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Au(I)-catalyzed tandem [3,3]-sigmatropic rearrangement–cycloisomerization cascade as a route to spirocyclic furans

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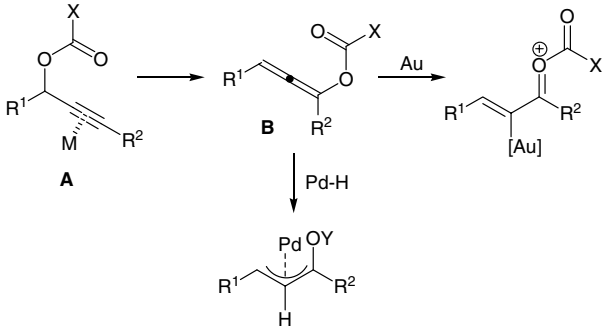
Abstract—Gold-catalyzed reaction of 1-(3-hydroxypropynyl)cycloalkanol derivatives was studied. The reaction profile was highly dependent on the ring size, migrating group, as well as reaction conditions. An efficient route to spirocyclic furans via tandem [3,3]-sigmatropic rearrangement–cycloisomerization is reported.

Transition metal catalyzed [3,3]-sigmatropic rearrangement of propargyl ester, phosphate, and sulfonate are important transformations in organic synthesis.[1] Particularly, it opens a promising venue for selective transformations by providing in situ access to *O*-allenes, which are often difficult to prepare otherwise.[2] Recently, alkynophilic gold complex turned out to be an excellent catalyst for the [3,3]-rearrangement of a range of propargylic substrates, including propargyl ester, enol ether, and vinyl silane, thus allowing various subsequent tandem transformations.[3,4] In this context, we recognized that propargyl esters **A** is a mechanistic synthon for the corresponding *O*-acetyl allenes **B** and initiated a program to investigate its application under gold-catalysis (Scheme 1).[5] Mechanistically interesting aspect is the regioselectivity of Au-catalyzed activation of O-substituted allene: While Pd-catalyzed reaction is known to occurs via metallation on C1 (or C3) of O-substituted allene (i.e., hydropalladation) leading to π-allyl species,[6] Au-catalyst adds on the central carbon of allene leading to oxocarbenium ion.[7] The latter species are known to participate in a variety of reactions, including nucleophilic attack by indol,[7a] 1,3-diene formation,[7b] Nazarov cyclization,[7d] and cycloisomerization.[7e]

We were interested in the reaction of propargyl cyclobutanol **C**, where three distinct mechanistic pathways could be envisioned (Scheme 2). Ring expansion of alkynyl cycloalkanol as reported by Toste, would lead to **D** (route A).[8] On the other hand, intervention of allenyl intermediate via [3,3]-sigmatropic rearrangement followed by Wagner–Meerwein type 1,2-alkyl shift would lead to **E** (route B),[9] which would compete with cycloisomerization into **F** (route C) as reported by Gagosz.[2a,7e] In this Letter, we report our investigation of the reactivity of cycloalkanol derivatives of **C** under gold catalysis that strongly depend on the ring size and the nature of the migrating group.



Scheme 1. Au- versus Pd-catalyzed reaction of *O*-allenes.

In this effort, we report a novel approach for assembling spirocyclic furans via tandem [3,3]-sigmatropic rearrangement–cycloisomerization sequence. Spirofurans are direct precursor to conformationally restricted nucleoside analogs and find useful applications as antiviral agents in nucleoside mimic.[9] This spurred us to further investigate a route to various ring-sized analogs of spirofurans.

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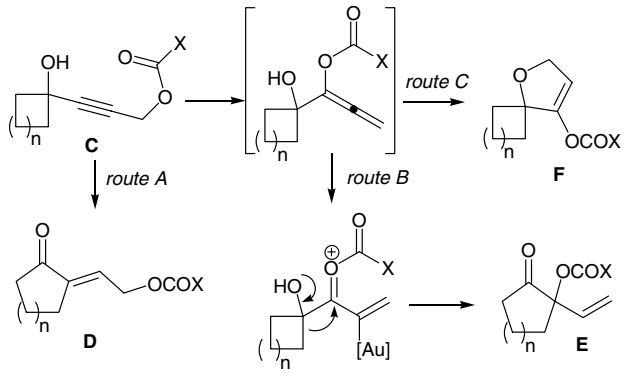
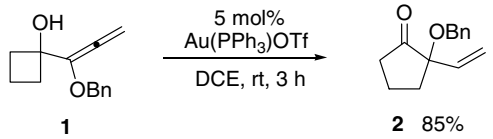


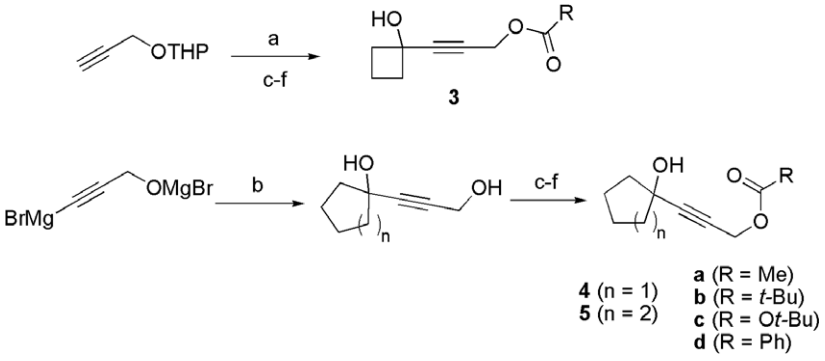
Scheme 2. Evolution of propargyl ester **C** under Au-catalysis.

Initially we were interested in gold-catalyzed ring expansion (route B, Scheme 2) and tested reaction of BnO-allene-substituted cyclobutanol (Eq. 1).[10] Under 5 mol % of $Au(PPh_3)OTf$ in 1,2-dichloroethane at rt, **1** was smoothly converted into α-vinylated cyclopentanone **2** in good yield.[11]



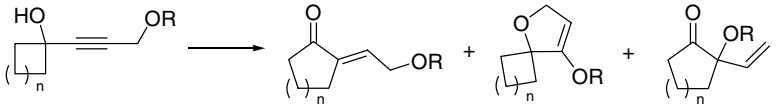
(1)

Encouraged by the result, we prepared a series of propargylic ester derivatives **3**–**5** according to Scheme 3 and investigated their reactions. For the preparation of



Scheme 3. Preparation of substrates **3a**–**d**, **4a**–**d**, and **5a**–**d**. Reagents and conditions: (a) (1) *n*-BuLi, THF, then cyclobutanone, 0 °C, (2) $TsOH·H_2O$, MeOH, (3) $(Boc)_2O$, DMAP, Et_3N, THF; (b) cyclopentaone (or cyclohexanone), $CeCl_3$, THF, 0 °C; (c) Ac_2O, Py; (d) PivCl, Py; (e) $(Boc)_2O$, DMAP, Et_3N; (f) BzCl, Py.

Table 1. Reactions of **3**–**5** under Au(I)-catalysis



Entry	Substrate	Condition[a]	Product, yield[b] (%)
1	**3a** R = Ac	A	**6a** (96)[c]
2	**3b** R = Piv	A	**7b** (60)
3	**3b** R = Piv	B	**7b** (73)
4	**3c** R = Boc	A	**7c** (68)
5	**3c** R = Boc	B	**7c** (75)
6	**3d** R = Bz	A	**7d** (66)
7	**4a** R = Ac	A	**10a** (16), **11a** (5)[d]
8	**4a** R = Ac	B	**10a** (61)
9	**4a** R = Ac	C	**9a** (11), **10a** (2)[d]
10	**4a** R = Ac	D	**10a** (34)
11	**4b** R = Piv	B	**10b** (81)
12	**4c** R = Boc	B	**10c** (84)
13	**4d** R = Bz	B	**10d** (98)
14	**5a** R = Ac	B	**13a** (92)
15	**5b** R = Piv	B	**13b** (66)
16	**5c** R = Boc	B	**13c** (63)
17	**5d** R = Bz	B	**13d** (93)

[a] All reactions were conducted in CH_2Cl_2 at rt. Condition A: $Au(PPh_3)OTf$ (5 mol % formed in situ), Condition B: Au[*t*-Bu_2P(*o*-biphenyl)]OTf (5 mol %), Condition C: $Au[P(C_6F_5)_3]OTf$ (5 mol %), Condition D: $Au[P(o\text{-tol})_3]OTf$ (5 mol %).

[b] Isolated yield after chromatography.

[c] 1 mol % of catalyst was used in this case.

[d] Other byproducts could not be identified.

cyclobutanol analogs, a four step sequence involving THP protection was required. However, for 5- and 6-membered substrates, a sequence involving reaction of dianion with cycloalkanone, followed by appropriate protection, efficiently delivered desired substrates.

Treatment of propargyl acetate **3a** with 1 mol % of $Au(PPh_3)OTf$ pre-catalyst in dichloromethane at rt for 1 h, direct ring expansion without [3,3]-rearrangement (route A, Scheme 2) occurred to give cyclopentanone **6a** in an excellent yield (96%, Table 1, entry 1).[12] Changing protecting group as in **3b–d** led to faster [3,3]-rearrangement and completely diverted the reaction path into rearrangement followed by cycloisomerization (route C, Scheme 2), giving **7** in modest yields (entries 2, 4, and 6). In these cases, **6** or **8** could not be isolated in any significant amounts. The reactivity of **3b–d** shows that the resulting *O*-acyl-allenyl intermediate cycloisomerize faster than ring-expansion, which is in contrast to BnO-allenyl derivative **1** (Eq. 1) and this could be rationalized by the lack of electron-donation of ester oxygen to bring about activation of allene. Interestingly, changing ligand into Au[*t*-Bu_2P(*o*-biphenyl)]OTf further increased the yield of **7** (entries 3 and 5).[13] In an attempt to decrease the rate of cycloisomerization, **3d** was converted into TMS ether and was subject to the condition A in the presence of 2 equiv of isopropanol. Unsuccessfully, the reaction gave cycloisomerized **7d** in 62% yield in a much slower reaction.

Reaction of **4** which is free of ring strain showed more complex reaction profile. Using $Au(PPh_3)OTf$ (5 mol %), small amount of ring expansion product **11a** (route B, Scheme 2) was observed from the complex reaction mixture, but most of the mass balance was attributed to an unidentified product (entry 7). Use of electron-deficient ligand gave a small amount of ring expansion product **9a** through route A (Scheme 2), albeit in low yield (entry 9). Use of Au[*t*-Bu_2P(*o*-biphenyl)]OTf (5 mol %) significantly improved the yield of **10a** and delivered the spirocycle in 61% yield (entry 8). Other derivatives of **4** gave more efficient conversion into spirocycles **10** in 81–98% yield (entries 11–13). Spirocyclization of six membered ring-substrates **5a–d** also went uneventfully giving the corresponding spirocycles **13a–d** in moderate to excellent yields (entries 14–17).

In summary, we reported a novel gold-catalyzed route to conformationally biased spirocyclic furans having various ring sizes. Our report shows the fate of 1-(3-hydroxypropynyl)cycloalkanol substrates is highly dependent upon the ring size as well as migrating group. Further effort to utilize this spirofuran skeleton in the synthesis of nucleoside analogs is underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.067.

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13. A representative procedure for cycloisomerization of **3b**: Au[*t*-Bu_2P(*o*-biphenyl)]Cl (10.0 mg, 0.019 mmol) and AgOTf (4.9 mg, 0.019 mmol) was weighed in a test tube. Starting propargyl pivalate **3b** (80.0 mg, 0.38 mmol) in dichloromethane (1.0 mL) was added and the resulting mixture was stirred 3 h. To the mixture was added three drops of triethylamine and the resulting mixture was filtered through a short pad of silica gel. The eluent was evaporated to dryness and the resulting oil was purified by flash chromatography (EtOAc–hex = 1:10) to give 58.5 mg (73%) of **7b** as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.78 (br s, 1H), 4.63 (d, $J = 1.5$ Hz, 2H), 2.48–2.22 (m, 4H), 1.82–1.60 (m, 2H), 1.31 (s, 9H). ^{13}C (100 MHz, $CDCl_3$): δ 175.6, 148.4, 104.9, 86.4, 72.3, 39.7, 35.3, 37.3, 12.2.