Synthesis of γ,δ-Unsaturated Esters and Amides via Au(I)-Catalyzed Reactions of Aryl Ynol Ethers or Ynamides with Allylic Alcohols

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Key words: gold, ynol, ynamide, hydroalkoxylation, Claisen rearrangement, ester, amide

Addition of nucleophiles to alkynes through activation of the C–C triple bond by transition metal complexes is a straightforward and atom-economical methodology for synthesis of functionalized alkenes. Au(I) complexes are widely used for this purpose in a process in which Au(I) activates the alkyne due to its π-Lewis acidity. A number of reactions of alkynes with nucleophiles (especially, heteroatom nucleophiles) using such catalyst have been reported. Among these, the Au(I)-catalyzed reaction of alkynes with allyl alcohols is of great interest because [3,3]-sigmatropic rearrangement sequentially occurs after hydroalkoxylation of the alkyne to afford γ,δ-unsaturated ketones in a one-pot reaction. For instance, Aponick and Nolan independently reported the synthesis of γ,δ-unsaturated ketones via a Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade starting from alkynes and allyl alcohols (Scheme 1a). In both reactions however, the regioselectivity of the addition of the allyl alcohol to the alkynes, when unsymmetrical internal alkynes were employed, was difficult to control, resulting in a mixture of isomers. Of note, polarized alkynes such as ynol ethers and ynamides have unique properties due to the delocalization of a lone electron pair of oxygen and nitrogen, and it is well known that addition of a nucleophile to ynol ethers or ynamides usually occurs at the α-position of the alkyne (Scheme 1b).

Background of Au(I)-catalyzed hydroxylation/Claisen rearrangement cascade reactions of alkynes.

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In the context of our continued interest in the reactivity of ynon ethers and ynamides,\(^7\) we envisaged utilization of these polarized alkynes in the Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade (Scheme 1c). Our hypothesis, in this case, was that the hydroalkoxylation by allyl alcohols would regioselectively occur at the α-position, followed by Claisen rearrangement, giving γ,δ-unsaturated esters or amides. Although there has been one report disclosing Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade reaction of polarized alkynes,\(^8\) a comprehensive exploration of this fascinating transformation has not been carried out, and the scope and limitations of this reaction still remain unclear. In this paper, we report Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade reactions of aryl ynon ethers and ynamides with allylic alcohols.\(^9\)

Initially, we investigated the reaction of aryl ynon ether 5a with allyl alcohol (2a) in THF [a solvent selected on the basis of conditions reported by Aponick\(^3\)] in the presence of various Au(I) catalysts, and key results are summarized in Table 1. Reactions using Au(I) catalysts bearing the phosphine ligands PPh\(_3\) and JohnPhos gave the desired product 7aa in 16% and 34% yields, respectively (Entries 1 and 2). N-heterocyclic carbene (NHC) ligands appear to be more effective than phosphines (Entries 3-5), and the reaction using 1 mol% Au(IPr)NTf\(_2\) affording 5a in 57% yield. The use of an isolated [Au(IPr)NTf\(_2\)]\(^{[6,11]}\) catalyst showed almost the same result (Entry 6) as that in Entry 5 using a catalyst formed by mixing [Au(IPr)Cl] (1 mol%) and AgNTf\(_2\) (1 mol%) prepared just prior to use. When we carefully examined and identified by-products formed during the reactions, we noticed the formation of m-cresol. Thus, the reactions were carried out at lower temperature to possibly get rid of this side-product. In spite of the milder reaction conditions, the yield of 7aa was not improved (Entries 7 and 8). We speculated that an excess of allyl alcohol could operate as a proton source in the presence of a trace amount of Tf\(_2\)NH derived from the catalyst, resulting in decomposition of the intermediate 4. We therefore proceeded with slow addition of a THF solution of 2a to the mixture of 5a and with the [Au(IPr)NTf\(_2\)] catalyst. In this manner, the yield of 7aa was greatly improved to 86% (Entry 9).

**Table 1** Screening of conditions for reaction of 5a with 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au(I) catalyst</th>
<th>Temp. (°C)</th>
<th>7aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>[Au(PPh(_3))Cl]/AgNTf(_2)</td>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>2(^a)</td>
<td>[Au(JohnPhos)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>34</td>
</tr>
<tr>
<td>3(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>42</td>
</tr>
<tr>
<td>4(^a)</td>
<td>[Au(IPr)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>45</td>
</tr>
<tr>
<td>5(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>57</td>
</tr>
<tr>
<td>6(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>7(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>8(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>40</td>
<td>45</td>
</tr>
<tr>
<td>9(^a)</td>
<td>[Au(ligand)Cl]/AgNTf(_2)</td>
<td>60</td>
<td>86 (82)</td>
</tr>
</tbody>
</table>

\(^a\) Yields were determined by \(^1\)H-NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yield is given in parentheses. \(^b\) The mixture of 5a, 2a, and Au(I) catalyst was stirred at the indicated temperature for 24 h. \(^1\) The Au(II) catalyst was prepared from [Au(ligand)Cl] (1 mol%) and AgNTf\(_2\) (1 mol%) prior to use. \(^2\) A solution of 2a in THF was slowly added (ca. 10 min) to the mixture of 5a and [Au(IPr)NTf\(_2\)] at 60 °C, and then the mixture was stirred at the same temperature for 24 h.

Next, we examined the reaction of ynamide 6a with allyl alcohol (2a). When the reaction of 6a with 2a was carried out under the above-mentioned optimal conditions, the desired product 8aa was obtained in a modest yield, 56% (Table 2, Entry 1). Thus, we rescreened conditions in order to improve the yield, and representative results are summarized in Table 2. When the reaction was carried out at 80 °C, the yield of 8aa was improved to 77% yield (Entry 2). Solvent screening revealed that toluene is suitable in this reaction (Entries 3-6). The use of a [Au(IPr)NTf\(_2\) catalyst prepared from [Au(IPr)Cl] (1 mol%) and AgNTf\(_2\) (1 mol%) prior to use showed the same reactivity as that of the isolated catalyst (Entry 7). In this reaction, the catalyst loading can be reduced to 0.1 mol% without any loss of reactivity, giving 8aa in 86% yield (Entry 8). It is noteworthy that the slow addition of 2a is not necessary in this reaction, and the mixture of 5a, 2a, and the catalyst in toluene can be simply heated to 80 °C. This is surely due to the increased stability of ynamides as well as the intermediate derived from ynamides compared to ynon ethers.

**Table 2** Re-screening of conditions for reaction of 6a with 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>solvent</th>
<th>8aa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>THF</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>THF</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>DMF</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>CH(_2)CN</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>Dichloroethane</td>
<td>65</td>
</tr>
</tbody>
</table>
The scope of the allylic alcohol was next investigated in the reaction of ynamide 6a (Figure 3). In the reaction of 6a with allyl alcohol 2b or 2c, having a substituent at the C2-position, the desired products 8ba and 8ac were obtained in good yields. Interestingly, the reaction with 2d also proceeded to give γ,δ,ε,ζ-unsaturated amide 8ad in 81% yield as a single isomer.

In the case of the reaction using allyl alcohol having a substituent at the C3-position, the product possesses two chiral carbon centers, in which the diastereoselectivity is of interest. Thus, the reaction of ynamides with E- or Z-crotyl alcohol (2e) was investigated (Figure 4). The reaction of 6a with (E)-2e under the optimized conditions produced anti-8ae as a major isomer in 65% yield as a 30:70 mixture of diastereomers. On the other hand, in the reaction with (Z)-2e under the same conditions, syn-8ae was formed as a major isomer in comparable yield to that of the reaction with (E)-2e but with higher diastereoselectivity. The reaction of 6f with (E)- or (Z)-2e showed the same trend as that for 6a in which anti-8fe or syn-8fe was formed as a major isomer from (E)-2e or (Z)-2e, respectively. The diastereoselectivity found for the reaction using (Z)-2e was quite low compared to that of 6a and (Z)-2e. The relative configuration of 8fe was determined as follows (Figure 5): a diastereomixture of 8fe (78:22), which was obtained in the reaction of 6f and (E)-2e, was converted to the carboxylic acid 9 by hydrolysis. The spectral data of both syn-9 and anti-9 have been reported in the literature.12 By a comparison of 1H-NMR of a mixture of 8fe and the reported data, we unambiguously determined that anti-8fe was formed as the major isomer in the reaction of 6f and (E)-2e. The relative configuration of 8ae was inferred by analogy to the spectral data of 8fe.
8fe was preferentially produced as the major diastereomer via transition state C-2 from (Z)-4ae or (Z)-4fe (Figure 6).

However, we wondered if the diastereoselectivity shown in Figure 4 was lower than that of previously reported cases, especially in the reaction of 6f with (Z)-2e. We therefore explored the selectivity at the stage of the nucleophilic attack of alcohol to activated ynamide by the Au(I) complex by using ynamide 6f and MeOH as the nucleophile under the optimized conditions and examining the temperature as a variable (Figure 7). The expected product (Z)-13 was obtained in 29% yield as the minor isomer, while (E)-13 was formed in 46% yield as the major isomer. This result indicates that hydroalkoxylation of ynamides is not very stereoselective compared to that of simple alkynes. It is well known that a keteniminium species like 14 is formed from ynamides through activation by a Au(I) complex, in which a known that a keteniminium species like 14 is formed from ynamides through activation by a Au(I) complex.

Counter Inc.) (for THF, Toluene, DMF, CH3CN) or distilled under an N2 atmosphere from CaH2 (ClCH2CH2Cl). All other solvents and reagents were purified under high vacuum and backfilled with argon. A solution of 1,1-dimethoxy-1-alkene (1.52 g, 6.30 mmol) in dry and degassed toluene (12.5 mL) was next added. The test tube was sealed with screw cap and the heterogeneous mixture was heated at 110 °C for 60 hours. The reaction mixture was then cooled to room temperature, filtered over a plug of silica gel (washed with AcOEt), and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (hexane) followed by gel permeation chromatography (eluent: CHCl3).

The residue was dissolved in MeOH as the nucleophile under the optimized conditions and examined the temperature as a variable (Figure 7). The expected product (Z)-13 was obtained in 29% yield as the minor isomer, while (E)-13 was formed in 46% yield as the major isomer. This result indicates that hydroalkoxylation of ynamides is not very stereoselective compared to that of simple alkynes. It is well known that a keteniminium species like 14 is formed from ynamides through activation by a Au(I) complex, in which a known that a keteniminium species like 14 is formed from ynamides through activation by a Au(I) complex.

Figure 6 Transition state of Claisen rearrangement of (E)- or (Z)-4ae and 4fe.

Figure 7 Stereoselectivity in the addition of MeOH to ynamide 6f.

In conclusion, we have developed Au(I)-catalyzed hydroalkoxylation/Claisen rearrangement cascade reactions involving aryl ynel ethers and ynamides with allylic alcohols, giving γ,δ-unsaturated esters and amides, respectively. In this reaction, attack of allylic alcohols occurs in a perfectly regioselective manner due to the inherent property of polarized alkynes. The use of a [Au(IPr)NTf2] catalyst is most effective, and the reaction proceeds under mild conditions. This reaction is an atom-economical methodology for synthesis of γ,δ-unsaturated esters or amides, and further studies including application to the synthesis of natural products are currently underway making use of alternative catalysts possibly rendering even more user-friendly.

Solvants were purified under N2 using The Ultimate Solvent System (Glass Counter Inc.) for THF, Toluene, DMF, CH3CN or distilled under an N2 atmosphere from CaH2 (ClCH2CH2Cl). All other solvents and reagents were purified under high vacuum and backfilled with argon. A solution of 1,1-dimethoxy-1-alkene (1.52 g, 6.30 mmol) in dry and degassed toluene (12.5 mL) was next added. The test tube was sealed with screw cap and the heterogeneous mixture was heated at 110 °C for 60 hours. The reaction mixture was then cooled to room temperature, filtered over a plug of silica gel (washed with AcOEt), and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (hexane) followed by gel permeation chromatography (eluent: CHCl3).

General Procedure for the Reaction of Alkaloid Ethers with Allyl Alcohol

A solution of allyl alcohol (0.3 mmol) in THF (0.3 mL) was added dropwise over 10 min to a solution of [Au(IPr)NTf2] (0.003 mmol) and ynel ether (0.3 mmol) in THF (0.3 mL) with stirring at 60 °C. The mixture was stirred at this temperature for 24 h. After removal of volatiles under vacuum, the residue was purified by column chromatography on silica gel to give the product.
**Synthesis**

**m-Toly 2-allylhexanoate (7aa) (Table 1, Entry 9).** According to the General Procedure for the Reaction of Aryl Ynoyl Ethers with Allyl Alcohol, a crude material was obtained from the reaction of 5f (51.4 mg, 0.295 mmol), 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=10:1) as a colorless oil.

**IR (neat):** 3076, 2926, 2852, 1755, 1642, 1592 cm⁻¹.

**HRMS (ESI):** m/z [M+Na]+ calcd for C30H36NaO3Si: 495.2330; found: 495.2333.

**Phenyl 2-allylhexanoate (7da) (Figure 1).** According to the General Procedure, 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=10:1) as a colorless oil.

**IR (neat):** 3077, 2931, 2860, 1575, 1642, 1593 cm⁻¹.


**Phenyl 2-allylheptanoate (7aa) (Table 1, Entry 9).** According to the General Procedure, 7aa (55.4 mg, 0.295 mmol), 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=20:1) as a colorless oil.

**IR (neat):** 3077, 2931, 2860, 1575, 1642, 1593 cm⁻¹.


**o-Toly 2-allylhexanoate (7ca) (Figure 1).** According to the General Procedure, 7ca (58.3 mg, 0.80%) was obtained as a colorless oil from the reaction of 5c (55.5 mg, 0.295 mmol), 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=10:1) as a colorless oil.

**IR (neat):** 3077, 2931, 2860, 1575, 1642, 1594, 1508 cm⁻¹.

**HRMS (ESI):** m/z [M+N]⁺ calcd for C16H22NaO2: 269.1512; found: 269.1512.

**4-Chlorophenyl 2-allylhexanoate (7da) (Figure 1).** According to the General Procedure, 7da (69.3 mg, 88%) was obtained as a colorless oil from the reaction of 5d (61.6 mg, 0.295 mmol), 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=10:1) as a colorless oil.

**IR (neat):** 3071, 2931, 2857, 1757, 1575, 1591 cm⁻¹.

**HRMS (ESI):** m/z [M+N]⁺ calcd for C16H22NaO2: 269.1512; found: 269.1512.

**Phenyl 2-cyclohexyl-4-pentenonate (7ea) (Figure 1).** According to the General Procedure, 7ea (60.8 mg, 80%) was obtained as a colorless oil from the reaction of 5e (59.1 mg, 0.295 mmol), 2a (20.0 µL, 0.294 mmol), and [Au(IPr)NTf2] (2.5 mg, 0.003 mmol) after purification by column chromatography (n-hexane: diethyl ether=10:1) as a colorless oil.

**IR (neat):** 3076, 2926, 2852, 1755, 1642, 1592 cm⁻¹.


**Preparation of Ynamides**

Ynamides, used as a substrate, were synthesized according to the reported method.**

**General Procedure for the Reaction of Ynamides with Aliphatic Alcohols**

A solution of ynamide (0.6 mmol) and allylic alcohol (0.6 mmol) in toluene (0.6 mL) was added to a mixture of [Au(ligand)Cl] (0.006 mmol, 1 mol% to a substrate) and AgNTf2 (0.006 mmol, 1 mol% to a substrate) in toluene (0.6 mL) under N₂. The mixture was stirred at 80 °C for 24 h. After removal of the volatiles under vacuum, the residue was purified by column chromatography on silica gel to give the product.
2-Allyl-N-methyl-N-tosylhexanamide (8aa) (Table 2, Entry 7).

According to the General Procedure for the Reaction of Ynamides with Allylic Alcohols, a crude material was obtained from the reaction of 6a (158.9 mg, 0.60 mmol), 2a (0.60 mL of 1.0 M solution in toluene, 0.60 mmol), [Au(IPr)Cl] (3.7 mg, 0.006 mmol), and AgNTf2 (2.4 mg, 0.006 mmol), from which the yield of 8aa was determined to be 92% by 1H-NMR by using 1,3,5-trimethoxybenzene as an internal standard.

IR (neat): 2925, 1719, 1610 cm⁻¹.

1H NMR (400 MHz, CDCl3): 8 = 7.76 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 7.26-7.21 (m, 4H), 5.60-5.49 (m, 1H), 4.97-4.91 (m, 2H), 4.45 (t, J = 7.4 Hz, 1H), 3.92 (s, 3H), 3.21 (s, 3H), 2.76-2.69 (m, 2H), 2.42-2.35 (m, 4H).


2-Allyl-N-methyl-N-tosylpent-4-enamide (8ba) (Figure 2).

According to the General Procedure, a crude product, which was prepared from ynamide 6a (158.6 mg, 0.598 mmol), 2a (0.60 mL of 1.0 M solution in toluene, 0.60 mmol), [Au(IPr)Cl] (0.006 mmol, 1 mol%), and AgNTf2 (0.006 mmol, 1 mol%) to a substrate) in toluene (1.2 mL) at 80 °C for 24 h, was purified by column chromatography on silica gel (n-hexane/EtOAc = 20/1) to give 8ba (79.0 mg, 50% yield) as a colorless liquid.

IR (neat): 2960, 1694, 1593 cm⁻¹.

1H NMR (400 MHz, CDCl3): 8 = 7.79 (d, J = 2.1 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 5.52-5.41 (m, 1H), 4.86-4.78 (m, 2H), 3.29 (s, 3H), 3.10-2.93 (m, 1H), 2.42 (s, 3H), 2.40-2.35 (m, 1H), 1.92-1.85 (m, 1H), 0.94 (s, 9H).

13C NMR (100 MHz, CDCl3): 8 = 146.6, 143.3, 136.7, 135.8, 129.5, 128.1, 117.2, 53.4, 34.5, 33.7, 33.5, 27.8, 21.7.

According to the General Procedure, a crude product, which was prepared from ynamide 6a (158.0 mg, 0.595 mmol), allylic alcohol 2d (1.2 mmol), [Au(IPr)Cl] (0.006 mmol, 1 mol%), and AgNTf₂ (0.006 mmol, 1 mol%) to a substrate) in toluene (1.2 mL) at 80 °C for 24 h, was purified by column chromatography on silica gel (n-hexane/乙酸乙酯 = 10/1) to give Bad (168.7 mg, 81% yield) as a colorless liquid.

IR (neat): 2957, 1697, 1598, 1357, 1163 cm⁻¹.


Spectral data of Bad (a mixture of diastereomers)
Determination of Relative Configuration of 8f (Figure 5). 2,3-Dimethylpent-4-en-1-olic acid (9). A solution of 8f (d = 78.22, 87.5 mg, 0.30 mmol) was obtained from the reaction of 6f and (E)-2e in THF (0.3 mL) was added to a cooled solution of LiOH·H2O (27.7 mg, 0.6 mmol) and H2O2 (30% (v/v) aqueous solution, 0.3 mL, 1.2 mmol), and the mixture was stirred at 50 °C for 16 h. The solution was washed with CH2Cl2 (3 × 15 mL), then the aqueous phase was acidified and extracted with CH2Cl2 (3 × 15 mL). The combined organic extracts were washed with brine and dried over MgSO4. After removal of the solvent, the crude material was obtained as an enough quality for comparison with 1H-NMR of known compounds in the literature. By comparison, we found that anti-8f was formed as the major product in reaction of 6f and (E)-2e.

Spectral data of 9-a mixture of diastereomers (syn/anti = 24/76)

<table>
<thead>
<tr>
<th>IR (neat)</th>
<th>3080, 2976, 1707, 1460, 1291 cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1H NMR (400 MHz, CDCl₃)</td>
<td>δ = 11.35 (bs, 1H), 5.84-5.73 (m, 1H, syn), 5.70-5.61 (m, 1H, anti), 5.09-5.00 (m, 2H), 2.55-2.31 (m, 2H), 1.14-1.00 (m, 6H)</td>
</tr>
<tr>
<td>13C NMR (100 MHz, CDCl₃)</td>
<td>δ = 141.3, 140.6, 115.5, 114.8, 45.9, 44.6, 40.2, 18.5, 16.1, 14.5, 13.3</td>
</tr>
</tbody>
</table>

HRMS (ESI): m/z [M+Na]+ calcd for C₁₂H₁₇NNaO₃S: 278.0825; found: 278.0825.

Acknowledgment

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Supporting Information

Is there Supporting Information to be published? Click here to indicate YES or NO (text and links will be updated prior to publication).

Conflict of Interest

There are no conflicts to declare.

References


(8) Liu et al. reported that y,β-unsaturated amidines were produced as undesired products in some cases in their study on Au(I)-catalyzed...


