



Gold Catalysis

Dual Gold-Catalyzed Three-Component Reaction: Efficient Synthesis of Indene-Fused Esters, Acids, and Lactones through Gold Vinylidene Intermediates

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Abstract: A dual gold(I)-catalyzed three-component reaction was developed to prepare indene-fused carboxylic acid derivatives from diynes, alcohols, and pyridine *N*-oxides in both interand intramolecular fashions. The pyridine *N*-oxides were found to exhibit distinct selectivity unlike the α -oxo gold carbene in-

termediates in the well-developed gold-catalyzed oxidative functionalization of alkynes. Experimental studies and DFT calculations support double nucleophilic substitution of a gold vinylidene intermediate.

Introduction

Multicomponent transformations have emerged as powerful tools in organic synthesis owing to their innate simplicity, efficiency, and elegance.^[1] Among these transformations, transition-metal-catalyzed three-component reactions have attracted broad research interest, as they show unique reactivities.^[2] Clearly, the development of novel multicomponent reactions for the efficient synthesis of synthetically useful molecular scaffolds remains in high demand.

The past decade has seen rapid developments in the area of homogeneous gold catalysis.^[3] In several early studies, gold vinylidenes were proposed as reactive intermediates^[4–8] that underwent facile C–H or Nu–H insertion [Equation (1)]. Only a few reports appeared in which a gold vinylidene was trapped with one nucleophile such as water^[9] or a methoxy group^[10] [Equation (2)]. In line with our interests in exploring new reactivities of Au vinylidenes, we continue to be inspired by other metal vinylidene complexes such as Ru, Rh, and W.^[11] In 2013, Kim and Lee reported an elegant pyridine *N*-oxide mediated oxidation of a rhodium vinylidene to a ketene,^[12] which led to a variety of carboxylic acid derivatives [Equation (3)]. We wondered if a similar strategy could be applied to gold vinylidenes. Herein, we report that pyridine *N*-oxide indeed serves as a

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unique oxygen-transferring agent to gold vinylidenes to give highly functionalized indene-fused esters, acids, and lactones. Temporary mechanistic studies and theoretical calculations suggest ketene formation is a viable reaction pathway [Equation (4)].



Results and Discussion

Our study began with evaluating the feasibility of a reaction to induce ethanol addition to a dialkyne with a commercially available pyridine *N*-oxide as the oxygen-transferring agent in the presence of IPrAuNTf₂ [IPr = 1,3-bis(diisopropylphenyl)imid-azol-2-ylidene, Tf = trifluoromethylsulfonyl]. To our delight, the desired indene-fused ester product was isolated. After numer-

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ous trials, the optimized reaction conditions were found to include IPrAuNTf₂ (5 mmol-%), 3,5-dichloropyridine *N*-oxide (1.5 equiv.), and 1,2-dichloroethane (DCE)/ethanol (1:1, 0.03 M) at 70 °C to give **2a** in 88 % yield [Equation (5)].



With the optimal reaction conditions in hand, the substrate scope was promptly investigated by examining various alkynes and alcohols nucleophiles. As summarized in Table 1, almost all natures of aliphatic alcohols, including primary, secondary, and tertiary alcohols, were good substrates for the three-component oxygenative cyclization reactions (see products **2a**–**h**). The reaction also tolerated benzylic and allylic alcohols (see products **2i** and **2j**). Pharmaceutically interesting monofluoro and trifluoromethyl groups did not interfere with the reaction (see

Table 1. Intermolecular reactions of gold vinylidenes.^[a]



[a] Yields of the isolated products are given. [b] About 10 % of the diyne was recovered.

products **2k** and **2l**). A synthetically useful acetone functionality was also successfully engaged in the addition reaction (see product **2m**). Variations on the diyne aromatic backbone were also briefly investigated. Substituents such as Me, Cl, and OMe on the benzene ring were well tolerated (see products **2n**–**p**). Upon changing the methyl group on the alkyne (i.e., R¹) to another group such as a bromo or cyclopropyl group, the reactions also proceeded well (see products **2q** and **2r**). To broaden the universality of this reaction, many other nucleophiles were explored. We were pleased to find that water and ethyl acetoacetate were also reactive nucleophiles, and the latter gave **2v** in vinyl ester form. However, amino alcohols and thiols were not effective nucleophiles under the current reaction conditions.

Lactones are a diverse group of natural products with a wide range of biological activities. We envisioned that an intramolecular version of our protocol might offer an approach to the lactone scaffold. We first subjected **3a**' to the optimized conditions; however, a known furan was isolated,^[5a] presumably as a result of downstream aromatization once the gold vinylidene was trapped by the secondary alcohol [Equation (6)].



To inhibit the aromatization, tertiary alcohol **3a** was prepared, and it gave the indene-fused lactone product under the established intermolecular reaction conditions. Optimization of the conditions finally led to product **4a** in 82 % yield (Table 2). The scope and limitations of this intramolecular oxygenative

Table 2. Intramolecular reactions of gold vinylidenes.[a]



[a] Yields of the isolated products are given.



lactonization were subsequently investigated (Table 2). Tertiary alcohols with different ring sizes and skeletons reacted well (see products **4b**–**d**). The benzene backbone could be substituted with CF₃, Me, and Cl groups (see products **4e**–**g**). To our delight, noncyclized tertiary alcohols were successfully engaged in the oxidative lactonization (see products **4h**–**k**). The enhanced synthetic utility of this methodology was demonstrated in the preparation of seven-membered lactones, which represent another important molecular motif (see products **4l**–**n**). Unfortunately, our attempts to generate six-membered or even larger macrolactones were not successful.

Next, we turned our attention to mechanistic studies. Several control experiments were performed. Upon using deuterated ethanol (EtOD) as a cosolvent, the methylene group of the product was deuterated by 95 % [Equation (7)], which suggested a dual gold catalysis nature. Vinyl ethyl ether **6** was isolated from the reaction mixture in the absence of a pyridine *N*-oxide, and no desired ester was observed from the reaction of **6** [Equation (8)]. This result indicated that oxygen transfer from the pyridine *N*-oxide might have occurred first.



Therefore, a tentative mechanism is proposed (Scheme 1). The generation of gold–vinylidene intermediate **II** initiates the reaction cascade. Intermediate **II** can be trapped with a pyridine *N*-oxide as a nucleophile; this is followed by leaving of the pyridine, which leads to species **IV**. Then, formation of key ketene **V**^[11i,12] and nucleophilic addition of the alcohol and demetalation provides **2a**.

To gain further insight and to support our outlined mechanism, we performed DFT calculations to investigate the energetics of the proposed mechanism; geometry optimizations and transitions-state searches were performed at the B3LYP^[13] level with the 6-31+G(d) basis set for the C, H, N, O, and Cl atoms and with LANL2DZ^[14] with relativistic effective core potentials for gold, as B3LYP was recently shown to give reasonable energy and geometry predictions for homogeneous gold catalysis;^[15] these basis sets were recently proven to be suitable for geometry predictions of similar systems involving gold atoms.^[16] Single-point calculations were performed at the M06 level with a mixed basis set of SDD for gold^[17] and 6-311+G(d,p) for all other atoms, as this was proven to provide reliable energy evaluation for similar gold catalysis.^[18] Solvation energy corrections were calculated by using the SMD model and with DCE as the solvent. All calculations were performed with the Gaussian 09 program package.^[19] All transition states were confirmed by intrinsic reaction coordinate (IRC) toward a set of





Scheme 1. Proposed mechanism for the dual gold-catalyzed three-component reaction.

pre- and postreaction complexes. $^{\circle{[20]}}$ Computed structures are displayed with CYLview. $^{\circle{[21]}}$

We started the calculations from gold vinylidene intermediate II.^[5a,5f,18] The activation barrier for nucleophilic attack by the pyridine N-oxide was calculated to be 9.9 kcal mol^{-1} (see Figure 1, TS1). This is comparable to the reported intramolecular C(sp³)-H insertion reaction in II, for which the calculated free energy barrier was 9.2 kcal mol⁻¹.^[5a,5f] The reaction was also investigated with vinylidene intermediate analogues II_a and **II_b** (Figure 1), and the activation barriers were found to be 7.8 and 7.7 kcal mol⁻¹, respectively, which are lower than that for II itself. In transition state TS1, the bond length for the newly formed C-O interaction is 2.63 Å. The C=C=Au angle is 167.3°, which bends by 12.7° from the linear structure in vinylidene II. This leads to the formation of intermediate III, which then undergoes decomposition to form intermediate IV with a barrier of 8.5 kcal mol⁻¹ (see **TS2**). In intermediate **IV**, Au is complexed to the C1 carbon center directly, the C1=C2 bond length is 1.36 Å, the C2=O bond length is 1.15 Å, and the C1-Au bond length is 2.21 Å (Figure 1, IV). Moreover, the C2-C1-Au bond angle is 98.8°, and the O=C=C bond is out of the phenyl cyclopentene plane by 47.6°. The bond lengths of the O=C=C moiety are similar to those for a ketene structure;^[22] therefore, we believe cleavage of the O-N bond in III can lead to the formation of ketene IV directly. The free energy of IV is much lower (by 72 kcal mol⁻¹) than that of **III**, which makes this a very favorable process. The Au complex in IV was found to be able to migrate to the benzene ring through C3 and C4 to form V directly. This process happens through transition TS3, with a very low activation barrier of 5.8 kcal mol⁻¹. This serves as one of the intermediate structures for gold slippage in the π system, and it can be transformed into gem-diaurated species VI (Scheme 1) directly or after nucleophilic attack by the







Figure 1. Computed free-energy profile for the reaction of 3,5-dichloropyridine N-oxide with a gold vinylidene.

alcohol, which, followed by gold and hydrogen exchange with **1a**, completes the catalytic cycle.

Conclusions

In summary, we were able to realize a dual gold-catalyzed three-component coupling by relying on new reactivity of a gold vinylidene intermediate. A pyridine *N*-oxide served as a unique oxygen-transfer agent, and it exhibited distinct selectivity unlike α -oxo gold carbenes. The oxygenative cyclized 1,1-difunctionalization reaction readily took place in both inter- and intramolecular settings, which led to a variety of indene-fused esters, acids, and lactones. Further investigations concerning gold vinylidene intermediates are currently underway in our laboratory.

Experimental Section

General Procedure for the Synthesis of Compound 2: In a flask, **1** (1.0 equiv.) was dissolved in DCE/R²OH (1:1 v/v, 0.03 M), and then IPrAuNTf₂ (5 mmol-%) and 3,5-dicholoropyidine *N*-oxide (1.5 equiv.) were added. The mixture was stirred at 70 °C until complete conversion was detected by TLC (3 h). Then, the mixture was concentrated, and the residue was purified by flash column chromatography (hexane/ethyl acetate = 20:1) to afford **2**.

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