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Gold-catalyzed ring expansions of 1-alkynylcyclobutanol derivatives via tandem hydration and α-ketol rearrangement

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ABSTRACT

We report herein the gold-catalyzed tandem hydration/α-ketol rearrangement of 1-alkynylcyclobutanol derivatives, leading to cyclopentanones bearing an α-hydroxy substituted quaternary center. In the presence of water, coordination of gold catalyst onto alkynyl moiety triggers hydration rather than a direct ring expansion, which followed by unprecedented Au-catalyzed α-ketol rearrangement. The details and the scope of this method are presented.

1. Introduction

Ring expansions of cyclobutanol derivatives have drawn significant interest because they provide versatile approaches to elaborate cyclopentanone scaffolds in terms of functionality and stereochemistry.[1] Among myriads of catalytic methods to trigger ring expansion of cyclobutanes, some recent developments are particularly notable, including organocatalytic approaches[2] as well as transition metal catalysis employing Pd, Fe, Ru, and Co.[3] Recently, gold catalysts are also known to be powerful activators for small ring expansion.[4] In 2005, Toste and co-workers reported 1-alkynylcyclopropanols and 1-alkynylcyclobutanols undergo direct ring expansion, leading to α-methylenecyclobutanones and α-methylenecyclopentanones, respectively (Scheme 1).[4b] We envisioned that incorporation of water in the reaction mixture would divert the reaction pathway from direct ring expansion to initial hydration followed by α-ketol rearrangement, based on the well-known reactivity of gold complexes as hydration catalysts.[5] This sequential catalysis would allow for a facile incorporation of an hydroxyl group at the α-quaternary center, which otherwise require oxidation of the corresponding cyclopentanone derivatives.[6] Herein, we disclose that both hydration and α-ketol rearrangement are catalyzed by Au(I) complexes and the scope of this new tandem catalysis are presented.

2. Results and discussion

2.1. Initial investigations

In order to realize the tandem reaction sequences outlined above, several challenges resulting from competing processes are to be addressed. In addition to the direct ring expansion pathway (formation of **A**), Au(I) complexes are also known to catalyze Meyer–Schuster rearrangement leading to **C**, as reported by Chung and co-workers employing closely related substrates.[7] Thus we started with identification of conditions that rapidly hydrate the 1-alkynylcyclobutaols, thereby ensuring selective formation of **B** rather than these competing processes.

As in Eq. 1, we prepared **1b** as a test substrate and examined its reaction in the presence of Au(IPr)Cl (5 mol %, IPr=*N*,*N*′-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) and $AgBF_4$ (5 mol %) in dioxane at 80 °C. Experiments conducted under anhydrous conditions afforded 38% of α-hydroxylcyclopentanone **2b** in addition to the direct expansion product **3b** (48% based on the crude ^1H NMR spectra), the former of which formed presumably from hydration by adventitious water. In contrast, when we added one drop of water (∼15 equiv) into the reaction mixture, a near complete selectivity toward **2b** could be achieved (>99% yield by NMR). To verify the possible intermediacy of α-ketol intermediate shown in Scheme 1, we then attempted to intercept the putative α-ketol intermediate utilizing substrate **1d** having a weaker ring strain due to Thorpe-Ingold effect and therefore lower propensity

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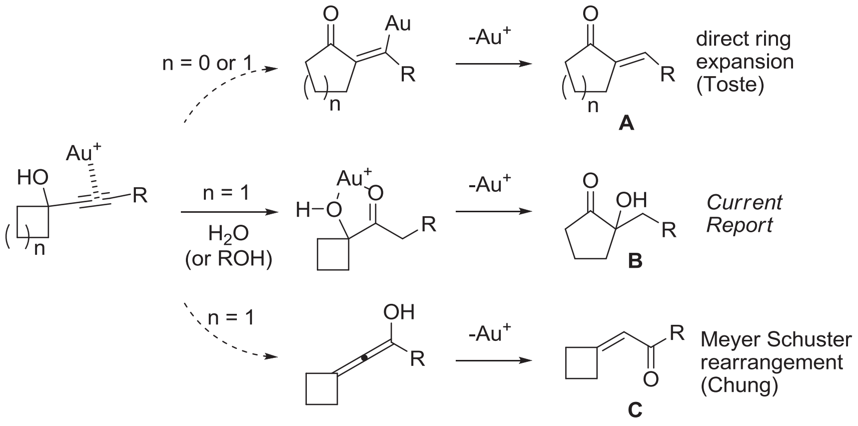
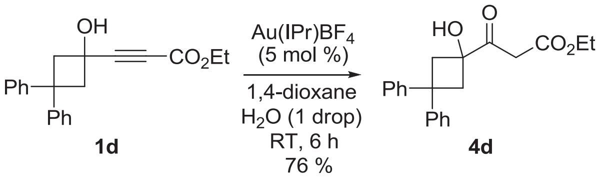


Scheme 1.

toward ring expansion.[8] As expected, the reaction of **1d** at rt under otherwise identical conditions led to an isolation of **4d** in 76% isolated yield after chromatographic separation (Eq. 2). This experiment undoubtedly confirmed the α-ketol is as an initial product of this tandem reaction and furthermore the isolated **4d** served as a probe for identifying the catalysts for the subsequent α-ketol rearrangement (Eq. 3). Simple heating **4d** in dioxane at 80 °C did not afford any product and **4d** remained intact even after 14 h. On the other hand, in the presence of Brönsted acid, HBF_4 (5 mol %) instead of Au(IPr)BF_4, the ring-expansion product **2d** (46%) was accompanied by a Rupe rearrangement product **5d** (52%). Finally, treating **4d** with Au(IPr)BF_4 (5 mol %) in 1,4-dioxane led to a clean formation of the desired product **2d** in excellent isolated yield (91%). These results confirmed that the hydration occurs faster than the competing direct 1,2-alkyl shift and the same Au(I) catalyst efficiently mediate both regioselective hydration and chemoselective α-ketol rearrangement, the latter of which presumably initiated by chelation of Au-catalyst onto α-ketols as in **D** (Scheme 2). To the best of our knowledge, the gold-catalyzed α-ketol rearrangement has not been reported prior to our work.



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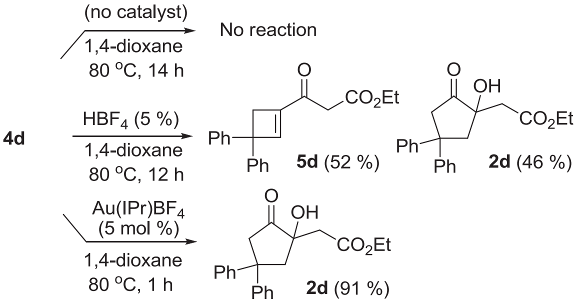
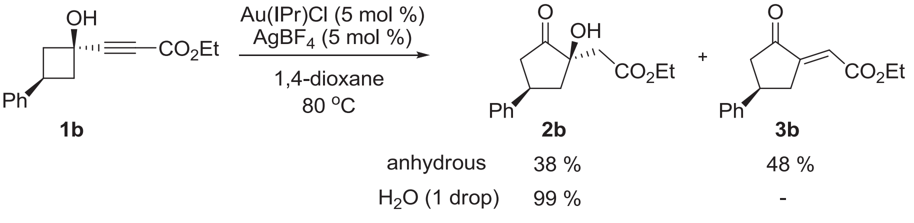


(3)

2.2. Optimization studies

To finely tune the reaction conditions that are generally applicable for diverse substrates, we conducted several screening studies using **1c** as a test substrate (Tables 1–3). As shown in Table 1, among the ligands tested, Buchwald-type ligands, that are bulky and relatively electron-rich, performed well for the desired transformation and JohnPhos ligand stood out as an optimal ligand (entry 3, Table 1). On the other hand, the reaction was also highly sensitive to the counter-anions. Among the silver salts examined, $AgSbF_6$ provided the best results in terms of



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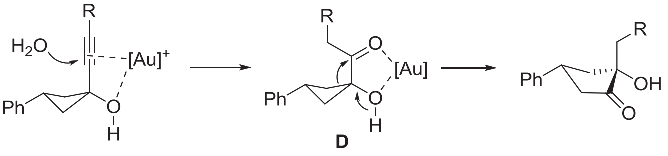

Scheme 2. A proposed tandem hydration/α-ketol rearrangement.