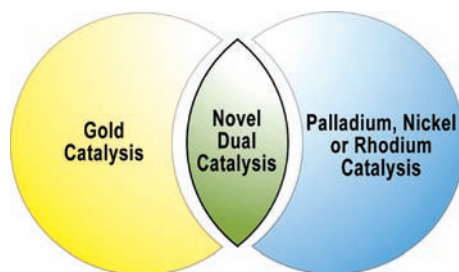


# Organogold Reactivity with Palladium, Nickel, and Rhodium: Transmetalation, Cross-Coupling, and Dual Catalysis

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## CONSPECTUS



Using two transition metals to simultaneously catalyze a reaction can offer distinct opportunities for reactivity and selectivity when compared to using single-metal catalyst systems. Creating dual transition metal catalytic systems is complicated, however, by challenges in predicting compatible reactivities and designing turnover pathways for both metals. In this Account, we describe our development of dual-metal catalysis reactions involving gold and a second transition metal.

The unique rearrangement intermediates accessible through gold-only catalysis, which exploits the soft Lewis acidity of Au(I), make gold an attractive partner for dual-metal catalysis reactions. Because of the complexity of achieving simultaneous turnover of two catalysts and predicting compatibilities, our approach has been to first gain a fundamental understanding of the reactivity of the two metals with each other, both in stoichiometric and monocatalyzed reactions. To this end, we have investigated the combined reactivity of organogold compounds with palladium, nickel, and rhodium.

We narrate the intricacies of turning over two catalysts simultaneously and thereby illuminate the valuable role of fundamental studies in identifying the optimal conditions to promote desirable two-metal reactivity and compatibility. Transmetalation, redox reactivity, and new mechanisms for dual-metal catalytic turnover were probed from this standpoint. We have applied the knowledge gained through these studies to the development of reactions that are dual-catalyzed by gold and palladium, as well as nickel- and rhodium-catalyzed reactions of organogold compounds. More broadly, these new reactions expand the reactivity available to catalytic organogold intermediates via trapping and functionalization reactions with other transition metals.

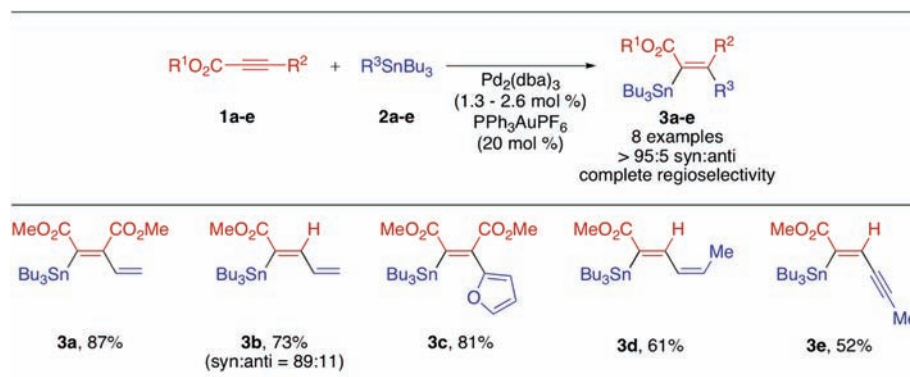
Our investigations reveal strategies useful for designing dual-metal reactions with gold. First, the versatility of gold as a transmetalation partner suggests that many potential methods may exist to intercept catalytic organogold intermediates with a second transition metal. Second, ligands on both metals should be selected carefully in order to prevent catalyst deactivation. Finally, reactions must be designed such that any oxidative steps involving the second metal outcompete undesired reactions with redox-active organogold compounds. We believe that the application of these principles will allow for the design of a diverse set of dual-catalyzed functionalizations befitting the wide variety of gold-catalyzed transformations already established.

## I. Introduction

We have focused our efforts toward dual-catalyzed transformations<sup>1–5</sup> combining gold catalysis with the unique reactivity of a second transition metal.<sup>6</sup> Gold is an attractive partner for dual-catalyzed reactions due to the unique rearrangement products accessible through gold-only catalysis.<sup>7–9</sup>

These rearrangement reactions make use of the soft Lewis acidity of gold(I) to install a wide range of molecular motifs.

These gold-only catalyzed reactions proceed through a common class of intermediates that contain gold–carbon  $\sigma$ -bonds.<sup>7–9</sup> Despite the diversity of products accessible with gold catalysis, the functionalization of the intermediate

**TABLE 1.** Representative Pd- and Au-Cocatalyzed Carbostannylation Products

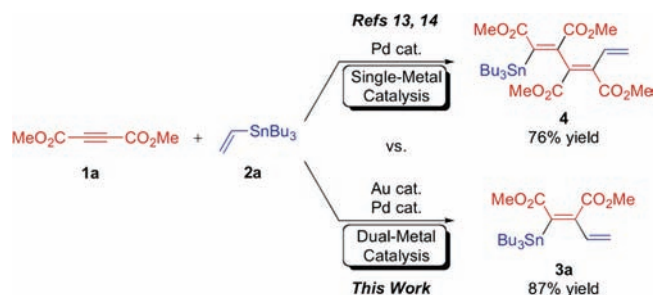
gold–carbon  $\sigma$ -bond remains an underdeveloped field, limited primarily to electrophilic trapping<sup>7–9</sup> and carbene insertion.<sup>10</sup> Concurrent with our work, Au-only cross-coupling reactivity has expanded the functionalization possibilities by employing Au(I)/Au(III) catalysis.<sup>11</sup> We reasoned that dual transition metal reactions would provide reactivity complementary to that which is already available through conventional functionalization methods.

In many instances, the challenges inherent in turning over two catalysts simultaneously have necessitated first studying related processes that are stoichiometric in gold. Developing the fundamental reactivity of organogold compounds with other transition metals has therefore become the pivotal step in connecting two catalytic cycles in the design of new dual-catalytic reactivity. Mechanistic investigations have accompanied the development of these reactions to provide broader insight into dual transition metal turnover and activation strategies, knowledge which facilitates the design of future reactions.

## II. Au and Pd Dual-Catalyzed Carbostannylation of Alkynes

The C–C bond-forming capability of Pd suggested this metal as an appropriate starting point for our study of the reactivity of Au with other transition metals. The wealth of knowledge regarding Pd organometallic transformations<sup>12</sup> allowed for fewer unknown steps while maximizing the opportunities to predict and intercept well-established intermediates. We postulated that the dual usage of Au and Pd catalysts could effect a carbostannylation reaction wherein a Sn–C bond could be broken and added across a C–C multiple bond.<sup>13</sup>

We tested our hypothesis by examining the Pd/Au dual-catalyzed addition of organostannanes across electron-deficient alkynes (Table 1). Notably, the Pd-only catalyzed vinylstannylation of alkynes developed by Shirakawa and

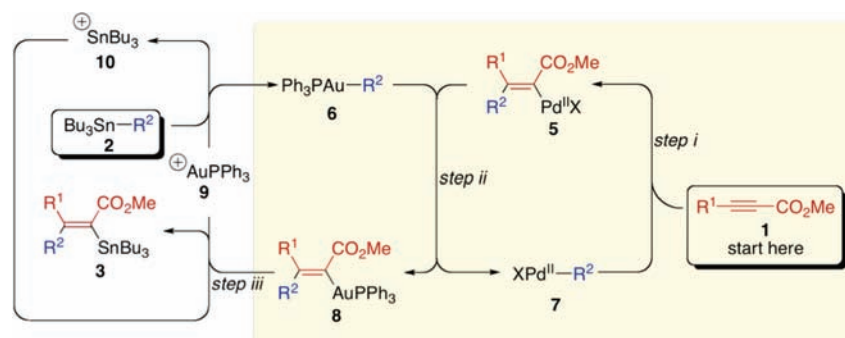
**SCHEME 1.** Contrast between the Pd-Only Catalyzed<sup>14,15</sup> and Au/Pd Dual-Catalyzed Carbostannylation of Alkynes<sup>13</sup>

Hiyama provides predominately double-addition products,<sup>14,15</sup> while our dual-catalyzed reaction is completely selective for monoaddition (Scheme 1). Attempted carbostannylation of alkynes in the presence of gold catalyst but in the absence of palladium did not produce any product.<sup>16</sup> These results provided our first demonstration that dual-metal catalyzed reactions involving gold allowed for reactivity and selectivity different from that available to their single-metal catalyzed counterparts.

The treatment of alkynes **1a–e** with stannanes **2a–e** in the presence of Pd and Au cocatalysts afforded tri- and tetrasubstituted olefin carbostannylation products **3a–e** with excellent regio- and stereoselectivity (Table 1). Our studies into the mechanism of this transformation later led to a proposal that involved a Au–C  $\sigma$ -bond intermediate.

## III. Mechanism of Dual-Catalyzed Carbostannylation: Intermediacy of a Au–C $\sigma$ -Bond

After developing the Pd and Au dual-catalyzed carbostannylation reaction, we elucidated the specific role of each metal catalyst building on a previous working hypothesis.<sup>17</sup> Our proposed mechanism elaborates substrate **1** in three steps: (i) migratory insertion of alkyne **1** into organopalladium intermediate **5**; (ii) transmetalation to Au to afford vinylgold

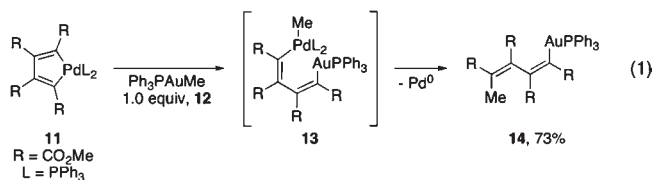
SCHEME 2. Revised Mechanism for the Au/Pd Dual-Catalyzed Carbostannylation of Alkynes<sup>a</sup>

<sup>a</sup>Generation of the active catalysts is omitted for clarity. Starting materials are demarcated with black boxes. The gold-shaded box demarcates a palladium-catalyzed carboauration reaction that operates as a subcycle within the broader carbostannylation cycle.

intermediate **8**; (iii) transmetalation to Sn to generate the final product **3** (Scheme 2). The mechanism involved a series of transmetalation reactions that shuttled the organic fragments between all three metals. Evidence for each these mechanistic steps were provided by independent experiments demonstrating their viability.

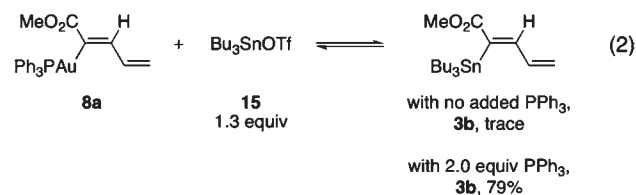
In order to prime the metal catalysts for reactivity, this mechanistic proposal invoked two successive transmetalation reactions of the organic fragment that started on the stannane (i.e., Sn-to-Au and then Au-to-Pd) rather than a direct Sn-to-Pd transfer in order to explain the fact that gold was required to be present in order to produce the observed product selectivity. Consistent with this proposed role of gold as a transmetalation “shuttle”, tributylvinylstannane transmetalated rapidly with triphenylphosphinegold triflate to produce (triphenylphosphine)vinylgold, a process which we could observe separately by <sup>1</sup>H NMR spectroscopy.

We next tested the possible transmetalation of an organic fragment from Pd to Au,<sup>17–20</sup> as proposed in step (ii). Treatment of known palladacycle **11** with methylgold **12** afforded dienyldgold complex **14** in reasonable yield (eq 1). The formation of **14** is consistent with the intermediacy of bimetallic transmetalation intermediate **13**, derived from transmetalation from methyl(triphenylphosphine)gold **12** to palladacycle **11**. This result demonstrates the plausibility of step (ii) of the mechanism.



In order to probe the viability of the previously unknown transmetalation of an organic fragment from Au to Sn as proposed in step (iii), vinylgold compound **8a** was treated

with the stannylating reagent Bu<sub>3</sub>SnOTf (eq 2). Transmetalation product **3b** was observed by <sup>1</sup>H NMR spectroscopy in accordance with the mechanistic hypothesis. The addition of PPh<sub>3</sub> was necessary in order to sequester the gold triflate coproduct as [Au(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup> in a way that mimicked catalytic conditions in which cationic gold would be consumed by catalyst turnover.



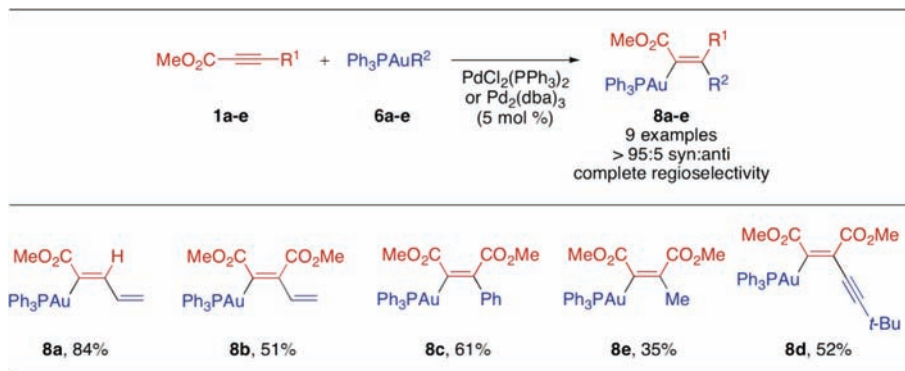
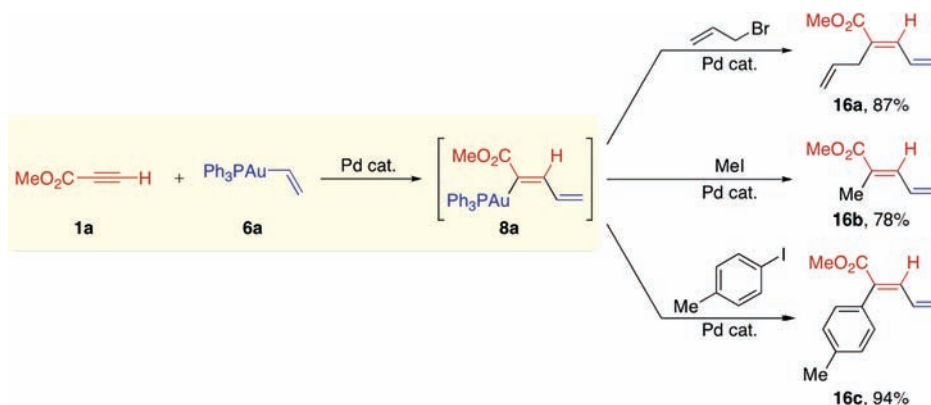
We noticed that the mechanism proposed in Scheme 2 suggested a previously unknown reaction: palladium-catalyzed carboauration of alkynes. This Pd-only catalyzed carboauration reaction formed part of the dual-catalytic cycle for carbostannylation, highlighted by the yellow box in Scheme 2. Indeed, we discovered that catalytic organogold intermediate **6** could be replaced by a stoichiometric organogold reagent in order to isolate carboauration products **8a–e** (Table 2)<sup>17</sup> with equally high and analogous regio- and stereoselectivity to that which occurs in the overall carbostannylation reaction.

Through our investigation of the carbostannylation reaction mechanism, the Pd/Au and Sn/Au transmetalation reactions and a palladium-catalyzed carboauration reaction were revealed. Knowledge of these fundamental processes has formed a basis for other studies within our laboratory.

#### IV. Pd-Catalyzed Cross-Coupling of Vinylgold Reagents

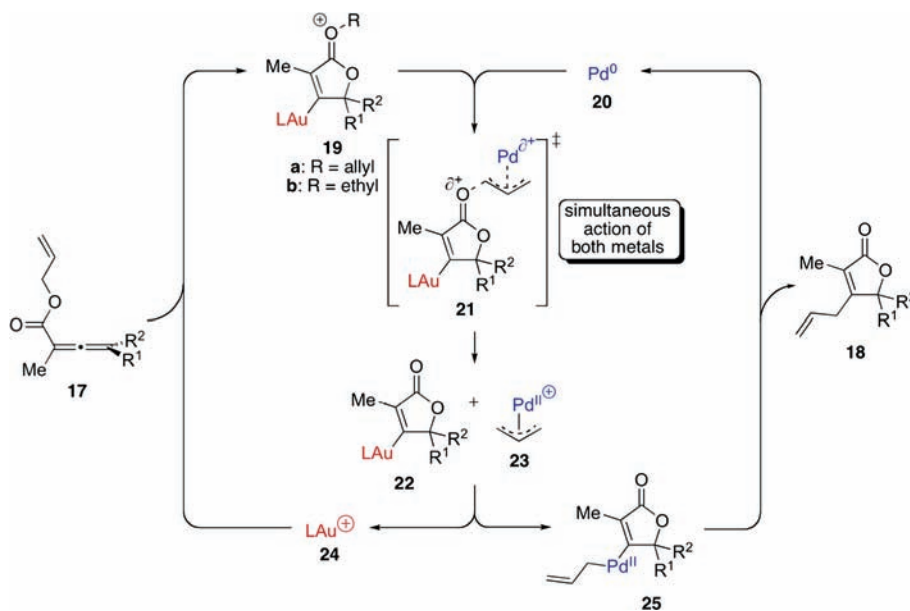
Inspired by the Au/Pd transmetalation that was uncovered during the course of our investigation into the carbostannylation mechanism, we developed a Pd-catalyzed cross-coupling of vinylgold reagents.<sup>17</sup> After the completion of the carboauration

TABLE 2. Representative Pd-Catalyzed Carboauration Products

SCHEME 3. One-Pot Tandem Carboauration of Alkynes and Cross-Coupling Reaction<sup>a</sup>

<sup>a</sup> Yellow-shaded box demarcates palladium-catalyzed carboauration. Unshaded portion shows palladium-catalyzed cross-coupling reactions of organogold compounds.

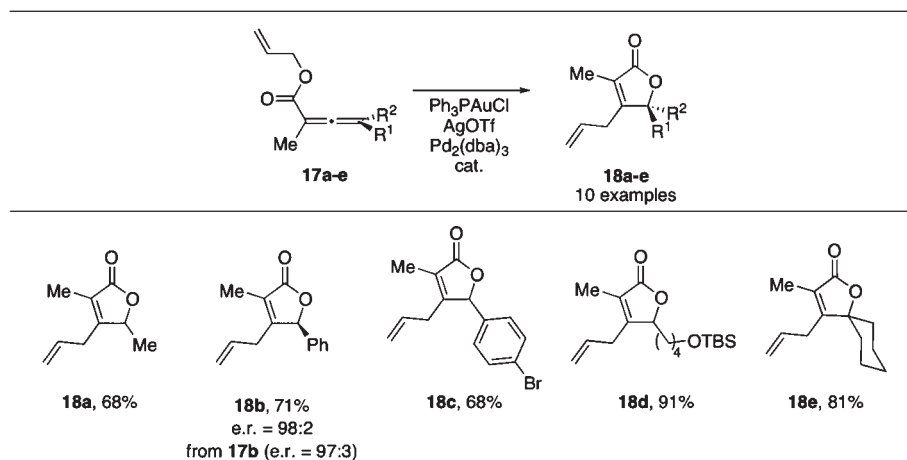
SCHEME 4. Proposed Mechanism for the Au and Pd Dual-Catalyzed Cyclization and Cross-Coupling Reaction



reaction forming **8a** (Scheme 3, yellow-shaded box), the addition of organohalides to the crude reaction mixture

generated cross-coupled products **16a–c** in high conversion (Scheme 3). The organogold reagents participated in



**TABLE 3.** Representative Products of the Pd and Au Dual-Catalyzed Rearrangement of Allenates

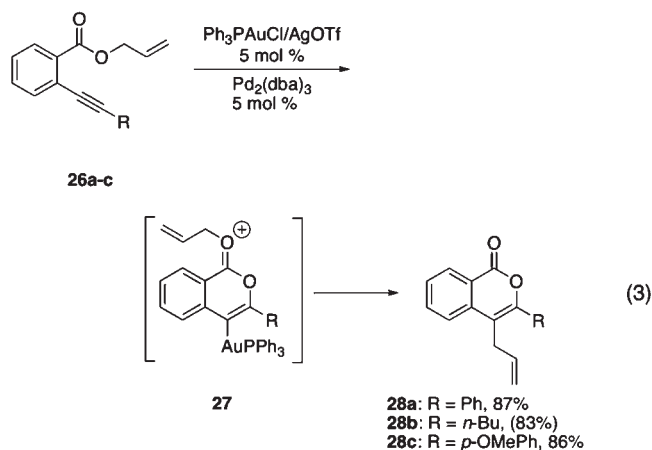
allylic (**16a**), alkyl (**16b**), and aryl (**16c**) cross-coupling reactions. These reactions were efficiently catalyzed by the residual Pd present in the crude carboauration reaction mixture. In each case, control reactions established that no reaction occurred in the absence of Pd. To the best of our knowledge, this is the first example of Au and Pd cross-coupling reactivity to be well-defined in the literature with a characterized organogold intermediate.<sup>19</sup> After our initial report, subsequent publication by the Hashmi group indicated that the idea of a stoichiometric Au/catalytic Pd cross-coupling reactivity manifold occurred to their group during a similar time frame.<sup>21</sup>

## V. Au and Pd Dual-Catalyzed Cyclization and Cross-Coupling Reaction

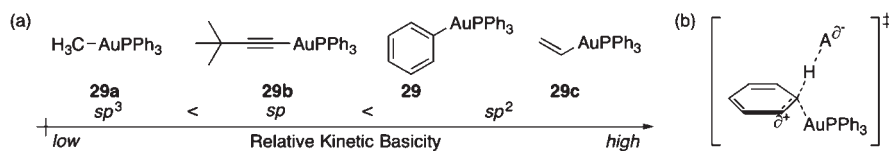
Through the Au/Pd cross-coupling reaction, we had established grounds from which to effectively pursue our goal of developing dual-metal catalyzed transformations with gold. The practical considerations of designing a reaction with two intercepting catalytic cycles are nontrivial at best.<sup>1–5,22,23</sup> We decided to combine the capacity of Au for cyclizations<sup>7–9</sup> with the C–C bond-forming and oxidative-addition power of Pd catalysis. In this vein, we were inspired by a timely report by Hammond et al. detailing the spectroscopic characterization of organogold rearrangement product **19b** (Scheme 4).<sup>24</sup> We considered that replacement of the ethyl group with allyl (**19a**) would prime a rearrangement of allyl allenates **17a–e** to substituted butenolides **18a–e** that proceeded via a unique mechanism that involved simultaneous activation of the substrate by gold and palladium (Table 3).<sup>25</sup>

A likely dual-catalytic cycle is shown in Scheme 4. Cationic gold complex **24** cyclizes allenolate **17** to organogold oxocarbenium **19a**,<sup>24</sup> activating the allyl group for oxidative addition<sup>26</sup> by Pd through bimetallic transition state **21**.

Transmetalation of neutral vinylgold **22** with the intermediate  $\pi$ -allyl Pd complex **23** then regenerates cationic gold catalyst **24**. Substituted butenolide **18** is then formed by reductive elimination from diorganopalladium intermediate **25**. Crossover experiments confirmed the intermolecular nature of this reaction. In order to highlight the potential generality of Au/Pd dual-catalyzed transformations, we also applied this reaction to the synthesis of substituted isocoumarins **28a–c** from benzoates **26a–c** (eq 3). Control experiments confirmed that this reactivity could not be attributed to either metal catalyst alone.



Our investigation into Pd sources revealed the importance of selecting the proper ligand for catalyst **20**. Specifically, phosphine ligands on Pd precatalysts were found to have an inhibitory effect on dual catalysis. When the optimal precatalyst Pd<sub>2</sub>(dba)<sub>3</sub> was replaced by the precatalyst Pd(PPh<sub>3</sub>)<sub>4</sub>, no formation of **18** was observed. Presumably, this complete inhibition of reactivity was due to the formation of catalytically inactive [Au(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup> OTf<sup>−</sup>, which formed



**FIGURE 1.** (a) Hybridization dependence on protodeauration rate. (b) Proposed transition state showing the donation of the Au–C bond into the organogold  $\pi$ -system.

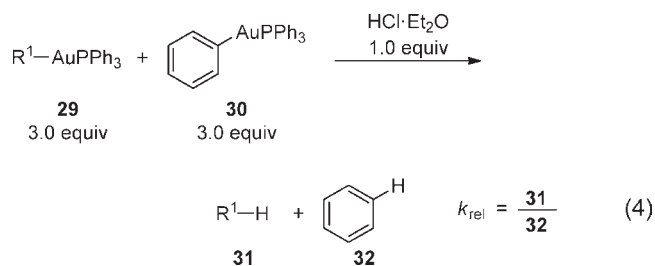
by scavenging the labile phosphine ligand from palladium. Spectroscopic identification indicated that this bisphosphine gold complex formed rapidly upon addition of stoichiometric triphenylphosphine to  $\text{PPh}_3\text{AuOTf}$ .

In addition to their ability to install a heterocyclic scaffold and to functionalize organogold intermediates, these reactions are interesting to us for the simultaneous metal–substrate–metal interactions that give rise to this unique reactivity. The term “dual-metal catalysis” encompasses many different mechanisms. As shown in the gold/palladium mechanism detailed in Scheme 4, we consider that the gold catalyst potentiates the subsequent palladium-catalyzed oxidative addition step: both metals communicate through substrate **17** via an electronic “push/pull” that activates the substrate toward oxidative addition.<sup>26</sup> We find it helpful conceptually to distinguish the potentiated activation as a “catalyzed catalysis” mechanism to differentiate it from more common dual-metal catalysis mechanisms wherein the two metals act in sequence. From a broad perspective, this dual-catalytic cross-coupling method presents an alternative means to functionalize the numerous organogold intermediates proposed in many catalytic cycles.<sup>7–9</sup> We therefore view these two rearrangements more as conceptual advances in reaction design rather than a new route to a specific class of compounds, illustrative of our paradigm that gold and a second transition metal catalyst can provide reactivity not accessible with only a single catalyst. Just as our investigation of the Au/Pd transmetalation step allowed us to develop this dual-catalyzed rearrangement, we envision that similar advances in the knowledge of fundamental metal–metal compatibility will allow for the future design of additional dual-catalyzed reactions.

## VI. Relative Kinetic Basicities of Organogold Compounds

In order to use a second metal catalyst to intercept organogold intermediates, a deeper knowledge of the stability and reactivity of organogold compounds was needed. Seeking to quantitatively understand the susceptibility of catalytic organogold intermediates toward protodeauration, which is commonly employed as a catalyst-regenerating step in

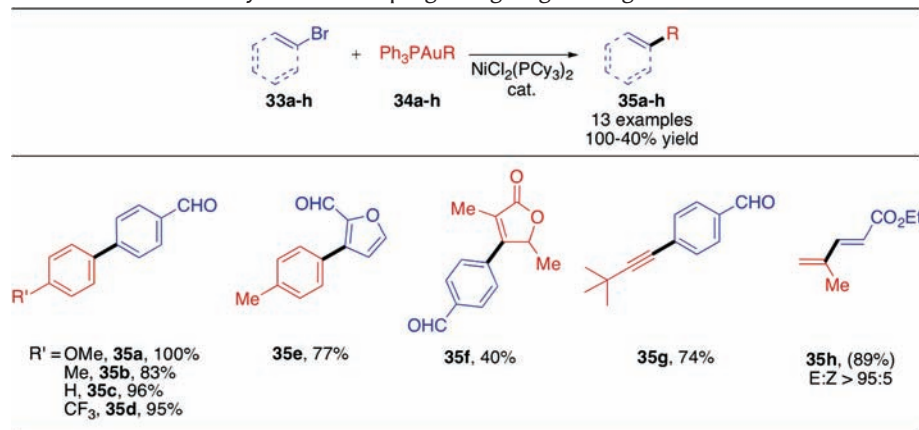
gold-only catalysis,<sup>7–9,27</sup> we examined the kinetic basicities of a variety of organogold compounds (**29**). Quantitative data on the relative kinetic basicities of organogold compounds were obtained relative to phenyl(triphenylphosphino)gold(I) (**30**) through a series of competition experiments (eq 4).<sup>28</sup> A full table of relative protodeauration rates is available in the original publication, but we find the broader conclusion of these results to merit highlighting in this narrative. The basicities of organogold compounds did *not* follow the hybridization trend that we expected on the basis of the  $\text{pK}_a$  values for the corresponding carbon acids (i.e., basicity increases  $\text{sp} < \text{sp}^2 < \text{sp}^3$ ). Organogold compounds instead exhibited a different basicity trend:  $\text{sp}^3 < \text{sp} < \text{sp}^2$  (Figure 1a). In analogy to the role of hyperconjugation in the protodemetalation of group 14 organometallics,<sup>29</sup> we reasoned that our hybridization dependence could be explained by a rate enhancement stemming from a hyperconjugative donation from the Au–C  $\sigma$ -bond into the  $\pi$ -system during the transition state (Figure 1b). Because  $\text{sp}^3$ -hybridized organogold compounds do not have a  $\pi$ -system, they are not subject to this donation and therefore undergo protodeauration at a slower rate. This understanding of the involvement of the organogold  $\pi$ -system in steps that functionalize the C–Au  $\sigma$ -bond has extended into other studies within our group: subsequent experimental data suggested a transition state analogy between protodeauration and transmetalation (see section VIII).



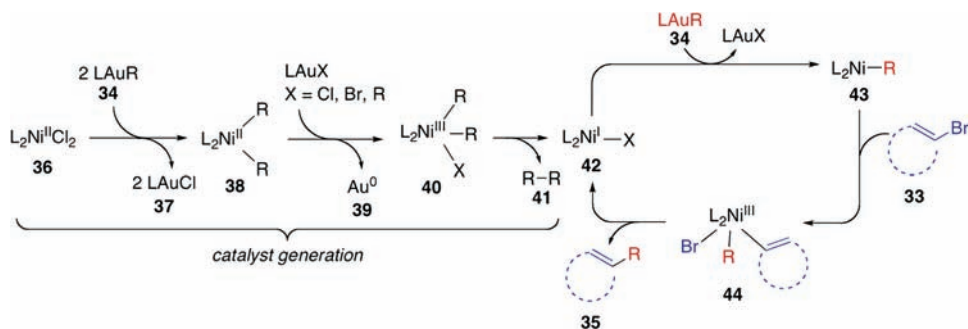
## VII. Ni-Catalyzed Cross-Coupling of Organogold Reagents

To this point in our research program, our investigation of dual-metal reactivity had been focused on Au and Pd. These successes taught us valuable lessons in reaction design,

TABLE 4. Representative Products of the Ni-Catalyzed Cross-Coupling of Organogold Reagents



SCHEME 5. Proposed Mechanism for Ni-Catalyzed Cross-Coupling of Organogold Compounds



allowing us to expand our aim to other combinations of two transition metals. We selected Au and Ni as our next target. Offering reactivity both parallel to<sup>30</sup> and unique from that of Pd,<sup>31</sup> Ni offered the potential to build on our previous experience with Pd while also providing access to eventual different classes of bond disconnections. Unlike Pd, however, Ni is more readily susceptible to single-electron redox processes, and the stability of organogold(I) compounds in the presence of a single-electron reducing metal was uncertain. We therefore explored the compatibility of the two metals<sup>18</sup> through a Ni-catalyzed cross-coupling of organogold reagents.<sup>32</sup> In the presence of a Ni catalyst, we found organogold reagents **34a–h** to undergo cross-coupling reactions with aryl and vinyl bromides **33a–h** in high yield under mild conditions (Table 4).

In analogy to other Ni-catalyzed cross-coupling reactions<sup>33</sup> and on the basis of EPR studies in our group, this reaction likely proceeds through a Ni(I)/Ni(III) catalytic cycle (Scheme 5). Notably, single-electron reduction of the organogold reagent was not detected under standard reaction conditions<sup>34</sup> after the Ni(I) catalyst-generating steps despite the potential thermodynamic favorability of this redox reaction.<sup>35</sup> Nevertheless, a reaction redox between an

organogold oxidant and nickel precatalyst **36** may be operative in generating Ni(III) precatalyst **40**, although the organobromide could serve as an alternative oxidant.<sup>36</sup> Additional insight into the redox processes available to organogold complexes and nickel is provided by examining the substrate scope illustrated in Table 4: electron-poor organobromides were required for high cross-coupling product yields. When electron-rich organobromides were employed, gold mirror was observed and cross-coupling product yields were low. In this case, the slower oxidative addition reactions of electron-rich organobromides<sup>37</sup> may permit kinetically competitive reduction reactions of organogold compounds by nickel intermediates to predominate. These results illuminate the valuable role of fundamental studies in identifying the optimal conditions that promote desirable two-metal reactivity and compatibility.

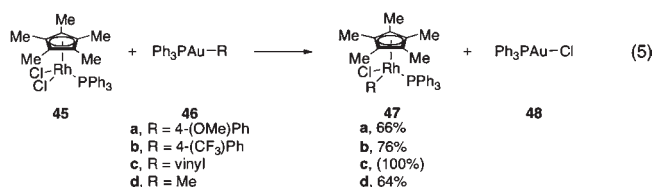
This new cross-coupling reaction is an early demonstration of the compatibility of homogeneous nickel and organogold complexes with one another.<sup>18</sup> This reactivity knowledge formed the basis for an investigation currently underway in our group to combine the unique reactivity of both Au and Ni catalytically. Using the lessons learned from

our Au/Pd studies as a guide, we believe that future Au/Ni dual-catalyzed transformations will be accessible.

## VIII. Au/Rh Transmetalation and Rh-Catalyzed Conjugate Addition to Alkynes

Most recently, we have expanded to studying the reactivity of Au and group IX metals. In order to further increase the scope of reactivity available to the many reported organogold intermediates beyond cross-coupling, Rh was selected as our next goal due to its well-documented capability for unique catalytic reactions.<sup>38</sup> As was the case with the Au/Pd and Au/Ni dual-metal transformations, the transmetalation of an organic fragment between the two metals would be the pivotal step in any potential Au/Rh dual reactivity.

Aryl-, vinyl-, and methylgold compounds **46a–d** were found to undergo transmetalation with Rh(III) complex **45** to afford organorhodium(III) products (eq 5).<sup>39</sup> Highlighting the stability of both organogold and rhodium(III) complexes, these transmetalation reactions could be conducted in vessels open to air and in wet solvents without diminished yields.

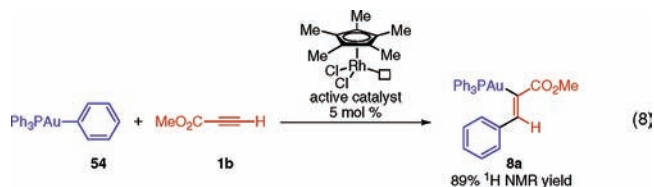
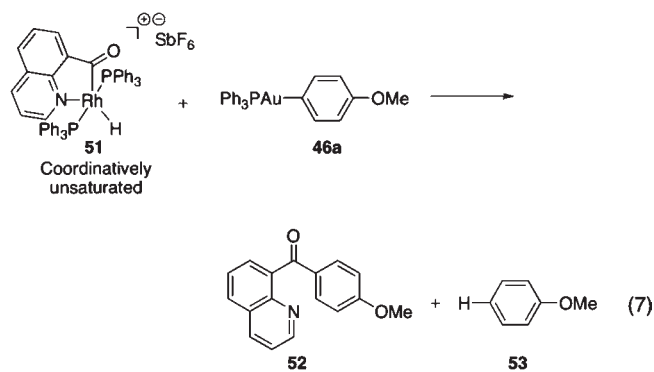
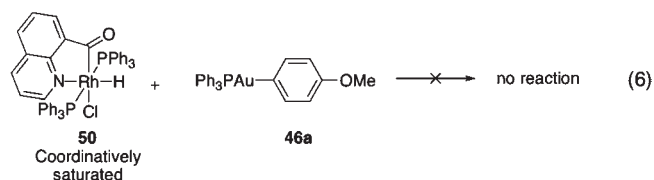


In order to better design future Au/Rh catalytic reactivity, we decided to first gain knowledge about the fundamental transmetalation step; advances in the understanding of transmetalation historically have been used to aid in the design of efficient catalytic cycles involving other metals.<sup>40</sup> Several transition states for the Au/Rh transmetalation reaction were considered based upon proposed transition states for other transmetalations (Figure 2). In transition state **49a**, the reaction occurs through a four-centered transition state with no loss of ligands.<sup>41</sup> Transition state **49b** requires the loss of a ligand from Rh to form an open coordination site,<sup>42</sup> and **49c** shows the loss of a ligand from Rh to allow for bimetallic  $\pi$ -complex character during transmetalation.<sup>43</sup> Notably, transition state **49c** is analogous to that previously reported for the metathesis between HCl and arylgold compounds (i.e., protodeauration, Figure 1b, section VI<sup>28</sup>). This model is also in accordance with the bimetallic Au–Au  $\pi$ -complex reported by Schmidbaur et al.<sup>44</sup>

The nature of the coordination environment about Rh was first examined in order to distinguish coordinatively saturated transition state **49a** from **49b** and **49c**. Addition of

an excess of PPh<sub>3</sub> to the otherwise effective reaction of Rh complex **45** and organogold compound **49a** completely inhibited transmetalation. This experiment suggested that the PPh<sub>3</sub> ligand must dissociate from Rh prior to transmetalation, thereby eliminating **49a** as a plausible transition state.

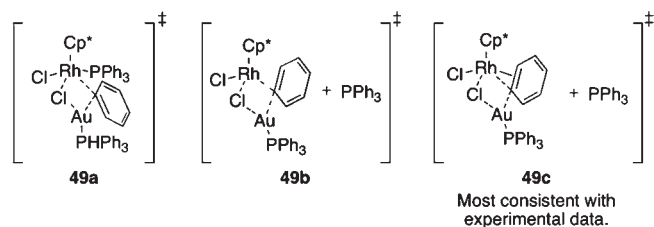
This mechanistic evidence had direct implications for the development of a C–C bond forming reaction between acylrhodium complex **50** and organogold complexes. We found that coordinatively saturated Rh **50** was unable to react with organogold **46a** (eq 6) because the required open coordination site was unavailable. Upon chloride abstraction to provide an open coordination site, the organogold complex transmetalated with the acylrhodium complex, allowing for formation of a new C–C bond (eq 7). An understanding of the optimal coordination environment of Rh for the Rh/Au transmetalation also allowed the rational design of a Rh-catalyzed addition of organogold complexes via conjugate addition chemistry (eq 8).<sup>39</sup>



## IX. Guiding Principles for Dual-Metal Reactivity with Gold

Our investigations indicate several broad lessons that are useful for the planning of new dual-metal reactions with Au. A primary cause of the current dearth of dual-catalyzed





**FIGURE 2.** Possible transition states for the Au/Rh transmetalation reaction with varying coordination environments about Rh.

reactions with gold may be the absence of a unified design strategy to overcome the challenges of compatible reactivity and simultaneous catalyst turnover. We have found it helpful to follow three guiding principles in our design of dual-metal reactions:

**1. Gold Is a Versatile Transmetalation Partner.** Gold has been shown to undergo transmetalation reactions with Ti,<sup>18,45,46</sup> Zr,<sup>45</sup> Hf,<sup>46</sup> V,<sup>46</sup> Nb,<sup>46</sup> Cr,<sup>46,47</sup> Re,<sup>48</sup> Fe,<sup>18</sup> Co,<sup>18</sup> Rh,<sup>39</sup> Ir,<sup>49</sup> Ni,<sup>18,32</sup> Pd,<sup>17–19,25</sup> Pt,<sup>18,50</sup> Au,<sup>18</sup> Hg,<sup>51,52</sup> B,<sup>11,53,54</sup> Si,<sup>55,56</sup> and Sn.<sup>13</sup> We believe that future studies will extend this compatibility of Au to many of the remaining *d* block elements. The breadth of this accessible transmetalation reactivity strongly suggests an abundance of potential methods to intercept and functionalize catalytic organogold intermediates by harnessing the unique reactivity of many different transition metals.

**2. Ligands Must Be Chosen Judiciously.** The weakly coordinating counterions typically required for gold(I) catalysis (e.g., OTf, SbF<sub>6</sub>) render the catalyst subject to deactivation by labile phosphine ligands on the second metal through the formation of the bisphosphine Au cation (e.g., [Au(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>). In our Au and Pd dual-catalyzed synthesis of butenolides and isocoumarins (section V),<sup>25</sup> the olefinic ligand dba was found to be the optimal Pd ligand to avoid Au catalyst deactivation.

Our investigation of the Rh–Au dual-metal system revealed the need for an open coordination site on Rh prior to transmetalation. We postulate that a coordinatively unsaturated intermediate may also be a prerequisite in the transmetalation of gold with other transition metals. Therefore, ligands that favor a coordinatively saturated second transition metal, such as chelating phosphines or nonlabile halides, may inhibit the interception of catalytic organogold intermediates.

**3. Oxidative Steps Involving the Second Metal Compete with Single-Electron Transfer to Au.** Organogold compounds are not redox innocent. Dual-metal reactions with Au must be designed such that any desired reactivity of the

second metal outcompetes the single-electron oxidation by Au. In our nickel-catalyzed cross-coupling reaction (section VII),<sup>32</sup> only electron poor aryl bromides were sufficiently fast oxidants for Ni<sup>I</sup> to allow for the desired reaction to occur; electron rich aryl bromides, which undergo oxidative addition at a lower rate,<sup>37</sup> resulted predominately in single-electron reduction of the organogold(I) compounds leading to homocoupling of the organogold fragment.

Recently, Gagné reported a competitive reduction and homocoupling of organogold compounds by palladium that provides additional insight. During an attempted Pd<sup>0</sup>-catalyzed cross-coupling of aryl triflates with organogold compounds,<sup>57</sup> the low-valent Pd intermediates were oxidized exclusively by Au<sup>I</sup>, resulting in Au mirror and the homocoupled product, possibly because the C–OTf oxidative addition was sluggish.<sup>41,58</sup> Notably, the use of the NHC ligands IPr and IMes on Au inhibited this redox reactivity, indicating that strongly donating ligands<sup>59</sup> may reduce single-electron reduction of catalytic Au in the presence of redox active metals.<sup>60</sup>

Promoting the desired oxidative-addition reaction via Lewis acid catalysis<sup>31d,e</sup> is a successful strategy for outcompeting the potential undesired single-electron transfer to gold. This strategy was demonstrated in our dual-catalyzed preparation of butenolides and isocoumarins (section V), wherein the gold Lewis acid lowered the barrier for palladium-catalyzed deallylation/oxidative addition.

## X. Conclusions and Outlook

In the past five years, our group has developed the compatibility and reactivity of Au with other transition metals. Mechanistic understanding gained through the investigation of the Au/Pd transmetalation allowed us to develop several Pd-catalyzed and Au/Pd dual-catalyzed reactions. The broad applicability of the Pd-catalyzed cross-coupling reaction of stoichiometric organogold compounds has since been demonstrated by the groups of Hashmi,<sup>21,61</sup> Sarandeses and Pérez Sestelo,<sup>62</sup> and Sarkar.<sup>63</sup> Echavarren et al. have further noted the possibility that a reaction previously thought to be catalyzed only by Au is in fact cocatalyzed by trace Pd impurities.<sup>64,65</sup> We envision that our investigations of the Au/Ni cross-coupling and Au/Rh transmetalation reactions could form a similar foundation for dual-catalyzed reactivity. Such functionalization methods are accessible even to acid-sensitive catalytic intermediates through understanding the basicities of organogold compounds. All of these advances were made possible by first gaining new

fundamental knowledge about the stability and reactivity of organogold compounds in the presence of other transition metals and potentially competing Brønsted acids. Pioneering studies in gold catalysis have given the synthetic community a variety of methods to form carbon–gold bonds; in light of ongoing work with dual-metal gold reactivity in our group and others, we are beginning to access a correspondingly diverse set of tools with which to functionalize them.

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## FOOTNOTES

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