

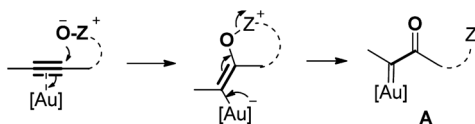
Electrophilicity of  $\alpha$ -oxo gold carbene intermediates: halogen abstractions from halogenated solvents leading to the formation of chloro/bromomethyl ketones†Weimin He,<sup>a</sup> Longyong Xie,<sup>a</sup> Yingying Xu,<sup>a</sup> Jiannan Xiang<sup>\*a</sup> and Liming Zhang<sup>\*b</sup>

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$\alpha$ -Oxo gold carbenes generated *via* intermolecular oxidation of terminal alkynes are shown to be highly electrophilic and can effectively abstract halogen from halogenated solvents such as 1,2-dichloroethane or 1,2-dibromoethane. Chloro/bromomethyl ketones are prepared in moderate efficiencies in one step using  $\text{Ph}_3\text{PAuNTf}_2$  as the catalyst and 8-methylquinoline *N*-oxide as the oxidant.

Among various types of gold catalysis developed in the past decade,<sup>1</sup> gold-catalyzed oxidation of alkynes, either intramolecularly<sup>2</sup> or intermolecularly,<sup>3</sup> has contributed significantly to the diversity and the versatility of gold chemistry and offers efficient access to an array of synthetically versatile structures. In most cases,  $\alpha$ -oxo gold carbene **A** is proposed as the reactive intermediate (Scheme 1). Albeit with exceptions,<sup>3a,e,4</sup> its intermediacy seems to offer the only reasonable rationale for the reaction outcome in many instances. Trapped mostly by optimally tethered nucleophiles or nucleophilic solvent,<sup>3g</sup> its reactivity is still not well understood, even to the extent of its electrophilicity. Only a few examples of formal C–H insertions and cyclopropanations<sup>3h,k</sup> are realized under optimal circumstances.<sup>5</sup> Herein, we disclose that the gold carbene intermediate is highly electrophilic and can abstract halides from halogenated solvents such as 1,2-



Scheme 1 Gold-catalyzed alkyne oxidation.

dichloroethane (DCE) and 1,2-dibromoethane; moreover, a one-step synthesis of versatile chloro/bromomethyl ketones from terminal alkynes is developed.

Recently some of us have developed a practical protocol for the generation of  $\alpha$ -oxo gold carbene **A** *via* gold-catalyzed intermolecular alkyne oxidation,<sup>3b-d,fg</sup> and derivatized pyridine/quinoline *N*-oxides are the oxidants of choice. Notably, this approach circumvents the use of  $\alpha$ -diazo compounds, typically employed for accessing  $\alpha$ -oxo metal carbenes.<sup>6</sup>

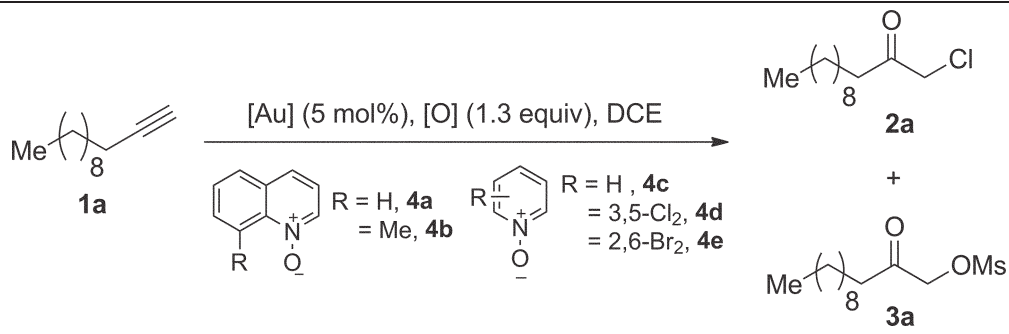
In some of our previous studies,<sup>4</sup> we noticed the formation of small amounts of  $\alpha$ -chloromethyl ketones when DCE was the reaction solvent. For example, 1-chlorododecan-2-one (*i.e.*, **2a**) was formed in 8% NMR yield when dodec-1-yne was treated with 8-methylquinoline *N*-oxide<sup>3c</sup> (*i.e.*, **4b**) in DCE (Table 1, entry 1). This reaction could be improved when a slight excess of MsOH was introduced (entry 2) and further by running the reaction at ambient temperature (entry 3). Mesylate **3a** was also formed but in small quantities, consistent with our previous observation.<sup>3b</sup> The origin of the chloride, although somewhat unexpected, was apparently from DCE, the reaction solvent. Moreover, chloride abstraction from methylene chloride by the same gold carbene also occurred albeit with a decreased efficiency (entry 4). Further evidence was provided by the formation of 2-chloroethyl mesylate in the case of entry 3, which identity was confirmed upon isolation.

The reaction outcome is rationalized in Scheme 2: the  $\alpha$ -oxo gold carbene intermediate **B** is first formed *via* intermolecular alkyne oxidation and then behaves as a highly electrophilic species, abstracting a chloride from the solvent *via* a chloronium intermediate (*i.e.*, **C**); the gold enolate intermediate **D** could then be protodeaurated to form **2a**; the solvent molecule, upon the loss of  $\text{Cl}^-$ , would become ethylene chloronium, which is then attacked by mesylate to form the observed 2-chloroethyl mesylate. Alternatively, the chloronium intermediate **C** might be first protonated to form the chloronium **E**, which could be attacked by mesylate to form either **2a** and 2-chloroethyl mesylate or **3a**, depending on the approaching point of the nucleophile. In addition, the gold carbene **B** might insert into mesylic acid to afford **3a**.

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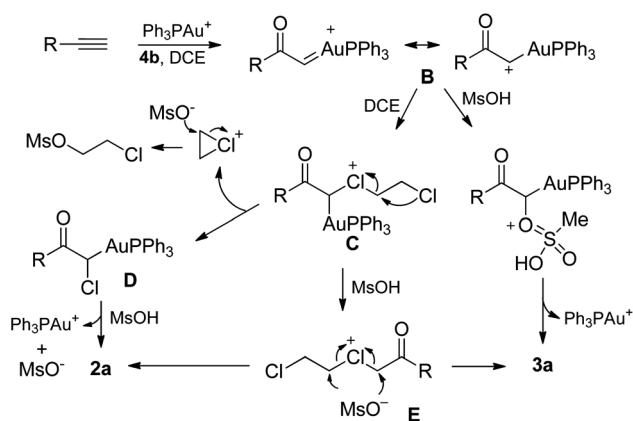
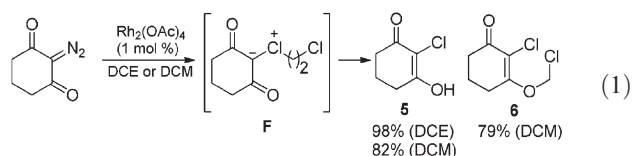
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**Table 1** Chloride abstraction by an  $\alpha$ -oxo gold carbene<sup>a</sup>


Entry	Gold catalyst	Oxidant	Acid (1.1 eq)	Reaction conditions	Yield <sup>b</sup> [%]	
					2a	3a
1	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4b	—	60 °C, 8 h	8	0
2	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4b	MsOH	60 °C, 8 h	39	6
3	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4b	MsOH	RT, 8 h	63 <sup>cd</sup>	5
4 <sup>e</sup>	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4b	MsOH	RT, 8 h	41	6
5	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4a	MsOH	RT, 8 h	60	5
6	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4c	MsOH	RT, 8 h	21	11
7	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4d	MsOH	RT, 8 h	24	15
8	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4e	MsOH	RT, 8 h	39	14
9	IPrAuNTf <sub>2</sub>	4b	MsOH	RT, 8 h	19	11
10	(RO) <sub>3</sub> PAuNTf <sub>2</sub> <sup>f</sup>	4b	MsOH	RT, 8 h	51	13
11	Au(III) <sup>g</sup>	4b	MsOH	RT, 8 h	4	13

<sup>a</sup> In vial; [1a] = 0.1 M. <sup>b</sup> Estimated by <sup>1</sup>H NMR spectroscopy using diethyl phthalate as an internal reference. <sup>c</sup> Isolated yield of 63%. <sup>d</sup> MsOCH<sub>2</sub>CH<sub>2</sub>Cl was formed in 46% yield. <sup>e</sup> CH<sub>2</sub>Cl<sub>2</sub> as solvent. <sup>f</sup> R = 2,4-(*t*-Bu)<sub>2</sub>Ph. <sup>g</sup> Dichloro(2-picolinato)gold(III).

**Scheme 2** Proposed reaction mechanism.

Notably, many reactions involving metal carbene/carbenoid intermediates are performed in DCM or DCE,<sup>6</sup> but only a few instances of chloride abstraction<sup>7,8</sup> have been documented to date. In 1995, Pirrung *et al.*<sup>7f</sup> reported that the rhodium carbenoid generated *via* dediazotization of 2-diazocyclohexane-1,3-

dione reacts with DCE and DCM to form 2-chloro-3-hydroxycyclohex-2-enone (*i.e.*, **5**, eqn (1)). The chloronium **F** is the proposed intermediate. Later, Lee showed that this type of rhodium carbenoids can abstract chloride from a range of other sources including acyl chloride, alkyl/benzyl halides besides halogenated solvents.<sup>7c</sup> In the case of DCM, however, he reported the isolation of dichloride **6** in 79% yield; the same result was obtained by Müller *et al.*<sup>7d</sup> It is important to point out that in these studies the highly electrophilic rhodium carbene/carbenoid intermediates are flanked by two electron-withdrawing carbonyl groups. In comparison, the gold carbene of type **B**, capable of similar chloride abstraction, has only one  $\alpha$ -carbonyl group. This indicates that gold is in general less capable of back bonding<sup>9</sup> than rhodium, therefore leading to a more electrophilic carbene center than that of a related rhodium species. An alternative explanation for the high electrophilicity of **B** by invoking a MsOH protonation of its oxo group prior to chloride abstraction is unlikely as **2a** was formed without acid (see Table 1, entry 1) and, moreover, such a protonated intermediate, if formed, would most likely lead to mesylate **3a** due to trapping by the counter anion, *i.e.*, MsO<sup>-</sup>, which should be more nucleophilic than the neutral solvent. Other  $\alpha$ -oxo metal carbenes capable of this type of chloride abstraction have been reported by Dias *et al.*<sup>7b</sup> and later Maseras and co-workers<sup>7e</sup> (Ag) and Davies and Albrecht<sup>2h</sup> (Pt), confirming that later transition metals (in relation to rhodium) tends to be poor in back bonding.

Further reaction conditions optimization using different *N*-oxides (Table 1, entries 5–8) and different gold catalysts (Table 1, entries 9–11) did not lead to an improved yield.

**Table 2** The reaction scope<sup>ab</sup>

$  \begin{array}{c}  \text{Ph}_3\text{PAuNTf}_2 \text{ (5 mol \%)} \\  \text{4b (1.3 equiv), MsOH (1.1 equiv)} \\  \text{DCE or 1,2-dibromoethane, rt, 8 h}  \end{array}  \rightarrow  \begin{array}{c}  \text{R}-\text{C}(=\text{O})-\text{CH}_2-\text{X} \\  \text{2 (X = Cl or Br)}  \end{array}  $		
1 	2 	3 
<b>2b</b> , 58%	<b>2c</b> , 42%	<b>2d</b> , 62%
4 	5 	6 
<b>2e</b> , 55%	<b>2f</b> , 65%	<b>2g</b> , 53%
7 	8 	9 
<b>2h</b> , 51%	<b>2i</b> , 56%	<b>2j</b> , 70%
10 	11 	12 
<b>2k</b> , 60%	<b>2l</b> , 41%	<b>2m</b> , 43%
13 	14 <sup>c</sup> 	15 <sup>c</sup> 
<b>2n</b> , 37%	<b>2o</b> , 68%	<b>2p</b> , 60%
16 <sup>c</sup> 	17 <sup>c</sup> 	18 <sup>c</sup> 
<b>2q</b> , 56%	<b>2r</b> , 43%	<b>2s</b> , 42%

<sup>a</sup> Reaction conditions: [1] = 0.1 M. <sup>b</sup> Isolated yield are given. <sup>c</sup> Using BrettPhosAuNTf<sub>2</sub> as the gold catalyst.

Chloro/bromomethyl ketones are versatile substrates<sup>10</sup> for various S<sub>N</sub>2 reactions and the Reformatsky reaction,<sup>11</sup> but their direct synthesis from the corresponding methyl ketones using electrophilic halogen sources such as molecular halogen,<sup>12</sup> NaClO<sub>2</sub>,<sup>13</sup> and NBS<sup>14</sup> can be plagued by poor regioselectivity and over-halogenation. This alkyne oxidation strategy offers a conceptually different preparative approach, which avoids the afore-mentioned issues and could be of synthetic utility. With this in mind, we proceeded to examine various alkynes substrates in order to reveal the scope of this chemistry.

As shown in Table 2, the reaction tolerated a range of functional groups including a free HO group (entry 1) and various protected/functionalized ones (entries 2–6), a chloro group (entry 7), protected amino groups such as tosylamide (entry 8) and phthalimide (entry 9), a carboxylic acid (entry 10), and phenyl groups (entries 11 and 12). Cyclohexyl chloromethyl ketone (**2n**) (entry 13) was also attainable albeit with a low yield, likely due to steric hindrance imposed by the secondary alkyl group. By using dibromoethane as the solvent, this alkyne oxidation strategy could be extended to access the corresponding bromomethyl ketones (entries 14–18). In all the cases, yields were mostly moderate but synthetically serviceable, reflecting the reactive nature of the α-oxo gold carbene intermediates. This reaction did not work with aliphatic internal alkynes due to facile enone formation.<sup>15</sup>

## Conclusions

We have reported a surprising halide abstraction by α-gold carbenes generated *via* gold-catalyzed intermolecular oxidation of terminal alkynes. Synthetically useful chloro/bromomethyl ketones can be prepared in one-step from terminal alkynes. Although the reaction efficiency is moderate, this method may find its usage in scenarios where functional group compatibility is critical, by masking the reactive halomethyl ketone as a terminal alkyne. Importantly, the strong electrophilicity of the gold carbene intermediates reveals that gold in general is less effective in back bonding than rhodium but perhaps similar to Ag. This conclusion forecasts that the chemistry of α-oxo gold carbenes, yet to be fully studied, could be very different from the well-studied Rh counterpart and may provide new opportunities for methodology development, especially *via* the alkyne oxidation strategy.

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