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Gold-Catalyzed Homogeneous Oxidative C−O Bond Formation: Efficient Synthesis of 1-Benzoxyvinyl Ketones

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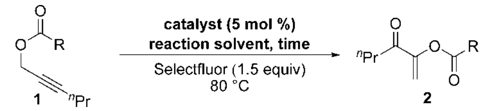
A variety of versatile synthetic methods have been recently developed via homogeneous gold catalysis.[1] The essential theme in most Au chemistry is initial Au activation of alkynes or allenes toward facile nucleophilic attack followed by transformations without involving Au oxidation state changes. While many more reactions based on this theme are to be developed, further expansion of Au chemistry demands revelation of new reactivities. Lately, homogeneous reactions involving Au(I)/Au(III) catalytic cycles have been reported. For example, Corma reported Au-catalyzed Suzuki and Sonogashira reactions likely involving arylhalide oxidation of Au(I) to Au(III) (i.e., oxidative addition, similar to Pd catalysis).[2] Alternatively, external oxidants have been employed to oxidize Au(I) to Au(III), leading to dimerizations.[3] The latter approach holds significant synthetic potential as one can combine contemporary Au catalysis based on alkyne or allene activation with external oxidant-enabled Au redox processes, opening up a new area for studying Au chemistry and offering more oxidized/functionalized products.[3b] Unfortunately, this novel reactivity mode has only been realized in synthetically less useful C−C bond-forming homodimerizations.[4] Recently, we developed the first example of C−C bond-forming cross-coupling reactions, leading to one-step synthesis of α-arylenones.[5] As a continuation of our effort to explore this novel reactivity mode, we herein report the first example of a Au-catalyzed homogeneous oxidative C−O bond-forming reaction. This chemistry offers an efficient synthesis of 1-benzoxyvinyl ketones and, furthermore, valuable mechanistic insights into this novel Au catalysis.

During our investigation with Au-catalyzed reactions of propargylic substrates in the presence of external oxidants, we discovered a rather surprising formation of 1-acetoxyvinyl propyl ketone **2a** from propargylic acetate **1a** when Selectfluor was used as the external oxidant (Table 1, entry 1). Optimization of the ester group (entries 2−6) revealed that benzoate **1c** was the best substrate and 1-benzoxyvinyl propyl ketone **2c** was formed in 83% isolated yield (entry 3). Further studies of the reaction conditions (i.e., the amount of H_2O, entries 7 and 8) and the catalyst (entries 9−11) with benzoate **1c** did not improve the reaction. Moreover, other oxidants such as $PhI(O_2CCF_3)_2$ and $(PhCO_2)_2$ were less effective (32% yield for the former and no product for the latter). As control experiments, $HNTf_2$ did not catalyze the reaction at all, and no product was detected when Selectfluor was omitted. No precipitates were formed during the reaction, and dynamic light scattering experiments offered further support to the homogeneous nature of this reaction.[6]

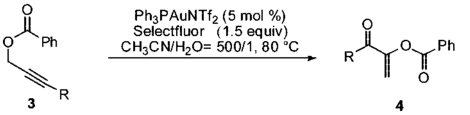
Table 1. Reaction Optimization



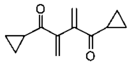
entry[a]	**1** (R)	catalyst	reaction solvent	time (min)	**2** (yield[b])
1	**1a** (Me)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	30	**2a** (46%)
2	**1b** (^{t}Bu)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	10	**2b** (68%)
3	**1c (Ph)**	$\mathbf{Ph_3PAuNTf_2}$	$\mathbf{CH_3CN/H_2O = 500:1}$	**10**	**2c (83%[c])**
4	**1d** (*p*-NO_2Ph)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	90	**2d** (14%)[d]
5	**1e** (*p*-MeOPh)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	10	**2e** (70%)
6	**1f** (MeO)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	40	–[e]
7	**1c** (Ph)	$Ph_3PAuNTf_2$	CH_3CN/H_2O = 100:1	30	**2c** (30%)
8		$Ph_3PAuNTf_2$	CH_3CN	10	**2c** (42%)
9		Au(III)[f]	CH_3CN/H_2O = 500:1	240	**2c** (70%)
10		Au(I)[g]	CH_3CN/H_2O = 500:1	10	**2c** (66%)
11		$PtCl_2$	wet toluene	240	**2c** (40%)[h]
12		$HNTf_2$	acidic condition	180	–[i]
13[j]		$Ph_3PAuNTf_2$	CH_3CN/H_2O = 500:1	120	–[i]

[a] The reaction concentration was 0.05 M, and anhydrous CH_3CN was used. [b] Estimated by ^1H NMR using diethyl phthalate as internal reference. [c] Isolated yield. [d] 32% of **1d** left. [e] The product appeared in 20 min but decomposed after 40 min. [f] Dichloro-(2-picolinato)gold(III). [g] (2-Biphenyl)$Cy_2PAuNTf_2$. [h] 17% of **1c** left. [i] No product was formed, and most **1c** remained unreacted. [j] No Selectfluor was used.

Table 2. Formation of 1-Benzoxyvinyl Ketones: Scope Study



Entry[a]	**3**	R	time	**4**	yield[b]
1	**3a**	cyclohexyl	10 min	**4a**	76%
2	**3b**	Ph	1.5 h	**4b**	66
3	**3c**	cyclopropyl	10 min	**4c**	56%[c]
4	**3d**	$BnOCH_2CH_2$	10 min	**4d**	71%
5	**3e**	$TBSOCH_2CH_2$	10 min	**6**[d]	62%
6	**3f**	$BzOCH_2CH_2$	10 min	**4f**	78%
7[e]	**3g**	$BrCH_2CH_2CH_2$	20 min	**4g**	70%
8	**3h**	$BrCH_2CH_2$	10 min[f]	**7**	60%
9	**3i**	$PhthNCH_2CH_2$	10 min	**4i**	71%



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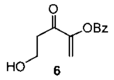

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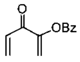

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[a] The reaction concentration was 0.05 M. [b] Isolated yield. [c] 28% of enone dimer **5** was formed. [d] The TBS group was cleaved during the reaction. [e] 2.2 equiv of Selectfluor was used. [f] The reaction mixture was further treated with excess Et_3N for 8 h.

The reaction scope was studied using benzoates with various substituents at the alkyne terminus. As shown in Table 2, cyclohexyl and phenyl were good substituents, affording 1-benzoxyvinyl ketones **4a** and **4b** in good yields, respectively. In the case of a cyclopropyl group (entry 3), the expected enone **4c** was isolated in 56% yield along with a 28% yield of enone dimer **5**.[7] A range of functional groups including protected OH groups (entries 4−6), phthalimide (entry 9), and bromide (entries 7−8) were generally allowed. Not surprisingly, the TBS group in **3e** was cleaved during the reaction as an equivalent of F^- was generated during the reaction. Interestingly, the corresponding propargylic benzoate with a free OH gave no observable **6**, suggesting that desilylation occurred after the Au catalysis. For bromide **3h**, the reaction initially gave a mixture of the expected 2-bromoethyl ketone and dienone **7**. To facilitate purification, the resulting reaction mixture was treated with excess Et_3N, and **7** was eventually isolated in 60% yield.

The mechanism of this reaction is proposed in Scheme 1. Hence, the cationic Au(I) complex first catalyzes tandem transformations

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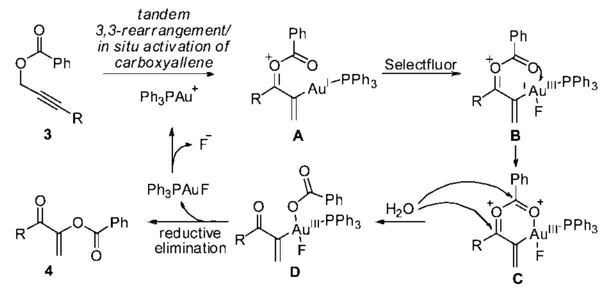
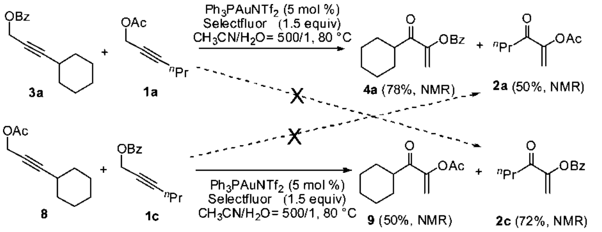
Scheme 1. Proposed Reaction Mechanism



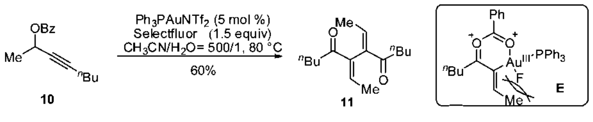
of propargylic benzoate **3**, leading to the formation of Au-containing oxocarbenium intermediate **A**.[8] Instead of hydrolysis,[8h] Au(I) complex **A** is efficiently oxidized by Selectfluor to afford Au(III) complex **B**. Subsequent cyclization of the benzoxy group in **B** to its cationic Au(III) center forms cyclic Au(III) complex **C** and thus initiates an intramolecular migration of the benzoxy group. Hydrolysis of **C** completes the benzoxy migration and affords intermediate **D**, which undergoes facile reductive elimination to yield 1-benzoxyvinyl ketone **4**. While reductive elimination by a Au complex to form a C−O bond has been previously reported,[9] this reaction would constitute the first catalytic, homogeneous case.

Our preliminary mechanistic investigations offer strong support for the intramolecularity of the benzoxy migration. First, externally added carboxylic acids such as acetic acid and *p*-methoxybenzoic acid were not incorporated into product **2c** at all. Second, reactions of a mixture of **3a** and **1a** (eq 1) did not give any cross products, and reversal of the substitution patterns likewise did not lead to any cross products (eq 2). Third, substrate **10** with a methyl group at the propargylic position surprisingly gave no 1-benzoxyvinyl product at all; instead, dimer **11** was isolated in 60% yield (eq 3);[7] this dramatic change in the reaction outcomes can be readily rationalized using the proposed benzoxy migration mechanism: square planar Au(III) complex **E** formed in this case is strongly destabilized by the detrimental steric interaction between one of its ligands (likely the smallest F) and the Me group due to their forced coplanarity.

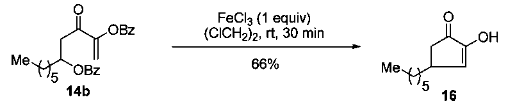


(1)

(2)

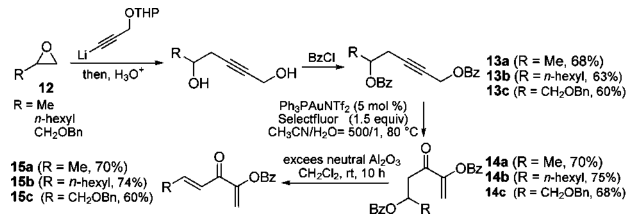


(3)



(4)

Scheme 2. Four-Step Synthesis of Dienones



From readily available propargylic benzoates, this method offers an efficient synthesis of 1-carboxyvinyl ketones, which embody captodative double bonds and often possess unique reactivities.[10] Moreover, dienones like **7** containing a unique combination of electron-deficient and captodative double bonds can be efficiently accessed using this gold catalysis as the key step. As shown in Scheme 2, dibenzoates **13**, easily prepared in two steps from epoxide **12**, were converted into 1-benzoxyvinyl ketones **14** in good yields, and subsequent elimination of benzoic acid from **14** afforded such dienones (i.e., **15**). Further synthetic utility of this chemistry was suggested by a direct conversion of **14b** to cyclopentane-1,2-dione **16** in the presence of $FeCl_3$ (eq 4).

In summary, we have developed the first example of a Au-catalyzed homogeneous oxidative C−O bond-forming reaction. Mechanistic studies suggest a unique intramolecular carboxy migration. From readily available propargylic benzoates, this chemistry allows efficient access to captodative alkenes and dienones, demonstrating the synthetic potential of incorporating Au(I)/Au(III) catalytic cycles into contemporary Au chemistry. The unique reactivity and the mechanistic insights help open a new area of studying Au catalysis.

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Supporting Information Available: Experimental procedures, compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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