Gold(I)-catalysed cycloisomerisation of 1,6-enynes into functionalised allenes†‡

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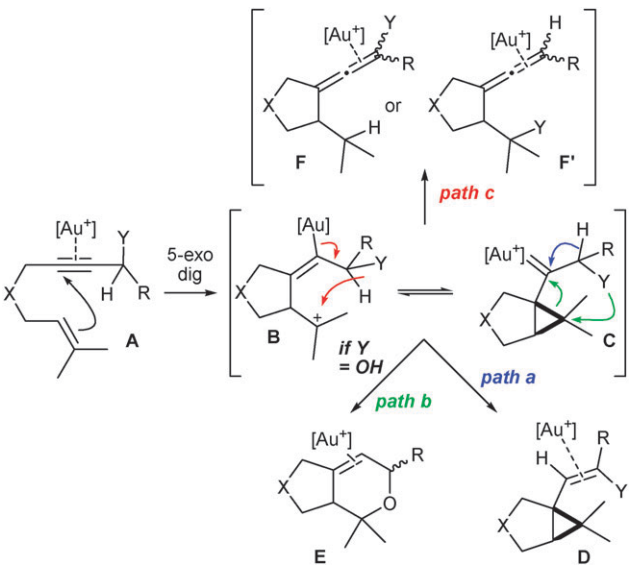
1,6-Enynes can be transformed into vinylidenecyclopentanes *via* gold-promoted 5-*exo* dig cyclisation followed by 1,5-hydride or -alkoxide shift.

Gold(I) and gold(III) salts have emerged lately as powerful catalysts for cycloisomerisations of polyunsaturated substrates.[1] Among them, 1,*n*-enynes (n = 5, 6, 7) have received considerable attention and proved to be versatile substrates for a myriad of selective transformations.[2] In spite of the numerous reports on that topic, we were interested in developing new synthetic opportunities, especially the direct transformation of enynes into allenes.[3] A few of these reactions have been described,[4] yet they are not coupled with ring formation.[5] One notable exception is the recently reported silver-catalysed hydrative cyclisation of enynols in wet CH_2Cl_2,[6] however, to the best of our knowledge, no investigation of that kind had been carried out using gold. Within this series, such a transformation would pave the way for cascade cyclisations,[7] since allenes are wonderful partners for a wide variety of transformations.[1,8]

The most classical cyclisation pathway for 1,6-enynes such as **A** is probably the 5-*exo* dig process,[9] which leads to carbocation **B**, in equilibrium with cyclopropylcarbene **C** (Scheme 1). 1,2-Hydride migration may follow to give vinylcyclopropane **D** (path a). Alternatively, if an hydroxy group is present, the formation of dihydropyran **E** is very likely to take place (path b). The challenging detour toward the formation of an allene framework such as **F** would be based on a 1,5-hydride shift, a process which could be assisted by an adjacent donor group Y (path c).[10] Conversely, if the donor group is also a good leaving one, one might expect its own migration to the carbocationic center to give **F′**. We report herein that the proper combination of tether (X), and propargylic substitution (Y) can funnel the reaction through this new pathway c.

We prepared a series of simple 1,6-enynes of type **1** exhibiting an electron-rich group Y susceptible of favouring the 1,5-hydride transfer (Table 1).§ Gratifyingly, enyne **1a**, which displays an oxygen tether and a propargyl acetate moiety, was selectively transformed into an allene of type vinylidenecyclopentane under Au(I) catalysis (entry 1). Yet this product arose from *1,5-OAc migration* and not from 1,5-H migration. Our second attempt rapidly revealed that the nature of the tether had a dramatic influence on the reaction outcome (entry 2). Indeed, the carbon-tethered enyne **1b** could be converted in good yield into allene **2b**, *this time as the result of a 1,5-H migration*! Not only did these two preliminary experiments validate our hypothesis, but they also showed that the two distinct types of allenes **2** and **2′** could be formed in a highly selective fashion. To gain further insight into this unprecedented type of cycloisomerisation, we next varied the nature of Y. The sterically crowded *tert*-butyldimethylsilyloxy group did not promote any type of 1,5-migration, enyne **2c** being converted into vinylcyclopropane **3c** as a sole product (entry 3). On the other hand, a phenyl group allowed the formation of allene **2d** in 75% yield (entry 4). Vinyl and 2-propenyl substituents also directed the reaction toward allenes **2e** and **2f**, respectively (entries 5 and 6).[11] Interestingly, the hydroxy group of **1g** also encouraged 1,5-H shift, giving rise to α,β-unsaturated aldehyde **2g** (entry 7). This product was accompanied by dihydropyran **4g**, which, although anticipated as the major product, was nonetheless obtained as the minor component of the mixture. Secondary alcohol



Scheme 1 Anticipated mechanistic scenario.

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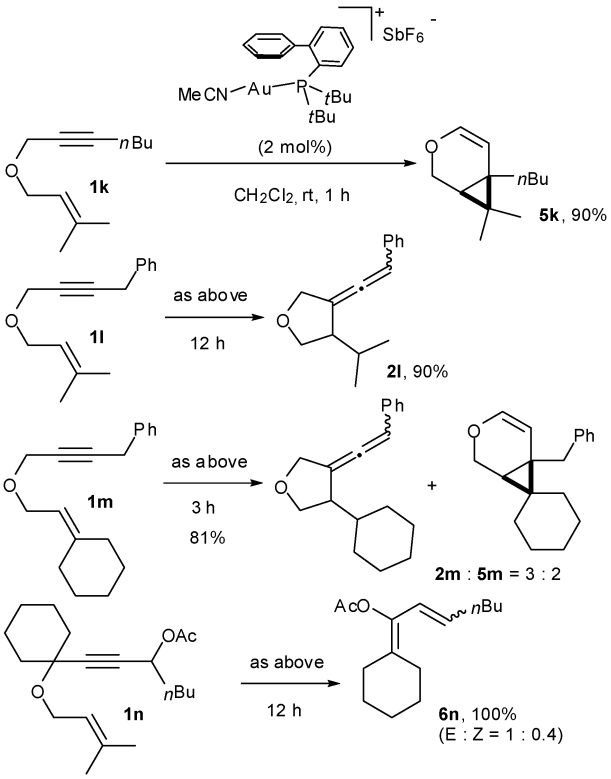
‡ Electronic supplementary information (ESI) available: Experimental section and NMR spectra. See DOI: 10.1039/b919240a

derivatives were briefly examined next. Compounds **2h** and **2′h** could be isolated from the reaction of acetate **1h** (entry 8). Although funnelled though the selective formation of allenes, no discrimination between 1,5-OAc and 1,5-H migration occurred in this case. Changing the acetate for a *p*-nitrobenzoate did not affect the reaction course (entry 9), nor did the nature of the catalyst, $AuClPPh_3/AgSbF_6$ and $AuPPh_3NTf_2$ giving the same 1 : 1 mixture in 60–70% in each case. Lastly, alcohol **1j** provided both the allene **2j** and the dihydropyran **4j** in almost equal amounts (entry 10).

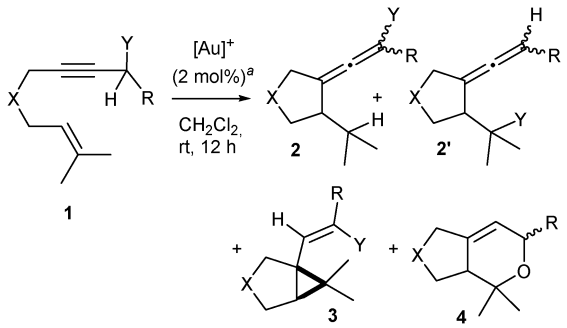
Clearly the gold catalyst promotes transformations that are very close-lying trajectories in terms of energy. This can be emphasized by the reaction of enyne **1k**, which, under the same experimental conditions used for the conversion of butyl-substituted enynes **1h–j**, transformed into a bicyclic product arising from 6-*endo* dig cyclisation in excellent yield (Scheme 2). Also the substitution at the double bond may affect the reaction course in such a way that *endo* products may ensue: whereas dimethylsubstituted enyne **1l** led to allene **2l** in 90% yield, the transformation of **1m**, which exhibits a methylene cyclohexane fragment, gave rise to a 3 : 2 mixture of the desired compound **2m** and of the *endo* cyclisation product **5m**. Lastly, enyne **1n** converted to diene **6n** which results from a mechanistically unclear elimination of 3-methylbutenal.

Due to its mechanistic value, the postulated 1,5-H migration process was probed by a deuterium labelling experiment during which compound [2D]-**1b** could be converted into

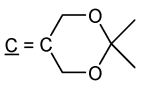


Scheme 2 Competitive reaction pathways.

Table 1 Scope and limitations of the title reaction



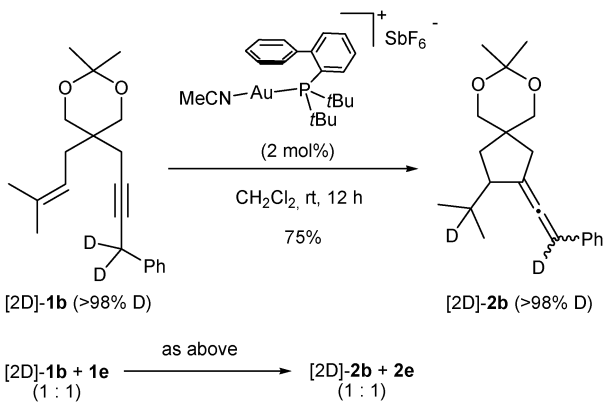
Entry	Substrate	Yield (% **2** : **2′** : **3** : **4**)
	R = H	
1	**1a**: X = O, Y = OAc	75 (0 : 1 : 0 : 0)[b]
2	**1b**: X = *C*, Y = OAc	78 (1 : 0 : 0 : 0)[c]
3	**1c**: X = *C*, Y = OTBDMS	80 (0 : 0 : 1 : 0)[d]
4	**1d**: X = *C*, Y = Ph	75 (1 : 0 : 0 : 0)
5	**1e**: X = $C(CO_2Me)_2$, Y = vinyl	71 (1 : 0 : 0 : 0)
6	**1f**: X = $C(CO_2Me)_2$, Y = C(Me)CH_2	71 (1 : 0 : 0 : 0)[e,f]
7	**1g**: X = *C*, Y = OH	60 (2 : 0 : 0 : 1)[g,h]
	R = *n*Bu	
8	**1h**: X = *C*, Y = OAc	83 (1 : 1 : 0 : 0)
9	**1j**: X = *C*, Y = OPNB	79 (1 : 1 : 0 : 0)
10	**1j**: X = *C*, Y = OH	85 (1 : 0 : 0 : 1.2)[h,i]



[a] [Au(MeCN)[P(*t*Bu)$_2$(2-biphenyl)]SbF_6. [b] 1 h. [c] 3 h. [d] 1 h. [e] Better yield using $AuClP(tBu)_3/AgSbF_6$. [f] 4 h. [g] 0 °C. [h] Products **2g** and **2j** are the corresponding aldehydes and ketones. [i] 2 h.

[2D]-**2b** (Scheme 3).[12] As expected, the reaction product exhibits a deuterated isopropyl group. Besides, the intramolecular nature of the migration was confirmed by reacting a 1 : 1 mixture of [2D]-**1b** with **1e**. No scrambling was observed, **2e** being isolated deuterium-free, while a complete deuterium incorporation was measured for [2D]-**2b**.

In conclusion, we have opened a new route to functionalised allenes by means of gold-catalysed cycloisomerisation of 1,6-enynes. Although we still do not control the factors that drive the migration process, we have shown that the reaction can occur in a selective fashion. Because of the strong influence of the nature of the tether on the reaction outcome, we believe that conformational aspects are a critical issue. Allylic interactions should also play a major role. Calculations are under way to shed light on that matter.



Scheme 3 Deuterium labelling experiments.

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Notes and references

§ Experimental procedure: (acetonitrile)[(2-biphenyl)di-*tert*-butylphos-phine]gold(I) hexafluoroantimonate (Aldrich, 11 mg) was added to a solution of **1e** (200 mg) in anhydrous DCM (0.025 M). The reaction progress was monitored by TLC. When the reaction was complete (*ca.* 12 h of stirring at rt), the mixture was filtered through a short pad of silica. The solvent was removed under vacuum, and the crude was purified by flash chromatography to afford **2e** (142 mg, 71% yield) as a colourless oil. IR (neat): ν = 2954, 1732, 1433, 1243, 898 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (dt, J = 17.2, 10.0, 1 H); 5.85 (m, 1 H); 5.14 (dd, J = 17.0, 4.0, 1 H); 4.94 (dd, J = 10.0, 6.8, 1 H); 3.73 (m, 6 H); 3.03–2.92 (m, 2 H); 2.66 (m, 1 H); 2.43 (dd, J = 12.8, 7.6, 1 H); 1.89 (q, J = 12.0, 1 H); 1.76 (m, 1 H); 0.94–0.83 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3 (2 C), 171.8 (4 C), 133.4 (2 C), 115.2 (2 C), 104.7 (2 C), 97.0 (2 C), 59.0 (2 C), 52.7 (4 C), 47.7 (2 C), 38.9 (2 C), 35.8 (2 C), 29.8 (2 C), 20.6 (2 C), 18.1 (2 C). HRMS (ES+) calculated for $C_{16}H_{22}O_4$ (M+Na): 301.1411; found 301.1405.

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