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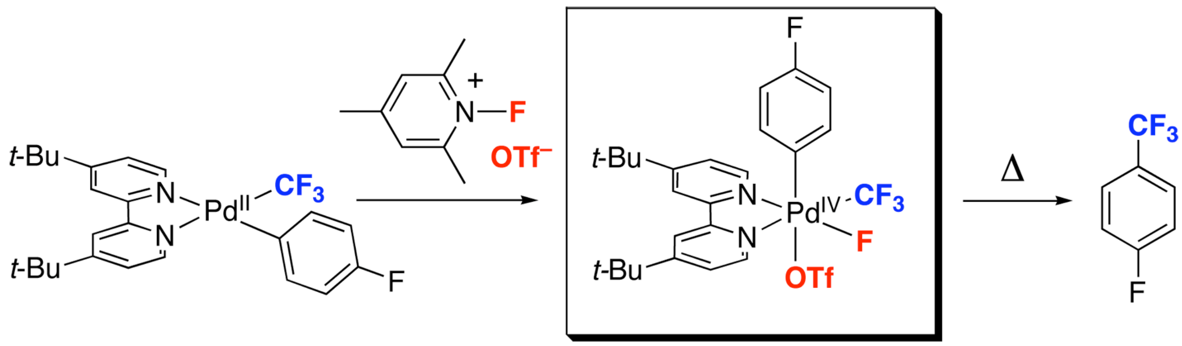
Aryl-CF_3 Bond-Forming Reductive Elimination from Palladium(IV)

Nicholas D. Ball, **Jeff W. Kampf**, and **Melanie S. Sanford***
Department of Chemistry, University of Michigan, 930 North University Ave, Ann Arbor, MI 48109

Abstract



This communication describes oxidatively-induced Ar–CF_3 bond-forming reductive elimination from new Pd^{II} complexes of general structure (L~L)Pd^{II}(Ar)(CF_3). The electrophilic fluorinating reagent *N*-fluoro-2,4,6-trimethylpyridinium triflate promotes these reactions in good to excellent yields. The palladium(IV) intermediate (^{t}Bu-bpy)Pd^{IV}(CF_3)(F)(OTf)(C_6H_4F) has been isolated, characterized, and demonstrated to undergo high yielding Ar–CF_3 coupling upon thermolysis. This work provides an attractive conceptual framework for the development of $Pd^{II/IV}$-catalyzed arene trifluoromethylation reactions.

Trifluoromethyl groups feature prominently in a wide variety of medicinal compounds.[1] The substitution of CH_3 for CF_3 can dramatically change the physical properties and biological activity of organic molecules. As a result, tremendous effort has been directed at the introduction of CF_3 groups into organic structures.[2] This has led to numerous methods for the efficient construction of sp^3 carbon–CF_3 bonds using nucleophilic (CF_3^-), electrophilic (CF_3^+) and radical (CF_3•)-based trifluoromethylating reagents.[2]

In contrast, the formation of aryl carbon–CF_3 bonds remains significantly more challenging.[3] This functional group is commonly prepared using the Swarts reaction (which requires high temperatures and reactive SbF_5)[4] or through the use of stoichiometric quantities of ill-defined and sensitive "Cu–CF_3" reagents.[5] Transition metal-catalyzed cross-coupling would provide a highly attractive alternative route to aryl–CF_3 linkages. While sporadic reports have suggested the viability of this approach,[6] general, efficient, and robust versions of such transformations have been slow to develop. The major challenge in this area is that CF_3 ligands are typically inert towards C–C bond-forming reductive elimination.[7]

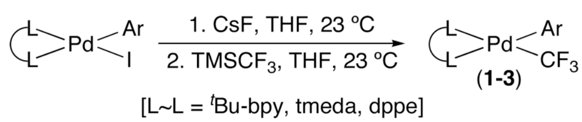
mssanfor@umich.edu.

Supporting Information Available: Experimental and crystallographic details and spectroscopic data for new compounds. This material is available free of charge via the internet at http://pubs.acs.org.

Several groups have made exciting recent progress towards addressing this challenge. For example, Vicic and coworkers have shown that the isolable *N*-heterocyclic carbene (NHC) copper complexes (NHC)Cu–CF_3 react stoichiometrically with aryl iodides to afford Ar–CF_3 products.[8] Vicic's group has also established that (dippe)Ni^{II}(Ph)(CF_3) undergoes H_sO-promoted Ph–CF_3 coupling in modest (22%) yield.[9] Finally, Grushin has demonstrated stoichiometric Ph–CF_3 coupling from (Xantphos)Pd^{II} (Ph)(CF_3).[10] This latter work is the only reported example of selective Ar–CF_3 bond-forming reductive elimination from a well-defined transition metal aryl/CF_3 complex. However, this reaction was limited to Ar = Ph and was also extremely sensitive to the nature of the ancillary ligand at Pd^{II}. A variety of P- and N-donor ligands including dppe,[11] dppb,[11] tmeda,[11] and PPh_3 were examined,[10,12] but only Xantphos was effective at promoting this transformation below 150 °C. Thus, the development of complementary and more general strategies for arene trifluoromethylation from M(Ar)(CF_3) species remains a topic of great current interest.

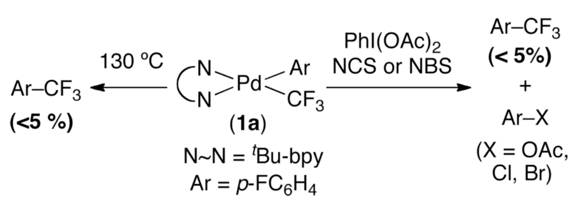
Our group[13] and others[14] have shown that Pd^{IV} complexes can participate in reductive elimination reactions that are challenging at other metal centers. Since high oxidation state palladium can be accessed following arene C–H activation[15] or transmetallation[16] processes, Ar–CF_3 coupling through this manifold would provide opportunities for the development of diverse new trifluoromethylation reactions. We report herein the first demonstration of Ar–CF_3 bond-forming reductive elimination from a Pd^{IV}(Ar)(CF_3) complex.

Our studies began with the synthesis of a series of new palladium(II) complexes of general structure (L) $_2Pd^{II}$(Ar)(CF_3) (**1–3**).[12b] These were prepared by treating the corresponding Pd^{II} aryl iodides with CsF followed by $TMSCF_3$ at 23 °C in THF (eq. 1).[10,21] The products were obtained in 32–76% yield as yellow solids (see Supporting Information for full details).



(1)

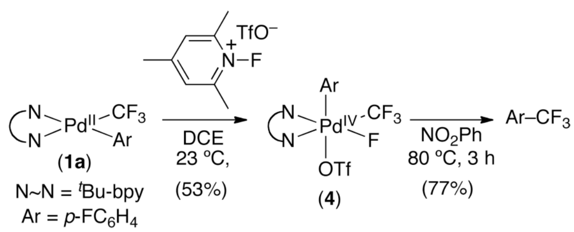
Heating complexes **1–3** at 130 °C for 3 d in nitrobenzene-d_5 produced <5% of Ar–CF_3 coupling products (eq. 2). This is consistent with literature reports showing that most Pd^{II}(Ar)(CF_3) complexes are poorly reactive towards Ar–CF_3 bond-forming reductive elimination.[10,12] We reasoned that 2e^- oxidation should yield Pd^{IV} species that might undergo more facile Ar–CF_3 coupling.[13–15] However, treatment of **1a** with $PhI(OAc)_2$, NCS,[11] or NBS[11] (oxidants known to promote the oxidation of Pd^{II} to Pd^{IV})[13] did not afford 1-fluoro-4-trifluoromethylbenzene; instead, the corresponding acetoxylated or halogenated products were obtained (eq. 2). This result suggests that Ar–X (X = OAc, Cl, Br) bond-forming reductive elimination is significantly faster than Ar–CF_3 coupling in this system.



(2)

We next examined the use of *N*-fluoro-2,4,6-trimethylpyridinium triflate (NFTPT) to effect Ar–CF_3 coupling from **1a**. This oxidant was selected based on the hypothesis that fluoride and triflate (the X-type ligands introduced to a putative Pd^{IV} intermediate by NFTPT) might undergo slower reductive elimination than CF_3.[17,18] Gratifyingly, treatment of **1a** with NFTPT at 80 °C for 3 h in nitrobenzene-d_5 resulted in clean formation of 1-fluoro-4-trifluoromethylbenzene in 85% yield (as determined by ^{19}F NMR spectroscopy) (Table 1, entry 1). As predicted, <5% of products derived from C–F or C–OTf coupling were observed. NFTPT also promoted Ar–CF_3 bond-formation from the other Pd^{II} complexes **1b–3** (Table 1). These transformations were efficient with strongly electron donating and electron withdrawing arene substituents (entries 2 and 3, respectively). In contrast, reactions of [Cu–CF_3] are often highest yielding with electron deficient aryl coupling partners.[6] Additionally, unlike Grushin's Ar–CF_3 coupling from Pd^{II} (which is very sensitive to the nature of the ancillary ligands),[10] this oxidatively induced transformation proceeded in modest to excellent yield with diverse N- and P-donor ligands, including ^{t}Bu-bpy, tmeda, and dppe.[11]

In an effort to detect intermediates in the Ar–CF_3 coupling process, we examined the reaction of **1a** with NFTPT at room temperature. In both nitrobenzene and DCE, a single major palladium-containing product (**4**) was observed. This species was isolated from DCE in 53% yield, and the analytically pure yellow solid exhibits four ^{19}F NMR signals in a 3 : 3 : 1 : 1 ratio. X-ray quality crystals were obtained by vapor diffusion of pentanes into a DCE solution of **4**. The X-ray crystal structure is shown in Figure 1 and confirms that **4** is the octahedral Pd^{IV} species (^{t}Bu-bpy)$Pd^{IV}(CF_3)(F)(OTf)(C_6H_4F)$. To our knowledge this is the first isolated example of a Pd^{IV} complex containing a perfluoroalkyl ligand.[19]



(3)

The reactivity of **4** towards Ar–CF_3 bond formation was next investigated. Heating a nitrobenzene-d_5 solution of **4** at 80 °C for 3 h resulted in smooth reductive elimination to form 1-fluoro-4-trifluoromethylbenzene in 77% yield (eq. 3). Similar to the reactions in Table 1, none of the products derived from Ar–F or Ar–OTf coupling were observed by ^{19}F NMR spectroscopy. This result demonstrates for the first time that Ar–CF_3 coupling can be kinetically accessible from mono-σ-aryl Pd^{IV} complexes; as such, it provides an attractive conceptual framework for the development of $Pd^{II/IV}$-catalyzed arene trifluoromethylation reactions.

In summary, we describe herein a new Ar–CF_3 bond-forming reaction mediated by Pd^{IV} centers. These transformations proceed under mild conditions with diverse nitrogen and phosphorus-based ancillary ligands. Efforts to gain further insights into the mechanism as well as to develop related catalytic transformations are currently underway in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. Xantphos = 4.5-bis(diphenylphosphino)-9,9-dimethylxanthene; ^{t}Bu-bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl; tmeda = *N,N*'-tetramethylethylene diamine; dppe = 1,2-bis(diphenylphosphino)ethane; dippe = 1,2- bis(diisopropylphosphino)ethane; NCS = *N*-chlorosuccinimide; NBS = *N*-bromosuccimide.
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19. Notably, related structures have been proposed as transient intermediates in the reactions of perfluoroalkyl iodides with Pd^{II}. See:Hughes RP, Overby JS, Williamson A, Lam K-C, Concolino TE, Rheingold AL. Organometallics 2000;19:5190.

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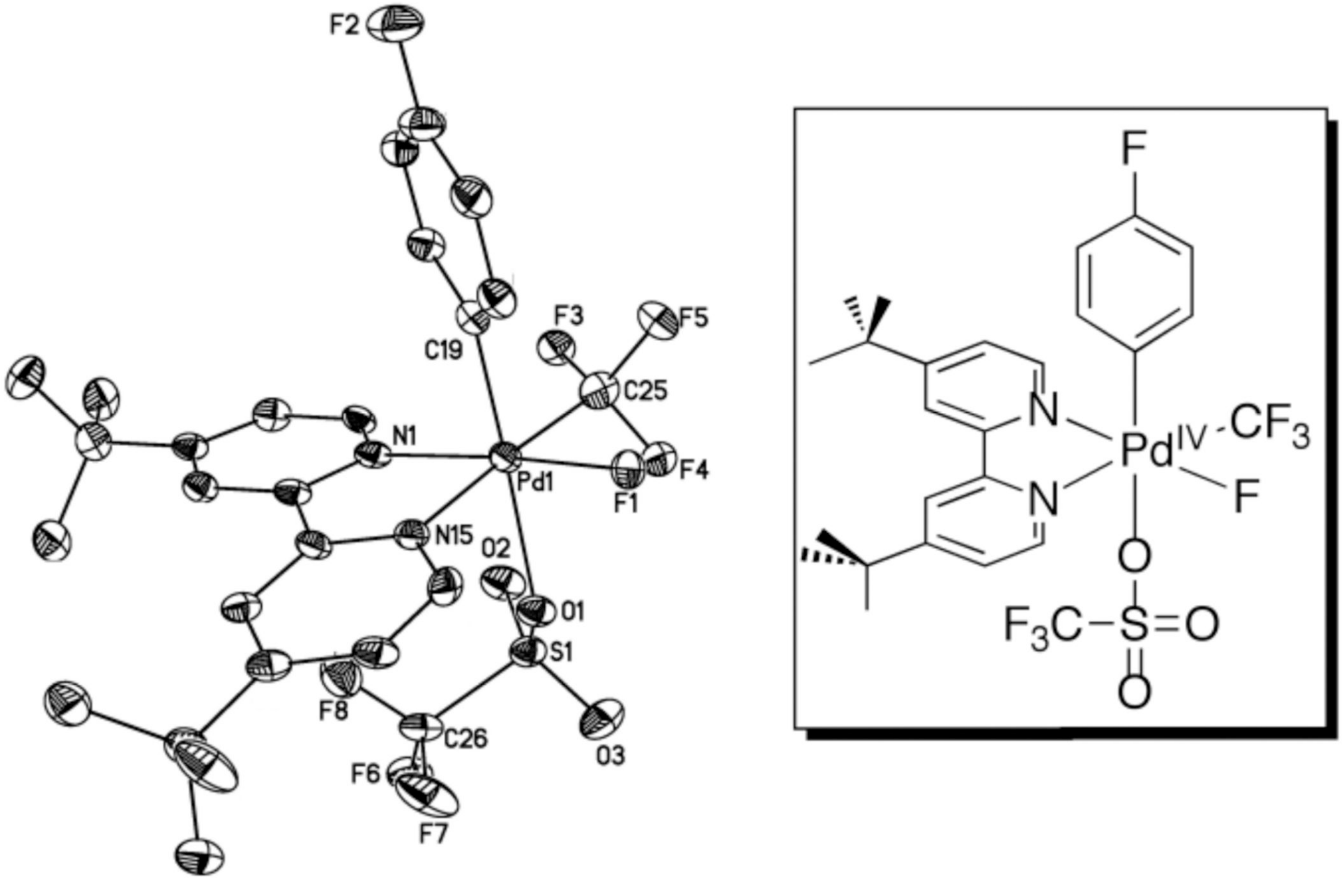
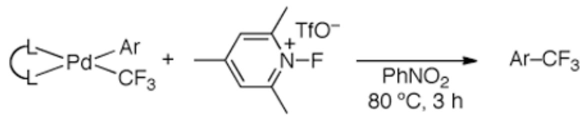


Figure 1.
ORTEP Diagram of **4**.

Table 1

Oxidatively Induced Ar–CF_3 Coupling from Complexes **1–3**



Entry	Compound	L_2	Ar	Yield Ar–CF_3[a]
1	**1a**	^{t}Bu-bpy	*p*-FC_6H_4	85%
2	**1b**	^{t}Bu-bpy	*p*-$CF_3C_6H_4$	61%
3	**1c**	^{t}Bu-bpy	*p*-$CH_3OC_6H_4$	86%
4	**1d**	^{t}Bu-bpy	*p*-PhC_6H_4	83%
5	**1e**	^{t}Bu-bpy	*p*-$CH_3C_6H_4$	85%
6	**2**	tmeda	*p*-FC_6H_4	89%
7	**3**	dppe	Ph	29%

[a]Determined by ^{19}F NMR spectroscopy