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Gold(I)-Catalyzed Synthesis of Highly Substituted 2-Cyclopentenones from 5-Siloxypent-3-en-1-ynes

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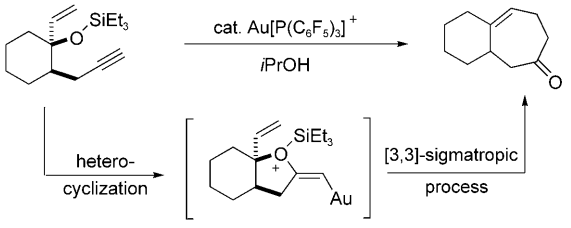
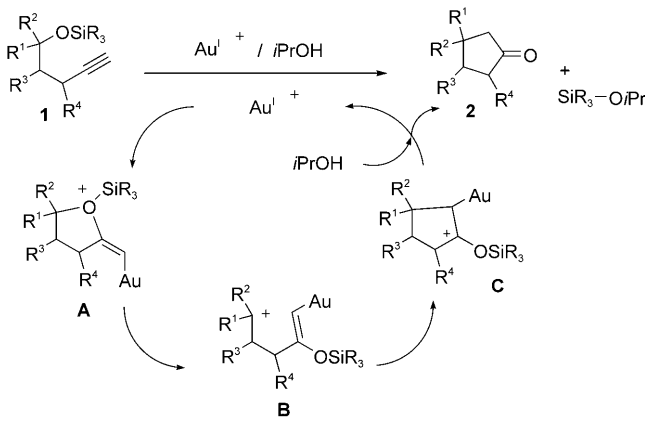
Intramolecular addition of nucleophiles to the Lewis acid activated alkynes represents one of the most powerful strategies for the synthesis of cyclic compounds.[1] In this context, recent advances in the catalytic reactions initiated by the intramolecular addition of alkyl and aryl ethers to alkynes are particularly noteworthy, because these groups are considered as relatively unreactive nucleophiles.[2,3] This type of reactivity led mostly to the development of novel syntheses of various cyclic ethers.[4]

Unlike the heterocycle formation, little is known about the carbocycle synthesis through a tandem alkoxycyclization/skeletal-rearrangement pathway. Toste and co-workers reported a gold(I)-catalyzed synthesis of indenyl ethers by an intramolecular carboalkoxylation process.[5] More recently, we reported the transformation of various 3-siloxy-1,6-enynes into 4-cycloheptenones through a tandem siloxycyclization/sigmatropic rearrangement [Eq. (1)].[6,7] A remarkable feature of this reaction is that even poorly reactive *O*-silyl ethers can add efficiently to the alkynes in the presence of cationic gold(I) complexes.[8]



(1)

In an effort to extend the scope of the reactions initiated by this intriguing siloxycyclization, we considered a catalytic reaction of 5-siloxypent-1-ynes **1** (Scheme 1). In this scenario, initial siloxycyclization of **1** followed by the ionization of C–O bond generates a carbocation intermediate **B**. Intramolecular carbocyclization and the subsequent elimination of cationic gold(I) via a cyclic intermediate **C** with the assistance of *i*PrOH will produce highly substituted cyclopentanone **2**.



Scheme 1. Proposed scheme for the gold(I)-catalyzed cyclopentanone formation.

Based on the proposed mechanism, we reasoned that the cation-stabilizing groups might be needed at the C-5 position.[9] This rationale was justified in preliminary studies using triethylsiloxypentyne **3a** [Eq. (2)]. The catalytic reaction of this compound gave the cyclopentanone **4** in 20% yield, when **6a** (10 mol%) was used (entry 1, Table 1).[10] Switching to a more electrophilic catalyst **6b** based on our previous experience in the related area significantly increased the yield to 44% (entry 2).[6,11]

At this stage, we decided to establish the relative reactivity of the methoxypentyne **3b** to siloxypentyne **3a**. Initially,

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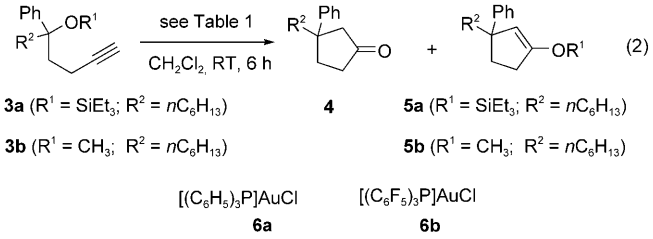
Table 1. Preliminary investigation of **3a** and **3b**.

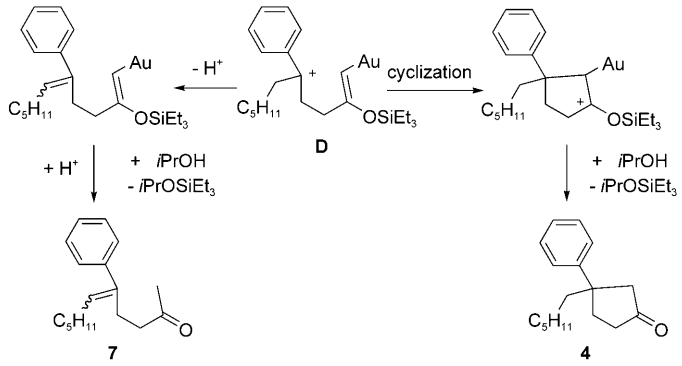
Entry	Substrate	Catalyst ([mol%])	Isolated yield [%]
1	**3a**	**6a** (10)/$AgSbF_6$ (5)	20 [a,b]
2	**3a**	**6b** (10)/$AgSbF_6$ (5)	44[a,b]
3	**3b**	**6b** (10)/$AgSbF_6$ (5)	trace[c]

[a] Only compound **4** was obtained.[12] [b] *i*PrOH (1 equiv) was added. [c] Combined yield of compound **4** and **5b**.



we surmised that **3b** would show higher reactivity, because the methoxy group is more nucleophilic than the triethylsiloxy group. Quite interestingly, methoxypentyne **3b** proved unreactive when catalyst **6b** (10 mol% of Au) was used (entry 3).

When **3a** was tested, enone **7** (Scheme 2) was obtained in 40% yield. Formation of this compound can be reasonably explained by the competing deprotonation from the carbocationic intermediate **D** and the subsequent alcoholysis of the vinylgold species (Scheme 2). This analysis confirms the involvement of the carbocationic intermediate in the proposed catalytic cycle. Moreover, the competition study of **3a** and **3b** strongly suggests that the efficiency of the proposed catalytic cycle depends mainly upon the cyclization of intermediate **B** rather than the initial formation of intermediate **A** (Scheme 1).



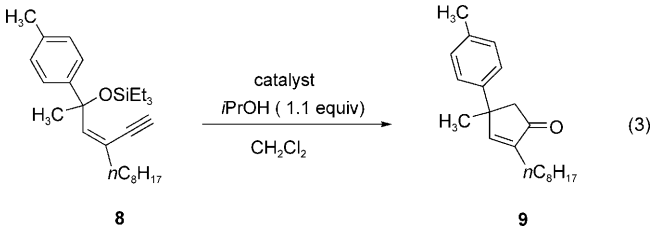
Scheme 2. Mechanism of the formation of compound **7**.

Based upon the mechanistic analysis of the preliminary studies, we envisioned that *cis*-5-trialkylsiloxypent-3-ene-1-ynes such as **8** would be more efficient than 5-trialkylsiloxypent-1-ynes, because the key cyclization should be faster for the former compounds.[13] Indeed, using substrate **8** provided the cyclopentenone **9** in 94% yield in the presence of catalyst **6a** [Eq. (3), Table 2, entry 1]. Using **6b** significantly shortened the reaction time, and slightly increased the yield of **9** (entry 2). Lowering the catalyst loading (5 mol% Au) little affected the yield (entry 3). Notably, the reaction performed at −15 °C was also successful with no negative effect on the yield of **9** (entry 4). In this run, the desired ketone **9** was obtained in 93% isolated yield. On the other hand, changing the counterion considerably decreased the yield of **9** (entry 5).[14,15] As illustrated in entry 6, using $AgSbF_6$ alone led to the decomposition of the starting material with no indication of the product formation.

Table 2. Optimization of the cyclization of substrate **8**.

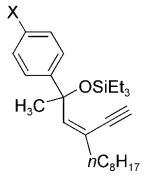
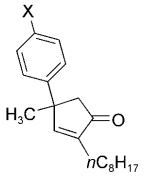
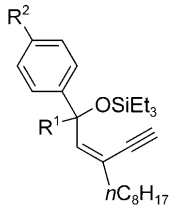
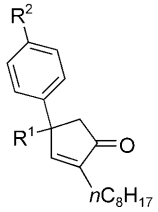
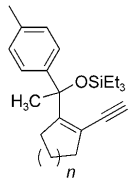
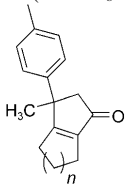
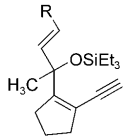
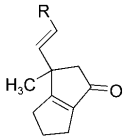
Entry	Catalyst ([mol%])	*T*	*t* [h]	Yield [%][a]
1	**6a** (10)/$AgSbF_6$ (5)	RT	1	94
2	**6b** (10)/$AgSbF_6$ (5)	RT	0.16	96
3	**6b** (5)/$AgSbF_6$ (2.5)	RT	0.16	93
4	**6b** (5)/$AgSbF_6$ (2.5)	−15 °C	0.16	97 (93[b])
5	**6a** (10)/AgOTf (5)	RT	1	53
6	$AgSbF_6$ (5)	RT	10	decomp

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield.



Using the optimized conditions in Table 2, an array of 5-siloxy-pent-3-en-1-ynes were converted into the corresponding cyclopentenones. As summarized in Table 3, the substituents on the phenyl ring significantly affected the yield of the cyclopentenones (entries 1–3). Substrate **10**, which possesses a phenyl group, showed a comparable result to compound **8** (entry 1), whereas, substrate **11**, with a more electron-donating *p*-methoxyphenyl group, significantly reduced the yield even though the starting material was completely consumed after 10 min (entry 2). On the other hand, poorer conversion was seen for the substrate with a more electron-withdrawing *p*-fluorophenyl group (**12**, entry 3). In this case, the reaction was completed after 7 h, providing the ketone **21** in 73% yield. As shown in entries 4 and 5, introducing longer alkyl group at the C-5 position little affected the catalytic activity. The cyclic substrates **15** and **16** also gave the bicyclic products in good yield (entries 6 and 7). Remarkably, the scope of the reaction was not limited to the substrates having aryl groups at the C-5 position. Thus, the compounds possessing alkenyl groups (**17** and **18**) were transformed smoothly into the cyclopentenones **26** and **27** in good yield (entries 8 and 9). In these cases, the tandem siloxycyclization-sigmatropic rearrangement shown in Equation (1) can compete with the proposed catalytic cycle.

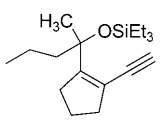
Table 3. Examples of cyclopentenone formation.[a,b]

Entry	Substrate	Method	t [h]	Product	Yield [%][c]
					
1	**10** (X = H)	B	0.16	**19** (X = H)	97
2	**11** (X = OMe)	A	0.16	**20** (X = OMe)	44
3	**12** (X = F)	B	7	**21** (X = F)	73
					
4	**13** (R^1 = Et, R^2 = H)	A	0.16	**22** (R^1 = Et, R^2 = H)	91
5	**14** (R^1 = nC_8H_{17}, R^2 = CH_3)	A	0.16	**23** (R^1 = nC_8H_{17}, R^2 = CH_3)	87
					
6	**15** (n = 1)	A	0.16	**24** (n = 1)	73
7	**16** (n = 2)	A	6	**25** (n = 2)	62
					
8	**17** (R = H)	B	12	**26** (R = H)	60
9	**18** (R = CH_3)	B	10	**27** (R = CH_3)	62

[a] Method A: catalyst **6b** (10 mol %)/$AgSbF_6$ (5 mol %) was used; Method B: catalyst **6b** (5 mol %)/$AgSbF_6$ (2.5 mol %) was used. [b] All reactions were performed at RT. [c] Isolated yield.

Quite interestingly, no seven-membered carbocyclic products generated from this competing process were detected.

As illustrated by the examples in Table 3, cation-stabilizing groups such as phenyl and alkenyl should be installed at the C-5 position for the efficient transformation. In fact, the substrate possessing two aliphatic alkyl groups at the C-5 position (such as compound **28**), and the substrate derived from secondary alcohol (such as compound **29**) gave the corresponding cyclopentenones only in trace yield.



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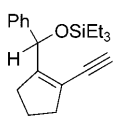

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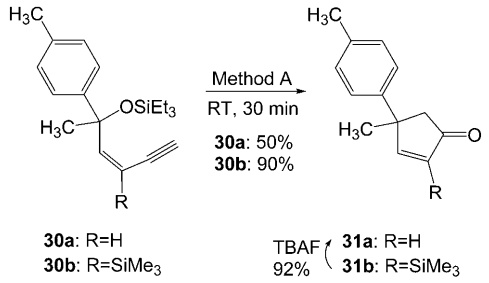
From a synthetic viewpoint, the catalytic reaction presented herein provides a highly efficient approach to 2-cyclopentenones with a quaternary carbon center; these are important building blocks in organic synthesis.[16,17] For example, the structural motif in compound **9** can be found in a number of bioactive cyclopentane sesquiterpene natural products possessing aryl groups[18] and in more structurally complex alkaloids such as meloscine and scandine.[19] Moreover, the carbocyclic structures of compounds **26** and **27** could be easily expanded to the synthesis of linear- and angular triquinane natural products.[20] In order to illustrate the synthetic potential of the proposed reaction, racemic synthesis of the key intermediate to cuparenone (**31a**) was pursued.[21] As shown in Scheme 3, this compound was obtained in moderate 50 % yield from substrate **30a** under the optimized conditions A (Table 3). On the other hand, substrate **30b** possessing trimethylsilyl group at the C-2 position afforded the corresponding ketone **31b** in significantly increased 90 % yield. Desilylation with TBAF using a modified literature procedure[22] smoothly proceeded to provide the target enone **31a** in 92 % yield.



Scheme 3. A formal synthesis of racemic cuparenone.

In summary, we have developed a highly efficient gold(I)-catalyzed approach towards densely functionalized cyclopentenones possessing a quaternary carbon center. It is worth noting that the activating power of the cationic gold(I) species allows the addition of relatively unreactive *O*-silyl ether nucleophiles, and also the efficiency of 5-siloxypent-3-en-1-ynes in the formation of 2-cyclopentenones. Also, the results described here provide a new insight into

the role of *O*-silyl ethers in organic synthesis. The scope of this reaction as well as further application to the synthesis of bioactive natural products with structural complexity is under investigation and will be reported in due course.

Experimental Section

Preparation of compound 9: Methylene chloride (3 mL) was added to a mixture of gold complex $[Au\{P(C_6F_5)_3\}Cl]$ (11.1 mg, 0.0145 mmol) and $AgSbF_6$ (2.5 mg, 0.0073 mmol); the resulting solution was stirred for 10 min. The reaction mixture was filtered through a pad of Celite and concentrated. The residue was dried over high vacuum for 2 h, and then cooled to −15 °C. A solution of **8** (121 mg, 0.29 mmol) and isopropyl alcohol (24.5 μL, 0.32 mmol) in CH_2Cl_2 (5.8 mL, 0.05 M, pre-cooled to −15 °C) was added to this residue. After stirring at room temperature for 10 min, the yellow mixture was passed through a pad of Celite and concentrated. The residual oil was purified by flash chromatography on silica gel (hexane/ethyl acetate 95:5) to give the compound **9** as a yellow oil (82 mg, 0.27 mmol, 93% yield). $R_f = 0.42$ (hexane/ethyl acetate = 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.7$ Hz, 3H), 1.21–1.31 (m, 10H), 1.48–1.56 (m, 2H), 1.58 (s, 3H), 2.20–2.25 (m, 2H), 2.33 (s, 3H), 2.57 (d, $J = 19$ Hz, 1H), 2.68 (d, $J = 19$ Hz, 1H), 7.11–7.18 (m, 4H), 7.25 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$, 21.1, 22.9, 24.7, 27.8, 27.9, 29.4, 29.5, 29.6, 32.0, 45.4, 52.7, 125.8, 129.5, 136.3, 143.4, 144.0, 164.8, 209.8 ppm; IR: $\tilde{\nu} = 2957$, 2925, 2855, 1709, 1514, 1456, 816 cm^{-1}; HRMS calcd for $C_{21}H_{30}O$: 298.2297; found: 298. 2298.

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Keywords: carboalkoxylation · cyclopentenone · gold · homogeneous catalysis · quaternary carbon

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[10] a) Using 1:1 complex of the Au catalyst and $AgSbF_6$ significantly lower the yield of the reaction. At this stage, it is unclear why the 2:1 complex gave higher yields of the product. It has been noted that that the chloro-bridged dinuclear gold complex is formed under this condition; A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709–713.

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[12] As observed in the previous study for the siloxycyclization-[3,3]-sigmatropic pathway of 3-siloxy-1,6-enynes, the reaction gave no silyl ether **5a**, even in the absence of any alcohol additives.

[13] a) For the detailed procedure for the synthesis of the substrates, see the Supporting Information; b) we also tried to investigate the reactivity of 5-methoxypent-3-en-yne derivative of **8**. However, all our efforts to prepare the 5-methoxy-3-en-1-ynes from the corresponding alcohols proved troublesome, because of the poor stability of the corresponding alcohols under the reaction condition. The reaction conditions investigated include; i) NaH/MeI in THF or DMF; ii) Ag_2O/MeI in various solvents; iii) $CH_3OC{=}NHCCl_3$ with various Lewis acids.

[14] a) Using other solvents (CH_3CN, THF, EtOAc) significantly decreased the yield of the reaction; b) we also examined various trialkylsilyl ethers: trimethylsilyl ethers provided the target in somewhat smaller yield, while triisopropylsilyl ethers significantly dropped the yield.

[15] a) The reaction performed in the presence of HF (up to 1 equiv) gave led to the complete decomposition of the starting material with no indication of the product formation; b) the catalytic reaction under aerobic conditions (open flask condition) gave comparable results to the reactions under N_2 atmosphere; c) the reaction of the corresponding alcohol led to decomposition of the staring material with no indication of the product formation; also, we found out that the TES silyl ethers of tertiary alcohols are stable in general under the reaction condition—based on these experiments, alternative explanation on the cyclopentenone formation promoted by the initial desilylation and the subsequent cyclization can be reasonably excluded; d) it should be noted that the scope of the reaction was strictly limited to the terminal alkynes; reaction of internal alkynes led to the decomposition of the staring material with no indication of formation of the cyclopentenones.

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