# Gold(I)-Catalyzed Enantioselective [2 + 2 + 2] Cycloadditions. An Expedient Entry to Enantioenriched Tetrahydropyran Scaffolds

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**ABSTRACT:** A straightforward and atom-economical enantioselective approach to highly substituted tetrahydropyrans is reported. The process, which consists of an intermolecular gold-catalyzed [2 + 2 + 2] cycloaddition between allenamides, alkenes and aldehydes, is efficiently catalyzed by both phosphoramidite- and chiral *N*-heterocyclic carbene-gold catalysts, occurs with complete chemo- and regioselectivity, moderate diastereoselectivity, and moderate to very good enantioselectivities.

**KEYWORDS**: Gold catalysis, enantioselective synthesis, tetrahydropyrans, N-heterocyclic carbenes, allenamide, cycloaddition

Tetrahydropyrans (THPs), and more in particular their 2,6-disubstituted derivatives, are privileged skeletons that can be found in many biologically active molecules and natural products (Figure 1).[1] During the last decades, many elegant methods have been developed for their preparation, including Prins-cyclizations, Ferrier rearrangements, intramolecular epoxide openings or oxa-Michael additions.[2] However, and despite these achievements, direct enantioselective methods that provide enantioenriched THPs from simple achiral materials are extremely scarce.[3-6] Indeed, after decades of extensive research on Prins-cyclizations, only isolated enantioselective variants have been achieved, and they are not suitable for the formation of 2,6-disubstituted THPs.[3] Alternatively, a handful of desymmetrizations,[4] hetero-Diels–Alder reactions,[5] and one-pot tandem processes[6] have also been reported, but their scopes are limited. Thus, new enantioselective, atom-economical and practical approaches to THPs are highly desirable.

In recent years, we have developed a series of Au(I)-catalyzed formal [m + n] annulations involving allenes,[7] together with some enantioselective versions.[8] More recently, we also developed multicomponent annulations,[9] including an intermolecular formal [2 + 2 + 2] cycloaddition between allenamides, alkenes and aldehydes, catalyzed by a phosphite-gold catalyst (Scheme 1).[9b] The reaction, which affords 2,6-disubstituted THPs with complete regioselectivity and moderate to complete diastereoselectivity, was proposed to proceed through the interception of intermediate **I** by the alkene to yield a key carbocationic species **II**, which might be partially stabilized by the gold atom.[9b] Lastly, carbonyl attack on **II**, followed by a Prins cyclization in the resultant oxonium **III**, affords the THP **4**.

Considering the synthetic potential of the transformation and the simplicity of the experimental protocol, we were prompted to investigate enantioselective variants that could provide optically active THPs **4**. However, the simultaneous control of the regio-, chemo-, stereo-, and enantio-selectivity represents an enormous challenge. Indeed, enantioselective transition metal catalyzed annulations involving three different components are virtually unknown.[10]

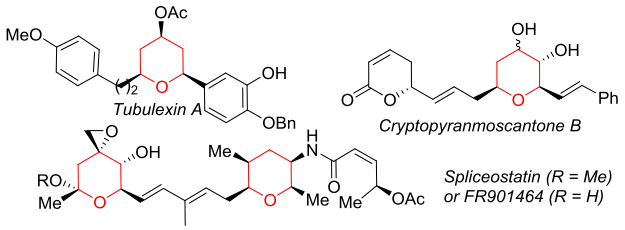
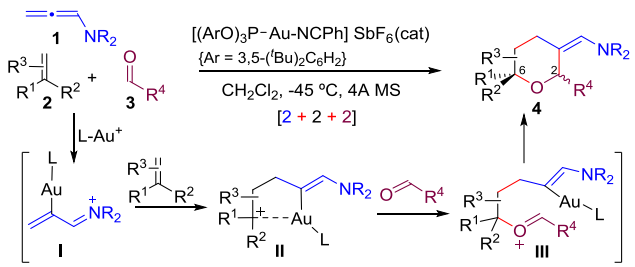



**Figure 1.** Selected examples of biologically relevant THPs



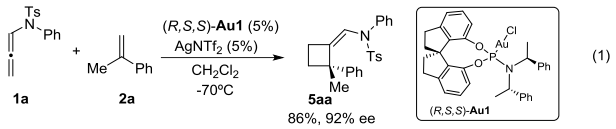

**Scheme 1.** Au-catalyzed [2+2+2] annulations to THPs **4**.[9b]

In our case, although the feasibility of the racemic process had been demonstrated,[9b] the generation of asym-

metry in such complex mechanistic scenario is not obvious, mainly because the presumable carbocationic nature of species **II**, which might prevent the asymmetric influence of the chiral ligand in the formation of the stereocenter in intermediate **III** (C6). Moreover, the subsequent Prins-cyclization might be likely governed by the stereocenter of **III**, rather than by the chiral ligand at gold. Importantly, an efficient chiral catalyst should also favor the [2 + 2 + 2] process over alternative [2 + 2] annulations,[11] or acyclic hydrofunctionalizations.[12] The complexity of the challenge was confirmed by analyzing the performance of the gold complex *(R,S,S)*-**Au1**/$AgNTf_2$, a previously reported highly efficient catalyst for allenamide-styrene [2 + 2] cycloadditions.[11b] Thus, while this gold complex catalyzed the [2 + 2] cycloaddition between allenamide **1a** and α-methyl styrene (**2a**) with excellent yield and 92% ee, (Scheme 2, eq 1),[11b] the analog reaction in presence of benzaldehyde (**3a**) as aldehyde partner, under otherwise identical reaction conditions, led to a mixture of products that include the [2 + 2] adduct **5aa** (15% yield, 92% ee) and a mixture of four [2 + 2 + 2] diastereoisomers (65% combined yield). The major products, the *E*- and *Z*-2,6-*cis* isomers (**4aaa**) were obtained with equal 68% ee, whereas the minor 2,6-*trans* isomers (*Z*- and *E*-**4aaa**'), were formed with ee's of 57% and 18%, respectively (Scheme 2, eq. 2)

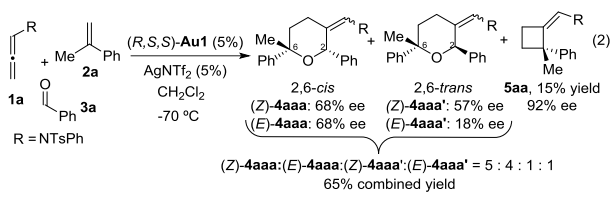
Despite the modest chemoselectivity, the formation of the desired products with reasonable ee's encouraged us

González et al.: [2 + 2] cycloaddition of **1a** and **2a** catalyzed by (*R,S,S*)-**Au1**[11b]




(1)

(*R,S,S*)-**Au1** performance on the [2 + 2 + 2] cycloaddition of **1a**, **2a** and benzaldehyde (**3a**)

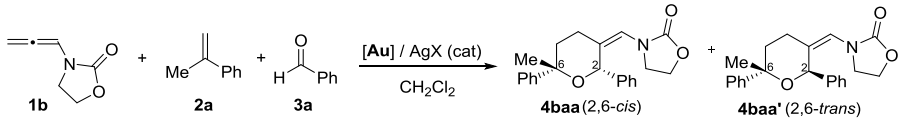



(2)

**Scheme 2**. Performance of (*R,S,S*)-**Au1** in a [2 + 2] cycloaddition[11b] and in the analog reaction with benzaldehyde (eq. 2).

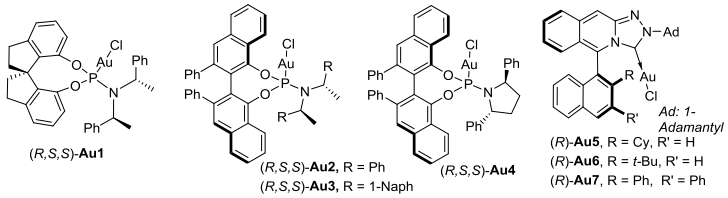
to further investigate the process.Table 1 summarizes the results obtained in the reaction of the allenamide **1b** with α-methyl styrene (**2a**) and benzaldehyde (**3a**), using different catalytic conditions. After extensive screening of different types of phosphoramidite-gold catalysts,[13] we found that the Vanol-derived gold(I) complex (*R,S,S*)-**Au2**/$AgNTf_2$ is able to efficiently catalyze this cycloaddition, to give after just 30 min at – 78 ºC, the desired THPs in an excellent 97% yield, and a moderate 2,6-*cis* /2,6-*trans* diastereomeric ratio (**4baa** : **4baa'** = 2 : 1), (entry 2). Moreover, both isomers were obtained with good enantioselectivities: 70% for the 2,6-*cis* isomer, and 81% ee for the 2,6-*trans* counterpart (entry 2).

**Table 1.** Preliminary screening of chiral gold-catalysts in a model [2 + 2 + 2] cycloaddition reaction[a]




| entry | [**Au**] (x mol%) | AgX | T (ºC) | t (h) | dr (**4baa**: **4baa'**) | Yield (%)[b] | **4baa**, ee (%) | **4baa'**, ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | (*R,S,S*)-**Au1** (5) | $AgNTf_2$ | -78 | 3 | 2 : 1 | 85 | 9 | 18 |
| 2 | (*R,S,S*)-**Au2** (5) | $AgNTf_2$ | -78 | 0.5 | 2 : 1 | 97 | 70 | 81 |
| 3 | (*R,S,S*)-**Au2** (5) | $AgNTf_2$ | -94 | 0.5 | 2 : 1 | 93 | 74 | 88 |
| 4 | (*R,S,S*)-**Au2** (5) | $AgBF_4$ | -94 | 0.5 | **4 : 1** | **91** | **74** | **90** |
| 5 | (*R,S,S*)-**Au3** (5) | $AgNTf_2$ | -78 | 0,2 | 1 : 1 | 91 | 10 | 66 |
| 6 | (*R,S,S*)-**Au4** (5) | $AgNTf_2$ | -78 | 0,1 | 3 . 1 | 97 | 50 | 26 |
| 7 | (*R*)-**Au5** (5) | $AgNTf_2$ | -70 -> -30 | 4 | 5 : 1 | 79 | 78 | 19 |
| 8 | (*R*)-**Au6** (5) | $AgNTf_2$ | -70 -> -30 | 20 | 5 : 1 | 37 | 77 | 4 |
| 9 | (*R*)-**Au7** (5) | $AgNTf_2$ | -70 -> -30 | 8 | 6 : 1 | 95 | 77 | 21 |
| 10 | (*R*)-**Au5** (10) | $AgNTf_2$ | -70 | 24 | **9 : 1** | **80** | **87** | **22** |

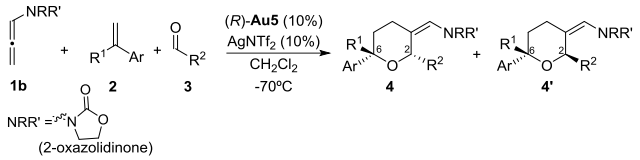
[a] **1b** (1 equiv) added to a solution of **2a** (2 equiv), **3a** (10 equiv), [**Au**] /AgX (x mol%) and 4Å MS, in $CH_2Cl_2$ at the indicated temperature. Conversions (>99%), and dr determined by $^1$H-NMR of the crude mixture using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated combined yield of **4baa** + **4baa'** (both isomers can be separated by chromatography).



Interestingly, the [2 + 2] adduct was not detected in the crude mixture. As can be deduced from entries 3 and 4, the enantioselection could be slightly improved by performing the reaction at -94 ºC (entry 3), while the 2,6-*cis*/2,6-*trans* ratio could be enhanced up to 4 : 1 by using $BF_4^-$ as counterion at this temperature (entry 4). Since further attempts to improve the ee by fine-tuning the reaction conditions or the phosphoramidite ligand were not successful (e. g. entries 5 and 6),[13] we analyzed the performance of other types of chiral gold catalysts. Thus, we found that the triazole-derived complex **Au5**/$AgNTf_2$, previously used for enantioselective [4 + 2] allenamide-diene cycloadditions,[8c] was also efficient, providing after 4h (slowly heating from -70 to -30 ºC), the THPs **4baa** and **4baa'**, in a 5 : 1 ratio, and 79% combined yield (entry 7). Remarkably, the major isomer, **4baa**, was obtained with 78% ee, whereas the minor, **4baa'**, with a modest 19% ee. Related catalysts featuring different substituents at the biaryl-moiety did not improve this result (entries 8 and 9);[13] however, by carrying out the reaction with **Au5** (10 mol%), at a constant temperature of -70 ºC, the diastereoselectivity could be improved up to 9 : 1, whereas the ee's were also increased to 87% (**4baa**) and 22% (**4baa'**) (entry 10).[14] Importantly, using X-Ray diffraction analysis (copper radiation), we could confirm that the absolute configuration at C6 was the same for the 2,6-*cis* and 2,6-*trans* isomers, **4baa** and **4baa'**, and as depicted in Table 1.[15,16]

With these results at hand, we next analyzed the scope of the enantioselective [2 + 2 + 2] cycloaddition using both, the triazole- and the phosphoramidite-based gold complexes, **Au5** and **Au2**. As indicated in Table 2, the cycloadditions between allenamide **1b**, α-methyl styrene (**2a**) and several aromatic or heteroaromatic aldehydes, such as mesitylaldehyde (**3b**), 2-furaldehyde (**3c**) or 2-thiofuraldehyde (**3d**), promoted by the gold-carbene complex **Au5**/$AgNTf_2$, provided the desired THPs with a diastereometic ratios of 4 to 1 (**4** : **4'**), and excellent combined yields (entries 2-4). Moreover, the ee of the major 2,6-*cis* isomers (**4bab** – **4bad**) were very good, varying from 81% (for **4bad**) to 91% ee (for **4bab**). As in the cycloaddition with benzaldehyde (entry 1), the ee's of the minor 2,6-*trans* isomers (**4'**) were significantly lower (from 13% to 41% ee, entries 2-4). An aliphatic aldehyde such as pentanal (**3e**) also participated in the cycloaddition, although a slightly higher reaction temperature was required to achieve full conversion (from -70 ºC to -50 ºC, for 8h). In this case, the 2,6-*cis* and 2,6-*trans* isomers were obtained with 66% ee and 54% ee, respectively (entry 5). On the other hand, α,β-unsaturated aldehydes were excellent partners. Thus, the reaction with tiglic aldehyde (**3f**) provided the desired THPs in a combined 85% yield (**4baf** : **4baf'** = 5 : 1) and an enantioselectivity for the major isomer (**4baf**) of 83% (entry 6). Likewise, other acyclic or cyclic enals like methacrolein, acrolein, (*E*)-2-methylcinnamaldehyde, or cyclohexenecarbaldehyde (entries 7-10) also provided the corresponding THPs with good yields, good 2,6-*cis*/2,6-*trans* isomeric ratios (from 4 : 1 to 7 : 1) and remarkable ee's for the major 2,6-*cis*-isomers, varying from 74% (**4bag**, entry 7) to 83% (entry 8). Gratifyingly, the cycloaddition also proceeds with different α-substituted styrenes (**2**). As can be seen in entry 11, the reaction of the allenamide **1b** with benzaldehyde and α-ethyl styrene (**2b**) provided the expected THPs in 76% yield (**4bba** : **4bba'** = 3 : 1) and the major isomer, **4bba,** was obtained with a very good 88% ee. Curiously, when α-*i*-Pr-styrene (**2c**) was employed, the 2,6-*cis* THP (**4bca**) was obtained as the minor isomer, with 76% ee (entry 12). Finally, the use of an electron-rich α-unsubstituted styrene, such as *p*MeO-styrene (**2d**), was also tolerated, exclusively affording the 2,6-*cis* isomer **4bda**, in 57% yield and 60% ee (entry 13).[17-19]

**Table 2.** Scope of the cycloaddition with **Au5**[a,19]



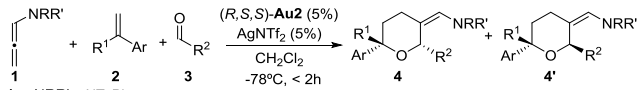

| entry | R¹, Ar (**2**) | R² (**3**) | dr (**4** : **4'**) | yield (%)[b] | **4**, ee (%) | **4'**, ee (%) |
|---|---|---|---|---|---|---|
| 1 | Me, Ph (**2a**) | Ph (**3a**) | 9 : 1 | 80 | **4baa**, 87 | **4baa'**, 22 |
| 2 | Me, Ph (**2a**) | Mesityl (**3b**) | 4 : 1 | 93 | **4bab**, 91 | **4bab'**, 13 |
| 3 | Me, Ph (**2a**) | 2-furyl (**3c**) | 4 : 1 | 76 | **4bac**, 88 | **4bac'**, 27 |
| 4 | Me, Ph (**2a**) | 2-thiofuryl (**3d**) | 4 : 1 | 92 | **4bad**, 81 | **4bad'**, 41 |
| 5[c,d] | Me, Ph (**2a**) | *n*-butyl (**3e**) | 5 : 1 | 51 | **4bae**, 66 | **4bae'**, 54 |
| 6 | Me, Ph (**2a**) |  (**3f**) | 5 : 1 | 85 | **4baf**, 83 | **4baf'**, 43 |
| 7 | Me, Ph (**2a**) |  (**3g**) | 5 : 1 | 60 | **4bag**, 74 | **4bag'**, 27 |
| 8 | Me, Ph (**2a**) |  (**3h**) | 6 : 1 | 85 | **4bah**, 83 | **4bah'**, 51 |
| 9 | Me, Ph (**2a**) |  (**3i**) | 4 : 1 | 80 | **4bai**, 78 | **4bai'**,39 |
| 10 | Me, Ph (**2a**) |  (**3j**) | 7 : 1 | 77 | **4baj**, 81 | **4baj'**, 25 |
| 11 | Et, Ph (**2b**) | Ph (**3a**) | 3 : 1 | 76 | **4bba**, 88 | **4bba'**, 5 |
| 12[c] | *i*-Pr, Ph (**2c**) | Ph (**3a**) | 1 : 2 | 52 | **4bca**, 76 | **4bca'**, 10 |
| 13 | H, *p*MeOPh (**2d**) | Ph (**3a**) | 1 : 0 | 57 | **4bda**, 60 | - |

[a] **1b** (1 equiv) added to a solution of **2** (2 equiv), **3** (10 equiv), [**Au5** / $AgNTf_2$] (10%) and 4Å MS, in $CH_2Cl_2$ at -70 ºC. Reaction times, from 4 to 24 h.[13] Conversions (>99%) and dr determined by $^1$H-NMR of the crude mixture. [b] Combined isolated yield (isomers can be generally separated by flash chromatography)[13]. [c] Slowly warmed from -70 to -50 ºC. [d] Carried out with (*S*)-**Au5**.

Having explored the scope with the triazole-based catalyst **Au5**/$AgNTf_2$, the performance of the Vanol-phosphoramidite gold complex **Au2**/$AgNTf_2$ was next investigated (Table 3). In general, the reactions with this catalyst were faster, leading to full conversions at -78 ºC in less than 30 min. In consonance with the results of the model reaction (table 3, entry 1), enantioselectivities of the 2,6-*cis* isomers turned out to be lower than those observed with **Au5**, whereas those of the 2,6-*trans* isomers (**4'**) were significantly higher. Indeed, while **Au5** provided the *trans* isomers with ee's typically below 50%,

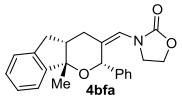
the phosphoramidite-based catalyst (*R,S,S*)-**Au2** generates these adducts with ee's higher than 75% on regular basis (entries 1-8). Moreover, using this catalyst, the proportion of the 2,6-*trans* THPs are higher than with **Au5**, and, in some cases, these products are even obtained as the major isomers (entries 2 and 3). Interestingly, a cyclic alkene such as **2f**, reacts with allenamide **1b** and benzaldehyde in presence of the complex (*R,S,S*)-**Au2**/$AgNTf_2$, to give a single stereoisomeric adduct (**4bfa**) in 50% yield and 82% ee (entry 11).[20] We also tested the cycloaddition using *N*-tosyl allenamide **1a**. In contrast to the results with (*R,S,S*)-**Au1** (Scheme 1), this Vanol-derived catalyst exclusively afforded [2 + 2 + 2] adducts of type **4** in an excellent 92% combined yield, as a *Z* / *E* mixture of isomers. The two 2,6-*cis* isomers (with *E* and Z *exo*-enamides) were obtained with 89% and 94% ee (entry 12).[21,22]

**Table 3.** Scope of the cycloaddition with (*R,S,S*)-**Au2**[a,19,22]



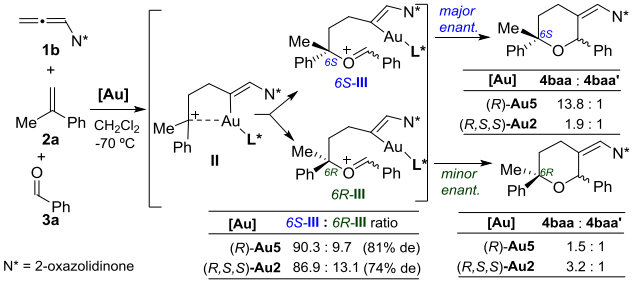

| entry | 1 | R¹, Ar (2) | R² (3) | dr 4 : 4' | yield (%)[b] | 4, ee (%) | 4', ee (%) |
|---|---|---|---|---|---|---|---|
| 1[c] | **1b** | Me, Ph (**2a**) | Ph (**3a**) | 4 : 1 | 91 | **4baa**, 74 | **4baa'**, 90 |
| 2 | **1b** | Me, Ph (**2a**) | Mesityl (**3b**) | 1 : 4 | 98 | **4bab**,49 | **4bab'**, 81 |
| 3 | **1b** | Me, Ph (**2a**) | 2-furyl (**3c**) | 1 : 3 | 81 | **4bac**, 65 | **4bac'**, 86 |
| 4 | **1b** | Me, Ph (**2a**) | 2-thiofuryl (**3d**) | 1 : 1 | 95 | **4bad**, 60 | **4bad'**, 75 |
| 5[d,e] | **1b** | Me, Ph (**2a**) | *n*-butyl (**3e**) | 2 : 1 | 42 | **4bae**, 33 | **4bae'**, 56 |
| 6 | **1b** | Me, Ph (**2a**) |  (**3f**) | 2 : 1 | 91 | **4baf**, 72 | **4baf'**, 77 |
| 7[e] | **1b** | Me, Ph (**2a**) |  (**3i**) | 1 : 1 | 98 | **4bai**, 65 | **4bai'**, 77 |
| 8 | **1b** | Me, Ph (**2a**) |  (**3j**) | 2 : 1 | 80 | **4baj**, 62 | **4baj'**, 75 |
| 9 | **1b** | *i*-Pr, Ph (**2c**) | Ph (**3a**) | 1 : 1 | 96 | **4bca**, 61 | **4bca'**, 45 |
| 10[c] | **1b** | Ph, Ph (**2e**) | Ph (**3a**) | - | 97 | **4bea**, 54 | |
| 11 | **1b** |  (**2f**) | Ph (**3a**) | 1 : 0 | 50 | **4bfa**,[f] 82 | -- |
| 12 | **1a** | Me, Ph (**2a**) | Ph (**3a**) | 5 : 1[g] | 92 | *Z*-**4aaa**, 89<br>*E*-**4aaa**, 94 | *Z*-**4aaa'**, 74<br>*E*-**4aaa'**, 25 |

[a] **1** (1 equiv) added to a solution of **2** (2 equiv), **3** (10 equiv), [(*R,S,S*)-**Au2** /$AgNTf_2$] (5%) and 4Å MS, in $CH_2Cl_2$ at – 78 ºC. Reaction times, < 2 h.[13] Conversions (> 99%) and dr determined by $^1$H-NMR of the crude mixture. [b] Combined isolated yield. [c] Carried out at -94 ºC with $AgBF_4$. [d] Slowly warmed from -70 to -50 ºC (14 h). [e] Carried out with (*S,R,R*)-**Au2**. [f] Structure of **4bfa** is drawn below. [g] **4aaa** and **4aaa'** were obtained as 1 : 1 *E* / *Z* mixtures

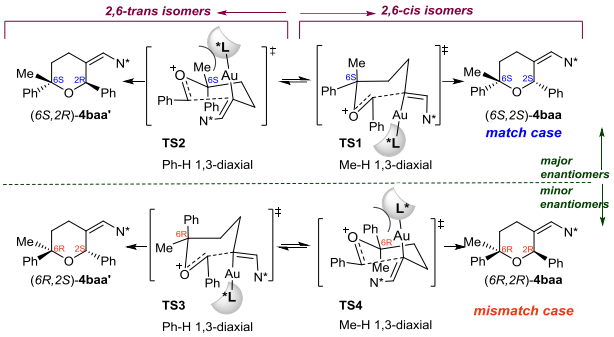



The above results confirm that despite the intrinsic complexity of the annulation, which requires the synchronous reactions of three different partners in presence of the catalyst, it is possible to obtain excellent chemoselectivities, and very good enantioselectivities. Noteworthy, while the above reactions were carried out using a relatively large excess of the aldehyde (10 equiv.), preliminary results indicate that the efficiency of the process is not significantly affected when the amount of aldehyde is reduced down to 5 or even 2 equivalents.[23]

Knowing that the major enantiomers of the 2,6-*cis* and 2,6-*trans* THP isomers obtained from the model reaction of **1b**, **2a** and **3a**, share the same absolute configuration at C6, it is possible to gain some insights into the stereoselection process. Indeed, combining this information with the dr and ee values obtained in the model cycloaddition catalyzed by (*R*)-**Au5** (Table 1, entry 10), we have calculated a diastereomeric excess (de) of 81% for the formal putative intermediate of type **III** (90.3 : 9.7 mixture of the epimers *6S*-**III** / *6R*-**III**).[13] The diastereoselectivity in the subsequent *Prins* cyclization would then be of 14 to 1 for the major epimer *6S*-**III**, whereas for the minor one, *6R*-**III,** would be significantly lower (1.5 : 1). In both cases, however, the formation the 2,6-*cis* isomer **4baa**, is favored (Scheme 3). Therefore, the cyclization of *6S*-**III** corresponds to a match case between the stereocenter of the THP (C6) and the chiral ligand, whereas that of *6R*-**III** reflects a mismatch case, albeit the influence of the C6 stereocenter still prevails.[24] The same analysis can be performed for the reaction promoted at -78 ºC by (*R,S,S*)-**Au2** (Table 1, entry 2). The intermediate **III** would be obtained with a diastereomeric excess of 74%, while in this case, the Prins cyclizations proceed with closer diastereoselectivities for the 6*S* and for the 6*R* isomers (1.9 : 1 and 3.2 : 1 ratios), again both in favor of the 2,6-*cis* product (**4baa**). These latter diastereoselectivities are very similar to those obtained with the racemic catalyst,[24] which suggests a marginal match/mismatch influence of the chirality of the ligand of (*R,S,S*)-**Au2** in the Prins cyclization. Therefore, and despite the assumed carbocationic character of intermediate **II**, the presence of a chiral ligand at gold allows for remarkable levels of stereocontrol. Since the diastereoselectivity of the Prins cyclizations is mainly influenced by the carbon stereocenter in C6, we can delineate the most favorable transition states of these cyclizations as those that minimize 1,3-diaxial interactions. Accordingly, for the model reaction of **1b**, **2a** and **3a** catalyzed by (*R*)-**Au5**, we tentatively proposed transition states like **TS1** and **TS4**, which involve chair-like conformations and present less disfavored Me-H 1,3-diaxial interactions, as those leading to 2,6-*cis* isomers (Scheme 4).[25,26]




**Scheme 3**. Mechanistic analysis of the stereoselectivity




**Scheme 4**. Proposed TS's for the Prins cyclizations in the reaction of **1b**, **2a** and **3a**, catalyzed by (*R*)-**Au5** (N* = 2-oxazolidinone).

In summary, we have developed an efficient, chemo- and stereoselective gold-catalyzed asymmetric [2 + 2 + 2] cycloaddition involving an allene, an alkene and an aldehyde. The method constitutes one of the first reports of any type of transition metal catalyzed enantioselective intermolecular annulation involving three different reaction components,[10] and provides a straightforward entry to optically active 2,6-disubstituted THPs. By the appropriate selection of the allenamide as well as the chiral gold catalyst (**Au2** or **Au5**), both, the 2,6-*cis* and 2,6-*trans* THP stereoisomers, can be obtained with good to very good enantiomeric ratios.

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## ASSOCIATED CONTENT

### Supporting Information

Full experimental procedures, optimization of the chiral catalyst and characterization of all new compounds, including $^{1}$H-, $^{13}$C-NMR spectra and chiral HPLC traces.

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## REFERENCES

(1) For recent reviews, see: (a) Perry, M. A.; Rychnovsky, S. D.; Sizemore, N. In *Synthesis of Saturated Oxygenated Heterocycles*; Cossy, J., Ed.; Topics in Heterocyclic Chemistry; Springer-Verlag: Berlin, **2014**, Vol 35, pp 43–95. (b). Han, X.; Peh, G.; Floreancig, P. E. *Eur. J. Org. Chem.* **2013**, 1193–1208.

(2) For selected reviews, see: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006,** 2045–2053. (b) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413–445. For selected recent methods for THP synthesis, see: (c) Xie, Y.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2014**, 53, 4926–4929. (d) Zeng, J.; Tan, Y. J.; Ma, J.; Leow, M. L.; Tirtorahardjo, D.; Liu X. W. *Chem. Eur. J.* **2014**, *20*, 405–409. (e) Shin, I.; Wang, G.; Krische, M. J. *Chem. Eur. J.* **2014**, *20*, 13382–13389.

(3) (a) Liu, L.; Kaib, P. S. J.; Tap, A.; List, B. *J. Am. Chem. Soc.* **2016,** *138*, 10822–10825. (b) Tsui, G. C.; Liu, L.; List, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 7703–7706. (c) Lalli, C.; van de Weghe, P. *Chem. Commun.* **2014**, 50, 7495–7498.

(4) (a) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (b) Roux, C.; Candy, M.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 766–770. (c) Chen, Z.; Sun, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 13593–13596.

(5) (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999,** *38*, 2398–2400. (b) Lin, Y.-J.; Du, L.-N.; Kang, T.-R.; Liu, Q.-Z.; Chen, Z.-Q.; He, L. *Chem. Eur. J.* **2015**, *21*, 11773–11778. (c) Cui, H.-L.; Tanaka, F. *Chem. Eur. J.* **2013,** *19*, 6213–6216.

(6) (a) Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 3774–3779. (b) Urbanietz, G.; Atodiresei, I.; Enders, D. *Synthesis* **2014**, *46*, 1261–1269. (c) Han, B.; Xie, X.; Huang, W.; Li, X.; Yang, L.; Peng, C. *Adv. Synth. Catal.* **2014**, *356*, 3676–3682. (d) Hahn, R.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 3636–3639. (e) Xie, J.-H.; Guo, L.-C.; Yang, X.-H.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 4758–4761.

(7) (a) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem. Eur. J.* **2009,** *15*, 3336–3339. (b) Faustino, H.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Sci.* **2011**, *2*, 633–637. (c) Faustino, H.; Bernal, P.; Castedo, L.; López, F.; Mascareñas, J. L. *Adv. Synth. Catal.* **2012**, *354*, 1658–1664. (d) Montserrat, S.; Faustino, H.; Lledós, A.; Mascareñas, J. L.; López, F.; Ujaque, G. *Chem. Eur. J.* **2013,** *19*, 15248–15260. (e) Bernal-Albert, P.; Faustino, H.; Gimeno, A.; Asensio, G.; Mascareñas, J. L.; López, F. *Org. Lett.* **2014**, *16*, 6196–6199.

(8) (a) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030. (b) Alonso, I.; Faustino, H.; López, F.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11496–11500. (c) Francos, J.; Grande-Carmona, F.; Faustino, H.; Iglesias-Siguenza, J.; Díez, E.; Alonso, I.; Fernández, R.; Lassaletta, J. M.; López, F.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 14322–14325. For a recent review on gold-catalyzed enantioselective annulations, see: (d) Li, Y.; Li, W.; Zhang, J. *Chem. Eur. J.* **2017,** *23*, 467–512.

(9) (a) Faustino, H.; Alonso, I.; Mascareñas, J. L.; López, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 6526–6530. (b) Faustino, H.; Varela, I.; Mascareñas, J. L.; López, F. *Chem. Sci.* **2015**, *6*, 2903–2908.

(10) To the best of our knowledge, only very recently the first transition metal catalyzed enantioselective intermolecular annulations involving three different reaction components were reported, see: (a) Hara, J.; Ishida, M.; Kobayashi, M.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2014**, 53, 2956–2959. (b) Yoshida, T.; Tajima, Y.; Kobayashi, M.; Masutomi, K.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2015,** *54*, 8241–8244. (c) Orgué, S.; León, T.; Riera, A.; Verdaguer, X. *Org. Lett.* **2015,** *17*, 250–253. For selected reviews, see: (d) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884–4908. (e) Amatore, M.; Aubert, C. *Eur. J. Org. Chem.* **2015**, 265–286. (f) Domínguez, G.; Pérez-Castells, J. *Chem. Eur. J.* **2016,** *22*, 6720–6739.

(11) For gold-catalyzed [2 + 2] allenamide - alkene intermolecular cycloadditions, see refs 7c, 7e and: (a) Suárez-Pantiga, S.; Hernández-Díaz, C.; Piedrafita, M.; Rubio, E.; González, J. M. *Adv. Synth. Catal.* **2012**, *354*, 1651–1657. (b) Suárez-Pantiga, S.; Hernández-Díaz, C.; Rubio, E.; González, J. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555. (c) Li, X. X.; Zhu, L. L.; Zhou, W.; Chen, Z. L. *Org. Lett.* **2012**, *14*, 436–439. (d) Wang, Y. D.; Zhang, P. C.; Liu, Y.; Xia, F.; Zhang, J. *Chem. Sci.* **2015**, *6*, 5564–5570. (e) Jia, M. Q.; Monari, M.; Yang, Q. Q.; Bandini, M. *Chem. Commun.* **2015**,

*51*, 2320–2323. (f) Hu, H.; Wang, Y.; Qian, D.; Zhang, Z.-M.; Liu, L.; Zhang, J. *Org. Chem. Front.* **2016,** *3*, 759-763.

(12) For selected examples of gold-catalyzed hydrofunctionalizations of allenamides, see: (a) Hill, A. W.; Elsegood, M. R.; Kimber, M. C. *J. Org. Chem.* **2010**, *75*, 5406–5409. (b) Kimber, M. C. *Org. Lett.* **2010,** *12*, 1128–1131. (c) Horino, Y.; Takata, Y.; Hashimoto, K.; Kuroda, S.; Kimura, M.; Tamaru, Y. *Org. Biomol. Chem*. **2008**, *6*, 4105–4107. For a review on allenamides, see: (d) Lu, T.; Lu, Z.; Ma, Z. X.; Zhang, Y.; Hsung, R. P. *Chem Rev* **2013,** *113*, 4862-4904.

(13) See the Supporting Information for complete details

(14) Replacing the $^{-}NTf_2$ counterion by alternative low-coordinating analogs did not improve neither the yield, diastereo- or enantio-selectivities of the process. [$^{-}SbF_6$: dr: 8 : 1, 30% yield, 82% ee (**4baa**), 18% ee (**4baa'**); $^{-}BArF_4$: dr 7 : 1, 65% yield, 82% ee (**4baa**), 40% ee (**4baa'**)]

(15) (a) Both catalysts (*R*)-**Au5** and (*R,S,S*)-**Au2** provide the same major enantiomers of **4baa** and **4baa**' [(*6S,2S*)-**4baa** and (*6S,2R*)-**4baa'**], as confirmed by chiral HPLC analysis. (b) As expected, when (*S*)-**Au5** or (*S,R,R*)-**Au2** are used as catalysts, identical results but opposite enantiomers of **4baa** and **4baa**' are obtained.

(16) CCDC 1520019 [**4baa** obtained from the reaction catalyzed by (*R*)-**Au5**] and CCDC 1520020 [**4baa'** obtained from the reaction with (*S,R,R*)-**Au2**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

(17) (a) The corresponding [2 + 2] adduct **5bd** was obtained as a side product in 26% yield. (b) α-Unsubstituted styrenes ($R^1$ = H) without electron-donating groups in the aryl ring, provide the [2 + 2] adduct as major product. (c) Simple ketones or α-ketoesters, do not efficiently participate in the [2+2+2] cycloaddition.

(18) The results with α-iPr-styrene (**2c**) (table 2, entry 12) and *p*-methoxy styrene (**2d**) (table 2, entry 13) support a strong influence of 1,3-diaxial interactions in the diastereoselectivity (**4** : **4**' ratio) of the process (vide infra).

(19) The depicted absolute configurations of the major enantiomers of THPs **4** and **4**' of Tables 2 and 3 are proposed by analogy with those unequivocally determined for **4baa** and **4baa'**.[16] The signs of their $[\alpha]_D$ values, as well as the chiral-HPLC chromatograms are fully consistent with this assumption.

(20) The analog reaction using **Au5** provided the corresponding [2+2] adduct as major adduct (44% yield), and only traces of the desired THP **4bfa**.

(21) The analog reaction between **1a**, **2a** and **3a** using **Au5**/AgNTf2 provides a 5: 1 mixture of Z-**4aaa** (81% ee) and Z-**4aaa'** (30% ee), in a low 15% combined yield.

(22) The major enantiomers of **4** and **4'** obtained with (*R,S,S*)-**Au2** (Table 3) are the same as those obtained with (*R*)-**Au5**, except for **4bab'** and **4bae**', which exhibit opposite absolute configuration.

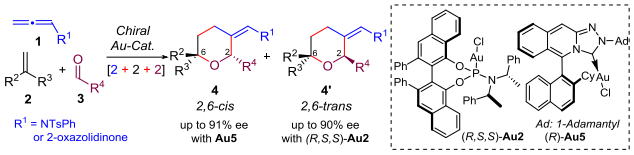
(23) Similar yields and selectivities were obtained in the model reaction using allenamide (**1b**) / alkene (**2a**)/ aldehyde (**3a**) molar ratios of 1 / 2 /5 and 1 / 1.2 / 2, either with (*S,R,R*)-**Au2** or (*S*)-**Au5.** See the Supporting Information for details.

(24) A racemic phosphite-gold catalyst affords at -78 ºC, a **4baa** : **4baa'** ratio of 3.5 : 1. See reference 9b.

(25) A Curtin-Hammett situation, based on a fast equilibrium between 6S-**III** and 6R-**III**, through intermediate **II** seems unlikely, but it cannot be fully discarded.

(26) Boat-like transition states such as **TS1'** - **TS4'** (Figure S1), although less likely, could also be operative in some cases.

# TOC GRAPHIC


1
2
3
Chiral
Au-Cat.
[2 + 2 + 2]
4
2,6-cis
up to 91% ee
with Au5
4'
2,6-trans
up to 90% ee
with (R,S,S)-Au2
R1 = NTsPh
or 2-oxazolidinone
(R,S,S)-Au2
Ad: 1-Adamantyl
(R)-Au5