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# Gold-Catalyzed Oxidative Hydrative Alkenylations of Propargyl Aryl Thioethers with Quinoline N-Oxides Involving a 1,3-Sulfur Migration

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**Supporting Information** 

ABSTRACT: This work reports gold-catalyzed oxidative alkenylations of quinoline N-oxides with propargyl aryl thioethers to afford 3-hydroxy-1alkylidenephenylthiopropan-2-one via a 1,3-sulfur group migration. The mechanism of this reaction is postulated to involve an  $\alpha$ -oxo gold carbene intermediate followed by formation of a four-membered sulfonium ring that is



ring-opened by one H<sub>2</sub>O to form a gold enolate. A final condensation of this enolate with a second quinoline N-oxide delivers an alkenylation product accompanied by a 1,3-sulfur shift.

ne noteworthy development in gold catalysis is to generate  $\alpha$ -oxo gold carbenes (I) from alkynes and pyridine-based oxides.<sup>1</sup> These  $\alpha$ -oxo metal carbenes (I) are versatile in reactions with small molecules to enable dipolar cycloaddition reactions,<sup>2</sup> skeletal rearrangements,<sup>3</sup>  $\tilde{X}$ -H insertions (X = C, N, O),<sup>4</sup> and cyclopropanations,<sup>5</sup> where most of these carbene functionalizations were intramolecular. In the presence of nucleophiles (Nu-H), the resulting  $\alpha$ -oxo gold carbenes are terminated with traditional 1,1-addition reactions (eq 1)<sup>4</sup> Oxidations of alkynes with nitrones generated similar

Organic

Previous systems: Oxidation/nucleophilic additions

$$\| + [N]^{+} O^{-} \xrightarrow{LAu^{+}} \left[ \bigvee_{O \ I \ H}^{R} \right] \xrightarrow{AuL} \frac{Nu \cdot H}{LAu^{+}} \bigvee_{O \ H}^{Nu}$$
(1)  
[N] = pyridine

Our recent work: Oxidative Cycloalkenvlation with N-oxides



This work: Oxidative hydrative alkenylation involving 1,3-thio migration



carbenes to afford 1,2-oxoamination products.<sup>6</sup> To design a new application of these  $\alpha$ -oxo carbenes, we reported gold-catalyzed oxidative cycloalkenylations of phenoxyethynes with nitrones to afford 3-alkylidenebenzofuran-2-ones; herein, gold enolate intermediates (II) undergo hydrogen bonding with a second

nitrone to induce a cycloalkenylation reaction (eq 2).<sup>7</sup> These gold-catalyzed oxidative cycloalkenylations were amenable to quinoline N-oxides to afford 3-alkylidenebenzofuran-2-ones efficiently (eq 3).<sup>8</sup> To seek new utility beyond our current work, herein we report the development of a new oxidative hydrative alkenvlation of aryl propargylic thioethers with quinoline Noxides and water to deliver 3-hydroxy-1-alkylidene phenylthiopropan-2-ones efficiently (eq 4). In this system, the Ph-S group does not attack the  $\alpha$ -oxo gold carbene via an arylation reaction, but reactive gold enolates (III) can be generated by a cooperative action of sulfide and H<sub>2</sub>O, and a final alkenylation results from the attack of gold enolates (III) on quinoline Noxides. This work manifests a new system to generate gold enolates via a 1,3-sulfur migration, thus enabling a novel oxidative hydrative alkenvlation of alkynes.

Table 1 shows the results of optimization of the reactions between phenyl propargyl thioether 1a (1.0 equiv) and 8methylquinoline oxide 2a (2.1 equiv) with commonly used gold catalysts. The use of IPrAuCl/AgNTf<sub>2</sub> (10 mol %) in hot DCE (70 °C, 12 h) delivered an oxidative hydrative alkenylation product 3a in 41% yield (entry 1): the molecular structure was confirmed by X-ray diffraction. A switch to  $P(t-Bu)_2(o$ biphenyl)AuCl/AgNTf2 increased the yield of compound 3a to 78% yield (entry 2). Other gold catalysts PPh<sub>3</sub>AuCl/AgNTf<sub>2</sub> and (PhO)<sub>3</sub>PAuCl/AgNTf<sub>2</sub> were less effective, giving species 3a in 25% and 49% yields, respectively; herein, starting 1a was recovered in 58% and 15% yields, respectively (entries 3 and 4). A change of silver salts with  $P(t-Bu)_2(o-biphenyl)AuCl/AgX$  (X =  $SbF_6$  and OTf) maintained the same efficiency to produce 3a in 75% and 69% yields (entries 5 and 6).  $P(t-Bu)_2(o$ biphenyl)AuCl/AgNTf<sub>2</sub> in other solvents gave compound 3a in the following yields: THF (55%), toluene (37%), and MeNO<sub>2</sub> in traces (entries 7–9). AgNTf<sub>2</sub> (10 mol %) alone in hot DCE (70 °C, 24 h) was catalytically inefficient to afford compound 3a in 4% yield (entry 10). This reaction pattern is unprecedented

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Table 1. Optimization of Reaction Conditions



<sup>*a*</sup>**1a** = 0.16 M, **2a** = 2.1 equiv. <sup>*b*</sup>Product yields are reported after purification from a silica gel column followed by trituration. <sup>*c*</sup>L =  $(t-Bu)_2(o-biphenyl)P$ ; IPr = 1,3-Bis(2,6-diisopropylph-enyl imidazol-2-ylidene). <sup>*d*</sup>Starting **2a** recovered in 31%. <sup>*c*</sup>Starting **2a** recovered in 55%.

and distinct from our previous oxidative cycloalkenylations in eqs 2 and 3 because the phenylthio group of initial **1a** does not participate in an arylation reaction.

Scheme 1 shows the scope of this new catalytic oxidation with various phenyl propargyl thioethers 1 and 8-substituted

Scheme 1. Scope of Propargyl Aryl Thioethers 1 and *N*-Oxides 2



<sup>*a*</sup>**1a** = 0.16 M, **2a** = 2.1 equiv, <sup>*b*</sup>Product yields are reported after purification from a silica gel column and trituration,  $L = (t-Bu)_2(o-biphenyl)P$ .

quinoline oxides **2** under the preceding optimized conditions. Phenyl propargyl thioethers 1b-d bearing *p*-phenyl substituents (X = F, Cl, and Br) were amenable to such catalytic reactions, delivering the desired products 3b-d in 70–74% yields (entries 1–3). For their 2-chloro and 3,5-dichlorophenyl analogues 1e,f, their corresponding products 3e,f were obtained in 71% and 77% yields, respectively (entries 4 and 5). The catalytic reaction of 2-naphthyl propargyl thioether **1g** yielded the corresponding product **3g** in 61% yield (entry 6). We also performed the oxidative hydrative alkenylations of other 8-substituted quinoline oxides **2b**-**d** (R= Et, *i*-Pr, and PhCH<sub>2</sub>), which yielded the desired products **3h**-**j** in 39–48% yields, with R = *i*-Pr being the least efficient (entries 7–9).

The results in Scheme 1 are inconclusive as to whether the alkenylation occurs on the alkynyl C(3)-carbon of thioethers 1 to generate products 3. We thus prepared various phenyl propargyl thioethers 4 bearing an alkyl group at the C(3)-carbon. The results are shown in Scheme 2, revealing a 1,3-sulfur migration and alkenylation at the alkynyl C(1)-carbon of initial thioethers.



<sup>*a*</sup>**4a** = 0.14 M, **2a** = 2.1 equiv, <sup>*b*</sup>Product yields are reported after purification from a silica gel column and trituration,  $L = (t-Bu)_2(o-biphenyl)P$ .

The <sup>1</sup>H NMR spectra reveal the presence of two product conformers, 5 and 5'. This structural assignment is supported by <sup>1</sup>H and <sup>13</sup>C NMR spectra and further confirmed by the X-ray structure of compound 5b. For compound 5b/5b', the two conformers were observed by <sup>1</sup>H NMR at 28 °C in toluene, but the <sup>1</sup>H resonances of the two conformers coalesced to signals of one species at 103 °C. To rationalize this conformational barrier, we postulate that major conformer 5b has its hydroxyl group bonding to the ketone via a hydrogen bond, whereas the other conformer 5b' has a hydroxyl group bonding to the sulfur. As shown in entries 1-4 (Scheme 2), gold-catalyzed oxidations of thioethers 4a-d (R<sup>1</sup>=Me, n-Bu, i-Pr, and 3-pentyl) and 8methylquinoline *N*-oxides 2a delivered the desired products 5a/ 5a'-5d/5d' in reasonable yields (57-67%). Cyclopentylsubstituted propargyl thioether 4e was an applicable substrate to yield product 5e/5e' in 62% (entry 5). Propargylic thioethers 4f-i bearing *para*-substituted phenyl groups (X = Cl, Br, Me, and OMe) were also applicable to these reactions, affording

compounds 5f/5f'-5i/5i' in 63–75% yields (entries 6–9). We tested the oxidations of thioether 4a with other 8-substituted quinoline oxides 2b-d (R = Et, *i*Pr, and PhCH<sub>2</sub>), which also yielded desired compounds 5j/5j'-5l/5l' in 59–66% yields (entries 10–12).

We examined the gold-catalyzed oxidation of allyl propargyl thioether 6 with 8-methylquinoline *N*-oxide 2a, which provided 2-allylthietan-3-one 7 in 96% yield (eq 5). Although we did not observe an alkenylation reaction in this case, the reaction outcome is helpful to elucidate the 1,3-sulfur migration mechanism.



We performed control experiments to determine the oxygen source of the hydroxyl groups in product 3a-O (eq 6).



Treatment of propargylic thioether 1a with quinoline N-oxide 2a in the presence of  $H_2^{18}O(2.0 \text{ equiv})$  resulted in product 3a-O with an oxygen content of  ${}^{16}O/{}^{18}O = 9.7:1$ . A low  ${}^{18}O$ -content for **3a-O** was attributed to the production of additional water (1 equiv) from this reaction sequence; this water was bound to gold and was proximate to the reaction inner sphere (vide infra). We prepared substrate  $d_2$ -1a bearing X = 0.72 D for each CH<sub>2</sub> hydrogen, and its corresponding reaction gave the desired product  $d_2$ -3a in bearing X = 0.23 D for each methylene hydrogen of the  $CH_2OH$  (eq 7). Nevertheless, the result in eq 7 is less meaningful because we have deuterium-scattered product  $d_n$ -3a when  $D_2O$  is present in the system (5 equiv, eq 8). We carried out a crossover experiment (eq 9) where 4b and 4f were treated with N-oxides 2a under standard conditions. We did not observe any crossover products and obtained only compounds 5b and 5f in 43% and 51% yield.

We postulate the mechanism in Scheme 3, involving  $\alpha$ -oxo gold carbenes C generated from the oxidation of propargyl phenyl thioethers 1 with quinoline *N*-oxide 2a. The attack of *N*oxide on gold  $\pi$ -alkyne A generates alkenylgold species B and gold carbene C sequentially. Intermediate C undergoes an intramolecular attack by PhS at the gold carbene functionality and forms a four-membered sulfonium ring D that is subsequently cleaved by water to produce C-bound gold enolate Scheme 3. Plausible Reaction Mechanism



E. A further tautomerization yields O-bound gold enolate intermediate F. We believe that O-bound gold enolate F attacks a second N-oxide to deliver alkylated intermediate G that undergoes dehydration to yield the desired product 3a. We surmise that the O-bound enolate F is likely to have a Econfiguration so that sulfur has a weak interaction to the gold center and its hydroxyl group can hydrogen bond with the Noxide; this association facilitates this alkenylation reaction. In the final step, we note that a water molecule is released from the loss of the oxygen of the N-oxide; this pathway indicates that the hydroxyl oxygen of products 3 or 5 may arise from either water or N-oxide. Water generated from the N-oxide is coordinated with LAu<sup>+</sup> to yield  $LAu(H_2O)^+$ , which is within the inner sphere of the reaction site. Accordingly, external H<sub>2</sub><sup>18</sup>O contributes little to the oxygen source of the hydroxyl groups of products 3 and 5, consistent with our <sup>18</sup>O experiment (eq 6).

This proposed mechanism also rationalizes the formation of 2-allylthietan-3-one 7 from gold-catalyzed oxidation of allyl propargyl thioether 6 (eq 5). After the attack of allyl sulfide at the gold carbene in species C, the resulting intermediate D' undergoes a [2,3]-Wittig rearrangement<sup>9</sup> to give the observed product 7.

This work reports gold-catalyzed oxidative hydrative alkenylations of propargyl aryl thioethers with quinoline *N*-oxides to afford 3-hydroxy-1-alkylidene phenylthiopropan-2-ones via a 1,3-sulfur migration. The reaction involves one alkyne, one water, and two discrete quinoline oxides. A reaction mechanism is postulated to involve an  $\alpha$ -oxo gold carbene that is *S*-attacked by a phenylthio group<sup>10,11</sup> to form a four-membered sulfonium intermediate. A ring cleavage of this sulfonium ring with water generates a gold enolate that reacts with a second quinoline *N*-oxide<sup>12</sup> to deliver an alkenylation product via 1,3-sulfur migration.<sup>13</sup>

### ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00705.

Experimental procedures, characterization data, crystallography data, and <sup>1</sup>H NMR and <sup>13</sup>C NMR for representative compounds (PDF)

## **Accession Codes**

CCDC 1897854–1897855 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by email-

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ing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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(11) We examined the oxidations of thioalkyne with 8-methylquinoline *N*-oxides; the reaction intermediates were elucidated to be ketenes instead of  $\alpha$ -oxo gold carbenes. In other words, this system serves as the first example to use alkynes as ketene precursors.



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(13) The very high cost and low concentration (3 wt %) of aqueous <sup>18</sup>O-containing  $H_2O_2$  (90% <sup>18</sup>O, USD 2,140/1g, Sigma-Aldrich) did not allow us to prepare <sup>18</sup>O-containing 8-methylquinoline oxide **2a**. In our proposed mechanism, this <sup>18</sup>O-containing sample is expected to give a positive result because it generates water. One reviewer suggests a mechanism as depicted below with this *N*-oxide as a nucleophile; we cannot exclude this process as a competitive reaction.

