



# Gold(I)-Catalyzed Cascade Cycloadditions between Allenamides and Carbonyl-Tethered Alkenes: An Enantioselective Approach to Oxa-Bridged Medium-Sized Carbocycles

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# Gold(I)-catalyzed Cascade Cycloadditions between Allenamides and Carbonyl-tethered alkenes: A straightforward, enantioselective approach to oxa-bridged medium-sized carbocycles

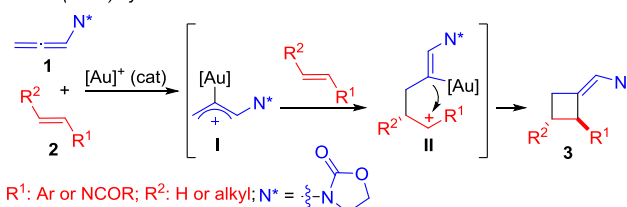
Hélio Faustino,<sup>†</sup> Isaac Alonso,<sup>†</sup> José L. Mascareñas\* and Fernando López\*

During the last decade, homogeneous gold catalysis has experienced an extraordinary growth, resulting in the discovery of a variety of powerful transformations.<sup>[1]</sup> Particularly relevant in terms of versatility and synthetic potential are those involving the cycloaddition of two or more unsaturated components, as they allow the rapid assembly of variety of cyclic and polycyclic systems in an efficient and usually stereoselective manner.<sup>[2]</sup> In this context, we and others have reported several intramolecular gold-catalyzed cycloadditions involving allenes,<sup>[3]</sup> as well as intermolecular cycloadditions of allenamides to dienes [(4 + 2)] or to alkenes [(2 + 2)].<sup>[4,5]</sup> The high regioselectivity observed in the (2 + 2) annulations,<sup>[5a]</sup> together with the intrinsic requirement of a carbocation-stabilizing group at the alkene, suggests that this reaction proceeds through a cationic pathway such as that depicted in the Scheme 1 (upper).<sup>[6]</sup>

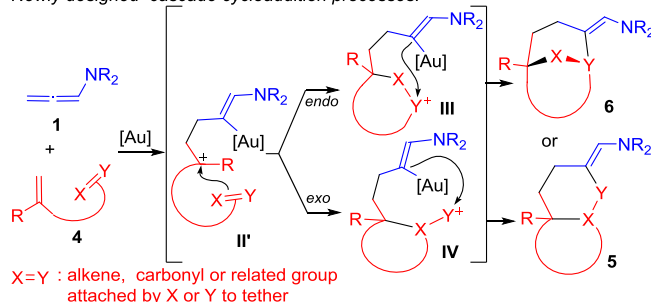
In light of this mechanism, we envisioned that interception of the carbocationic intermediate **II** by an internal nucleophile might allow to assemble interesting bicycles according to the cationic cascade shown in the Scheme 1 (bottom).<sup>[7]</sup> Depending on the *endo* or *exo* trapping of the cation **II**<sup>+</sup>, the process could yield either fused- or bridged-bicyclic skeletons of type **5** or **6**. Herein, we demonstrate the viability of the *endo* route when a carbonyl group (X=Y is O=CR) is used as carbocation intercepting unit.<sup>[8]</sup> The process provides a straightforward, robust and versatile access to synthetically appealing oxa-bridged systems of type **6** (X=O, Y=

carbon) embedding seven, eight or even nine-membered carbocycles. Additionally, we also disclose several examples of an enantioselective variant promoted by chiral diposphine- and/or phosphoramidite-gold catalysts, which provides a practical asymmetric approach to 8-oxabicyclo[3.2.1]octanes,<sup>[9]</sup> and the first direct enantioselective entry to oxygen-bridged eight-membered carbocycles.<sup>[10]</sup>

Previous (2 + 2) cycloaddition:<sup>[5a]</sup>

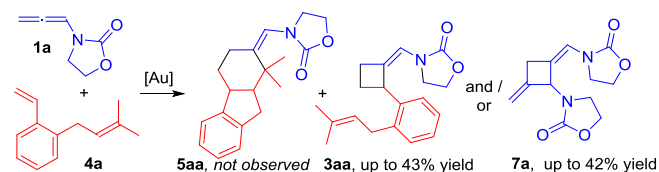


Newly designed cascade cycloaddition processes:



**Scheme 1.** Previously reported (2 + 2) cycloadditions and the proposed “cascade” formal cycloaddition.

Our study began by assessing the viability of engaging the bis-alkene **4a** in a cascade cycloaddition with **1a**. We reasoned that the different nature of the alkenes in **4a** could bias a selective annulation leading the tricycyclic **5aa** (Scheme 1, *exo* mode). However, treatment of these components with several gold catalysts, under different reaction conditions, failed to give **5aa**, and always led to a relatively complex mixture of products, among which we could identify and even isolate the (2 + 2) adduct **3aa** and the allenamide homodimer **7a**.<sup>[11]</sup> (Scheme 2).



**Scheme 2.** Preliminary experiments with **1a** and bis-alkene **4a**.

Therefore, we explored an alternative cascade process relying

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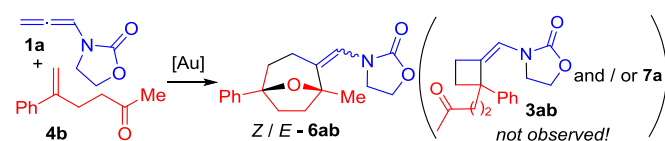
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have equally contributed to this work.

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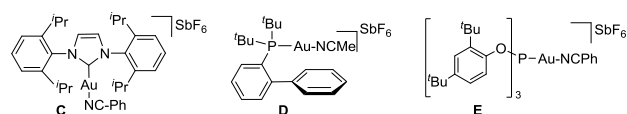
on the use of a carbonyl group as internal nucleophile. Interception of **II'** by the carbonyl oxygen might generate a cyclic oxocarbenium ion (Scheme 1, **III**, X = O, Y = CR), susceptible of undergoing a *Prins*-like terminal cyclization with the vinyl gold moiety.<sup>[12]</sup> Gratifyingly, slow addition over 1 hour of a solution of allenamide **1a** to a mixture of **4b** and Ph<sub>3</sub>PAuCl/AgSbF<sub>6</sub> (**A**) led to a 1.2:1 mixture of the *Z*- and *E*- 8-oxabicyclo[3.2.1]octane derivatives **6ab**, which were isolated in 75% yield (Table 1, entry 1).<sup>[13]</sup> Similar results, but with higher *Z* selectivity, were achieved with gold catalysts **B-E** (entries 3-6). Significantly, by using the phosphite-gold complex **E**, the catalyst loading could be reduced down to 1 mol% (entry 7), and the allenamide can be added in one portion (entry 8), providing *Z*-**6ab** in 87% yield.<sup>[14]</sup> The robustness and practicality of the process was further demonstrated by performing the reaction on a 8 mmol scale (**1a**), with a 0.5 mol% of catalyst, which produced 2.0 g of *Z*-**6ab** (84% yield) after just 5 min (entry 9).

**Table 1.** Cascade cycloadditions with carbonyl-tethered alkene **4b**.



| entry <sup>[a]</sup> | [Au]   | mol% | <i>Z</i> : <i>E</i> <sup>[b]</sup> | <b>6ab</b> , yield (%) |
|----------------------|--|------|------------------------------------|------------------------|
| 1                    | Ph <sub>3</sub> PAuCl / AgSbF <sub>6</sub> ( <b>A</b> )                | 5    | 1.2 : 1                            | 75                     |
| 2                    | Ph <sub>3</sub> PAuCl / AgSbF <sub>6</sub> ( <b>A</b> ) <sup>[c]</sup> | 5    | 3.2 : 1                            | 70                     |
| 3                    | Ph <sub>3</sub> PAuNTf <sub>2</sub> ( <b>B</b> )                       | 5    | 5.5 : 1                            | 75                     |
| 4                    | <b>C</b>   | 5    | 7.5 : 1                            | 79                     |
| 5                    | <b>D</b>   | 5    | 50 : 1                             | 75                     |
| 6                    | <b>E</b>   | 5    | 15 : 1                             | 76                     |
| 7                    | <b>E</b>   | 1    | 22 : 1                             | 74                     |
| 8 <sup>[d]</sup>     | <b>E</b>   | 1    | 22 : 1                             | 87                     |
| 9 <sup>[d,e]</sup>   | <b>E</b>   | 0.5  | 22 : 1                             | 84                     |

[a] **1a** (1 equiv) added over one hour to a solution of **4b** (1.5 equiv) and [Au] (mol%), in CH<sub>2</sub>Cl<sub>2</sub> at -15°C, unless otherwise noted. Conversions > 99% (<sup>1</sup>H-NMR) after 5 min. [b] *Z*/*E* ratios determined by <sup>1</sup>H NMR spectroscopy of the crude mixtures. [c] Catalyst was filtered through Celite prior to its use. [d] **1a** was added in one portion. [e] Performed on an 8.0 mmol scale (**1a**).



We next analysed the scope of the process. As can be seen in Table 2, not only a methyl ketone was competent to productively intercept intermediate **II'**. The cycloaddition also works with a phenyl ketone (**4c**), an aldehyde (**4d**) or a methyl ester (**4e**), to give the corresponding 8-oxabicyclo[3.2.1]octane derivatives (**6ac-6ae**) in good yields (entries 1-4). On the other hand, substrates in which a phenyl ring holds the alkene and the carbonyl moiety (**4f** and **4g**), provided the corresponding oxa-tricyclic systems, **6af** and **6ag**, in 41% and 65% yields, respectively (entries 5 and 6).

The strategy also allows to build 5,7-bicarbo-cyclic systems such as **6ah**, by using cyclopentanone precursors like **4h** (entry 7). This reaction was completely diastereoselective and the relative configuration of the product was determined by X-ray diffraction analysis.<sup>[15]</sup> The effect of additional substituents at the styrene moiety was investigated in the substrate **4i** (*E*/*Z* = 1.3:1, entry 8). In consonance with previous results in the (2 + 2) cycloaddition processes,<sup>[5a]</sup> we only observed the reaction of the *trans* counterpart

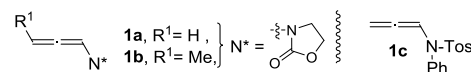
(*E*-**4i**),<sup>[16]</sup> which efficiently afforded the oxabicyclic system **6ai** (77% yield, entry 8), featuring the oxygen-bridge and the methyl group in a *syn* disposition (Figure 1).<sup>[17]</sup>

Importantly, the cascade cycloaddition is not restricted to phenyl-substituted alkenes, which might be particularly biased to participate in the process owing to the generation of benzylic carbocation intermediates (e.g. **II'**, R = Ph, Scheme 1). Indeed, the presence of a methyl substituent (**4j**) is enough to warrant the annulation, with the product **6aj** being isolated in a 63% yield (entry 9).<sup>[18]</sup> On the other hand, oxo-enamides are also effective precursors, producing amino derivatives like **6ak** and **6al**, in good yields (entries 10 and 11). Substituted allenamides like **1b**, and the *N*-phenyl-*N*-tosylallenamide **1c**, equally provided the corresponding bicyclic products, **6bb** and **6cb**, in moderate to good yields (entries 12 and 13).

**Table 2.** Scope of the Au-catalyzed cascade cycloaddition between allenamides (**1**) and carbonyl-tethered alkenes (**4**).<sup>[a]</sup>

| entry | <b>1</b>  | oxo-alkene ( <b>4</b> )                            | product | <b>6</b>   | yield <sup>[b]</sup> |
|-------|-----------|--|---------|------------|----------------------|
| 1     | <b>1a</b> | <b>4b</b> , R <sup>2</sup> = Me                    |         | <b>6ab</b> | 87                   |
| 2     | <b>1a</b> | <b>4c</b> , R <sup>2</sup> = Ph                    |         | <b>6ac</b> | 86                   |
| 3     | <b>1a</b> | <b>4d</b> , R <sup>2</sup> = H                     |         | <b>6ad</b> | 90                   |
| 4     | <b>1a</b> | <b>4e</b> , R <sup>2</sup> = OMe                   |         | <b>6ae</b> | 75 <sup>[c]</sup>    |
| 5     | <b>1a</b> | <b>4f</b> , R <sup>3</sup> = H                     |         | <b>6af</b> | 41 <sup>[d,e]</sup>  |
| 6     | <b>1a</b> | <b>4g</b> , R <sup>3</sup> = Me                    |         | <b>6ag</b> | 65 <sup>[d,f]</sup>  |
| 7     | <b>1a</b> | <b>4h</b>  |         | <b>6ah</b> | 51, dr 1:0           |
| 8     | <b>1a</b> | <b>4i</b> , <i>E</i> / <i>Z</i> = 1.3:1            |         | <b>6ai</b> | 77, dr 1:0           |
| 9     | <b>1a</b> | <b>4j</b> , R <sup>3</sup> = Me                    |         | <b>6aj</b> | 63                   |
| 10    | <b>1a</b> | <b>4k</b> , R <sup>3</sup> = NMeCO <sub>2</sub> Bn |         | <b>6ak</b> | 65                   |
| 11    | <b>1a</b> | <b>4l</b> , R <sup>3</sup> = N <sup>*</sup>        |         | <b>6al</b> | 75                   |
| 12    | <b>1b</b> | <b>4b</b>  |         | <b>6bb</b> | 57, dr 3:1           |
| 13    | <b>1c</b> | <b>4b</b>  |         | <b>6cb</b> | 77 <sup>[g]</sup>    |

[a] Allenamide **1** (1 equiv) was added to a mixture of **4** (1.5 equiv) and **E** (1%) in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) at -15 °C; Conversions >99% (<sup>1</sup>H-NMR) after 5-15 min. [b] Isolated yields of **6** (%); *Z*/*E* ratios, determined by <sup>1</sup>H NMR of the crude mixtures, are > 20:1, unless otherwise noted. [c] Cyclobutane **3ae** was also obtained in 14% yield. [d] The allenamide dimer **7a** was also obtained in 30% yield. [e] *Z*/*E* = 9:1. [f] *Z*/*E* = 10:1. [g] *Z*/*E* = 3:1.

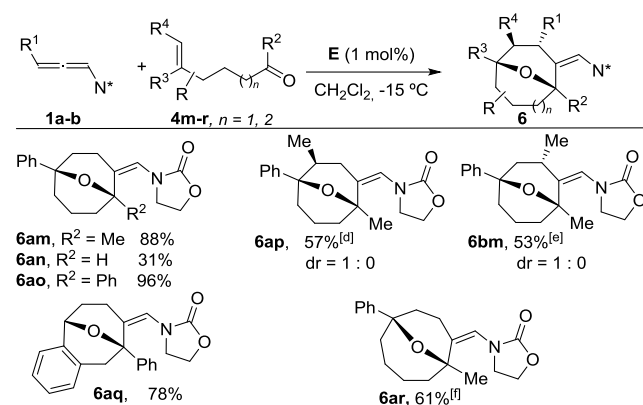


The efficiency of the above process suggested that the strategy might be used to construct eight or even nine-membered carbocycles, simply by using oxo-alkenes featuring longer carbon tethers. Assembling these medium-sized carbocycles continues to be a major challenge, owing to their presence in a large number of relevant products and the well-known difficulties associated to their construction.<sup>[19,20]</sup> Gratifyingly, the gold-catalyzed annulation of **1a** with **4m-4o** provided the desired 9-oxabicyclo[3.3.1]nonanes **6am-6ao**, in moderate to excellent yields (Table 3). Moreover, and

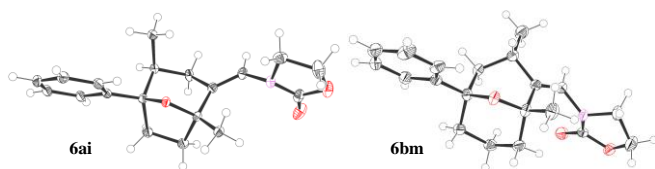
similarly to the cycloadditions leading to the seven-membered cycles, the reaction also proceeds with more substituted alkenes (**4p**, R<sup>4</sup> = Me) or disubstituted allenamides (**1b**), providing the oxa-bridged cyclooctanes **6ap** and **6bm** with complete diastereoselectivity. An unambiguous confirmation of the stereochemistry of **6bm** could be obtained by X-ray diffraction analysis (Figure 1).<sup>[21]</sup> The method also provides an immediate entry to the 6,8-fused bicyclic derivatives like **6aq** (78% yield) and, importantly, can be even used to make cyclononane derivatives like **6ar**.

Overall, these results highlight the great potential and versatility of the methodology, which provides a direct and practical access to highly valuable oxa-bridged seven, eight and even nine-membered carbocycles using readily accessible starting materials.<sup>[22]</sup>

**Table 3.** Access to 8- and 9-membered oxa-bridged carbocycles.<sup>[a-c]</sup>



[a]-[c]: See Table 2. [d] The cyclobutane derivative **3ap** (12% yield) was also obtained. [e] **3bm** (12% yield) was also obtained. [f] Carried out at  $-78^\circ\text{C}$  for 6h. **3ar** (26% yield), was also obtained.



**Figure 1.** X-Ray structures of **6ai** and **6bm**.

The recent progress in asymmetric gold catalysis called for exploring the viability of achieving these annulations in an enantioselective manner.<sup>[23]</sup> Curiously, despite the synthetic value of oxa-bridged medium-sized carbocycles, catalytic enantioselective approaches to these systems are very scarce, and essentially limited to the seven-membered derivatives.<sup>[9,10]</sup>

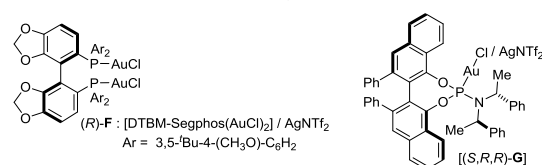
A preliminary screening of different types of chiral gold complexes, allowed to identify the DTBM-Segphos complex (*R*)-**F** and the phosphoramidite-gold complex (*S,R,R*)-**G** as suitable catalysts to achieve the cycloaddition of **1a** with several oxo-alkenes (**4**), in good yields and moderate-to-high levels of enantioselectivity (Table 4).<sup>[24]</sup> In the case of the oxa-bridged seven membered carbocycles, the best enantiomeric ratios were obtained with (*S,R,R*)-**G**, and ranged from 82:18 to 90:10. (entries 1–4). Interestingly, these er values could be increased up to 98:2, by performing a partial crystallization (e.g. entries 1 and 2). In the case of the cyclooctanes, while the phosphoramidite gold catalyst (*S,R,R*)-**G** provided good enantioselectivities (er's from 87:13 to 90:10),<sup>[24]</sup> the Segphos complex (*R*)-**F** provided the cycloadducts **6am**, **6ao** and **6ap** with enantiomeric ratios between 91:9 and 96:4 (entries 5–7). Despite there is still room for improvement, these

results represent the first highly enantioselective entries to oxa-bridged eight-membered carbocycles and one of the very few enantioselective approaches to any type of cyclooctanes.<sup>[10]</sup>

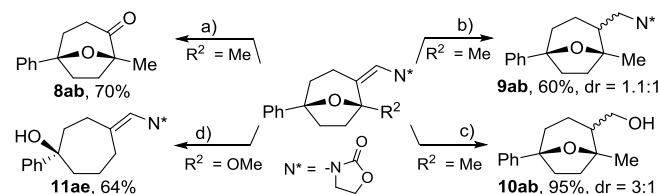
**Table 4.** Enantioselective cycloadditions of **1a** and oxo-alkenes **4**.

| Entry <sup>[a]</sup> | <b>4</b>  | [Au] (5 mol %)             | <b>6</b> , yield (%) <sup>[b]</sup> | er <sup>[c]</sup>      |
|----------------------|-----------|----------------------------|-------------------------------------|------------------------|
| 1                    | <b>4b</b> | ( <i>S,R,R</i> )- <b>G</b> | <b>6ab</b> , 63                     | 83 : 17 <sup>[d]</sup> |
| 2                    | <b>4c</b> | ( <i>S,R,R</i> )- <b>G</b> | <b>6ac</b> , 69                     | 82 : 18 <sup>[e]</sup> |
| 3 <sup>[f]</sup>     | <b>4d</b> | ( <i>S,R,R</i> )- <b>G</b> | <b>6ad</b> , 83                     | 84 : 16                |
| 4                    | <b>4i</b> | ( <i>S,R,R</i> )- <b>G</b> | <b>6ai</b> , 72 <sup>[g]</sup>      | 90 : 10                |
| 5 <sup>[h]</sup>     | <b>4m</b> | ( <i>R</i> )- <b>F</b>     | <b>6am</b> , 52                     | 95 : 5                 |
| 6 <sup>[h]</sup>     | <b>4o</b> | ( <i>R</i> )- <b>F</b>     | <b>6ao</b> , 80                     | 91 : 9                 |
| 7 <sup>[h]</sup>     | <b>4p</b> | ( <i>R</i> )- <b>F</b>     | <b>6ap</b> , 45                     | 96 : 4                 |

[a]: **1a** (1 equiv), **4** (1.5 - 2 equiv) and [Au] (5 mol%) in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ , unless otherwise noted. Conversions > 99% after 10-180 min. [b] Isolated yields of **6**. Z : E ratios are > 20 : 1. [c] Determined by HPLC. [d] er = 95:5 after crystallization (iPrOH/hexane). [e] er = 98:2 after crystallization. [f] Carried out from  $-78$  to  $-60^\circ\text{C}$ , for 5h. [g] dr = 1:0. [h] Carried out from  $-78$  to  $-35^\circ\text{C}$ , for 4-12h.



Finally, we also did a preliminary exploration of the manipulability of the oxa-bridged carbocycles, which confirmed that the presence of the *exo*-enamide provides for rapid and versatile transformations. Treatment of adduct **6ab** with  $\text{RuO}_2/\text{NaIO}_4$  cleanly afforded the ketone **8ab** (70% yield). Alternatively, the enamide group could be hydrogenated to give **9ab** (60% yield), or reduced to the epimeric alcohols **10ab** in 95% yield. On the other hand, the presence of the methoxy group in **6ae** allowed to perform a Lewis acid-induced opening of the bridge to yield cycloheptane **11ae**.



**Scheme 3.** Conditions: a)  $\text{RuO}_2$ ,  $\text{NaIO}_4$ , THF / H<sub>2</sub>O, 70%. b) H<sub>2</sub>, Pd/C; 60%. c) i) HCl<sub>aq</sub> ii) NaBH<sub>4</sub>; 95%. d) TiCl<sub>4</sub>, Et<sub>3</sub>SiH,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; 64%.

In summary, we have discovered a simple and highly versatile cascade cycloaddition between allenamides and carbonyl-tethered alkenes. The reaction can be performed at mild temperatures with just 1 mol% of the catalyst, and provides a straightforward entry to oxa-bridged seven, eight and even nine-membered rings. Moreover, we have also demonstrated that using chiral gold catalysts it is possible to obtain the products with good or high enantioselectivities. In particular, the method provides the first enantioselective entries to eight-membered carbocycles by means of a formal intermolecular cycloaddition reaction.

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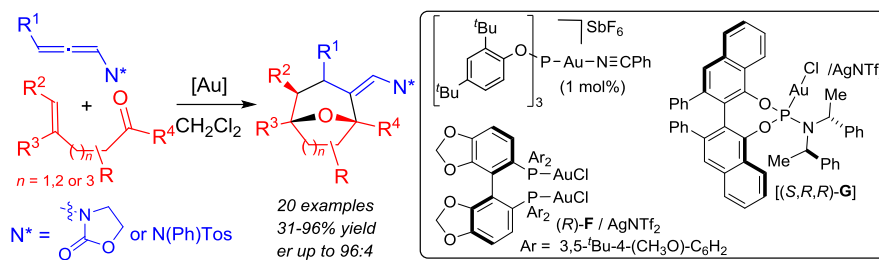
**Keywords:** gold • enantioselective • catalysis • annulation • cascade

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- [13] Slow addition of the allenamide is aimed to avoid the formation of **7a**.
- [14] The structure of **6ab** could be further confirmed by X-ray analysis CCDC 917326 contains the crystallographic data of **6ab**, which can be obtained via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [15] CCDC 930627 contains the crystallographic data of **6ah**, which can be obtained via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [16] The Z isomer, **Z-4i**, is recovered from the crude reaction mixture.
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## ((Catch Phrase))

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Gold(I)-catalyzed Cascade  
Cycloadditions between Allenamides  
and Carbonyl-tethered alkenes: A  
straightforward, enantioselective  
approach to oxa-bridged medium-sized  
carbocycles



Allenamides react with aldehydes or ketones equipped with  $\gamma$ ,  $\delta$  or  $\varepsilon$  alkenyl groups, upon activation with suitable gold catalysts, to provide oxa-bridged systems embedding carbocycles of seven to nine members, in a formal cascade cycloaddition process. The reaction requires low catalyst loadings (typically 1 mol%) and achieves full conversion within few minutes at mild temperatures. Moreover, using chiral phosphoramidite- or bisphosphine-gold catalysts it is possible to obtain the oxa-bridged seven- and eight-membered rings with good or high enantioselectivities.