Gold-Catalyzed Reaction of Propargyl Esters and Alkynylsilanes: Synthesis of Vinylallene Derivatives through a Twofold 1,2-Rearrangement

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Dedicated to Professor Gerhard Erker on occasion of his 75th birthday

Abstract: The reaction of propargyl esters with alkynylsilanes under gold catalysis provides vinylallene derivatives through consecutive [1,2]-acyloxy/[1,2]-silyl rearrangements. Good yields, full atom-economy, broad substrate scope, easy scale-up and low catalyst loadings are salient features of this novel transformation. Density Functional Theory (DFT) calculations suggest a reaction mechanism involving initial [1,2]-acyloxy rearrangement to generate a gold vinylcarbene intermediate which upon regioselective attack of the alkynylsilane affords a vinyl cation which undergoes a type II-dyotropic rearrangement involving the silyl group and the metal fragment. Preliminary results on the enantioselective version of this transformation are also disclosed.

Metal-carbene complexes have reached an indisputable position as intermediates in organic synthesis and catalysis. This is due not only to the ample spectrum of reactivity exhibited by these species but also to the wide variety of available precursors for their catalytic generation.[1] Among these carbenoid precursors, propargylic esters have found widespread uses, particularly in combination with gold-based catalysts.[2] In these gold-catalyzed transformations of propargylic esters, the generation of the carbene intermediate is proposed employing alkenes[4] and dienes[4d,5] as trapping reagents, whereas a diverse range of transformations has been developed employing alkynes[6] and dienes[4d,5] as trapping reagents, methods based on the use of alkynes as counterparts remain, however, largely underdeveloped. In fact, although some intramolecular processes have been reported, the intermolecular trapping by alkynes of gold carbene intermediates generated from propargyl esters remains challenging.[6,7] To the best of our knowledge, the regioselective synthesis of functionalized cyclopentadienes by gold-catalyzed cyclization of ynamides and propargyl esters reported by Hashmi and co-workers in 2013 represents the only example of intermolecular interception of gold carbene intermediates arising from propargyl esters with a carbon-carbon triple bond (Scheme 1, top).[6] To the best of our knowledge, the regioselective synthesis of functionalized cyclopentadienes by gold-catalyzed cyclization of ynamides and propargyl esters reported by Hashmi and co-workers in 2013 represents the only example of intermolecular interception of gold carbene intermediates arising from propargyl esters with a carbon-carbon triple bond (Scheme 1, top).[6]

Inspired by Hashmi’s elegant work and as part of our ongoing interest in the reactivity of gold vinylcarbene precursors toward unsaturated organosilicon reagents,[9] we became interested in exploring the behavior of propargyl esters toward alkynylsilanes under gold catalysis. We hypothesized that the bulkiness of the silyl group in the alkynylsilane, which might hinder a cyclization reaction, together with the ability of the C-Si o-bond to stabilize an adjacent carboxylation (the so-called β-silicon effect),[10] could provide a favorable sce-

Scheme 1. Intermolecular trapping of gold carbene intermediates arising from propargyl esters with alkynes.
nary for alternative pathways. We report herein that this transformation does not lead to [3+2] cycloadducts but to vinylallene derivatives (Scheme 1, bottom), which are not only common structural motifs in several natural products[11] but also valuable building blocks.[12] A detailed mechanism for this unusual double 1,2-rearrangement,[13] supported by DFT calculations, is also proposed.

At the outset, we first studied the reaction of 1-phenyl-prop-2-yn-1-yl acetate (1a) and 1-phenyl-2-trimethylsilylacetylene (2a, 2 equiv) in the presence of a variety of Au[III] and Au[1] catalysts (see Table S1 in the Supporting Information for a summary of the screening). To our delight, we found that commercially available IPrAuNTf2 (1 mol%) in DCE at 50°C produced vinylallene derivative 3a in 78% isolated yield (Scheme 2). In agreement with previous gold-catalyzed transformations of propargyl esters, compound 3a was isolated as a single (Z)-isomer.

Interestingly, although the gold-catalyzed cycloisomerization of vinylallenes to cyclopentadienes has been reported,[14] no cyclic isomers of vinylallene 3a were observed. Also of note, attempted reaction of propargyl ester 1a with 1-phenyl-1-propyne failed to provide any product, thus revealing that the trimethylsilyl (TMS) group plays a crucial role in the reaction outcome.

Having established effective reaction conditions for the synthesis of 3a, we explored then the scope of this transformation (Table 1). First, 1-phenylprop-2-yn-1-yl pivalate (1b, R’ = Bu) was also found to be amenable to the transformation providing the corresponding allene 3b in good yield (69%) when reacted with 2a. On the other hand, propargyl esters with substituted aryl groups also engaged in this transformation as demonstrated by the synthesis of vinylallene 3c in moderate yield.

Regarding the alkynesilane component, we first demonstrated that the reaction also worked well when the TMS group was replaced with a tert-butyldimethylsilyl (TBS) group, as illustrated the formation of allene derivatives 3d–3g in good to excellent yields (65–91%) when tert-butyldimethyl(phenylethynyl)silane (2b) was reacted with a variety of differently substituted propargyl esters. Regarding the substitution on the aryl ring of the alkynesilane component, we found that electron-rich substrates such as those featuring p-methyl- and p-methoxyphenyl groups are particularly well-suited to the process providing the corresponding products 3h–3m in good to excellent yields (69–98%). p-Halophenyl substituted alkynesilanes also proved to be effective substrates for this transformation affording the expected products 3n–3s in moderate to good yields (58–88%). Aryl-substituted alkynesilanes with electron-withdrawing p-methoxycarbonyl and p-trifluoromethyl groups were also compatible with the present transformation delivering the corresponding allenylsilanes 3t and 3u in moderate yields (58 and 33%, respectively). Conversely, the reactions with alkynesilanes featuring p-acetyl- and p-nitrophenyl groups failed to deliver the expected products. Substituents at the meta position were well-tolerated under the reaction conditions as demonstrated by the formation of vinylallene 3v in good yield (74%). In contrast, the use of an o-methylphenyl group resulted in essentially no reaction. Pleasingly, a 1-naphthyl-substituted alkynesilane was also an amenable reagent, providing the corresponding allenylsilane 3w in 91% yield. Interestingly, an alkynesilane containing a ferrocenyl group proved to be a suitable substrate, delivering the expected product 3x (41%).

Interestingly, the reaction of propargyl esters 1 with alkynesilanes 2 is not limited to the use of aryl-substituted alkynesilanes. For example, a representative alkyl-substituted alkynesilane, namely (cyclohex-1-en-1-yl)trimethylsilyl, was also a viable substrate in this transforma-
tion providing the respective bis-vinylallene 3y in a decent yield (58%). Under the developed conditions, cycloalkyl-substituted alkynylsilanes were also transformed into the corresponding allenylsilane derivatives 3z and 3aa albeit in low isolated yields. In these cases, we found that increasing the catalyst loading to 5.0 mol% had a positive effect on the reaction outcome allowing the isolation of the desired products in good yields (73% for 3z and 66% for 3aa). Under otherwise similar conditions, the reaction of (oct-1-yn-1-yl)silane, proceeded sluggishly to afford the corresponding product 3ab in lower isolated yield (36%).

A possible pathway for the formation of allene derivatives 3 is depicted in Scheme 3. After the initial generation of gold carbene intermediate I through 1,2-acyloxy shift, regioselective attack of the alkynylsilane to the electrophilic carbene carbon atom would generate cationic intermediate II, stabilized by the β-silicon effect. Then, elimination of the [Au]+ fragment with concurrent 1,2-silyl shift would account for the formation of the final product.

To gain more insight into the reaction mechanism of this novel reaction, DFT calculations were carried out (see computational details in the Supporting Information). To this end, the transformation involving substrate 1a and alkynylsilane 2a leading to 3a (see Scheme 2) catalyzed by a model cationic active Au²⁺-catalyst (where the IPr ligand was replaced by the 1,3-bis-phenyl-imidazol-2-ylidene ligand) was computationally explored. The results are shown in Figure 1, which gathers the corresponding relative free energies (ΔG_R, at 298 K) in DCE as solvent (PCM-B3LYP-D3/def2-TZVPP/PCM-B3LYP-D3/def2-SVP level).

As previously proposed, the process begins with the exergonic coordination of the C=C triple bond of 1a to the [Au]²⁺ catalyst. The resulting initial intermediate INT0 undergoes a standard stepwise 1,2-acyloxy shift via the five-membered intermediate INT1 to produce INT2 in an exergonic transformation (ΔG_R = -4.4 kcal mol⁻¹, from INT0). The computed exergonicity and the low barriers involved in this initial rearrangement, which are similar to those reported for related systems,¹⁵ are compatible with the mild reaction conditions used experimentally (see Table S1 in the Supporting Information). Once the gold(I)-vinylcarbene INT2 is formed, the nucleophilic addition of the alkynylsilane 2a takes place. Two possible additions can be envisaged, namely that involving the carbon atom attached to the TMS group (via TS3) and the analogous process involving the carbon atom attached to the phenyl group (via TS3'). Our calculations clearly indicate that the former process is kinetically favored over the latter (ΔΔG_R = 5.8 kcal mol⁻¹), which is fully consistent with the complete regioselectivity observed experimentally. This regioselectivity is mainly due to the β-effect of silicon which greatly stabilizes the benzylic carbo-cationic intermediate INT3. This species finally evolves into

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**Figure 1.** Computed reaction profile for the gold-catalyzed reaction of propargyl ester 1a and alkynylsilane 2a. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal mol⁻¹ and angstroms, respectively. All data have been computed at the PCM-B3LYP-D3/def2-TZVPP/PCM-B3LYP-D3/def2-SVP level.
INT4 through the transition state TS4 with a very low barrier ($\Delta G^\ddagger = 3.0 \text{ kcal mol}^{-1}$) and in a strongly exergonic transformation ($\Delta G_\text{r} = -28.3 \text{ kcal mol}^{-1}$). As depicted in Figure 1, the latter saddle point is associated with the 1,2-shift of the TMS group and the concomitant migration of the transition-metal fragment to the newly formed C=C double bond. Therefore, this step can be viewed as a type II-dyotropic rearrangement, defined as the simultaneous and intramolecular migration of two atoms/groups without positional interchange.[14] Final decooordination releases the observed allene 3a and the active [Au$^+$] catalyst, which can reenter into a new catalytic cycle.

According to our calculations, an alternative mechanism involving the initial formation of a silyl-substituted cyclopropene intermediate and subsequent rearrangement to the allenylsilane seems unlikely.[17]

We next turned our attention to assessing the scalability of our transformation. Pleasingly, we found that the reaction of propargyl ester 1b and alkynylsilane 2e proceeded uneventfully on a 10 mmol-scale, even when the catalyst loading was reduced to 0.4 mol %, delivering 3.93 g (85 %) of the corresponding allene derivatives. Final decoordination releases the observed allene 3a and the active [Au$^+$] catalyst, which can reenter into a new catalytic cycle.

Table 2: Preliminary study on the development of an enantioselective version.[9]

| R$^1$; R$^2$; R$^3$ | [S] | t [h] | Yield [%] | er [%] |
|------------------|-----|------|----------|-------|
| Ph; Me; Ph       | 3a  | 24   | 62       | 52:48 |
| Ph; Me; Ph       | 3d  | 4    | 51       | 82:18 |
| Ph; Bu; Ph       | 3e  | 24   | 62       | 77:23 |
| Ph; Bu; p-Tolyl  | 3j  | 24   | 57       | 84:16 |
| Ph; Me; p-MeOC$_6$H$_4$ | 3k | 4    | 75       | 85:15[4] |
| Ph; Bu; p-MeOC$_6$H$_4$ | 3l | 15   | 67       | 95:5[5] |
| Ph; Bu; p-MeOC$_6$H$_4$ | 3m | 20   | 85       | 92:8  |

[a] (Ar = 6-Methoxynaphthalen-2-yl). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 99:1 er after crystallization from pentane.

These preliminary results seem to suggest that the structure of the alkynylsilane plays an important role in the enantioselectivity of the reaction. Specifically, TBS-substituted alkynylsilanes provided much better er values than those featuring a TMS group. Although further studies are required to elucidate the actual structural factors governing the enantioselectivity of this process, this exploratory study would demonstrate the feasibility of accessing axially chiral compounds in enantioenriched form, a challenging process in asymmetric gold catalysis.

In summary, we have reported an efficient and perfectly atom-economical approach to functionalized vinylallene derivatives from readily available propargyl esters and alkynylsilanes. This novel transformation represents an unusual example of intermolecular trapping of a gold carbene species with alkynes. DFT calculations are consistent with a stepwise mechanism involving the regioselective attack of the alkynylsilane to the gold carbene intermediate and subsequent dyotropic rearrangement of the resulting cationic...
intermediate as key steps. Because of its scalable character and the promising results achieved in the enantioselective version, the reported protocol could serve as a convenient platform for accessing enantiomerically enriched compounds by exploiting the multiple potential reactive sites present in the available products. Further investigations toward this objective are currently in progress in our group.

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Conflict of Interest

The authors declare no conflict of interest.

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