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Gold-Catalyzed Cycloisomerization of Siloxy Enynes to Cyclohexadienes

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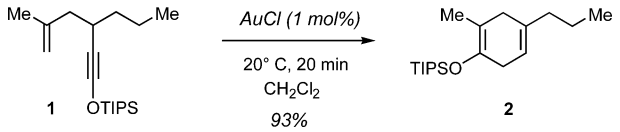
Metal-catalyzed enyne cycloisomerizations provide rapid and efficient access to a variety of cyclic structural motifs for a range of synthetic applications.[1] Particularly noteworthy are the latest advances in platinum(II)[2] and gold(I)[3] catalysis of these transformations. In this communication, we describe our discovery and subsequent investigation of the first Au-catalyzed skeletal reorganization of 1-siloxy-5-en-1-ynes to furnish highly substituted siloxy cyclohexadienes. Furthermore, we demonstrate that the presence of a siloxy alkyne moiety is crucial for enabling the skeletal reorganization process, which proceeds via a novel reaction mechanism involving a series of alkyl migrations.

In the course of our investigation of basic reactivity of siloxy alkynes,[4] we found that treatment of siloxy enyne **1** with a catalytic amount of AuCl resulted in efficient formation of a new product that was identified as siloxy cyclohexadiene **2** (Scheme 1). Structural

Scheme 1

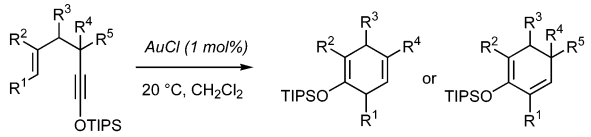


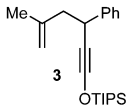
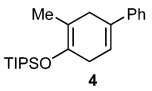
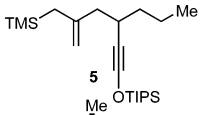
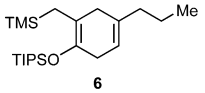
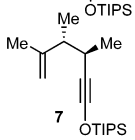
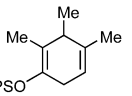
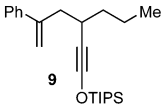
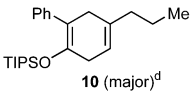
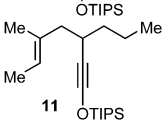
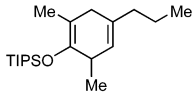
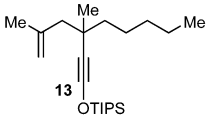
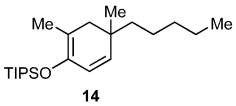
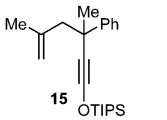
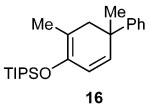
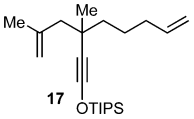
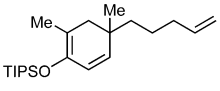
assignment of **2** was based on a series of NMR studies, including COSY, NOESY, HMQC, and HMBC experiments. The remarkable catalytic efficiency of this process is highlighted by the fact that the reaction proceeded to completion within 20 min at room temperature using only 1 mol % AuCl. While addition of phosphine resulted in inhibition of catalytic activity, the efficiency can be recovered using $Au(PPh_3)Cl$ in the presence of $AgBF_4$, presumably due to the generation of a cationic gold complex.[3] In the absence of Au(I), neither $AgBF_4$ nor AgOTf promoted formation of **2**. The cycloisomerization can be catalyzed by $PtCl_2$ (10 mol %); the reaction, however, requires to be conducted at 80 °C and proceeds with lower efficiency (66% yield). These studies revealed that AuCl proved to be the most effective catalyst for the cycloisomerization of siloxy enyne **1**.

Our investigation of the scope of the Au-catalyzed skeletal reorganization of siloxy enynes is summarized in Table 1. Subjection of the 3-aryl-substituted enyne **3** to the general cycloisomerization protocol afforded the expected diene **4** in 73% yield (entry 1). The 5-trimethylsilylmethyl group was retained in the cyclization product **6** despite the labile nature of this material (entry 2). 4-Alkyl substitution of enyne **7** was well tolerated (entry 3). Cycloisomerizations of 5-phenyl-substituted enyne **9** afforded a 4:1 mixture of nonconjugated and conjugated cyclohexadienes (entry 4).

A similar outcome (3:1 ratio of dienes, entry 5) was observed in the cycloisomerization of enyne **11** containing a trisubstituted alkene moiety. To explore the possibility of exclusive formation of conjugated cyclohexadienes, we prepared enynes **13**, **15**, and **17** containing quaternary stereogenic centers at the 3-position. To our delight, subjection of enynes **13** and **15** to the general cycloisomerization conditions afforded conjugated diens **14** and **16** in 88 and 89% yields, respectively (entries 6 and 7). Finally, cycloisomerization of dienyne **17** proceeded with complete chemoselectivity to afford **18** as a single reaction product (entry 8). Additional studies revealed that while both di- and trisubstituted alkenes efficiently

Table 1. Gold-Catalyzed Cycloisomerization of Siloxy Enynes

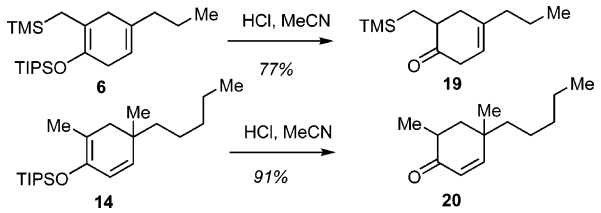


Entry	Siloxy Alkyne	Product[a]	Yield, %[b]
1	 **3**	 **4**	73
2	 **5**	 **6**	50
3	 **7**	 **8** (major)[c]	82
4	 **9**	 **10** (major)[d]	99
5	 **11**	 **12** (major)[e]	99
6	 **13**	 **14**	88
7	 **15**	 **16**	89
8	 **17**	 **18**	84

[a] General reaction protocol: Siloxy enyne (0.2 mmol) was dissolved in CH_2Cl_2 (4 mL) and treated with AuCl (0.002 mmol). The resulting solution was stirred at 20 °C for 30 min. After treatment of the reaction mixture with a drop of Et_3N, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel. [b] Refers to isolated yields of spectroscopically pure products that were fully characterized by NMR, IR and MS. [c] Ratio of 1,4- to 1,3-cyclohexadienes = 6:1. [d] Ratio of 1,4- to 1,3-cyclohexadienes = 4:1. [e] Ratio of 1,4- to 1,3-cyclohexadienes = 3:1.

10.1021/ja046112y CCC: $27.50

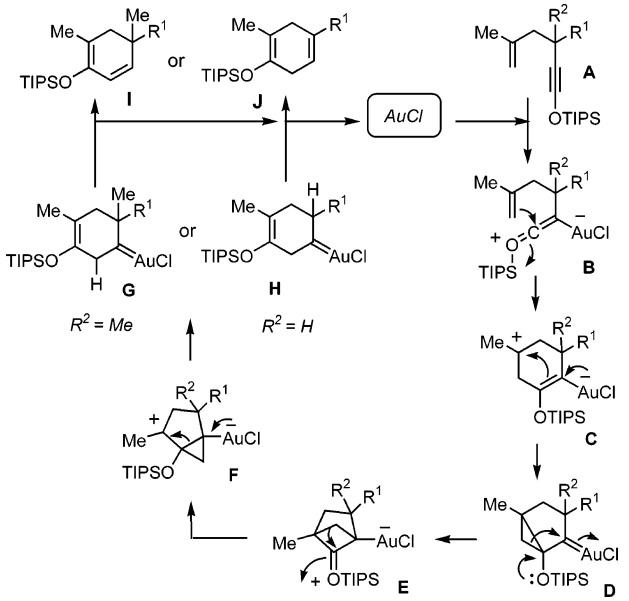
Scheme 2



participated in the cycloisomerization process, terminal monosubstituted alkenes proved to be unreactive during the current catalytic protocol.

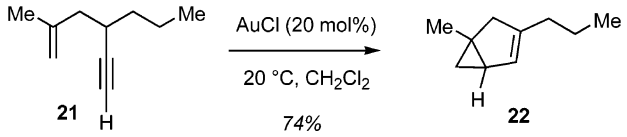
Siloxy cyclohexadiene products of the cycloisomerizations can be efficiently converted to 1,2- and 1,3-cyclohexenones, highlighting the general synthetic utility of this process. Protodesilylation of silyl enol ether **6** afforded nonconjugated enone **19** (Scheme 2). Subjection of siloxy diene **14** to the same protocol afforded conjugated enone **20**.

Scheme 3



Formation of the cyclohexadiene products can be rationalized using the mechanistic analysis presented in Scheme 3. Coordination of the π-acidic AuCl with siloxy alkyne **A**, followed by intramolecular attack by the proximate alkene (structure **B**), promotes cyclization to give cyclopropyl gold carbene **D**.[5] Formation of similar intermediates has been postulated in the reported Pt- and Au-catalyzed cycloisomerizations of enynes to give [3,1,0] and [4,1,0] bicyclic structures.[2,3] The presence of the siloxy moiety, however, dramatically alters the subsequent mechanistic scenario. We propose that the formation of the observed cyclohexadiene products can be explained by the subsequent 1,2-alkyl shift to give oxocarbenium ion **E**, which undergoes another 1,2-shift, followed by fragmentation of the intermediate **F**. Depending on the nature of the R^2 substituent at the 3-position of the enyne, the subsequent intermediate gold carbenoid can undergo two alternative 1,2-hydride shifts (structures **G** and **H**). Subsequent elimination of AuCl results

Scheme 4



in regeneration of the active catalyst and formation of two isomeric diene products **I** and **J**. To further probe the effect of 1-siloxy substitution, we subjected enyne **21** (Scheme 4) to the standard cyclization protocol. The reaction produced cyclopropane **22** as a single product, highlighting the crucial role of the siloxy alkyne moiety in the outcome of the enyne cycloisomerization, presumably due to the stabilization of cationic intermediate **E**.

In summary, we have developed a highly efficient Au-catalyzed cycloisomerization of siloxy enynes that features low catalyst loading and exceedingly mild reaction conditions. This new catalytic process provides rapid access to highly substituted siloxy cyclohexadienes and the corresponding 1,2- and 1,3-cyclohexenones. Importantly, the siloxy alkyne moiety is uniquely responsible for a novel reaction mechanism of the cycloisomerization, which is proposed to involve a cascade of 1,2-alkyl shifts.

Acknowledgment. We thank Randy Sweis for preparation and cycloisomerization of enyne **21**. S.A.K thanks the Dreyfus Foundation for a Teacher−Scholar Award and Amgen, Inc., for a New Investigator's Award. S.A.K. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Full characterization of new compounds and selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Structure **C** is used to illustrate the movement of electron density during the conversion of Au−alkyne complex **B** to carbene **D**, which may proceed directly as previously suggested in ref 3a.

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