Gold Catalysis

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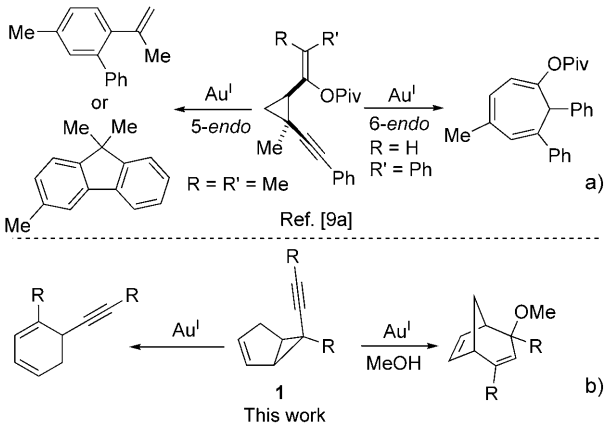
Gold-Catalyzed Rearrangements: Reaction Pathways Using 1-Alkenyl-2-alkynylcyclopropane Substrates**

José Barluenga, Eva Tudela, Rubén Vicente, Alfredo Ballesteros, and Miguel Tomás*

In memory of Rafael Suau

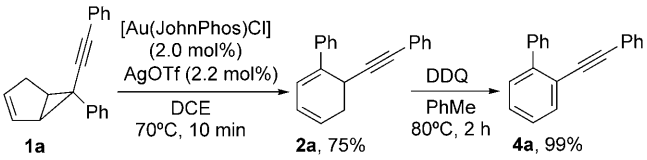
In the past decade, homogeneous gold catalysis have irrupted in organic chemistry with a vast array of novel transformations.[1] In particular, the ability of gold catalysts to activate alkynes, alkenes, or allenes enables profound skeletal rearrangements.[2] Whereas gold-catalyzed 1,*n*-enyne cycloisomerization reactions have been extensively developed,[3] the involvement of the cyclopropane unit as a C-3 surrogate in metal-catalyzed cycloisomerization reactions has been much less studied. For instance, simple alkynylcyclopropanes undergo gold-catalyzed cyclopropane–cyclobutane ring expansion in the presence of amines[4] or diphenylsulfoxide.[5] Alkynylcyclopropanes with additional functionalities (hydroxy,[6] acyl,[7] or epoxy[8]) allowed to design useful transformations based on the cleavage of the cyclopropane ring. In this scenario, it seemed to us that the catalytic transformations of substrates containing the alkene–cyclopropane–alkyne connectivity might be a promising approach. Surprisingly, transformations based on the 1-alkenyl-2-alkynylcyclopropane framework (1,5-enyne arrangement) are very rare.[9,10] Thus, Toste and co-workers[9a] reported the gold(I)-catalyzed cycloisomerization of *cis*-PivO-vinyl-alkynyl-cyclopropane units into arene and cycloheptatriene derivatives through 5-*endo-dig* and 6-*endo-dig* cyclization reactions (Scheme 1a).

Our recent report[11] on a straightforward access to 6-alkynylbicylo[3.1.0]hexen-2-enes **1** prompted us to study their behavior toward metal catalysis. Although this structure features the required *cis*-alkene–cyclopropane–alkyne connectivity, the fact that the alkenyl function is constrained in a cyclic substructure would likely impose new reaction pathways. Herein, it is reported that 1) gold(I) catalyzes the cycloisomerization of compounds **1** and, 2) divergent structural rearrangements are observed in the absence/presence of nucleophiles (Scheme 1b).



Scheme 1. Gold-catalyzed rearrangements of 1-alkenyl-2-alkynylcyclopropanes. Piv = pivaloyl.

After some optimization studies, we found that an in situ generated cationic JohnPhos–gold(I) complex catalyzes the cycloisomerization of the alkynylcyclopropane **1a**, thus affording the alkynylcyclohexadiene **2a** in synthetically useful yield (75%; Scheme 2).[12] The structure of compound **2a** was elucidated on the basis of one- and two-dimensional NMR data and confirmed by aromatization to the known arene **4a**.[13]



Scheme 2. Gold-catalyzed rearrangement of alkynylcyclopropane **1a**. DCE = 1,2-dichloroethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Several features related to the behavior of the alkynylcyclopropane system toward cationic gold(I) are noteworthy. First, the distal cyclopropane C–C bond suffered selective cleavage, and second, the alkyne function remained unaltered. Moreover, the overall process consisting of a formal cyclopentadiene–cyclohexadiene ring expansion and a [1,2]-alkynyl shift represents a novel transformation.

Further studies were performed using various types of substrates (Table 1).[14] First, the homosubstituted cyclopropanes **1b–d** ($R^1 = R^2 = Ar$) yielded **2b–d** (70–88%) as single

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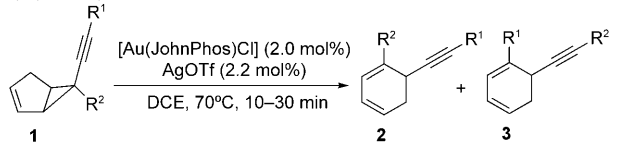
Table 1: Gold-catalyzed rearrangement of alkynylcyclopropanes **1** into 6-alkynyl-1,3-cyclohexadienes **2**,**3**.



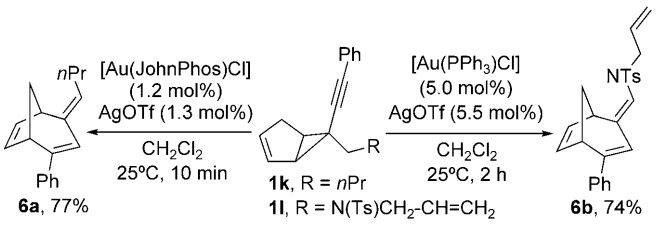
Entry	R^1	R^2	**2** (Yield [%])[a]	**3** (Yield [%])[a]
1	Ph	Ph	**2a** (75)	–
2	*p*-ClC_6H_4	*p*-ClC_6H_4	**2b** (88)	–
3	*p*-MeC_6H_4	*p*-MeC_6H_4	**2c** (73)	–
4	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**2d** (70)[b]	–
5	*p*-ClC_6H_4	Ph	**2e**+**3e** (70, 1.4:1)[c]	–
6	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	**2f**+**3f** (62, 3:1)[b,c]	–
7	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	**2f**+**3f** (55, 2.4:1)[b,c]	–
8[d]	*p*-$MeOC_6H_4$	*p*-CNC_6H_4	–	**3g** (>45)
9	Ph	*c*Pr	**2h** (54)	–
10	Ph	*t*Bu	**2i** (47)	–
11	Ph-C≡C-	Ph	**2j** (66)[b]	–

[a] Yields of isolated products. [b] Around 5% of *gem*-disubstituted cyclohexadiene **5** was detected in the crude reaction mixture. See Ref. [15]. [c] Isolated as a mixture. The selectivity was determined by ^{1}H NMR spectroscopic analysis. [d] Reaction conditions: $PtCl_4$ (5 mol%), CO (1 atm), 70°C, 5 h. **3g** was further dehydrogenated yielding **4g** in 45% overall yield. See Ref. [16].

isomers (entries 2–4).[15] Unexpectedly, variable mixtures of regioisomers **2**/**3** were formed from heterosubstituted cyclopropanes ($R^1 \neq R^2$; entries 5–6). Thus, inseparable mixtures of **2e**/**3e** (1.4:1; R^1/R^2 = *p*-ClC_6H_4/Ph) and **2f**/**3f** (3:1; R^1/R^2 = *p*-ClC_6H_4/*p*-$MeOC_6H_4$) were obtained. Interestingly, the regioisomeric cyclopropane **1f′** (R^1/R^2 = *p*-$MeOC_6H_4$/*p*-ClC_6H_4, entry 7) yielded a mixture of regioisomers **2f**/**3f** in a ratio of 2.4:1. Thus, the regioselectivity appeared to be dependent on the electronic demand of the aryl groups. Accordingly, it was found that cyclohexadiene **3g** was exclusively formed ($PtCl_4$, 5 mol%, CO, 70°C, 5 h) from **1g** having aryl groups of opposite electronic nature (R^1 = *p*-$MeOC_6H_4$; R^2 = *p*-CNC_6H_4; entry 8). As a result of its low stability, compound **3g** was dehydrogenated to form **4g** (DDQ, 80°C; 45% overall yield from **1g**).[16] Importantly, a general discrimination between phenyl and alkyl groups was discovered (entries 9–10). Thus, cyclopropyl- and *t*Bu-substituted substrates **1h**,**i** yielded **2h** and **2i**, respectively, as single isomers (47–54% yield). On the other hand, the replacement of the alkynyl unit with a diynyl unit (**1j**; R^1 = phenylethynyl; entry 11) resulted in the chemo- and regioselective formation of the butadiynyl-substituted adduct **2j** in a satisfactory yield.

Surprisingly, a completely different transformation occurred from cyclopropane derivatives having a primary alkyl substituent (Scheme 3). Stirring **1k**,**l** in the presence of a gold(I) catalyst at ambient temperature provided stereoselectively the bicyclic structures **6a**,**b**. It is also noteworthy that the process tolerated both amino and alkene functionalities.

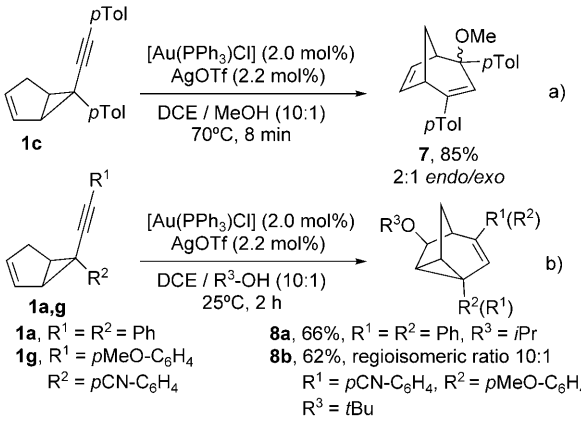
Based on the assumption that cationic species might be involved, further experiments were conducted in the presence of an alcohol as the nucleophile (Scheme 4). Thus, the



Scheme 3. Gold-catalyzed rearrangement of alkynylcyclopropanes **1k**,**l** bearing an unbranched alkyl substituent. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

treatment of alkynylcyclopropane **1c** ($R^1 = R^2$ = *p*-MeC_6H_4) with a cationic gold(I) catalyst in the presence of excess of MeOH resulted in the formation of 4-methoxybicyclo[3.2.1]octadiene **7** (85% yield) as a separable *endo*/*exo* mixture (Scheme 4a). On the other hand, bulkier alcohols (*i*PrOH, *t*BuOH) reacted with **1a**,**g** leading selectively to tricyclo[3.2.1.$0^{2,7}$]octenes **8a**,**b** (Scheme 4b).[17,18]

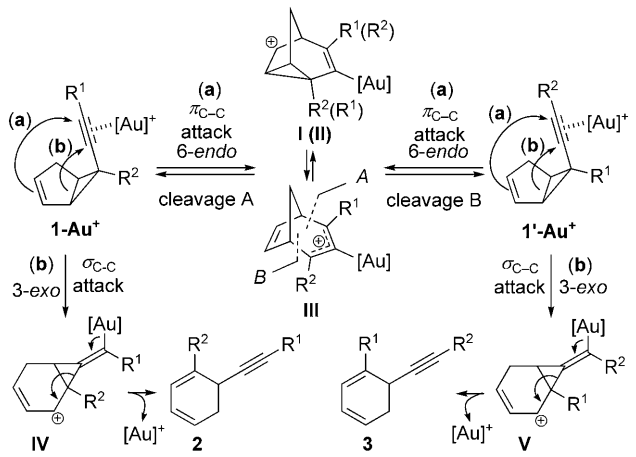
A tentative mechanism to account for these transformations is depicted in Scheme 5. First, we propose that regioisomers **2**/**3** originate specifically from complexes **1-**



Scheme 4. Gold-catalyzed rearrangement of alkynylcyclopropanes **1** in the presence of alcohols. Tol = tolyl.

Au$^+$/**1′-Au**$^+$, which in turn, result from the gold(I)-catalyzed equilibration of **1**. Such a reversible process can be explained by the 6-*endo-dig* π_{C-C} attack (**a**) in **1**/**1′**, thus resulting in the cationic species **I**/**II** that equilibrate into **III**. Then, a retro 6-*endo* cyclization from **III** provides both alkynylcyclopropanes **1-Au**$^+$ (cleavage A) and **1′-Au**$^+$ (cleavage B).[19] The proposed intermediate species **III** and **I**/**II** were trapped with methanol and bulky alcohols, respectively (compounds **7**,**8**; Scheme 4). In the same way, intermediates **III** arising from **1k**,**l** (R^2 = CH_2-R) underwent rapid proton elimination to form **6a**,**b** (Scheme 3).

Then, the formation of **2**/**3** from **1-Au**$^+$/**1′-Au**$^+$, could be explained by the irreversible 3-*exo-dig* nucleophilic attack by the σ_{C-C} bond (**b**)[20] that results in the allylic cationic species **IV**/**V**. The latter intermediates would then provide **2**/**3** through metal elimination and cleavage of the C–C bond. The kinetic selectivity toward **2**/**3** can be rationalized in terms



Scheme 5. Mechanism rationale for gold-catalyzed equilibration of alkynylcyclopropanes **1**/**1′** and formation of compounds **2**,**3**.

of the different electrophilicity of the alkyne function in **1-Au**$^+$ versus **1′-Au**$^+$.

In summary, we have disclosed a new reactivity pattern for alkynyl, cyclopentene-fused cyclopropane units (1,5-enyne arrangement) toward gold(I) catalysts. The process results in a novel five-to-six-membered ring expansion that involves cleavage of the bridging C–C bond and formal [1,2]-alkynyl shift. An unexpected equilibration of regioisomers **1**/**1′** is invoked that takes place through a cationic allyl–gold complex. Although both π systems result unaffected, they play a definitive role in both the occurring processes.[21] As the starting material is directly prepared from cyclopentadiene,[11] herein it is reported a simple two-step transformation of cyclopentadiene into 1,6-disubstituted cyclohexadienes.[22] Moreover, the reaction course can be diverted in the presence of alcohols to provide bicyclo[3.2.1]octadiene and bicyclo[3.2.1.0^{2,7}]octane derivatives. Further studies focused on related structural frameworks as well as on the heteroatom-containing substrates are in progress.

Experimental Section

Representative procedure for the preparation of ((2-phenylcyclohexa-2,4-dienyl)ethynyl) benzene (**2a**; Table 1, entry 1): a previously prepared stock solution of [Au(JohnPhos)Cl] (3.2 mg, 2.0 mol%) and AgOTf (1.7 mg, 2.2 mol%) in DCE (1.0 mL) was added to a solution of alkynylcyclopropane **1a** (77 mg, 0.30 mmol) in DCE (2.0 mL) under an atmosphere of Ar, at ambient temperature. The resulting mixture was immediately placed into a oil bath preheated at 70°C. After 10 min, SiO_2 was added and the solvent was removed under vacuum. The remaining residue was purified by column chromatography (SiO_2, hexane/CH_2Cl_2, 10:1), thus yielding **2a** (57 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 7.6$ Hz, 2H), 7.45–7.35 (m, 4H), 7.34–7.26 (m, 4H), 6.44 (d, $J = 5.6$ Hz, 1H), 6.23 (tdd, $J = 9.5$, 5.6, 1.7 Hz, 1H), 5.97 (dt, $J = 9.5$, 4.6 Hz 1H), 3.83 (dd, $J = 5.9$, 5.6 Hz, 1H), 2.68 ppm (ddd, $J = 5.6$, 4.6, 1.7 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 139.8$ (C_q), 135.3 (C_q), 131.7 (2× CH), 128.4 (2× CH), 128.0 (2× CH), 127.6 (CH), 127.2 (CH), 125.3 (2× CH), 124.9 (CH), 124.3 (CH), 123.7 (C_q), 121.3 (CH), 90.8 (C_q), 80.5 (C_q), 29.8 (CH_2), 28.2 ppm (CH). HRMS (IE) calc. for $C_{20}H_{16}$ $[M]^+$ 256.1252, found 256.1254.

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Keywords: alkynes · cyclopropanes · gold · rearrangement · ring expansion

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[12] A longer reaction time resulted in lower yield (20°C, 3 h; 15% yield). An independent experiment confirmed that **2a** slowly decomposes in the presence of gold catalyst.

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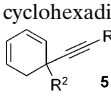
[14] Although other gold catalysts also catalyzes the process, the complex [Au(JohnPhos)Cl] proved to be superior in most instances.

[15] In some cases (entries 4, 6, 7, and 11), *gem*-disubstituted cyclohexadienes **5** were formed in ca. 5% yield. Compound **5f** ($R^1 = p$-$MeOC_6H_4$; $R^2 = p$-ClC_6H_4) could be isolated in pure form and characterized by NMR spectroscopy.



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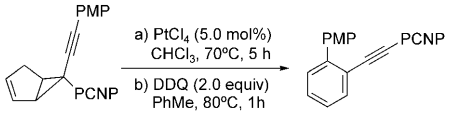
[16] The cycloisomerization of **1g** into **3g** was accomplished with $PtCl_4$. The adduct **3g** it was in situ aromatized to **4g** and characterized. (PMP = p-$MeOC_6H_4$; PCNP = p-CNC_6H_4).



1g **4g**, 45%

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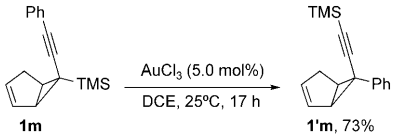
[18] CCDC 804280 (**8b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] In accordance with this hypothesis, clean $AuCl_3$-catalyzed isomerization of **1m** into **1m′** was observed at room temperature TMS = trimethylsilyl.



1m **1'm**, 73%

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