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Au(I)-catalyzed efficient synthesis of α-acyloxy-α′-silyl ketones from α-acyloxy-α-alkynylsilanes

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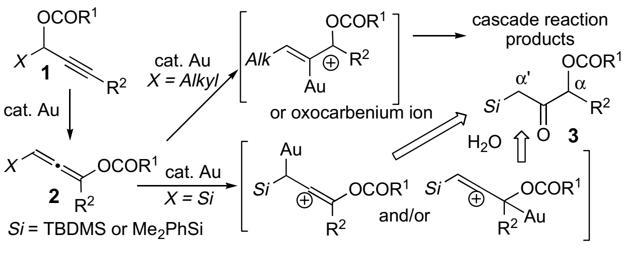
Dedicated to the late Professor Yoshihiko Ito

Abstract—The Au(I)-catalyzed novel conversion of α-acyloxy-α-alkynylsilanes to α-acyloxy-α′-silyl ketones is reported. $Ph_3PAuOTf$ in dioxane in the presence of 1 equiv of H_2O efficiently catalyzed both the [3,3] sigmatropic rearrangement and allenic transformation of the resulting ester to give the α-acyloxy-α′-silyl ketones in a one-pot procedure.

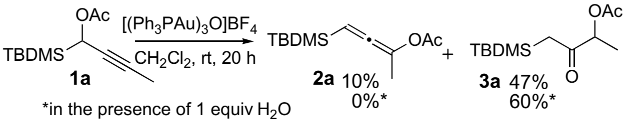
The α-acyloxy ketone is not only a significant synthetic building block,[1] but also a possible precursor of α-hydroxy ketone which is present in substantial numbers of both biologically active natural and synthetic molecules.[2] On the other hand, α-silyl ketones can be used for the regioselective generation of an enolate equivalent.[3] Furthermore, oxidative cleavage of a carbon–silicon bond with an electron-withdrawing silicon substituent allows the conversion of the silyl group to a hydroxy group.[4] Therefore, the regioselective preparation of an α-acyloxy ketone with an additional functionality would expand its utility in organic synthesis. In this Letter, we describe a novel method to access the titled α-acyloxy ketone bearing a synthetically useful α-silyl ketone by the Au(I)-catalyzed reaction of α-acyloxy-α-alkynylsilanes.

Au salts are powerful soft Lewis acids and readily activate alkynes and allenes toward attacks by a variety of nucleophiles.[5] The catalyst plays a dual role for the [3,3] sigmatropic rearrangement of a propargyl ester and activation of the resulting allene to give a series of cascade reaction products via a cationic vinyl-Au species (putatively, an allyl cation) at the allenic terminus (Scheme 1).[6] We hypothesized that a propargyl ester **1** attached to an α-silyl group[7] would undergo the Au-catalyzed rearrangement to give allene **2** whose successive activation by the Au salt would generate a vinyl cation at the allenic center stabilized by the silyl group.[8–10] The unprecedented generation of the cation and its trapping with H_2O would give rise to an α-acyloxy-α′-silyl ketone **3** (Scheme 1).



Scheme 1.

To examine this hypothesis, the readily available α-acetoxy-α-alkynylsilane **1a**[7] was treated with 3 mol % of $[(Ph_3PAu)_3O]BF_4$, used for the Claisen rearrangement of a propargyl vinyl ether[11] in CH_2Cl_2. To our delight, the reaction produced a mixture of an allene **2a** (10%) and α-acetoxy-α′-silyl ketone **3a** (47%). Apparently, **2a** is a product of the Au(I)-catalyzed [3,3] rearrangement.



Scheme 2.

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Table 1. Catalyst optimization using **1a**[a]

Entry	Catalyst	mol %	Temperature (°C)	Time (h)	**2a**[b] (%)	**3a**[b] (%)
1	$[(Ph_3PAu)_3O]BF_4$	3	rt	24	0	74
2	$Ph_3PAuCl/AgBF_4$	3	rt	2	0	41
3	$Ph_3PAuCl/AgSbF_6$	5	rt	4	0	74
4	$Ph_3PAuCl/AgOTf$	3	rt	4	0	91
5	AuCl	5	rt	1	45	0
6	$AuCl_3$	2	rt	0.25	40	0
7	$AgSbF_6$	5	100	22	0	0
8	$AgBF_4$	5	100	22	66	0
9	AgOTf	5	100	6	0	0
10	$PtCl_2$	3	80	3	35	0
11	$Hg(OAc)_2$	5	rt	12	0	0

[a] All the reactions were carried out using dioxane in the presence of 1 equiv of H_2O.

[b] Isolated yield (%) after column chromatography.

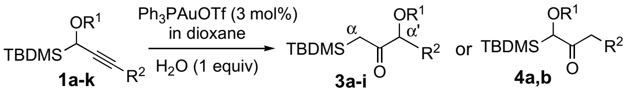
We considered that ketone **3a** was produced from the Au-catalyzed allenic transformation of **2a** via the initial formation of the putative vinyl cation species and subsequent trapping with contaminated water in the solvent. In fact, the addition of 1 equiv of H_2O to the reaction resulted in the exclusive formation of **3a** (60%, Scheme 2).[12] It was found that dioxane in the presence of 1 equiv of H_2O was an appropriate solvent system for this transformation (74%; CH_3CN, 19%; DMF, 29%; THF, 50%).

The catalyst screening indicated that $Ph_3PAuOTf$ (3 mol %), prepared in situ from Ph_3PAuCl and AgOTf, in dioxane–H_2O (1 equiv) was found to be superior to the other Au catalysts (Table 1).[13] The reaction was completed within 4 h at room temperature to give **3a** (91%, entry 4). Au salts, such as AuCl and $AuCl_3$, catalyzed the [3,3] rearrangement to give **2a**, but did not catalyze any further reactions (entries 5 and 6). Among other catalysts, $AgBF_4$ and $PtCl_2$ catalyzed the rearrangement (entries 8 and 10). These results indicated that more electrophilic Au catalyst plays a dual role for activation of both the propargyl ester **1a** and resulting allenol ester **2a**.

We next applied the optimized reaction conditions to other substrates possessing various acyl groups and alkyne substituents (Table 2). The reaction tolerates sterically bulky pivaloyl and electron-donating *p*-methoxybenzoyl esters to give the corresponding products **3b**,**d** in good yields, respectively (entries 2 and 4). An alkyl, phenyl, or *p*-methoxyphenyl alkyne substituent also gave **3g**–**i** in good to excellent yields (entries 7–9). It is noteworthy that *N*-Boc amino acid esters **1e**,**f** also rearranged into the corresponding α-acyloxy ketones **3e**,**f** (entries 5, 6, vide infra). On the other hand, the *p*-nitrophenyl substituted and unsubstituted alkynes **1j**,**k** gave α-acyloxy-α-silyl ketones **4a**,**b** (entries 10 and 11).[5j] In these cases, the generation of a β-silylvinyl cation or 5-*exo*-dig cyclization would take place over the [3,3] rearrangement (Scheme 3).[14] The regioselectivity upon generation of either the vinyl or allyl cation species apparently depends on the α-substituent of the propargyl esters. Treatment of *t*-butyl propargyl acetate **5** under the same reaction conditions gave the α,β-unsaturated ketone **6** (92%).[15,16] This result is in good agreement with the cationic vinyl gold intermediate as proposed by Zhang et al. (Schemes 1 and 3).[6a,b,d,i]

To gain mechanistic insights into the transformation of **1** to **3**, the optically active (*R*)-**1a** (>95% ee) was treated with the optimized reaction conditions. The reaction gave **3a** with complete loss of the starting optical purity. The use of D_2O gave deuterated **3a** in which the D atoms were incorporated into both the α- and α′-positions (α, 70% D; α′, 58% D). The excess incorporation of the D atom would be due to the Au-catalyzed epimerization of **2**.[17] The reaction of the diastereomerically

Table 2. Au-Catalyzed formation of α-acyloxy-α′-silyl ketones



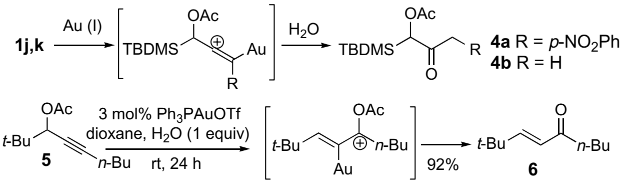
Entry	R^1	R^2	Time (h)	Product	Yield[a] (%)
1	Ac (**1a**)	Me	4	**3a**	91
2	Piv (**1b**)	Me	4	**3b**	89
3	Bz (**1c**)	Me	14	**3c**	0[b]
4	*p*-OMeBz (**1d**)	Me	5	**3d**	68
5	Boc-Gly (**1e**)	Me	6	**3e**	85
6	Boc-L-Phe (**1f**)	Me	7	**3f**	74[c]
7	Ac (**1g**)	*n*-Bu	4	**3g**	91
8	Ac (**1h**)	Ph	22	**3h**	65[d]
9	Ac (**1i**)	*p*-MeOPh	5	**3i**	95
10	Ac (**1j**)	*p*-NO_2Ph	10	**4a**	83
11	Ac (**1k**)	H	8	**4b**	79

[a] Isolated yield after column chromatography.

[b] Recovery of **1c**.

[c] A mixture of 1:1 diastereomers.

[d] With 5 mol % catalyst employed and 22% recovery of **1h**.

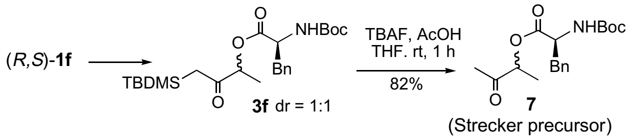


Scheme 3.

pure (*R*,*S*)-**1f** also afforded a 1:1 mixture of diasteromers **3f**, which were obtained from **1f** (entry 6), whose methanolysis gave an optically pure Boc-L-Phe (Supplementary data). These results suggested that the allene epimerization and/or non-stereoselective protonation occurred at the ester counterparts during the Au-catalyzed allenic transformations (Scheme 1). The removal of the silyl group from **3f** afforded α-acyloxy ketone **7**, a precursor for the asymmetric Strecker synthesis of α-methylthreonines (Scheme 4).[18]

Next, we examined the present reaction using other silyl groups. An intriguing entry is the use of the dimethylphenylsilyl group, which can be viewed as a masked hydroxy group.[4] However, the Au-catalyzed reaction of **8** under the optimized conditions resulted in almost the recovery of **8** even after 15 h. We considered that the highly electrophilic Au catalyst was inactivated for the [3,3] rearrangement by interacting with the phenyl group attached to the silicon. Thus, switching the catalyst and solvent systems to a less electron deficient $[(Ph_3PAu)_3O]BF_4$ in CH_2Cl_2–H_2O (1 equiv), which was very effective for this transformation, gave **9** in 86% yield (Scheme 5). The silicon–carbon bond was cleaved after converting **9** to **10** to give alcohol **11** (88%, dr = 2:1). As an attempt for the regioselective aldol condensation of **9**, treatment with benzaldehyde in the presence of BF_3–OEt_2 gave a mixture of the aldol diastereomers **12** (87%, dr = 7:1).[3a]

In summary, various α-acyloxy-α′-silyl ketones were synthesized by the Au(I)-catalyzed reactions of α-acyloxy-α-alkynylsilanes. The reaction proceeded in a mild and regioselective manner via the putative vinyl cation stabilized by the silyl group. The rearranged product possessing an amino acid ester group adds a new and efficient entry for the preparation of the asymmetric Strecker precursor, which leads to various α,α-disubstituted α-amino acids. The α′-silyl ketone moiety also allowed its conversion to the C–O bond formation and the aldol condensation. Further studies are underway to expand the scope of the present method and to use the rearranged products for further conversion.



Scheme 4.

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Supplementary data

Experimental and spectral data of all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.023.

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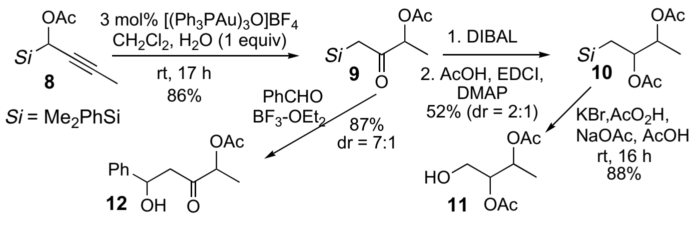

Scheme 5.

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