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 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 \(\pi\)-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,5,7 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 carbyclics (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 6,9 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 \((E)\)-\(\beta\)-methylstyrene (2a) and benzaldehyde (3a)
THP 4aaa, was also detected, but only in trace amounts. Similarly, other frequently used gold catalysts such as Ph3PAuN(Tf2) 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).

At this point, we envisioned that an additional stabilization of the putative carbocationic species of type I, resulting from the addition of the alkenes to intermediate 1 (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 (4aaa) and 2,6-trans (4aaa) diastereoisomers (entry 6). The same result was obtained when 1a was added in one portion (entry 7). Gold catalysts such as JohnPhosAuNCMeSbF6 (Au1), Ph3PAuN(Tf2) or IPrAuNCMeSbF6 (Au2), also provided the desired [2 + 2 + 2] cycloadduct 4aaa as the major adduct; however, yields and chemoselectivities were significantly lower than those obtained with the phosphate-gold catalyst {Au3} (entry 7 vs. 8–10). Moreover, with this latter catalyst the diastereoselectivity could

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### Table 1 Preliminary evaluation of the [2 + 2 + 2] cycloaddition

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Au] (mol%)</th>
<th>2</th>
<th>R′</th>
<th>R″</th>
<th>Conv.</th>
<th>4 (%)</th>
<th>5 (%)</th>
<th>6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Au1 (5%)</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>99%</td>
<td>4aaa, 2</td>
<td>5aa, 4</td>
<td>6a, 44</td>
</tr>
<tr>
<td>2</td>
<td>Ph3PAuN(Tf2) (3%)</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>60%</td>
<td>4aaa, 2</td>
<td>5aa, 0</td>
<td>6a, 7</td>
</tr>
<tr>
<td>3</td>
<td>Au2 (5%)</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>99%</td>
<td>4aaa, 15</td>
<td>5aa, 7</td>
<td>6a, 22</td>
</tr>
<tr>
<td>4</td>
<td>Au3 (2%)</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>99%</td>
<td>4aaa, 21</td>
<td>5aa, 60</td>
<td>6a, 8</td>
</tr>
<tr>
<td>5</td>
<td>Au2 (2%)</td>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>99%</td>
<td>4aaa, 35</td>
<td>5aa, 37</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>Au3 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 95^{-d}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>Au3 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 99^{-d}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>Au1 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 51^{-d}</td>
<td>5ab, 17</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>Ph3PAuN(Tf2) (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 77^{-f}</td>
<td>5ab, 14</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>Au2 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 80^{-d}</td>
<td>5ab, 6</td>
<td>—</td>
</tr>
<tr>
<td>11^{-e}</td>
<td>Au3 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 98^{-h}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12^{-f}</td>
<td>Au3 (2%)</td>
<td>2b</td>
<td>Me</td>
<td>H</td>
<td>99%</td>
<td>4aba, 98^{-h}</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*a 1a (1 equiv.) added over 2 h to a solution of 2 (2 equiv.), 3a (10 equiv.), [Au] (X mol%) and 4 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)2C6H3 as internal standard (IS). Carried out at −45 °C (1 h).

*c Overall yield for the mixture of 2,6-cis (4aba) and trans (4aba) dr = 2 : 1. The major isomer is that drawn. ^d 1a added in one portion.

D Overall yield. dr 1.5 : 1. ^e Carried out at −78 °C (1 h). ^f 90% overall isolated yield, dr 3.5 : 1 (4aba : 4aaa). ^g Carried out in F3C–Ph at −25 °C (4 h).
be improved by either performing the reaction at $-78 \, ^\circ\mathrm{C}$ (dr
3.5 : 1, 90% isolated yield, entry 11) or by using $\alpha, \beta, \gamma$-tri-
fluorotoluene 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 $\beta$-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 $\alpha$-phenylstyrene
provided the desired THP (4afa) in an excellent 86% yield,
whereas the use of exo-methylene such as 1-methylene-tetra-
hydronaphthalene allowed an efficient access to spirotetray-
dropropan derivatives like 4aha, which was isolated in an
excellent 94% yield (dr 1.5 : 1).16

Remarkably, cyclic alkenic derivatives were also excellent
partners for this process. Thus, the cycloadditions of allen-
amide 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 (4aja–aja) stereoselectivity.17
X-ray analysis of crystals of 4aha and 4aja 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 $\gamma$-methyl-substituted allenamide
1b (see Table 2, footnote) with $\alpha$-methylstyrene and benzalde-
hyde provided the $[2 + 2 + 2]$ adduct 4bba, featuring three new
stereogenic centers, in 70% yield and with excellent diaster-
eselectivity (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 $\alpha$-methylene 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 $\alpha$-methylstyrene, allen-
amide 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. $\alpha, \beta,$
Unsaturated aldehydes such as 2-methylbut-2-enal or meth-
acrolein also participated in the annulation yielding the desired

Table 2 Scope of the Au-catalyzed $[2 + 2 + 2]$ intermolecular
cycloaddition$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkenene</th>
<th>Aldehyde</th>
<th>$N$-tosylphenyl</th>
<th>$2/1$ $\delta$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cfa</td>
<td>4 : 1</td>
<td>84%</td>
</tr>
<tr>
<td>1b</td>
<td>2-methylbut-2-enal</td>
<td>1b</td>
<td>4cka</td>
<td>3 : 1</td>
<td>77%</td>
</tr>
<tr>
<td>1c</td>
<td>2-methylbut-2-enal</td>
<td>1c</td>
<td>4cfa</td>
<td>5 : 1</td>
<td>70%</td>
</tr>
<tr>
<td>1d</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cfa</td>
<td>11 : 1</td>
<td>77%</td>
</tr>
<tr>
<td>1e</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>3 : 1</td>
<td>84%</td>
</tr>
<tr>
<td>1f</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>11 : 1</td>
<td>77%</td>
</tr>
<tr>
<td>1g</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>3 : 1</td>
<td>84%</td>
</tr>
<tr>
<td>1h</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>11 : 1</td>
<td>77%</td>
</tr>
<tr>
<td>1i</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>3 : 1</td>
<td>84%</td>
</tr>
<tr>
<td>1j</td>
<td>2-methylbut-2-enal</td>
<td>2a</td>
<td>4cka</td>
<td>11 : 1</td>
<td>77%</td>
</tr>
</tbody>
</table>

$^a$ 1 (1 equiv.) added to a solution of 2 (2 equiv.), aldehyde (10 equiv.), [Au3] (2 mol%) and 4 Å MS, in CH2Cl2 at $-45 \, ^\circ\mathrm{C}$, unless otherwise noted. Conversions $\geq 99\%$ (4H-NMR). When a mixture of 2,6-isomers is formed, the major is that drawn. $^b$ Carried out at $-45 \, ^\circ\mathrm{C}$ with a 1/2/3
molar ratio of 1/1.25/2. $^c$ Carried out at $-78 \, ^\circ\mathrm{C}$. $^d$ 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. $^h$ Traces of 7aj (5% yield) were also isolated. $^i$ 17% yield of 5bb was also isolated. $^j$ For the structure of the minor isomers, see the ESI.
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).\textsuperscript{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
distance (\textit{e.g.} C6).\textsuperscript{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 (Table 2, footnote b, results in
parentheses). Thus, using these conditions, THPs 4aba, 4afa,
4aga, 4ala, 4abb, 4abc, 4afd, 4abe, 4afb or 4afg were obtained in
yields varying from 60% to 90% (Table 2).\textsuperscript{20} Additionally, more
complex polycyclic systems like 4aha–4aja could also be
obtained in yields from 45% to 68%.\textsuperscript{14}

We next explored some manipulations of the \textit{exo}-enamide
moiety of the products (Scheme 2). Thus, THPs like 4afdf or
4acca can be dihydroxylated to afford the \textit{exo}-hydroxy aldehydes 11
and 12 in excellent yields and with very good or complete di-
stereoselectivity (Scheme 2, eqn (1)). Moreover, both types of
enamides (\textit{e.g.} 4afdf and 4acca) 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 inter-
molecular 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 \textit{trans} position of the alkene,
the [2 + 2 + 2] adduct 4aaa displays these groups in a \textit{cis}
disposition (Table 1, entry 5). On the contrary, poly cyclic [2 + 2 + 2]
adducts like 4aha, 4aaa 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 \textit{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-4acbc (38% yield)
and d-5ac (43% yield), respectively. Interestingly, d-5ac incor-
porates the Ph and the deuterium atom in a \textit{trans} disposition,
whereas the [2 + 2] adduct, d-4acb, holds these groups in a \textit{cis}
arrangement. These results strongly suggest the formation of an
intermediate of type II that preserves the stereochemical infor-
mation of the alkene due to an stabilizing electrostatic interaction
between the gold atom and the benzylic carbocation (Scheme 3).\textsuperscript{21} A subsequent nucleophilic \textit{anti} attack of the
carbonyl moiety would lead to intermediate III and, eventually,
to the product d-4acbc. The preferential formation of this THP
with the C2 and C6 substituents in \textit{cis} is in agreement with a
transition state that places these groups in equatorial disposi-
tion (Prins-like cyclization from III to 4). On the other hand, if
species II collapses to render a [2 + 2 + 2] adduct, the Ph and the D
atom would retain the initial \textit{trans} arrangement, as observed in
d-5ac.

We also analysed the cycloaddition with deuterated
\textit{α}-methylstyrene (d-2b) as a model for \textit{α}-substituted alkenes
(Scheme 4). Curiously, the expected [2 + 2 + 2] isomeric adducts
d-4abb and d-4abbb were obtained as mixtures of \textit{cis}/\textit{trans} (Ph/D)
isomers. Accordingly, an acyclic carbocation species like \textit{II}' or,
alternatively, a fast equilibrium between the Ph/D-\textit{trans} and \textit{cis}
intermediates II and II" could account for this result.\textsuperscript{22,23}
Considering this proposal, the exclusive formation of the \textit{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
corresponding [2 + 2 + 2] adducts were obtained in both cases but, interestingly, the stereochemistry of each deuterated cycloadduct (d-4acb, d-5ac and d-4abbc), turned out to be identical to that obtained with Au3.14 Thus, the σ-donor and 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 σ-unsaturated components. The process shows a broad scope with regard to the alkenes and aldehydes that can be easily used, and provides an efficient, atom-economical and stereo-selective access to a variety of 2,6-disubstituted THPs from easily accessible or even commercially available materials.

Acknowledgements

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Notes and references

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 ESIF 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/4abα) were established by NMR and, additionally, those of the major isomer (4aba), with the Ph groups in cis, were further confirmed by X-ray ESIF.11
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. ESIF
17 The ring fusion was exclusively cis in all these polycyclic systems. Therefore, d refers to the substituents at the 2,6-THP positions.
18 An α-alkyl-substituted allenamides such as 3-(buto-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

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. 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-4aca (64% yield) and traces of the [2 + 2] adduct d-5ae, both as almost equimolar mixtures of cis and trans (pMeOPh/D) isomers. 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.