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Gold Catalyzed Diastereoselective Cascade Allylation/Enyne Cycloisomerization to Construct Densely Functionalized Oxygen Hetereocycles

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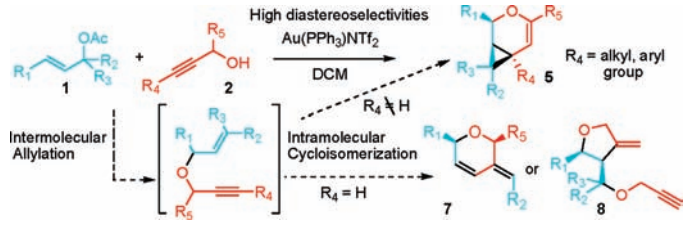
ABSTRACT



A new tandem allylation/enyne cycloisomerization reaction was developed to construct densely functionalized oxygen hetereocycles with high diastereoselectivities from the intermolecular reaction of allylic acetates with propargylic alcohols via gold catalysis. Terminal and nonterminal propargylic alcohols take different reaction routes either to provide 3-oxa-bicyclo[4.1.0]hept-4-ene derivatives 5 or to give endocyclic rearrangement products 7 and alkoxycyclization adducts 8. Cyclopropane's stereochemistry was mainly determined by allylic substituents.

Transition metal-catalyzed cycloisomerization of 1,*n*-enynes is one of the most attractive strategies for the synthesis of the complicated cyclic molecules.[1,2] Almost all reported results to date in this area are intramolecular reactions, which require additional synthetic steps to prepare the enyne substrates. An intermolecular-type reaction, if possible, would not only minimize the use of chemicals and the waste production, but also improve the reaction efficiency and broaden substrate diversity. However, extending these intramolecular rearrangements to intermolecular processes is very difficult, due to the unfavored entropic binding penalties, and inefficient regio- and stereocontrol. A partial approach to this transformation has just been reported in the research of the Pauson−Khand reaction by using a pseudointermolecular process, which combined the synthesis of enyne and its further cyclization into a one-pot reaction, induced by either one or two metal complexes.[3,4] Despite these achieve-

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(1) Selected general reviews: (a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Top. Organomet. Chem.* **2006**, *19*, 259. (d) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

(2) Selected reviews on Pt- or Au-catalyzed reactions involving enyne cycloisomerizations: (a) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (c) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (g) Ma, S.-M.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (h) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (i) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (j) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (k) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (l) Añorbe, L.; Dominguez, G.; Pérez-Castells, J. *Chem.—Eur. J.* **2004**, *10*, 4938. (m) Mendez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*, 397. (n) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

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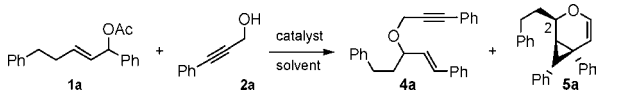
Table 1. Gold-Catalyzed Intermolecular Reaction of (*E*)-1,5-Diphenyl Pent-2-enyl Acetate **1a** and 3-Phenylprop-2-yn-1-ol **2a** To Give 3-Oxa-bicyclo[4.1.0]hept-4-ene Derivatives **5a**[a]



		1a/2a	time/temp	yield of 4a (%)[b]	yield of 5a (%)[b]
1	5% Au(pph$_3$CI/AgOTf	1/1.5	1 h/rt	15	<5
2	5% Au(PPh$_3$)NTf$_2$	1/1.5	0.5 h/rt	8	45
3	5% Au(PPh$_3$)NTf$_2$	1/6	1 h/30 °C	trace	86

[a] Unless noted, all reactions were carried out at 0.1 mmol scale in 3 mL of CH_2Cl_2 at 25 °C. [b] Isolated yields.

ments, there are few reports of employing a similar method in the study of the enyne cycloisomerization reaction.[4]

In this paper, we will report a convenient new method to construct densely functionalized 5- or 6-membered oxygen hetereocycles with high diastereoselectivities from the intermolecular reaction of allylic acetates with propargylic alcohols via gold catalysis. This is the first report, to the best of our knowledge, of a two-step tandem process involving intermolecular allylic substitution[5] and intramolecular 1,6-enyne cycloisomerization[6] in which the Au(I) catalyst played a mechanistically distinctive dual role.

The reaction of (*E*)-1, 5-diphenylpent-2-enyl acetate **1a** with 3-phenylprop-2-yn-1-ol **2a** was chosen as the model system for our initial investigation. When 1 equiv of **1a** and 1.5 equiv of **2a** were treated with 5% equiv of Au(PPh$_3$)Cl/AgOTf in DCM for 1 h, **1a**'s rearrangement isomer **3a** was obtained in 70% yield,[5c,d] along with enyne ether **4a** (15% yield), and a trace amount of cyclic product **5a** (Table 1, entry 1).

The structure of **5a**, as shown in Figure 1, was identified to be a polysubstituted 3-oxa-bicyclo[4.1.0]hept-4-ene

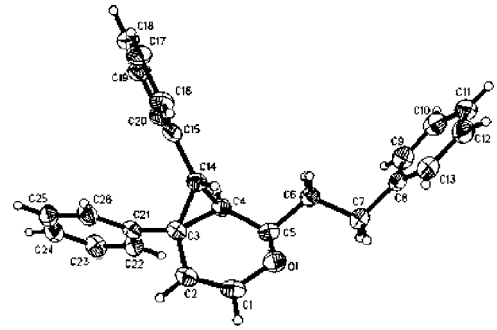


Figure 1. X-ray chromatograph of compound **5a**.

derivative,[6c,d,7] in which the 2-phenylethyl group and the cyclopropyl group are located on the same side of the dihyropyran ring (the reaction in Table 1). It was notable that **5a** was obtained as the single diastereomer.

Further experiments proved that Au(PPh$_3$)NTf$_2$ (5% equiv) performed better than other catalysts (Table 1, entry 2). Optimization of the **1a**/**2a** ratio, catalyst loading, and reaction time/temperature identified a set of best conditions to give **5a** in 86% yield (Table 1, entry 3).[8]

Under the conditions from entry 3 in Table 1, the scope and limitations for this reaction were then explored.[9] Some representative examples for the preparation of 3-oxa-bicyclo[4.1.0]hept-4-ene derivatives **5** were summarized in Table 2.[6c,d] The reactions of a number of disubstituted allylic acetates with mono- or disubstituted propargylic alcohols were investigated to determine the influence of various substitution patterns (R_1−R_5). Both aromatic and aliphatic substituents worked well at the R_4 position, in which substrates with electron-rich aryl groups worked better than that with electron-deficient aryl groups and alkyl groups (**2a**−**f**, Table 2, entries 1−6). At the R_2, R_3 position, both aryl (**1a**, **1b**,**c**) and dialkyl (**1d**) substrates gave the desired products in moderate to good yields (Table 2, entries 1 and 7−9). The low reaction yield of **5h** is due to the low reactivity of the in situ generated enyne ether intermediate.[9] At the R_1 position, replacement of the phenylethyl group with the bulky phenyl group (**1e,** Table 2, entries 10 and 11) lowered the reaction yield. Disubstituted propargylic alcohols were also examined in this reaction. The reaction of **1a** with **2g** or **2i** gave the desired product **5m** and **5o** in moderate yields (Table 2, entries 12 and 14), while the reaction of **1e** with **2h** gave **5n** in low yield (Table 2, entry 13). As shown in Table 2, when "R_5" is a hydrogen atom,

(3) Selected reviews on intermolecular cascade reactions: (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (c) Aubert, C.; Fensterbank, L.; Gandon, V.; Malacria, M. *Top. Organomet. Chem.* **2006**, *19*, 259. (d) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (e) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

(4) Examples of intermolecular allylation/Pauson−Khand cascade reactions: (a) Malacria, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *Org. Lett.* **2005**, *7*, 1661. (b) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (c) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220.

(5) Gold-catalyzed cyclization of allylic acetate: (a) Wang, Y.-H.; Zhu, L.-L.; Zhang, Y.-X.; Chen, Z. *Chem. Commun.* **2010**, *46*, 577. (b) Porcel, S.; López-Carrillo, V.; Garcssa-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1883. (c) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653. (d) Gourlaouen, C.; Marion, N.; Nolan, S. P.; Maseras, F. *Org. Lett.* **2009**, *11*, 81.

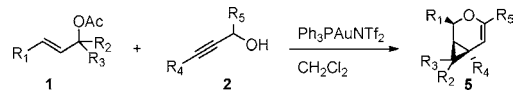
(6) Selected examples of Au-catalyzed 1,6-enyne cyclization: (a) Cabello, N.; Jiménez-Núez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Lpez, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1677. (c) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. W. *J. Org. Chem.* **2006**, *71*, 9366. (d) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. Pt-catalyzed reaction: (e) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (f) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (g) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (h) Blum, J.; Berr-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567. (i) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988. (j) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191.

(7) CCDC 771930 contains the supplementary crystallographic data for compound **5a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.Uk/ data_request/cif.

(8) See the Supporting Information for the detailed reaction optimizations.

(9) The enyne ether intermediates can be monitored by the TLC method in the reactions in Table 2.

Table 2. Gold-Catalyzed Intermolecular Reaction of Allylic Acetates **1** with Nonterminal Propargylic Alcohols **2**[a,b]



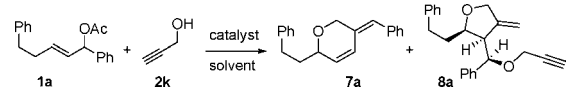
entry	1	2	time	yield of **5**[c]
1	**1a**	**2a**, R = H	1 h	**5a**, 86%
2	**1a**	**2b**, R = CH_3	1 h	**5b**, 88%
3	**1a**	**2c**, R = CH_2CH_3	2 h	**5c**, 92%
4	**1a**	**2d**, R = ^{n}Bu	1 h	**5d**, 85%
5	**1a**	**2e**, R_4 = *m*-FPh	2 h	**5e**, 62%
6	**1a**	**2f**, R_4 = $PhCH_2CH_2$	2 h	**5f**, 67%
7	**1b**, R = Me **1c**, R = Cl	**2a**	1 h	**5g**, 84%
8	**1b**, R = Me **1c**, R = Cl	**2a**	12 h	**5h**, 42%
9	**1d**	**2a**	2 h	**5i**, 65%
10	**1e**	**2f**	3 h	**5j**, 42%
11	**1e**	**2a**	1 h	**5k**, 73%
12	**1a**	**2g**	0.5 h	**5m**, 53%
13	**1e**	**2h**	1 h	**5n**, 37%
14	**1a**	**2i**	1 h	**5o**, 65% dr = 30/1[c]
15	**1a**	**2j**	2 h	**6**, 71%

[a] Unless noted, all reactions were carried out at 0.1 mmol scale in 3 mL of CH_2Cl_2 at 25 °C with 5 mol % equiv of $Ph_3PAuNTf_2$ as catalyst (**1**/**2** = 1/6). [b] Unless noted, all products were obtained as the single diastereomers. [c] Isolated yields. [d] The dr value was determined by separated yields.

all products were obtained as the single diastereomers (**5a**−**k**). When "R_5" is an alkyl group, the reaction yields (**5m**−**o**) were somewhat lower than that of their primary alcohol analogues. But their dr values were still very high. Only **5o** was obtained as a mixture of two diastereomers (dr ∼ 30/1). No diastereomers were detected in the reaction of **1a** with **2g** and **2h**. Moreover, the reaction of **1a** with but-2-yne-1,4-diol **2j** was also tested, which afforded a ring-opening product **6** in 71% yield (Table 2, entry 15).[10]

We then turn to investigating the reaction of terminal alkynyl alcohols (Table 3). The reaction of **1a** (1 equiv) with 3-propynyl alcohol **2k** (1.5 equiv) afforded endocyclic

Table 3. Gold-Catalyzed Intermolecular Reaction of (*E*)-1,5-Diphenyl Pent-2-enyl Acetate **1a** and Prop-2-yn-1-ol **2k**[a]



	ratio (**1a**/**2k**)	catalysts/equiv	time (min)	yield of **7a** (%)[b]	yield of **8a** (%)[b]
1	1/1.5	$Au(PPh_3)NTf_2$/5%	10	49	7
2[c]	1/10	$Au(PPh_3)NTf_2$/5%	10	trace	88

[a] Unless noted, all reactions were carried out at 0.1 mmol scale in 3 mL of CH_2Cl_2 at 25 °C. [b] Isolated yields. [c] Reaction temperature is 30 °C.

rearrangement product **7a** in 49% yield,[6a,d] along with a trace amount of **8a** (Table 3, entry 2). A "concentration effect" was observed in the reaction of **1a** with **2k**.[8] As shown in Table 3, optimization of the reaction temperature and the **1a**/**2k** ratio provide a set of best conditions to give **8a** exclusively in 88% yield (Table 3, entry 8).

As shown in Table 4, a series of alkoxycyclization adducts **8a**−**e** were then prepared in good yields by using the

Table 4. Gold-Catalyzed Intermolecular Reaction of Allylic Acetates **1** and Prop-2-yn-1-ol **2k**[a]

entry	reactant **1**	reaction time	product **4**[b]	yield(%)[c]
1	**1a**, R = H	**1a**, 30 min	**4a**, R = H	**8a**, 88
2	**1b**, R = Cl	**1b**, 50 min	**4b**, R = Cl	**8b**, 80
3	**1f**, R = MeO	**1c**, 30 min	**4c**, R = MeO	**8c**, 93
4	**1d**	1 h	**4d**	**8d**, 65
5	**1e**	1 h	**4e**	**8e**, 60

[a] All reactions were carried out at 0.1 mmol scale in 3 mL of CH_2Cl_2 at 30 °C with 5 mol % equiv of $Ph_3PAuNTf_2$ as the catalyst (**1**/**2k** = 1/10). [b] All products were obtained as the single diastereomers. [c] Isolated yields.

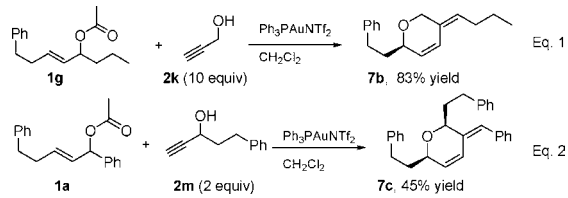
condition from entry 8 in Table 3.[6b,d,11] The reaction of **1c** with **2k** give the highest reaction yield (Table 4, entry 3). The reaction yields for substrates **1d** and **1e** were relatively low (Table 4, entries 4 and 5).

A similar "concentration effect" could not be observed in the reaction of dialkyl allylic acetate **1g** with **2k** (Scheme 1, eq 1) or in the reaction of **1a** with substituted termial alkynyl alcohol **2m** (Scheme 1, eq 2).[11] The former reaction gave tetrahydropyran derivative **7b** exclusively in 83% yield, while the reaction of **1a** with **2m** (Scheme 1, eq 2) give **7c** in 45%

(10) The stereochemistry of compounds **6**, **7c**, and **10** were determined by their NOESY NMR spectral data.

(11) The enyne ether intermediates cannot be detected by TLC monitoring in these reactions.

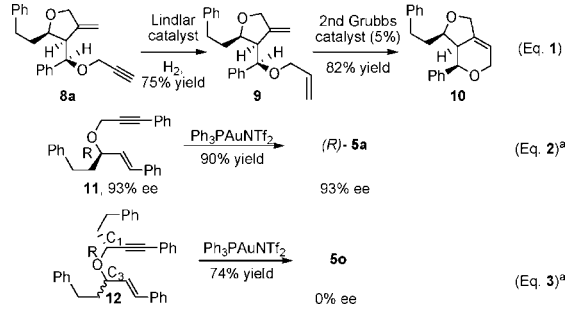
Scheme 1. Gold-Catalyzed Intermolecular Reaction of Allylic Acetate **1** with Terminal Propargylic Alcohol **2**



yield,[10,12] along with a mixture of some inseparatable products.

The derivation of compound **8a** was then performed to determine the relative stereochemistry of products **8a**−**e**. As shown in Scheme 2, hydrogenation of **8a** over Lindlar's

Scheme 2. Derivation of **8a** and Investigating Substitution Effect on Cyclopropane's Stereochemistry



catalyst followed by alkene metathesis under the second generation Grubbs catalyst provided a bicyclo product **10** in 82% yield (Scheme 2, eq 1).[10,13]

To examine the effect of different substitution patterns on stereochemistry, chiral substrate (*R*)-**11** (93% ee) was prepared and treated with $Au(PPh_3)NTf_2$ in DCM, which gave **5a** in 93% ee (Scheme 2, eq 2). However, when compound **12** (dr = 0%, ee = 92% for one diastereomer) was examined in the same condition,[14] only racemic **5o** was obtained in 74% yield (Scheme 2, eq 3). These results indicated that the stereochemistry of cyclopropane was mainly determined by the allylic substituents (R_1).

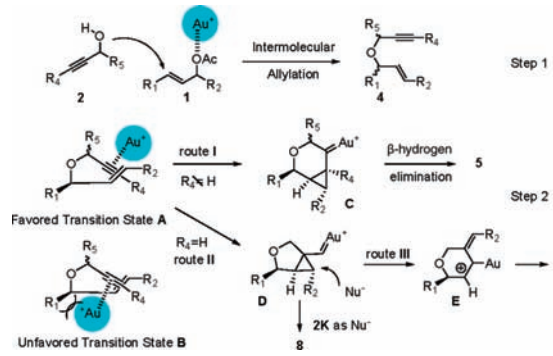
A plausible mechanism was then proposed. As shown in Scheme 3, enyne ether intermediates **4**, in situ generated from

(12) The reason for the formation of one diastereomer in the reaction of **1a** with **2m** is still unclear.

(13) (a) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (b) Samojblowicz, G. C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708.

(14) **12** was obtained as a mixture of two diastereomers. The ee value of one diastereomer was determined to be 92%.

Scheme 3. A Plausible Mechanism for the Synthesis of Compounds **5**, **7**, and **8**



intermolecular allylation,[5a] underwent subsequent cycloisomerization to yield a series of oxygen heterocycles. In the second step, trapping the gold activated triple bond by the alkene group was favored to proceed though transition state **A**, in which allylic R_1 group pointed away from the alkyne bond to avoid the steric hindrance between R_1 and gold complexes (Scheme 3). The stereochemistry of bicyclo[4.1.0]-heptylidene gold(I) carbene **C** (route I) and bicyclo[3.1.0]-hexylidene gold carbene **D** (route II) was then determined by the favored transition state **A**. Product **5** was obtained from intermediate **C** by β-hydrogen elimination. Trapping intermediate $\mathbf{D_1}$ with 3-propynyl alcohol **2k** afforded **8**, while intermediate **D** rearranged with ring-opening to provide **E**, which then gave **7** via β-elimination.[6a]

In summary, we have developed an efficient new method to construct the densely functionalized oxygen hetereocycles with high diastereoselectivities from the intermolecular reaction of allylic acetates with propargylic alcohols via gold catalysis, in which gold promoted two mechanistically distinct processes, including intermolecular allylation and intramolecular enyne cycloisomerization. Different substitution patterns affected the reaction's regioselectivity and cyclopropane unit's stereochemistry. It was found that cyclopropane stereochemistry was mainly determined by the allylic substituents. The effort to extend this reaction and broaden its application is still underway in this laboratory.

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Supporting Information Available: Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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