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Gold catalysis: up to six new bonds by a domino [3+2]/[2+1]/[2+1] cycloaddition

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Abstract—In the presence of the *N*-heterocyclic carbene gold catalyst (IPrAuNCPbSbF₆, **2**), propargyl ester **1** undergoes a formal [3+2] cycloaddition reaction with vinyl ethers at room temperature. If the reaction was allowed to continue with excess propargyl ester, one or two sequential cyclopropanations occur on the enolate double bond of the [3+2] reaction product. The one-pot domino cycloaddition reactions created cyclopropanation products with multiple rings, formed multiple new sigma bonds, and new stereocenters. When 2-methoxypropene was allowed to react with excess propargyl ester **1** in the presence of the Au(I) catalyst **2**, two tandem cyclopropanations occurred on the initial [3+2] cycloaddition product, which yields a product with a tricyclic carbon frame, six new sigma bonds, and eight new stereocenters. Hence the observation sets a new record for gold-catalyzed domino reactions. The assignment of the product stereochemistry was performed by NMR spectroscopy and confirmed by an X-ray structure analysis.

Keywords:

gold catalysis

domino cycloaddition

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One of the fundamental objectives of organic synthesis is the construction of complex molecules from simpler ones. During the construction of the complex target molecules, a challenging task involves the consideration of atom economy.¹ Gold catalyzed reactions have emerged as an extraordinary tool to create molecular complexity with high atom economy.²⁻⁴ Au(I) complexes are especially active as catalysts in many cyclization and cycloaddition reactions because of the unique ability of gold complexes to activate carbon-carbon π -systems.⁵⁻⁸ During our pursuit of a promoter to initiate a transannular [4+3] cycloaddition, we discovered that gold complexes are most suitable for such transformations by providing Au-stabilized allylic cations.⁹⁻¹⁰ Recently we have further demonstrated that propargyl esters (**1**) could add to vinyl ethers (**3**)

Scheme 1.

by either a direct [3+2] cycloaddition via a Au-stabilized allylic cation (**A**) or a tandem [2+1] cycloaddition/rearrangement via a gold carbene intermediate (**B**). Both gave five-membered rings (**4**), but with different stereochemistry, Scheme 1.¹¹

In our recent study,¹¹ some of the cyclopropanation products such as **5** were isolated although no similar product was observed with 1-methoxycyclohexene as the substrate (Scheme 1). The vinyl cyclopropane **5** was easily converted to the corresponding cyclopentene derivative (**6**, Scheme 2) with the Au(I) catalyst **2** (IPrAu⁺NPhSbF₆⁻). In the absence of the Au(I) catalyst, vinyl cyclopropane **5** was resistant to change even at high temperatures up to 110 °C.¹¹ We proposed a likely two step mechanism for the Au(I)-catalyzed ring expansion reaction. First, the initial coordination of the enolate ester double bond of **5** to the cationic Au(I) center leads to the opening of the cyclopropane ring and the concurrent formation of an oxycarbenium ion (**C** in Scheme 2). Secondly this highly strained intermediate (due to the cis-configuration of the double bond) led to the five member ring formation and deauration producing product **6**. Thus the Au(I) catalyst not only activates the reactant propargyl esters, but also activates the initial product, the vinylcyclopropane (**5**) to give the cyclopentene product (**6**).

Intrigued by the multiple roles played by the Au(I) catalyst, we become interested in the possibility of using propargyl esters as the substrates in a gold-catalyzed domino reaction^{12–14} sequence to prepare compounds with multiple five-membered rings. To explore the likelihood of the hypothesis, the reactivity of the vinyl ester **4** was tested using gold catalyst **2**, Scheme 3. Similar cyclopropanation of vinyl esters have been reported by Fiksdahl, but the substrate was much simpler and a different Au catalyst was used.¹⁵ In the presence of gold catalyst **2**, propargyl ester **1** and vinyl ester **4** reacted smoothly at room temperature to afford the vinyl cyclopropane **7** in 75% yield, Scheme 3.

With the successful cyclopropanation of **4**, we set out to test the one-pot cascade [3+2]/[2+1] cycloadditions starting from 1-methoxycyclohexene **3**, Scheme 4. We are pleased to identify two diastereomers (**8a** and **8b**) as cis/trans isomers

when three equivalents of propargyl ester **1** and one equivalent of **3** were allowed to react at r.t. for 4 h in the presence of Au(I) catalyst **2**. According to the definition put forth by Tietze,¹⁶ this is a domino cycloaddition reaction.¹⁴ A domino reaction has been defined as a reaction involving two or more bond-forming transformations that take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation in the previous step. The first stage of the Au(I)-catalyzed reaction in Scheme 4 creates the vinyl ester functionality (syn or anti-**4**) to enable it to engage in the second reaction, which affords the cyclopropane enolate. It was not necessary to isolate the intermediate **4** or add additional catalyst.

To study the scope of this Au(I)-catalyzed domino reaction, the substrates are expanded to include different cyclic vinyl ethers. Unfortunately, the reaction is sensitive to vinyl ether ring sizes, Scheme 5. With the 7- and 8-membered cyclic vinyl ethers **9** and **11**, the domino cycloadditions occurred in about 60% of the total product distribution. The other products include the previously identified cyclopropanation products **5** and **12c**, and the initial [3+2] product **6**, Scheme 5.¹¹

Scheme 5

The stereochemistry of the domino [3+2]/[2+1] cycloaddition reaction product was determined by two-dimensional NMR spectroscopy including NOESY. The NOE effect between the vinyl proton of the enolate and the two cyclopropane protons for compound **10** is illustrated in Figure 1.

Figure 1. The stereochemistry of the *exo*-enol ester group relative to the cyclopropane ring was determined by NOSEY NMR spectroscopy.

To further identify the structures, we attempted the Au(I)-catalyzed ring expansion reaction on the domino cycloaddition products. However we found that these products are extremely resistant to change, even after being heated to 200°C in CH_2Cl_2 in a sealed tube with fresh Au(I) catalyst, Scheme 6. Our attempts to hydrolyze the ester groups by treatment with K_2CO_3 and MeOH were also unsuccessful with recovery of 80% of the starting material after 9 hours at room temperature, Scheme 6.

It became clear that the steric bulk of the enol ether play an important role on the product distribution. This was demonstrated by the exciting observation of the experiment of 2-methoxypropene **13**, Scheme 7. Under the same conditions, i.e., three equivalents of the propargyl ester **1** and 5% of the Au(I) catalyst **2** ($IPrAu^+NCPhSbF_6^-$), the reaction with 2-methoxypropene did not stop after the first cyclopropanation. A second cyclopropanation occurred on the double bond of the vinyl cyclopropane **14a**. Thus product **14b** with a tricyclic carbon frame, six new sigma bonds, and eight new stereocenters was isolated and identified, Scheme 7.

Figure 2. Crystal structure of domino product **14b**. Carbon: gray; Oxygen: red.

The structures of **14a** and **14b** were assigned by a combination of two-dimensional NMR methods, including COSY, HSQC, and NOESY spectroscopy. The relative configuration was confirmed by X-ray crystallography analysis, Figure 2. The domino cycloaddition product **14b** is believed to arise through the initial [3C+2C]-cycloaddition/cyclopropanation product **14a**, followed by an additional cyclopropanation to give cycloadduct **14b**.

From the results of this and previous studies on gold-catalyzed reactions between propargyl esters and enol ether or enol esters,^{11,15} product distribution depends mainly on the structure of the enols. Enol ethers may lead to formal [3+2] cycloaddition products, but enol esters produce primarily cyclopropanation products. In this report, we used only propargyl toluate ester **1** as the other reactant. However, propargyl acetate and pivalate have been used previously by Fiksdahl and cyclopropanation products were also observed if enol esters were used.¹⁵ It would be interesting to expand the gold-catalyzed cyclopropanation reaction to propargyl thioesters and amides in a future study.

In summary, we have discovered a domino [3+2]/[2+1]/[2+1] cycloaddition that produced a product with six new sigma bonds, and eight new stereocenters. Our current efforts are directed towards identifying the scope of the domino cycloaddition. Potential mixed versions of this reaction using different propargyl esters including thioesters and amides will be explored.

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