Gold Catalysis

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

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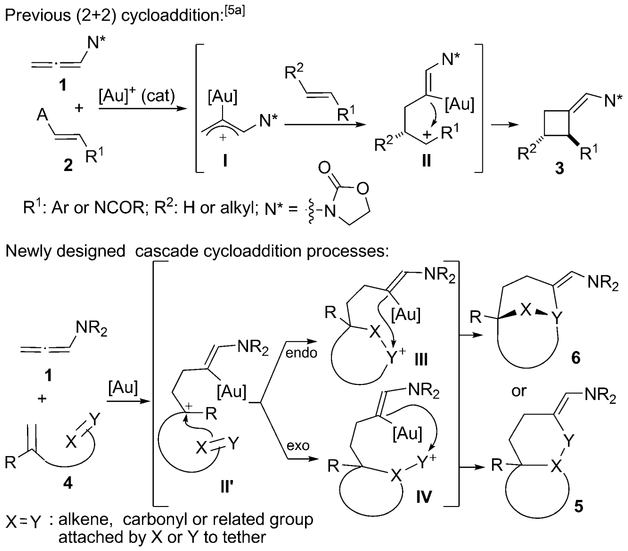
During the last decade, research in homogeneous gold catalysis has experienced an extraordinary growth, resulting in the discovery of a variety of powerful transformations.[1] Particularly relevant, in terms of versatility and synthetic potential, are those reactions involving the cycloaddition of two or more unsaturated components, as a variety of cyclic and polycyclic systems can be rapidly assembled in an efficient and usually stereoselective manner.[2] In this context, we and others have reported several intramolecular gold-catalyzed cycloadditions involving allenes,[3] as well as intermolecular cycloadditions of allenamides to dienes, (4+2), or to alkenes, (2+2).[4,5] The high regioselectivity observed in the (2+2) annulations,[5a] 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).[6]

In light of this mechanism, we envisioned that interception of the carbocationic intermediate **II** by an internal nucleophile might result in the assembly of interesting bicycles through the cationic cascade shown in the Scheme 1 (bottom).[7] Depending on the *endo* or *exo* trapping of the cation **II′**, the transformation 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.[8] The reaction provides a straightforward, robust, and versatile access to synthetically appealing oxa-bridged systems of type **6** (X = O, Y = carbon) containing seven-, eight-, or even nine-membered carbocycles. Additionally, we also disclose several examples of an enantioselective variant promoted by chiral diphosphine/gold and/or phosphoramidite/gold catalysts that provides a practical asymmetric approach to 8-oxabicyclo[3.2.1]octanes,[9] and the first direct enantiocatalytic entry to oxygen-bridged eight-membered carbocycles.[10]



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

Our study began by assessing the viability of a cascade cycloaddition between the bisalkene **4a** and **1a**. We reasoned that the different nature of the alkenes in **4a** could bias the annulation to selectively give the tricarbocycle **5aa** (Scheme 1, *exo* mode). However, treatment of these substrates 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**.[11] (Scheme 2).

Therefore, we explored an alternative cascade process relying on the use of a carbonyl group as an internal nucleophile. Interception of **II′** by the carbonyl oxygen might generate a cyclic oxocarbenium ion (**III**, X = O, Y = CR; Scheme 1), susceptible of undergoing a Prins-like terminal cyclization with the vinyl gold moiety.[12] Gratifyingly, slow addition over 1 hour of a solution of allenamide **1a** to a mixture of **4b** and $[Ph_3PAuCl]/AgSbF_6$ (**A**) led to a 1.2:1 mixture of the *Z*- and *E*-configured 8-oxabicyclo[3.2.1]octane

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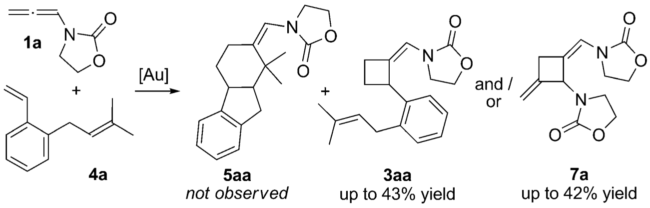
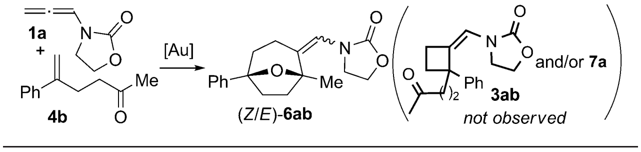


Scheme 2. Preliminary experiments with **1a** and bisalkene **4a**.

derivatives **6ab**, which were isolated in 75 % yield (Table 1, entry 1).[13] Similar results, but with higher Z selectivity, were achieved with gold catalysts **B**–**E** (Table 1, entries 3–6). Significantly, by using the phosphite/gold complex **E**, the catalyst loading could be lowered to 1 mol % (Table 1, entry 7), and the allenamide can be added in one portion (Table 1, entry 8), to provide (*Z*)-**6ab** in 87 % yield.[14] The robustness and practicality of the method was further demonstrated by performing the reaction on an 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).

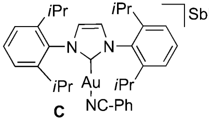
We next evaluated the scope of the method (Table 2). Not only was a methyl ketone competent to productively intercept intermediate **II′**, but the cycloaddition also worked with a phenyl ketone (**4c**), an aldehyde (**4d**), and a methyl ester (**4e**), to give the corresponding 8-oxabicyclo[3.2.1]octane derivatives (**6ac**–**6ae**) in good yields (Table 2, entries 1–4). Also, substrates in which the alkene and the carbonyl moiety (**4f** and **4g**) are attached by a phenyl ring, provided the corresponding oxa-tricyclic systems, **6af** and **6ag**, in 41 % and 65 % yields, respectively (Table 2, entries 5 and 6).

Table 1: Cascade cycloadditions with carbonyl-tethered alkene **4b**.[a]



Entry	[Au]	Mol %	Z/E[b]	Yield of **6ab** [%]
1	$Ph_3PAuCl/AgSbF_6$ (**A**)	5	1.2:1	75
2	$Ph_3PAuCl/AgSbF_6$ (**A**)[c]	5	3.2:1	70
3	$Ph_3PAuNTf_2$ (**B**)	5	5.5:1	75
4	**C**	5	7.5:1	79
5	**D**	5	50:1	75
6	**E**	5	15:1	76
7	**E**	1	22:1	74
8[d]	**E**	1	22:1	87
9[d,e]	**E**	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_2Cl_2 at −15 °C, unless otherwise noted. Conversion was > 99 %, as determined by ^1H NMR spectroscopy, after 5 min. [b] Z/E ratios determined by ^1H 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**). Tf = trifluoromethanesulfonyl.



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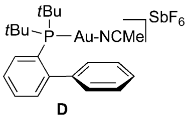

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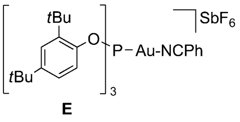
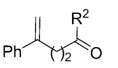
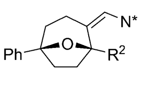
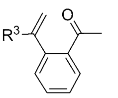
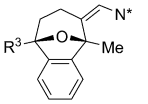
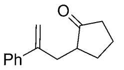
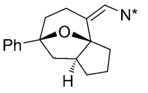
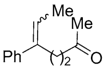
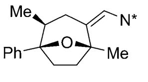
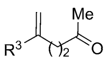
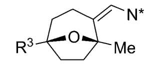
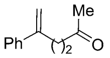
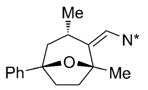
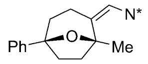
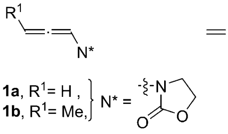


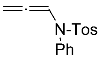
E

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

Entry	1	Oxoalkene (4)		Product	6	Yield [%][b]
1	**1a**		**4b**, $R^2 = Me$		**6ab**	87
2	**1a**		**4c**, $R^2 = Ph$		**6ac**	86
3	**1a**		**4d**, $R^2 = H$		**6ad**	90
4	**1a**		**4e**, $R^2 = OMe$		**6ae**	75[c]
5	**1a**		**4f**, $R^3 = H$		**6af**	41[d,e]
6	**1a**		**4g**, $R^3 = Me$		**6ag**	65[d,f]
7	**1a**		**4h**		**6ah**	51 d.r. 1:0
8	**1a**		**4i** $E/Z = 1.3:1$		**6ai**	77 d.r. 1:0
9	**1a**		**4j**, $R^3 = Me$		**6aj**	63
10	**1a**		**4k**, $R^3 = NMeCO_2Bn$		**6ak**	65
11	**1a**		**4l**, $R^3 = N*$		**6al**	75
12	**1b**		**4b**		**6bb**	57 d.r. 3:1
13	**1c**		**4b**		**6cb**	77[g]

[a] Allenamide **1** (1 equiv) was added to a mixture of oxoalkenes **4** (1.5 equiv) and catalyst **E** (1 %) in CH_2Cl_2 (0.1 м) at −15 °C; Conversion was > 99 %, as determined by ^1H NMR spectroscopy, after 5–15 min. [b] Yield of isolated **6**; Z/E ratios, as determined by ^1H NMR spectroscopy 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] $Z/E = 3:1$.

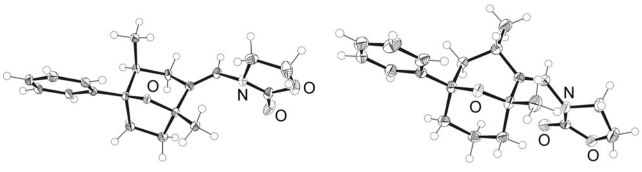




1c

This strategy also enables the synthesis of 5,7-bicarbocyclic systems such as **6ah**, by using cyclopentanone precursors like **4h** (Table 2, entry 7). This reaction was completely diastereoselective and the relative configuration of the product was determined by X-ray diffraction analysis.[15] The effect of additional substituents at the styrene moiety was investigated in the substrate **4i** (*E*/*Z* = 1.3:1: Table 2, entry 8). In agreement with previous results for (2+2) cycloadditions,[5a] we only observed the reaction of the *trans* compound ((*E*)-**4i**),[16] which efficiently afforded the oxabicylic system **6ai** (77 % yield; Table 2, entry 8), featuring the oxygen bridge and the methyl group in a *syn* disposition (Figure 1).[17]

Importantly, the cascade cycloaddition is not restricted to phenyl-substituted alkenes, which might be particularly

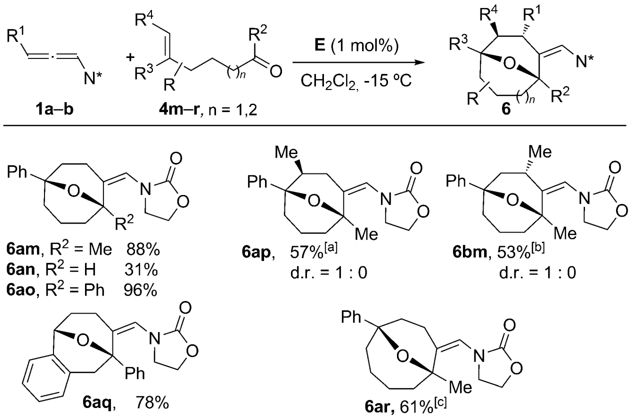


6ai **6bm**

Figure 1. X-Ray structures of **6ai** and **6bm** (thermal ellipsoids are set at 50% probability).

biased to participate in the transformation 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 (Table 2, entry 9).[18] Oxoenamides are also effective precursors, producing amino derivatives, such as **6ak** and **6al**, in good yields (Table 2, entries 10 and 11). Substituted allenamides, such as **1b** and the *N*-phenyl-*N*-tosylallenamide (**1c**), also provided the corresponding bicyclic products, **6bb** and **6cb**, in moderate to good yields (Table 2, entries 12 and 13).

The efficiency of the above transformation suggested that the strategy might be used to construct eight- or even nine-membered carbocycles, simply by using oxoalkenes featuring longer carbon tethers. Assembling these medium-sized carbocycles, which are present in a large number of relevant products, continues to be a major challenge in organic synthesis, owing to the well-known difficulties associated with their construction.[19,20] 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 (Scheme 3). Moreover, and similarly to the cycloadditions leading to the seven-membered cycles, the reaction also proceeds with more-substituted alkenes (**4p**, R^4 = Me) or disubstituted allenamides (**1b**), to provide the oxa-bridged cyclooctanes **6ap** and **6bm** with complete diastereoselectivity. Unambiguous confirmation of the stereochemistry of **6bm** was obtained by X-ray diffraction analysis (Figure 1).[21] The method also provides direct entry to 6,8-fused bicarbocycles such as **6aq** (78% yield) and, importantly, can be even be used to make cyclononane derivatives such as **6ar** (61% yield).



Scheme 3. Synthesis of 8- and 9-membered oxa-bridged carbocycles. Reaction conditions: Allenamide **1** (1 equiv) was added to a mixture of **4** (1.5 equiv) and **E** (1%) in CH_2Cl_2 (0.1 M) at −15 °C. Conversions are >99%, as determined by ^1H NMR spectroscopy, after 5–15 min. Yields are of the isolated products. *Z*/*E* ratios, as determined by ^1H NMR spectroscopy of the crude mixtures, are >20:1, unless otherwise noted. [a] The cyclobutane derivative **3ap** (12% yield) was also obtained. [b] **3bm** (12% yield) was also obtained. [c] Carried out at −78 °C for 6 h. **3ar** (26% yield), was also obtained.

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

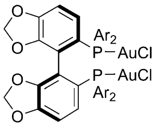
Owing to the recent progress in asymmetric gold catalysis,[23] we were interested in exploring the viability of achieving these annulations in an enantioselective manner. Curiously, despite the synthetic value of oxa-bridged medium-sized carbocycles, catalytic enantioselective approaches to these systems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

A preliminary screening of different types of chiral gold complexes identified 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 oxoalkenes **4**, in good yields and moderate-to-high levels of enantioselectivity (Table 3).[24] 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. (Table 3, entries 1–4). Interestingly, these e.r. values could be increased up to 98:2, by performing a partial crystallization (Table 3, entries 1 and 2). In the case of the cyclooctanes, although the phosphoramidite gold catalyst (*S*,*R*,*R*)-**G** provided good enantioselectivity (e.r. from 87:13 to

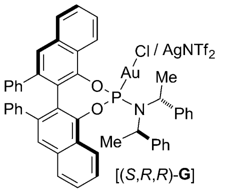
Table 3: Enantioselective cycloadditions of **1a** and oxoalkenes **4**.

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

[a] **1a** (1 equiv), **4** (1.5–2 equiv) and [Au] (5 mol%) in CH_2Cl_2 at −78 °C, unless otherwise noted. Conversion was >99% after 10–180 min. [b] Yield of isolated **6**; *Z*/*E* ratios are >20:1. [c] Determined by HPLC. [d] e.r. = 95:5 after crystallization (*i*PrOH/hexane). [e] e.r. = 98:2 after crystallization. [f] At −78 to −60 °C, for 5 h. [g] d.r. = 1:0. [h] At −78 to −35 °C, for 4–12 h.



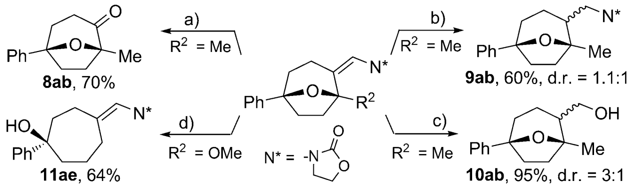
(*R*)-**F** : [dtbm-segphos($(AuCl)_2$] / $AgNTf_2$
Ar = 3,5-*t*Bu-4-(CH_3O)C_6H_2



[(*S*,*R*,*R*)-**G**]

90:10),[24] the Segphos complex (*R*)-**F** provided the cycloadducts **6am**, **6ao**, and **6ap** with higher enantiomeric ratios (between 91:9 and 96:4; Table 3, entries 5–7). Although there is still room for improvement, these results represent the first highly enantioselective syntheses of oxa-bridged eight-membered carbocycles and one of the very few enantiocatalytic approaches to cyclooctanes.[10]

Finally, we also did a preliminary exploration of the manipulability of the oxa-bridged carbocycles, and confirmed that the presence of the *exo*-enamide enables a variety of transformations (Scheme 4). Treatment of adduct **6ab** with RuO$_2$/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. Also, the presence of the methoxy group in **6ae** enabled a Lewis acid induced opening of the bridge to yield cycloheptane **11ae**.



Scheme 4. Reaction conditions: a) RuO$_2$, NaIO$_4$, THF/H$_2$O, 70 %. b) H$_2$, Pd/C; 60 %. c) i) HCl (aq); ii) NaBH$_4$; 95 %. d) TiCl$_4$, Et$_3$SiH, CH$_2$Cl$_2$, −78 °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 by using chiral gold catalysts it is possible to obtain the products with good to high enantioselectivities. In particular, the method provides the first enantiocatalytic entries to eight-membered carbocycles by means of a formal intermolecular cycloaddition reaction.

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[11] Other bisalkenes led exclusively to (2+2) adducts of type **3**. See the Supporting Information for more details.

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[13] Slow addition of the allenamide is aimed to avoid the formation of dimer **7a**.

[14] CCDC 917326 (**6ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] CCDC 930627 (**6ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] The *Z* isomer, (*Z*)-**4i**, is recovered from the crude reaction mixture.

[17] CCDC 917327 (**6ai**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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