Ag(I)-Catalyzed C−H Activation: The Role of the Ag(I) Salt in Pd/Ag-Mediated C−H Arylation of Electron-Deficient Arenes

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S *Supporting Information*

ABSTRACT: The use of stoichiometric Ag(I)-salts as additives in Pd-catalyzed C−H functionalization reactions is widespread. It is commonly proposed that this additive acts as an oxidant or as a halide scavenger promoting Pd-catalyst turnover. We demonstrate that, contrary to current proposals, phosphine ligated Ag(I)-carboxylates can efficiently carry out C−H activation on electron-deficient arenes. We show through a combination of stoichiometric and kinetic studies that a (PPh_3)Ag-carboxylate is responsible for the C−H activation step in the Pd-catalyzed arylation of $Cr(CO)_3$-complexed fluorobenzene. Furthermore, the reaction rate is controlled by the rate of Ag(I)-C−H activation, leading to an order zero on the Pd-catalyst. H/D scrambling studies indicate that this Ag(I) complex can carry out C−H activation on a variety of aromatic compounds traditionally used in Pd/Ag-mediated C−H functionalization methodologies.

Over the past decade C−H functionalization has emerged as a promising synthetic tool capable of significantly streamlining access to complex materials from nonprefunctionalized starting compounds.[1] In particular, the functionalization of aromatic C−H bonds is under intense development, and several transition metals have been shown to catalyze C−H activation, including Pd, Ir, Rh, Cu, Ru, and Au.[1] Due to its versatility in mediating the C−H functionalization of a broad range of aromatics, Pd has been one of the most studied transition metals to date. While several mechanistic pathways have been proposed for Pd-mediated C−H activation, carbonate or carboxylate assisted concerted metalation−deprotonation (CMD) stands out as a likely mechanism for a wide variety of electron-rich and -poor aromatics, as well as those containing directing groups.[2] Often, Pd-catalyzed C−H functionalizations are carried out in the presence of stoichiometric Ag(I)-salts.[3] The need for these Ag-additives is commonly attributed to one of two secondary roles in these processes: as a terminal oxidant in oxidative functionalizations, or as a halide scavenger, particularly when iodoarenes are used as coupling partners.[4] In both of these roles, the Ag(I)-salts are needed to regenerate catalytically active Pd species as the reaction proceeds. However, in many of these processes the Ag(I)-salts cannot be successfully replaced with other oxidants or halide scavengers. This raises the question of whether Ag-salts may play additional roles in these C−H functionalization processes. Recent computational[5] and deuteration[6] studies on the oxidative coupling of pentafluorobenzene

and benzene suggested that silver could be performing the C−H activation in this case, and a recent computational mechanistic study suggested that Ag could interact with Pd in a cooperative manner for enhanced heterobimetallic C−H activation.[7] However, experimental evidence for these proposals under catalytic conditions has not been forthcoming.[8]

We report that *Ag(I)-carboxylates on their own* are, in fact, highly efficient catalysts for the C−H activation of electron-deficient arenes. We demonstrate that a Ag(I)-carboxylate, and not a Pd(II) species as previously believed, is responsible for C−H activation in a Pd/Ag-mediated C−H arylation system, likely via a concerted metalation−deprotonation similar to that proposed for Pd. These results suggest that the role of Ag(I) in many other Pd/Ag C−H functionalization processes may have been underestimated.

We recently reported a Pd-catalyzed methodology for the C−H arylation of electron-deficient $(arene)Cr(CO)_3$ complexes with iodoarenes as coupling partners (Scheme 1).[9] As is common

Scheme 1. Pd/Ag-Mediated Direct Arylation of (2-Fluorotoluene)Cr(CO)₃ (1) with 4-Iodoanisole (2)
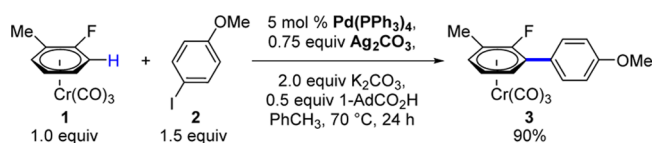
in this type of process, we found that stoichiometric Ag_2CO_3 was required, nominally to scavenge the iodide formed during the reaction. A typical Pd(0/II)-type catalytic cycle (mechanistic proposal A in Scheme 2), as proposed in most C−H arylation methodologies, could account for these results. The role of the Ag(I)-salt would be simply to abstract I from Pd-species **II**, generating Pd(II)-carboxylate **III**. Species **III** would then perform C−H activation of **1** via CMD, followed by reductive elimination to form biaryl product **3**. However, during optimization of this process we observed that lower yields were obtained when the ratio PPh_3/Pd was decreased from 4:1 to 2:1 or 0:1.[10] Intrigued by these results, we set out to investigate whether there was an alternative species performing the C−H activation step in this reaction.
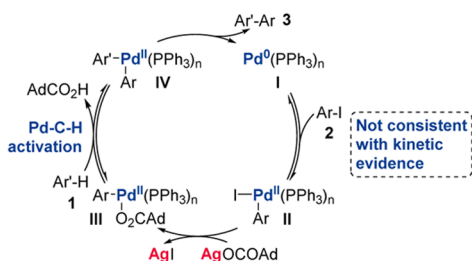
In order to identify the species performing the C−H activation we attempted H/D exchange experiments on arene-complex **1**
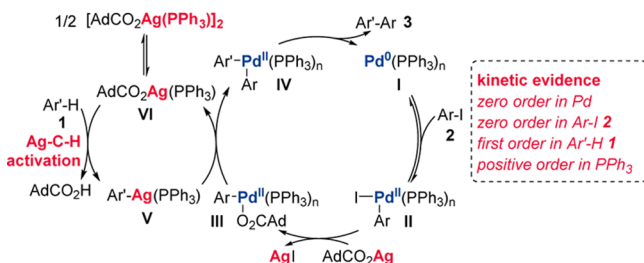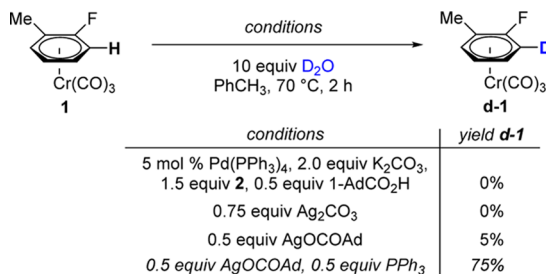
Scheme 2. Mechanistic Hypotheses

a) Mechanistic proposal A: Pd(II)-mediated C-H activation

b) Mechanistic proposal B: Ag(I)-mediated C-H activation

(Scheme 3). Treatment of **1** under the standard reaction conditions in the presence of D_2O, but in the absence of Ag_2CO_3,

Scheme 3. H/D Exchange Experiments on Arene−Cr 1

conditions	yield **d-1**
5 mol % $Pd(PPh_3)_4$, 2.0 equiv K_2CO_3, 1.5 equiv **2**, 0.5 equiv 1-$AdCO_2H$	0%
0.75 equiv Ag_2CO_3	0%
0.5 equiv $AgOCOAd$	5%
0.5 equiv AgOCOAd, 0.5 equiv PPh₃	*75%*

led to recovery of starting material after 2 h. Similarly, treatment of **1** with 0.75 equiv of Ag_2CO_3 afforded no deuteration of the starting material **1**. The use of 0.5 equiv of $AdCO_2Ag$, on the other hand, led to a small amount of deuteration (5%). Interestingly, when 0.5 equiv of $AdCO_2Ag$ was used in combination with 0.5 equiv of PPh_3, 75% deuteration to **d-1** was observed. This suggested that the additional PPh_3 needed in the arylation reaction was complexing and solubilizing an Ag-carboxylate species which then performs the C−H activation. ^1H and ^{31}P NMR experiments in d_8-$PhCH_3$ confirmed that the highly insoluble $AdCO_2Ag$ is fully solubilized upon addition of 1 equiv of PPh_3, leading to the formation of a 1:1 complex with the empirical formula $AdCO_2Ag(PPh_3)$.[11] Accordingly, Scheme 2b outlines mechanistic proposal B for the arylation reaction in which $AdCO_2Ag(PPh_3)$ species (**VI**) would carry out C−H activation, forming Ag(I)-aryl species **V**. Subsequently, **V** would transmetalate with Pd(II)-carboxylate **III** to form **IV**.

To confirm this hypothesis, we monitored the kinetics of the arylation reaction with increasing amounts of added PPh_3. We found a positive effect of the phosphine on the rate of the reaction reaching saturation at 0.04 M (Figure 1). Considering that the precatalyst $Pd(PPh_3)_4$ can liberate two molecules of PPh_3 into the solution after formation of intermediate **III**, the amount of PPh_3 available to coordinate AgO_2CAd under those
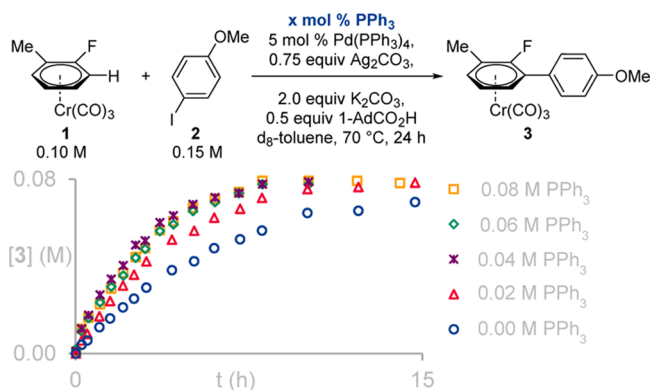

Figure 1. Saturation concentration of PPh_3.

conditions is approximately 0.05 M. This value is the concentration of $AdCO_2H$ used and therefore the upper limit concentration of **VI** that can be formed. These results suggest that the $AdCO_2Ag(PPh_3)$ complex **VI** is involved in the rate-determining step of the overall reaction.

To perform further mechanistic studies of such a complex system, we used the experimental design of reaction progress kinetic analysis (RPKA)[12] and novel analysis methods for integrative data recently developed.[13] Under the standard conditions (Scheme 1), the same excess experiments analyzed by the time-adjusted method[12c] showed neither significant deactivation nor product inhibition, indicating that the system can be studied by these methods.[14] Different excess experiments revealed a zero order in iodoarene **2** and a positive order in arene **1**.[14] A first order in arene **1** was further determined by initial rate measurements.

Measuring the order in Pd is nontrivial because the precatalyst, $Pd(PPh_3)_4$, liberates PPh_3 which in turn has a positive effect in the rate of the reaction. To avoid this interference, the order in Pd must be measured under PPh_3 saturation conditions. When the reaction was performed adding 0.06 M of PPh_3, the orders in iodoarene **2** and arene **1** remained the same as under standard conditions.[14] Remarkably, *the order in Pd was found to be zero*, as shown by the identical kinetic profiles of the reactions with 2.5, 5, and 10 mol % of $Pd(PPh_3)_4$ (Figure 2).
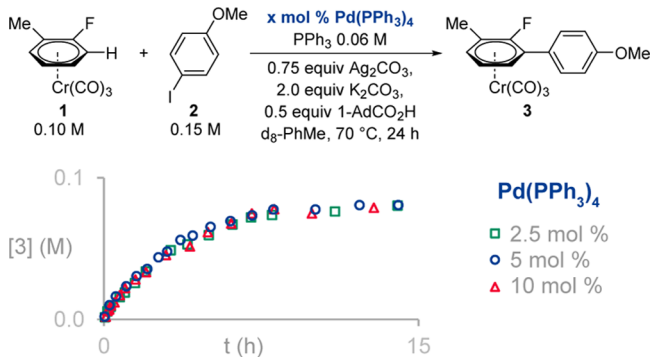

Figure 2. Order zero in Pd under PPh_3 saturation.

To the best of our knowledge, this is the first time that a null effect of the Pd concentration has been observed in a Pd-catalyzed cross-coupling. A zero order in catalyst can be observed in cases where a process external to the catalytic cycle is limiting the rate of the overall reaction.[15] In mechanistic proposal A (Scheme 2a), the only out-cycle process that could limit the rate

of the overall reaction is the formation of AgO$_2$CAd from Ag$_2$CO$_3$ and AdCO$_2$H. This hypothesis would be consistent with the positive order in PPh$_3$ because its coordination would increase the solubility of Ag(I) salts. However, it would be incompatible with the observed positive order in arene **1**. On the other hand, mechanistic proposal B has an additional out-cycle process that could limit the rate of the overall reaction: the Ag(I)-mediated C−H activation. This scenario would be compatible with the positive effect of PPh$_3$, its saturation above the concentration of AdCO$_2$H, and the positive order in arene **1** since it is a driving force of this step.[16]

The key species in the reaction is, therefore, AdCO$_2$Ag(PPh$_3$) **VI**. It was not possible to measure the concentration of this complex from reaction aliquots, and so order on this catalyst was evaluated using the deuteration system (Scheme 3) as a simplified model. The order on Ag was found to be 0.6, consistent with an inactive dimeric resting state of the type [AdCO$_2$Ag(PPh$_3$)]$_2$ and a low concentration monomeric active species **VI**.[17] The 0.6 order on Ag, taken together with the positive order on arene **1** and the zero order observed on Pd in the arylation reaction, provides strong support for mechanistic proposal B in Scheme 2b.

In addition to the kinetic evidence supporting mechanistic proposal B, we were also able to identify by ^{1}H and ^{31}P NMR *trans*-(PPh$_3$)$_2$Pd(OCOAd)(p-C$_6$H$_4$OMe) (**5**, Figure S32) corresponding to the trans isomer of proposed Pd(II)-carboxylate intermediate **III**, as the major Pd-catalytic intermediate in the reaction. The identity of **5** was confirmed by independent synthesis. This observation is in agreement with mechanistic proposal B, where the Ag(I)-mediated C−H activation is the rate limiting step of the entire catalytic system. In this situation, the rate-determining step of the Pd-catalytic cycle must be the transmetalation of Ag(I)-aryl species **V** with Pd(II) species **III**. Using species **5** as the Pd-precatalyst instead of Pd(PPh$_3$)$_4$ for the arylation process led to identical reaction kinetics, provided two additional equivalents of PPh$_3$ are added.[14]

This kinetic evidence points toward mechanistic proposal B being in operation (Scheme 2b), with Ag(I)-mediated C−H activation as the rate limiting step in the process. A KIE of 2.3 had previously been measured for this reaction, in agreement with this hypothesis.[9a] In order to gather further evidence, we tested the reactivity of Pd-species **5**, a plausible resting state for Pd during the reaction, with arene−Cr complex **1** (Scheme 4). As expected, Pd-carboxylate **5** did not react with **1** under a variety of conditions, including addition of 2 equiv of K$_2$CO$_3$. No reaction was observed either when running the reaction under O$_2$.[18] On the other hand, addition of AdCO$_2$Ag and PPh$_3$ led to formation of the C−H arylation product **3** in 26% yield. Decomposition of
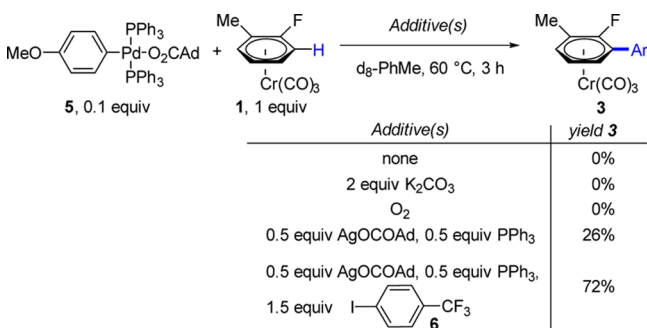
5 is also observed, accounting for the low yield. We hypothesized that this decomposition was accelerated by formation of trace amounts of Pd(0). Indeed, when the reaction was carried out in the presence of an iodoarene, **6**, able to react rapidly with any low valent Pd species, a yield of 72% of **3** was obtained. These results are fully consistent with mechanistic proposal B (Scheme 2b) and inconsistent with mechanistic proposal A.[19]

Further studies will be needed to understand the exact mechanism of C−H activation by AdCO$_2$Ag(PPh$_3$). However, by analogy with previous studies on Pd−O$_2$CR, a plausible CMD can be proposed. This was probed by DFT calculations of the CMD pathway of (fluorotoluene)Cr(CO)$_3$ with the simplified AcOAg(PPh$_3$) which revealed a feasible free energy barrier of 29.5 kcal/mol (Figure 3).[20,21]
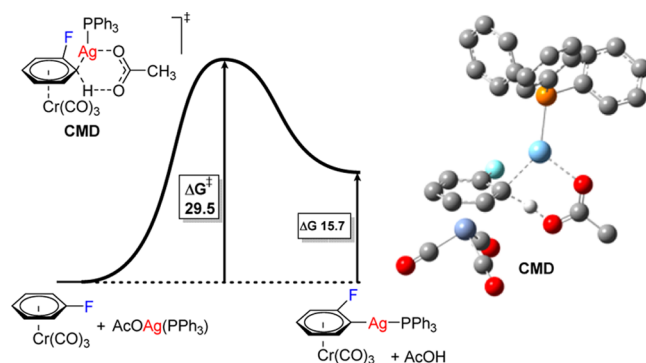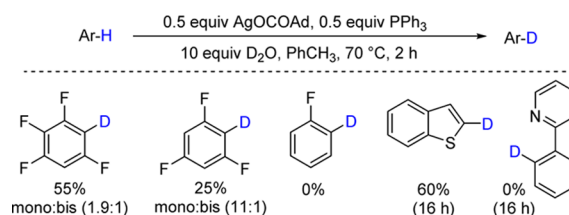

Figure 3. DFT study of a plausible CMD process in the gas phase (B3LYP/DGDZVP/SDD/6-31G(d)). Gibbs free energies (G) in kcal/mol.

From a practical point of view, the observation of zero-order kinetics on the Pd-catalyst at PPh$_3$ saturation conditions suggests that Pd-catalyst loadings could be significantly reduced below the 5 mol % typically used. Gratifyingly, we found that in the presence of 60 mol % added PPh$_3$ the reaction of **1** and **2** proceeded efficiently with only 0.1 mol % Pd(PPh$_3$)$_4$, affording **3** in 61% yield in 40 h. The longer reaction times and lower yield suggest that at low Pd-catalyst loadings this cycle becomes kinetically relevant. Indeed, under these conditions of PPh$_3$ we observed an order one for Pd at loadings below 0.5 mol %.[14]

Due to the ubiquity of Pd/Ag-mediated C−H functionalization methodologies we investigated whether AdCO$_2$Ag(PPh$_3$) may be also able to mediate C−H activation on other commonly used arenes. Gratifyingly, H/D exchange experiments using 50% of this Ag(I)-salt showed significant deuteration after 3 h at 70 °C in benzo[*b*]thiophene, pyridine-*N*-oxide, 1,3,5-trifluorobenzene, and 1,3,4,5-tetrafluorobenzene (Scheme 5). On the other hand, fluorobenzene and 2-phenylpyridine did not undergo deuteration. These results suggest that Ag(I)-salts may be the actual species performing C−H activation in several previously

Scheme 4. Stoichiometric Reactions of Aryl-Pd(II) 5 a

Additive(s)	yield 3
none	0%
2 equiv K$_2$CO$_3$	0%
O$_2$	0%
0.5 equiv AgOCOAd, 0.5 equiv PPh$_3$	26%
0.5 equiv AgOCOAd, 0.5 equiv PPh$_3$, 1.5 equiv I—⟨⟩—CF$_3$ **6**	72%

Scheme 5. Ag(I)-Catalyzed H/D Exchange Experiments

reported Pd/Ag C−H functionalization methodologies. More studies will be necessary to assess the extent of the contribution of Ag(I) to C−H activation in these cases.

In conclusion, with a combination of stoichiometric and kinetic mechanistic studies we have demonstrated that phosphine ligated Ag(I)-carboxylates are excellent catalysts for C−H activation of electron-deficient arenes. These studies show that the ratio of PPh₃, AdCOOH, and Pd determine the rate-determining step of the overall Pd/Ag-mediated C−H arylation of (arene)−Cr(CO)₃ complexes with iodoarenes. Furthermore, deuteration studies suggest that the role of Ag(I)-salts in C−H activation should be considered in many other Pd/Ag-mediated C−H functionalization reactions.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04726.

> Experimental procedures and characterization data for new compounds (PDF)

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(16) This result would also be compatible with C−H activation by K₂CO₃ or KO₂CAd. We have discounted this hypothesis since we observed no deuteration in the absence of Ag(I)-salt.

(17) For a reaction with a dimerization off-cycle equilibrium the order on these species must be in the range 0.5 to 1. See ref 13 and SI.

(18) "Ligandless" Pd(II)−aryl species, generated through O₂-oxidation of the phosphine ligands, can carry out C−H activation of benzene in DMA at 110 °C. See: Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 3308. In our case, only decomposition of Pd-complex **5** was observed under O₂.

(19) A related study by Hartwig showed that a cyclometallated Pd(II) phosphine carboxylate complex performed the C−H activation of electron-deficient arenes and that the arene was then transferred to a second Pd(II) complex containing the second arene coupling partner. This process is very unlikely to be operating here due to the observed zero order on Pd. See: Tan, Y.; Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

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(21) While direct comparisons are not possible due to the use of different basis sets, the calculated barrier is comparable to those previously calculated for Pd-mediated CMD. See ref 2b and: Gorelsky, S. I. *Coord. Chem. Rev.* **2013**, *257*, 153.