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Gold(I)-catalyzed [2 + 2 + 2] cycloaddition of allenamides, alkenes and aldehydes: a straightforward approach to tetrahydropyrans†

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Allenamides participate as two-carbon components in an intermolecular [2 + 2 + 2] cycloaddition with alkenes and aldehydes when treated with catalytic amounts of a phosphite gold complex. The reaction is highly regio- and chemoselective, and works with different types of alkenes, including styrenes, enol ethers or enamides, as well as with aromatic and aliphatic aldehydes. Accordingly, different types of 2,6-disubstituted tetrahydropyrans can be stereoselectively assembled in a single step from commercial or very accessible starting materials.

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Introduction

Transition metal catalyzed [2 + 2 + 2] cycloadditions constitute one of the most attractive methodologies for the construction of six-membered cyclic systems.¹ Despite the significant achievements reported in this field, intermolecular examples involving three different cycloaddition partners are extremely scarce, most probably because of the chemo- and regioselectivity issues associated with these multicomponent annulations.² The few examples reported so far involve the use of Rh, Ru, Nb or Ni catalysts and at least one alkyne as cycloaddition component.² Curiously, and despite the fact that gold catalysis has proven to be very efficient for unveiling novel types of cycloadditions,³ fully intermolecular [2 + 2 + 2] examples are almost unknown⁴ and, to the best of our knowledge, those of three different two-atom components are unprecedented.⁵

Herein, we are pleased to report a fully intermolecular gold-catalyzed [2 + 2 + 2] cycloaddition involving three different π -unsaturated components, namely an allene, an alkene and an aldehyde. The reaction takes place with excellent chemo- and regioselectivity and provides a straightforward and atom-economical entry to tetrahydropyrans (THPs). THPs, and in particular their 2,6-disubstituted counterparts, are privileged scaffolds that are present in a myriad of biologically active

molecules (Fig. 1).⁶ Although many elegant methods have been developed to construct these motifs,^{6,7} none of them encompass the coupling of three readily available components in a single catalytic annulation step.⁸

Over the past few years, we have developed different types of Au-catalyzed annulations,⁹ including a cycloaddition between allenamides and oxoalkenes that affords oxabridged medium-sized carbocycles (Scheme 1, eqn (1)).^{10,11} This annulation was proposed to proceed through the intermediate **I**,¹² which evolves to the product by the sequential formation of species **II** and **III**. On this basis, we then wondered whether it would be possible to achieve an annulation between the allenamide, alkene and carbonyl units in a fully intermolecular way, a process that would directly afford 2,6-disubstituted THPs like **4** (Scheme 1, eqn (2)). Despite the fact that the process could be viewed as an intermolecular version of the previous annulation, the timely assembly of three different components in a programmed manner is extremely challenging. Indeed, the feasibility of the reaction could be seriously compromised since more simple [2 + 2] adducts of type **5** and **6**,^{9c} acyclic products like **7**, or alternative [2 + 2 + 2] adducts (**8/9**) could be likewise expected.¹³

Results and discussion

We began our studies by analyzing the reactivity of allenamide **1a** with (*E*)- β -methylstyrene (**2a**) and benzaldehyde (**3a**)

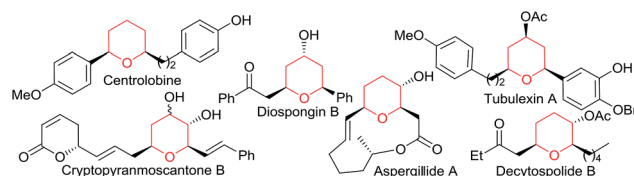


Fig. 1 Tetrahydropyran frameworks in biologically active products.

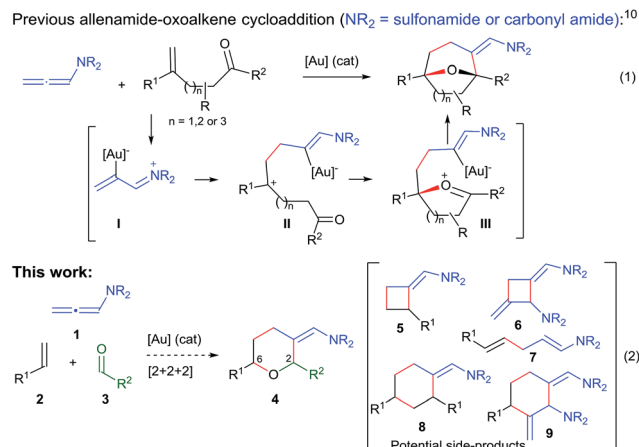
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Scheme 1 Previous gold-catalyzed cascade cycloadditions and current proposal.

(Table 1). Initial assays confirmed the expected difficulties for controlling the chemoselectivity of the process. Indeed, despite using an excess of the aldehyde (10 equiv.), and adding the allenamide over 2 hours, the gold complex **Au1** induced the formation of the $[2+2]$ allenamide dimerization adduct **6a** in 44% yield, together with a minor amount of the cyclobutane **5aa**,^{9c} resulting from the $[2+2]$ cycloaddition between **1a** and **2a** (entry 1). A $[2+2+2]$ adduct, eventually identified as the 2,6-*cis*

THP **4aaa**, was also detected, but only in trace amounts. Similarly, other frequently used gold catalysts such as $\text{Ph}_3\text{PAuNTf}_2$ or the NHC-gold complex **Au2** provided very low yields of the $[2+2+2]$ adduct **4aaa** (entries 2 and 3), with poor mass recovery balances in all these cases. Interestingly, when using the phosphite-gold complex **Au3**, we observed a significant increase in the global yield of the reaction, which provided **5aa** in 60% yield along with the $[2+2+2]$ adduct **4aaa** in 21% yield (entry 4). This last yield could be further improved up to 35% by carrying out the reaction at -45°C (entry 5).¹⁴

At this point, we envisioned that an additional stabilization of the putative carbocationic species of type **II**, resulting from the addition of the alkene to intermediate **I** (Scheme 1), could eventually facilitate its intermolecular capture by the aldehyde.

In consonance with this hypothesis, we were pleased to find that the use of α -methylstyrene (**2b**) instead of β -methylstyrene (**2a**) provided, under otherwise identical conditions, the desired THP in an excellent 98% yield, as a 2 : 1 mixture of 2,6-*cis* (**4aba**) and 2,6-*trans* (**4aba'**) diastereoisomers (entry 6).¹⁵ The same result was obtained when **1a** was added in one portion (entry 7). Gold catalysts such as JohnPhosAuNCMeSbF₆ (**Au1**), $\text{Ph}_3\text{PAuNTf}_2$ or IPrAuNCMeSbF_6 (**Au2**), also provided the desired $[2+2+2]$ cycloadduct **4aba** as the major adduct; however, yields and chemoselectivities were significantly lower than those obtained with the phosphite-gold catalyst **Au3** (entry 7 vs. 8–10). Moreover, with this latter catalyst the diastereoselectivity could

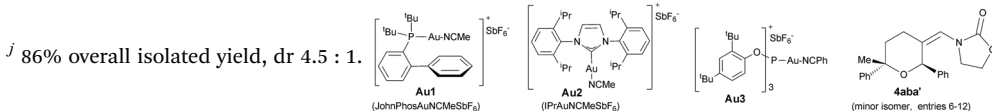
Table 1 Preliminary evaluation of the $[2+2+2]$ cycloaddition^{a,b}

Entry	[Au] (mol%)	2	R ¹	R ²	Conv.	4 (%)	5 (%)	6 (%)
1	Au1 (5%)	2a	H	Me	99%	4aaa , 2	5aa , 4	6a , 44
2	$\text{Ph}_3\text{PAuNTf}_2$ (5%)	2a	H	Me	60%	4aaa , 2	5aa , 0	6a , 7
3	Au2 (5%)	2a	H	Me	99%	4aaa , 15	5aa , 7	6a , 22
4	Au3 (2%)	2a	H	Me	99%	4aaa , 21	5aa , 60	6a , 8
5 ^c	Au3 (2%)	2a	H	Me	99%	4aaa , 35	5aa , 37	—
6	Au3 (2%)	2b	Me	H	99%	4aba , 98 ^d	—	—
7 ^e	Au3 (2%)	2b	Me	H	99%	4aba , 99 ^d	—	—
8	Au1 (2%)	2b	Me	H	99%	4aba , 51 ^d	5ab , 17	—
9	$\text{Ph}_3\text{PAuNTf}_2$ (2%)	2b	Me	H	99%	4aba , 77 ^f	5ab , 14	—
10	Au2 (2%)	2b	Me	H	99%	4aba , 80 ^d	5ab , 6	—
11 ^{e,g}	Au3 (2%)	2b	Me	H	99%	4aba , 98 ^h	—	—
12 ^{e,i}	Au3 (2%)	2b	Me	H	99%	4aba , 98 ^j	—	—

^a **1a** (1 equiv.) added over 2 h to a solution of **2** (2 equiv.), **3a** (10 equiv.), $[\text{Au}]$ (X mol%) and 4 Å MS, in CH_2Cl_2 at -15°C , unless otherwise noted.

^b Conversion of **1a** and yields of **4-6** determined by $^1\text{H-NMR}$ of the crude mixture using 1,3,5-(MeO)₃C₆H₃ as internal standard (IS). ^c Carried out at -45°C , (1 h). ^d Overall yield for the mixture of 2,6-*cis* (**4aba**) and *trans* (**4aba'**); dr = 2 : 1. The major isomer is that drawn. ^e **1a** added in one portion.

^f Overall yield. dr 1.5 : 1. ^g Carried out at -78°C , (1 h). ^h 90% overall isolated yield, dr 3.5 : 1 (**4aba** : **4aba'**). ⁱ Carried out in $\text{F}_3\text{C-Ph}$ at -25°C (4 h).



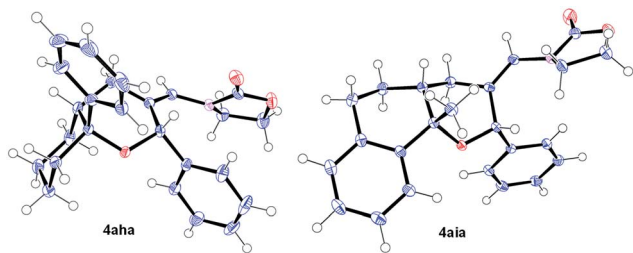


Fig. 2 X-ray structures of **4aha** (left, major isomer) and **4aia** (right).¹⁴

THPs (**4abf**, **4aff**, **4afg**) in yields above 90%. Moreover, the cycloaddition of the γ -substituted allenamide **1b** with an aliphatic aldehyde such as 2-methylbut-2-enal was also feasible, providing **4bbf** in 84% yield (dr 10 : 2 : 1).¹⁴

Overall, it is important to highlight that the current method constitutes one of the very few catalytic approaches that affords THPs featuring fully substituted carbons at the oxygen-adjacent position (e.g. C6).¹⁹ On the other hand, while the above reactions were carried out using a relatively large excess of the aldehyde, gratifyingly, we found that in most of the cases the reaction can be efficiently performed using an allenamide (**1**)/alkene (**2**)/aldehyde (**3**) molar ratio of 1/1.2/2 (Table 2, footnote *b*, results in parentheses). Thus, using these conditions, THPs **4aba**, **4afa**, **4aga**, **4ala**, **4abb**, **4abc**, **4afd**, **4abe**, **4abf** or **4afg** were obtained in yields varying from 60% to 90% (Table 2).²⁰ Additionally, more complex polycyclic systems like **4aha**–**4aja** could also be obtained in yields from 45% to 68%.¹⁴

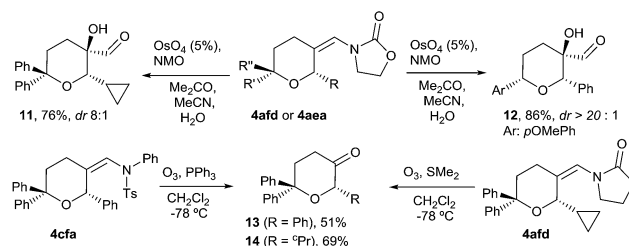
We next explored some manipulations of the *exo*-enamide moiety of the products (Scheme 2). Thus, THPs like **4afd** or **4aia** can be dihydroxylated to afford the α -hydroxy aldehydes **11** and **12** in excellent yields and with very good or complete diastereoselectivity (Scheme 2, eqn (1)). Moreover, both types of enamides (e.g. **4afd** and **4cfa**) could be easily converted into their corresponding ketones upon ozonolysis (Scheme 2, eqn (2)).

With regard to the mechanism of the annulation, the general proposal indicated in Scheme 1 could also apply for this intermolecular process; however, we found some results that were indicative of a more complex scenario. In particular, it is curious that while the [2 + 2] product (**5aa**) obtained from **1a** and *E*- β -methylstyrene retains the *trans* configuration of the alkene, the [2 + 2 + 2] adduct **4aaa** displays these groups in a *cis* disposition (Table 1, entry 5). On the contrary, polycyclic [2 + 2 + 2] adducts like **4aha**, **4aia** or **4aja** retained the configuration of the parent alkene. To shed light on this divergence, we carried out the cycloaddition of **1a** and pentanal with the *trans*-deuterated styrene *d*-*E*-**2c** (Scheme 3). As expected, the reaction provided a mixture of the [2 + 2 + 2] and [2 + 2] adducts **d**-**4acb** (38% yield) and **d**-**5ac** (43% yield), respectively. Interestingly, **d**-**5ac** incorporates the Ph and the deuterium atom in a *trans* disposition, whereas the [2 + 2 + 2] adduct, **d**-**4acb**, holds these groups in a *cis* arrangement. These results strongly suggest the formation of an intermediate of type **II** that preserves the stereochemical information of the alkene due to an stabilizing electrostatic interaction between the gold atom and the benzylic carbocation (Scheme 3).²¹ A subsequent nucleophilic *anti* attack of the

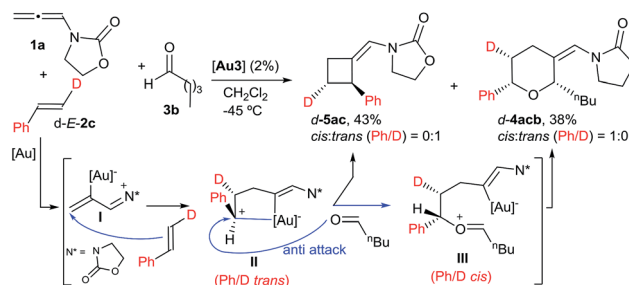
carbonyl moiety would lead to intermediate **III** and, eventually, to the product **d**-**4acb**. The preferential formation of this THP with the C2 and C6 substituents in *cis* is in agreement with a transition state that places these groups in equatorial disposition (Prins-like cyclization from **III** to **4**). On the other hand, if species **II** collapses to render a [2 + 2] adduct, the Ph and the D atom would retain the initial *trans* arrangement, as observed in **d**-**5ac**.

We also analysed the cycloaddition with deuterated α -methylstyrene (**d**-**2b**) as a model for α -substituted alkenes (Scheme 4). Curiously, the expected [2 + 2 + 2] isomeric adducts **d**-**4abb** and **d**-**4abb'** were obtained as mixtures of *cis/trans* (Ph/D) isomers. Accordingly, an acyclic carbocation species like **II'** or, alternatively, a fast equilibrium between the Ph/D-*trans* and *cis* intermediates **II** and **II''**, could account for this result.^{22,23} Considering this proposal, the exclusive formation of the *cis*-fused polycyclic THPs **4aha**–**4aja** from cyclic alkene precursors can be also understood.

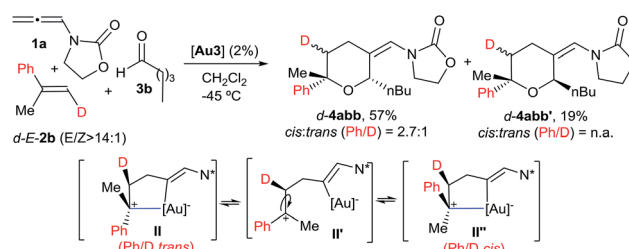
Finally, we carried out the above cycloadditions of Schemes 3 and 4 using the NHC–gold catalyst **Au2**, instead of **Au3**. Not unexpectedly, lower chemoselectivities and yields of the



Scheme 2 Functionalization of the *exo*-enamide moiety.



Scheme 3 Cycloaddition of *d*-*E*-**2c** and the proposed key intermediate **II**.



Scheme 4 Cycloaddition of *d*-*E*-**2b** and the proposed key intermediate **II'**.



corresponding [2 + 2 + 2] adducts were obtained in both cases but, interestingly, the stereochemistry of each deuterated cycloadduct (d-**4acb**, d-**5ac** and d-**4abb**), turned out to be identical to that obtained with **Au3**.¹⁴ Thus, the σ -donor or π -acceptor characteristics of the ligand at the gold atom do not seem to significantly affect the nature of the intermediate of type **II**.

Conclusions

In summary, we have developed a gold-catalyzed fully intermolecular [2 + 2 + 2] cycloaddition that constitutes one of the few transition metal catalyzed annulations involving three different π -unsaturated components. The process shows a broad scope with regard to the alkenes and aldehydes that can be used, and provides an efficient, atom-economical and stereoselective access to a variety of 2,6-disubstituted THPs from easily accessible or even commercially available materials.

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- When a diastereoisomeric mixture is formed in the reactions of Table 2, the 2,6-*cis* and *trans* isomers could usually be separated by standard chromatography. ESI.†
- The ring fusion was exclusively *cis* in all these polycyclic systems. Therefore, dr refers to the substituents at the 2,6-THP positions.
- An α -alkyl-substituted allenamides such as 3-(buta-2,3-dien-2-yl)oxazolidin-2-one provided a complex mixture of products.
- (a) Previously reported approaches are essentially limited to the formation of THPs with monosubstituted C2 or C6



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- 23 Similarly, the cycloaddition of an electron-rich styrene such as *trans*-deuterated *p*-methoxystyrene (*d-E-2e*) with **1a** and benzaldehyde provided *d-4aea* (64% yield) and traces of the [2 + 2] adduct *d-5ae*, both as almost equimolar mixtures of *cis* and *trans* (*p*MeOPh/D) isomers.¹⁴ Thus, an intermediate of type **II'** (or an equilibrium between the *cis* and *trans* cyclic isomers **II**, Scheme 4) might also operate in this case.

