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Gold-Catalyzed Formation of Oxonium Ions from Enynes and Their Intra- and Intermolecular Trapping with Allylsilanes

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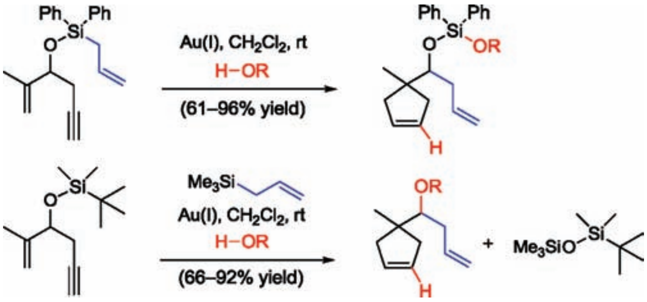
ABSTRACT



Gold-catalyzed ring closure of 1,5-enyne containing a silyl ether at the allylic position induces a skeletal rearrangement to form an oxonium intermediate, which then undergoes a smooth allylation in both an intra- and intermolecular manner. In the intramolecular allyl transfer, the additive alcohol becomes positioned on the silicon of the silyl ether by forming a new Si–OR bond, whereas, in the intermolecular allylation, the alcohol is incorporated in the homoallylic carbon by forming a C–OR bond.

Gold complexes are powerful carbophilic Lewis acids that activate alkynes to generate cationic or carbenoid intermediates depending on the functional groups within the molecules containing the alkyne. These reactive intermediates are known to undergo an array of transformations to engender diverse carbon frameworks.[1]

It has been shown that gold-catalyzed activation of 1-hexen-5-yn-3-ol or its silyl ether affords a cyclopentene carboxaldehyde (Scheme 1).[2] This reaction is believed to proceed via an intermediate **I** arising from a nucleophilic attack of the alkene to the activited alkynyl functionality in a 6-*endo*-dig carbocyclization mode, which then undergoes an irriversible pinacol-type rearrangement to another intermediate **II** followed by loss of a proton or a silyl group, yielding **III**. We envisaged that a carbocationic intermediate **I** could be intercepted by an allylsilane, before it undergoes a skeletal rearrangement to **II**, to generate a [5.4.0]bicyclic intermediate **IV**, which then would undergo C–Si bond cleavage to deliver a cyclohexene derivative **V**.[3] On the other hand, if the formation of rearranged oxonium intermediate **II** still takes precedence over the direct trapping of **I** by the allyl group,[4] an alternative carbocationic intermediate **VI** would arise. Finally, the C–Si bond cleavage next to the carbocationic center would lead to a cyclopentene derivative **VII**. Herein we describe an efficient and general allylation reaction to form cyclopentene derivatives **VII** exclusively over cyclohexene structures **V** in both an intra- and intermolecular manner.

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(1) For selected reviews on gold catalysis, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (g) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.

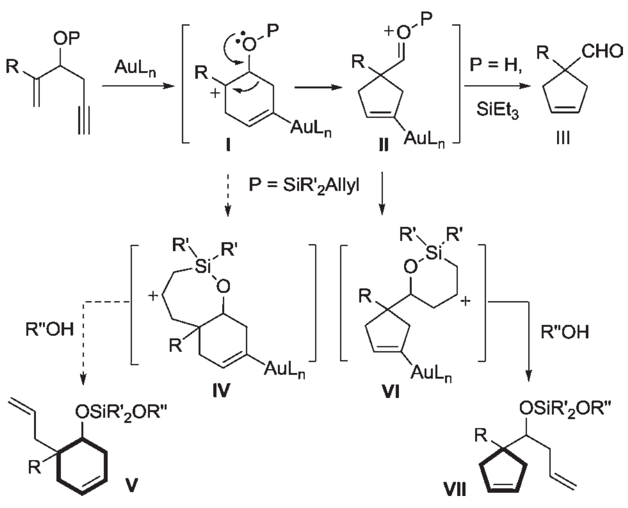
(2) (a) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310. (b) Menz, H.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Kirsch, S. F.; Klahn, P.; Liébert, C. *Tetrahedron* **2009**, *65*, 1880.

(3) (a) Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539. (b) Lim, C.; Rao, M. S.; Shin, S. *Synlett* **2010**, 368. (c) Lee, Y.; Lim, C.; Kim, S.; Shin, S. *Bull. Korean Chem. Soc.* **2010**, *31*, 670.

(4) Examples of oxonium species trapped by allylsilanes: (a) Nishiyama, Y.; Shimoura, K.; Sonoda, N. *Tetrahedron Lett.* **2008**, *49*, 6533. (b) Jung, M. E.; Maderna, A. *J. Org. Chem.* **2004**, *69*, 7755.

10.1021/ol203206k

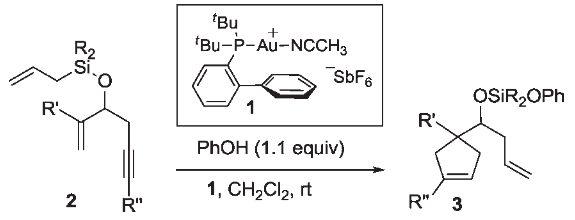
Scheme 1. Intramolecular Trapping of Oxonium Intermediates in Au(I)-Catalyzed Tandem Reaction Sequence



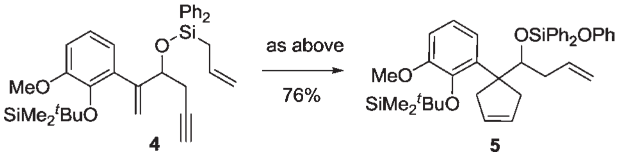
To examine the behavior of the carbocationic intermediates toward trapping with an allylsilane moiety, 2-methylhex-1-en-5-yn-3-yloxy allyldimethylsilyl ether **2a** was prepared via propargylation of methacrolein (propargyl bromide, Zn, aq NH_4Cl−DMF)[5] followed by silylation. With cationic gold complex **1** (1 mol %),[6] reaction of **2a** in the presence of *tert*-butanol (1.1 equiv) in dichloromethane provided cyclopentene derivative **3a** in 86% yield (entry 1 in Table 1). The corresponding cyclohexene derivative was not observed, but a nonnegligible amount of cyclopentene caboxaldehyde (**III**) was isolated. However, it was found that the combined use of allyldiphenylsilyl ether[7] and phenol as opposed to allyldimethylsilyl ether and *tert*-butanol could minimize the formation of the cyclopentene carboxaldehyde byproduct.[8] Under the optimized conditions, various enyne substrates **2b**−**f** afforded homoallylic silxoane **3b**−**f** in good yields. Compound **3c**−**e** derived from internal alkynes **2c**−**e** provided mixtures of diastereomers (entries 3−5), but products **3b** and **3f** derived from terminal alkyne are single diastereomers because the quaternary carbon center is not stereogenic (entries 2). Similarly, relatively complex substrate **4** containing an aromatic moiety with oxygen substituents afforded **5** in good yield (76%) without complication.[9]

Although the gold-catalyzed tandem ring closure of enynes followed by intramolecular allylation was an efficient process, the preparation of a substrate containing the allyldiphenylsilyl moiety was found to be tedious. To remove this inconvenience, we envisaged an intermolecular trapping of the oxonium intermediate with externally added allyltrimethylsilane. Initially, triethylsilyl protected 2-methyl-1-hexen-5-yn-3-ol **6a** was employed. But under the typical reaction conditions with allyltrimethylsilane, **6a** provided only 1-methylcyclopent-3-ene carbaldehyde without any allylation (Scheme 2). To diminish the O−Si bond cleavage by the attack of the additive alcohol on the silicon center, a more sterically hindered silyl

Table 1. Au(I)-Catalyzed Tandem Reaction with Intramolecular Allylation[a]



entry	enyne	R	R'	R"	product	yield (%)[b]
1	**2a**	Me	Me	H	**3a**	86[c]
2	**2b**	Ph	Me	H	**3b**	96
3	**2c**	Ph	Me	Ph	**3c**	81
4	**2d**	Ph	Me	Br	**3d**	74
5	**2e**	Ph	Me	allyl	**3e**	61
6	**2f**	Ph	$(CH_2)_3OPiv$	H	**3f**	76



[a] **1** (1 mol %), PhOH (1.1 equiv). [b] Isolated yield. [c] *tert*-Butanol (1.1 equiv) was used instead of phenol.

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(5) Barbier, P. *Compt. Rend.* **1899**, *128*, 110.

(6) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

(7) (a) Ito, H.; Saito, T.; Miyahara, T.; Zhong, C.; Sawamurat, M. *Organometallics* **2009**, *28*, 4829. (b) Ito, H.; Takagi, K.; Miyahara, T.; Sawamura, M. *Org. Lett.* **2005**, *7*, 3001.

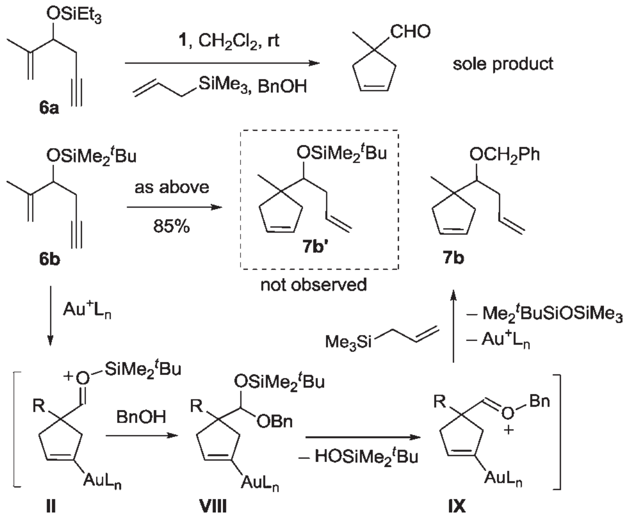
(8) For the effect of additive alcohols, see: (a) Horino, Y.; Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 11364. (b) Park, S.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 10664.

(9) Compared to *tert*-butyldimethylsilyl phenyl ether **4**, a related methoxymethyl phenyl ether provided an acetal product due to a neighboring oxygen atom participation with intermediate **II**.

(10) For related seminal publications on the Sakurai reaction, see: (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, *5*, 941–942. (b) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. For in situ generated oxoniums from alkoxysilanes and carbonyl compounds and their trapping by allylic silanes, see: (c) Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, *16*, 1121. (d) Markó, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211. (e) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790. (f) Lipshutz, B. H.; Burgess-Henry, J.; Roth, G. P. *Tetrahedron Lett.* **1993**, *34*, 995. (g) Tietze, L. F.; Wulff, C.; Wegner, C.; Schuffenhauer, A.; Schiemann, K. *J. Am. Chem. Soc.* **1998**, *120*, 4276. (h) Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147. (i) Watahiki, T.; Akabane, Y.; Mori, S.; Oriyama, T. *Org. Lett.* **2003**, *5*, 3045. (j) Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 3231. (k) Anzalone, P. W.; Baru, A. R.; Danielson, E. M.; Hayes, P. D.; Nguyen, M. P.; Panico, A. F.; Smith, R. C.; Mohan, R. S. *J. Org. Chem.* **2005**, *70*, 2091. (l) Pospíšil, J.; Kumamoto, T.; Markó, I. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3357. (m) Spafford, M. J.; Anderson, E. D.; Lacey, J. R.; Palma, A. C.; Mohan, R. S. *Tetrahedron Lett.* **2007**, *48*, 8665. (n) Kampen, D.; Ladépêche, A.; Claßen, G.; List, B. *Adv. Synth. Catal.* **2008**, *350*, 962. (o) Kataki, D.; Phukan, P. *Tetrahedron Lett.* **2009**, *50*, 1958. For allenylsilane trappings, see: (p) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2689. For in situ generated oxoniums from alcohol and carbonyl compounds and their trapping by allylic silanes, see: (q) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808. (r) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765. (s) Tietze, L. F.; Dölle, A.; Schiemann, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1372.

protecting group was empolyed. When *tert*-butyldimethyl silyl protected enyne substrate **6b** was treated with gold complex **1** (1 mol %) in the presence of benzyl alcohol (1.1 equiv) and allyltrimethylsilane (3 equiv), an efficient allylation took place. However, the isolated product was not the expected silyl ether **7b′** but the additive alcohol-incorporated ether **7b**. This suggests that the initially formed oxonium intermediate **II** reacted with the added alcohol instead of allylsilane to generate a new oxonium species **IX** via an acetal intermediate **VIII**, which then reacted with allylsilane to provide the observed allylated product (Scheme 2).[10]

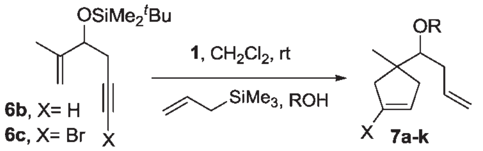
Scheme 2. Au(I)-Catalyzed Formation of an Oxonium Intermediate and Its Intermolecular Allylation[a]

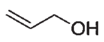
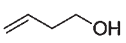
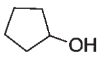
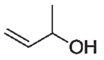
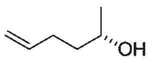
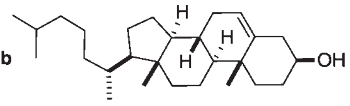


[a] **1** (1 mol %), allyltrimethylsilane (3.0 equiv), BnOH (1.1 equiv).

To test the generality of the Au(I)-catalyzed tandem cyclization of an enyne–alkoxy exchange–intermolecular allylation sequence, we examined the reaction of enyne substrate **6b** in the presence of a variety of additive alcohols (Table 2). It was found that most alcohols could participate in this reaction in roughly the same efficiency except *tert*-butanol (entry 3). Water and acetic acid were found to be unsuitable as an additive for this reaction. Not surprisingly, both 3-buten-2-ol and (*S*)-5-hexen-2-ol gave diastereomeric mixtures (entries 8 and 9), and cholesterol provided diastereomers in a 15:1 ratio (entry 10). In the presence of isopropanol, substrate **6c** containing a brominated alkyne efficiently generated the corresponding diastereomeric mixture of isopropyl ethers in a 1:1 ratio (entry 11).

Table 2. Au(I)-Catalyzed Tandem Reaction Alkoxy Allylation with Different Alcohols[a]



entry	enyne	ROH	product	yield (%)[b]
1	**6b**	CH_3CH_2OH	**7a**	72
2	**6b**	$PhCH_2OH$	**7b**	85
3	**6b**	$(CH_3)_3COH$	**7c**	0
4	**6b**	$(CH_3)_2CHOH$	**7d**	92
5	**6b**		**7e**	91
6	**6b**		**7f**	66
7	**6b**		**7g**	81
8	**6b**		**7h** (1:1.1)	84
9	**6b**		**7i** (1:1.4)	89
10	**6b**		**7j** (15:1)	72
11	**6c**	$(CH_3)_2CHOH$	**7k**	73

[a] **1** (1 mol %), allyltrimethylsilane (3.0 equiv), ROH (1.1 equiv). [b] Isolated yields.

With the involvement of carbocationic intermediates along the reaction sequence, we predicted that the initially formed oxonium species could be intercepted by suitably tethered heteroatom-based nucleophiles such as alcohols, ethers, and amides to form a new oxonium or iminium species after elimination of silanol, which then undergoes the expected final allylation, providing the corresponding spirobicyclic products.[11] As expected, a tethered alcohol-containing substrate **8** provided an allylated spirobicyclic ether **9** in good yield (Scheme 3). However, substrate **10** containing a three-carbon tether between the incipient carbocation and a hydroxyl group provided spirobicyclic ether **11** without allylation. This implies that the intramolecular trapping of the initially formed carbocation **I** by a tethered nucleophile to form a five-membered ring should be more favorable than its skeletal rearrangement to an oxonium species **II**. An altered pairing of reacting counterparts, such that the trapping of the cationic intermediate with an alcohol additive would be intermolecular but the subsequent allylation would be intramolecular, would generate a product of different connectivity. Indeed, when the mixture of **6b** and 5-trimethylsilyl-pent-3-en-1-ol was treated with catalyst **1**, cycylopentene derivative **12** containing

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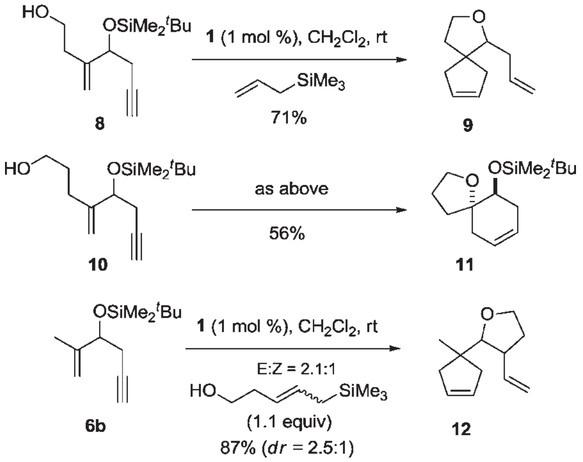
(11) For gold-catalyzed formation of oxonium ions and their intramolecular trapping by a hydroxyl group, see: (a) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. For gold-catalyzed formation of carbocations and their intramolecular trapping by nucleophiles, see: (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (c) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888. (d) Tarselli, M. A.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 3490. (e) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.

an alternative substituent pattern was obtained in good yield (87%).

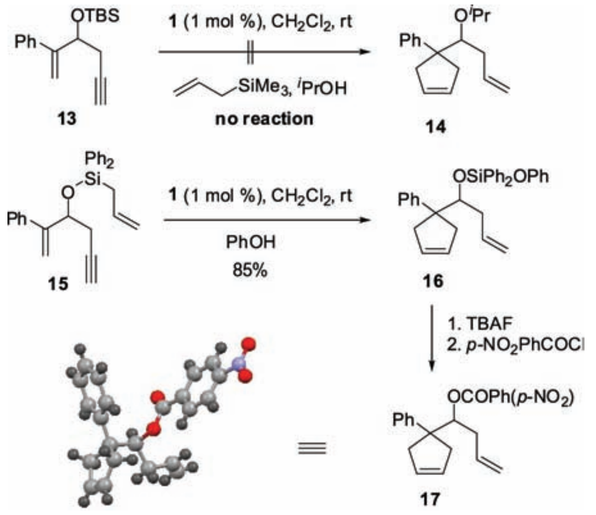
Scheme 3. Intramolecular Trapping of an Oxonium Intermediate with a Tethered Hydroxy Group



A subtle influence of substituents on the reactivity of enynes toward gold-catalyzed ring closure was observed (Scheme 4). Enyne substrate **13** with a phenyl substituent on the internal position of the alkene moiety was inert under the intermolecular allyl transfer conditions and recovered intact. On the other hand, the reaction of closely related enyne **15** containing an allyl-transferring silyl ether moiety delivered allylated product **16** in 85% yield. Unambiguous structural determination of **16** was realized by X-ray crystallographic analysis of its *p*-nitrobenzoate derivative **17**.

In conclusion, we demonstrated two efficient gold(I)-catalyzed tandem reactions of 3-silyloxy-1,5-enynes, which involves an initial carbocyclization of an enyne moiety, pinacol-type skeletal reorganization, and intra- or intermolecular allyl transfer induced by an additive alcohol. These reactions provide a rapid access to cyclopentene derivatives containing a quaternary carbon center and a homoallyl ether moiety. Further exploration of this methodology in the context of natural product synthesis will be reported in due course.

Scheme 4. Reactivity Difference between Intra- And Intermolecular Allyl Transfer



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