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Gold-catalyzed synthesis of oxepinones: an experimental mechanistic evidence

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ABSTRACT

The isolation of a bicyclic lactone and its room temperature isomerization in $CDCl_3$ to the expected oxepinone allows confirmation of a previously proposed mechanism for the gold-catalyzed synthesis of oxepinones from donor–acceptor alkynylcyclopropanes. However, the unsuccessful conversion of another bicyclic lactone into its corresponding oxepinone points out to a substrate-dependent mechanism.

The synthesis of seven-membered cyclic compounds remains as a highly challenging task,[1] much more than the formation of five- or six-membered cyclic structures, due to ring-strain and entropic reasons.[2] In particular, very few methods have been developed for the synthesis of the oxepin-2-one skeleton (especially when compared to the isoelectronic azepin-2-one), even though it is present in natural products, such as transtaganolides or basiliolides **1**–**6** (Fig. 1), which display appealing SERCA-ATPases inhibitory activities.[3]

On the other hand, we have taken advantage of the known properties of gold catalysts as π-acids for alkyne activation.[4] In this context, we have developed a novel cascade reaction consisting of a sequential intramolecular nucleophilic addition/cyclopropane ring-opening on alkynylcyclopropanes **7** bearing donor–acceptor (DA) substituents in the cyclopropane ring (push–pull cyclopropanes),[5] leading to oxepin-2-ones **8** (Scheme 1).[6] The scope of the process was found to be quite general and it furnishes good to excellent yields of oxepinones with R = alkyl, alkenyl and aryl groups. Remarkably, the cascade process takes place with complete regioselectivity under mild reaction conditions (room temperature) provided that the cyclopropane ring bears both a donor and acceptor substituents, due to the known intrinsic vulnerability of DA cyclopropanes to undergo ring-opening reactions.[7,8]

In the mechanism proposed in our original manuscript for the cascade sequence,[6] we suggested an initial activation of the triple bond of **7** by complexation of the gold catalyst to form intermediate **I** (Scheme 1). Intermediate **I** could then evolve by three different routes: (1) a regioselective 6-*endo*-*dig* nucleophilic addition of the carboxylic acid to the activated triple bond in **I**, which is probably favored over the 5-*exo*-*dig* by coordination of the methoxy group with the metal atom, would lead to **II** (Via A); a subsequent cyclopropane ring-opening would render seven-membered ring intermediate **III**, which after a final protodemetalation would give product **8** and would regenerate the catalyst. (2) Alternatively, cyclopropane ring-opening may happen prior to the nucleophilic attack to the triple bond on **I** and the formation of **III** would take place through acyclic intermediate **IV** (Via B). (3) The third option would imply a concerted mechanism with simultaneous nucleophilic attack and ring-opening (Via C).

During the optimization of the reaction conditions some cyclopropane ring-opening derived byproducts were isolated, such as lactone **9** or ketoacid **10**;[6] these findings suggest that the cyclopropane may undergo ring-opening prior to the nucleophilic addition to the triple bond, at least under specific reaction conditions (mainly the catalyst system employed). On the other hand, bicyclo[4.1.0]lactone **11** was also isolated as the minor product while exploring the scope of the reaction; this result proved that, at least in this case, the nucleophilic addition to the triple bond was previous to the cyclopropane ring-opening, thus pointing out to Via A as

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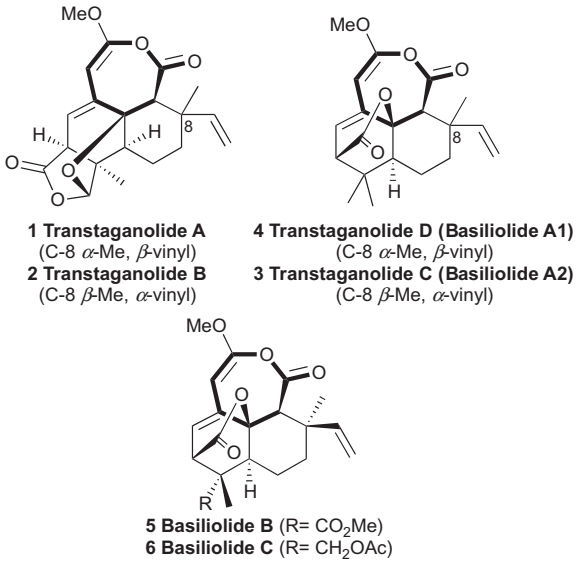
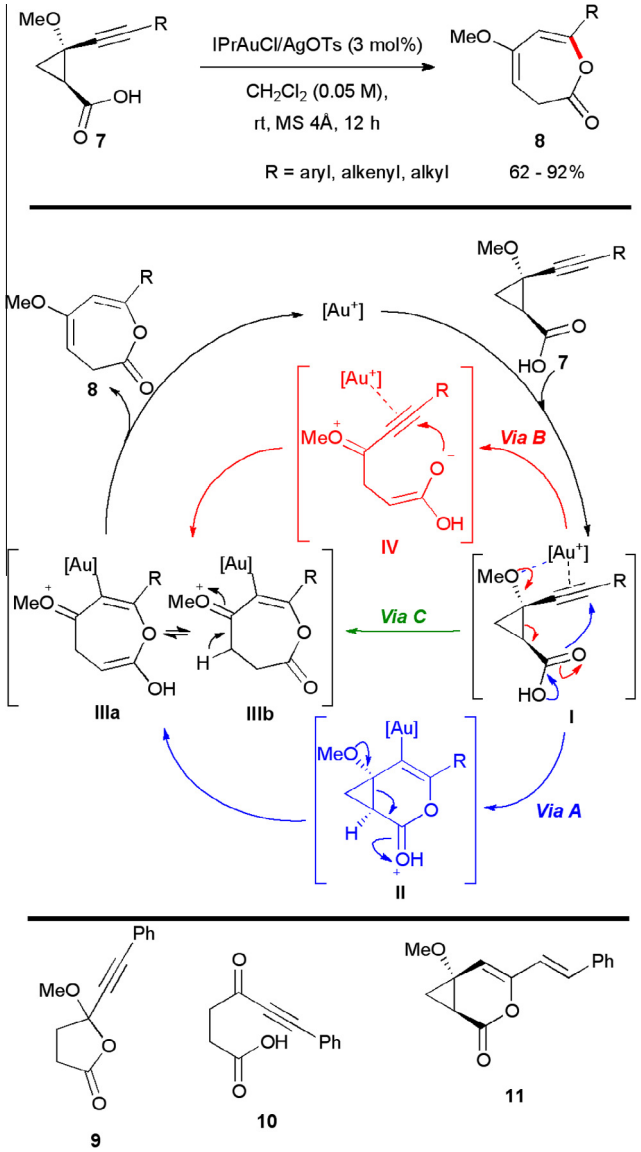


Figure 1. Natural products bearing the (dihydro)oxepin-2-one skeleton.



Scheme 1. State of the Art (Ref. 6).

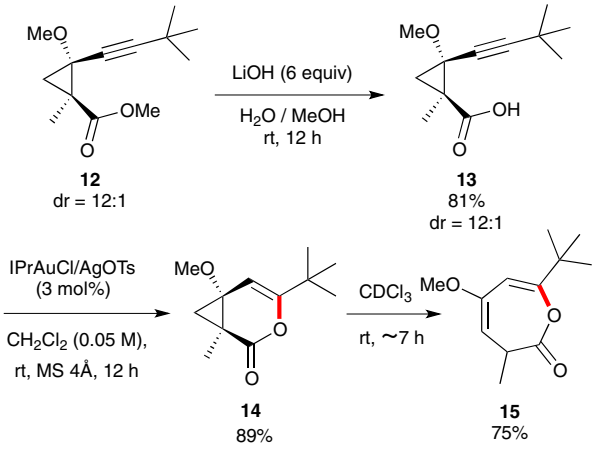
the most probable mechanism.[6] However, none of lactones **9** or **11** was later converted into the corresponding oxepinones.

So far, all the tested alkynylcyclopropanecarboxylic acids **7** displayed the carboxylic group as the only substituent at position 1 of the cyclopropane ring. We decided to check the effect of placing a second substituent at that position. To this end, alkynylcyclopropanecarboxylic acid **13** was synthesized in 12:1 diastereomeric ratio by basic hydrolysis of previously prepared methyl 2-(3,3-dimethylbut-1-yn-1-yl)-2-methoxy-1-methylcyclopropanecarboxylate **12**, derived from methyl methacrylate,[5] with lithium hydroxide at room temperature (81% yield). No epimerization was observed in this reaction. The treatment of alkynylcyclopropanecarboxylic acid **13** under the optimized reaction conditions for the formation of oxepinones [IPrAuCl/AgOTs (3 mol %), CH_2Cl_2, rt] led to bicyclic lactone **14** in 89% isolated yield (Scheme 2).[9] The minor diastereomer of **13** remained unreacted. It seems clear that 3-oxabicyclo[4.1.0]hepten-2-one **14** should be formed by a protodemetalation step from an intermediate analogous to **II** but bearing a methyl group at position 1. Unexpectedly, for this particular substrate **13**, the sequence cyclization/cyclopropane ring-opening did not take place under the optimized reaction conditions as no traces of the expected oxepinone **15** were detected.

However, while compound **14** was being characterized and its NMR data were being acquired in $CDCl_3$, its conversion into oxepinone **15** was observed in the NMR tube and it could be monitored. For instance, as shown in Figure 2, the intensity of signals of reference at 3.38 ppm (which corresponds to the methoxy group) and 5.51 ppm (belongs to the olefinic proton) of **14** diminished while two new signals, assigned to the corresponding hydrogen atoms in **15**, appeared with increasing intensity at 3.57 and 5.77 ppm. A NMR-recorded spectrum pointed out the complete disappearance of bicyclic lactone **14** after 439 min monitoring. Once the conversion finished, flash column chromatography allowed the recovery of oxepinone **15** in 75%.[10] Some other minor signals were also observed (see signal of reference at 3.50 ppm, Fig. 2), which suggest that oxepinone **15** may also undergo further transformation into a yet undefined product.

The conversion of **14** into **15** could be attributed to the acidity of $CDCl_3$, which has probably enhanced the electron-withdrawing ability of the ester carbonyl group and also, as a consequence, the 'push–pull' nature of the DA cyclopropane ring, thus favoring its ring-opening.

These findings are of relevance as the isolation of bicyclic lactone **14** and its subsequent transformation into oxepinone **15** clearly allows confirmation of Via A pathway in the previously proposed



Scheme 2. Synthesis and gold-catalyzed cyclization of alkynylcyclopropanecarboxylic acid **13**.