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COMMUNICATIONS

Published on Web 09/12/2006

Facile Ar−CF_3 Bond Formation at Pd. Strikingly Different Outcomes of Reductive Elimination from [$(Ph_3P)_2Pd(CF_3)Ph$] and [(Xantphos)Pd(CF_3)Ph]

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Biological activity is commonly exhibited by selectively fluorinated molecules. "As many as 30−40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine, including half of the top 10 drugs sold in 2005."[1] Hence, the demand for new reactions to introduce fluorine and fluorine-containing groups into organic molecules is increasingly high.[1] New methods to selectively fluorinate and trifluoromethylate aromatic compounds are particularly important and intensely sought. Although a few interesting findings have recently been reported,[2−4] the problem is far from being solved and still represents a major synthetic challenge.

As an alternative to the Swarts reaction,[5] it would be desirable to develop Pd-catalyzed coupling of haloarenes with a CF_3-transferring nucleophile, for example Ruppert's reagent, CF_3SiMe_3. Such process must involve Ar−CF_3 reductive elimination from Pd(II) as the key product forming step. The feasibility of this step, however, is in question because late transition metal-CF_3 bonds are generally strong and notoriously inert.[6] Unlike [(LL)Pd(CH_3)(Ph)] (LL = dppe[7] or dppp[8]) that reductively eliminate toluene at as low as 15−40 °C, their CF_3 congeners [(dppbz)Pd(CF_3)(*o*-Tol)][9] and [(LL)Pd(CF_3)(Ph)] (LL = dppe or dppp)[10] do not produce $ArCF_3$ for days at 130 °C. Only at 145 °C was the low-yield formation of $PhCF_3$ from the dppe and dppp complexes observed as a result of the sluggish and poorly selective reaction.[10] In this communication, we describe the first example of facile and clean CF_3−Ar reductive elimination from a Pd(II) complex under mild conditions.

Trifluoromethyl palladium aryls reported to date are all derivatives of strongly chelating bidentate ligands.[9,10] In this work, we prepared analogous complexes, stabilized by a monodentate phosphine and a trans-chelating phosphine, to determine how these ligands would influence the ability of the Pd center to reductively eliminate Ar−CF_3. Triphenylphosphine was chosen because of the reported[11] formation of perfluoroalkylarenes from perfluoroalkyl iodides, iodoarenes, and Zn in the presence of [$(Ph_3P)_2PdCl_2$] under sonication. The choice of Xantphos as a bidentate phosphine was determined by its wide bite angle[12] and both cis- and trans-chelating ability,[12,13] factors that are expected[8,12] to strongly influence reductive elimination from Pd(II).[14]

The starting materials for the synthesis of [$(Ph_3P)_2Pd(Ph)CF_3$] (**1**) and [(Xantphos)Pd(Ph)CF_3] (**2**) were well-known [$(Ph_3P)_2Pd$-(Ph)I] and new [(Xantphos)Pd(Ph)I] (**3**). The latter was prepared by reacting [$Pd_2(dba)_3$] with Xantphos and PhI in toluene at room temperature, a standard procedure for the synthesis of various palladium aryls, including a few Xantphos derivatives.[13,14] Complex **3** was trans in solution and in the solid state (NMR, X-ray; see Supporting Information).

† Contribution No. 8741.

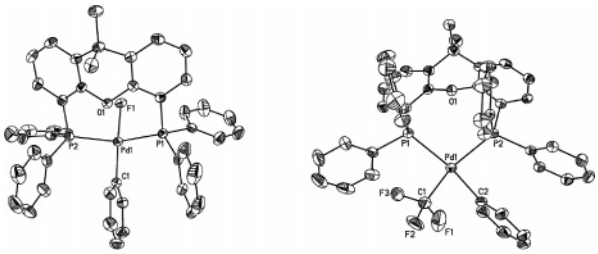
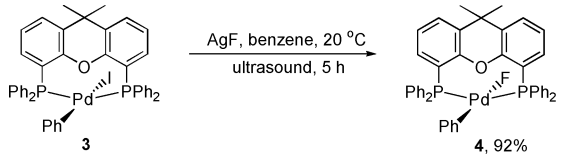


Figure 1. ORTEP drawings of **4** (left) and **2** (right).

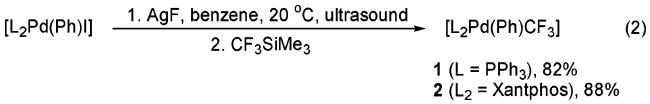
Our previous attempts[10] to synthesize **1** from [$(Ph_3P)_2Pd(Ph)I$] and CF_3SiMe_3/CsF were unsuccessful owing to facile displacement of the phosphines on Pd with the CF_3 groups.[15a] Because **3** behaved similarly,[15b] we attempted the synthesis of **1** and **2** from the corresponding fluorides.[16] Both known [$(Ph_3P)_2Pd(Ph)F$] and new [(Xantphos)Pd(Ph)F] (**4**) were prepared using our previously developed method for the synthesis of metal fluorides from the corresponding iodides and AgF under sonication (eq 1).[17] The I/F exchange on **3** (eq 1) smoothly produced **4** that was isolated pure in 92% yield.



(1)

The new fluoride **4** was fully characterized, including ^1H, ^{19}F, and ^{31}P NMR spectra and single-crystal X-ray diffraction. In the solid state and in solution, **4** is trans, as established by the X-ray (Figure 1) and NMR data.[18] Thermolysis of **4** in dry benzene under N_2 at 60 °C overnight led, as expected,[19] to only P−F bond formation and no Ph-F reductive elimination.

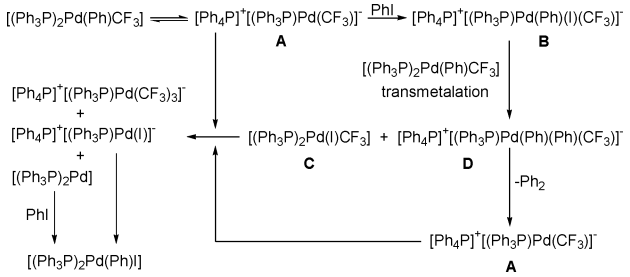
Treatment of [$(Ph_3P)_2Pd(Ph)F$][17] or **4** with CF_3SiMe_3 in benzene afforded, within the time of mixing, [$(Ph_3P)_2Pd(Ph)CF_3$] (**1**) and [(Xantphos)Pd(Ph)CF_3] (**2**), respectively. More conveniently, **1** and **2** were made without isolation of the fluoride intermediates. After the I/F exchange had gone to completion, the reaction mixtures were quickly filtered through Celite *in air*, and the filtrates were treated with CF_3SiMe_3 to afford pure **1** and **2** in high yield (eq 2). Complex **1** was trans in solution[20] and as a solid (X-ray; see Supporting Information). The Xantphos derivative **2** was a 10:1 mixture of cis and trans isomers in benzene but exclusively cis in more polar CH_2Cl_2 or THF and in the crystal structure (Figure 1).[20]



(2)

10.1021/ja064935c CCC: $33.50

Scheme 1. Proposed Mechanism for Reaction 3.



Decomposition of **1** in the presence of PhI in benzene-d_6 at 60 °C (eq 3) gave a mixture of two complexes, $[(Ph_3P)_2Pd(Ph)I]$ (NMR) and $[Ph_4P]^+[(Ph_3P)Pd(CF_3)_3]^-$ (X-ray).[21]

$$3[(Ph_3P)_2Pd(Ph)CF_3] + 2PhI \xrightarrow{C_6D_6,\ 60\ ^\circ C} 2[(Ph_3P)_2Pd(Ph)I] + [(Ph_4P)^+\ (Ph_3P)Pd(CF_3)_3]^- + Ph_2 \quad (3)$$

1

Extra PPh_3 was found to strongly inhibit reaction 3. This points to P−C reductive elimination as the first step (Scheme 1) that is known[19,22] to require phosphine predissociation. The resulting Pd(0) species **A** oxidatively adds PhI to give **B**, followed by well-established[10] transmetalation resulting in **C** and **D**, with the latter undergoing reductive elimination of Ph_2 to reform **A**. Complex **C** is fully expected[15a] to easily exchange its I and PPh_3 ligands for CF_3 in the presence of a strongly nucleophilic CF_3-donor, such as **A** (as shown in Scheme 1) or **B**. Both byproducts of this exchange, $[(Ph_3P)_2Pd]$ and $[Ph_4P]^+[(Ph_3P)Pd(I)]^-$, transform to $[(Ph_3P)_2Pd(Ph)I]$ upon oxidative addition of PhI and the $[Ph_4P]^+$, respectively.

In sharp contrast with **1** and $[L_2Pd(CF_3)(Ar)]$ (L_2 = dppbz,[9] dppe,[10] and dppp;[10] see earlier), **2** underwent remarkably clean and smooth Ph−CF_3 reductive elimination at as low as 50−80 °C. Heating a benzene solution of **2** and Xantphos (1:1) under N_2 at 80 °C for 3 h led to the exclusive formation of $PhCF_3$ and $[(Xantphos)_2Pd]$[23] (X-ray) at ca. 100% conversion (eq 4).

$$[(Xantphos)Pd(\mathbf{CF_3})\mathbf{Ph}] + Xantphos \xrightarrow[100\%]{C_6H_6,\ 80^\circ C,\ 3\ h} \boxed{\mathbf{PhCF_3}} + [(Xantphos)_2Pd] \quad (4)$$

When the experiment was repeated using PhI in place of Xantphos as a trap for the Pd(0), the formation of Ph_2 and $[(Xantphos)Pd(I)CF_3]$ (**5**; X-ray) competed with the main pathway leading to $PhCF_3$ and $[(Xantphos)Pd(Ph)I]$ (**3**). This result was expected.[10] As the Ph-CF_3 reductive elimination occurs, the Pd(0) formed oxidatively adds PhI to give $[(Xantphos)Pd(Ph)I]$ (**3**). The latter and the as yet unreacted **2** undergo transmetalation[10] giving rise to **5** and $[(Xantphos)PdPh_2]$ which is transformed back to **3** via Ph−Ph reductive elimination, followed by oxidative addition of PhI. The transmetalation path is favored by higher concentrations, conversion, and temperature. At 95−100% conversion of **1**, the $PhCF_3$ to **5** ratio was measured (^{19}F NMR) at 2.3 (60 °C, 20 h), 2.0 (70 °C, 8 h), and 1.2 (80 °C, 2 h).

In conclusion, facile and highly selective perfluoroalkyl−aryl reductive elimination from a metal center (Pd) has been demonstrated for the first time. The role of Xantphos on Pd for the CF_3−Ph bond formation is critical.[14] Replacement of the Xantphos ligand on Pd with PPh_3 or cis-chelating dppbz,[9] dppe,[10] dppp,[10] and tmeda[10] blocks the Ar−CF_3 bond forming path. The dramatic change in reactivity of $[L_2Pd(Ar)CF_3]$ when going from the rigid L_2 (dppbz, dppe, dppp) to adaptable Xantphos is remarkably reminiscent of the key importance of flexibility for the reactions of cyclic iodonium cations with nucleophiles, which proceed via reductive elimination from tricoordinate iodine.[24]

Supporting Information Available: Experimental details, NMR data (pdf), and X-ray analysis data (cif) for **1**−**5**, $[Ph_4P]^+[(Ph_3P)Pd(CF_3)_3]^-$, and $[(Xantphos)_2Pd]$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) NMR data for **4** (C_6D_6, 25 °C): ^{19}F: $\delta = -300.7$ ppm (br. t). ^{31}P: $\delta =$ 4.4 ppm (d); $J_{P-F} = 10$ Hz.
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(20) NMR data (benzene-d_6; 25 °C; δ). For **1**: ^1H: 6.4 (m, 2H, *m*-PhPd); 6.6 (m, 1H, *p*-PhPd); 7.0 (m, 2H, *o*-PhPd); 7.1 (m, 18H, *m*, *p*-PhP); 7.8 (m, 12H, *o*-PhP). ^{19}F: −16.1 (t, $J_{P-F} = 13.9$ Hz). ^{31}P: 28.6 (q, $J_{P-F} =$ 13.9 Hz). For *trans*-**2**: ^{19}F: −13.1 (t, $J_{P-F} = 16.0$ Hz). ^{31}P: 17.7 (q, $J_{P-F} = 16.0$ Hz). For *cis*-**2**: ^{19}F: −14.6 (br m); ^{31}P: 4.8 (br m, 1P); 9.6 (br s, 1P). There is no fast exchange on the NMR time scale between *cis*- and *trans*-**2** in benzene at 25 °C. The ^{19}F and ^{31}P NMR spectra of **2** display sharp multiplets from *trans*-**2** but broadened resonances from *cis*-**2**. This line broadening might be due to P-site exchange via dissociation (strong trans effects of both Ph and CF_3) and can be frozen out at lower temperatures. ^{19}F NMR (CD_2Cl_2, −70 °C), δ: −17.5 (dd, trans-$J_{P-F} =$ 48 Hz, cis-$J_{P-F} = 15$ Hz). ^{31}P NMR (CD_2Cl_2, −70 °C), δ: 8.4 (dq, trans-$J_{P-F} = 48$ Hz, cis-$J_{P-P} = 24$ Hz, 1P); 12.6 (m, 1P). The −70 °C NMR data is fully consistent with the cis solid-state structure.
(21) The anion $[(Ph_3P)Pd(CF_3)_3]^-$ has been previously characterized.[15a] In the structure of the $[Ph_4P]^+$ $[(Ph_3P)Pd(CF_3)_3]^-$ from reaction 3, each CF_3 group is slightly disordered with iodide, with the percentages of CF_3 being 84.3% (trans to PPh_3) and 93.2% and 89.1% (mutually trans). The sum of the iodide and CF_3 occupancies independently refined to 0.999, 1.003, and 0.997, indicating that each position is well represented by either CF_3 or iodide.
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JA064935C