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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.¹⁻⁵ Considerably less is known about strategies for designing dual-catalyzed reactions than about their single-metal counterparts.¹ 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 carbophilic⁶ 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;^{6,7} however, their reactivity has been dominated by protodemetalation,^{6,7} with electrophilic trapping as a notable alternative.⁸⁻¹⁰ Our Au/Pd crosscoupling reaction enhances the synthetic usefulness of these intermediates by providing dual-catalytic C-C bond formation as an alternative to protodemetalation.¹¹ We have showcased this reaction in the synthesis of substituted butenolides and isocoumarins, structural motifs present in numerous biologically active compounds.^{12,13}

We anticipated that the Au-catalyzed rearrangement of allenoate 1 would produce allyl oxonium 2, in analogy to the stoichiometric formation of the ethyloxonium ion reported by Hammond¹⁴ (Scheme 1). We hypothesized that this rearrangement^{15,16} would enhance the reactivity of the ester toward deallylation¹⁷ by Pd(0) because of the increased rate of oxidative addition of Pd(0) toward allylic substrates bearing cationic leaving groups.¹⁸ Subsequent transmetalation between neutral vinylgold complex 3 and π -allyl Pd complex 4¹¹ followed by C-C bond-forming reductive elimination¹⁹ 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).18 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.²⁰

In order to explore this hypothesis, allenoate **1a** was treated with 5 mol % PPh₃AuCl/AgOTf and 5 mol % Pd₂dba₃ in CD₂Cl₂ (Table 1). As predicted, this reaction produced butenolide **5a** (97%) and required both Au and Pd.²¹ The reaction proceeded in high conversion with a variety of substituents at the R¹, R², and R³ 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







^a Using 10 mol % PPh₃AuCl/AgOTf and 10 mol % Pd₂dba₃.

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 (\mathbb{R}^3) at the internal position was also tolerated [**5h** (78%) and **5i** (85%)] despite the increased acid sensitivity of the starting allenoates **1h** and **1i** toward Lewis acid-catalyzed ionization.

To probe the intermediacy of π -allyl palladium complex **4** and vinylgold complex **3** in this reaction, a crossover experiment between allenoates **1b** and **1h** was examined.²² Specifically, 5 mol % PPh₃AuCl/AgOTf and 5 mol % Pd₂dba₃ 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 ¹H 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.¹⁹ 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 ¹H NMR spectroscopic kinetic experiments revealed a first-order kinetic dependence on the concentration of Pd₂dba₃, confirming the role of Pd in the reaction (at 5 mol % PPh₃AuOTf and 0.10 M **1b**, $k_{obs} = 0.0014$, 0.0016, and 0.0026 M⁻¹ s⁻¹ at 5, 7.5, and 10 mol % Pd, respectively).²³ Over this loading range, the reaction displayed zeroth-order substrate saturation kinetics.²⁴ While the presence of Au was required for the observed product formation, loadings of over 5 mol % PPh3AuOTf 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 ¹H NMR spectroscopy) (eq 2) Specifically, addition of the precatalyst



Pd(PPh₃)₄ did not initiate cross-coupling reactivity but instead quickly regenerated the starting material, presumably by trapping PPh₃AuOTf as the catalytically inactive $[(PPh_3)_2Au]^+$, as was observed when 1 equiv of PPh3 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.^{6,7}

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 π -allyl palladium cations 4 with L = dba and (PPh₃)₂ were identified in the reaction mixture by highresolution MS prior to completion of the reaction, supporting the proposed mechanism.²⁵ 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 π -allyl-Pd alkylation reactions¹⁹).

Extension of the Au/Pd cross-coupling reaction to benzoate substrates established the generality of this methodology. The Auonly rearrangement of benzoates 6a and 6b previously was proposed to proceed through vinylgold oxonium intermediates 7a and 7b (eq 3), followed by protodemetalation.²⁶ Addition of 5 mol % Pd₂dba₃



to 6a-c in the presence of 5 mol % PPh₃PAuCl/AgOTf resulted in cross-coupling of 7a-c to produce isocoumarins 8a-c (89%, 83%, 98% respectively).²⁷ This result demonstrated that the vinylgold intermediate need not be previously reported as observable²⁶ in order to serve as an efficient cross-coupling partner.

In conclusion, we have established a fundamental pattern of dualcatalytic cross-coupling reactivity and turnover with carbophilic Lewis acidic Au catalysts and Lewis basic Pd catalysts. More broadly, this C-C cross-coupling²⁸ method represents a practical alternative to protodemetalation for elaborating the large number of recently reported organogold oxonium intermediates.^{6,7}

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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.

References

- (1) Sammis, G. M.; Danio, H.; Jacobsen, E. N. J. Am. Chem. Soc. 2004, 126, 9928.
- Balmas, G., K., Dallo, H., Balcott, J., Roy, U. K.; Roy, S. J. Org. Chem. 2007, 72, 3100. Shi, Y.; Peterson, S. M.; Haberaecker, W. W., III; Blum, S. A. J. Am. (2)
- (3)Chem. Soc. 2008, 130, 2168.
- For a Ag/Pd cross-coupling reaction limited to carboxylic acids, see: Ma, S.; Shi, Z. J. Org. Chem. 1998, 63, 6387. For a Pd-only reaction, see: Ma, S., Sin, Z. J. Org. Chem. 1996, 60, 0361. For a relong reaction, see. IV S.; Yu, Z. J. Org. Chem. 2003, 68, 6149.
 (5) Chinchilla, R.; Nájera, C. Chem. Rev. 2007, 107, 874.
 (6) Gorin, D. J.; Sherry, B. D.; Toste, F. D. Chem. Rev. 2008, 108, 3351.
 (7) Hashmi, A. S. K. Chem. Rev. 2007, 107, 3180.
 (8) D. K. E. D. L. G. M. G. M. C. 100, 10062.

- (8) Dubé, P.; Toste, F. D. J. Am. Chem. Soc. 2006, 128, 12062.
- (9) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. Org. Lett. 2007, 9, 4081.
- (10) Luzung, M. R.; Mauleón, P.; Toste, F. D. J. Am. Chem. Soc. 2007, 129, 12402.
- (11) We previously reported a series of Au/Pd cross-coupling reactions that were stoichiometric in Au and catalytic in Pd: Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275. While the current manuscript was under revision, another example of a Au/Pd cross-coupling reaction that is also stoichiometric in Au and catalytic in Pd was reported: Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. Angew. Chem., Int. Ed. 2009, 48, 1
- (12) Alali, F. W.; Liu, X. S.; McLaughlin, J. L. J. Nat. Prod. 1999, 62, 504.
- (13) Hill, R. A. Prog. Chem. Org. Nat. Prod. 1986, 49, 2.
- (14) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. J. Am. Chem. Soc. 2008. 130. 17642.
- (15) Kang, J.-E.; Lee, E.-S.; Park, S.-I.; Shin, S. Tetrahedron Lett. 2005, 46, 7431.
- (16) Piera, J.; Krumlinde, P.; Strübing, D.; Bäckvall, J.-E. Org. Lett. 2007, 9, 2235.
- (17) Fürstner, A.; Stelzer, F.; Szillat, H. J. Am. Chem. Soc. 2001, 123, 11863.
 (18) Amatore, C.; Jutand, A.; Mensah, L.; Meyer, G.; Fiaud, J.-C.; Legros, J.-
- Y. Eur. J. Org. Chem. **2006**, 1185. (19) Trost, B. M.; Van Vranken, D. L. Chem. Rev. **1996**, 96, 395.
- (20) Recent reports from Nakao and Hiyama and from our group provide examples of the use of this mechanism as a unified concept for reaction design (see ref 3 and: Nakao, Y.: Yada, A.: Ebata, S.: Hivama, T. J. Am. Chem. Soc. 2007, 129, 2428) A previous example of this mechanistic phenomenon is the Sonogashira reaction (see ref 5).
- (21) No conversion was observed with AgOTf or Pd₂dba₃ separately or with only PPh3AuCl/AgOTf. The combination of AgOTf and Pd2dba3 catalyzed the reaction less effectively alone than it did in the presence of PPh₃AuCl (49% at 1.5 h and 60% at 24 h, compared with 97% at 1.5 h when Au was also present). Employing premade PPh₃AuOTf and Pd₂dba₃ in the absence of Ag confirmed the presence of a purely Au/Pd dual-catalyzed reaction. Addition of $PtCl_2$ did not result in product formation.
- (22) Blum, S. A.; Tan, K. L.; Bergman, R. G. *J. Org. Chem.* **2003**, *68*, 4127. (23) We estimate the error to be $\pm 0.0001-0.0002$ M⁻¹ s⁻¹ on the basis of
- triplicate runs at each loading level. Anslyn, E. V.; Dougherty, D. A. Modern Physical Organic Chemistry; University Science Books: Sausalito, CA, 2006; p 396. (24)
- (25) We considered the possibility that cationic 2 rather than neutral 3 was the cross-coupling partner with 4. In the ethyl series, dealkylation of the oxonium ion did not occur, so we could query this point. Cationic ethyl 9 did not participate in cross-coupling, suggesting that neutral 3 rather than cationic 2 was the more likely transmetalation partner:



- Aikawa, H.; Tago, S.; Umetsu, K.; Haginiwa, N.; Asao, N. Tetrahedron (26)2009, 65, 1774.
- Separately, PPh₃AuCl/AgOTf or Pd₂dba₃ did not catalyze this transformation
- Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angew. Chem., Int. Ed. 2005, (28)44, 4442.

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