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Gold(I)-Catalyzed Domino Reaction : An Access to furooxepines.

Roméric Galéa, Gaëlle Blond*

Université de Strasbourg, CNRS, Laboratoire d'Innovation Thérapeutique, UMR 7200, 67000 Strasbourg, France

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Abstract. We report herein the synthesis of [7,5]-fused bicyclic acetals, also named furooxepines derivatives through a gold(I)-catalyzed domino reaction. During this transformation, two molecules of homopropargyl alcohol react together, in a sequence including an intramolecular hydroalkoxylation, condensation, a 1,6-enyne cycloisomerization, acetalization and an isomerization. This gold(I)-catalyzed domino reaction allow the formation of three bonds, two heterocycles and a tetrasubstituted carbon stereocenters in a one-step operation with 100% atom economy. Post-functionalizations allow the formation of tetrahydrofurans.

Keywords: domino reactions; gold catalysis; furooxepines; hydroalkoxylation; 1,6-enyne cycloisomerization

Bicyclic acetals represent structural architectures frequently found in natural products, agrochemicals and pharmaceuticals.^[1] Their unique 3D structures and the presence of adjacent pair of oxygens, able to form hydrogen bonds, make those structures very interesting pharmacophores.^[2] Bicyclic acetals are found in natural products as spiroacetals, bridge bicyclic acetals, fused bicyclic acetals or a combination of them. Among fused bicyclic acetals, the three most frequent ring combinations were found to be [5,5], [6,5] and [6,6]-fused bicyclic acetal scaffolds. Even if [7,5]-fused bicyclic acetals, also named furooxepines, are a structure present in azadirachtin, these scaffolds are less represented in natural products and in synthesis (Figure 1).^[3]

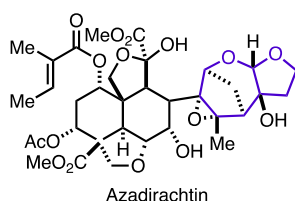
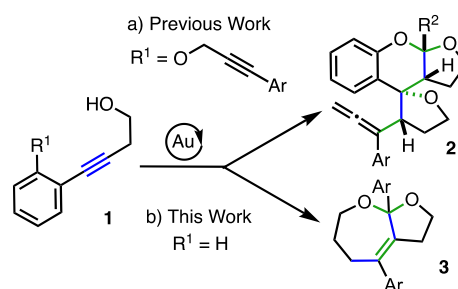


Figure 1. [7,5]-fused bicyclic acetal in natural product.

Homogeneous gold catalysis allowed significant advances toward the synthesis of heterocyclic

compounds.^[4] Moreover, as part of domino processes, it represents interesting tools to rapidly build molecular complexity and was the subject of intense research.^[5] In this context, we have previously reported the synthesis of complex polycyclic molecules **2** containing [6,5]-fused bicyclic acetals through a gold(I)-catalyzed domino reaction including a hetero Diels-Alder (HDA) (Scheme 1).^[6] Continuing our exploration in this field, we report herein the synthesis of new [7,5]-fused bicyclic acetals **3**, starting from the simple starting material **1** ($R^1 = H$), obtained in only one steps from but-3-yn-1-ol. During this transformation, two molecules of **1** react together ~~in intermolecular fashion~~, forming three bonds, two heterocycles and a tetrasubstituted carbon stereocenters in a one-step operation with 100% atom economy.



Scheme 1. Gold(I)-catalyzed cascade reaction for the synthesis of [6,5] and [7,5]-fused bicyclic acetal **2** and **3**.

Our initial investigation was performed with **1a** as model substrate for optimization of the reaction conditions (Table 1, see SI for the full optimization). The first experiment was carried out in dichloroethane (DCE) as solvent in the presence of a pre-activated cationic gold(I) complex, the commercially available catalyst [(JohnPhos)Au(MeCN)][SbF₆] (**A**), at room temperature for 30 min (entry 1). Pleasingly, these reaction conditions afforded the furooxepine compound **3a** in 53% estimated yield. The structure of **3a** was unambiguously determined by ¹H and ¹³C NMR experiments. Nevertheless, a sub-product **4a**

was also formed with this reaction condition resulting either from a regioselective hydration of the triple bond due to the presence of water in our reaction mixture, either from the hydrolysis of the intramolecular hydroalkoxylation product.^[7] With this promising result in hand, we next optimized the reaction conditions.

Table 1. Optimization of the reaction conditions.

Entr y	Catalyst	Solvent	[1] mol/L	3a/4a (%) ^{a)}
1	Cat. A	DCE	0.102	53/32
2	Cat. A	DCE	0.205	63/26
3	Cat. A	DCE	0.41	70/22 ^e
4 ^b	Cat. A	DCE	0.41	81/6
5	Cat. A^c	DCE	0.41	65/17
8	Cat. B /AgOTf	DCE	0.41	65/19
11	Cat. C / AgSbF ₆	DCE	0.41	53/27
12	Cat. C / AgOTf	DCE	0.41	54/20
16	Cat. A	Dioxane	0.41	65/25
17	Cat. A	THF	0.41	19/23
18	Cat. A	DCM	0.41	55/14
19	Cat. A	HFIP ^d	0.41	45/25
20 ^b	Cat. A	MeCN	0.41	19/40

^{a)} Calculated yield by integration of the ¹H-NMR of the crude product relatively to the internal reference (caffeine).
^{b)} with 4 Å molecular sieves. ^{c)} 2 mol% ^{d)} HFIP : hexafluoroisopropanol. ^{e)} 63 % isolated yield for **3a**.

We first studied the influence of the concentration of **1a** in the reaction mixture (up to 0.82 mol/L) and we obtained our best results with 0.41 mol/L with 70 % estimated yield and 63 % isolated yield (entries 1-3 and SI). To decrease the amount of water present in the reaction mixture, 4 Å molecular sieves was added and we succeeded to reduce the amount of **4a** to obtain **3a** with 81% estimated yield (entry 4). Reducing the amount of **Cat. A** to 2 mol% gave similar results (entries 3 and 5). Poorer results were obtained with gold(I) catalysts bearing other phosphine ligands and NHC ligands (entries 8-12 and SI). Then, several solvents (1,4-dioxane, THF, DCM, HFIP, MeCN) were tested with the use of **Cat. A** as the best catalyst, without any improvement (entries 16-20). Eventually, the use of **Cat. A** in DCE at room temperature for 30 min in the presence of 4 Å

molecular sieves proved to be the best conditions of choice to obtain **3a** (entry 4, 81 % estimated yield). We then examined the scope of this new gold(I)-catalyzed process. As illustrated in Scheme 2, this transformation is efficient on a broad range of substrates **1** with yields between 20% and 74%. A requirement is to use aromatic or heteroaromatic substituted alkynes; terminal alkyne or methyl substituted alkyne gave complex mixtures. A variety of aryls exhibiting electron-donating or -withdrawing groups at the *meta* or *para* positions were well tolerated (**3b-3m**). With *ortho*-chloro substituted aryl groups, the steric hindrance hampers the reaction. Heteroaromatics such as furane, thiophene and benzothiophene gave modest results (30, 20 and 44% yield respectively for **3o**, **3p** and **3q**). For the scale-up reaction (up to 1 mmol of **1a**), we decided for economic reasons to use the optimized reaction conditions with only 2.5 mol% of **Cat. A** instead of 5 mol%, and we obtained **3a** with 74 % isolated yield. Crystals obtained from **3h** and **3k**, allow to unambiguously confirm their structure by X-ray crystallographic analysis (Figure 2).^[8] It is interesting to note that type **3** compounds are stable for months but sensitive to acid conditions.

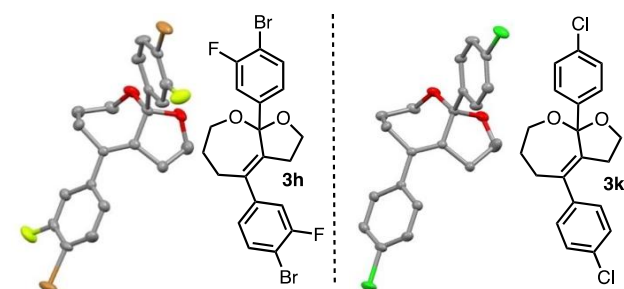
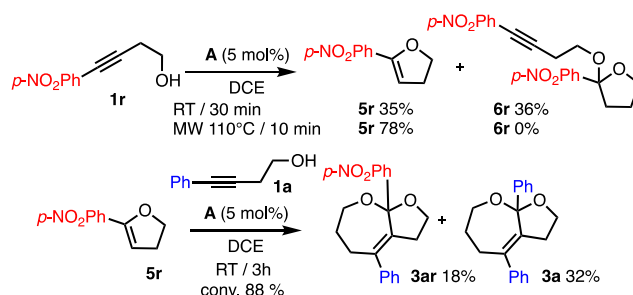
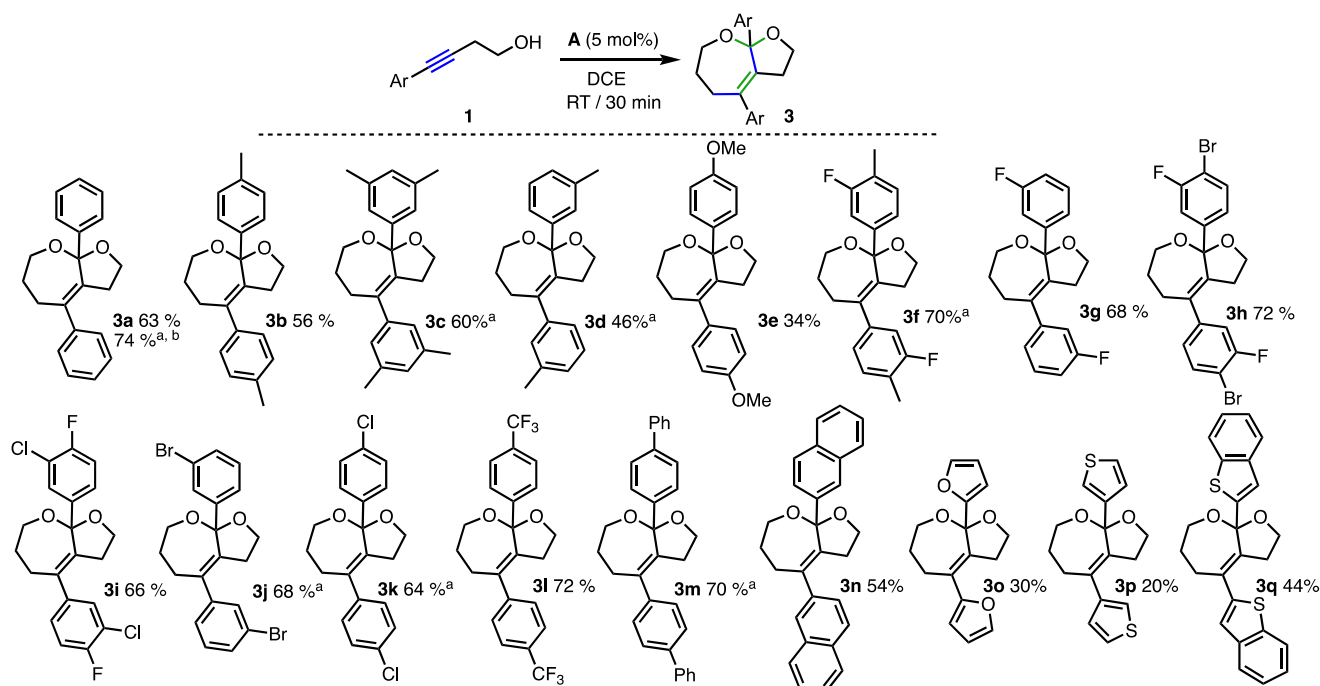


Figure 2. X-ray structures of furooxepines **3h** and **3k**. Hydrogen atoms are omitted for clarity.

During our investigations, when homopropargyl alcohol bearing a *para*-nitrosubstituted aryl group (**1r**) was used, we observed a mixture of two products (**5r** and **6r**, Scheme 3). Compound **5r** comes from an intramolecular hydroalkoxylation reaction of **1r** and **6r** from an intermolecular condensation between **5r** and **1r**. Surprisingly furooxepine **3r** was not observed in this case, even at higher temperature. These results have suggested us that type **5** and **6** compounds could be intermediaries in the formation of furooxepines **3**.

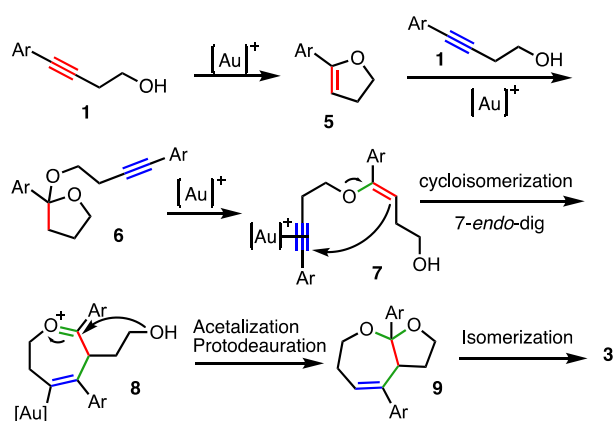


Scheme 3. **1r** reactivities and mechanistic investigation.



Scheme 2. Synthesis of furooxepine derivatives **3**. [a] with molecular sieves, [b] scale up with 2.5 mol%

To confirm this hypothesis, **5r** was subjected to gold reaction conditions in presence of **1a**. Within 3 hours, full conversion of **5r** was attained with furooxepines **3ar** and **3a** formed in respectively 18% and 32% yield. Therefore, we proposed the following mechanism to explain the formation of furooxepines **3** (Scheme 4).

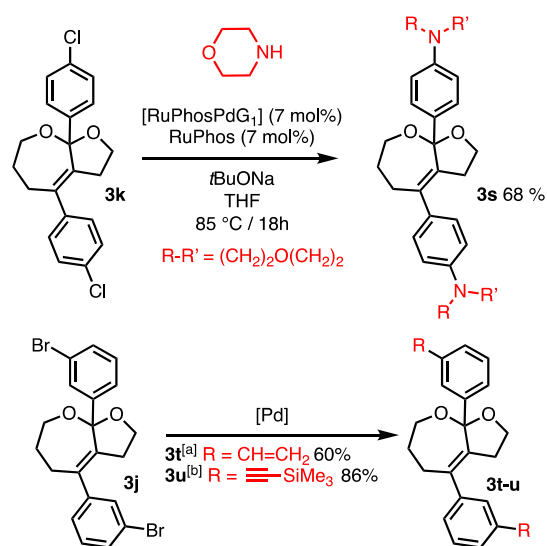


Scheme 4. Proposed mechanism for the formation of **3**.

The coordination of the homopropargyl alcohol **1** by the cationic gold(I) complex leads to the intramolecular hydroalkoxylation giving 2-phenyl-2,3-dihydrofuran **5** after a protodeauration. The last one reacts with a second molecule of **1**, giving **6** which undergoes a ring opening and generating the intermediate **7**.^[9] The previously formed 1,6-enyne **7** cyclizes via a 7-endo-dig cycloisomerization, leading

to the seven membered ring formation.^[10] An acetalization occurred, followed by a second protodeauration and an isomerization giving the desired furooxepine **3**.

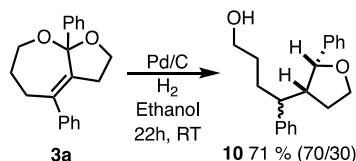
In order to increase the molecular diversity, we decided to introduce nitrogen group on those new scaffolds (scheme 5). Starting with furooxepine **3k**, a Buchwald reaction^[11] allowed us to form compound **3s** bearing a morpholine group with 68% yield. Other palladium couplings were used on **3j** allowing the formation of **3s** and **3t** with respectively a Stille and Sonogashira coupling.^[12]



Scheme 5. Functionalization. [a] Pd(PPh₃)₄ (10 mol%), vinyltributylstannane (3 eq.), toluene, 80°C, 16h. [b]

PdCl₂(PPh₃)₂ (5 mol%), CuI (5 mol%), PPh₃ (10 mol%), trimethylsilylacetylene (3 eq.), Et₃N (0.13 M), 70°C, 16h.

Moreover, hydrogenation reaction conditions were used starting from **3a** leading to the formation of two diastereoisomers **10** bearing tetrahydrofuran scaffolds (scheme 6). The stereochemistry of the cis-protons in both diastereoisomers of **10** was established by ¹H-NOESY experiments. A sequence of 7-membered ring opening reaction and the hydrogenations occurs giving those later compounds with 71 % overall yield and 70/30 ratio.



Scheme 6. Furooxepine reduction.

In conclusion, we have developed a gold-catalyzed domino reaction giving access to furooxepine derivatives of type **3**. The sequence includes a hydroalkoxylation, condensation, a 7-endo-dig cycloisomerization, an acetalization and an isomerization. 21 furooxepines are described with 20 to 74 % yields. It is also possible to introduce nitrogen group on the structure or to obtain tetrahydrofuran through post-functionalization of the structures **3**.

Experimental Section

In a dried MW tube under argon, homopropargylic alcohol (1 eq) was dissolved in DCE to a concentration of 0,41M. Then Echavarren catalyst **A** (0.05 eq) catalyst is added to the solution and the mixture was stirred 30 minutes at room temperature (20° C) and monitored by TLC (2/1 Heptane/AcOEt). Once TLC showed complete conversion of homopropargylic substrate, the reaction mixture was filtered through a pad of Celite with AcOEt as eluent and concentrated to give the crude product as an oil. After caffeine dosage in NMR, the latter was purified by flash column chromatography to afford the pure furooxepine **3**.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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