Beilstein Journal of Organic Chemistry

# Gold-catalyzed alkylation of silyl enol ethers with *ortho*-alkynylbenzoic acid esters

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Letter

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Keywords:
alkylation; gold catalysis; leaving group; silyl enol ether; substitution reaction

*Beilstein J. Org. Chem.* **2011,** *7,* 648–652.
doi:10.3762/bjoc.7.76

Received: 01 April 2011
Accepted: 13 May 2011
Published: 20 May 2011

This article is part of the Thematic Series "Gold catalysis for organic synthesis".

Guest Editor: F. D. Toste

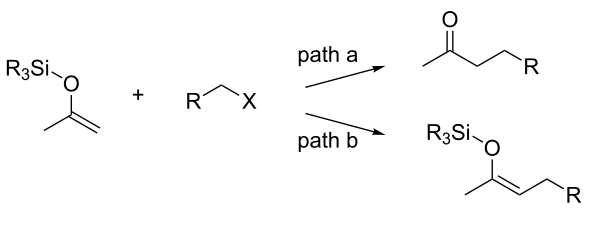


## Abstract

Unprecedented alkylation of silyl enol ethers has been developed by the use of *ortho*-alkynylbenzoic acid alkyl esters as alkylating agents in the presence of a gold catalyst. The reaction probably proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack on the silyl enol ethers. The generated leaving compound abstracts a proton to regenerate the silyl enol ether structure.

## Findings

Silyl enol ethers have been widely used in organic synthesis as effective carbon nucleophiles for the construction of carbon frameworks [1-4]. Generally, they react with a variety of electrophiles to give carbonyl compounds as products due to cleavage of the silicon–oxygen bond. For example, the Lewis acid-catalyzed reaction of silyl enol ethers with alkyl halides is well known as one of the most efficient preparative methods for regio-defined α-alkylated ketones (path a in Scheme 1) [5-17]. In contrast, in this paper, we report a gold-catalyzed reaction of silyl enol ethers with *ortho*-alkynylbenzoic acid esters which leads to the formation of α-alkylated silyl enol ethers (path b).



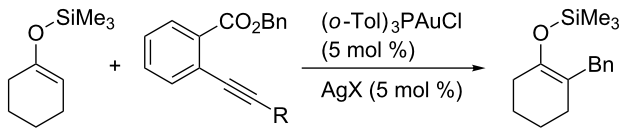

**Scheme 1:** Alkylation of silyl enol ethers.

We examined the reactions of silyl enol ether **1a** with *ortho*-alkynylbenzoic acid benzyl esters **2** in the presence of gold catalysts under several reaction conditions and the results are summarized in Table 1 [18-21]. With a cationic gold catalyst, derived from $Ph_3PAuCl$ and $AgClO_4$, the reaction of **1a** with **2a** proceeded at 80 °C over 2 h and the benzylated silyl enol ether **3a** was obtained in 35% yield, along with the eliminated isocoumarin **4a** and recovered **2a** in 32% and 65% yields, respectively (entry 1). On the other hand, no products were obtained from the reaction of **1a** with benzyl benzoate (having no alkynyl group at the *ortho*-position) under similar reaction conditions. These results clearly show that the alkynyl moiety of ester **2a** is essential for the formation of **3a**. It is well known that concerted pericyclic ene-type reaction of silyl enol ethers with electrophiles, such as aldehydes or ketones, gives functionalized silyl enol ethers without desilylation [22-36]. To the best of our knowledge, however, this is the first example of the introduction of simple alkyl groups through a substitution-type reaction [37-40]. The chemical yield was increased to 55% by use of sterically hindered $(o\text{-Tol})_3PAuCl$ as the gold catalyst (entry 2). Besides benzene, $(CH_2Cl)_2$ and 1,4-dioxane were also suitable solvents (entries 3 and 4). The use of 5 equiv of **1a** improved the chemical yield and **3a** was obtained in 72% yield (entry 5). The catalyst derived from AgOTf gave a better yield, although a longer reaction time was required (entry 6). Analogously, the reaction with **2b**, with a butyl group at the alkynyl terminus, gave **3a** in 75% yield (entry 7). In the current catalyst system using AgOTf, TfOH might be produced during the reactions due to the decomposition of AgOTf with a trace amount of water, which could be present in the reaction medium. However, the alkylation of **1a** with **2a** did not proceed at all with 5 mol % of TfOH. This result clearly indicates that the gold complex functions as a catalyst in the current transformations.

We next examined the substrate generality with several types of silyl enol ethers **1** and esters **2** (Table 2). Treatment of five-membered silyl enol ether, cyclopentenyloxytrimethylsilane (**1b**), with **2b** in the presence of the gold catalyst gave the corresponding benzylated product **3b** in 61% yield (entry 1). It is worth mentioning that benzo-fused silyl enol ether **1c** is suitable for this transformation as shown in entries 2 and 3, whereas it cannot be used for ene-reaction due to the lack of a hydrogen atom at the α'-position. Not only cyclic silyl enol ethers but also an acyclic silyl enol ether underwent the reaction. Thus, **1d** reacted stereoselectively with **2a** to yield *E*-**3e**. Interestingly, the formation of the isomeric *Z*-**3e** was not detected at all (entry 4) [41]. The reaction of **1a** with allyl ester **2d** proceeded smoothly and the corresponding allylated product **3f** was obtained in 70% yield (entry 5) [42].

A plausible mechanism for the gold-catalyzed alkylation of silyl enol ethers is shown in Scheme 2. The gold catalyst enhances the electrophilicity of the alkynyl moiety of **2**, leading to the formation of a cationic intermediate **6** via the intramolecular nucleophilic attack of the carbonyl oxygen on the alkyne as shown in **5**. Due to the high leaving ability of the isocoumarin moiety of **6**, the silyl enol ether **1** attacks the R group to give the intermediate **7** together with the gold complex **8** as a leaving compound [43-46]. In the case of ordinary substitution reactions with alkyl halides (path a in Scheme 1), generated halide ions would attack the silyl group, due to their strong affinities

**Table 1:** Gold-catalyzed alkylation of silyl enol ether[a].

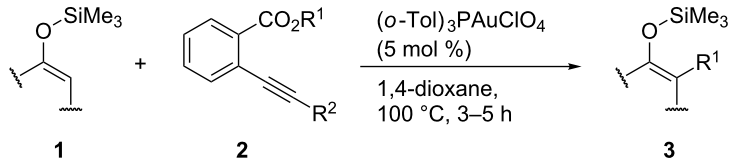



**1a** **2a:** R = Ph **2b:** R = Bu **3a**

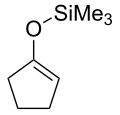
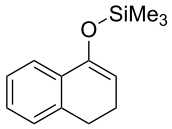
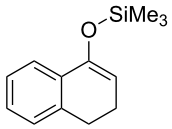
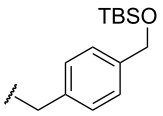
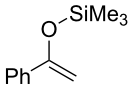
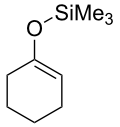
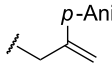
| Entry | 2 | AgX | Solvent | Conditions | Yield (%)[b] |
|---|---|---|---|---|---|
| 1[c] | **2a** | $AgClO_4$ | benzene | 80 °C, 2 h | 35 |
| 2 | **2a** | $AgClO_4$ | benzene | 80 °C, 2 h | 55 |
| 3 | **2a** | $AgClO_4$ | $(CH_2Cl)_2$ | 80 °C, 2 h | 44 |
| 4 | **2a** | $AgClO_4$ | dioxane | 100 °C, 2 h | 58 |
| 5[d] | **2a** | $AgClO_4$ | dioxane | 100 °C, 1 h | 72 |
| 6[d] | **2a** | AgOTf | dioxane | 100 °C, 10 h | 80 |
| 7[d] | **2b** | AgOTf | dioxane | 80 °C, 5 h | 75 |

[a]Reaction conditions: 0.25 M solution of **2** was treated with **1a** (3 equiv) in the presence of the gold catalyst. [b]NMR yield using $CH_2Br_2$ as an internal standard. [c]$Ph_3PAuCl$ was used instead of $(o\text{-Tol})_3PAuCl$. [d]5 equiv of **1a** was used.

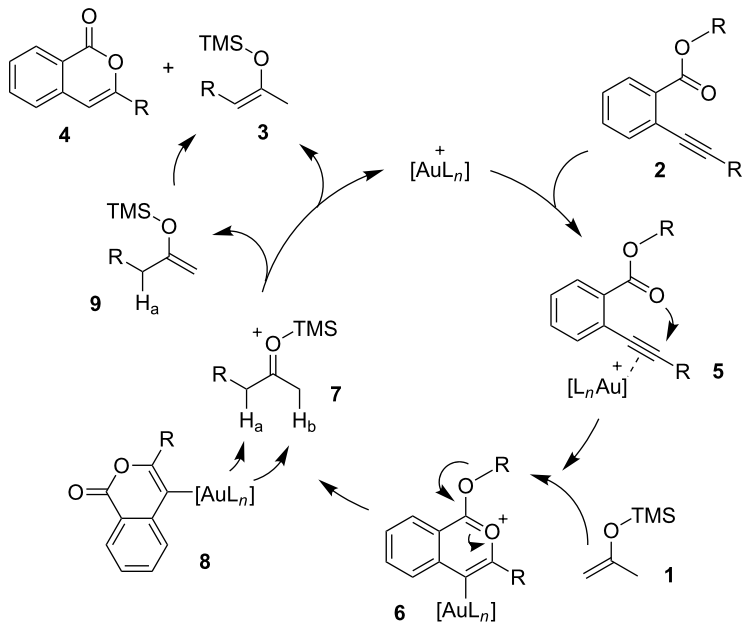
**Table 2:** Gold-catalyzed alkylation of silyl enol ether[a].




**1** **2** **3**

| Entry | | **1** | **2** | $R^1$ | $R^2$ | **3** | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1[c] | **1b** |  | **2b** | Bn | Bu | **3b** | 61 |
| 2 | **1c** |  | **2b** | Bn | Bu | **3c** | 70 |
| 3[d] | **1c** |  | **2c** |  | Ph | **3d** | 60[e] |
| 4[c,f] | **1d** |  | **2a** | Bn | Ph | **3e** | 61 |
| 5 | **1a** |  | **2d** |  | Ph | **3f** | 70 |

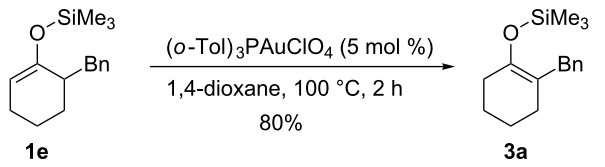
[a]Reaction conditions: 0.25 M solution of **2** was treated with **1** (5 equiv) in the presence of the gold catalyst. [b]NMR yield using $CH_2Br_2$ as an internal standard. [c]10 mol % of the catalyst was used. [d]3 equiv of **1** was used. [e]Yield of isolated product. [f]AgOTf was used instead of $AgClO_4$.



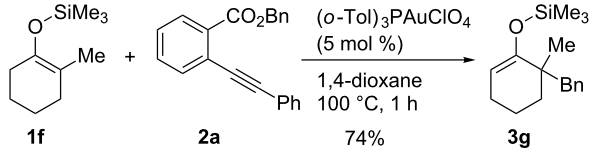

**Scheme 2:** Plausible mechanism for the alkylation of silyl enol ether.

with the silicon atom, and cleave the silicon–oxygen bond of **7**. However, in the present reaction system, intermediate **8** would prefer to act as a base and abstract a proton, $H_a$, from the α-position rather than attack the silyl group as a nucleophile, probably due to steric and electronic reasons. For these reasons, deprotonation of **7** occurs to give the product **3** together with **4** as a final leaving compound.

On the other hand, in the case of reactions with silyl enol ethers having a proton, $H_b$, at the α'-position, compound **9** might be produced through the deprotonation of $H_b$ by **8**. However, such products were not obtained in any of the examples studied. These results imply that isomerism from **9** to **3** would occur during the reaction. Thus, compound **1e** was prepared according to a known procedure and treated with the gold catalyst at 100 °C for 2 h (Scheme 3). As expected, the isomerization of the double bond occurred and **3a** was obtained in 80% yield. This result shows that the indirect pathway from **7** to **3** via deprotonation of $H_b$ is also possible. In addition, it was found that the reaction of **1f**, having no hydrogen at the α-position, proceeded smoothly and α,α-dialkyl silyl enol ether **3g** was obtained in good yield (Scheme 4). Obviously, this result supports the possibility of the indirect pathway.




**Scheme 3:** Gold-catalyzed isomerism of silyl enol ether.




**Scheme 4:** Gold-catalyzed alkylation of tetra-substituted silyl enol ether.

In conclusion, we have developed an unprecedented alkylation method for silyl enol ethers, using a gold catalyst and *ortho*-alkynylbenzoic acid esters as alkylating agents. The reaction probably proceeds through the gold-induced in situ construction of a leaving group and subsequent nucleophilic attack on the silyl enol ether. Unlike ordinary leaving groups, such as halide ions, the generated leaving compound **8** acts as a base and abstracts a proton to regenerate the silyl enol ether structure. The current protocol can also be used with substrates having no hydrogen at the α-position, such as **1f**. Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are underway.

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