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Gold-catalyzed selective oxidation of 4-Oxahepta-1,6-diyynes to 2H-pyran-3(6H)-ones and chromen-3(4H)-ones via the β-gold vinyl cation intermediates

Kegong Ji,* Xiang Liu, Bowen Du, Fang Yang, Jinming Gao

The α-oxo gold carbones generated in situ via gold-catalyzed selective oxidation of 4-oxahepta-1,6-diyynes were effectively trapped by internal alkynes, resulting in the formation of 2H-pyran-3(6H)-ones 3 and chromen-3(4H)-ones 4 upon facile trapping the vinyl cation intermediates by external N-oxide and internal aryl ring system.

Recently, gold-catalyzed oxidation of alkynes offered an expedient access to synthetically versatile α-oxo gold carbenes to synthesize various useful molecules that display significant utility for chemical synthesis, medicines, and functionalized materials. This strategy is safer and greener to construct C-X (X=C, N, O, S and Cl) bonds by internal/external nucleophiles trapping the in situ generated α-oxo gold carbones, which circumvents the use of hazardous and potentially explosive α-diazo ketone precursors (eq 1). Various efficient synthetic methods have been developed by Zhang, Hashimi, Liu, Ye, Gagosz and others based on trapping α-oxo gold carbene intermediates. While, the alkyn as nucleophile trapped the α-oxo gold carbene intermediates generated in situ proves to be very challenging because of the selective of oxidation of diynes and other intractable side reactions. Recently Hashimi and co-workers have reported the gold catalyzed oxidation of 1,5-enediyynes to indenones with internal alkynes trapping the gold carbones through 1,6–carbene transfer intermediates (eq 2). We envisioned that the α-oxo gold carbene intermediates were tapped by alkynes might alternatively have a β-C-gold vinyl cation intermediates following by nucleophiles trapping (eq 3). To further develop alkynes as surrogates of hazardous α-diazo ketones in gold catalysis, we focused here on expanding the scope of suitable internal nucleophiles like alkynes. Our first target was 1,6-oxadiynes (eq 4) and notably, the reaction, if developed, would offer a novel and rapid access to synthetically versatile 2H-pyran-3(6H)-ones 3 and chromen-3(4H)-ones 4 with N-oxide and aromatic ring trapping the β-C-gold vinyl cation intermediates. Meanwhile, the reaction would prove the β-C-gold vinyl cation intermediates experimentally.

At the outset, we used 4-oxahepta-1,6-diyne 1a and pyridine 1-oxide as the oxidant, and the results of reaction optimization are shown in Table 1. Initially, we started by using 0.3 mmol of 1a and 2,6-dichloropyridine 1-oxide 2a (2.5 equiv) with Me₂BuXPhosAuCl (5 mol %)/ NaBARF₄ (10 mol %) as catalyst, to our delight, the double oxidation product of 5-benzoyl-6-methyl-2H-pyran-3(6H)-one 3a was obtained in 82% isolated yield after 5 h in 1,2-dichloroethane (DCE) at room temperature (entry 1). Other N-oxides were also investigated, like 2b-2e, however no superior results were observed even after longer time (entries 2-5). The oxidant 2a loading was also tested, no exciting results were observed.

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Electronic Supplementary Information (ESI) available: 1H NMR, 13C NMR and IR, HRMS of new compounds. For crystallographic data of 5 in CIF or other electronic format See DOI: 10.1039/000000000000
achieved (for details, see SI). While, decreased the gold catalyst loading to 2 mol % with 4 mol % NaBARF, an acceptable result (82 % yield) was observed after 10h (entry 6). Other cationic gold complexes derived from typical ligands such as Ph3P, IPr were largely ineffective, thus resulting in 1, 6-diyne 1a remaining with little desired product (entries 7-8). Mor-DalPhosAuNTf2 (2 mol %) can also promote the reaction with less effective (entry 9). Solvent effect was also considered, such as acetone, acetonitrile and toluene, but no effective solvent was observed.

Table 1 Screening conditions a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Additive (mol %)</th>
<th>Yield b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me2BuXPhosAuCl(5)</td>
<td>NaBARF2 (10)</td>
<td>82% c</td>
</tr>
<tr>
<td>2</td>
<td>Me2BuXPhosAuCl(5)</td>
<td>NaBARF2 (10)</td>
<td>58% d</td>
</tr>
<tr>
<td>3</td>
<td>Me2BuXPhosAuCl(5)</td>
<td>NaBARF2 (10)</td>
<td>55% e</td>
</tr>
<tr>
<td>4</td>
<td>Me2BuXPhosAuCl(5)</td>
<td>NaBARF2 (10)</td>
<td>57% f</td>
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<tr>
<td>5</td>
<td>Me2BuXPhosAuCl(5)</td>
<td>NaBARF2 (10)</td>
<td>73% g</td>
</tr>
<tr>
<td>6</td>
<td>Me2BuXPhosAuCl(2)</td>
<td>NaBARF2 (4)</td>
<td>82%</td>
</tr>
<tr>
<td>7</td>
<td>Ph3PAuCl(2)</td>
<td>NaBARF2 (4)</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>8</td>
<td>IPrAuCl(2)</td>
<td>NaBARF2 (4)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>9</td>
<td>Mor-DalPhosAuNTf2</td>
<td>-</td>
<td>72%</td>
</tr>
<tr>
<td>10</td>
<td>Mor-DalPhosAuNTf2</td>
<td>NaBARF2 (4)</td>
<td>&lt;3% h</td>
</tr>
<tr>
<td>11</td>
<td>Mor-DalPhosAuNTf2</td>
<td>NaBARF2 (4)</td>
<td>45%</td>
</tr>
<tr>
<td>12</td>
<td>Mor-DalPhosAuNTf2</td>
<td>NaBARF2 (4)</td>
<td>&lt;3% i</td>
</tr>
</tbody>
</table>

a The reaction was run with everything in a vial capped with a septum, initially, [1a]=0.1M. b Isolated yield. c Reaction time 5h. d 2b as The N-oxide. e 2c as The N-oxide. f 2d as The N-oxide (for detail see SI). g Acetonitrile as the solvent. h Toluene as the solvent.

With the optimized reaction conditions given in Table 1, entry 6, the scope of the transformation was first examined with various 4-oxahepta-1,6-diyne. As shown in Table 2. Thus, a tandem double oxidation of substituted 4-oxahepta-1,6-diyne 1a-m except 1k with one carbon-carbon double bond formation proceeded smoothly to provide corresponding products 2a-j and 2l-m in moderate to good yields. The reaction works well with aromatic R groups. Electron-donating aryl groups showed slight better results than those with an electron-withdrawing group in the reaction (1b vs 1d). Various electron-withdrawing R group were tolerance. Steric effect of R ary groups was also considered and the o-methyl aryl group showed better yield than o-bromide aryl group by installing the methyl and bromide group on ortho position (1c vs 1g). 4-oxahepta-1,6-diyne 1j with a heteroaromatic R group can also afford the desired product 2j in 70% yield, while a substrate like 1k with an aliphatic R group gave no reaction. It is reasonable to accept that the reaction needs a cation-stabilizing aryl group. Other 1,6-diyne like 1l with different R' groups can also afford corresponding 2H-pyran-3(6H)-one 2l in acceptable yield. 4-oxahepta-1,6-diyne 1m with orthobenzyl aryl R group also investigated, a moderate yield of desired product 3m was obtained. However, almost no 4m was observed from crude NMR.

Furthermore, to expand the scope of this reaction, we also investigated 4-oxahepta-1,6-diyne 1o with 2 mol % of Mor-DalPhosAuNTf2 as the catalyst by installing the ethynyl group on R' position. To our delight, the desired double oxidation product 3o was obtained in 30% yield along with 5-phenyl-4,10,11,11a-tetrahydrobenzo[4,5]cyclohepta[1,2-b]pyran-3(2H)-one 5 in 33 % yield and some complex mixture (eq 5). The relative configuration of the product 5 was unambiguously assigned by X-ray crystallography. For this phenomenon, we proposed that the phenyl ring trapped the vinyl cation intermediate as describe in eqs 4.

While considering synthetically useful transformations, we also sought to gather additional experimental evidence for the mechanism. To this end, we examined the direct conversion of 4-
oxahepta-1,6-diynes 1aa-1ah by installing the benzyl group on R’ position in the presence of 2 mol% of Mor-DalPhosAuNTf₂. Much to our delight, this strategy worked well with different substituents of R group affording various functionalized 10,10a-dihydro-2H-benzo[g]chromen-3(4H)-ones 4aa-4ah in acceptable yield with two new C-C bonds formation as shown in Table 3. For the substrates 1ag-h with an o-bromophenyl and naphthalene substituents, the reaction worked well and afforded the corresponding products 4ag-h in 45% and 81% yield respectively with 5:4 diastereoselectivity.

Table 3. Scope of 10,10a-dihydro-2H-benzo[g]chromen-3(4H)-ones 4.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Yield</th>
<th>Diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4aa</td>
<td>63%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ab</td>
<td>58%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ac</td>
<td>56%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ad</td>
<td>55%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ae</td>
<td>76%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4af</td>
<td>75%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ag</td>
<td>45%</td>
<td>dr=5:4</td>
</tr>
<tr>
<td>4ah</td>
<td>81%</td>
<td>dr=5:4</td>
</tr>
</tbody>
</table>

A interesting phenomenon was observed when 4-oxahepta-1,6-diyne 1p was investigated in this reaction. The product 6,6-dimethyl-5-phenyl-5,6,7,7a-tetrahydrocyclopenta[b]pyran-3(2H)-one 6 was obtained in 80% yield. We proposed that the reaction was occurred through the vinyl cation intermediate and 1,5-H migration process to afford 6 (Fig 1). This case is an additional experimental evidence for the vinyl cation intermediates.

On the basis of the above observations, we propose the following plausible mechanisms for this transformation (Fig 2). i) Coordination of the diynes moiety with the cationic gold complexes and N-oxide selectively attacked the terminal alkyne to form the vinyl cation intermediates A. ii) The gold complexes donated the electron to remove the 2,6-dichloropyridine and gave the α-oxo gold carbene intermediates B, followed by internal alkynes attacking to form the vinyl cation intermediates C. iii) The vinyl cation intermediates C were trapped by external N-oxide to form the intermediates D followed by removing the 2,6-dichloropyridine to give 3. Alternatively, if R’ contained an aryl ring in suitable position, the vinyl cation intermediates C might be trapped by internal aryl ring to give products 4.

In summary, we have described a gold-catalyzed selectively oxidation of 4-oxahepta-1,6-diynes to various 2H-pyran-3(6H)-ones 3 and 10,10a-dihydro-2H-benzo[g]chromen-3(4H)-ones 4 in the presence of 2 mol% catalyst loading. We also observed the interesting product 6 with 1,5-H migration. The reaction proceeded smoothly to provide corresponding products through the α-oxo gold carbene intermediates generated in situ and β-C-gold vinyl cation intermediates which can be trapped by external N-oxide and internal aryl ring systems. A more detailed investigation on the mechanism, as well as the scope of this cascade, is ongoing in our laboratory.

We are grateful for the financial support from Northwest A&F University (Z111021404).

Notes and references
2. For a monograph, see: M. P. Doyle, M. A. McKervey and T. Ye, Modern catalytic methods for organic synthesis with diazo


13. For X-ray structure of 5, the CCDC number is 1058971.