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Phosphine-Scavenging Cationic Gold(I) Complexes: Alternative Applications of Gold Cocatalysis in Fundamental Palladium-Catalyzed Cross-Couplings

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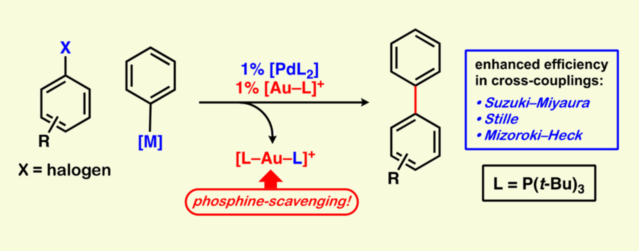
Supporting Information

ABSTRACT: We have demonstrated that air-stable cationic gold(I) cocatalysts have the capacity to enhance the efficiency of palladium-catalyzed cross-couplings. Specifically, we determined that a 1:1 $[Pd\{P(t\text{-}Bu)_3\}_2]/[Au\{P(t\text{-}Bu)_3\}(NTf_2)]$ system provides superior reactivity relative to $[Pd\{P(t\text{-}Bu)_3\}_2]$, across Suzuki−Miyaura, Stille, and Mizoroki−Heck reactions performed under mild conditions. Our results are consistent with cationic gold(I) species serving primarily as phosphine scavengers in this chemistry, as recently predicted by density functional theory (DFT).



INTRODUCTION

Palladium-catalyzed cross-couplings represent a fundamentally important class of synthetic transformations of both academic and industrial significance.[1] Arylphosphine ligands have been employed to great effect as versatile supporting ligands in these reactions, as have bulky, electron-rich trialkylphosphines.[1] The latter family of ligands, particularly venerable $P(t\text{-}Bu)_3$, has enabled efficient Pd-catalyzed reactions under mild conditions.[2] Indeed, in 2010, $P(t\text{-}Bu)_3$ was described as "the most widely used single ligand in modern cross coupling chemistry".[2d]

In contrast to many other Pd/PR_3 catalyst systems, it is generally accepted that the oxidative addition of aryl electrophiles to $P(t\text{-}Bu)_3$-ligated Pd(0) species predominantly proceeds via monophosphine-ligated intermediate $[Pd\{P(t\text{-}Bu)_3\}]$.[3,4] It has also been reported that catalytically inactive $[Pd\{P(t\text{-}Bu)_3\}_2]$ comprises the catalyst resting state in various Mizoroki−Heck and Suzuki−Miyaura couplings.[3a,c] Thus, ~1:1 ratios of $Pd/P(t\text{-}Bu)_3$ are often employed in catalysis performed at lower temperatures, and the active species is often generated in situ from standard palladium precatalysts.[2c,3a,5]

Beyond the development of new ligands that provide enhanced reactivity, a number of strategies have been used to augment various features of Pd-mediated couplings, and the emergence of homo- and heterobimetallic systems in homogeneous catalysis are examples of this.[6] Gold complexes have been employed in the latter capacity.[6a,b] Many of these studies describe Au(I) species serving as transmetalating intermediates derived from various alkyne/allene activation processes characteristic of Au(I) complexes or from preformed organogold complexes.[7] Au(I) species have been employed as cocatalysts in Pd-catalyzed Stille reactions to facilitate efficient cross-couplings with sterically hindered nucleophiles, and tin/gold transmetalation mechanisms are suggested to operate in this system.[8] Other modes of reactivity have also been invoked. For example, Blum and co-workers reported a detailed study demonstrating the viability of a Pd/Au cocatalyst system to promote the carbostannylation of alkynes.[9] The mechanism is consistent with the coordination of a Lewis acidic Au(I) species to the alkyne, which is key to activation in this manifold.[9,10]

In 2017, Ariafard's density functional theory (DFT) computational study first predicted the phosphine-scavenging ability of cationic Au(I) complexes (Figure 1).[11] Specifically, this work suggested that this property could be exploited to lower the barrier leading to the catalytically active monophosphine-ligated $[Pd\{P(t\text{-}Bu)_3\}]$ from its stable (catalytically inactive) bis-ligated precursor. This prompted us to postulate

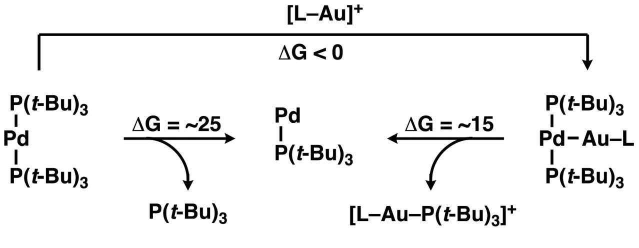


Figure 1. Calculated Gibbs free energies (kcal/mol) for the formation of $[Pd\{P(t\text{-}Bu)_3\}]$ from $[Pd\{P(t\text{-}Bu)_3\}_2]$ in the presence or absence of $[Au–L]^+$.[11]

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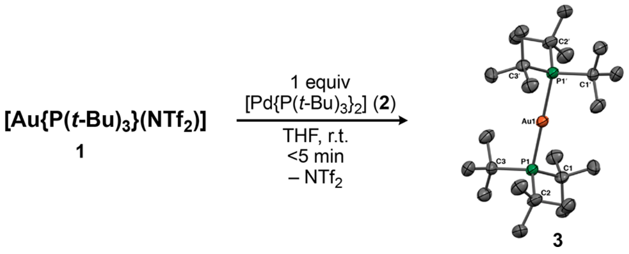
that Pd/Au cocatalysis could be exploited to enhance the reactivity of this catalyst system and perhaps other Pd/PR_3 catalyst systems under mild conditions by sequestering free phosphine. Herein, we illustrate the validity of this postulate in practice.

Our results provide evidence for the capacity of cationic Au(I) complexes to formally abstract P(*t*-Bu)$_3$ from [Pd{P(*t*-Bu)$_3$}$_2$]. Furthermore, we determined that [Pd{P(*t*-Bu)$_3$}$_2$]/[Au{P(*t*-Bu)$_3$}(NTf_2)] systems can provide superior efficiency relative to [Pd{P(*t*-Bu)$_3$}$_2$] in key couplings, including Suzuki–Miyaura, Stille, and Mizoroki–Heck reactions. These data are consistent with the gold cocatalyst playing a key role primarily as a phosphine scavenger.

■ RESULTS AND DISCUSSION

First, we investigated the capacity of [Au{P(*t*-Bu)$_3$}(NTf_2)] (**1**) to formally abstract P(*t*-Bu)$_3$ from bis(phosphine)-ligated Pd(0) complex [Pd{P(*t*-Bu)$_3$}$_2$] (**2**) (Scheme 1). After the addition of Au complex **1** to Pd complex **2**, a new signal (δ 97.0 ppm) appeared, consistent with the rapid formation of [Au{P(*t*-Bu)$_3$}$_2$]$^+$, as judged by ^{31}P NMR spectroscopy.[12,13] We also isolated and crystallographically characterized linear mononuclear [Au{P(*t*-Bu)$_3$}$_2$]NTf_2 (**3**).[14]

Scheme 1. Reaction of Au Complex 1 with Pd Complex 2 to Afford [Au{P(*t*-Bu)$_3$}$_2$]NTf_2 (3)[a]



[a]In the structural representation of Au complex **3**, thermal ellipsoids are drawn at the 50% probability level and the [NTf_2]$^-$ counteranion and hydrogen atoms are omitted for clarity.

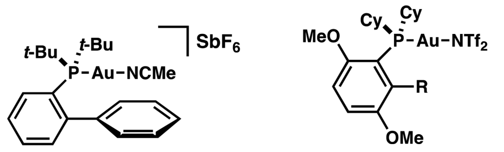
Next, we explored the capacity of Au complex **1** to promote the oxidative addition of *p*-bromotoluene to a Pd species derived from [Pd{P(*t*-Bu)$_3$}$_2$] (**2**). In the absence of Au complex **1**, reaction of the aryl bromide with Pd complex **2** was not observed after 24 h, as judged by ^{31}P NMR spectroscopy (Scheme 2). This is in agreement with germane findings.[3a] In stark contrast, the presence of equimolar quantities of Au complex **1** rapidly promoted oxidative addition in minutes. Specifically, ^{31}P NMR spectroscopy indicated the presence of a new signal (δ 61.5 ppm),[15] which was consistent with the presence of Pd(II) species **4**. The conversion of Pd(0) complex **2** to Pd(II) complex **4** was complete within 0.25 h, and we also observed the concomitant formation of [Au{P(*t*-Bu)$_3$}$_2$]$^+$ by ^{31}P NMR spectroscopy.[12]

We obtained analogous results employing other commercially available, air-stable cationic Au(I) complexes **5**–**7** in equivalent experiments. In each case, oxidative addition to form Pd(II) complex **4** promptly occurred at ambient temperature. This property of species **1** and **5**–**7** is notable as Fu and co-workers have suggested that (catalytically inactive) Pd complex **2** comprises the catalyst resting state in various Mizoroki–Heck and Suzuki–Miyaura couplings.[3a,c] The presence of free phosphine has also been shown to reduce the efficiency of transmetalation in Suzuki–Miyaura and Stille cross-coupling reactions mediated by Pd/PPh_3 systems.[16,17]

Scheme 2. Investigating the Capacity of Au Complexes 1 and 5–7 and Cu Complex 8 to Promote the Oxidative Addition of a Pd Species to *p*-Bromotoluene

$$\underset{\mathbf{2}}{[\mathrm{Pd\{P(}t\mathrm{\text{-}Bu)_3\}_2}]} \xrightarrow[\text{THF-}d_8\text{, r.t.}]{\substack{\text{1 equiv [M]} \\ \text{1 equiv } p\text{-tol–Br}}} \underset{\mathbf{4}}{[\mathrm{Pd\{P(}t\mathrm{\text{-}Bu)_3\}(}p\mathrm{\text{-}tol)(Br)}]}$$

[M]	conversion of Pd 2
–	0% after 24 h
[Au{P(*t*-Bu)$_3$}(NTf_2)] (**1**)	100% after 0.25 h
[Au(PPh_3)(NTf_2)] (**5**)	100% after <5 min
[Au(JohnPhos)(MeCN)]SbF_6 (**6**)	100% after 0.25 h
[Au(BrettPhos)(NTf_2)] (**7**)	100% after 0.25 h
[Cu(MeCN)$_4$]PF_6 (**8**)	100% after 5 min



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7 {R = *o*,*m*,*p*-(*i*-Pr)$_3$$C_6H_2$}

The capacity of substoichiometric quantities of copper salts to accelerate and enhance the efficiency of Pd-catalyzed Stille and Suzuki–Miyaura couplings is well established.[18,19] Much of the pioneering work exploring the role of copper additives in Stille chemistry was undertaken by Liebeskind, and excellent reviews discussing this "copper effect" within the context of Pd cross-coupling chemistry have been published more recently.[6b,20] Although it can be difficult to unambiguously determine the mechanistic basis of this phenomenon in every instance, two primary effects have been proposed.[6b] Specifically, the operation of possible tin/copper transmetalation mechanisms have been invoked in these Stille processes (particularly in very polar solvents such as NMP, DMF, and DMSO),[6b,17b,21] in addition to the phosphine-scavenging capacity of copper species.[17b,c,18a,22] The latter effect is thought to be most pronounced when free, strong donor phosphine ligands are present in ethereal solutions because their presence can impede transmetalation.[6b,17b,c,23]

Donnelly and Finet first suggested that phosphine-scavenging processes may be operative in Suzuki–Miyaura reactions performed in the presence of CuI.[19a] Furthermore, Hobbs noted that a specific 1:2 Pd/Cu cocatalyst ratio provided optimal results in Sonogashira reactions employing [Pd(PPh_3)$_4$] and proposed that this type of behavior may also be present.[24] Ariafard's DFT studies also support the phosphine-scavenging ability of cationic Cu(I) complexes.[11] Consequently, we also determined that [Cu(MeCN)$_4$]PF_6 (**8**) could rapidly promote the oxidative addition of *p*-bromotoluene to an active species derived from [Pd{P(*t*-Bu)$_3$}$_2$] (Scheme 2). We also isolated and crystallographically characterized mononuclear complex [Cu{P(*t*-Bu)$_3$}$_2$]PF_6 (**9**).[25]

To explore the viability of our proposed phosphine-scavenging strategy in synthesis, we investigated the effects of Pd complex **2**/Au complex **1** (and Pd complex **2**/Cu complex **8**) cocatalyst systems in Pd-catalyzed cross-coupling processes under simple and mild reaction conditions. In each case, we compared the respective rates of product formation employing these two cocatalyst systems and benchmarked these data against equivalent experiments featuring Pd complex **2** exclusively.

The enhanced efficiency provided by our Pd/Au cocatalyst system was clearly evident in a Suzuki−Miyaura cross-coupling involving *p*-bromotoluene and phenylboronic acid (Figure 2).

$$p\text{-tol—Br} + \underset{1.1\ \text{equiv}}{\text{Ph—B(OH)}_2} \xrightarrow[\substack{3:1\ \text{THF/ H}_2\text{O}\\ 50\ ^\circ\text{C}}]{\substack{1\%\ \text{Pd}\ \mathbf{2}\\ 0\ \text{or}\ 1\%\ [\text{M}]\\ 4\ \text{equiv Na}_2\text{CO}_3}} p\text{-tol—Ph}$$

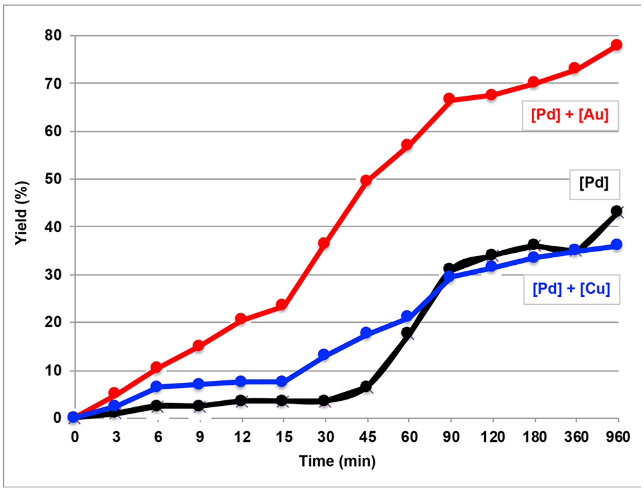

Figure 2. Effects of cocatalysts Au complex **1** (red line) or Cu complex **8** (blue line) on the progress of Pd-mediated Suzuki−Miyaura cross-couplings. The experiment employing only Pd catalyst **2** is represented with a black line.[29]

In the absence of additive **1**, the reaction essentially featured an induction period (∼0.5 h). In contrast, the process using 1% [Au{P(*t*-Bu)$_3$}(NTf$_2$)] (**1**) provided an enhanced rate of product formation.[26,27] Employing 3% Au complex **1** afforded negligible differences in reactivity relative to 1% loading (Supporting Information), which is consistent with the phosphine-scavenging capacity of Au complex **1** playing a key role in improving the efficiency of this transformation.[28] Similar results were also obtained when a 1% Pd(dba)$_2$/1% [HP(*t*-Bu)$_3$]BF$_4$ catalyst system was utilized in this transformation (Supporting Information).

In a recent study,[16,30] we identified that the poor turnover of key on-cycle intermediate *trans*-[Pd(PPh$_3$)$_2$(Ar)(I)] in the presence of free PPh$_3$ was responsible for the surprisingly poor reactivity of aryl iodides in [Pd(PPh$_3$)$_4$]-catalyzed Suzuki−Miyaura cross-couplings performed at relatively low temperatures (Scheme 3A,B).[31] Our report also illustrated the drastic difference between this process and the equivalent reaction utilizing aryl bromides (Scheme 3A). With this in mind, we investigated whether gold cocatalysis could ameliorate the aforementioned issues affecting catalyst turnover in this transformation. Although a 1% loading of [Au(PPh$_3$)(NTf$_2$)] (**5**) provided a negligible effect, 2% Au complex **5** facilitated a much more efficient process (Scheme 3C).

Scheme 3. Suzuki−Miyaura Reactions[a,b]

A

$$\underset{\text{X = I, Br}}{p\text{-tol—X}} + \underset{1.1\ \text{equiv}}{\text{Ph—B(OH)}_2} \xrightarrow[\substack{4:1\ n\text{-PrOH/ H}_2\text{O}\\ 50\ ^\circ\text{C, 0.5 h}}]{\substack{1\%\ [\text{Pd(PPh}_3)_4]\\ 4\ \text{equiv Na}_2\text{CO}_3}} p\text{-tol—Ph}$$

X	yield (%)[a]
I	8 (7)
Br	61 (29)

B

$$p\text{-tol—I} + \underset{1.1\ \text{equiv}}{\text{Ph—B(OH)}_2} \xrightarrow[\substack{4:1\ n\text{-PrOH/ H}_2\text{O}\\ 50\ ^\circ\text{C, 0.5 h}}]{\substack{1\%\ trans\text{-[Pd(PPh}_3)_2(p\text{-tol)(I)]}\\ \text{X\% PPh}_3\text{, 4 equiv Na}_2\text{CO}_3}} p\text{-tol—Ph}$$

PPh$_3$ (%)	yield (%)[a]
0	32 (23)
2	<2 (<2)

C

$$p\text{-tol—I} + \underset{1.1\ \text{equiv}}{\text{Ph—B(OH)}_2} \xrightarrow[\substack{2:1:1\ n\text{-PrOH/THF/H}_2\text{O}\\ 50\ ^\circ\text{C, 0.5 h}}]{\substack{1\%\ [\text{Pd(PPh}_3)_4]\\ 0\text{–}3\%\ [\text{M}]\\ 4\ \text{equiv Na}_2\text{CO}_3}} p\text{-tol—Ph}$$

[M]	yield (%)[a]
–	15 (14)
1% Au **5**	17 (13)
2% Au **5**	64 (45)
3% Au **5**	66 (47)
1% Cu **8**	30 (22)
2% Cu **8**	36 (25)

D

$$\underset{\mathbf{5}}{[\text{Au(PPh}_3)(\text{NTf}_2)]} \xrightarrow[\substack{\text{THF-}d_8\text{, r.t.}\\ <5\ \text{min}\\ -\ \text{NTf}_2}]{\substack{1\ \text{equiv}\\ [\text{Pd(PPh}_3)_4]}} \underset{\mathbf{10}}{[\text{Au(PPh}_3)_3]^+}$$

[a]Yields after 0.25 h are provided in parentheses.[29] [b](A) Reported inefficient Pd-catalyzed Suzuki−Miyaura couplings of aryl iodides.[16] (B) Reported poor turnover of *trans*-[Pd(PPh$_3$)$_2$(Ar)(I)] in the presence of free PPh$_3$.[16] (C) Investigation of the effects of cocatalyst **5** or **8** on the efficiency of Pd-catalyzed Suzuki−Miyaura reactions with *p*-iodotoluene. (D) Reaction of Au complex **5** with [Pd(PPh$_3$)$_4$] to afford [Au(PPh$_3$)$_3$]$^+$ (**10**).

Employing 3% [Au(PPh$_3$)(NTf$_2$)] afforded essentially the same results relative to 2% **5**. Significant reactivity differences were observed when 1:1 and 1:2 ratios of [Pd(PPh$_3$)$_4$] and [Au(PPh$_3$)(NTf$_2$)] were employed in these Suzuki−Miyaura couplings. In contrast, similar results were obtained using 1:2 and 1:3 ratios of [Pd(PPh$_3$)$_4$]/[Au(PPh$_3$)(NTf$_2$)]. These data are consistent with the phosphine-scavenging capacity of Au complex **5** playing a role in enhancing the efficiency of this process.[28,32] We also investigated the ability of [Au(PPh$_3$)(NTf$_2$)] (**5**) to formally abstract PPh$_3$ from [Pd(PPh$_3$)$_4$] (Scheme 3D). After the addition of Au complex **5** to a solution containing this Pd(0) species, a new signal (δ 22.1 ppm) was observed, consistent with the formation of [Au(PPh$_3$)$_3$]$^+$ (**10**) as judged by ^{31}P NMR spectroscopy.[33] This demonstrates the capacity for Au complex **5** to scavenge PPh$_3$.[34]

Next, we demonstrated the superior results provided by our Pd/Au cocatalyst system in a Stille cross-coupling involving *p*-iodotoluene and tributylphenylstannane (Figure 3). Specifically, the process featuring 1% Au complex **1** provided a more efficient process relative to the reaction featuring only Pd complex **2**.[26,27] Employing 3% Au complex **1** provided negligible improvements in reactivity relative to 1% Au complex **1** (Supporting Information). However, we cannot exclude the possibility that tin/gold transmetalation mechanisms may also be operative under these conditions. The enhanced efficiency we observed in each of the Pd-catalyzed Stille and Suzuki−Miyaura cross-couplings investigated in this study is consistent with the Au cocatalyst scavenging phosphine, thus accelerating the respective rates of transmetalation in these processes.

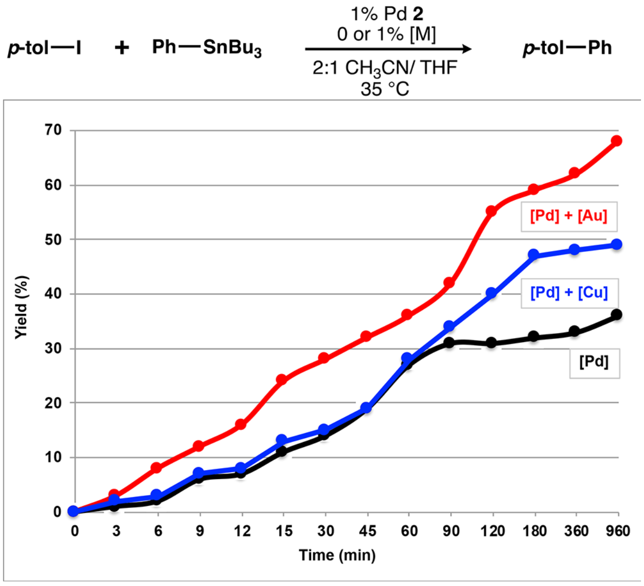

Figure 3. Effects of cocatalysts Au complex **1** (red line) or Cu complex **8** (blue line) on the progress of Pd-mediated Stille cross-couplings. The experiment employing only Pd catalyst **2** is represented with a black line.[29]

The improved results provided by our Pd/Au cocatalyst system were also demonstrated in a Mizoroki–Heck cross-coupling involving *p*-iodotoluene and ethyl acrylate (Figure 4).[26,27] Our results indicated that the process featuring 2% [Au{P(*t*-Bu)$_3$}(NTf$_2$)] (**1**) provided a more efficient process relative to the reaction featuring only Pd complex **2**. Employing 4% Au complex **1** provided minor improvements in reactivity relative to 2% Au complex **1** (Supporting Information). Similar results were also obtained when a 2% Pd(dba)$_2$/2% [HP(*t*-Bu)$_3$]BF$_4$ catalyst system was employed to effect this transformation (Supporting Information).

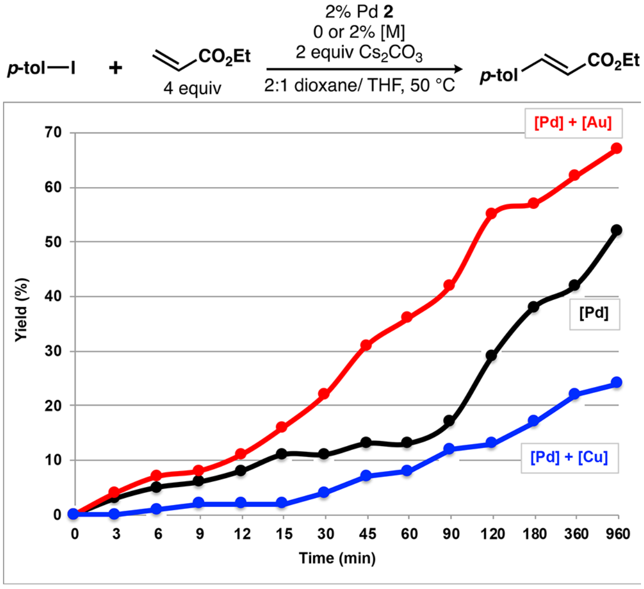

Figure 4. Effects of cocatalysts Au complex **1** (red line) or Cu complex **8** (blue line) on the progress of Pd-mediated Mizoroki–Heck cross-couplings. The experiment employing only Pd catalyst **2** is represented with a black line.[29]

■ CONCLUSIONS

We have demonstrated that substoichiometric quantities of air-stable cationic Au(I) complexes can accelerate and enhance the efficiency of Pd-catalyzed cross-coupling reactions. Our observations are consistent with Au(I) cocatalysts serving primarily as phosphine scavengers in these processes, and these findings reinforce the predictions of a recently published DFT study.[11] Our results also suggest that gold additives may be more effective than copper salts in this regard, which should be investigated further in the future.

Arguably, the viability and general utility of this Au(I) cocatalysis approach in augmenting the development of Pd-catalyzed reactions under mild conditions will be influenced by factors including the donor capacity of the ligand employed, the binding affinity of the gold complex, the choice of solvent, and the additives present. Subsequent studies will seek to investigate the broader implications and further applications of this strategy in other metal-catalyzed transformations, including olefin polymerization processes,[35] and to utilize this approach to facilitate new reaction development under mild conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00294.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1875861–1875862 contain the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(5) Generating the active catalyst in situ from various Pd(0) or Pd(II) precatalysts and [HP(*t*-Bu)$_3$]BF$_4$ allows for easier handling because free P(*t*-Bu)$_3$ is susceptible to oxidation by oxygen (ref 2c). [Pd{P(*t*-Bu)$_3$}$_2$] is an air-stable solid and can be handled in air (refs 2c and 3c).

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(26) Essentially no cross-coupled product was formed in reactions featuring either Au complex **1** or Cu complex **8** in the absence of Pd complex **2**.

(27) The use of Cu complex **8** as an additive was not as effective as Au complex **1**. Experiments were also performed using CuI as an additive, which was also not as effective as Au complex **1** (Supporting Information).

(28) The possibility that boron/gold transmetalation mechanisms may also be operative under these conditions cannot be excluded.

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