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New vistas in transmetalation with discrete "AgCF₃" species: Implications in Pd-mediated trifluoromethylation reactions

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Abstract: This work describes the employment of discrete "AgCF₃" complexes as efficient transmetalating agents to Pd^{II}to surmount overlooked challenges related to the transmetalation step in Pd-catalyzed trifluoromethylation processes. We report the participation of a unique silver ate (Cs)[Ag(CF₃)₂] complex, under stoichiometric and catalytic conditions, in the unprecedented one-pot formation of PhCF₃ using PhI as starting material. Moreover, we show that the transmetalation step, which is often ignored in these transformations, can also determine the success or failure of the coupling process.

Over the past few years, organosilver(I) intermediates have demonstrated their potential as nucleophilic coupling partners in Pd-catalyzed transformations.¹ However, their ability as transmetalating agents is far from being fully exploited, most likely due to their instability (e.g. photosensitivity).² Therefore, important fundamental questions such as the scope of the transferred group or the reactivity of silver(I) ate complexes remains essentially unexplored. In this context, a particularly interesting test case is the synergistic Ag/Pd cooperation for the transfer of a CF₃ moiety. This group is a prevalent structural motif in high-value molecules and organometallic scaffolds due to its unique capability to modify physicochemical and/or biological properties.³ A priori, the design of new CF3 shuttles for their use in Pd^{0/II}-catalyzed aryl trifluoromethylation could seem unnecessary since the reductive elimination step is considered the central problem associated with these processes.⁴ However, a close look at the literature reveals that the transmetalation step can also dramatically hamper the C-

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 CF_3 bond-forming reaction (Figure 1). A slow nucleophilic trifluoromethylation leads to undesired reactions by "mismatched" group exchanges. $^{4a\cdot b,d\cdot e,h,5}$ Furthermore, CF_3^- ions can displace the stabilizing ligands on Pd, forming inactive $\mathsf{Pd}^{II}(\mathsf{CF}_3)_n$ species. $^{4a,d\cdot e,h,i,6}$

Intrigued by these overlooked challenges, we envisioned to surmount these limitations by exploring "AgCF₃" complexes as selective and rapid CF₃ shuttles to Pd^{II}. We support our hypothesis on the well-known lability of the Ag–CF₃ bond of in situ generated "AgCF₃" species which readily form a silver(I) ate [Ag(CF₃)₂]⁻ complex through a CF₃ exchange reaction in polar solvents.⁷ Herein, we reveal the exceptional transmetalating activity of well-defined isolated "AgCF₃" compounds to Pd^{II} metal centers (Figure 1), including: 1) their relative reactivity to a benchmark complex and their comparison to commercially available nucleophilic reagents; and 2) the high efficiency of [Ag(CF₃)₂]⁻ species, only detected by NMR spectroscopy to date and whose reactivity has been unrecognized for decades,^{7b-d} in one of the few productive Pd^{II} systems, in which the transmetalation has been pointed out as a challenging step.

Potential unproductive transmetalations in Pd^{0/II}-catalyzed Ar-CF₃ couplings
 Ligand Displacement
 Mismatched Transmetalation



Figure 1. Exploration of trifluoromethylsilver(I) nucleophiles as efficient CF_3 shuttle to Pd^{II} systems.

We started our study by exploring the relative reactivity of "AgCF₃" complexes towards a Pd^{II} model system (Scheme 1). Several considerations were taken into account for this initial investigation. Firstly, (dppp)Pd(Ph)I (**1**; dppp = 1,3-bis(diphenylphosphino)propane) was selected as benchmark complex because it contains a strong coordinating ligand that

prevents the formation of inactive poly(trifluoromethyl)palladium compounds and the resulting product (2) does not undergo Ph–CF₃ coupling.⁸ Secondly, only well-defined isolable trifluoromethylsilver(I) complexes were targeted to avoid potential reproducibility issues associated with in situ generated species. Finally, we pursued fast I-for-CF₃ exchanges (< 30 minutes), to minimize possible undesired by-products related to long reaction times.



✓ benchmark Pd^{II} system ✓ well-defined isolable "AgCF₃" ✓ rapid transmetalation

Scheme 1. Requirements for the initial study

Before exploring the CF₃ group transfer from Ag to (dppp)Pd(Ph)I, we established as touchstone the trifluoromethylation of 1 with the widely used nucleophilic trifluoromethyl sources R₃SiCF₃ (R = Me,⁹ Et^{4b,h-i}) in combination with CsF. After 30 minutes, we only observed 2 in 19% and traces using Me₃SiCF₃ and Et₃SiCF₃. respectively (Figure 2a).¹⁰ With these results as a reference, we then focused on the activity of the scarce examples of isolated trifluoromethylsilver(I) compounds reported in the literature to date: SIPrAaCF311 (SIPr bis(1,3-bis(2,6diisopropylphenyl)imidazole-2-ylidene) and (bathophenanthroline)Ag(CF₃).¹² The treatment of (dppp)Pd(Ph)I with 1.5 equiv of SIPrAgCF3 (3)13 resulted in <5% yield of (dppp)Pd(Ph)(CF₃) after 30 minutes (Figure 2a). We discarded the exploration of the other known LAgCF₃, bearing the bathophenanthroline ligand,12 due to stability issues under our reaction conditions.¹⁴ Notably, after some experimentation, using bathocuproine, we were able to prepare 4 in THF, as a mixture of $(Bc)Aq(CF_3)$ (4a: Bc = bathocuproine) in equilibrium with an ionic $[Ag(CF_3)_2]^-$ species (4b) (Figure 2b). Initially, we hypothesized that the structure of 4b was [(Bc)₂Ag][Ag(CF₃)₂], by analogy to related copper compounds.¹⁵ However, a detailed NMR spectroscopic analysis, including DOSY experiments, confirmed the absence of [(Bc)₂Ag]⁺ as the cation of **4b**, on the basis of the higher hydrodynamic radius measured for [(Bc)₂Ag](SbF₆) (5) (6.86 Å), compared to 4 (4.33 Å). Challenged by this unexpected outcome, we performed computational studies which suggested,¹⁶ as the most stable cation for **4b**, a structure that contains the silver center coordinated to a bathocuproine ligand along with two molecules of THF, and a second Bc bound to the system through stabilizing $\pi - \pi$ interactions.¹⁷ In line with the DFT calculations, we observed the formation of [(Bc)Ag(THF)](SbF₆) (6), characterized by X-ray diffraction, upon exposure of 5 to THF. With the structural information of 4a/4b in hand, we assessed the reactivity of this equilibrium mixture. Gratifyingly, the trifluoromethylation of (dppp)Pd(Ph)I with 1.5 equiv of 4 proceeded cleanly and quantitatively in 10 minutes to afford 2 and an iodo-bridged dimeric compound with Ag-Ag interactions (7) (Figure 2a).



Figure 2. (a) Reactivity of Me_3SiCF_3, Et_3SiCF_3, 3 and 4 towards 1. (b) Synthesis and characterization of 4.

Inspired by the extraordinary transmetalating ability of 4, and prompted by its different behavior from 3, we wondered whether [Ag(CF₃)₂]⁻ could be a non-innocent spectator and participate as CF₃ shuttle.⁷ To unravel this key question, we targeted the synthesis of two well-defined (Cat)[Ag(CF₃)₂] salts, Cat = NBu₄ (8NBu4) or Cs (8Cs) to evaluate their relative stability and reactivity. As shown in Figure 3, the reaction of AgOAc with 4 equiv of Me₃SiCF₃, in THF at room temperature, in the presence of 4 equiv of KF and 1 equiv of NBu₄OAc afforded a white crystalline solid, 8_{NBu4}, in 83% isolated yield. Following a similar synthetic route but using 2 equiv of CsF instead of the combination KF/NBu₄OAc, we synthesized (Cs)[Ag(CF₃)₂] in 85% yield as a yellow solid. The structures of both salts, that can be stored for months at -30 °C under inert atmosphere in the dark,18 were unambiguously confirmed by NMR spectroscopy, ESI-MS and single crystal X-ray diffraction. It is worth mentioning the different bonding situation between these ionic species. The X-ray structure of 8NBu4 shows a linear bis(trifluoromethyl)argentate paired together with the NBu₄ cation. In sharp contrast, 8_{Cs} presents a rather unique structure, with the silver atoms forming linear chains, and the cesium cations interacting with twelve different fluorine atoms.¹⁹ Having synthesized and fully-characterized these singular ionic species, we next investigated their efficiency as nucleophilic trifluoromethyl sources. To our delight, the reaction of (dppp)Pd(Ph)I with 0.75 equiv of either of the two silver salts resulted in the quantitative formation of 2 in 10 minutes, when using 8_{cs}, and in 93% yield for 8_{NBu4}.²⁰



Figure 3. Synthesis, Characterization and Reactivity of $(Cat)[Ag(CF_3)_2]$ (Cat = NBu₄, Cs)

Next, we aimed at evaluating the real potential of our silver nucleophiles, focusing our attention on one of the few PdII systems which affords relatively facile PhCF₃ coupling. In 2006, Grushin et al. reported the first example of C-CF₃ bond-forming reductive elimination from an isolated Xantphos-based Pd^{II} derivative, synthetized by treatment of (Xantphos)Pd(Ph)F with Me₃SiCF₃.^{4a} In this work and subsequent elegant mechanistic studies,^{4d} the authors explained in detail, not only the challenges associated to the reductive elimination from this system, but also the appealing difficulties related to unfruitful attempts to achieve the nucleophilic trifluoromethylation of (Xantphos)Pd(Ph)I (9) using Me₃SiCF₃/CsF, such as: i) ligand displacement by CF₃-; and/or ii) the formation of unproductive Ph-Ph homocoupling. Encouraged by our previous results, we envisioned that our silver nucleophiles could overcome these shortcomings and provide the unprecedented formation of PhCF₃ using 9 as starting material (Scheme 2). Following the same strategy used for 1, we first defined as touchstone the reactivity of **9** with R_3SiCF_3/F^- (R = Me, Et), under comparable reaction conditions to those reported previously for the high-yielding formation of PhCF3 from (Xantphos)Pd(Ph)(CF₃) (10).4a,d As expected, we observed the formation of the coupling product in low yields in the presence of CsF (14% and 20%, for Me₃SiCF₃ and Et₃SiCF₃ respectively). Then, we examined the reactivity of 9 with our most efficient Ag-CF₃ sources, 4a,²¹8_{NBu4} and 8_{Cs}. We were pleased to observe that all these transformations led to the targeted product in moderate to excellent yields (4: 70%,²² 8_{NBu4}: 42%, and 8_{cs}: 84%). The lower reactivity of (Bc)Ag(CF₃) and (NBu₄)[Ag(CF₃)₂] can be ascribed to unproductive pathways: ²³ ligand scrambling between both metals which affords (Bc)Pd(Ph)(CF₃) for 4, and the formation of poly(trifluoromethyl)complexes and decomposition to Ag^{III} for 8_{NBu4} .^{18,23} For 8_{Cs} , we corroborated the rapid and selective CF₃ transfer by observing full conversion of 9 into 10 in less than 10 minutes in C₆H₆ at room temperature.



Scheme 2. Thermolysis of **9** with different "CF₃⁻⁻" sources. ^aReaction conditions: **9** (0.006 mmol), Xantphos (0.006 mmol), C₆H₆ (0.01 M) under Ar. ^{b 19}F NMR analysis using fluorobenzene or 4,4'-difluorobiphenyl as internal standards.

Based on these promising data, we next examined the compatibility of 8cs with all elementary steps involved in the catalytic cycle, under stoichiometric conditions in the presence of excess of PhI. As previously described, the accumulation of the oxidative addition product, (Xantphos)Pd(Ph)I, could favor the mismatched transmetalation shown in Figure 1. Delightfully, using Pd(dba)₂ as Pd⁰ source and 30 equiv of PhI, we observed the desired product (11) in slightly higher yield (91%) when compared to the entry 5 of Scheme 2 (Scheme 3), along with the regeneration of the oxidative addition product.²⁴ This result points out the capability of 8cs for precluding the side-product formation that could potentially lead to dead-end routes under catalytic conditions using Xantphos as ligand. Indeed, as a proof-ofconcept, preliminary results show the formation of 11 in 56% yield by slow addition of 8cs under catalytic conditions in the presence of 60 equiv of PhI (Scheme 3).25



Scheme 3. Stoichiometric and catalytic reactions. ^{a19}F NMR analysis using fluorobenzene as internal standard.

In summary, this work presents the potential of discrete "AgCF₃", including a unique (Cs)[Ag(CF₃)₂] salt, as CF₃ shuttle to Pd^{II} systems. Our results, not only provide the first reported example of stoichiometric and catalytic one-pot formation of Ph–CF₃ starting from PhI, but also confirm the crucial role of the nucleophile in the transmetalation step, which can be decisive, enabling or preventing the product formation. Further work towards unravelling the potential of silver nucleophiles as transmetalating agents is currently ongoing in our laboratory.

Acknowledgements

We thank the CERCA Programme/Generalitat de Catalunya and the Spanish Ministry of Economy, Industry and Competitiveness (MINECO: CTQ2017-87792-R, CTQ2016-79942-P, CTQ2015-64436-P, AIE/FEDER, EU, and Severo Ochoa Excellence Accreditation 2014-2018, SEV-2013-0319) for the financial support. S. M. S. thanks Severo Ochoa Excellence Accreditation for post-doctoral contract. A. L. M. thanks La Caixa-Severo Ochoa programme for a predoctoral grant. We thank to the Research Support Area of ICIQ. The authors also thank Prof. Rubén Martín and Dr. Alex Shafir for useful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: organometallic synthesis • silver • structural elucidation • transmetalation • trifluorometalation

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