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Research Article

Ag/Pd Cocatalyzed Direct Arylation of Fluoroarene Derivatives with Aryl Bromides

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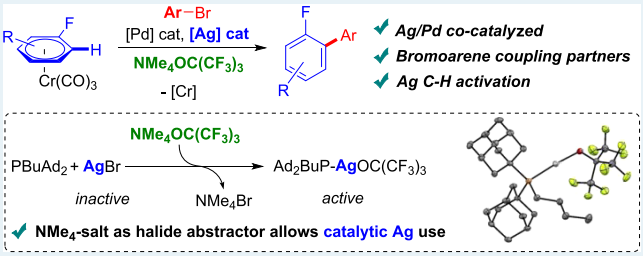
ABSTRACT: Diverse C−H functionalizations catalyzed by Pd employ Ag(I) salts added as halide abstractors or oxidants. Recent reports have shown that Ag can also perform the crucial C−H activation step in several of these functionalizations. However, all of these processes are limited by the wasteful requirement for (super)stoichiometric Ag(I) salts. Herein, we report the development of a Ag/Pd cocatalyzed direct arylation of (fluoroarene) chromium tricarbonyl complexes with bromoarenes. The small organic salt, $NMe_4OC(CF_3)_3$, added as a halide abstractor, enables the use of a catalytic amount of Ag, reversing the rapid precipitation of AgBr. We have shown through H/D scrambling and kinetic studies that a (PR_3)Ag-alkoxide is responsible for C−H activation, a departure from previous studies with Ag carboxylates. Furthermore, the construction of biaryls directly from the simple arene is achieved via a one-pot chromium tricarbonyl complexation/C−H arylation/decomplexation sequence using (pyrene)$Cr(CO)_3$ as a $Cr(CO)_3$ donor.



KEYWORDS: *silver catalysis, palladium, C−H activation, arene exchange, homogeneous, (arene) chromium tricarbonyl*

1. INTRODUCTION

In recent years, direct C−H arylation has become a versatile tool for the construction of biaryls. This transformation typically involves in situ metalation of an aryl C−H bond and subsequent coupling with an aryl donor. Many different transition metals have been found to catalyze this transformation, including Rh,[1] Ru,[2] Ir,[3] Co,[4] Cu,[5] Fe,[6] and Au,[7] but the most frequently used continues to be Pd.[8]

In contrast to the mild conditions possible for C−H arylations using bis(aryliodonium) salts and iodoarenes as coupling partners,[9] the use of bromoarenes in Pd-catalyzed direct arylation reactions typically requires high temperature and electron-donating phosphine ligands to facilitate the more challenging oxidative addition step.[10] Intriguingly, Hartwig demonstrated that the electron-donating phosphine ligand actually inhibits the Pd(II)-mediated C−H activation step of simple arenes.[11] This presents a quandary for how to approach reaction design for direct arylation with bromoarenes, as any ligand used must strike a delicate balance between promoting oxidative addition and inhibiting C−H activation. With this issue in mind, we envisaged that a cooperative bimetallic catalytic system, in which an electron-rich Pd undergoes oxidative addition and mediates C−C bond formation while another metal performs C−H activation, could provide a resourceful solution.

Ag(I) salts are often employed as stoichiometric halide abstractors in Pd-catalyzed direct arylation reactions, particularly those using iodoarenes as coupling partners, to prevent inhibition of the Pd catalyst.[9,12] We recently demonstrated through H/D exchange, stoichiometric and kinetic studies that phosphine-ligated Ag-carboxylate salts are actually responsible for the crucial C−H activation step in the Pd-catalyzed arylation of electron-deficient arenes (Scheme 1a).[13] Simultaneously, Sanford reported similar observations on the oxidative homocoupling of thiophenes and fluoroarenes (Scheme 1b).[14] Hartwig further demonstrated that AgOPiv mediated the C−H activation in a regioselective Pd-catalyzed allylation of simple arenes (Scheme 1c).[15] Recently, we uncovered an unexpected mechanistic switch in the direct arylation of (benzo)-thiophenes, in which a Pd-catalyzed β-arylation was outcompeted by a Ag-mediated (but still Pd-catalyzed) α-arylation at low concentrations of Pd (Scheme 1d).[16] In all of these methodologies, however, super-stoichiometric Ag salts were found to be required for reactivity.

More recently, a Ag/Au cocatalyzed oxidative coupling between fluoroarenes and pyrazoles was demonstrated to proceed via Ag-catalyzed C−H activation of the electron-deficient coupling partner.[17] Although no analogous Ag/Pd cocatalyzed system has yet been developed, we reasoned that such a system would make an ideal direct arylation with

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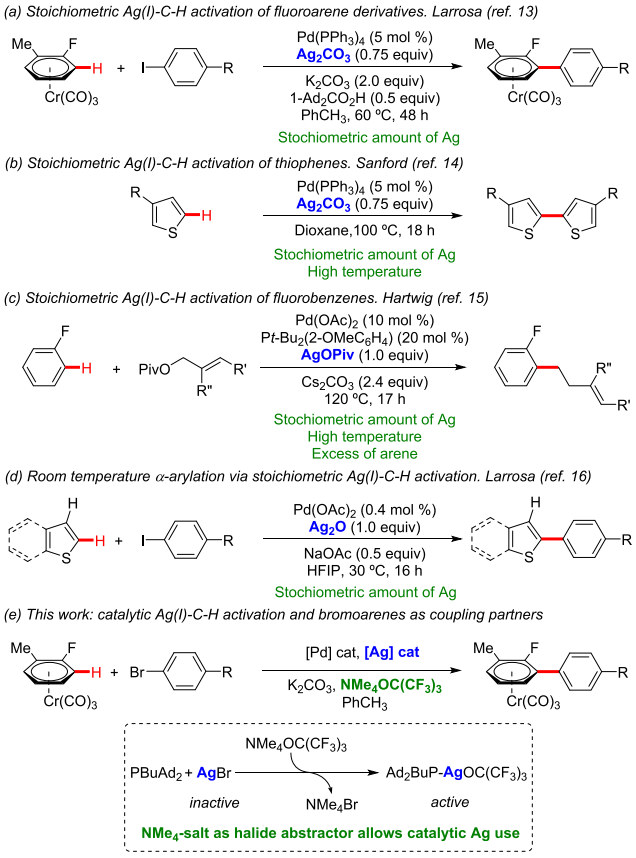
Scheme 1. Ag(I)-Mediated C−H Functionalizations in Pd/Ag Systems

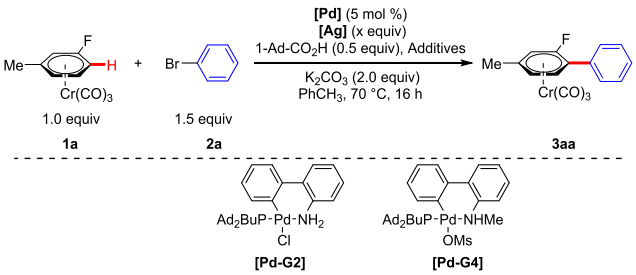


bromoarene coupling partners. However, a number of challenges would need to be addressed to develop such a process: (1) Ag(I) salts are oxidizing agents and can oxidize electron-rich Pd(0)-species to Pd(II), which could present a problem when using bromoarenes instead of the more reactive iodoarenes; (2) Ag(I) forms highly insoluble bromide salts, which would quickly remove the catalyst as the reaction progresses. Herein, we report the development of the first Ag/Pd cocatalyzed C−H arylation system and its application to the mild arylation of fluorobenzene derivatives with bromoarenes (Scheme 1e).

2. RESULTS AND DISCUSSION

2.1. Development of a Ag/Pd Cocatalyzed C−H Arylation Process Using Bromoarenes as Coupling Partners. We began our investigation testing conditions we previously developed for the direct arylation of (fluoroarene)-$Cr(CO)_3$ with iodoarenes.[18] When these conditions were applied to the arylation of 3-fluorotoluene chromium tricarbonyl **1a** with bromobenzene **2a**, no reaction was detected (Table 1, entry 1), in line with our previous observation.[18] Our group recently reported that adding up to 60 mol % of PPh_3 had a beneficial effect on the reaction rate for the Pd-catalyzed direct C−H arylation with iodoarenes, due to a faster Ag-mediated C−H activation step.[13] In this case, however, this additive did not enable reactivity (entry 2). The results in entries 1 and 2 suggested that the oxidative addition step with less reactive bromobenzene (vs iodoarenes) may be problematic. Accordingly, the addition of 20 mol % of SPhos, a more electron-donating ligand than PPh_3, resulted in a small amount of desired product **3aa** (entry 3). We postulated that deactivation of Pd(0) via oxidation to Pd(II) by the Ag(I) salt could be competing with the oxidative addition of bromoarene **2a**. Thus, a reduction of the amount of Ag(I) salts employed could be beneficial by reducing the rate of undesired Pd oxidation. Our group has previously reported on the use of NMe_4 salts as halide abstractors as an alternative to Ag(I) salts

Table 1. Effect of the Change in Reaction Variables on the Direct Arylation of 3-Fluorotoluene Chromium Tricarbonyl 1e with Bromobenzene 2a



entry	[Ag] (equiv)	[Pd]	additives (equiv)	3aa (%)[a]
1	Ag_2CO_3 (0.75)	$Pd(PPh_3)_4$		0
2	Ag_2CO_3 (0.75)	$Pd(PPh_3)_4$	PPh_3 (0.6)	<1
3	Ag_2CO_3 (0.75)	$Pd(PPh_3)_4$	SPhos (0.2)	6
4	Ag_2CO_3 (0.10)	$Pd(PPh_3)_4$	SPhos (0.2), $NMe_4OC(CF_3)_3$ (1.5)	12
5	Ag_2CO_3 (0.10)	**Pd-G2**	SPhos (0.2), $NMe_4OC(CF_3)_3$ (1.5)	51
6[b]	AgOCOAd (0.20)	**Pd-G2**	$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5)	61
7[b]	AgOCOAd (0.20)	**Pd-G4**	$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5)	65
8[b]	AgOCOAd (0.20)	**Pd-G4**	$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5), K_2CO_3 (4.0)[d]	73
9[b,c]	AgBr (0.20)	**Pd-G4**	$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5), K_2CO_3 (4.0)[d]	90
10[b,c]		**Pd-G4**	$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5), K_2CO_3 (4.0)[d]	0
11[b,c]	AgBr (0.20)		$PBuAd_2$ (0.2), $NMe_4OC(CF_3)_3$ (1.5), K_2CO_3 (4.0)[d]	0

[a]Reaction carried out on a scale of 0.1 mmol of **1a** and yield determined by ^1H nuclear magnetic resonance (NMR) using nitrobenzene as internal standard. [b]1-$AdCO_2H$ not added to this reaction. [c]Reaction carried out at 75 °C. [d]4 equiv of K_2CO_3 was used in total.

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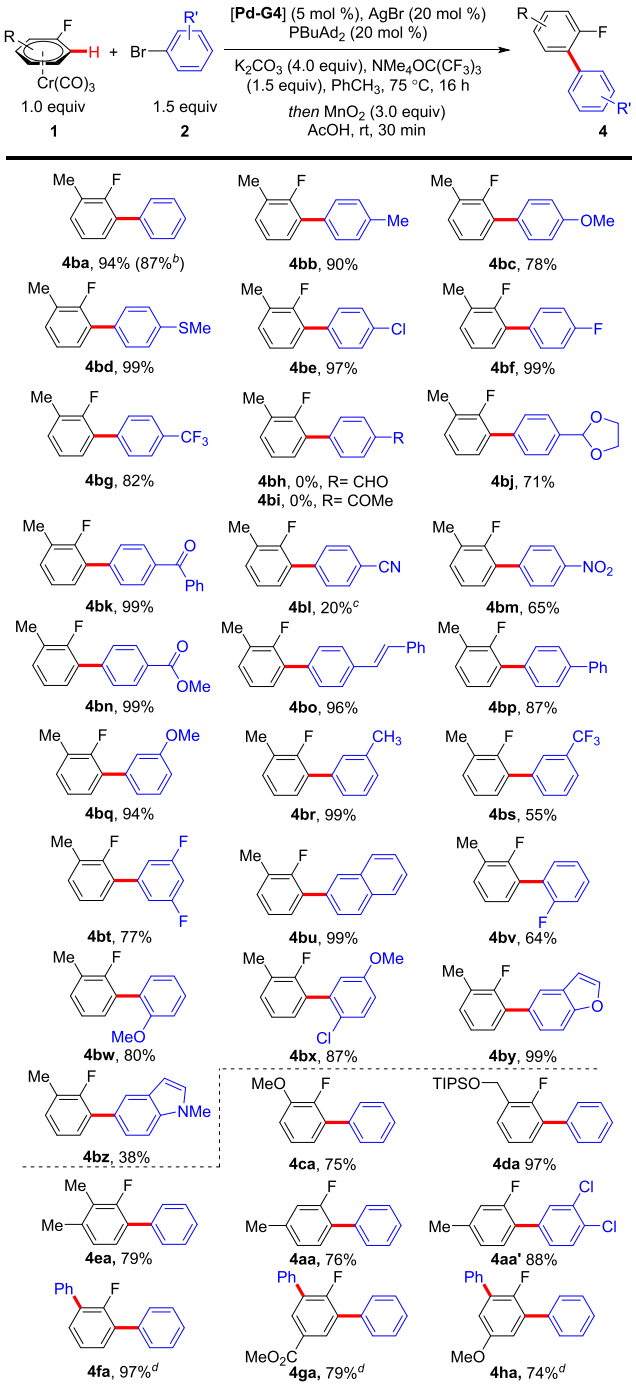
in a range of Pd- and Ru-catalyzed direct arylations.[19] We hypothesized that NMe_4 salts may be able to regenerate active Ag(I)-species from unreactive AgBr and thus be suitable stoichiometric bromide abstractors for this process (Scheme 1e, box). This would allow the use of the Ag(I) salt to mediate C−H activation in a catalytic fashion, while slowing down the deleterious Pd(0)-oxidation pathway. To test this hypothesis, we lowered the Ag(I) salt loading to 0.1 equiv of Ag_2CO_3, in combination with 1.5 equiv of $NMe_4OC(CF_3)_3$ (entry 4). Gratifyingly, the 7.5-fold reduction in the Ag loading led to a marked increase in reactivity, providing a 12% yield of **3aa**. Further optimization revealed that Buchwald's precatalyst **Pd-G2** led to a significant improvement in the yield of **3aa** to 51% (entry 5). Replacing the Ag_2CO_3 catalyst and $AdCO_2H$ additive, with just 20 mol % of AgOCOAd, in combination with $PBuAd_2$ as a ligand further increased the yield of **3aa** (entry 6). The use of a more active Pd precatalyst, **Pd-G4**, in which Cl is avoided, led to an additional small yield increase (entry 7). Increasing the loading of K_2CO_3 to 4 equiv resulted in 73% of **3aa** (entry 8). Remarkably, the use of AgBr instead of AgOCOAd resulted in a significant increase in the reaction efficiency, affording an excellent 90% yield of **3aa** (entry 9). This result reveals that the carboxylate base is not needed to carry out the C−H activation in this system, a role that may be played instead by either carbonate or the perfluoro-*tert*-butylalkoxide.[20] Conversely, the reaction did not proceed at all in the absence of either the Pd or the Ag catalysts (entries 10 and 11), confirming that both are essential for the observed reactivity. Note that the mass balance of the reaction was accounted for with unreacted **1a** being recovered.

2.2. Scope of the Ag/Pd Cocatalyzed C−H Arylation.

Next, the scope of the direct C−H arylation of fluoroarene−chromium tricarbonyl complexes **1** with aryl bromides **2** as coupling partners (Table 2) was investigated. The reaction tolerated a variety of functionalities at the *para* positions of the aryl bromide, affording the corresponding biaryls (**4ba**−**4bp**) in moderate to excellent yields. Halo groups such as −Cl (**4be**) and −F (**4bf**) showed excellent reactivity, widening the opportunity for further functionalization. Bromoarenes with trifluoromethyl (**4bg**) and nitro (**4bm**) electron-withdrawing groups afforded 82 and 65% yields, respectively. Aldehyde- and methylketone-bearing bromoarenes **2h** and **2i** were not compatible with our reaction conditions, with starting material recovered unreacted in both cases. On the other hand, a protected aldehyde (**4bj**) and a phenylketone (**4bk**) exhibited very good reactivity. Low reactivity was observed with cyano (**4bl**) substituent; nonetheless, CO_2Me (**4bn**) and alkene (**4bo**) functional groups were compatible with the system. More electron-donating SMe (**4bd**), Me (**4bb**), and OMe (**4bc**) substituents gave good yields. This methodology was also applicable to *meta*- (**4bq**−**4bu**) and *ortho*-substituted bromoarenes (**4bv**−**4bx**). Additionally, bromoheteroarenes containing benzofuran (**4by**) and indole (**4bz**) cores reacted to afford biaryl products in 99 and 38% yields, respectively. Aryl triflates and tosylates were found to be unreactive in this system. Finally, the reaction of **1b** with **2a** was scaled up to a 2 mmol scale, giving the desired arylation product **4ba** in an 87% yield.

We then turned our attention to the exploration of the scope of fluoroarene−chromium complexes with bromobenzene **2a** as the coupling partner. The reaction was compatible with both electron-donating and -withdrawing functionalities such as OMe (**4ca**), CH_2OTIPS (**4da**), and CO_2Me (**4ga**). When a

Table 2. Scope of the Direct C−H Arylation of Fluoroarene−Chromium Tricarbonyl Complexes 1 with Bromoarenes 2[a,b,c,d]



[a]Reactions carried out on a scale of 0.5 mmol of **1**. [b]Performed on a 2 mmol scale. [c]Yield determined by ^1H NMR analysis using nitrobenzene as an internal standard. [d]3 equiv of bromoarene used.

methyl group was present at the *meta* position, the arylation primarily took place at the less hindered site (**4aa**−**4aa′**). Finally, when a substituent was present at *para* position, bisarylated adducts **4ga**−**4ha** were obtained with 3 equiv of bromobenzene **2a** in good to very good yields.

2.3. Mechanistic Proposal and Mechanistic Studies.

The mechanistic proposal for our Ag/Pd cocatalyzed C−H arylation of fluorobenzene complex **1** has been outlined in

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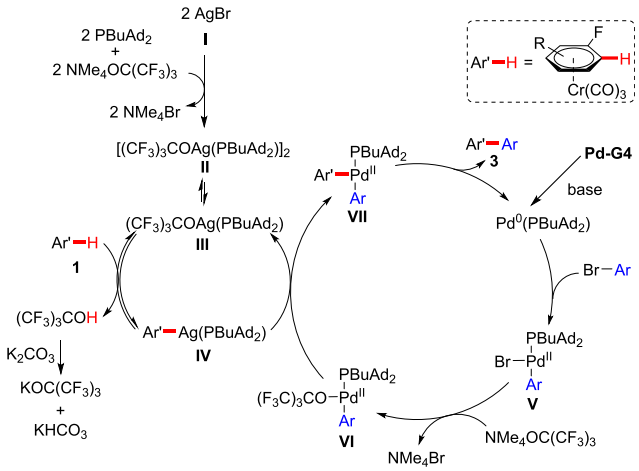
Scheme 2. We hypothesized that phosphine-ligated Ag(I)-alkoxide **III**, formed in situ by the reaction of $PBuAd_2$, AgBr,

Scheme 2. Proposed Mechanism for Ag(I)/Pd Cocatalyzed C−H Arylation of Fluorobenzene Derivatives with Bromoarenes



and $NMe_4OC(CF_3)_3$, performs C−H activation on arene complex **1**, forming Ag(I)-aryl species **IV**. These, in turn, enter into a Pd(0)/Pd(II) catalytic cycle through transmetalation with Pd(II)-alkoxide **VI** to form **VII**, while regenerating Ag(I)-species **III**. Bis-aryl-Pd species **VII** then undergoes reductive elimination to form the product **3**.

We first investigated the proposed Ag-catalyzed C−H activation step. By treating complex **1b** with various components from our reaction system, in the presence of D_2O, we studied the H/D exchange resulting from a reversible C−H activation process (Table 3). The use of 20 mol % of AgBr only and in combination with either 20 mol % of $PBuAd_2$ or 1.5 equiv $NMe_4OC(CF_3)_3$ afforded no deuteration of **1b** (Table 3, entries 1−3). As predicted, when all three components were used in combination, 50% deuteration of **1b** was observed after only 2 h (Table 3, entry 4). This result indicates that perfluoro-*tert*-butoxide is a suitable base to carry out C−H activation in combination with Ag(I), despite its monodentate nature, but only in the presence of the phosphine ligand. Further addition of K_2CO_3 as a terminal base further enhanced the deuteration of **1b**, yielding 83% of deuterated starting material **1b** (Table 3, entry 5). The beneficial effect of K_2CO_3 could be explained through the removal of perfluoro-*tert*-butanol from the mixture, as shown in Scheme 2, thus favoring the C−H activation equilibrium toward **IV**. When **1b** was instead treated with D_2O under the standard coupling conditions but in the absence of AgBr, no deuteration or biaryl coupling was observed (Table 3, entry 6), further demonstrating key role of the Ag(I) salt in the C−H activation step. These results point toward a similar overall mechanism to those observed in our previous studies of Ag-mediated C−H activation,[13,16] albeit with subtly different kinetically relevant steps. Here, instead of rate-limiting transmetalation or C−H activation, we observe a situation where both of these steps are kinetically relevant.

Given the well-known affinity of Ag(I) for bromide,[21] we carried out stoichiometric NMR studies to determine whether $NMe_4OC(CF_3)_3$ is indeed able to abstract the bromide and generate the proposed Ag(I)-alkoxide. When $PBuAd_2$ and AgBr were mixed with $NMe_4OC(CF_3)_3$, the formation of $(PBuAd_2)AgOC(CF_3)_3$ could be confirmed by ^{31}P and ^{19}F NMR (see Figures S3 and S4 in the Supporting Information). The identity and structure of $(PBuAd_2)AgOC(CF_3)_3$ (**III**) were confirmed by single-crystal X-ray diffraction analysis (Figure 1). These experiments are consistent with both the formation of Ag-alkoxide **III** from AgBr and its proposed role on the C−H activation of **1** (Scheme 2).

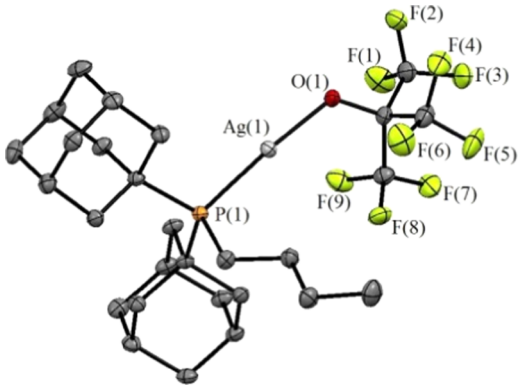
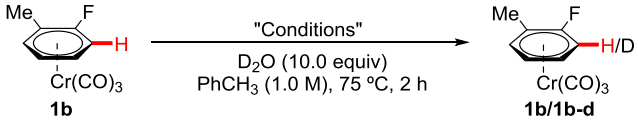


Figure 1. ORTEP plot of $(PBuAd_2)AgOC(CF_3)_3$ (**III**). Selected bonds and angles: P−Ag, 2.332 Å; O−Ag, 2.086 Å; O−Ag−P 173.6°. All hydrogen atoms are omitted for clarity.

To further investigate the reaction mechanism, we applied reaction progress kinetic analysis (RPKA)[22] and variable-time normalization analysis (VTNA).[23] We began by examining the stability of the catalysts during the reaction by carrying out two

Table 3. H/D Scrambling of Fluoroarene−Chromium Complex 1b



entry	conditions	1b/1b-d[a]
1	AgBr (20 mol %)	100:0
2	$PBuAd_2$ (20 mol %) + AgBr (20 mol %)	100:0
3	AgBr (20 mol %) + $NMe_4OC(CF_3)_3$ (1.5 equiv)	100:0
4	$PBuAd_2$ (20 mol %) + AgBr (20 mol %) + $NMe_4OC(CF_3)_3$ (1.5 equiv)	50:50
5	$PBuAd_2$ (20 mol %) + AgBr (20 mol %) + $NMe_4OC(CF_3)_3$ (1.5 equiv) + K_2CO_3 (4.0 equiv)	17:83
6	**Pd-G4** (5 mol %) + PhBr (1.5 equiv) + K_2CO_3 (4.0 equiv) + $NMe_4OC(CF_3)_3$ (1.5 equiv)	100:0

[a]Ratios were determined by ^1H NMR.

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kinetic runs under "same-excess" conditions (Figure 2). A time-adjusted plot[24] (Figure 2a) from reactions carried out

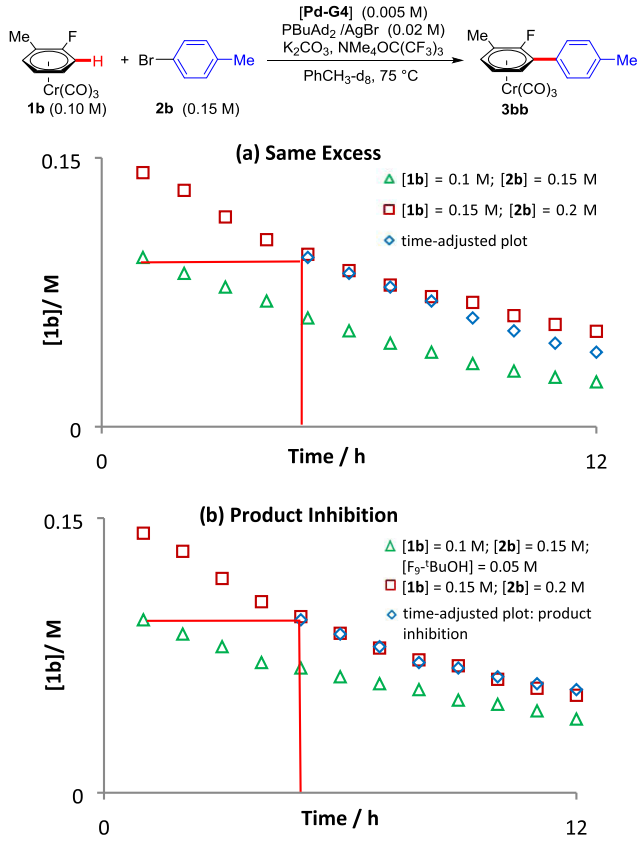

Figure 2. Time-adjusted (a) same-excess experiment and (b) same-excess experiment in the presence of F_9-^{t}BuOH.

with initial concentrations of either 0.1 or 0.15 M of **1b** (and an [excess] of 0.05 M) showed a small but reproducible deviation between the two traces. This suggested that either product inhibition and/or catalyst deactivation were occurring. We thought that perfluoro-*tert*-butanol, formed in the C−H activation step, may be responsible for the slight inhibition observed. When the same-excess experiment was repeated under standard conditions with 0.05 M of added perfluoro-*tert*-butanol, a good match was obtained (Figure 2b) between the two kinetic runs, confirming the small inhibitory effect of this side product and indicating that no significant catalyst decomposition is occurring. Therefore, VTNA could still be applied to determine the orders on the different components in the reaction (Figure 3).[23] The kinetic analyses revealed positive orders on both catalysts, Pd and Ag, and arene **1b** and an order zero on bromoarene **2b**. These data are consistent with both the transmetalation (**IV** and **VI** to **III** and **VII**) and the C−H activation (**III** and **1** to **IV**) steps contributing to the rate of the reaction simultaneously, with the C−H activation step being in quasi-equilibrium. An order of 0.5 in Ag catalyst suggests the existence of an inactive Ag(I)-dimer resting state (such as **II**) in equilibrium with active monomeric Ag(I)-alkoxide **III**, which performs kinetically relevant C−H activation.[25] The partial order in Pd is typical of cocatalyzed processes where the order may range from 0 to 1, depending on the rate of the interconnecting step. For example, in our case, the partial order in Pd is consistent with a relatively fast, but still relevant, transmetalation step. An order

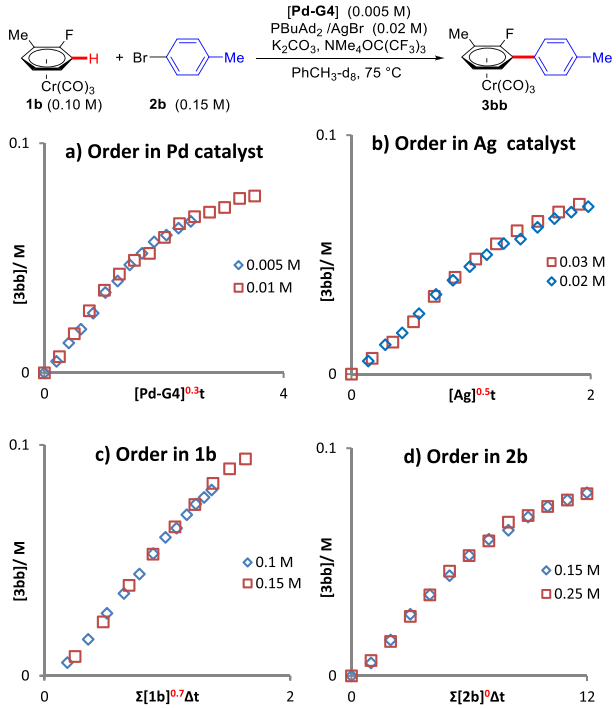

Figure 3. Determination of orders of reaction of the different components using VTNA.

of 0.7 in **1b** indicates that the C−H activation step is an equilibrium displaced toward **1b**. An order of 0 in bromoarene **2b** indicates that the oxidative addition to Pd(0) is not involved in the rate of the reaction and suggests that this step is fast. The order in $NMe_4OC(CF_3)_3$ salt could not be determined due to its very low solubility in toluene; however, kinetic runs with different stirring rates provided identical reaction profiles, suggesting that the order may be zero.[26] Taken together with the H/D exchange experiments in Table 3, these results are strongly consistent with the proposed mechanism. In support of our analysis, we simulated the proposed mechanism using COPASI,[27] which allowed the identification of a set of kinetic constants replicating the observed kinetic orders for all reaction components (see Figure S13 in the Supporting Information).

2.4. One-Pot Protocol with in Situ Formation of Cr Complex. Finally, we considered whether we could further improve the practical utility of this C−H arylation methodology by developing a one-pot protocol that would start from the fluoroarene, rather than its Cr complex. Achieving such a process would require developing a mild set of complexation conditions that would be compatible with the subsequent arylation step. Typical standard conditions for the synthesis of (arene)$Cr(CO)_3$ complexes involve reflux in ^{n}Bu$_2$O for prolonged periods and would therefore be unsuitable for a one-pot protocol. Previous studies have shown that polyarene−Cr complexes are able to undergo arene exchange under relatively mild conditions.[28] A survey of such polyarene complexes revealed (pyrene)$Cr(CO)_3$ (**1l**) as a suitable $Cr(CO)_3$ donor for the efficient formation of fluorobenzene complexes (Scheme S10 and Table S9 in the Supporting Information). Accordingly, a mixture of **1l** and fluorotoluene **5b** in dioxane heated at 90 °C for 16 h afforded **1b** in an excellent 86% yield (Scheme 3a). Gratifyingly, this protocol for the preparation of **1b** was found to be compatible with the

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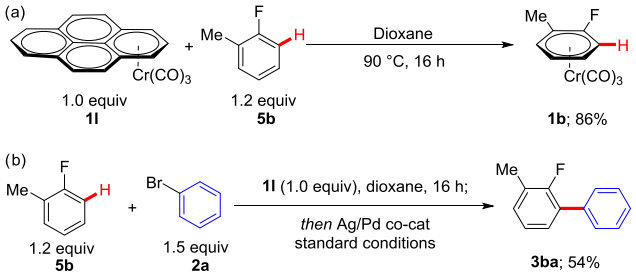
Scheme 3. (a) Arene Exchange and (b) One-Pot Sequential Complexation/C−H Arylation of Fluoroarene



subsequent arylation reaction conditions. Thus, simple addition to the same flask of bromoarene **2a** and the other arylation components, followed by in situ decomplexation, afforded **3ba** in a 54% yield (Scheme 3b). This proof-of-principle reaction sets the stage for the extension of this methodology with free fluoroarene substrates in one pot without isolating the chromium tricarbonyl complex, thus increasing its practicality and synthetic utility.

3. CONCLUSIONS

In conclusion, we have developed the first Ag/Pd cocatalyzed C−H arylation process. This catalytic system is capable of regioselective direct C−H arylation of fluoroarenes with bromoarenes using π-complexation to $Cr(CO)_3$ to enhance the fluoroarene reactivity. Key to developing this protocol was the identification of $NMe_4OC(CF_3)_3$ as a halide abstractor capable of removing Br from AgBr, to regenerate the catalytic Ag-species. This system is able to operate under relatively mild conditions using Ag(I) to carry out the C−H activation and Pd to carry out the bromoarene oxidative addition and reductive elimination steps, in a synergistic system. Our proposed mechanism is fully consistent with H/D exchange experiments, in situ NMR identification of catalytic intermediates, and observed partial kinetic orders on both catalysts and the arene substrate. We have also developed a new one-pot sequential arene complexation/arylation technique for the synthesis of biaryls. This investigation opens the door for the future development of Ag/Pd cocatalyzed systems for C−H functionalization.

4. EXPERIMENTAL SECTION

4.1. General Procedure for Biaryl Synthesis via Pd/Ag Catalytic System. A mixture of **Pd-G4** (18.6 mg, 0.025 mmol, 5 mol %), AgBr (18.8 mg, 0.1 mmol, 20 mol %), $PBuAd_2$ (37.7 mg, 0.1 mmol, 20 mol %), K_2CO_3 (276.4 mg, 4.0 equiv, 2.0 mmol), $NMe_4OC(CF_3)_3$ (232.6 mg, 1.5 equiv, 0.75 mmol), arene−chromium complex **1** (1.0 equiv, 0.5 mmol), and bromoarene **2** (1.5 equiv, 0.75 mmol) in $PhCH_3$ (0.5 mL) was stirred at 75 °C for 16 h in a flame-dried reaction vial. The reaction setup was covered with aluminum foil to prevent photodecomposition. After this time, MnO_2 (130.4 mg, 1.5 mmol, 3 equiv) in AcOH (3.0 mL) was added and stirred at room temperature for 30 min. The resulting mixture was filtered through celite, concentrated under reduced pressure, and purified through column chromatography to afford the desired biaryl products **4**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.9b05334.

Representative ^{1}H NMR; effect of additives on the direct arylation; screening of different palladium precatalysts, silver salts, and ligands; effect of TMP on the direct arylation; temperature screening of the direct arylation; previously reported chromium complexes; experimental procedures; and characterization data (PDF)

X-ray data for $C_{104}H_{172}Ag_4Br_4Cl_6P_4$ (CIF)

X-ray data for $C_{28}H_{39}AgF_9OP$ (**III**) (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected examples of Rh-catalyzed C−H arylation: (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. Arylation of Heterocycles via Rhodium-Catalyzed C−H Bond Functionalization. *Org. Lett.* **2004**, *6*, 35−38. (b) Bouffard, J.; Itami, K. Rhodium-Catalyzed C−H Bond Arylation of Arenes. *Top. Curr. Chem.* **2009**, *292*, 231−280. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010**, *110*, 624−655. (d) Zhang, B.; Wang, H.-W.; Kang, Y.-S.; Zhang, P.; Xu, H.-J.; Lu, Y.; Sun, W.-Y. Rhodium-Catalyzed Direct Ortho C−H Arylation using Ketone as Directing Group with Boron Reagent. *Org. Lett.* **2017**, *19*, 5940−5943. (e) Qiu, X.; Deng, H.; Zhao, Y.; Shi, Z. Rhodium-Catalyzed, P-Directed Selective C7 Arylation of Indoles. *Sci. Adv.* **2018**, *4*, No. eaau6468.

(2) Selected examples of Ru-catalyzed C−H arylation: (a) Arockiam, P. B.; Bruneau, C.; Dixneauf, P. H. Ruthenium(II)-Catalyzed C−H Bond Activation and Functionalization. *Chem. Rev.* **2012**, *112*, 5879−5918. (b) Nareddy, P.; Jordan, F.; Szostak, M. Recent Developments in Ruthenium-Catalyzed C−H Arylation: Array of Mechanistic Manifolds. *ACS Catal.* **2017**, *7*, 5721−5745. (c) Shan, C.; Zhu, L.;

Qu, L.-B.; Bai, R.; Lan, Y. Mechanistic View of Ru-Catalyzed C−H Bond Activation and Functionalization: Computational Advances. *Chem. Soc. Rev.* **2018**, *47*, 7552−7576. (d) Simonetti, M.; Cannas, D. M.; Just-Baringo, X.; Vitorica-Yrezabal, I. J.; Larrosa, I. Cyclometallated Ruthenium Catalyst Enables Late-Stage Directed Arylation of Pharmaceuticals. *Nat. Chem.* **2018**, *10*, 724−731.

(3) Selected examples of Ir-catalyzed C−H arylation: (a) Shin, K.; Park, S.-W.; Chang, S. Cp*Ir(III)-Catalyzed Mild and Broad C−H Arylation of Arenes and Alkenes with Aryldiazonium Salts leading to the External Oxidant-Free Approach. *J. Am. Chem. Soc.* **2015**, *137*, 8584−8592. (b) Gao, P.; Liu, L.; Shi, Z.; Yuan, Y. Iridium(III)-Catalyzed Regioselective Direct Arylation of sp^2 C−H Bonds with Diaryliodonium Salts. *Org. Biomol. Chem.* **2016**, *14*, 7109−7113. (c) Shin, K.; Park, Y.; Baik, M.-H.; Chang, S. Iridium-Catalysed Arylation of C−H Bonds enabled by Oxidatively Induced Reductive Elimination. *Nat. Chem.* **2018**, *10*, 218−224.

(4) Selected examples of Co-catalyzed C−H arylation: (a) Sezen, B.; Sames, D. Cobalt-Catalyzed Arylation of Azole Heteroarenes via Direct C−H Bond Functionalization. *Org. Lett.* **2003**, *5*, 3607−3610. (b) To, C. T.; Chan, T. L.; Li, B. Z.; Hui, Y. Y.; Kwok, T. Y.; Lam, S. Y.; Chan, K. S. C−H Arylation of Unactivated Arenes with Aryl Halides Catalyzed by Cobalt Porphyrin. *Tetrahedron Lett.* **2011**, *52*, 1023−1026. (c) Tilly, D.; Dayaker, G.; Bachu, P. Cobalt Mediated C−H Bond Functionalization: Emerging Tools for Organic Synthesis. *Catal. Sci. Technol.* **2014**, *4*, 2756−2777. (d) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C−H Activation. *ACS Catal.* **2016**, *6*, 498−525. (e) Li, Y.; Qian, F.; Wang, M.; Lu, H.; Li, G. Cobalt-Catalyzed Decarboxylative C−H (Hetero)Arylation for the Synthesis of Arylheteroarenes and Unsymmetrical Biheteroaryls. *Org. Lett.* **2017**, *19*, 5589−5592.

(5) Selected examples of Cu-catalyzed C−H arylation: (a) Do, H.-Q.; Daugulis, O. Copper-Catalyzed Arylation of Heterocycle C−H Bonds. *J. Am. Chem. Soc.* **2007**, *129*, 12404−12405. (b) Do, H.-Q.; Khan, R. K. M.; Daugulis, O. A General Method for Copper-Catalyzed Arylation of Arene C−H Bonds. *J. Am. Chem. Soc.* **2008**, *130*, 15185−15192. (c) Do, H.-Q.; Daugulis, O. Copper-Catalyzed Arene C−H Bond Cross-Coupling. *Chem. Commun.* **2009**, 6433−6435. (d) Phipps, R. J.; Gaunt, M. J. A Meta-Selective Copper-Catalyzed C−H Bond Arylation. *Science* **2009**, *323*, 1593−1597. (e) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. Copper-Catalyzed C−H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (f) Honraedt, A.; Raux, M.-A.; Grognec, E. A.; Jacquemin, D.; Felpin, F.-X. Copper-Catalyzed Free-Radical C−H Arylation of Pyrroles. *Chem. Commun.* **2014**, *50*, 5236−5238. (g) Jia, N.-N.; Tian, X.-C.; Qu, X.-X.; Chen, X.-X.; Cao, Y.-N.; Yao, Y.-X.; Gao, F.; Zhou, X. L. Copper-Catalyzed Direct 2-Arylation of Benzoxazoles and Benzoimidazoles with Aryl Bromides and Cytotoxicity of Products. *Sci. Rep.* **2017**, *7*, No. 43758.

(6) Selected examples of Fe-catalyzed C−H Arylation: (a) Liu, W.; Cao, H.; Lei, A. Iron-Catalyzed Direct Arylation of Unactivated Arenes with Aryl Halides. *Angew. Chem., Int. Ed.* **2010**, *49*, 2004−2008. (b) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed C−H Bond Activation. *Chem. Rev.* **2017**, *117*, 9086−9139. (c) Gallego, D.; Baquero, E. A. Recent Advances on Mechanistic Studies on C−H Activation Catalyzed by Base Metals. *Open Chem.* **2018**, *16*, 1001−1058. (d) Doba, T.; Matsubara, T.; Ilies, L.; Shang, R.; Nakamura, E. Homocoupling-Free Iron-Catalysed twofold C−H Activation/Cross-couplings of Aromatics via Transient Connection of Reactants. *Nat. Catal.* **2019**, *2*, 400−406.

(7) Selected examples of Au-catalyzed C−H arylation: (a) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. Gold-Catalyzed Direct Arylation. *Science* **2012**, *337*, 1644−1648. (b) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. Au-Catalyzed Cross-Coupling of Arenes via Double C−H Activation. *J. Am. Chem. Soc.* **2015**, *137*, 15636−15639. (c) Hata, K.; Ito, H.; Segawa, Y.; Itami, K. Pyridylidene Ligand facilitates Gold-Catalyzed Oxidative C−H Arylation of Heterocycles. *Beilstein J. Org. Chem.* **2015**, *11*, 2737−2746. (d) Cresswell, A. J.; Lloyd-Jones, G. C. Room-Temperature Gold-Catalysed Arylation of Heteroarenes: Complementarity to Palladium Catalysis. *Chem. − Eur. J.* **2016**, *22*, 12641−12645. (e) Gauchot, V.; Sutherland, D. R.; Lee, A.-L. Dual Gold and Photoredox Catalysed C−H Activation of Arenes for Aryl−Aryl Cross Couplings. *Chem. Sci.* **2017**, *8*, 2885−2889. (f) Corrie, T. J.; Ball, L. T.; Russell, C. A.; Lloyd-Jones, G. C. Au-Catalyzed Biaryl Coupling to generate 5- to 9-Membered Rings: Turnover-Limiting Reductive Elimination versus π-Complexation. *J. Am. Chem. Soc.* **2017**, *139*, 245−254. (g) Robinson, M. P.; Lloyd-Jones, G. C. Au-Catalyzed Oxidative Arylation: Chelation-Induced Turnover of *Ortho*-Substituted Arylsilanes. *ACS Catal.* **2018**, *8*, 7484−7488.

(8) Selected examples of Pd-catalyzed C−H arylation: (a) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010**, *110*, 1147−1169. (b) Simonetti, M.; Cannas, D. M.; Larrosa, I. Biaryl Synthesis via C−H Bond Activation: Strategies and Methods. *Adv. Organomet. Chem.* **2017**, *67*, 299−399. (c) Dey, A.; Agasti, S.; Maiti, D. Palladium Catalysed Meta-C−H Functionalization Reactions. *Org. Biomol. Chem.* **2016**, *14*, 5440−5453. (d) Choy, P. Y.; Wong, S. M.; Kapdi, A.; Kwong, F. Y. Recent Developments in Palladium-Catalysed Non-Directed Coupling of (Hetero)arene C−H Bonds with C−Z (Z = B, Si, Sn, S, N, C, H) Bonds in Bi(hetero)aryl Synthesis. *Org. Chem. Front.* **2018**, *5*, 288−321. (e) Felpin, F.-X.; Sengupta, S. Biaryl Synthesis with Arenediazonium salts: cross-coupling, CH-Arylation and Annulation Reactions. *Chem. Soc. Rev.* **2019**, *48*, 1150−1193.

(9) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. Room Temperature Palladium-Catalyzed 2-Arylation of Indoles. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973. (b) Lebrasseur, N.; Larrosa, I. Room Temperature and Phosphine Free Palladium Catalyzed Direct C-2 Arylation of Indoles. *J. Am. Chem. Soc.* **2008**, *130*, 2926−2927. (c) René, O.; Fagnou, K. Room-temperature Direct Arylation of Polyfluorinated Arenes under Biphasic Conditions. *Org. Lett.* **2010**, *12*, 2116−2119. (d) Colletto, C.; Islam, S.; Juliá-Hernández, F.; Larrosa, I. Room-temperature Direct β-Arylation of Thiophenes and Benzo[*b*]thiophenes and Kinetic Evidence for a Heck-type Pathway. *J. Am. Chem. Soc.* **2016**, *138*, 1677−1683.

(10) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756. (b) Lafrance, M.; Shore, D.; Fagnou, K. Mild and General Conditions for the Cross-Coupling of Aryl Halides with Pentafluorobenzene and other Perfluoroaromatics. *Org. Lett.* **2006**, *8*, 5097−5100. (c) Wang, X.; Gribkov, D. V.; Sames, D. Phosphine-Free Palladium-Catalyzed C−H Bond Arylation of Free (N−H)-Indoles and Pyrroles. *J. Org. Chem.* **2007**, *72*, 1476−1479. (d) Caron, L.; Campeau, L.-C.; Fagnou, K. Palladium-Catalyzed Direct Arylation of Nitro-substituted Aromatics with Aryl Halides. *Org. Lett.* **2008**, *10*, 4533−4536. (e) Campeau, L. C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. Palladium-Catalyzed Direct Arylation of Azine and Azole N-oxides: Reaction Development, Scope and Applications in Synthesis. *J. Am. Chem. Soc.* **2009**, *131*, 3291−3306. (f) Zeng, Y.; Zhang, C.; Yin, C.; Sun, M.; Fu, H.; Zheng, X.; Yuan, M.; Li, R.; Chen, H. Direct C−H Functionalization of Pyridine via a Transient Activator Strategy: Synthesis of 2,6-Diarylpyridines. *Org. Lett.* **2017**, *19*, 1970−1973. (g) Kim, J.; Hong, S. H. Ligand-promoted Direct C−H Arylation of Simple Arenes: Evidence for a Cooperative Bimetallic Mechanism. *ACS Catal.* **2017**, *7*, 3336−3343.

(11) Tan, Y.; Hartwig, J. F. Assessment of the Intermediacy of Aryl Palladium Carboxylate Complexes in the Direct Arylation of Benzene: Evidence for C−H Bond Cleavage by "Ligandless" Species. *J. Am. Chem. Soc.* **2011**, *133*, 3308−3311.

(12) (a) Daugulis, O.; Zaitsev, V. G. Anilide *Ortho*-Arylation by using C−H Activation Methodology. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046−4048. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp^3 C−H Bonds Catalyzed by Palladium Acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. Two Methods for Direct *Ortho*-Arylation of Benzoic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 9879−9884. (d) Shabashov, D.; Maldonado, J. R. M.; Daugulis, O. Carbon-

Hydrogen Bond Functionalization Approach for the Synthesis of Fluorenones and Ortho-Arylated Benzonitriles. *J. Org. Chem.* **2008**, *73*, 7818−7821. (e) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. Synthesis of Fluorenones from Aromatic Aldoxime Ethers and Aryl Halides by Palladium-Catalyzed Dual C−H Activation and Heck Cyclization. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462−9465.

(13) (a) Whitaker, D.; Burés, J.; Larrosa, I. Ag(I)-catalyzed C−H Activation: the Role of the Ag(I) Salt in Pd/Ag-Mediated C−H Arylation of Electron-Deficient Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 8384−8387. (b) Batuecas, M.; Luo, J.; Gergelitsová, I.; Krämer, K.; Whitaker, D.; Vitorica-Yrezabal, I. J.; Larrosa, I. Catalytic Asymmetric C−H Arylation of (η^6-Arene)Chromium Complexes: Facile Access to Planar-Chiral Phosphines. *ACS Catal.* **2019**, *9*, 5268−5278.

(14) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. Role of Silver Salts in Palladium-Catalyzed Arene and Heteroarene C−H Functionalization Reactions. *Organometallics* **2017**, *36*, 165−171.

(15) Lee, S. Y.; Hartwig, J. F. Palladium-Catalyzed, Site-Selective Direct Allylation of Aryl C−H Bonds by Silver-Mediated C−H Activation: A Synthetic and Mechanistic Investigation. *J. Am. Chem. Soc.* **2016**, *138*, 15278−15284.

(16) Colletto, C.; Panigrahi, A.; Fernández-Casado, J.; Larrosa, I. Ag(I)-C−H Activation enables Near-Room-Temperature Direct α-Arylation of Benzo[*b*]thiophenes. *J. Am. Chem. Soc.* **2018**, *140*, 9638−9643.

(17) While evidence for Ag(I) involvement in the C−H activation step was already shown and discussed in ref 7b, this was further demonstrated in thorough mechanistic studies: (a) Li, W.; Yuan, D.; Wang, G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Cooperative Au/Ag Dual-Catalyzed Cross-Dehydrogenative Biaryl Coupling: Reaction Development and Mechanistic Insight. *J. Am. Chem. Soc.* **2019**, *141*, 3187−3197. (b) Liu, J.-R.; Duan, Y.-Q.; Zhang, S.-Q.; Zhu, Y.-Y.; Jiang, Y.-Y.; Bi, S.; Hong, X. C−H Acidity and Arene Nucleophilicity as Orthogonal Control of Chemoselectivity in Dual C−H Bond Activation. *Org. Lett.* **2019**, *21*, 2360−2364.

(18) Ricci, P.; Krämer, K.; Cambeiro, X. C.; Larrosa, I. Arene-Metal π-Complexation as a Traceless Reactivity Enhancer for C−H Arylation. *J. Am. Chem. Soc.* **2013**, *135*, 13258−13261.

(19) (a) Arroniz, C.; Denis, J. G.; Ironmonger, A.; Rassias, G.; Larrosa, I. An Organic Cation as a Silver(I) Analogue for the Arylation of sp^2 and sp^3 C−H Bonds with Iodoarenes. *Chem. Sci.* **2014**, *5*, 3509−3514. (b) Simonetti, M.; Perry, G. J. P.; Cambeiro, X. C.; Juliá-Hernández, F.; Arokianathar, J. N.; Larrosa, I. Ru-Catalyzed C−H Arylation of Fluoroarenes with Aryl Halides. *J. Am. Chem. Soc.* **2016**, *138*, 3596−3606.

(20) The pKa of perfluoro-tert-butyl alcohol at 25 °C in water is 5.4. See: Dyatkin, B. L.; Mochalina, E. P.; Knunyants, I. L. The Acidic Properties of Fluorine-containing Alcohols, Hydroxylamines and Oximes. *Tetrahedron* **1965**, *21*, 2991−2995.

(21) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*; John Wiley & Sons: New York, 1988.

(22) Blackmond, D. G. Reaction Progress Kinetic Analysis: a Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302−4320.

(23) (a) Burés, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem., Int. Ed.* **2016**, *55*, 2028−2031. (b) Burés, J. Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem., Int. Ed.* **2016**, *55*, 16084−16087.

(24) Blackmond, D. G. Kinetic Profiling of Catalytic Organic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852−10866.

(25) Burés, J. What is the Order of a Reaction? *Top. Catal.* **2017**, *60*, 631−633.

(26) Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. Rational Ligand Design for the Arylation of Hindered Primary Amines guided by Reaction Progress Kinetic Analysis. *J. Am. Chem. Soc.* **2015**, *137*, 3085−3092.

(27) Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. COPASI—a COmplex PAthway SImulator. *Bioinformatics* **2006**, *22*, 3067−3074.

(28) (a) Kündig, E. P.; Perret, C.; Spichiger, S.; Bernardinelli, G. Naphthalene Complexes: V. Arene Exchange Reactions in Naphthalenechromium Complexes. *J. Organomet. Chem.* **1985**, *286*, 183−200. (b) Howell, J. A. S.; Ashford, N. F.; Dixon, D. T.; Kola, J. C.; Albright, T. A.; Kang, S. K. The Arene-Exchange Reaction in Naphthalene and Pyrene Chromium Tricarbonyl. *Organometallics* **1991**, *10*, 1852−1864.

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