

## Catalyzed Catalysis Using Carbophilic Lewis Acidic Gold and Lewis Basic Palladium: Synthesis of Substituted Butenolides and Isocoumarins

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Reactions catalyzed by two different metals at the same time, or dual-catalyzed reactions, can access reactivity and selectivity not available to single-metal systems while offering the attractive environmental and cost benefits of substoichiometric use of both metals.<sup>1–5</sup> Considerably less is known about strategies for designing dual-catalyzed reactions than about their single-metal counterparts.<sup>1</sup> This paucity of predictive power arises in part from questions regarding the compatibility of the two metals with each other and the additional complexity of initiating the catalytic turnover of both metals. In this work, we have developed a valuable new strategy, catalyzed catalysis, to achieve turnover of both metals and novel reactivity. Specifically, we employ a carbophilic<sup>6</sup> Lewis acidic Au catalyst to catalyze the cross-coupling reactivity of a second Lewis basic Pd catalyst in order to functionalize vinylgold intermediates arising from intramolecular substrate rearrangements. In the past decade, vinylgold intermediates have been indicated in the rearrangement of numerous heteroatom-containing substrates;<sup>6,7</sup> however, their reactivity has been dominated by protodemetalation,<sup>6,7</sup> with electrophilic trapping as a notable alternative.<sup>8–10</sup> Our Au/Pd cross-coupling reaction enhances the synthetic usefulness of these intermediates by providing dual-catalytic C–C bond formation as an alternative to protodemetalation.<sup>11</sup> We have showcased this reaction in the synthesis of substituted butenolides and isocoumarins, structural motifs present in numerous biologically active compounds.<sup>12,13</sup>

We anticipated that the Au-catalyzed rearrangement of allenolate **1** would produce allyl oxonium **2**, in analogy to the stoichiometric formation of the ethyloxonium ion reported by Hammond<sup>14</sup> (Scheme 1). We hypothesized that this rearrangement<sup>15,16</sup> would enhance the reactivity of the ester toward deallylation<sup>17</sup> by Pd(0) because of the increased rate of oxidative addition of Pd(0) toward allylic substrates bearing cationic leaving groups.<sup>18</sup> Subsequent transmetalation between neutral vinylgold complex **3** and  $\pi$ -allyl Pd complex **4**<sup>19</sup> followed by C–C bond-forming reductive elimination<sup>19</sup> would complete both metals' catalytic cycles and form substituted butenolide **5**. In essence, the Au therefore would catalyze both the initial rearrangement step and the subsequent Pd oxidative addition step, first by lowering the energy of the allene antibonding orbital in **1** and then by redistributing this electron deficiency through the substrate's rearrangement via lowering of the energy of the allyl–oxygen antibonding orbital in oxonium **2**, thus lowering the barrier for oxidative addition by the second Pd catalyst (Scheme 1).<sup>18</sup> In this proposed pathway, Au catalytically creates a different species with increased reactivity toward catalytic oxidative addition of Pd. The term *catalyzed catalysis* is applied to convey this mechanistic process.<sup>20</sup>

In order to explore this hypothesis, allenolate **1a** was treated with 5 mol % PPh<sub>3</sub>AuCl/AgOTf and 5 mol % Pd<sub>2</sub>dba<sub>3</sub> in CD<sub>2</sub>Cl<sub>2</sub> (Table 1). As predicted, this reaction produced butenolide **5a** (97%) and required both Au and Pd.<sup>21</sup> The reaction proceeded in high conversion with a variety of substituents at the R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> positions (Table 1, 1.5–24 h). For example, geminal substitution on the allenyl moiety was tolerated in the formation of spirocyclic

### Scheme 1. Proposed Mechanism

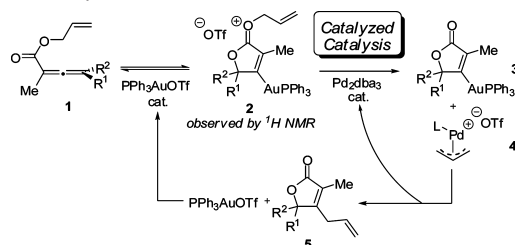
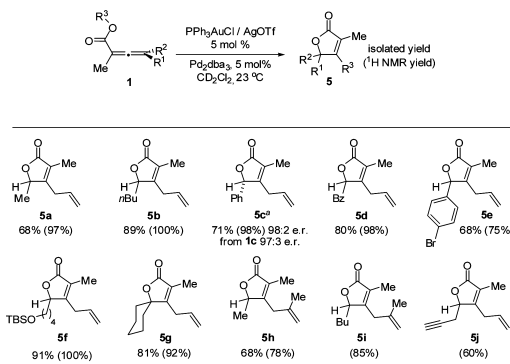


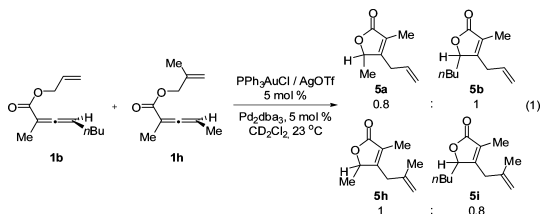
Table 1. Scope of Au/Pd-Catalyzed Butenolide Rearrangement



<sup>a</sup> Using 10 mol % PPh<sub>3</sub>AuCl/AgOTf and 10 mol % Pd<sub>2</sub>dba<sub>3</sub>.

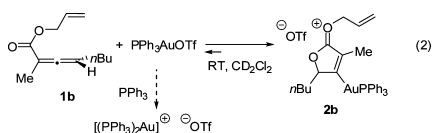
product **5g** (92%). The robustness of the Brønsted acid-sensitive *tert*-butyldimethylsilyl protecting group toward the reaction conditions showcased the selective reactivity of the carbophilic Lewis acid Au while providing a handle for subsequent orthogonal reactivity. Similarly, the dual-catalyzed reaction conditions avoided potential side reactions from oxidative addition into the aryl bromide bond (**5e**, 75%). Substitution of the allyl moiety (R<sup>3</sup>) at the internal position was also tolerated [**5h** (78%) and **5i** (85%)] despite the increased acid sensitivity of the starting allenolates **1h** and **1i** toward Lewis acid-catalyzed ionization.

To probe the intermediacy of  $\pi$ -allyl palladium complex **4** and vinylgold complex **3** in this reaction, a crossover experiment between allenolates **1b** and **1h** was examined.<sup>22</sup> Specifically, 5 mol % PPh<sub>3</sub>AuCl/AgOTf and 5 mol % Pd<sub>2</sub>dba<sub>3</sub> was added to 0.5 equiv of **1b** and 0.5 equiv of **1h** in a single reaction vessel (eq 1). The crude reaction mixture was analyzed by <sup>1</sup>H NMR spectroscopy and mass spectrometry (MS), which revealed that products **5b** and **5h** and crossover products **5a** and **5i** were produced in a 1:1:0.8:0.8 ratio. The observed crossover is consistent with the intermediacy of **3** and **4** followed by intermolecular transmetalation and reductive elimination.<sup>19</sup> The unequal ratio of crossover to noncrossover products could arise from a small difference in the rates of reactivity between the differentially substituted starting materials.



A series of  $^1\text{H}$  NMR spectroscopic kinetic experiments revealed a first-order kinetic dependence on the concentration of  $\text{Pd}_2\text{dba}_3$ , confirming the role of Pd in the reaction (at 5 mol %  $\text{PPh}_3\text{AuOTf}$  and 0.10 M **1b**,  $k_{\text{obs}} = 0.0014, 0.0016, \text{ and } 0.0026 \text{ M}^{-1} \text{ s}^{-1}$  at 5, 7.5, and 10 mol % Pd, respectively).<sup>23</sup> Over this loading range, the reaction displayed zeroth-order substrate saturation kinetics.<sup>24</sup> While the presence of Au was required for the observed product formation, loadings of over 5 mol %  $\text{PPh}_3\text{AuOTf}$  resulted in decreased conversion, consistent with catalyst decomposition prior to the completion of the reaction at higher Au loadings.

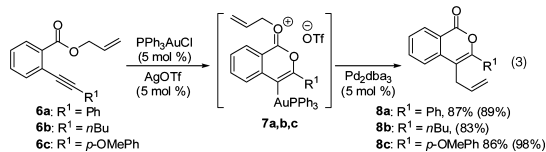
We next examined which step was rate-determining. We discovered that reactant **1b** and rearrangement product **2b** reach a rapid equilibrium strongly favoring **2b** (>95% by  $^1\text{H}$  NMR spectroscopy) (eq 2). Specifically, addition of the precatalyst



$\text{Pd}(\text{PPh}_3)_4$  did not initiate cross-coupling reactivity but instead quickly regenerated the starting material, presumably by trapping  $\text{PPh}_3\text{AuOTf}$  as the catalytically inactive  $[(\text{PPh}_3)_2\text{Au}]^+$ , as was observed when 1 equiv of  $\text{PPh}_3$  was added to 1 equiv of **2b** (>95% regeneration of **1b** within 20 min). This is an early example of an experimentally detected Au-catalyzed substrate rearrangement in which the equilibrium and the back reaction could be observed and kinetically probed. This result suggested that a low energy barrier and equilibrium may be present in the initial rearrangement step for numerous other recently reported Au-catalyzed reactions.<sup>6,7</sup>

The presence of substrate saturation kinetics suggested that the catalyst resting state should be an observable intermediate with the substrate bound to one or both of the metal catalysts. Indeed, vinylgold complex **3** and the  $\pi$ -allyl palladium cations **4** with  $\text{L} = \text{dba}$  and  $(\text{PPh}_3)_2$  were identified in the reaction mixture by high-resolution MS prior to completion of the reaction, supporting the proposed mechanism.<sup>25</sup> The observed equilibrium between **1b** and **2b** and the buildup of intermediates **3** and **4** suggested that the intermolecular combination of **3** and **4** was the rate-determining step under saturation conditions (likely via transmetalation and/or reductive elimination to form **5**, in analogy to other known  $\pi$ -allyl-Pd alkylation reactions<sup>19</sup>).

Extension of the Au/Pd cross-coupling reaction to benzoate substrates established the generality of this methodology. The Au-only rearrangement of benzoates **6a** and **6b** previously was proposed to proceed through vinylgold oxonium intermediates **7a** and **7b** (eq 3), followed by protodemetalation.<sup>26</sup> Addition of 5 mol %  $\text{Pd}_2\text{dba}_3$



to **6a–c** in the presence of 5 mol %  $\text{PPh}_3\text{AuCl}/\text{AgOTf}$  resulted in cross-coupling of **7a–c** to produce isocoumarins **8a–c** (89%,

83%, 98% respectively).<sup>27</sup> This result demonstrated that the vinylgold intermediate need not be previously reported as observable<sup>26</sup> in order to serve as an efficient cross-coupling partner.

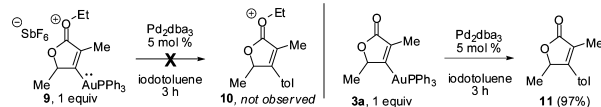
In conclusion, we have established a fundamental pattern of dual-catalytic cross-coupling reactivity and turnover with carbophilic Lewis acidic Au catalysts and Lewis basic Pd catalysts. More broadly, this C–C cross-coupling<sup>28</sup> method represents a practical alternative to protodemetalation for elaborating the large number of recently reported organogold oxonium intermediates.<sup>6,7</sup>

**Acknowledgment.** We thank the ACS-PRF, the NSF (a CAREER Award), and the University of California Irvine for funding, the Allergan Foundation for a fellowship to Y.S., Dr. John Greaves for help with MS, and Mr. Stephen Canham for HPLC assistance.

**Supporting Information Available:** Experimental procedures, kinetic data, and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA9068497