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Homogeneous gold-catalyzed efficient oxidative dimerization of propargylic acetates

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ABSTRACT

A highly efficient gold-catalyzed oxidative dimerization of propargylic acetates is developed. In this chemistry, Selectfluor oxidation of Au(I) to Au(III) is readily incorporated into Au-catalyzed tandem reactions of propargylic acetates, and transmetallation and reductive elimination on Au(III) intermediates are likely involved.
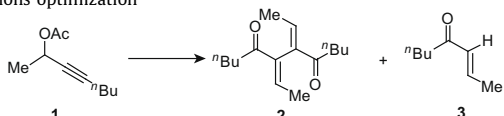
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Homogeneous gold chemistry based on Au(I) or Au(III) catalysis has attracted much attention lately, and various practically useful synthetic methods have been developed.[1] In these reactions, the gold catalysts often do not change their oxidation state.[2] However, homogeneous reactions involving catalytic interconversion of Au(I) and Au(III) has just started to emerge. For example, Au complexes were reported to catalyze Suzuki and Sonogashira reactions at 130 °C, where the arylhalides were likely the oxidant for converting Au(I) into Au(III) (i.e., oxidative addition, similar to Pd catalysis).[3] Alternatively, external oxidants have been employed to oxidize Au(I) to Au(III). For example, an oxidative dimerization[4] of non-activated arenes using HAuCl$_4$ as catalyst and PhI(OAc)$_2$ as external oxidant was reported by Tse and co-workers.[5] A second example was recently reported by Wegner,[6] where aryl propiolates dimerized following an initial cyclization using AuCl$_3$/3AgOTf as catalyst and ^{t}BuOOH as oxidant. In the latter example, a combination of contemporary Au catalysis based on alkyne or allene activation and external oxidant-enabled Au redox processes was achieved. Considering the large array of Au-catalyzed reactions based on alkyne/allene substrates, the introduction of Au(I)/Au(III) interconversion would potentially add a new dimension to gold chemistry. However, protodeauration was a major side reaction in this dimerization of aryl propiolates and the reaction yields were mostly low, thus casting doubts on the synthetic potential of this concept. Herein, we report a highly efficient homogeneous Au-catalyzed oxidative dimerization. In this reaction, Selectfluor oxida-

tion of Au(I) to Au(III) was readily incorporated into Au-catalyzed tandem reactions of propargylic acetates. In addition, dynamic light scattering experiments offered support for the homogeneity of this reaction.

In our attempts to develop a Au-catalyzed synthesis of α-fluoroenones from propargylic acetates,[7] Selectfluor was chosen as an electrophilic fluorinating reagent. To our surprise, when propargylic acetate **1** was treated with Ph$_3$PAuNTf$_2$[8] (5 mol %) and Selectfluor in acetone in a sealed vial at 80 °C, enone dimer **2** was formed in 19% yield along with 11% of enone **3**[9] and some unreacted starting material (Table 1, entry 1). No desired α-fluoroenones was observed. Solvent screening revealed that MeCN was better than acetone, toluene, THF and MeNO$_2$ for this dimerization, and the yield was dramatically increased to 72% (Table 1, entry 2). Among different gold catalysts and PtCl$_2$, (2-biphenyl)Cy$_2$PAuNTf$_2$ (i.e., **5**)[10] gave the best result (Table 1, entry 7). Noteworthy is that neither PtCl$_2$ (Table 1, entry 5) nor Au(III) complex **4** (Table 1, entry 6) gave any discernable dimer **2**. Much to our surprise, Ph$_3$PAuCl, catalytically inert in our previous studies with propargylic esters, also catalyzed this reaction (Table 1, entry 3). Using (2-biphenyl)Cy$_2$PAuNTf$_2$ as catalyst, the reaction yield was lower with less Selectfluor (1.2 equiv, Table 1, entry 8) or at 60 °C (Table 1, entry 9). We surmised that H$_2$O could affect efficiency of this reaction as it was involved in the reaction (vide infra). To our delight, when the volume ratio of CH$_3$CN (anhydrous) and H$_2$O was 500:1, this reaction became highly efficient, affording dimer **2** in 91% isolated yield (Table 1, 12); moreover, only *E,E*-**2** was detected, and no enone **3** was observed. The reaction mixture was transparent throughout, suggesting its homogeneous nature. Control

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E-mail address: lzhang@unr.edu (L. Zhang).

Table 1
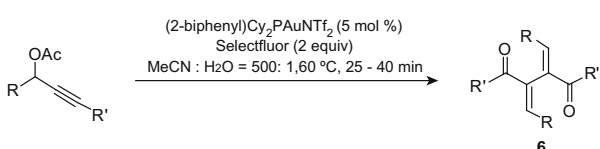Au-catalyzed homo-coupling reactions: reaction conditions optimization[a]

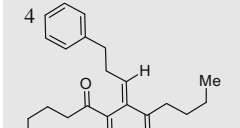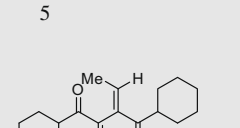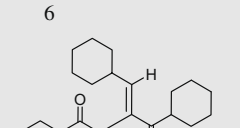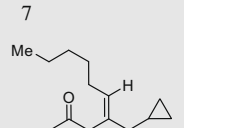| Entry	Catalyst (5 mol %)	Reaction conditions	Yield (%)[b]		% of **1** left
			2	**3**	
1	Ph$_3$PAuNTf$_2$	Acetone, 80 °C, 36 min	19	11	25
2	Ph$_3$PAuNTf$_2$	MeCN, 80 °C, 25 min	72	6	–
3	Ph$_3$PAuCl	MeCN, 80 °C, 60 min	78	<2	–
4	(4-CF$_3$Ph)$_3$AuNTf$_2$	MeCN, 80 °C, 25 min	76	–	–
5	PtCl$_2$	MeCN, 80 °C, 4 h	–	–	16
6	**4**[c]	MeCN, 80 °C, 4 h	20	–	7
7	**5**[d]	MeCN, 80 °C, 11 min	82	–	–
8[e]	**5**	MeCN, 80 °C, 50 min	71	2	–
9	**5**	MeCN, 60 °C, 25 min	71	–	–
10[f]	**5**	MeCN (anhyd), 60 °C, 25 min	53	–	–
11[f]	**5**	MeCN:H$_2$O = 300:1, 60 °C, 25 min	70	4	–
12[f]	**5**	MeCN:H$_2$O = 500:1, 60 °C, 25 min	91[g]	–	–
13[f]	–	MeCN:H$_2$O = 500:1, 60 °C, 25 min	–	–	79
14[f]	HNTf$_2$ (1 equiv)	MeCN:H$_2$O = 500:1, 60 °C, 25 min	–	24	–
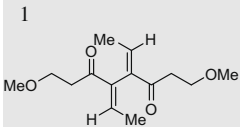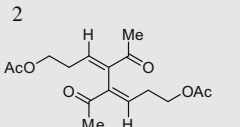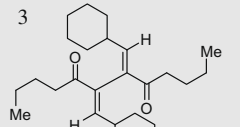
[a] Vial reactions with regular solvent. The reaction concentration was 0.05 M. Selectfluor (2 equiv) was used.
[b] Estimated by ^{1}H NMR using diethyl phthalate as internal reference.
[c] Dichloro-(2-picolinato)Au(III).
[d] (2-biphenyl)Cy$_2$PAuNTf$_2$.
[e] 1.2 equiv of Selectfluor was used.
[f] Flask reaction with anhyd MeCN.
[g] Isolated yield.

experiments (Table 1, entries 13 and 14) suggested that Au catalysts were essential for this dimerization.

The scope of this chemistry was studied using the optimized conditions in Table 1, entry 12. As shown in Table 2, propargylic acetates with oxygen-functionalized alkyl chains on either side of the propargyl moiety worked well, giving enone dimer **6a** and **6b** in excellent yields (entries 1 and 2), respectively. Sterically demanding cyclohexyl group were well tolerated, again affording excellent yields of corresponding products (entries 3, 5 and 6). Particularly noteworthy is that highly hindered enone dimer **6f** was formed with ease and high efficiency. A phenyl group at the propargylic position, however, led to mostly enone formation[9a] along with small amount of the corresponding α-fluoroenone;[7] a phenyl group at the alkyne terminus did not work well, either. However, a

Table 2
Reaction scope studies[a]

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phenyl group removed from the propargyl moiety was well tolerated, giving dimer **6d** in 81% yield (entry 4). In addition, a cyclopropyl group at the alkyne terminus was allowed. For substrates without substitution at the alkyne terminus or propargylic position,[11] no dimer was observed.

6h,   R = Me,   83%
6i,   R, R = (CH₂)₄, 31%

7 (15%)

(1)
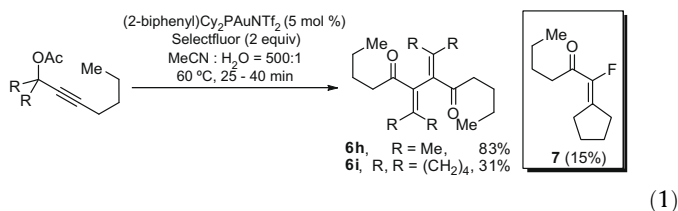
For tertiary propargylic acetates, the substrate prepared from cyclopentanone upon reaction gave only a 31% yield of dimer **6i** (Eq. 1) along with 15% of α-fluoroenone **7**. However, the sterically less demanding dimethyl substrate reacted smoothly to afford dimer **6h** in 83% yield.

The mechanism of this highly efficient homo-coupling reaction is proposed in Scheme 1. As established in studies by us[7,9a,12] and others,[13] propargylic acetates undergo Au(I)-catalyzed tandem reactions, affording oxocarbenium intermediate **A** with LAu(I) at the enone α-position. Hydrolysis of **A** leads to α-auroenone **B**, which would form enones[9a] such as **3** via protodeauration. However, Selectfluor appears readily oxidizing Au(I) complex **B** into Au(III) complex **C**. The lack of enone formation (e.g., **3**) indicates that intermediate **B** undergoes this oxidation much faster than protodeauration. Although this oxidation of organogold(I) to organogold(III) by Selectfluor is previously unknown, this change of gold oxidation states is necessary for subsequent C–C bond formation. Transmetallation between **B** and **C** would then yield Au(III) complex **D** with two identical 1-acylalkenyl ligands, which can undergo reductive elimination to afford enone dimer **2** or **6**. Similar reductive elimination of dialkenylgold(III),[4a] diarylgold(III)[4b,14] and alkoxyalkylgold(III)[15] intermediates have been previously proposed. The essential oxidation of **B** to **C** by Selectfluor is most likely facilitated by the formally negatively-charged 1-acylalkenyl ligand; alternative oxidation of (2-biphenyl)Cy₂PAuNTf₂ to Au(III) is less likely due to the cationic nature of Au(I). Moreover, oxidation of (2-biphenyl)Cy₂P to the corresponding phosphine oxide was not observed during the reaction by both ³¹P NMR and ES⁺ MS, suggesting the (2-biphenyl)Cy₂PAu moiety was most likely intact during the reaction.

Importantly, no precipitates were observed during these reactions. To provide further support for the homogeneous nature of the reaction, we performed dynamic light scattering experiments on the reaction mixture using **1** as substrate.[16] Using Microtrac Nanotrac™ ULTRA with a particle size detecting lower limit of 0.8 nm, the filtered reaction solution,[17] while still containing

catalytically active gold catalysts,[18] could not be effectively measured due to the lack of light scattering.[19] This negative result supported the homogeneous nature of this oxidative dimerization reaction.

In summary, a Au-catalyzed homogeneous oxidative dimerization of propargylic acetates has been developed, leading to highly efficient formation of enone dimers from readily available propargylic acetates. This chemistry is proposed to involve Selectfluor-promoted Au(I)/Au(III) catalytic cycles and proceed with transmetallation and reductive elimination on Au(III) intermediates in a homogeneous system. The oxidation of Au(I) into Au(III) by Selectfluor efficiently outcompetes protodeauration frequently observed in gold catalysis. This work would help the introduction of a new area in Au catalysis, where gold oxidation states can be tuned and contemporary Au chemistry based on alkyne/allene activation can be coupled with oxidative metal-catalyzed reactions.

Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.127.

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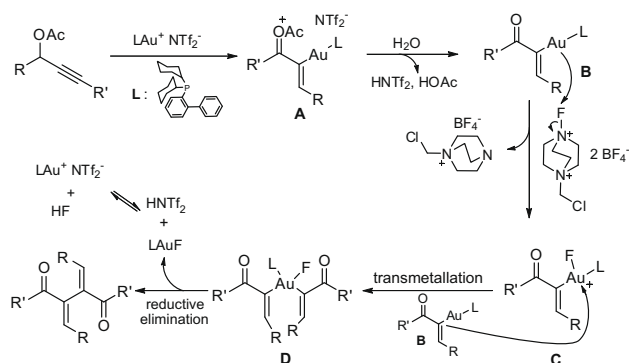
Scheme 1. Proposed reaction mechanism.

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16. For details, see the Supplementary data.

17. Although the reaction mixture is clear, filtration before the measurement using a millex syringe-driven filter unit (450 nm diameter) is necessary to get rid of the contaminating dust; otherwise, the measurement gave particle sizes of ~700 nm, which cannot be due to gold particles as they will become visible.

18. More propargylic acetate **1** and Selectfluor were added to the filtrate, and heating the mixture led to the conversion of **1** to product **2** without further addition of any gold catalyst.

19. By forcing the instrument to perform the measurement, the result was 2.50 nm. As a control experiment, we did the same measurement of the reaction solvent (filtered), which was also used for zeroing the instrument, and an identical number (i.e., 2.50 nm) was obtained, suggesting that the machine could not effectively give negative results.