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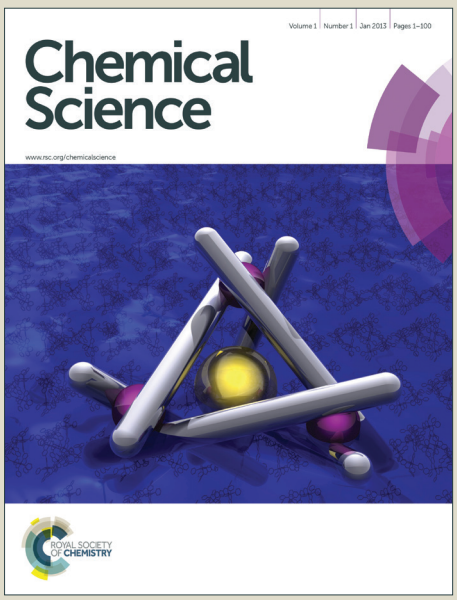

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Gold(I)-catalyzed [2+2+2] Cycloaddition of Allenamides, Alkenes and Aldehydes: A Straightforward Approach to Tetrahydropyrans

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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.

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 so far reported involve the use of Rh, Ru, Nb or Ni catalysts and, at least, one alkyne as cycloaddition component.[2] Curiously, and despite gold catalysis has proven to be very efficient for unveiling novel types of cycloadditions,[3] fully intermolecular [2 + 2 + 2] examples are almost unknown[4] 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 the 2,6-disubstituted counterparts, are privileged scaffolds that are present in a myriad of biologically active molecules (Figure 1).[6] Although many elegant methods have been developed to construct these motifs,[6,7] none of them encompasses the coupling of three readily available components in a single catalytic annulation step.[8]

During the last 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, eq 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, eq 2). Despite 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]

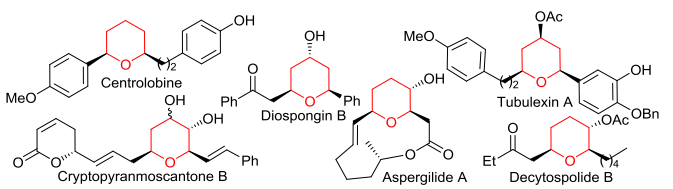
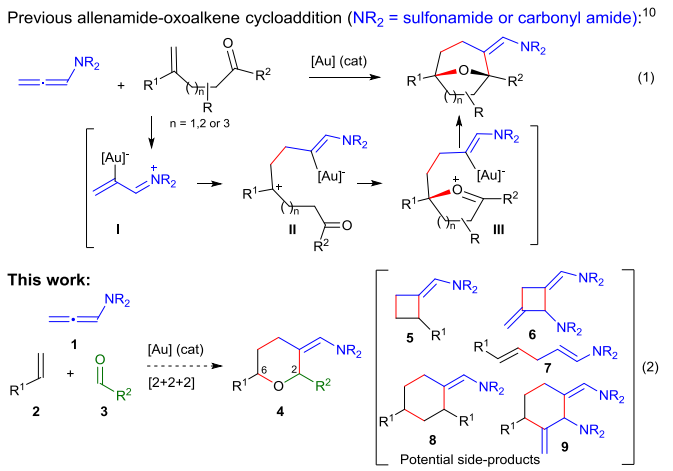


Figure 1 Tetrahydropyran frameworks in biologically active products.

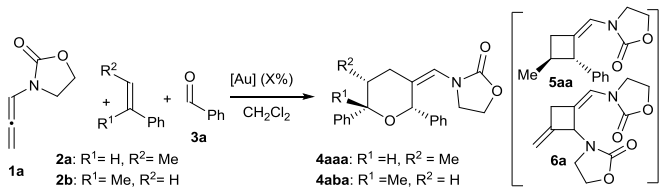


Scheme 1 Previous gold-catalyzed cascade cycloadditions and current proposal.

Results and discussion

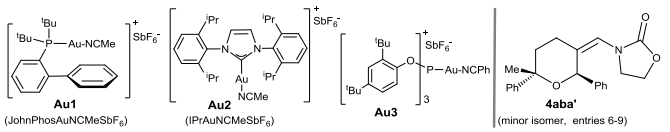
We began our studies by analyzing the reactivity of allenamide **1a** with (*E*)-β–methylstyrene (**2a**) and benzaldehyde (**3a**) (Table 1). Initial assays confirmed the expected difficulties for controlling the chemoselectivity of the process. Indeed, despite using an excess of the aldehyde (10 equiv), 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**,[8b] 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 $Ph_3PAuNTf_2$ 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 of 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 ºC (entry 5).[14]

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	$Ph_3PAuNTf_2$ (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	$Ph_3PAuNTf_2$ (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), [Au] (X mol%) and 4Å MS, in CH_2Cl_2 at -15 ºC, unless otherwise noted. [b] Conversion of **1a** and yields of **4-6** determined by ^{1}H-NMR of the crude mixture using 1,3,5-$(MeO)_3C_6H_3$ as internal standard (IS) [c] Carried out at -45 ºC, (1 h). [d] *dr* (2,6-*cis* : *trans*) = 2 : 1; the major isomer is that drawn. [e] **1a** added in one portion. [f] *dr* 1.5 : 1; [g] Carried out at -78 ºC, (1 h). [h] 90% isolated yield, *dr* 3.4:1 (**4aba** : **4aba'**). [i] Carried out in F_3C-Ph at -25 ºC (4 h) [j] 86% isolated yield, *dr* 4.5:1.



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 JohnPhosAuNCMeSbF$_6$ (**Au1**), $Ph_3PAuNTf_2$ or IPrAuNCMeSbF$_6$ (**Au2**), also provided the desired [2 + 2 + 2] cycloadduct **5aba** as the major adduct; however, yields and chemoselectivities were significantly lower to those obtained with the phosphite-gold catalyst **Au3** (entry 7 *vs* 8-10). Moreover, with this latter catalyst the diastereoselectivity could be improved by either performing the reaction at -78 ºC (*dr* 3.5:1, 90% isolated yield, entry 11) or by using α,α,α-trifluorotoluene as solvent (*dr* 4.5:1, 86% yield, entry 12).

With these results in hand, we next analyzed the scope of the process (Table 2). In consonance with the performance of β–methylstyrene (**2a**, Table 1, entry 5), the cycloaddition of styrene (**2c**) with **1a** and benzaldehyde provided the desired 2,6-disubstituted THP (**4aca**) in a moderate 37% yield, but with complete 2,6-*cis* selectivity (**5ac** was also isolated in 46% yield). Gratifyingly, use of styrenes with an electron-donating groups (e.g. *p*-MeO or *o*-MeO) allowed to significantly improve the chemoselectivity, so the corresponding THPs, **4ada** and **4aea**, were isolated in good yields (60-65% yield) and with complete 2,6-*cis* diastereoselectivity.

On the other hand, the cycloaddition with α-phenylstyrene provided the desired THP (**4afa**) in an excellent 86% yield, whereas the use *exo*-methylenes such as 1-methylene-tetrahydronaphthalene allowed an efficient access to spirotetrahydropyran derivatives like **4aga**, which was isolated in an excellent 94% yield (*dr* 1.5:1).

Remarkably, cyclic alkene derivatives were also excellent partners for this process. Thus, the cycloadditions of allenamide **1a** and benzaldehyde with 1-phenylcyclohexene, 4-methyl-1,2-dihydronaphthalene or 3-methyl-1H-indene, provided the corresponding THPs (**4aha**-**4aja**) in good yields (57 – 84% yield) and moderate (**4aha**) or complete (**4aia**-**aja**) stereoselectivity.[16] X-ray analysis of crystals of **4aha** and **4aia** unambiguously confirmed their structures and relative stereochemistry (Figure 2).[17]

We next explored the use of alternative electron-rich alkenes. Gratifyingly, the cycloaddition could also be performed with enol ethers such as 2-methoxyprop-1-ene or ethoxyethene, to obtain the corresponding cyclic acetals (**4aka**-**4ala**) with moderate to good yields. Similarly, the cycloaddition between **1a**, **3a** and 1-vinylpyrrolidin-2-one was also feasible, providing the cyclic hemiaminal ether **4ama** in 45% yield and with complete diastereoselectivity.

These annulations are also feasible with other allenamides. For instance, the reaction of γ-methyl-substituted allenamide **1b**

(see Table 2, footnote) with α–methylstyrene and benzaldehyde provided the [2 + 2 + 2] adduct **4bba**, featuring three new stereogenic centers, in 70% yield and with excellent diastereoselectivity (*dr* 11 : 1).[18] On the other hand, *N*-tosylphenyl allenamides such **1c** were also suitable partners. Thus, the [2 + 2 + 2] adduct **4cfa**, resulting from the cycloaddition of **1c**, benzaldehyde and α-phenylstyrene was obtained in 77% yield, whereas the adduct **4cka**, from 2-methoxyprop-1-ene, was obtained in 84% yield and, importantly, with complete 2,6-*cis* stereoselectivity.

Remarkably, the scope of the method is not limited to benzaldehyde. Indeed, the reaction of α-methylstyrene, allenamide **1a** and an aliphatic aldehyde such as pentanal led to the desired adduct, **4abb**, in 97% yield (*dr* 3:1). Other aldehydes such as isobutyraldehyde, cyclopropanecarbaldehyde or pent-4-enal also gave the THPs **4abc**-**4abe** in excellent yields. α,β-Unsaturated aldehydes such as 2-methylbut-2-enal or methacrolein (**3g**) also participated in the annulation yielding the desired 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 under parenthesis). Thus, using these conditions, the 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]

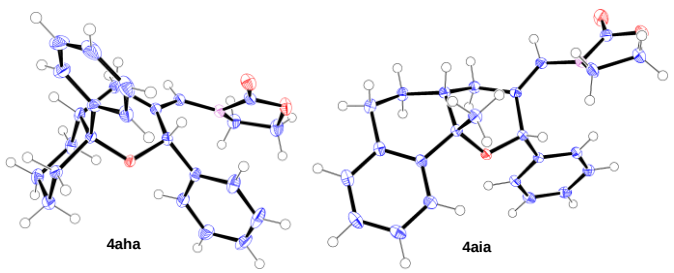
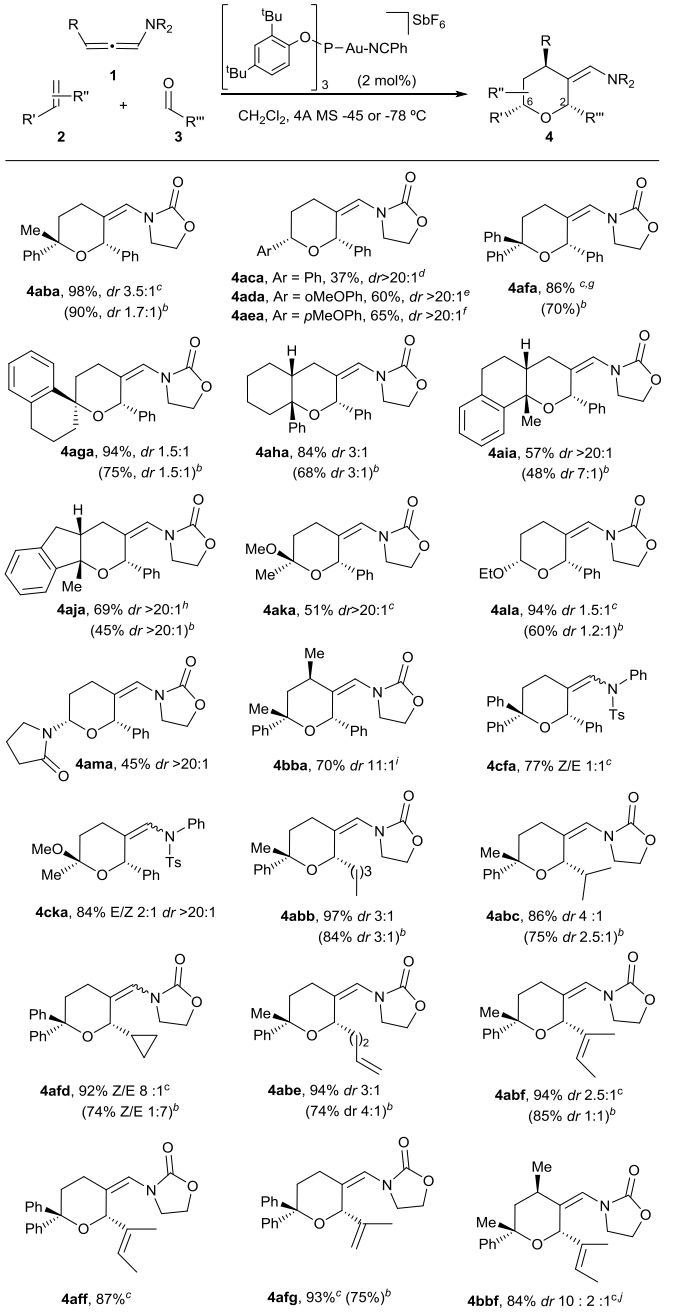


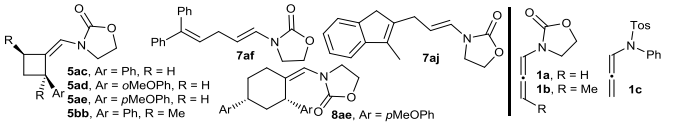
Figure 2 X-Ray structures of **4aha** (left, major isomer) and **4aia** (right).[14]

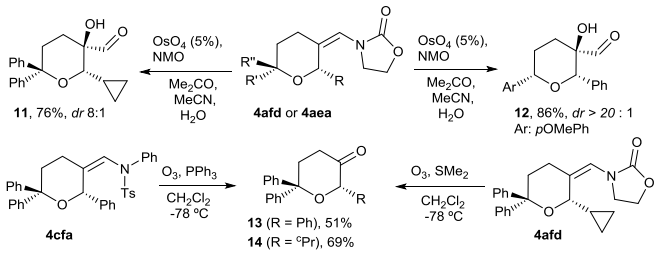
We next explored some manipulations of the *exo*-enamide moiety of the products (Scheme 2). Thus, THPs the like **4afd** or **4aea** can be dihydroxylated to afford the α-hydroxo aldehydes **11** and **12** in excellent yields and with very good or complete diastereoselectivity (Scheme 2, eq. 1). Moreover,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

Table 2 Scope of the Au-catalyzed [2 + 2 + 2] intermolecular cycloaddition[a,b]



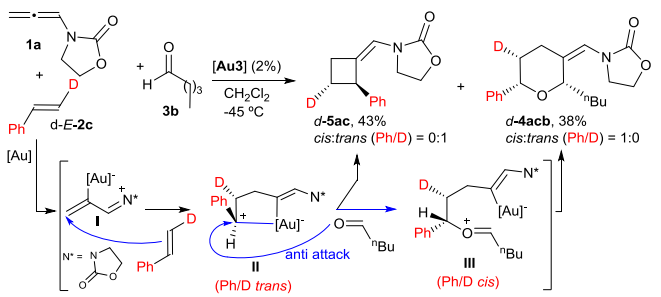
[a] **1** (1 equiv) added to a solution of **2** (2 equiv), aldehyde (10 equiv), [**Au3**] (2 mol%) and 4Å MS, in CH_2Cl_2 at -45 ºC, unless otherwise nwoted. Conversions > 99% (^{1}H-NMR). When a mixture of 2,6-isomers is formed, the major is that drawn. [b] Carried out at -45 ºC with a **1** / **2** / **3** molar ratio of 1 / 1.25 / 2. [c] Carried out at -78 ºC. [d] 45% of **5ac** was also isolated. [e] 21% of **5ad** was also isolated. [f] Traces of **5ae** and **8ae** (5% yield) were also isolated. [g] 5% yield of **7af** was also isolated. [h] 5% yield of **7aj** was also isolated. [i] 17% yield of **5bb** was also isolated. [j] For the structure of the minor isomers, see the ESI.





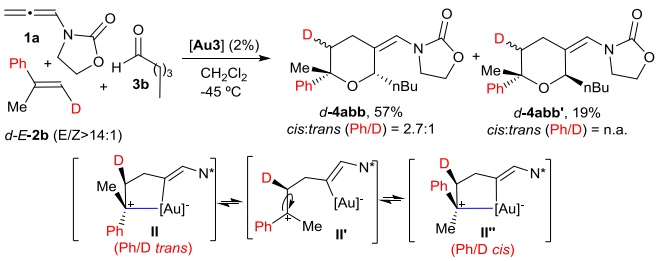
Scheme 2 Functionalization of the *exo*-enamide moiety.

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). 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 4).[21] A subsequent nucleophilic *anti* attack of the carbonyl moiety would lead intermediate **III** and, eventually, to the product *d*-**4acb**. The preferential formation of this THP with the C2 and C6 substituents in *cis* disposition, 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**.



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

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 easily understood.



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

Finally, we carried out the above cycloadditions of Schemes 4 and 5 using the *NHC*-gold catalyst **Au2**, instead of **Au3**. Not unexpectedly, lower chemoselectivities and yields of the 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 gold 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 high 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 very accessible or even commercially available materials.

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Notes and references

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† HF and IV equally contributed to this work. Electronic Supplementary Information (ESI) available: [Characterization data and experimental procedures]. See DOI: 10.1039/b000000x/

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11 For a review on allenamides, see: T. Lu, Z. Lu, Z. X. Ma, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2013, **113**, 4862.

12 a) S. Montserrat, H. Faustino, A. Lledós, J. L. Mascareñas, F. López and G. Ujaque, *Chem.-Eur. J.* 2013, **19**, 15248. See also: (b) Y. Horino, Y. Takata, K. Hashimoto, S. Kuroda, M. Kimura and Y. Tamaru, *Org. Biomol. Chem.*, 2008, **6**, 4105; (c) M. C. Kimber, *Org. Lett.*, 2010, **12**, 1128.

13 (a) [2+2] adducts of type **5** and **6** were previously reported, see ref. 9c; For addition products related to **7**, see: (b) A. W. Hill, M. R. Elsegood and M. C. Kimber, *J. Org. Chem.*, 2010, **75**, 5406.

14 See the Electronic Supplementary Information for further details.

15 (a) The [2 + 2] adducts **5ab**, **6a**, or other side-products, were not detected in the crude mixture (^{1}H-NMR); (b) The structure and relative stereochemistry of both THP isomers (**4aba** / **4aba'**) were established by NMR and, additionally, those of the major isomer (**4aba**), with the Ph groups in *cis*, were further confirmed by X-ray (CCDC 1038447).[14]

16 The ring fusion was exclusively *cis* in all these polycyclic systems. Therefore, *dr* refers to the substituents at the 2,6-THP positions.

17 CCDC 1038448 (for **4aha**) and CCDC 1038449 (for **4aia**).[14]

18 An α-alkyl-substituted allenamides such as 3-(buta-2,3-dien-2-yl)oxazolidin-2-one provided a complex mixture of products.

19 (a) Previously reported approaches are essentially limited to the formation of THPs with monosubstituted C2 or C6 carbons,[6a] something that significantly facilitates a high stereoselection; For isolated catalytic examples yielding products with fully substituted-C2 or C6 carbons, see: (b) M. Jacolot, M. Jean, N. Levoin and P. van de Weghe, *Org. Lett.*, 2012, **14**, 58; (c) M. P. Castaldi, D. M. Troast and J. A. Porco Jr, *Org. Lett.*, 2009, **11**, 3362; (d) J. S. Yadav, B. V. Subba Reddy, G. G. K. S. Narayana Kumar and S. Aravind *Synthesis*, 2008, 395; (e) When a diastereoisomeric mixture is formed (Table 2) the 2,6-*cis* and *trans* isomers could be usually separated by standard chromatography.[14]

20 **4aba** can even be obtained using a 1:1:1 ratio in 86% yield (*dr* 1.8:1).

21 (a) A. Z. Gonzalez, D. Benitez, E. Tkatchouk, W. A. Goddard and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 5500; (b) See also ref 12a.

22 The preferential formation of the THP **4abb**, is also in agreement with a preferred *Prins*-like transition state that holds the bulkier groups at C2 and C6 in equatorial disposition.

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.