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Regioselective synthesis of oxepinones and azepinones by gold-catalyzed cycloisomerization of functionalyzed cyclopropyl alkynes†

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A regioselective synthesis of oxepinones and azepinones in good to excellent yields from alkynylcyclopropanecarboxylic acid derivatives is described. This novel cycloisomerization cascade process consists of a nucleophilic addition followed by a cyclopropane ring-opening, where both donor and acceptor groups are required as substituents of the cyclopropane ring.

The synthesis of seven-membered cyclic compounds remains as a highly challenging task in organic synthesis, despite the blooming development of powerful tools such as the RCM methodology.[1] In particular, very few methods have been developed for the synthesis of the oxepin-2-one skeleton, even though it is present in natural products displaying remarkable biological activities.[2] On the other hand, gold-catalyzed cycloadditions and cycloisomerizations have been widely explored in recent years.[3] In this regard, we have employed gold catalysis to prepare six-membered heterocycles (pyridines and dihydropyridones)[4] and carbocycles[5] from push–pull conjugated dienynes.[6] Alkynyl cyclopropanes have also recently served as starting materials for gold-catalyzed transformations.[7] In this context, we envisioned that alkynyl cyclopropanes bearing donor–acceptor (DA) substituents in the cyclopropane ring (push–pull cyclopropanes)[8] might offer a straightforward access to the oxepin-2-one skeleton, *via* an intramolecular cascade reaction involving a regioselective 6-*endo* nucleophilic attack of the carboxy group and the opening of the cyclopropyl ring (Fig. 1).[9] Cascade reactions are some of the most useful strategies for achieving synthetic efficiency,[10] and on the other hand, mild reaction conditions should be expected for this transformation due to the intrinsic vulnerability of DA cyclopropanes to undergo ring-opening reactions.[11]

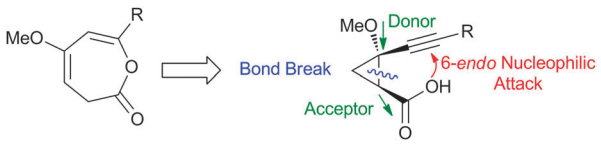
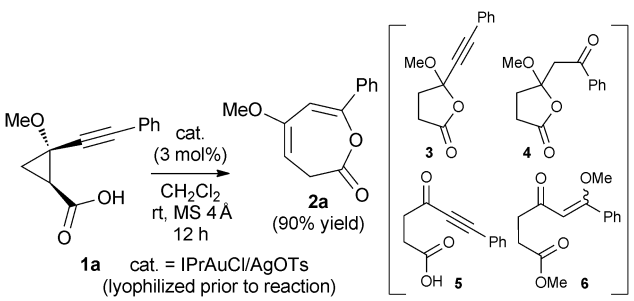


Fig. 1 Proposed synthetic strategy.

Compound **1a** was selected as a model system for checking the viability of the proposed strategy and a variety of parameters were screened. Due to the highly functionalized nature of the starting material several alternative reactions may occur, which makes the control of the selectivity an important issue in this transformation. Thus, up to four side products **3–6** were observed in variable amounts using different catalysts (Scheme 1).[12a] Gratifyingly, the combination IPrAuCl–AgOTs led to a completely selective reaction allowing the isolation of desired oxepin-2-one **2a** in a remarkable 90% yield provided that strictly anhydrous conditions are employed [both gold and silver complexes (or essentially, the hygroscopic silver salt) were lyophilised prior to carrying out the reaction, and MS of 4 Å were used] (Scheme 1).[12b]

With the proof of concept established, the scope of the reaction was checked. The optimized conditions shown to be useful for a wide range of DA alkynylcyclopropane carboxylic acids (Table 1). Thus, good to excellent yields were reached for oxepinones bearing aromatic substitutents with electron-donating (**2b–e**) or electron-withdrawing groups (**2f,g**) either in the *para* (**2b–d,f,g**), *meta* (**2c**) or *ortho* (**2e**) position, as well as heteroaromatics (**2h**). Alkenyl substituents



Scheme 1 Proof of concept.

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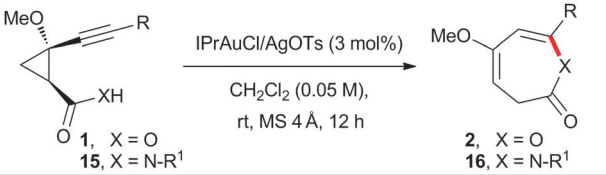
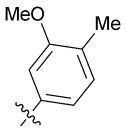
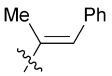
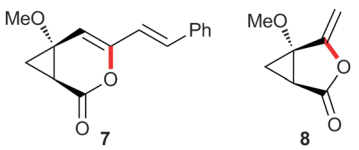
† Electronic supplementary information (ESI) available: Full experimental details (including the catalyst lyophilisation process), optimization of the reaction conditions, a proposal to explain the lack of reactivity of *trans*-DA alkynylcyclopropanes, and copies of ^{1}H- and ^{13}C-NMR spectra of both new starting materials and reaction products. See DOI: 10.1039/c3cc46238b

Table 1 Scope of the reaction



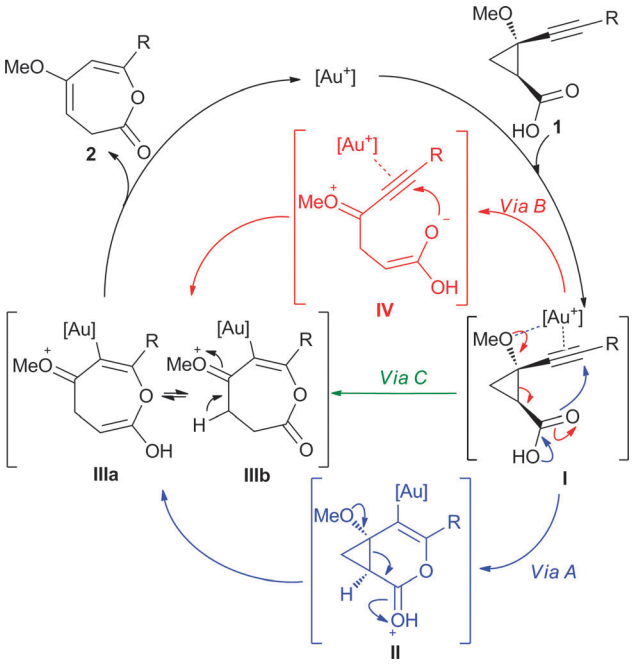
Entry	Product	X	R	Yield[a]
1	**2b**	O	*p*-(C_6H_4)-OMe	78
2	**2c**	O		84
3	**2d**	O	*p*-(C_6H_4)-Me	92
4	**2e**	O	*o*-(C_6H_4)-Me	72
5	**2f**	O	*p*-(C_6H_4)-Cl	75
6	**2g**	O	*p*-(C_6H_4)-CF_3	86
7	**2h**	O	Thiophen-2-yl	62
8	**2i**	O		82
9	**2j**	O	*n*-Bu	89
10	**2k**	O	Cyclopentyl	87
11	**2l**	O	*t*-Bu	74
12	**2m**	O	*E*-styryl	30[b]
13	**2m**	O	*E*-styryl	75[c]
14	**2n**	O	H	30[d]
15	**2n**	O	H	71[c,d]
16	**16a**	NH	Ph	85[e]
17	**16b**	NMe	*o*-(C_6H_4)-Me	76[e]
18	**16c**	N-*p*-(C_6H_4)-OMe	*p*-(C_6H_4)-Me	62[e]

[a] Isolated yields. [b] Bicyclo[4.1.0]lactone **7** (30%) was also isolated. [c] Reactions carried out in refluxing dichloromethane. [d] Combined yield of non-separated **2n** and **8** (ratio **2n**/**8**: 54/46, entry 14; 52/48, entry 15). [e] Reactions carried out in 1,2-dichloroethane (DCE) at 110 °C.



were also tolerated (**2i**), as well as primary, secondary or tertiary alkyl groups (**2j–l**). Remarkably, in all these examples the process took place with complete regioselectivity without the formation of the corresponding 5-*exo* adducts.

In our proposed mechanism,[13] we suggest an initial activation of the triple bond of **1** by complexation of the gold catalyst to form intermediate **I** (Scheme 2). This intermediate may evolve by three different routes. According to *Via A* a regioselective 6-*endo-dig* nucleophilic addition of the carboxylic acid to the activated triple bond in **I**, which is probably favoured over the 5-*exo-dig* by coordination of the methoxy group with the metal atom,[14] would lead to **II**. A subsequent cyclopropane ring-opening would render seven-membered ring intermediate **III**, which after a final protodemetalation would give product **2** and would regenerate the catalyst. Alternatively, as stated in *Via B*, cyclopropane ring-opening may occur prior to the nucleophilic attack to the triple bond on **I** and the formation of **III** would take place through acyclic intermediate **IV**. Finally, a concerted mechanism implying a simultaneous nucleophilic attack and ring-opening could also operate (*Via C*).

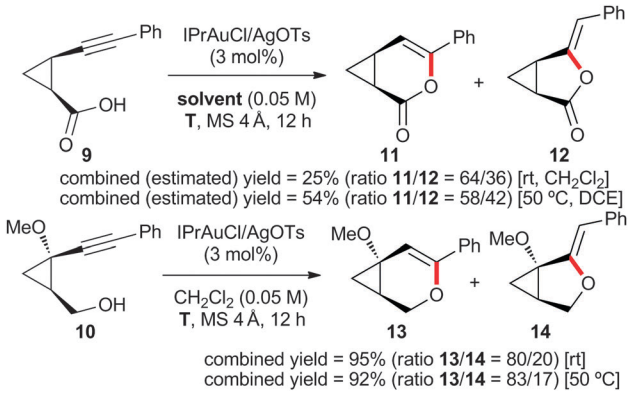


Scheme 2 Proposed mechanism.

We have obtained some evidence that led us to consider *Via A* as the most probable route (see Table 1, entries 12–15). First, reaction of substrate **1m** under the optimized reaction conditions afforded a 1 : 1 ratio of oxepinone **2m** and bicyclo[4.1.0]lactone **7** (entry 12), although **2m** could be selectively obtained in good yield when the reaction was performed at reflux (entry 13).

On the other hand, DA cyclopropane **1n**, bearing a terminal alkyne moiety, led to a mixture of oxepinone **2n** and bicyclo[3.1.0]-lactone **8**, coming from a 5-*exo-dig* cyclization, in an almost 1 : 1 ratio, both at room temperature and at reflux (Table 1, entries 14 and 15). The latter results are not surprising as, in gold-catalyzed reactions, the 5-*exo-dig* cyclization is expected to be favoured for terminal alkynes.[15] The structural features of lactones **7** and **8**, which retain the cyclopropane moiety, as well as the absence of **7** in the reaction of **1m** performed at reflux support the assumption that the nucleophilic addition to the triple bond takes place prior to the opening of the cyclopropane ring. Moreover, the diastereomeric DA cyclopropanes bearing the alkynyl group and the carboxylic acid in relative *trans* positions remain unaltered under the optimized reaction conditions,[12c] which is also in agreement with proposed *Via A*.

Next we turned our attention to evaluate the role of the substituents of the cyclopropane in the efficiency of the transformation. As pointed out before, we expected the DA nature of the cyclopropane to be a requirement for the ring opening under such mild conditions. To test our hypothesis, alkynyl cyclopropane **9**, which does not present an electron-donating group in its structure, and **10**, which lacks an electron-withdrawing substituent, were prepared and subjected to the optimized reaction conditions (Scheme 3). Bicyclic products still bearing the cyclopropane ring (**11–14**) were isolated in these experiments, even at 50 °C, thus supporting our thesis. Moreover, the higher levels of regioselectivity observed for the cycloisomerization of substrates **1** and **10** in comparison with **9**



Scheme 3 Reactions with non-DA alkynyl cyclopropanes.

seem to support the coordination between the methoxy group and the gold atom suggested in *Via A*.

Then, we decided to explore if this type of sequential reaction could also be used to prepare azepinones.[16] To our delight, alkynyl cyclopropanamides **15** proved to be active although they required warming at 110 °C to form azepinones **16** in good isolated yields (Table 1, entries 16–18). In these preliminary results, azepinones bearing *N*-H (**16a**), *N*-alkyl (**16b**) and *N*-aryl (**16c**) groups have been prepared. Not surprisingly, harsh conditions were required for the gold-catalyzed reaction sequence, probably due to difficulties associated with the intramolecular triple bond amidation step,[17] but in all cases the regioselectivity was complete towards the 6-*endo-dig* isomer.

In conclusion, we have developed a novel cascade reaction consisting of a sequential intramolecular nucleophilic addition/cyclopropane ring-opening on alkynyl DA-cyclopropanes leading to oxepin-2-ones in excellent yields. The cascade process takes place at room temperature with complete regioselectivity provided that the cyclopropane ring bears both donor and acceptor substituents. Moreover, the developed strategy could also be employed for the synthesis of other seven-membered heterocyclic compounds as we have demonstrated with isolobal azepin-2-ones.

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