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Role of Silver Salts in Palladium-Catalyzed Arene and Heteroarene C-H Functionalization Reactions

Monica D. Lotz,[†] Nicole M. Camasso,[†] Allan J. Canty,^{*,‡} and Melanie S. Sanford^{*,†}

[†]Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States [‡]School of Physical Sciences, University of Tasmania, Private Bag 75, Hobart, Tasmania 7001, Australia

Supporting Information

ABSTRACT: Silver carboxylate salts are widely used as additives in palladium-catalyzed C–H functionalization reactions. However, the role of these silver additives is often not fully understood. This paper describes an investigation of the role of AgOPiv in the stoichiometric activation of C_6F_5H at a well-defined Pd^{II} complex as well as in the Pd^{II}-catalyzed oxidative dimerization of 2-alkylthiophenes. Both in situ NMR spectroscopy and H/D exchange studies of the reactions of C_6F_5H implicate a role for AgOPiv in the C–H cleavage event, generating Ag– C_6F_5 as an intermediate. The catalytic studies show similar trends despite the different conditions and



substrates, suggesting that AgOPiv promotes a similar metalation of the thiophene in the catalytic transformations. This proposal is supported by DFT calculations, which show energetically feasible pathways for concerted metalation–deprotonation of both 2-methylthiophene and pentafluorobenzene at $[Ag(OPiv)]_2$. These studies suggest that initial metalation of C–H substrates at Ag^I carboxylates should be considered as a plausible pathway in C–H functionalization reactions involving mixtures of Ag and Pd salts.

C ilver carboxylate and carbonate salts are commonly Semployed as additives in Pd-catalyzed C–H bond functionalization reactions.¹⁻⁴ In many of these systems, the presence of the silver salt dramatically enhances the reaction rate and/or yield. However, the mechanistic origin of this enhancement is often poorly understood. The most commonly proposed roles for silver carboxylate salts in Pd-catalyzed C-H functionalization reactions are (1) AgO₂CR serving as a source of carboxylate for the Pd^{II} center (often via halide abstraction), which in turn facilitates carboxylate-assisted C-H cleavage at Pd^{II} (Scheme 1i)^{1,2} or (2) AgO₂CR acting as a terminal oxidant to (re)generate the active Pd^{II} catalyst A (Scheme 1v).^{1,3} Several other possible roles have also been proposed, including (3) AgO₂CR promoting C–C coupling (Scheme 1iv),⁴ (4) AgO₂CR reacting with Pd to form bi- or multimetallic Pd-Ag intermediates that facilitate C-H cleavage at Pd^{II} (Scheme 1iii);^{3a,d,5} and (5) AgO₂CR directly promoting C–H cleavage to form a Ag-arene intermediate (Scheme 1ii).^{3i,k,6,7} However, experimental work aimed at establishing which of these possibilities is operating in a given transformation remains relatively rare.

In this paper, we report studies aimed at unraveling the role of AgO₂CR in the stoichiometric activation of C₆F₅H. We provide spectroscopic evidence that AgOPiv reacts with C₆F₅H to afford a Ag $-C_6F_5$ complex that then undergoes transmetalation to Pd. In addition, we use experimental and DFT studies to demonstrate that the findings from this stoichiometric activation of C₆F₅H are potentially relevant to a Pdcatalyzed, AgOPiv-mediated C–H oxidative coupling of 2-alkylthiophenes.

RESULTS AND DISCUSSION

We initially focused on a stoichiometric model system to explore the role of Ag carboxylates in Pd-mediated C–H cleavage. We set two criteria for this model reaction. First, we sought an aryl–H substrate and a palladium precursor that would react to yield a stable, isolable Pd– σ -aryl product.⁸ This could enable us to selectively investigate the C–H cleavage step. Second, we sought an aryl–H substrate that was relevant to catalysis. These criteria led us to the reaction of (dtbpy)Pd(OAc)₂ (1; dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) with C₆F₅H, a substrate that has been widely used in Pd-catalyzed, Ag-mediated cross-coupling reactions.^{1f}

Our initial studies showed that the reaction of 1 with C_6F_5H in the presence of certain Ag additives affords a mixture of the Pd^{II} —pentafluorophenyl complexes 2 and 3 (Table 1). These Pd^{II} products are stable and do not undergo C–C bond-forming reductive elimination over 24 h at 60 °C. We conducted a detailed investigation of the impact of the Ag salt structure on the conversion of 1 to 2/3. As shown in Table 1, entry 1, heating complex 1 with C_6F_5H in THF at 60 °C for

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Scheme 1. Potential Roles of Silver in C–H Functionalization Reactions

Table 1. Effect of Additives on the Reaction of 1 with C_6F_5H To Afford $2/3^a$



^{*a*}Conditions: 1 (0.025 mmol), additive (0.075 mmol), C_6F_5H (1.8 mmol) in THF at 60 °C for 18 h. Yields are based on 1 serving as the limiting reagent. ^{*b*}M = Na, Cs, NMe₄. ^{*c*}M = Li, Na, Cs.

18 h afforded $\leq 1\%$ conversion to the organometallic products 2 and 3.⁹ Under otherwise identical conditions, the addition of a Ag carboxylate or carbonate salt resulted in a dramatic enhancement in conversion. AgOPiv provided a high yield of the bis(pentafluorophenyl)-Pd^{II} complex 3 (entry 2), while Ag₂CO₃, AgOAc, and AgOTFA afforded mixtures of **2** and **3** under otherwise identical conditions (entries 3–5). In contrast, Ag salts bearing weakly basic anionic ligands such as tetrafluoroborate and hexafluorophosphate provided $\leq 1\%$ of the organometallic products. The presence of Ag appears to be important for achieving high yields of **2**/3 under these conditions. For example, other M₂CO₃ and MOPiv salts (M = Li, Na, Cs, NMe₄) afforded a maximum of 9% of **2** and 2% of **3** under otherwise identical conditions (entries 8 and 9).

These initial results allow us to rule out several potential roles for AgOPiv in this specific transformation. This transformation is a redox-neutral process, and complex 3 is inert to reductive elimination. This eliminates contributions from the possibilities given by Scheme 1iv,v in this system. The low reactivity of other metal pivalate salts suggests that AgOPiv is not simply serving as a pivalate source (Scheme 1i). Thus, we hypothesized that the AgOPiv plays a role in the C–H cleavage step by forming either a Pd/Ag bimetallic or a Ag–C₆F₅ intermediate (Scheme 1ii,iii).

In an effort to observe one or both of these intermediates, we next monitored the reaction of C_6F_5H with 1/AgOPiv via ¹⁹F NMR spectroscopy. After 30 min at 60 °C, compound 4 was detected based on a diagnostic signal at approximately -105 ppm (Figure 1a). Compound 4 was consumed over the course



Figure 1. ¹⁹F NMR spectra (between -95 and -140 ppm): (a) reaction of 1, AgOPiv, and C₆F₅H after 0.5 h at 60 °C; (b) reaction of AgOPiv and C₆F₅H after 1 h at 60 °C; (c) authentic sample of Ag-C₆F₅ (synthesized from AgOTFA and LiC₆F₅).

of the reaction, with concomitant generation of products 2 and 3. As shown in Figure 1b, this same intermediate was formed when C_6F_5H and AgOPiv were combined in THF at 60 °C in the absence of Pd. In contrast, no new ¹⁹F NMR signals were observed in the reaction of C_6F_5H with CsOPiv under analogous conditions.

To confirm the assignment of 4 as a $Ag-C_6F_5$ complex, we independently synthesized this Ag complex from LiC_6F_5 and AgOTFA according to a literature procedure.¹⁰ As shown in Figure 1c, the ¹⁹F NMR spectrum of this independently prepared Ag-C_6F_5 matches that of compound 4 formed in situ from AgOPiv/C_6F_5H.¹¹ Additionally, the treatment of complex

1 with 3 equiv of an authentic sample of $Ag-C_6F_5$ produced 3 in 91% yield. 12,13

We next studied H/D exchange between C_6F_5H and D_2O (5 equiv relative to C_6F_5H) catalyzed by MOPiv. ^{17,31,k,6} The ratio of C_6F_5H to MOPiv in this experiment was the same as that in the reactions in Table 1. As shown in eq. 1, analysis by ²H NMR



spectroscopy showed 63% deuterium incorporation in reactions with AgOPiv under these conditions. In contrast, 9% and <1% deuterium incorporation were detected with CsOPiv and NMe₄OPiv, respectively, under otherwise identical conditions.¹⁴ Moreover, no deuterium exchange was observed when complex 1 was subjected to the reaction conditions in the absence of a MOPiv additive.

Collectively, these data provide evidence that AgOPiv and C_6F_5H react to generate Ag $-C_6F_5$, which can undergo transmetalation at Pd to form products 2/3.^{15,16} Notably, Nolan proposed a similar Ag-arene intermediate in the Au(IPr)(OH)/Ag₂O-catalyzed carboxylation of 1,3,5-trifluor-obenzene.^{6a} Furthermore, similar intermediates have been proposed in a number of Pd-catalyzed C₆F₅H cross-coupling reactions.^{1f,3i,k,6} However, this is a rare example of the spectroscopic observation of an organometallic Ag intermediate in such transformations.

We next sought to probe the catalytic relevance of these findings. Our initial studies focused on the 1-catalyzed oxidative dimerization of $C_6F_5H^{17}$ in the presence of AgOPiv. However, the stability of Pd intermediate 3 precluded product formation under all of the conditions examined. As such, we next examined the 1-catalyzed oxidative dimerization of 2-methyl-thiophene and 2-trifluoromethylthiophene (Table 2). Notably, the Pd-catalyzed C–H functionalization of thiophenes is well-precedented;^{18,19} furthermore, silver carboxylates and other Ag salts are commonly used as additives in these systems.^{18,19} In the literature, the role of the silver salts is primarily proposed to involve regeneration of the active catalyst by oxidation of Pd⁰ to Pd^{II} (Scheme 1v).

After some optimization, we identified conditions for the 1catalyzed oxidative dimerization of 2-methylthiophene to afford product 5 in 50% yield (TON = 5.0; Table 2, entry 2). Silver additives proved critical for this transformation (entries 2-5), with AgOPiv leading to the highest yield/TON (entry 2). The AgOPiv serves as a terminal oxidant (Scheme 1v), as indicated by the formation of a silver mirror at the end of the reaction. However, several pieces of evidence implicate an additional role for AgOPiv in this system. First, soluble Ag^I salts bearing noncoordinating counterions (e.g., AgPF₆) proved ineffective for promoting this transformation (entry 6), despite the fact that they should be competent oxidants for Pd^{0,20} Second, the use of other metal pivalate salts (e.g., Na, Cs, or NMe₄OPiv) resulted in <1 turnover of the oxidative dimerization product (entry 7). While these other metal pivalates cannot oxidize Pd^0 to Pd^{II} , if they operate in an otherwise similar fashion to AgOPiv, they should be capable of promoting 1 turnover of 1.

Table 2. 1-Catalyzed Oxidative Coupling of 2-Methylthiophene and 2-Trifluoromethylthiophene with Various Additives

R.	/ ^S 、_H	1 (0.015 mmol) additive (0.30 mmol		,s _√ R
1.0 mmol		dioxane 100 °C, 18 h	(5)	
entry	R	additive	yield of 5, $\%^a$	TON ^b
1	CH_3	none		<1
2	CH ₃	AgOPiv	50	5.0
3	CH ₃	Ag_2CO_3	19	1.9
4	CH ₃	AgOAc	15	1.5
5	CH_3	AgF	7	<1
6	CH_3	AgPF ₆	<2	<1
7	CH_3	MOPiv		<1 ^c
8	CF_3	none		<1
9	CF_3	AgOPiv	61	6.1
10	CF_3	Ag ₂ CO ₃	17	1.7
11	CF_3	AgOAc	19	1.9
12	CF_3	AgF	29	2.9
13	CF_3	AgPF ₆	<2	<1
14	CF_3	MOPiv		<1 ^c

"Yields determined on the basis of Ag^{I} , which serves as the limiting reagent and as a 2e⁻ oxidant. ^bTON of 5 reported on the basis of Pd complex 1. ^cM = Na, Cs, Me₄N.

Notably, analogous results were obtained using 2-trifluoromethylthiophene as a substrate (Table 2, entries 8-14). In this case, the AgOPiv conditions afforded the dimer in 61% yield (TON = 6.1; entry 9).

Third, as shown in eq 2, AgOPiv was found to promote H/D exchange at the 5-position of both 2-methylthiophene and 2-

trifluoromethylthiophene.²¹ This H/D exchange occurs in the absence of palladium, under conditions otherwise analogous to the catalytic oxidative dimerization reaction (1.0 mmol of thiophene, 0.30 mmol of AgOPiv in dioxane for 18 h at 100 °C, but with 20 mmol of added D₂O). In contrast, <1% deuterium incorporation was observed with CsOPiv or NMe₄OPiv under these conditions.^{22,23}

A variety of experiments were conducted in an effort to spectroscopically observe the proposed Ag-thiophene intermediate (6 with R = CF₃; eq 2) via ¹⁹F NMR spectroscopy.⁸ However, these experiments were inconclusive, possibly due to the low equilibrium population and/or the instability of 6 at the temperatures required to form this species. In view of the inability to experimentally observe putative intermediate 6, we turned to DFT to probe the feasibility of accessing this (or related) species, in conjunction with analogous computation for pentafluorobenzene reactivity as a model system.^{24,25} In considering potential mechanisms for metalation at Ag, we noted that Ag^I carboxylates typically exist as dimers containing a weak argentophilic interaction.^{26,27} For example, in the solid state, AgOAc exhibits linear "AgO2" coordination, with a Ag... Ag interaction as well as weak axial coordination from neighboring molecules to give the approximately planar motif "O".Ag(AcO- μ -O,O')₂Ag".O".^{26a} We hypothesized that in dioxane and THF solutions the solvent would likely serve as an axial ligand. These considerations are related to those adopted in studies of metalation at bimetallic Pd/Ag systems.^{5a,2}

Our calculations confirm that dimeric structures bearing two axial dioxane ligands (d) are lower in energy than the dimer with free axial coordination site(s) ($\Delta G = -4.4 \text{ kcal/mol}$). In contrast, THF has little influence, as $[\text{AgOPiv}]_2$ ·THF has a value of -0.3 kcal/mol and $[\text{AgOPiv}]_2$ ·2THF of +0.2 kcal/mol. Although these small energy differences are influenced by estimated values for corrections to the translational contribution of entropy changes,²⁹ the computed lowest energy ground state species were used as the reference energy for reaction profiles. Overall, DFT shows that monomeric AgOPiv is unlikely to be the reactive species in these transformations.³⁰

Transition structures were obtained by employing the concerted metalation-deprotonation (CMD) model³¹ applied to binuclear four-coordinate Ag^I cores. As shown in Figure 2, a variety of related transition structures were found, and these can generally be grouped into categories a and b. Category a transition states show metalation at the silver atom that is not coordinated by the carboxylate group that participates in CMD. In contrast, those in category b show CMD occurring at a single Ag^I center. The eight structures shown in Figure 2 are comprised of four closely related pairs, e.g. TS3 thi and TS4 thi, differing only in the number of coordinated solvent molecules. Each pair exhibits ΔG^{\ddagger} values within 0.4–2.0 kcal/ mol. In light of the high relative concentration of solvent and, in some cases, the presence of weak Ag---solvent interactions (e.g., 2.746 Å in TS2 thi), it is difficult to definitively select between these species for a preferred pathway in each pair. Notably, TS3 thi and TS4 thi show a possible role for the sulfur atom of 2-methylthiophene.

For the metalation of 2-methylthiophene, the transition structures **TS1_thi** and **TS2_thi** are favored over **TS3_thi** and **TS4_thi** by ~5 kcal/mol, and complete reaction profiles involving **TS1_thi** and **TS2_thi** are shown in Figure 3. The four pentafluorobenzene transition structures have similar activation barriers ($\Delta G^{\ddagger} = 24.8-25.5$ kcal/mol), and reaction profiles for these together with those for **TS3_thi** and **TS4_thi** (all supported by intrinsic reaction coordinate (IRC) analysis and potential energy scans) are provided as Supporting Information.³² Gaussview diagrams for **TS2_thi** (a representative category a transition structure) together with **TS3_C₆F**₅ (a representative category b transition structure) are shown in Figure 4.

(a) Transition structures for CMD across two Ag centers



(b) Transition structures for CMD across one Ag center



Figure 2. Potential transition structures for concerted metalation– deprotonation (CMD) of 2-methylthiophene and pentafluorobenzene at binuclear silver centers. Category a involves metalation across two Ag^I centers. Category b involves metalation at a single Ag^I center. Energies $\Delta G^{\ddagger} (\Delta H^{\ddagger})$ in kcal/mol are with respect to [AgOPiv]₂. THF. Abbreviations: d = dioxane; THF = tetrahydrofuran.

For 2-methylthiophene, the formation of an O··H interaction and a weak η^2 interaction in IIIA,B leads directly to transition structures followed by dissociation of pivalic acid to give VA,B (Figure 3). In these profiles, the weak Ag···Ag interactions are computed to cover the range of 2.684–2.805 Å. The shortest distances are observed for intermediates VA (2.794 Å) and VB (2.684 Å), where the 2-methylthienyl groups are participating in a bridging three-center-two-electron interaction (Ag-C 2.153–2.235 Å).

Computed structures for the initial products arising from the eight transition structures in Figure 2 are shown as VA,B in Figure 3 and VI–VIII in Figure 5. Ag^I species are expected to be labile, and a representative μ -C₆F₅ structure (IX) is shown for comparison with VA,B. We also note the similarity of products VA,B and IX to crystallographically characterized polymeric Ag^I pentafluorophenyl complexes containing μ -C₆F₅ groups.^{33b,34}

For 2-methylthiophene the highest calculated barrier for the process illustrated in Figure 3 (23.0 kcal/mol) should be experimentally feasible under the catalytic oxidative coupling conditions (100 $^{\circ}$ C in dioxane). In addition, these calculations



Figure 3. Energy profile for the reaction of silver pivalate with 2-methylthiophene in dioxane (d) via transition structures **TS1_thi** and **TS2_thi** showing selected distances (Å). Energies ΔG (ΔH) are given in kcal/mol. Additional data for **TS2_thi** are presented with Figure 4. Abbreviations: d = dioxane; THF = tetrahydrofuran.



Figure 4. Examples of computed TS structures for the metalation of (i) 2-methylthiophene (**TS2_thi**) via a category a transition state and (ii) pentafluorobenzene (**TS3_C**₆**F**₅) via a category b transition state. Selected bond distances are shown in Å.

demonstrate that the metalated Ag–2-methylthiophene intermediate VB is 14.4 kcal/mol uphill relative to I and 7.0 kcal/ mol higher than the analogous Ag–C₆F₅ intermediate IX.³⁵ This energy difference is consistent with our inability to detect this species experimentally. Transmetalation to Pd^{II} is then expected to be a low-energy process involving VA,B or related intermediates, on the basis of reports of related facile transmetalation from Ag^I to Pd^{II. 36,37}

In summary, this paper describes a study of the role of AgOPiv salts in the stoichiometric C–H activation of C_6F_5H



Figure 5. Computed products from the four transition structures shown in Figure 2, together with a structure calculated for a μ -C₆F₅ species (**IX**). Energies ΔG (ΔH) in kcal/mol are with respect to [AgOPiv]₂·THF.

and in the catalytic oxidative dimerization of 2-methylthiophene and 2-trifluoromethylthiophene catalyzed by $(dtbpy)Pd(OAc)_2$. Both in situ NMR spectroscopy and H/D exchange studies of the stoichiometric reactions implicate a role for AgOPiv in the C-H cleavage event, generating Ag-C₆F₅ as an intermediate. The catalytic studies show similar trends despite the different conditions and substrates, suggesting that AgOPiv promotes a similar metalation of 2-alkylthiophenes in the catalytic transformations. This proposal is supported by DFT calculations, which show energetically feasible pathways for concerted metalation-deprotonation of both 2-methylthiophene and pentafluorobenzene at $[Ag(OPiv)]_2$. These studies suggest that initial metalation of C-H substrates at Ag¹ carboxylates should be considered as a plausible pathway in C-H functionalization reactions involving mixtures of Ag carboxylates and Pd salts.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.6b00437.

Experimental and spectral details for all new compounds and all reactions reported as well as DFT energy parameters, Cartesian coordinates of all optimized structures, and Gaussview diagrams for species not shown above (PDF)

Crystallographic data for 3 (CIF) Crystallographic data for S-1 (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail for A.J.C.: Allan.Canty@utas.edu.au.

*E-mail for M.S.S.: mssanfor@umich.edu.

Notes

The authors declare no competing financial interest.

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(20) For a complete list of Ag additives screened under the reaction conditions, see the Supporting Information.

(21) These reactions were conducted on the benchtop using reagent grade dioxane in order to mimic the catalytic conditions. As such, significant quantities of residual H_2O are present, which is expected to dilute the extent of H/D exchange.

(22) Ag_2CO_3, AgOAc, and AgF all afforded ${\leq}1\%$ deuterium incorporation.

(23) No C-C coupling was detected during H/D exchange.

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(25) Computation employed the B3LYP functional for geometry optimization with dioxane or tetrahydrofuran as solvent utilizing the SDD basis set on Ag and the 6-31G(d) basis set for other atoms. Single-point energy calculations for all structures at the M06 level employed the quadruple- ξ valence def2-QZVP basis set on Ag along with the corresponding ECP and the 6-311+G(2d,p) basis set on other atoms. See the Supporting Information for further details.

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(30) A mononuclear mechanism with a transition structure similar to **TS3_thi** proceeds with a prohibitively high activation energy (59.3 kcal/mol relative to **I**). As such, we deem this pathway unlikely. See the Supporting Information for full details.

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(32) Computation for acetate analogues of the transition structures shown in Figure 2 provided trends identical with those for OPiv, illustrating discrimination between 2-methylthiophene species (ΔG^{\ddagger} = 23.0, 22.7, 28.3, and 27.6 kcal/mol for the analogues of **TS1–4_thi**) and a narrow range of values for C₆F₅H (ΔG = 25.8, 25.2, 26.7, and 24.9 kcal/mol for the analogues of **TS1–4_C₆F₅**) (see the Supporting Information for full details). We preliminarily hypothesize that the lower observed reactivity of AgOAc versus AgOPiv in these systems is due to the lower solubility of the former.

(33) Ag– C_6F_5 likely exists as a polymer. (a) Ibad, M. F.; Schulz, A.; Villinger, A. Organometallics **2015**, *34*, 3893. (b) Kuprat, M.; Lehmann, M.; Schulz, A.; Villinger, A. Organometallics **2010**, *29*, 1421.

(34) Structure **IX** resembles the reported solid-state structure of Ag– C₆F₅ when it is crystallized from acetonitrile. The acetonitrile adduct is polymeric ((··Ag··Ag··)_n 2.802(1) Å) with C₆F₅ forming three-center– two-electron bridges (i.e., $[Ag(\mu-C_6F_5) (NCMe)Ag]_n)$.

(35) A separate estimation of this energy difference, using optimizations for all species in the same solvent (dioxane) applied to $VA + C_6F_5H = IX + 2$ -methylthiophene, provides an energy difference of 6.5 kcal/mol.

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