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# Expanding the Horizon of Intermolecular Trapping of In-Situ Generated $\alpha$ -Oxo Gold Carbenes: Efficient Oxidative Union of Allylic Sulfides and Terminal Alkynes via C-C Bond Formation

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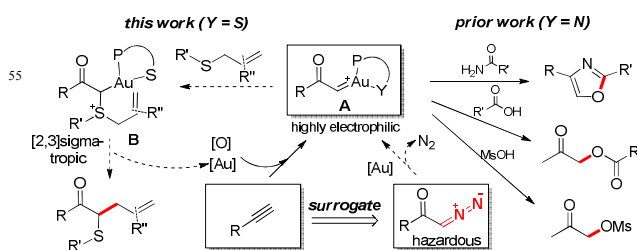
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With a new *P,S*-bidentate phosphine as ligand to gold(I), the  $\alpha$ -oxo gold carbenes generated in situ via gold-catalyzed intermolecular oxidation of terminal alkynes were effectively trapped by various allylic sulfides, resulting in the formation of  $\alpha$ -aryl(alkyl)thio- $\gamma,\delta$ -unsaturated ketones upon facile [2,3]sigmatropic rearrangements.

A few years ago we developed a strategy of generating  $\alpha$ -oxo gold carbenes via gold-catalyzed intermolecular oxidation of alkynes,<sup>1</sup> which offers a facile access to their versatile reactivities and, most importantly, circumvents the use of hazardous and potentially explosive diazo carbonyl compounds<sup>2,3</sup> (Scheme 1). While we<sup>1,4</sup> and others<sup>5</sup> have demonstrated that they can be trapped effectively in intramolecular manners, their intermolecular reactions, owing to the highly electrophilic nature, have been rather challenging. Gold catalysts derived from typical phosphines or NHC ligands in most cases led to low yields;<sup>4c, 6</sup> however, we recently showed that *P,N*-bidentate phosphines such as Mor-DalPhos<sup>7</sup> and our later modified ones,<sup>4h</sup> were uniquely effective in promoting the reactions of the  $\alpha$ -oxo gold carbenes with stoichiometric external nucleophiles. So far we have reported reactions using carboxamides,<sup>4g</sup> carboxylic acids<sup>4h</sup> and MsOH<sup>6, 8</sup> as the stoichiometric trapping reagents. In these cases, the formed bonds that unite the reacting partners are invariable carbon second-row heteroatom bonds (Scheme 1, the right half). To expand the horizon of intermolecular trapping of in-situ generated  $\alpha$ -oxo gold carbene, herein we disclose that the soft sulfur in the form of an allylic sulfide can react smoothly with it, and the oxidative gold catalysis coupled with a facile [2,3]sigmatropic rearrangement (i.e., [2,3]-thio Wittig rearrangement) leads eventually to the union of the sulfide and a terminal alkyne by a newly formed C-C bond.

At the outset, we envisioned that the  $\alpha$ -oxo gold carbene intermediate **A** would react with an external allylic sulfide (Scheme 1, the left half). The gold-substituted sulfonium intermediate **B**<sup>9</sup> thus-generated would then undergo a [2,3]sigmatropic rearrangement<sup>2, 10</sup> either with a prior dissociation of the gold catalyst or without, leading to the formation of an  $\alpha$ -aryl(alkyl)thio- $\gamma,\delta$ -unsaturated ketone product. Importantly, the two reacting partners, the alkyne and the sulfide, were united by a newly formed C-C bond, which is of central importance in organic synthesis. In contrary to the well-practiced preparation of this type of ketone products based on terminal  $\alpha$ -diazo ketones,<sup>2, 10</sup> this strategy, if worked, would enable the

replacement of those hazardous and potentially explosive chemicals with readily accessible and comparably much safer terminal alkynes.

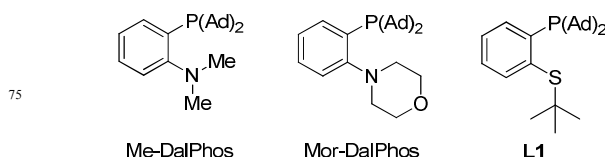


**Scheme 1.** Intermolecular trapping in-situ generated  $\alpha$ -oxo gold carbenes by stoichiometric nucleophiles: precedents and a new design with allylic sulfide as the reacting partner.

**Table 1.** Reaction discovery and optimization.<sup>a</sup>

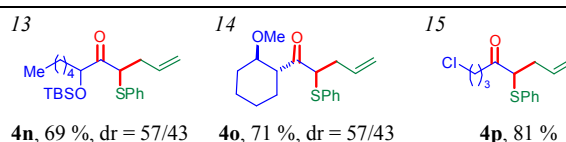
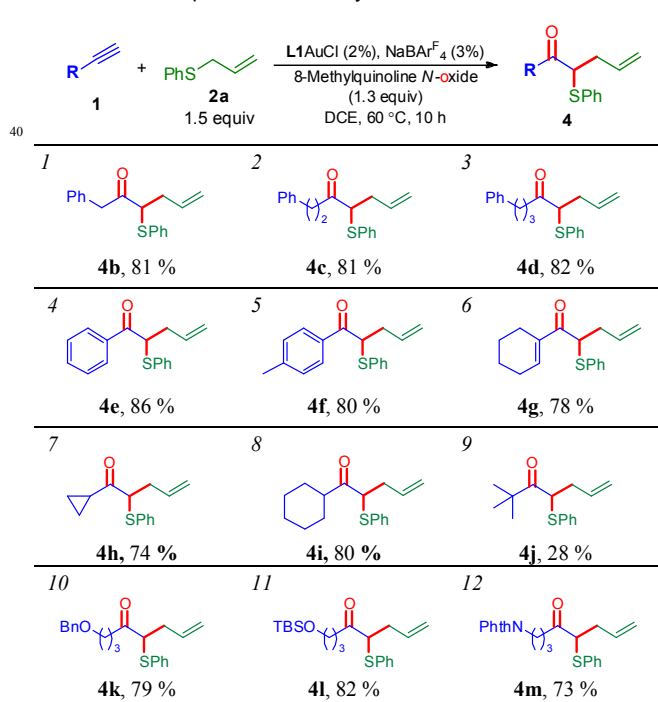
Entry	[Au] (y%)	2a/3 (equiv)	Additive (1.5 • y %)	Yield (conversion) <sup>b</sup>
1	Ph <sub>3</sub> PAuNTf <sub>2</sub> (5)	2.0/1.5	\	5% (70%)
2	BrettPhosAuNTf <sub>2</sub> (5)	2.0/1.5	\	5% (89%)
3	Me-DalPhosAuCl (5)	2.0/1.5	NaBAR <sub>4</sub> <sup>F</sup>	86% (>99%)
4	Mor-DalPhosAuCl (5)	2.0/1.5	NaBAR <sub>4</sub> <sup>F</sup>	87% (>99%)
5	L1AuCl (5)	2.0/1.5	NaBAR <sub>4</sub> <sup>F</sup>	88% (>99%)
6	L1AuCl (2)	1.5/1.3	NaBAR <sub>4</sub> <sup>F</sup>	83% <sup>c</sup> (>99%)
7 <sup>d</sup>	L1AuCl (2)	1.5/1.3	NaBAR <sub>4</sub> <sup>F</sup>	39% (70%)
8 <sup>e</sup>	L1AuCl (2)	1.5/1.3	NaBAR <sub>4</sub> <sup>F</sup>	34% (80%)

<sup>a</sup> A solution of **3** in DCE was introduced into the reaction in a septum-capped vial via a syringe pump at the rate of 0.1 mL/h; the nominal final concentration of **1a** was 0.05 M. <sup>b</sup> Estimated by <sup>1</sup>H NMR using diethyl phthalate as the internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> **3** was added into the reaction in one portion at the beginning. <sup>e</sup> The reaction was run at the room temperature.



To reduce the design into practice, we employed 1-dodecyne (**1a**) as the substrate and phenyl allyl sulfide (**2a**, 2 equiv) as the trapping reagent. With the oxidant 8-methylquinoline *N*-oxide (**3**)<sup>4a</sup> added via syringe pump, the reaction run in DCE at 60 °C led to little desired product **4a** in the presence of gold catalysts derived from monodentate ligands including Ph<sub>3</sub>P (entry 1) and BrettPhos (entry 2), which were nevertheless expected based on our previous studies.<sup>4g, 4h</sup> In line with the unique ability of *P,N*-bidentate ligands to facilitate intermolecular trapping<sup>4g, 4h</sup> via the likely formation of tricoordinated and hence less electrophilic  $\alpha$ -oxo gold carbenes, the reaction was highly efficient when Me-DalPhosAuCl (entry 3) or Mor-DalPhos (entry 4) in the presence of the halide scavenger NaBARF<sub>4</sub>, confirming that sulfide can be a suitable nucleophile to trap attenuated  $\alpha$ -oxo gold carbene intermolecularly. Notably, the sulfide moiety in **2a** and **4a**, though capable of coordination to the cationic gold complex, did not affect the oxidative gold catalysis nor get oxidized by **3** during the reaction. To expand the ligand repertoire for effecting this oxidative gold catalysis, we tested the ligand **L1**, a new *P,S*-bidentate ligand possessing a bulky di-(1-adamantyl)phosphinyl group. Comparing to its *di-t*-butylphosphinyl counterpart we used previously,<sup>4g, 4i</sup> the Ad<sub>2</sub>P group is preferred due to its ease of installation via cross coupling.<sup>7a</sup> To our delight, the reaction proceeded with similar ease and comparable efficiency (entry 5). To showcase the synthetic utility of this new ligand, we decided to focus on using it to develop this gold catalysis. To make the reaction more economical, the catalyst loading was lowered from 5% to 2%, and the amount of the sulfide **2a** and the oxidant **3** were decreased to 1.5 equiv. and 1.3 equiv., respectively; however, to our delight, the reaction yield remained excellent (entry 6). The slow addition of **3** into the reaction mixture was to minimize competing gold carbene oxidation. Without using this technique, the yield expectedly decreased substantially (entry 8). A low yield was also resulted when the reaction was run at ambient temperature (entry 8), likely due to the diminished rate of the [2,3]sigmatropic rearrangement at the lower temperature.<sup>9</sup>

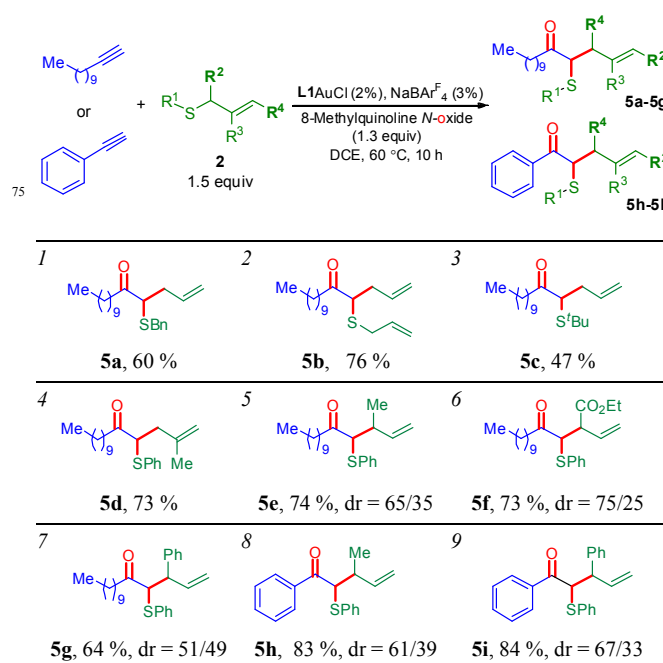
**Table 2.** The scope of terminal alkynes<sup>a</sup>

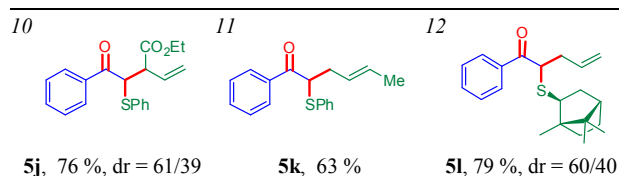


<sup>a</sup> A solution of **3** in DCE was introduced into the reaction via a syringe pump; isolated yields are reported.

With the best conditions outlined in Table 1, entry 6 in hand, we promptly investigated the scope of terminal alkynes. As shown in Table 2, phenyl/aryl-substituted alkynes such as 3-phenylprop-1-yne (entry 1), 4-phenylbut-1-yne (entry 2), 5-phenylpent-1-yne (entry 3), phenylacetylene (entry 4), and *p*-tolylacetylene (entry 5) participated in the reaction smoothly, affording the corresponding products all in good yields. Notably in these cases the Friedel-Crafts-type cyclization by the electrophilic gold carbene center was not observed, highlighting the substantial attenuation of the electrophilicity of the carbene center by the *P,S*-bidentate ligand **L1**. 1-Ethynylcyclohex-1-ene was also a good substrate (entry 6), and the resulting enone **4g** possesses an interesting array of functional groups. Similarly, cyclopropylacetylene reacted without incident, affording the  $\alpha$ -phenylthio ketone **4h** in 74% yield. A secondary alkyl group at the alkyne end (e.g., entry 8) was inconsequential, but a *t*Bu group led to a significant decrease in the yield (entry 9). Our further examination of functional group compatibility of this reaction revealed its general tolerance. For example, a variety of protected hydroxyl groups at different locations (entries 10, 11, 13 and 14), a protected amino group in the form of PhthN (entry 12), and a chloride (entry 15) were all allowed. It is worthwhile to point out that similar to the cases with phenyl groups these functional groups are all electrophilic in nature but did not interfere to a notable extent with the nucleophilic trapping by external sulfides. Notably, very low diastereoselectivities were detected in the entries 13 and 14.

**Table 3.** The scope of allylic sulfides<sup>a</sup>

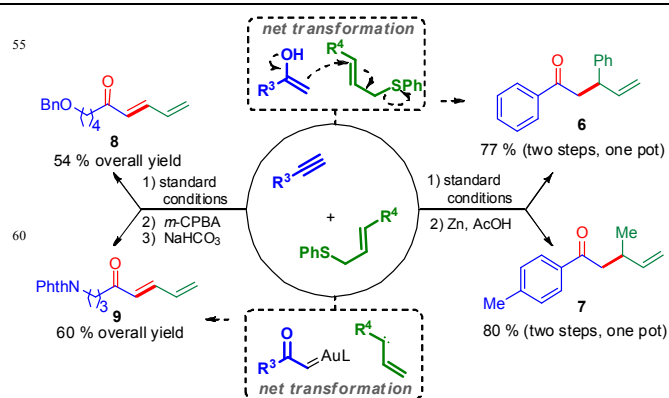




<sup>a</sup> A solution of **3** in DCE was introduced into the reaction via a syringe pump; isolated yields are reported.

The scope of the allylic sulfides was also probed first by using 1-dodecyne as the alkyne substrate (Table 3, entries 1-7). Replacing the phenyl group of **2a** with a benzyl (entry 1), an allyl (entry 2), or a <sup>t</sup>Bu (entry 3) was mostly uneventful although the yields were lower. The last case suffered a particularly notable yield decrease, likely the consequence of the steric bulk of the <sup>t</sup>Bu group. Perturbing the allyl group of **2a** provided valuable opportunities to increase the structural diversity of the enone product with much synthetic flexibility. A methyl group posed little problem to the reaction, and the product **5d** was isolated in 73% yield (entry 4). Substitutions at the allyl distal end by a methyl group (i.e., a crotyl group, entry 5), an ester group (entry 6), and a phenyl group (i.e., a cinnamyl group, entry 7) were all readily allowed, and the corresponding products were isolated in fair to good yields albeit with low diastereoselectivities. The reactions of these three sulfides with phenylacetylene also occurred smoothly, offering generally higher yields than those with 1-dodecyne (entries 8-10). The allylic sulfide could also accommodate substitution at the allylic position, as exemplified by the case shown in entry 11; the yield was moderate, presumably caused by the more hindered nature of the sulfide. The attempt to generate a ketone product with an enantioenriched thio-substituted  $\alpha$ -chiral center using an allyl sulfide derived from (-)-borneol (for its synthesis, see SI) was thwarted by the low diastereoselectivity, although the yield was good (entry 12).

To illustrate the synthetic utility of this oxidative gold catalysis, some of the  $\alpha$ -phenylthio ketone products were subjected to either reductive or oxidative desulfuration. In the former case, the direct treatment of the resulting reaction mixtures with Zn/HOAc led to clean removal of the phenylthio group, delivering the  $\beta$ -substituted- $\gamma,\delta$ -unsaturated ketones **6** and **7**, respectively, in good overall yields (Scheme 2). Of note, the low diastereoselectivities of the gold catalysis in these cases were inconsequential. The net transformation of this one-pot, two-step process is a novel  $S_N2'$  substitution of an allylic sulfide with a hydrated alkyne (i.e., an enol). Alternatively, the oxidation of the sulfide into a sulfoxide followed by basic elimination could result in the formation of a conjugated dienone. For two examples shown in Scheme 2, the  $\alpha$ -phenylthio ketones formed upon the gold catalysis were better purified before subjected to the one-pot oxidation and elimination, and the overall yields were respectful. The net result of this three-step, two-pot process is a C-C double bond union between an  $\alpha$ -oxo gold carbene and formally a vinyl carbene from the sulfide (see Scheme 2).



**Scheme 2.** Conversion of the  $\alpha$ -phenylthio ketone products via reductive or oxidative desulfuration.

Gold-catalyzed intermolecular oxidation of alkynes provides a facile access to typically highly reactive  $\alpha$ -oxo gold carbenes without resorting to hazardous and potentially explosive diazo carbonyl substrates. With the attenuation of their electrophilicities by the use of a new *P,S*-bidentate ligand, we have in this study expanded the scope of external nucleophiles that could effectively trap them in stoichiometric amount or in slight excess from those based on second-row, hard heteroatoms to soft nucleophilic sulfides. By coupling with a subsequent facile [2,3]sigmatropic rearrangement, a union of the two reacting partners, a terminal alkyne and an allylic sulfide, is achieved via a newly formed C-C bond, which is the first example of this type of oxidative gold catalysis. The reaction scope is fairly general with both substrates, tolerating various functional groups, and the reaction yields in most cases are good. This chemistry makes the corresponding well-practiced diazo approach obsolete by replacing the hazardous reagents with readily accessible and comparably much safer terminal alkynes. In combination with a one-pot reductive desulfuration, this chemistry offers a new and efficient synthetic strategy for  $\gamma,\delta$ -unsaturated ketones. On the other hand, subsequent oxidative desulfuration provides access to synthetically useful conjugated dienones in acceptable yields.

## Notes and references

- <sup>†</sup> Jiabin Li and Kegong Ji contributed equally to this work.  
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<sup>b</sup> College of Science, China Pharmaceutical University, Nanjing, 210009, P. R. China.  
<sup>†</sup> Electronic Supplementary Information (ESI) available: experimental procedure, <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra. See DOI: 10.1039/b000000x/  
<sup>‡</sup> We are grateful of the financial support of NSF (CHE-1301343) and NIGMS (R01 GM084254). JL thanks the fellowship of Jiangsu Overseas Research & Training Program for the University Prominent Young & Middle-aged Teachers and Presidents.
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