

Au–Pd Bimetallic Catalysis: The Importance of Anionic Ligands in Catalyst Speciation

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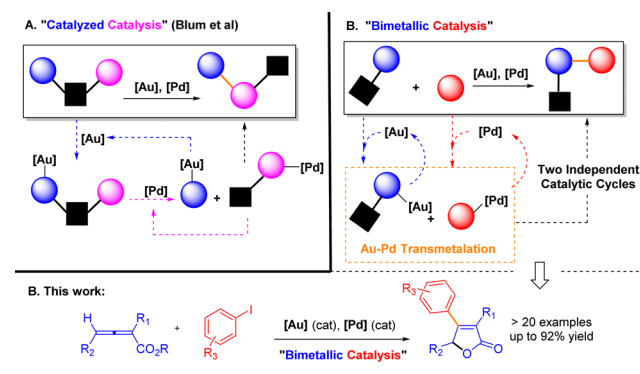
S Supporting Information

ABSTRACT: Synergistic gold–palladium catalytic processes have been intensively sought during the past decade, because the combination of the carbophilic Lewis acidity of Au with the redox properties of Pd within a catalytic cycle is particularly appealing for the synthesis of novel functionalized compounds. We demonstrate here the feasibility of a Au–Pd bimetallic catalytic system based on the generation of competent Au and Pd species by anionic ligand exchange. This strategy enabled the preparation of a variety of substituted butenolides in a simple and efficient way.

Transmetalation with stoichiometric amounts of toxic and expensive main-group organometallic derivatives is often involved in palladium-catalyzed transformations. More user-friendly bimetallic catalytic systems in which two transition metals work synergistically¹ in independent catalytic cycles connected by a transmetalation step have thus been sought.² In this context, the tandem Au–Pd results particularly attractive given the privileged carbophilicity and thus unparalleled ability to activate unsaturated moieties of the former³ and the efficient redox turnover of the latter. A few reports have already featured the Pd-catalyzed cross-coupling of aryl-, vinyl-, alkynyl-, and alkylgold stoichiometric reagents with aryl halides.⁴ In contrast, besides the seminal work of Laguna and Sarkar on Sonogashira reactions in which Au replaced the more classical copper(I) salts,⁵ cooperative Au–Pd catalytic cross-couplings have only been scarcely demonstrated. Blum et al. pioneered the concept of Au–Pd “catalyzed catalysis”⁶ to describe processes in which the catalytic cycle of Pd can only be turned on once the catalytic cycle of Au has been initiated (Scheme 1A). Later work by Hashmi⁷ and Gagné⁸ demonstrated the difficulty of implementing two truly independent Au–Pd catalytic cycles. Even in substrates that enable an intramolecular transmetalation step,⁷ envisioned to be rate-determining in these processes, only moderate yields of the cross-coupling products could be obtained. More importantly, in the above-mentioned cases, comparable amounts of the desired products were also obtained in the presence of Pd or Ag alone, thus pointing toward Pd–Ag competent catalytic cycles which question the occurrence of an unambiguous Au–Pd catalytic transmetalation.⁹

The development of bimetallic Au–Pd catalyzed cross-coupling reactions is hampered by multiple challenges. First, the simultaneous turnover of the two metals is cumbersome, since the best working conditions for each metal might not to

Scheme 1. (A) Catalyzed Catalysis. (B) This Work: Au–Pd Bimetallic Catalysis via Au–Pd Transmetalation



be compatible.⁸ Second, the Au and Pd intermediates generated in situ need to be stable toward proto-demetalation or reaction with other species present in the reaction media. In addition, the recycling of the active metal catalysts after the first turnover needs to be highly efficient, which seems to be particularly challenging for Au, as formation of catalytically inactive neutral LAuX (X = halogen) complexes is thermodynamically driven. Finally, the transmetalation between the two catalytic species, present in scarce amount in the reaction media, also requires exquisite control to prevent competing homocoupling or decomposition reactions. We thus set out to develop a Au–Pd intermolecular synergistic catalytic process using the Au-catalyzed cycloisomerization of allenates and the Pd-catalyzed cross-coupling of aryl/heteroaryl iodides as benchmark reactions (Scheme 1B). Here we present the realization of this concept with the preparation, in high yields, of a variety of functionalized butenolides, motifs commonly found in many biologically relevant natural products and drugs,¹⁰ via bimetallic Au–Pd catalysis.

Allenoate **1** and iodobenzene (**2a**) were selected as model substrates to explore the desired reactivity (Table 1).¹¹ Our study commenced using PPh₃AuCl in high load (20 mol%), [PdCl₂(dppf)] (5 mol%), and an excess of **2a** over the allene with binary mixtures of solvents containing MeOH at 70 °C. Small amounts of product could be detected in the reaction mixtures upon addition of an excess of NaOAc (Table 1, entry 1). PPh₃AuCl was replaced by the more active PPh₃AuOAc, which combined with 2 equiv of CsOAc and an optimal ratio **1**:**2a** (2:1) in a more concentrated mixture at higher

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Table 1. Optimization of the Reaction Conditions¹¹

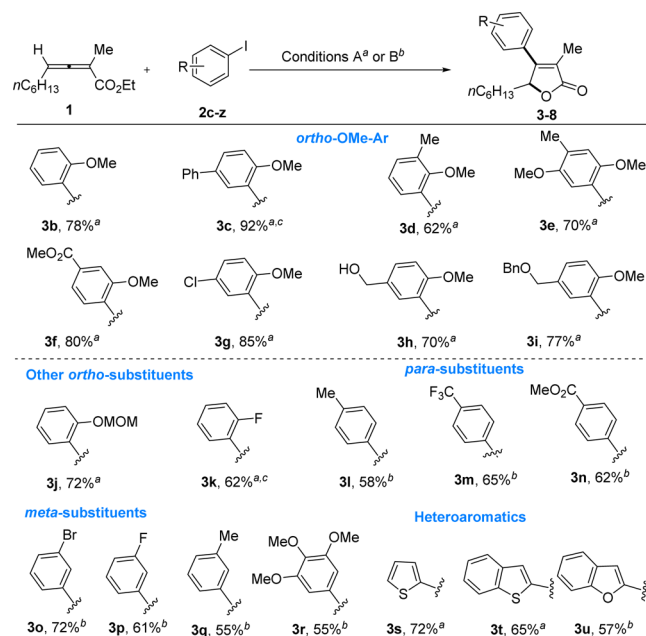
entry	reaction conditions	product, yield (%) ^a
1	Ph ₃ PAuCl (20 mol%), [PdCl ₂ (dppf)] (5 mol%), NaOAc (200 mol%), DCE/MeOH (1:1) [0.3 M], 70 °C, 21 h; Y = 1 equiv; 2a , Z = 1.5 equiv	3a , 5 ^{b,c}
2	Ph ₃ PAuOAc (5 mol%), [PdCl ₂ (dppf)] (5 mol%), CsOAc (200 mol%), DCE/MeOH (1:1) [1.2 M], 80 °C, 21 h; Y = 2 equiv; 2a , Z = 1 equiv	3a , 17 (24 ^b)
3	(<i>p</i> -CF ₃ Ph) ₃ PAuCl (5 mol%), [PdCl ₂ (dppf)] (5 mol%), CsOAc (10 mol%), toluene/MeOH (1:1) [1.2 M], 80 °C, 21 h; Y = 2 equiv; 2a , Z = 1 equiv	3a , 46
4	(<i>p</i> -CF ₃ Ph) ₃ PAuOAc (5 mol%), [PdCl ₂ (dppf)] (5 mol%), CsOAc (10 mol%), toluene/MeOH (1:1) [1.2 M], 80 °C, 21 h; Y = 2 equiv; 2b , Z = 1 equiv	3b , 78 ^d (conditions A)
5	as entry 4, but with [PdCl ₂ (dppf)] (2.5 mol%)	3b , 67 ^d
6	as entry 4, but with (<i>p</i> -CF ₃ Ph) ₃ PAuOAc (2.5 mol%)	3b , 46 ^d
7	as entry 4, but with [PdCl ₂ (DPEPhos)] (5 mol%), 100 °C	3b , 78 ^d (conditions B)

^aIsolated yield after column chromatography in silica gel. ^bYields determined by GC-MS using dodecane as internal standard. ^cIn the initial screening, reactions were carried out in parallel reactor vessels. All others were performed in a J-Young Schlenk tube or with a bullet-shaped Supelco vial. ^dReaction scale: 0.48 mmol (limiting reagent). Reaction scale in all the other entries: 0.14 or 0.24 mmol. [PdCl₂(DPEPhos)] = dichloro[bis(2-(diphenylphosphino)phenyl)-ether]palladium(II).

temperature afforded **3a** in 17% yield (Table 1, entry 2). To further increase the reactivity of the Au catalyst, different ancillary ligands were tested, of which (*p*-CF₃Ph)₃P turned out to be the most suitable. In subsequent experiments, the amount of CsOAc could be significantly reduced to a sub-stoichiometric amount in a toluene/MeOH (1:1) solvent mixture, furnishing **3a** in 46% yield (Table 1, entry 3). When these optimized conditions were applied to substrate **2b**, the desired cross-coupled product **3b** could be isolated in a satisfying 78% yield (Table 1, entry 4). Fine-tuning the amounts and ratios of CsOAc and both metals did not improve the yield (Table 1, entries 5 and 6). Diverse bidentate phosphines, which seem to prevent ligand exchange between the two catalysts,¹² were also tested on the Pd catalyst. DPEPhos-palladium(II) dichloride at 100 °C afforded the desired product in yields comparable to those obtained under the standard conditions (Table 1, entry 7).

With these two sets of optimal reaction conditions in hand (Table 1, entries 4 and 7, conditions A and B, respectively), we set out to explore the scope of this Au–Pd-catalyzed process (Scheme 2). Under conditions A, an array of 2-iodoanisole derivatives afforded the corresponding aryl-substituted lactones in good to excellent yields (**3b–i**). Free alcohol, ether, and ester groups were tolerated under these conditions. In addition, the reaction is chemoselective, as shown by the efficient transformation of 4-chloro-2-iodoanisole, which furnished **3g** in 85% yield without participation of the C_{sp}²–Cl bond. MOMO- and F-*ortho*-substituted aryl iodides could be also successfully cross-coupled in good yields, as shown by products **3j** and **3k**. Coupling partners bearing electron-donating or electron-withdrawing groups in the *para*- and/or *meta*-position broadened the scope of this reaction, as the corresponding

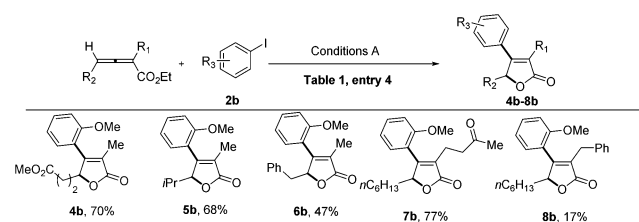
Scheme 2. Substrate Scope on Aryl/Heteroaryl Iodides



^aConditions A, see Table 1, entry 4. ^bConditions B, as conditions A but with [PdCl₂(DPEPhos)] (5 mol%), 100 °C, see Table 1, entry 7. ^cAverage of two independent runs.

products (**3l–r**) could also be isolated in synthetically useful yields using conditions B. Compound **3o**, featuring a potentially competitive C_{sp}²–Br bond, showcased once again the exquisite chemoselectivity of this cross-coupling reaction. The reactivity of different heteroaromatic rings was investigated next. We were pleased to find that our bimetallic Au–Pd catalytic system successfully furnished thiophene-, benzothiophene-, and benzofuran-substituted butenolides **3s–u** in good yields under both sets of reaction conditions.

Variations in the allene were also well tolerated (Scheme 3). Ethylcarboxymethyl, isopropyl, and benzyl groups could be

Scheme 3. Substrate Scope on Allenolates^a

^aConditions A, see Table 1, entry 4.

installed at the C₄ position of the allene, providing the corresponding butenolide derivatives (**4b**, **5b**, and **6b**) in good yields.

Variations at C₂ could also be accommodated, as shown by the reactions producing **7b** and **8b**. Double substitution at C₄ was not pursued, as these allenolates are known to efficiently cyclize in the sole presence of Pd or acid catalysts.^{7,13}

The contribution of each metal to the cooperative catalysis was investigated next (Table 2). Control experiments showed that both [PdCl₂(dppf)] and (*p*-CF₃Ph)₃PAuOAc were required to achieve the described reactivity. Although the background reaction in the absence of Au can take place (Table

Table 2. TON Control Experiments

entry	conditions	isolated yield (%)	bimetallic catalysis (%)	TON
1	conditions A ^a	78		
2	conditions A, without Au	9 ^b	69	14 (on Au)
3	conditions A, without Pd	0		0
4	conditions A, without Cs	37	37	4 (on Cs)

^aConditions A, see Table 1, entry 4. ^bAverage of two independent runs.

2, entry 2),¹⁴ substantial TONs (~14) can be unambiguously assigned to the Au metal center. As expected, the reaction did not proceed in the absence of the Pd catalyst (Table 2, entry 3), and Cs was also necessary to achieve high conversion to the product, with a TON of ~4 (Table 2, entry 4). SEM-EDX and ICP-MS analyses of the Au, Pd, and Cs complexes used in these reactions ruled out a potential cross-contamination between metals.¹¹

Additional experiments revealed the lack of reactivity of LAuX (X = Cl, I) with CsOAc, in sharp contrast to [PdCl₂(dppf)], which showed fast conversion to a mixture of Pd(II)(Y)(X) (X = OAc, Y = OMe, Cl) complexes, as confirmed by MS and ³¹P NMR experiments (Figure 1, eqs 1

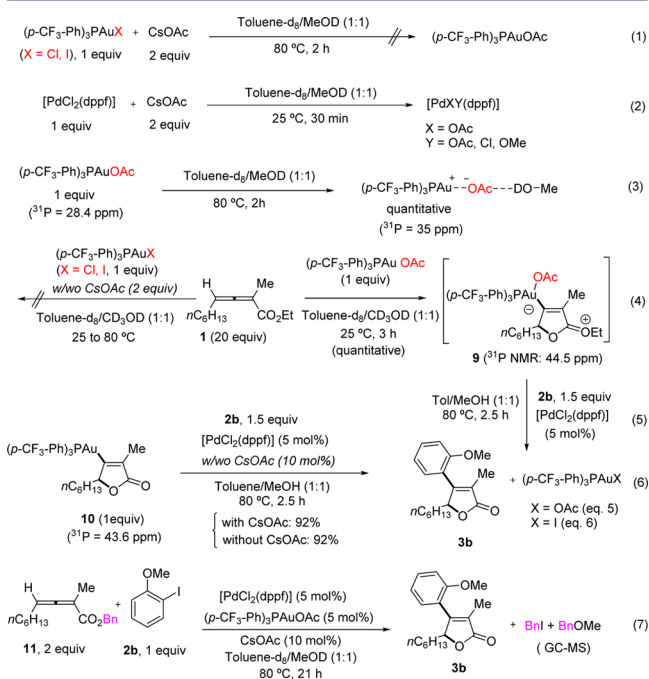


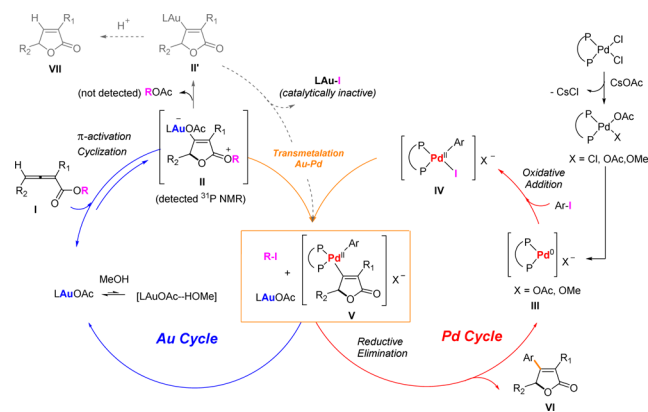
Figure 1. Control experiments.

and 2).¹¹ Interestingly, (*p*-CF₃-Ph)₃PAuOAc (³¹P NMR 28.4 ppm) in the presence of a Tol/MeOH solvent mixture delivered a new ³¹P NMR signal at 35 ppm, in line with recent reports describing the activation of neutral Au(I) species in the presence of MeOH,¹⁵ presumably via associative ligand substitution favored in the polar media (eq 3).¹¹ As expected, gold halide complexes (*p*-CF₃-Ph)₃PAuX (X = Cl, I) were inactive in the cycloisomerization of allenolate **1**, even at high temperature (eq 4, left), in line with the high thermodynamic stability reported for the Au–X bond.^{3c} In contrast, the reaction

of (*p*-CF₃-Ph)₃PAuOAc with an excess of the allenolate **1** led to a quantitative consumption of the Au complex at room temperature, forming a single compound with a characteristic ³¹P NMR signal at 44.5 ppm (eq 4, right). This product was tentatively assigned to zwitterionic complex **9** based on ¹H and ³¹P NMR spectra, which are consistent with those observed by Hammond et al. on similar systems.^{11,16} When this reaction mixture was spiked with independently prepared neutral vinylgold lactone **10** (³¹P NMR 43.7),¹⁷ ³¹P NMR showed the presence of two distinct species.¹¹ Interestingly, when a 1:1 ratio of allenolate **1** and (*p*-CF₃-Ph)₃PAuOAc was used, poor conversion to **9** was observed, indicating the presence of an equilibrium in the formation of this zwitterionic species (data not shown).¹¹ Both **9** and **10** proved to be competent transmetalating agents with coupling partner **2b** under the standard reaction conditions, even in absence of CsOAc (eqs 5 and 6), thus supporting the idea that cesium is not involved in the transmetalation step.¹⁸ With the previous results in hand, we hypothesized that the iodine atom stemming from the Ar-I partner could collapse with the alkyl group on the zwitterionic vinylgold lactone intermediate, delivering Alk-I as byproduct in these transformations. We thus set out to explore whether this highly indicative byproduct could be detected by GC-MS analysis of the crude reaction mixture. When allenolate **11** was used as starting material, benzyl iodide and benzyl methyl ether were detected, whereas BnOAc could not be observed in appreciable amounts in the reaction media, which provided a hint of the mechanism for the Au–Pd bimetallic catalysis (eq 7). Altogether, the collected data suggest a role for CsOAc connected to the generation of a more labile Pd complex by sequestering the Cl[−] anions from the reaction mixture in the form of CsCl, which avoids the formation of gold(I) halide species along the catalytic cycle. This hypothesis is in agreement with its use in 1:1 ratio with respect to the Cl[−] present in the Pd precatalyst (i.e., 10 mol%). In addition, the active participation of the MeOH cosolvent in these transformations was also revealed, as acetate–OMe exchange reactions seem to occur under the reaction conditions at both Au and Pd centers to generate the reactive species involved in the bimetallic catalysis.

The previous set of data supports a reaction mechanism with two co-existing but independent catalytic cycles for Au and Pd, as depicted in Scheme 4. Allenolate **1** is activated in the presence of (*p*-CF₃-Ph)₃PAuOAc, forming zwitterionic intermediate **II** in an equilibrium process favored by the excess of the former

Scheme 4. Mechanistic Proposal



present in the reaction media. At the same time, the $[\text{PdCl}_2(\text{dppf})]$ precatalyst evolves in the presence of CsOAc to a short-lived Pd^0 anionic complex **III**,¹⁹ which is known to undergo facile associative oxidative addition with Ar-I to form Pd^{II} anionic complex **IV**,²⁰ as supported by control experiments.¹¹ Reduction of $\text{Pd}(\text{II})$ to $\text{Pd}(0)$ can be rationalized at the expense of the homocoupling of the organogold species initially formed in the reaction^{6,12} or oxidation of the phosphine ligands¹⁹ present in the reaction media. The key transmetalation step between species **II** and **IV** takes place to give Pd^{II} intermediate **V**, as demonstrated by Figure 1, eq 5. Intermediate **V** evolves via reductive elimination to provide the desired butenolide **VI**, with concomitant formation of a new $\text{C}_{\text{sp}^2}\text{-C}_{\text{sp}^2}$ bond and release of the active Pd^0 anionic species needed to commence the Pd-catalytic cycle. In this process, the catalytically active LAuOAc species is produced, which re-enters the Au catalytic cycle, as supported by experiments summarized in eq 7. Equation 6 shows that neutral vinyl lactone **II'** could also be a productive transmetalation partner. However, if that were to be the predominant pathway, thermodynamically stable LAuI would be the Au species produced after the first turnover. Experiments summarized in eqs 1 and 4 proved LAuI to be catalytically incompetent as well as unreactive toward anionic ligand exchange to produce the catalytically active LAuOAc under the reaction conditions, so that zwitterionic form **9** is proposed as the productive intermediate in these transformations. Finally, even if **II** and **II'** could undergo protonation, sufficient lifetime seems granted under the reaction conditions for the reaction with the intermediate organopalladium species to take place, as vinyl lactones **VII** generally could not be observed in these reactions.

In conclusion, an efficient example of Au–Pd bimetallic catalysis using allenates and aryl and heteroaryl iodides as starting materials is presented here. Two independent catalytic cycles join in a key transmetalation step involving a vinylgold(I) intermediate and an Ar– Pd^{II} –I species. The success of this transformation relies on the generation of catalytically competent LAuOR species connected to the speciation of the Pd catalyst used for the cross-coupling by chloride abstraction with a catalytic amount of CsOAc . Applications of this method to other systems are currently being explored and will be reported in due course.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10277.

Compound synthesis and characterization (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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