## Gold-catalyzed oxidative cleavage of aryl-substituted alkynyl ethers using molecular oxygen. Simultaneous degradation of C–H and single and triple carbon–carbon bonds under ambient conditions<sup>†</sup>

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We report the gold-catalyzed oxidative cleavage of arylsubstituted alkynyl ethers using molecular oxygen under ambient conditions; the transformation involves a remarkable cleavage of C-H, C-C and C $\equiv$ C bonds simultaneously.

The metal-catalyzed cleavage of a carbon-carbon triple bond has stimulated new conceptual strategies in organic synthesis.<sup>1,2</sup> The use of oxygen to cleave a carbon-carbon bond catalytically is economically and environmentally important. Although the catalytic cleavage of C–C and C=C bonds using oxygen as the oxidant has achieved reasonable progress,<sup>3</sup> very limited examples have been documented for the oxygeninduced oxidative cleavage of a  $C \equiv C$  bond.<sup>2d,e</sup> Previously, Liu et al. reported the gold-catalyzed tandem cyclizationoxidative cleavage of cis-enynols with O2, with the key carboncarbon cleavage step occurring on cyclized enol ether intermediates.<sup>2d</sup> Wang and Jiang reported the Pd-catalyzed oxidative cleavage of alkynes, but the reactions were run with elevated temperature, pressurized oxygen (5 atm) and co-catalyst.<sup>2e</sup> There is no precedent for a simultaneous oxidative cleavage of single and triple carbon-carbon bonds using oxygen. We report herein, the gold-catalyzed oxidative transformation of 3-aryl-3-alkoxy-1-alkynes to alkyl aryloates under mild conditions: air (10%  $O_2$  in  $N_2$ ), no co-catalyst, 25 °C and 3 mol% catalyst, which suffice for a remarkable cleavage of C–H, and C–C and C $\equiv$ C bonds simultaneously (eqn (1)).



Table 1 shows the use of molecular oxygen to cleave 4-phenyl-4-methoxy-2-butyne (1a) over PPh<sub>3</sub>AuCl–AgNTf<sub>2</sub> (3 mol%), which was chosen because of its best activity among commonly used Pt(II), Ag(I) and Au(I) catalysts.<sup>4</sup> The reaction was performed under a dilute oxygen atmosphere (10% in N<sub>2</sub>) in dry CH<sub>2</sub>Cl<sub>2</sub> at 25 °C, giving methyl benzoate (2a) and enone 3a in 19 and 43% yields, respectively (entry 1). The formation of ester 2a is astonishing because an oxo group replaces C–H

| Table 1  | Gold-catalyzed | oxidative | cleavage | reactions |
|----------|----------------|-----------|----------|-----------|
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|                                       | Ph<br>RO 1a-c Me C                                                                         | 3 mol%<br>n <sub>3</sub> AuCl/AgN<br>:H <sub>2</sub> Cl <sub>2</sub> , 25 ° | $\frac{\text{ITf}_2}{\text{C}}  \text{PhCO}_2\text{R}  +  -  -  -  -  -  -  -  -  -$                                   | + Me<br>COMe                       | 2CO <sub>2</sub> R<br><b>4a-c</b>                                                                 |
|---------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------------|
|                                       |                                                                                            | ROH                                                                         |                                                                                                                        |                                    |                                                                                                   |
| Entry                                 | Substrate <sup>a</sup>                                                                     | Gas                                                                         | R'OH (equiv.)                                                                                                          | Time/h                             | Products (yields) <sup>cd</sup>                                                                   |
| 1                                     | $\mathbf{R} = \mathbf{Me} \ (\mathbf{1a})$                                                 | 10%                                                                         | _                                                                                                                      | 24                                 | <b>2a</b> (19%),<br><b>3a</b> (43%).                                                              |
| 2                                     | 1a                                                                                         | 10%                                                                         | $\mathbf{R}' = \mathbf{Me} \ (3)$                                                                                      | 15                                 | $ \begin{array}{c} \mathbf{4a} (nd)^{e} \\ \mathbf{2a} (81\%), \\ \mathbf{3a} (4\%) \end{array} $ |
| 3                                     | 1a                                                                                         | 10%                                                                         | $\mathbf{R}' = \mathbf{H} (3)$                                                                                         | 15                                 | $\begin{array}{c} 3a \ (470), \\ 4a \ (85\%) \\ 2a \ (6\%), \\ 3a \ (82\%) \end{array}$           |
| 4<br>5                                | $\begin{array}{l} \mathbf{1a} \\ \mathbf{R} \ = \ \mathbf{Et} \ (\mathbf{1b}) \end{array}$ | 10%<br>10%                                                                  | R' = Me(3)<br>R' = Et(3)                                                                                               | 15<br>20                           | <b>4a</b> (nd)<br><b>3a</b> (23%)<br><b>2b</b> (76%),                                             |
| 6                                     | $\mathbf{R} = n - \Pr\left(\mathbf{1c}\right)$                                             | 10%                                                                         | $\mathbf{R}' = n - \Pr\left(3\right)$                                                                                  | 24                                 | 3a (12%),<br>4b (78%)<br>2c (56%),                                                                |
| 7                                     | $\mathbf{R} = \mathbf{H} \left( \mathbf{1d} \right)$                                       | 10%                                                                         | $\mathbf{R}' = \mathbf{Me}\left(3\right)$                                                                              | 24                                 | 3a (22%),<br>4c (57%)<br>3a (72%)                                                                 |
| <sup>a</sup> [Sub<br>report<br>determ | strate] = 0.25 M<br>ed after purification<br>ined from <i>in situ</i>                      | M. <sup>b</sup> 90%<br>on from<br>NMR i                                     | $%$ N <sub>2</sub> , 1 atm. $e^{-3}$<br>a silica column. $d^{-4}$<br>n CD <sub>2</sub> Cl <sub>2</sub> . $e^{-4}$ nd = | Yields of<br>Yields of<br>not dete | <b>2a–2c</b> are <b>4a–4c</b> were rimined.                                                       |

and unstrained  $C-C \equiv C$  sigma bonds. We envisage that residual water promotes the conversion of 1a to enone 3a releasing the methanol that serves to form desired ester 2a. To test this hypothesis, we added MeOH (3.0 equiv.), which greatly increased the yield of ester 2a up to 81%, whereas external water (3.0 equiv.) gave enone 3a in 83% yield via a Meyer-Schuster rearrangement.<sup>5</sup> In entry 2, we identified methyl acetate (4a) (ca. 85%) to be the concurrent product by GC-MS and in situ NMR studies in CD<sub>2</sub>Cl<sub>2</sub>. GC analysis of the gas phase,<sup>6</sup> identified CO in 38% yield in addition to  $CO_2$ (2%) and H<sub>2</sub> (5%) in small proportions; no trace of formic acid or methyl formate was found therein.<sup>7</sup> The use of argon or oxygen-free nitrogen gave messy products, from which we isolated only enone 3a in 23% yield. This oxidative cleavage was applicable to substrates 1b and 1c bearing an ethoxy and propoxy group, which reacted with ROH (R = Et, n-Pr) to give desired ethyl and propyl benzoates 2b and 2c in 76% and 56% yields, respectively; ethyl- and propyl acetates 4b and 4c were identified and estimated by in situ NMR spectra. We also prepared alcohol 1d that gave enone 3a in 72% yield.

We prepared substrates **5a–5m** to examine the generality of this oxidative cleavage reaction; the yields of desired esters **6a–6m** 

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<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: General procedure, screening of metal catalyst, <sup>1</sup>H and <sup>13</sup>C NMR data and spectra of compounds **1a–8b**. See DOI: 10.1039/b908338c

 Table 2
 Substrates used for the gold-catalyzed cleavage transformation

|       | R <sup>1</sup><br>R <sup>2</sup><br>5a-51 OMe R <sup>1</sup><br>R <sup>2</sup><br>R <sup>2</sup> | +<br>6a-6l | e 7g                  |
|-------|--------------------------------------------------------------------------------------------------|------------|-----------------------|
| Entry | Substrate                                                                                        | Time/h     | Ester (yield)         |
| 1     | $R^{1} = \bigcirc_{O} \bigoplus_{Me} (CH_{2})_{2^{-}}, R^{2} = H (5a)$                           | 3          | <b>6a</b> (71%)       |
| 2     | $R^1 = $ $C_0^{-}$ $(CH_2)_{2^-}$ $R^2 = H$ (5b)                                                 | 8          | <b>6b</b> (68%)       |
| 3     | $R_{2}^{1} = Me(O = C) - (CH_{2})_{2},$                                                          | 12         | <b>6c</b> (66%)       |
| 4     | $R^{2} = H (5c)$<br>$R^{1} = PhCH_{2}OCH_{2}-,$<br>$R^{2} = H (5d)$                              | 6          | <b>6d</b> (73%)       |
| 5     | $R^{1} = MeCO_{2} - (CH_{2})_{3} -,$                                                             | 8          | <b>6e</b> (69%)       |
| 6     | $R^{-} = H$ (Se)<br>$R^{1} = (t-Bu)Me_{2}SiO(CH_{2})_{3}$ -,<br>$R^{2} = H$ (Sf)                 | 12         | <b>6f</b> (69%)       |
| 7     | $R^1 = t$ -Bu, $R^2 = H$ (5g)                                                                    | 2          | 6a (69%), 7a (20%)    |
| 8     | $R^1 = n$ -Bu, $R^2 = H$ (5h)                                                                    | 10         | <b>6h</b> (71%)       |
| 9     | $\mathbf{R}^1 = trans$ -PhMe=CH-,<br>$\mathbf{P}^2 = \mathbf{H}$ (5i)                            | 24         | <b>6i</b> (71%)       |
| 10    | $R^{1} = OMe R^{2} = H(5i)$                                                                      | 15         | <b>6i</b> (74%)       |
| 11    | $R^1 = R^2 = OMe(5k)$                                                                            | 15         | <b>6k</b> (63%)       |
| 12    | $R^1, R^2 = 5$ (51)                                                                              | 10         | <b>61</b> (59%)       |
| 13    | OMe (5m)                                                                                         | 24         | $G_{\rm S}$ $CO_2 Me$ |
|       |                                                                                                  |            | on (or so)            |

<sup>*a*</sup> Conditions: 3 mol% PPh<sub>3</sub>AuCl–AgNTf<sub>2</sub>, 10% O<sub>2</sub> in N<sub>2</sub>, MeOH (3 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, [substrate] = 0.25 M. <sup>*b*</sup> Product yields are given from silica column separation.

are summarized in Table 2. Under running conditions (CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, MeOH), enone byproducts were obtained in small proportions (< 8%) in most instances without isolation. Entries 1–6 show the tolerance of this catalysis towards various organic functionalities, with applicability to substrates **5a–5f** bearing dioxolane, dioxane, ketone, benzyl ether, ester and siloxy ether groups; the corresponding benzoate products **6a–6f** were isolated in satisfactory yields (66–79%). This gold-catalyzed reaction is suitable for substrates **5g–5i**, which bear *para*-substituents of *tert*-butyl, *n*-butyl and 2-methylstyrene, respectively; the resulting esters **6g–6i** were produced efficiently (69–71% yields). In entry 7, we obtained a 20% yield of byproduct **7g**, which assists the



Scheme 1 A proposed mechanism for gold-catalyzed oxidative cleavage.

| Table 3 | Substrates | with | an | altered | alkynyl | substituent. |
|---------|------------|------|----|---------|---------|--------------|
|---------|------------|------|----|---------|---------|--------------|

|   |             | Me<br>P | eO<br>h 8a-8              | کــر<br>ه          | OR O2<br>3% PPh <sub>3</sub> A<br>CH <sub>2</sub> Cl <sub>2</sub> , 2 | uCl/AgX         | PhCO <sub>2</sub> Me +<br><b>2a</b>                            | ester<br>4d-4e                  |
|---|-------------|---------|---------------------------|--------------------|-----------------------------------------------------------------------|-----------------|----------------------------------------------------------------|---------------------------------|
|   | Subst       | rate    | O <sub>2</sub><br>(% in 1 | N <sub>2</sub> ) A | .gX                                                                   | MeOH/<br>equiv. | Products (y                                                    | vield)                          |
| 1 | R =<br>(8a) | Bn      | 10%                       | Х                  | $L = NTf_2$                                                           | 3               | <b>2a</b> (81%)<br>BnO(CH <sub>2</sub> )<br>( <b>4d</b> , 73%) | <sub>3</sub> CO <sub>2</sub> Me |
| 2 | R =<br>(8b) | Н       | 50%                       | Х                  | $L = SbF_6$                                                           | 0               | <b>2a</b> (75%), 1                                             | ( <b>4e</b> , 78%)              |
|   |             |         |                           |                    |                                                                       |                 |                                                                |                                 |

<sup>*a*</sup> Conditions: 3 mol% PPh<sub>3</sub>AuCl–AgX, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, [substrate] = 0.25 M. <sup>*b*</sup> Product yields are given from silica column separation.

understanding of the mechanism (see Scheme 1). The reaction is extendable to electron-rich benzenes **5j–5k**, which provided esters **6j** and **6k** in 74% and 63% yields, respectively. For naphthyl substrate **5l**, its gold catalysis gave the expected ester **6l** in 59% yield. Application of this catalysis to thiophene-containing substrate **5m** gave desired ester **6m** in 51% yield.

This catalytic cleavage worked for substrate **8a** bearing a benzyl pentynyl ether, and its oxidative degradation with 3% PPh<sub>3</sub>AuNTf<sub>2</sub> and MeOH (3 equiv.) gave methyl benzoate (**2a**) and ester **4d** in 81% and 73% yields, respectively (Table 3). In the absence of MeOH, oxidative cleavage of **8b** was implemented by PPh<sub>3</sub>AuSbF<sub>6</sub> and oxygen in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C, through an initial intramolecular alkoxylation, giving methyl benzoate (**2a**) and  $\gamma$ -lactone (**4e**) in 75% and 78% yields, respectively. We obtained a messy mixture of products for substrates bearing an *n*-butyl or phenyl group at the alkyne functionality.

Eqns (2)–(4) show the results to assist the understanding of the reaction mechanism. Oxidative cleavage of species **1a** with PPh<sub>3</sub>AuNTf<sub>2</sub>, O<sub>2</sub> and CD<sub>3</sub>OD (3 equiv.) gave only PhCO<sub>2</sub>Me and MeCO<sub>2</sub>CD<sub>3</sub>, and this observation excluded the intermediacy of allene **I** (eqn (2)). We prepared an sample of **1a** enriched with <sup>18</sup>O at its methoxy oxygen (*ca.* 56% <sup>18</sup>O),<sup>8</sup> and its treatment with MeOH, O<sub>2</sub> and gold catalyst provided **2a** without a loss of the <sup>18</sup>O-content according to mass and IR analysis (eqn (3)); herein, the <sup>18</sup>O content of methyl acetate **4a** was insignificant. H<sub>2</sub>O is unlikely to be the oxygen source of the carbonyl oxygen of ester **2a** and methyl acetate (**4a**), as added H<sub>2</sub>O\* (99% <sup>18</sup>O content) failed to give <sup>18</sup>O-enrichment of these two esters under running conditions (eqn (3)).



Scheme 1 shows a plausible mechanism that excludes the involvement of enol ether A' as a reaction intermediate based on a control experiment in which formic acid and aldehyde C'are not reaction intermediates.<sup>7</sup> This proposed mechanism is distinct from those proposed by previous workers;<sup>2d,e</sup> it is supported by our isolation of side product 7g, from which we infer the participation of acylgold species C. We envisage that oxygen activation is likely to occur before hydrodeauration of gold enol ether A<sup>9</sup> because the gold fragment of species A is more electron-rich than cationic PPh<sub>3</sub>AuNTf<sub>2</sub> in the reduction of O<sub>2</sub> to form cyclic peroxide intermediates **B**. This O<sub>2</sub>activation process presumably proceeds through a radical process, because the catalytic reaction is inhibited by a radical scavenger such as 2,6-di-tert-butyl-p-cresol according to control experiment.<sup>10</sup> Cyclic peroxide intermediates **B** allow cleavage of the carbon-carbon bond to form methyl acetate and acylgold intermediate C. We propose that the enol form, **D**, is equally active as species **A** for the second reduction of  $O_2$ , giving gold-substituted formic acid via cyclic peroxide E. As metal-containing formic acid is the postulated intermediate for the water-gas shift reaction,11 we speculate that the decomposition of species F is expected to give CO and H<sub>2</sub>O, or CO<sub>2</sub> and H<sub>2</sub>, which were identified by GC analysis. Accordingly, side product 7g was presumably generated from the decarbonylation of gold intermediate C, followed by hydrodeauration.

In summary, we report the gold-catalyzed oxidative cleavage of aryl-substituted alkynyl ethers<sup>12</sup> using molecular oxygen under ambient conditions; the transformation involves a remarkable cleavage of C–H, C–C and C $\equiv$ C bonds simultaneously. This catalysis is mechanistically novel because the mechanism, on the basis of control experiments and product analysis, reveals that gold-containing enol ethers are the active species for the activation of oxygen. This new information enhances the use of gold complexes in the activation of molecular oxygen in organic synthesis under ambient conditions.

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