$_3$)/AgSbF$_6$ in anhydrous CH$_2$Cl$_2$. **1** was completely consumed in 0.5 h, and gratifyingly, the desired cyclopentenone **3** was formed in 8% yield along with unhydrolyzed cyclopentadienylic acetate **2**[8] (65% yield; Table 1, entry 1). When wet CH$_2$Cl$_2$[9] was used as reaction solvent, the yield of **3** was increased dramatically to 92%, while a small amount of **2** was observed by ^{1}H 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(PPh$_3$)/AgSbF$_6$ was evident, as other catalysts were either less efficient (e.g., AuCl$_3$ and PtCl$_2$; Table 1, entries 3−5) or incompetent (e.g., AgSbF$_6$ and TfOH; Table 1, entries 6 and 7).

Scheme 1. Proposed Au(I)-Catalyzed Formation of 2-Cyclopentenones

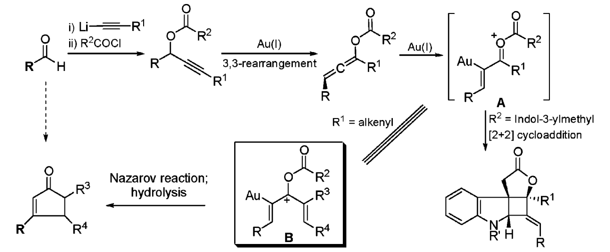
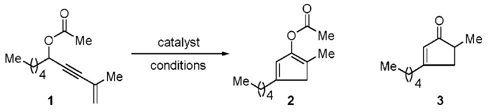


Table 1. Screen of Reaction Conditions for Cyclopentenone Formation



Entry	Catalyst	Conditions	Time (h)	Conv. (%)	yield (%)[a] 2	3
1	1% AuCl(PPh$_3$)/AgSbF$_6$	dry CH$_2$Cl$_2$, rt	0.5	>99	65[b]	8[c]
2	**1% AuCl(PPh$_3$)/AgSbF$_6$**	**wet CH$_2$Cl$_2$, rt**	**0.5**	**>99**	**<1**	**92[b]**
3	5% AuCl$_3$	dry CH$_2$Cl$_2$, rt	0.5	48	31	<1
4	5% AuCl$_3$	wet CH$_2$Cl$_2$, rt	0.5	96	5	64
5	5% PtCl$_2$	dry toluene, 80 °C	4	41	32	<1
6	5% AgSbF$_6$	wet CH$_2$Cl$_2$, rt	0.5	<1	<1	<1
7	5% TfOH	dry CH$_2$Cl$_2$, rt	0.5	62[d]	<1	<1

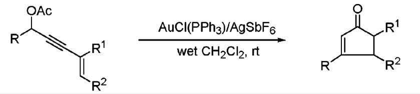
[a] Estimated by ^{1}H NMR using diethyl phthalate as internal standard. [b] Isolated yield. [c] Due to adventitious water. [d] Decomposed amount.

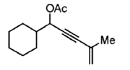
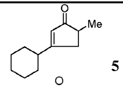
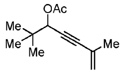
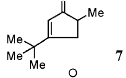
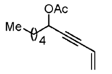
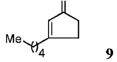
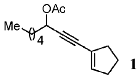
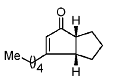
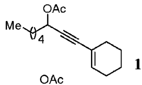
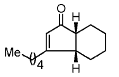
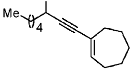
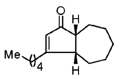
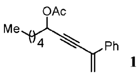
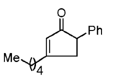
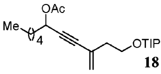
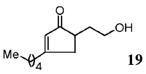
With these results in hand, we set out to examine the scope of this reaction. As shown in Table 2, enynyl acetates derived from α-branched aldehydes (i.e., compounds **4** and **6**) underwent smooth reaction, and the corresponding cyclopentenones were isolated in excellent yields (entries 1 and 2), 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(PPh$_3$)/AgSbF$_6$ 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(PPh$_3$)/AgSbF$_6$ (5 mol %) resulted in the formation of cyclopentadienylic acetate **21** in 91% yield even in wet CH$_2$Cl$_2$ (eq 1). Hydrolysis of **21** in the presence of HNTf$_2$ (1 mol %) gave enone **22** in excellent yield. Similarly, acetate **23** with a *p*-CF$_3$-substituted phenyl group underwent smooth cyclization, and enone **24** was isolated in 96% overall yield after hydrolysis.

10.1021/ja057327q CCC: $33.50

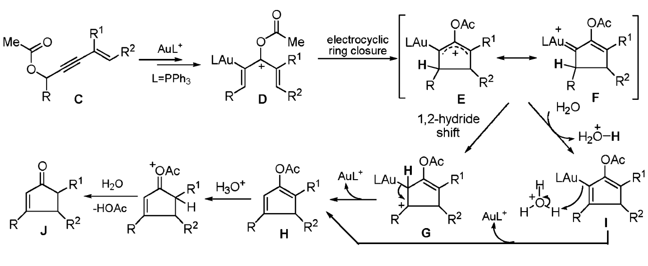
Table 2. $AuCl(PPh_3)/AgSbF_6$-Catalyzed Formation of Cyclopentenones[a]



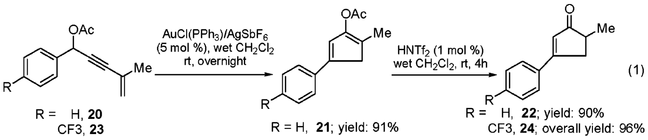
Entry	Enynyl acetate	Catalyst (mol %)	Time (h)	Cyclopentenone	Yield[b] (%)
1	 **4**	1	0.5	 **5**	95
2	 **6**	1	0.5	 **7**	88
3	 **8**	1	0.5	 **9**	79
4	 **10**	1	0.5	 **11**	57
5	 **12**	1	0.5	 **13**	84
6	 **14**	1	0.5	 **15**	90[c]
7	 **16**	5	2	 **17**	74
8	 **18**	5	0.5	 **19**	81[d]

[a] Substrate concentrations are 0.05 M. [b] Isolated yields. [c] Containing about 6% of the *trans*-5,7-fused enone and 6% of an isomer with the C−C double bond at ring juncture. [d] See text.

Scheme 2. Proposed Mechanism for the Formation of Cyclopentenones



However, a complex reaction mixture resulted when the phenyl group was substituted with a *p*-methoxy group.



(1)

The mechanism of this remarkable reaction is hypothesized in Scheme 2. Pentadienylic cation **D** is generated via cationic Au(I)-catalyzed tandem 3,3-rearrangement of enynyl acetate **C** and activation of the in situ generated allenylic acetate. Subsequent electrocyclic ring closure of **D** forms Au-containing cyclopentenylic cation **E**, which should be in resonance with Au carbenoid species **F**. While cyclopentadienylic 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 H_2O 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 CH_2Cl_2 saturated with D_2O 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 $H_3O^+SbF_6^-$, instead of $[Au(PPh_3)]^+SbF_6^-$, based on the following observations: (1) $AuCl(PPh_3)/AgSbF_6$ (up to 5 mol %) hydrolyzed **2** in wet CD_2Cl_2 very slowly; (2) $AuCl(PPh_3)/AgSbF_6$ (1 mol %) hydrolyzed **2** quickly (in less than 30 min) when **2** was mixed with 1 equiv of enynyl acetate **1**; (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 BnSMe,[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 $HNTf_2$. Presumably a small amount of $H_3O^+SbF_6^-$ was generated during the reaction of $[Au(PPh_3)]^+SbF_6^-$ with **1**. In the cases of aryl compounds **20** and **23**, either $H_3O^+SbF_6^-$ was not generated or it was consumed via the formation of a stable benzylic-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.

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(6) Exceptions include transition-metal-catalyzed isomerizations of 1-ethynyl-2-propenyl carboxylates to cyclopentenones. For Pd-catalyzed case, see: (a) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952. For Au-catalyzed case, see: (b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803.
(7) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805.
(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 CH_2Cl_2 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 ^2H NMR.
(11) BnSMe was used to poison the cationic Au(I) catalyst, while it is not basic enough to neutralize the acid generated during the reaction.

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