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Gold(I)-Catalyzed Divergence in the Reactivity of 3-Silyloxy 1,6-Enynes: Pinacol-Terminated vs Claisen-Terminated Cyclization Cascades

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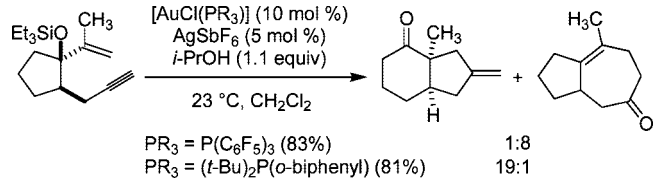
ABSTRACT



On activation with catalytic amounts of gold(I) complexes, 3-silyloxy 1,6-enynes can react through two alternative pathways. In one, a cascade reaction consisting of carbocyclization and subsequent pinacol rearrangement takes place. In the second pathway, a heterocyclization is followed by a Claisen rearrangement. The reaction outcome differs depending on the substitution pattern of the 3-silyloxy 1,6-enynes and, more importantly, the electronic properties of the gold-bound phosphane ligand.

Within the rapidly developing area of catalysis involving gold complexes as carbophilic π-acids,[1] enyne cycloisomerizations have been particularly well-studied.[2] In this context, cycloisomerizations of 1,5-enynes[3] and 1,6-enynes[4] were found to produce a great diversity of products via various reaction cascades. While noble metal-catalyzed reactions involving 1,*n*-enynes that bear a protected hydroxyl group at the 3-position are rare,[5] our preliminary results of employing 3-silyloxy 1,5-enynes[6] and 3-methoxy 1,6-enynes[7] in cascade reactions initiated by π-activation led us to investigate the reactivity of 3-silyloxy 1,6-enynes in the presence of π-acids.

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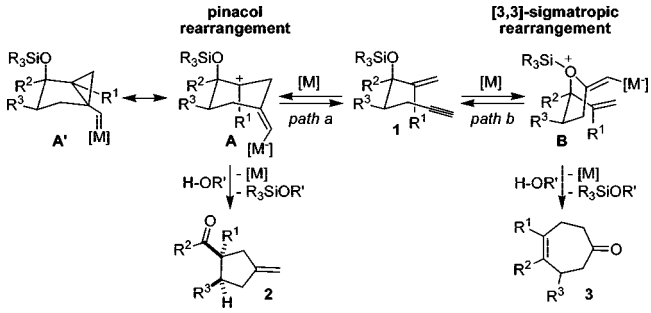
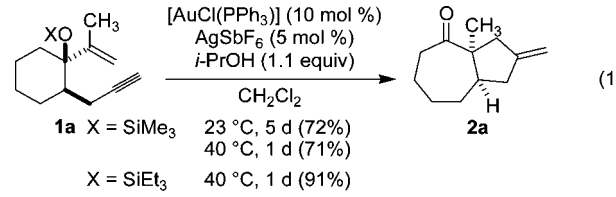


Figure 1. Divergent reactivity of 3-silyloxy 1,6-enynes.

We were intrigued by the possibility that 3-silyloxy 1,6-enynes **1** might undergo both a catalyzed domino reaction consisting of carbocyclization followed by a pinacol rearrangement and a domino reaction consisting of heterocyclization and subsequent Claisen rearrangement (Figure 1). In our projected sequence, the cationic intermediate **A** was expected to undergo a pinacol-type 1,2-shift[5c,6,8] to produce alkene **2** (path a). On the other hand, heterocyclization should generate the charged intermediate **B** that is prone to undergo a [3,3]-sigmatropic rearrangement upon formation of **3** (path b).[7] In this paper, we report the application of the divergent reactivity of 3-silyloxy 1,6-enynes in the presence of gold(I) complexes to the development of novel domino reactions.[9,10]

Our preliminary investigation focused on the cyclization−pinacol reaction of 1,6-enyne **1a** to ketone **2a** (eq 1).[11] Reaction of enyne **1a** to bicyclic compound **2a** in the presence of cationic triphenylphosphinegold(I) as the catalyst was examined initially under reaction conditions employed previously for the cyclization−pinacol reaction of 3-silyloxy 1,5-enynes.[6] Under these conditions, the reaction proceeded smoothly to afford **2a** with excellent cis diastereoselectivity in 72% yield after 5 d at room temperature. Increasing the reaction temperature to 40 °C led to the anticipated increase in reaction rate providing the desired product in good yields after 1 d (71% for X = $SiMe_3$, 91% for X = $SiEt_3$). Since the silylated compounds **1** lack the proton source required for the protodemetalation of the vinylgold(I) intermediate, isopropyl alcohol was required as an additive. The use of methanol under otherwise identical reaction conditions led to complete decomposition.



(1)

Under these conditions, a wide range of 3-silyloxy 1,6-enynes **1** having aryl, heteroaryl, and alkyl substituents at the alkyne terminus underwent the gold(I)-catalyzed domino reaction to carbonyl compounds **2** (eqs 2−4). Notably, the use of cyclohexanol derivatives led to the formation of cis-fused bicyclic compounds bearing an all-carbon quaternary stereocenter.[12] Generally, the exocyclic double bond was exclusively formed with *Z*-configuration;[13] as an exception, reaction of 2-thienyl compound **1f** gave a mixture of both double bond isomers (dr 45:55). Presumably due to the crucial stabilization of cationic intermediate **A**, the reaction proved strictly limited to 1,6-enynes possessing a substituent at the C2 position (Figure 1, R^1). In all cases, product formation is consistent with an initial 6-*exo*-*dig* cyclization of the alkene moiety onto gold(I)-complexed alkynes followed by a 1,2-alkyl migration that proceeds with ring contraction.

Interestingly, cyclopentanol-derived silyl ether **1i** was converted within 10 min into a 1:1 mixture of cyclization−pinacol product **2i**[13,14] and heterocyclization−Claisen product **3i** using Ph_3PAu^+ as the cationic catalyst (eq 5).[15] Changing the electronic properties of the phosphine ligand had a significant effect on the selectivity of this transformation. The use of $(C_6F_5)_3PAuCl$ as a less electron-rich gold(I) complex led to the formation of the seven-membered ring system **3i**[16] as the major product. Quite intriguingly, employ-

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(9) For reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(10) For recent examples of Au-catalyzed domino processes, see: (a) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614. (b) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (c) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (d) Buzas, A.; Istrate, F.; Gagosz, F. *Org. Lett.* **2006**, *8*, 1957. (e) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (f) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916. (g) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (h) Hashmi, A. S. K.; Grundl, L. *Tetrahedron* **2005**, *61*, 6231. (i) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (j) Barluenga, J.; Diéguez, A.; Fernandéz, A.; Rodríguez, F.; Fananás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091.

(11) For a related Pd(II)-catalyzed process, see: (a) Korotchenko, V. N.; Gagné, M. R. *J. Org. Chem.* **2007**, *72*, 4877. For related Lewis-acid mediated processes, see: (b) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.

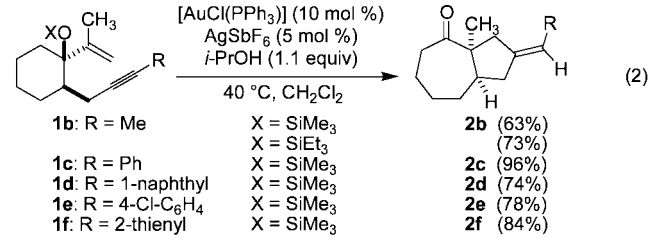
(12) Although not illustrated in this paper, cyclization−pinacol reaction of acyclic substrates **1** is generally low yielding (< 50%).

(13) The structures of compounds **2** were established by analysis of $^1H-^1H$ COSY, HMBC, and NOESY data.

(14) Compound **2i** was obtained as a single diastereomer.

(15) For the related discussion on the aza-Claisen rearrangement in the pyrrole formation, see: Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181.

(16) (a) Unlike the gold(I)-catalyzed cycloisomerization of 3-methoxy 1,6-enynes previously reported (ref 7), no silyl enol ethers were obtained in heterocyclization−Claisen rearrangement pathway. However, the protodesilylation of initially formed silyl enol ethers cannot be completely excluded. (b) In the absence of *i*-PrOH, the reaction gave the ketone **3i** in significantly lower yield (<30%), with no evidence of formation of the silyl enol ethers.



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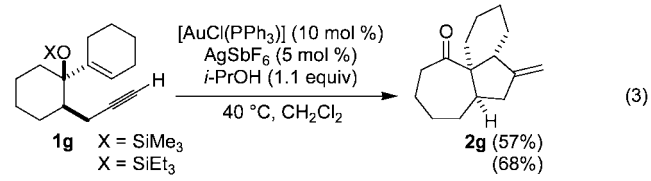

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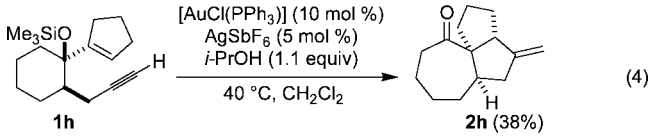
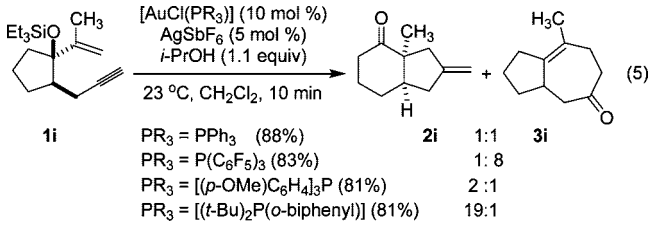


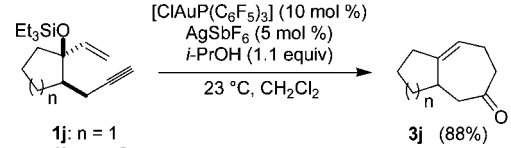
(4)

ing [*p*-MeO(C_6H_4)]$_3$PAuCl as a more electron-rich gold(I) complex inverted the selectivity, providing the cyclization−pinacol product as the major product over the heterocyclization−Claisen pathway. Switching to [(*t*-Bu)$_2$P(*o*-biphenyl]PAuCl significantly improved the selectivity for the cyclization−pinacol pathway, providing **2i** as the almost exclusive product. These results indicate that subtle variations on the equilibrium between **A**/**A′** and **B** such as the diminished backbonding capacity from the more electron-deficient complex, $(C_6F_5)_3PAu^+$, may account for the attack of the "hard" O-nucleophile to access [3,3]-sigmatropic rearrangement precursor **B** (Figure 1, path b).[17] On the other hand, effective back-bonding from electron-rich gold(I) complexes leading to metal−carbenoid intermediate **A′** could then facilitate a pinacol-type reaction outcome (Figure 1, path a).[1c,d]



(5)

On the basis of the requirement of a carbocation-stabilizing substituent at the C2-position (Figure 1, R^1) to provide cyclization−pinacol products **2**, we then hypothesized that alkenes **1** not bearing an additional substituent at C2 (e.g., R^1 = H) would instead furnish cyclohept-4-enones **3** in the presence of $(C_6F_5)_3$PAuCl as the precatalyst. Accordingly, a number of 3-silyloxy 1,6-enynes **1** were converted into the corresponding cyclic products **3**, whereas complete conversion in CH_2Cl_2 was generally observed after 10 min at room temperature (eqs 6 and 7). In sharp contrast to the pinacol-terminated reactions discussed above, both cyclic and acyclic substrates **1** were effectively reacted to give **3**. Of primary importance, product formation was not accompanied byproduct resulting from the competitive cyclization−pinacol sequence.



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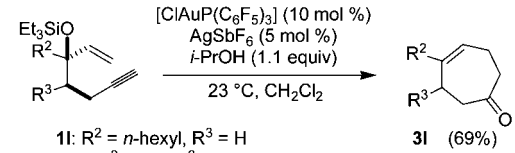

(7)

In summary, we described a synthetically useful gold(I)-catalyzed reaction from 3-silyloxy 1,6-enynes that provides access to either cyclization−pinacol products **2** or heterocyclization−Claisen products **3**. This is a remarkable example of divergence because the reaction outcome not only derives from substitution pattern of the substrate but is strongly influenced by the electronic properties of the gold-bound phosphane ligand. Further investigations on this and related types of noble metal-catalyzed rearrangements are ongoing and will be reported in due course.

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Supporting Information Available: Representative experimental procedures for catalytic formation of **2** and **3** and copies of ^{1}H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Although the formation of cycloheptenones could be explained by the initial alcoholysis of the silyl ethers under Lewis/protonic acid conditions and the subsequent alkoxycyclization−[3,3]-sigmatropic rearrangement of the corresponding alcohols (e.g., ref 10j), this alternative reaction pathway was reasonably excluded on the basis of the following observations: (i) Upon exposure to the reaction conditions described in eq 5 (5−10%, with or without *i*-PrOH (1.1 equiv)), the alcohol precursor of silyl ether **1i** led to the formation of an intractable mixture of compounds with no evidence of formation of compound **3i**. (ii) Compound **1i** did not form **3i** upon treatment with a catalytic amount of various protonic acids (5−10%, with or without *i*-PrOH (1.1 equiv)).