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Tandem Au-Catalyzed 3,3-Rearrangement−[2 + 2] Cycloadditions of Propargylic Esters: Expeditious Access to Highly Functionalized 2,3-Indoline-Fused Cyclobutanes

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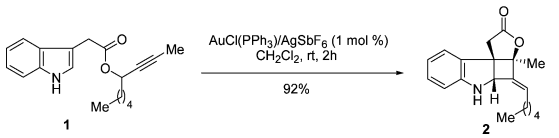
Gold salts have been recently demonstrated to be exceptional reagents for the activation of C−C triple bonds[1] toward addition of a range of nucleophiles, including H_2O/alcohols,[2] carbon[3] and nitrogen[4] nucleophiles, and carbonyl groups.[5] These catalytic reactions generally proceed under exceedingly mild reaction conditions and with high efficiency. However, the activation of related allenes by Au salts has been largely unexplored.[6,7] Herein, I report tandem cationic Au(I)-catalyzed activations of both propargylic esters and the in situ generated allenylic esters, resulting in the expeditious formation of highly functionalized 2,3-indoline-fused cyclobutanes via sequential 3,3-rearrangement and [2 + 2] cycloaddition.

During the study of the general reactivities of propargylic carboxylates in the presence of Au salts, non-2-yn-4-yl indole-3-acetate (**1**) was treated with 1 mol % of $AuCl(PPh_3)/AgSbF_6$ [8] at ambient temperature. A clean and complete conversion was observed in 2 h. The isolated product was identified as tetracyclic cyclobutane **2** with fused 2,3-indoline and γ-lactone rings and an exocyclic *E*-double bond (eq 1). The *Z*-double bond isomer was not observed. While the initial structural analysis relied on extensive NMR work, this assignment was subsequently confirmed by X-ray crystallography of **4c** (Figure 1).



(1)

The efficient formation of highly functionalized cyclobutane **2** from readily available propargylic ester **1** prompted us to further study its scope. As shown in Table 1, alkyl substitution at the indole nitrogen was tolerated, and *N*-methylindole-3-acetate **3a** reacted smoothly to give *N*-methylindoline derivative **4a** in good yield (entry 1). A phenyl group at the propargylic position did not affect the reactivity; for example, cyclobutane **4b** was obtained in 98% yield (entry 2). 3-Bromopropyl-substituted propargylic ester (**3c**) reacted smoothly in the presence of Au(I), giving cyclobutane **4c** in excellent yield (entry 3). The structure of **4c** was verified by X-ray crystallography. Aryl alkyne **3d** showed diminished reactivity, and 10 mol % of $AuCl(PPh_3)/AgSbF_6$ was needed to drive the reaction to completion; compound **4d** was obtained in 86% yield

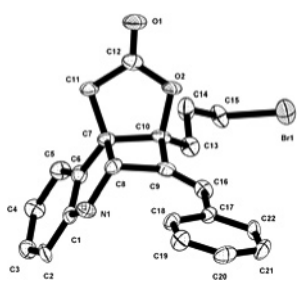
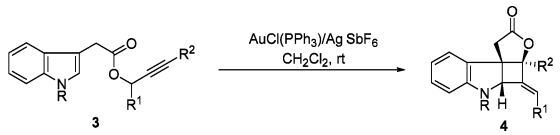
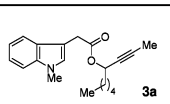
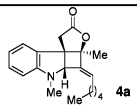
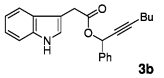
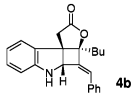
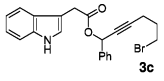
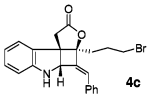
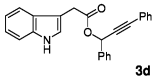
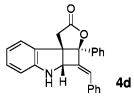
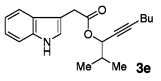
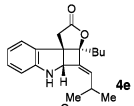
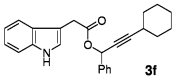
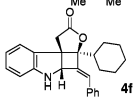
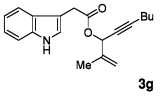
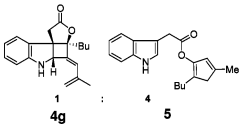


Figure 1. X-ray structure of cyclobutane **4c**.

Table 1. $AuCl(PPh_3)/AgSbF_6$-Catalyzed Formation of Highly Functionalized Cyclobutanes



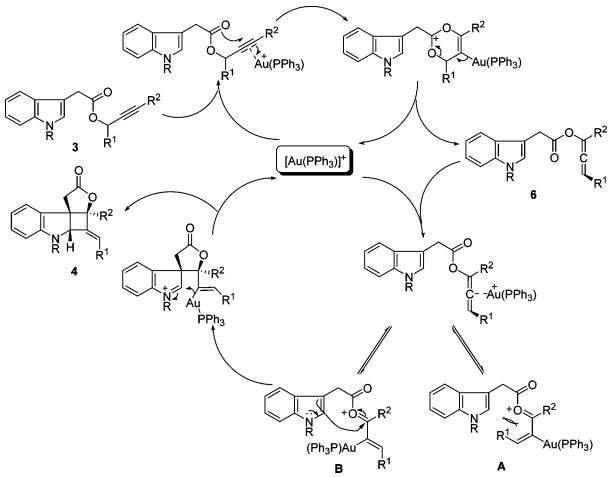
entry	Propargylic ester **3**	Cyclobutane **4**	Au$^+$ (mol%)	Time (h)	Yld. (%)
1	 **3a**	 **4a**	1	2	81
2	 **3b**	 **4b**	1	2	98
3	 **3c**	 **4c**	1	2	95
4	 **3d**	 **4d**	10	2	86
5	 **3e**	 **4e**	2[a]	12	84[b]
6	 **3f**	 **4f**	5	8	69
7	 **3g**	 **4g** : **5**	1	2	85[c]

[a] $AuCl(PPh_3)/AgSbF_6$ (1 mol %) was initially added; after 6h, an additional batch was added. [b] Compound **4e** is contaminated with an unknown impurity. [c] Combined yield of compound **4g** and **5**.

(entry 4). More bulky substituents at either the propargylic position (entry 5) or the alkyne terminus (entry 6) affected the reaction. Longer reaction times and higher catalyst loadings were necessary for the reaction of **3e** and **3f**. Cyclobutanes **4e** and **4f** were obtained in moderate to good yields. Interestingly, the treatment of ester **3g** with a 2-propenyl group at the propargylic position with 1 mol % of $AuCl(PPh_3)/AgSbF_6$ resulted in a 1:4 mixture of the desired cyclobutane **4g** and cyclopentenone derivative **5**,[9] respectively (entry 7). There was no reaction with the parent propargyl indole-3-acetate ($R = R^1 = R^2 = H$). When the propargylic position was substituted with two methyl groups ($R^2 = n$-Bu), the desired product was not detected, although the starting material was completely consumed. Surprisingly, there was no reaction with $R = H$, $R^1 = BnOCH_2$, and $R^2 = n$-Bu, while a complex reaction mixture was formed with $R = H$, $R^1 = n$-pentyl, and $R^2 = BnOCH_2$.

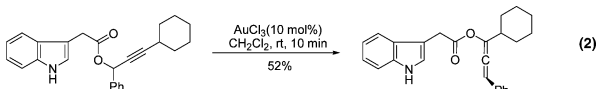
10.1021/ja056419c CCC: $30.25

Scheme 1. Proposed Mechanism for the Formation of Cyclobutane **4**



The proposed mechanism for the formation of cyclobutane **4** is shown in Scheme 1. Activation of the C−C triple bond in propargylic ester **3** by $[Au(PPh_3)]^+$ promotes a 3,3-rearrangement of the indole-3-acetoxy group, which leads to the formation of allenylic ester **6**. The allene moiety of **6** is further activated by the cationic Au(I) complex, resulting in the formation of either oxonium **A** with Au *trans* to the R^1 group or **B** with the opposite double bond geometry.[10] While **A** suffers $A^{1,3}$-strain, **B** is relatively less strained due to the long $C(sp^2)$−Au bond.[11] Consequently, equilibration of **A** and **B** via allenylic ester **6** would result in thermodynamically favored **B** as the predominant oxonium species. Cyclobutane **4** with an exocyclic *E*-double bond is formed via cyclization of the oxonium group in **B** to the 3-position of the indole ring, followed by intramolecular trapping of the iminium with the alkenylgold(I).[12]

This mechanism is supported by the ^{1}H NMR observation of allenylic ester **6f**. When propargylic ester **3f** with R^2 = cyclohexyl was treated with 1 mol % of $AuCl(PPh_3)/AgSbF_6$, a 1:1 inseparable mixture of **6f** and cyclobutane **4f** was isolated in 2 h. **6f** was independently prepared through $AuCl_3$-catalyzed 3,3-rearrangement of **3f** (eq 2). Not surprisingly, treatment of **6f** with the cationic Au(I) catalyst (5 mol %) for 8 h gave **4f** in 74% yield. Remarkably, $AuCl_3$ did not catalyze the formation of **4f**, and extended reaction led to the decomposition of **6f**. Other allenylic ester intermediates were not observed, likely because the [2 + 2] cyclizations of these allenylic esters were faster than the 3,3-rearrangements of the corresponding propargylic esters. In contrast, **6f** reacted with Au(I) slower than **3f** due to the steric bulk of the cyclohexyl group, resulting in the accumulation of **6f** and the slow formation of **4f**. It is noteworthy that Au salts have been shown previously to catalyze 2,3-rearrangements of propargylic esters[3d,13] but not their 3,3-rearrangements.[14]



In summary, we have demonstrated that the cationic Au(I) complex derived from $AuCl(PPh_3)/AgSbF_6$ activates both propargylic esters and allenylic esters. Tandem Au(I)-catalyzed 3,3-rearrangement−[2 + 2] cyclizations of readily available propargylic indole-3-acetates lead to the formation of highly functionalized 2,3-indoline-fused cyclobutanes with high efficiency. Further studies in utilizing this tandem process as well as the application of these cyclobutanes in alkaloid synthesis will be reported in due course.

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

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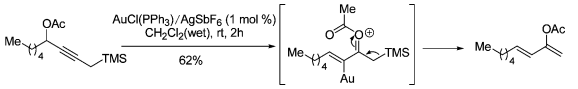
(9) Transition metal-catalyzed isomerizations of related 1-ethynyl-2-propenyl carboxylates to cyclopentenones have been previously reported. For the Pd-catalyzed case, see: Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952. For the Au-catalyzed case, see: Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803.

(10) The formation of oxonium species **A** and **B** is supported by the following observation. This result and further studies will be published soon.



(11) ConQuest searching of the Cambridge structural database resulted eight hits with similar $C(sp^2)$−Au(I)(PPh_3) bonds. The average bond length is 2.043 Å, while the bond length of $C(sp^2)$−$C(sp^3)$ is 1.50 Å.

(12) An alternative kinetic explanation for the exclusive formation of the *E*-double bond is that oxoniums **B** and **A** are in equilibrium with extremely fast interconversion rate, and **B** cyclizes much faster than **A**.

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