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Gold(ı)-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

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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 twoatom components are unprecedented.⁵

Herein, we are pleased to report a fully intermolecular goldcatalyzed [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 atomeconomical 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

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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

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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 mediumsized 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 $Ph_3PAuNTf_2$ 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 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), Ph₃-PAuNTf₂ or IPrAuNCMeSbF₆ (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 + 2]	cycloaddition ^{a,}	9
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	o, IÍ IÍ	$R^{2} + R^{1} + R^{1}$ 1a 2a : R ¹ = H, R ² = 2b: R ¹ = Me, R ²	O [Au] + ↓ Ph CH 3a Me 2ª= H	(X%) ₂ Cl ₂ R ¹ + Ph ⁴ 4aaa: R ¹ + 4aba: R ¹	Ph = H, R2 = H	$ \begin{array}{c} $		
Entry	[Au] (mol%)	2	R^1	R^2	Conv.	4 (%)	5 (%)	6 (%)
1	Au1 (5%)	2a	Н	Ме	99%	4aaa , 2	5aa, 4	6a , 44
2	$Ph_3PAuNTf_2$ (5%)	2a	Н	Me	60%	4aaa , 2	5aa , 0	6a , 7
3	Au2 (5%)	2a	Н	Me	99%	4aaa , 15	5aa, 7	6a , 22
4	Au3 (2%)	2a	Н	Me	99%	4aaa , 21	5aa , 60	6a , 8
5 ^c	Au3 (2%)	2a	Н	Me	99%	4aaa , 35	5aa, 37	_
6	Au3 (2%)	2 b	Me	Н	99%	4aba , 98 ^d	—	_
7 ^e	Au3 (2%)	2 b	Me	Н	99%	4aba , 99 ^d	—	_
8	Au1 (2%)	2b	Ме	Н	99%	4aba , 51 ^d	5ab, 17	_
9	$Ph_3PAuNTf_2$ (2%)	2 b	Me	Н	99%	4aba , 77 ^f	5ab , 14	—
10	Au2 (2%)	2b	Ме	Н	99%	4aba , 80 ^d	5 ab , 6	_
$11^{e,g}$	Au3 (2%)	2 b	Ме	Н	99%	4aba , 98 ^h	—	—
$12^{e,i}$	Au3 (2%)	2b	Ме	Н	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 4 Å MS, in CH₂Cl₂ at -15 °C, unless otherwise noted. ^{*b*} Conversion of **1a** and yields of **4–6** determined by ¹H-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 F₃C-Ph at -25 °C (4 h).



be improved by either performing the reaction at -78 °C (dr 3.5:1, 90% isolated yield, entry 11) or by using $\alpha_{\alpha,\alpha}$ -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 45% yield). Gratifyingly, use of styrenes with electron-donating groups (e.g. p-MeO or o-MeO) allowed significant improvement of 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 of exo-methylenes such as 1-methylene-tetrahydronaphthalene allowed an efficient access to spirotetrahydropyran derivatives like 4aga, which was isolated in an excellent 94% vield (dr 1.5 : 1).16

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.¹⁷ X-ray analysis of crystals of 4aha and 4aia unambiguously confirmed their structures and relative stereochemistry (Fig. 2).14

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 as 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 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-4enal also gave the THPs 4abc-4abe in excellent yields. α , β -Unsaturated aldehydes such as 2-methylbut-2-enal or methacrolein also participated in the annulation yielding the desired



Table 2 Scope of the Au-catalyzed [2 + 2 + 2] intermolecular

4bbf, 84% dr 10 : 2 :1^{cj}

^a 1 (1 equiv.) added to a solution of 2 (2 equiv.), aldehyde (10 equiv.), [Au3] (2 mol%) and 4 Å MS, in CH₂Cl₂ at -45 °C, unless otherwise noted. Conversions >99% (¹H-NMR). When a mixture of 2,6-isomers is formed, the major is that drawn. ^b Carried out at -45 °C with a 1/2/3molar ratio of 1/1.25/2. ^c Carried out at -78 °C. ^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 Traces of **7af** (5% yield) were also isolated. Traces of 7aj (5% yield) were also isolated. ¹ 17% yield of 5bb was also isolated.³ For the structure of the minor isomers, see the ESI.





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 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, 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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Notes and references

- 1 (a) D. L. J. Broere and E. Ruijter, *Synthesis*, 2012, 44, 2639; (b)
 G. Dominguez and J. Pérez-Castells, *Chem. Soc. Rev.*, 2011, 40, 3430.
- 2 (a) J. Hara, M. Ishida, M. Kobayashi, K. Noguchi and K. Tanaka, Angew. Chem., Int. Ed., 2014, 53, 2956; (b) M. Kobayashi, T. Suda, K. Noguchi and K. Tanaka, Angew. Chem., Int. Ed., 2011, 50, 1664; (c) Y. Satoh and Y. Obora, Org. Lett., 2011, 13, 2568; (d) S. Ogoshi, A. Nishimura and M. Ohashi, Org. Lett., 2010, 12, 3450; (e) N. Mori, S. Ikeda and Y. Sato, J. Am. Chem. Soc., 1999, 121, 2722.
- 3 For selected recent reviews, see (a) D. Garayalde and C. Nevado, ACS Catal., 2012, 2, 1462; (b) I. D. G. Watson and F. D. Toste, Chem. Sci., 2012, 3, 2899; (c) F. López and J. L. Mascareñas, Beilstein J. Org. Chem., 2011, 7, 1075; (d) G. Abbiati and E. Rossi, Beilstein J. Org. Chem., 2014, 10, 481.
- 4 For fully intermolecular (trimolecular) Au-catalyzed [2 + 2 + 2] cycloadditions of two different components, see (*a*) S. N. Karad and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2014, 53, 9072; (*b*) R. B. Dateer, B. S. Shaibu and R.-S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 113.
- 5 For selected examples of partially intermolecular (bimolecular) Au-catalyzed [2 + 2 + 2] cycloadditions of three different components, see (a) C. Obradors and A. M. Echavarren, *Chem.-Eur. J.*, 2013, **19**, 3547; (b) D. B. Huple and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 10975; (c) M. Schelwies, R. Moser, A. L. Dempwolff, F. Rominger and G. Helmchen, *Chem.-Eur. J.*, 2009, **15**, 10888; (d)

T.-M. Teng and R.-S. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 9298. For a review highlighting the challenges of Au-catalyzed intermolecular annulations, see: (*e*) M. E. Muratore, A. Homs, C. Obradors and A. M. Echavarren, *Chem.-Asian J.*, 2014, **9**, 3066.

- 6 For recent reviews, see (*a*) M. A. Perry, S. D. Rychnovsky and N. Sizemore, Synthesis of Saturated Tetrahydropyrans, in *Synthesis of Saturated Oxygenated Heterocycles*, ed. J. Cossy, Topics in Heterocyclic Chemistry, Springer-Verlag, Berlin, 2014; (*b*) X. Han, G. Peh and P. E. Floreancig, *Eur. J. Org. Chem.*, 2013, 1193.
- 7 For selected recent methods for THP synthesis, see (a) Y. Xie and P. E. Floreancig, Angew. Chem., Int. Ed., 2014, 53, 4926;
 (b) J. Zeng, Y. J. Tan, J. Ma, M. L. Leow, D. Tirtorahardjo and X. W. Liu, Chem.-Eur. J., 2014, 20, 405; (c) I. Shin, G. Wang and M. J. Krische, Chem.-Eur. J., 2014, 20, 13382.
- 8 For a tandem [[2 + 2] + 2] cycloaddition, see: A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 14202.
- 9 (a) F. López and J. L. Mascareñas, Chem. Soc. Rev., 2014, 43, 2904; (b) F. López and J. L. Mascareñas, Beilstein J. Org. Chem., 2013, 9, 2250; (c) H. Faustino, P. Bernal, L. Castedo, F. López and J. L. Mascareñas, Adv. Synth. Catal., 2012, 354, 1658; (d) H. Faustino, F. López, L. Castedo and J. L. Mascareñas, Chem. Sci., 2011, 2, 633; (e) I. Alonso, H. Faustino, F. López and J. L. Mascareñas, Angew. Chem., Int. Ed., 2011, 50, 11496.
- 10 H. Faustino, I. Alonso, J. L. Mascareñas and F. López, *Angew. Chem., Int. Ed.*, 2013, **52**, 6526.
- 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. 9*c*; 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 ESI[†] for further details.
- 15 (a) The [2 + 2] adducts 5ab, 6a, or other side-products, were not detected in the crude mixture (¹H-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 ESI.[†] ¹⁴
- 16 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.†
- 17 The ring fusion was exclusively *cis* in all these polycyclic systems. Therefore, dr refers to the substituents at the 2,6-THP positions.
- 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.

- 20 **4aba** can even be obtained using a 1 : 1 : 1 ratio (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. 12*a*.
- 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.

