Carbon(sp³)−Fluorine Bond-Forming Reductive Elimination from Palladium(IV) Complexes**

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The development of transition-metal-catalyzed reactions for the formation of C−F bonds has been an area of intense research over the past decade.[1–3] Traditionally, the C−F coupling step of these sequences has proven challenging because of the high kinetic barrier for C−F bond-forming reductive elimination from most transition-metal centers.[1] Our approach to address this challenge has involved the use of Pd[II] catalysts in conjunction with F⁺-based oxidants. Since 2006, a variety of Pd[II]-catalyzed reactions of F⁺ reagents have been developed to introduce fluorine at both C(sp²) and C(sp³) centers.[4–6] These transformations have been proposed to proceed through C−F bond-forming reductive elimination from transient, highly reactive Pd[IV] alkyl/aryl fluoride intermediates.

A detailed understanding of the high-valent organopalladium species that are involved in the key C−F coupling step has lagged considerably behind the development of catalytic reactions. In particular, the feasibility of C(sp³)−F bond formation from Pd[IV] complexes (a crucial step in the Pd-catalyzed fluorination of benzylic/alkyl C−H bonds[4c] and the fluorination of olefins)[5] has not yet been established. Several recent reports have described detailed investigations of related C(sp²)−F bond-forming reductive elimination from Pd[IV] aryl fluoride complexes.[7] In addition, both Vigalok[8] and Gagne[9] and their respective co-workers have demonstrated that Pt[II] alkyl complexes react stoichiometrically with F⁺ reagents to form alkyl fluorides. Both groups proposed C(sp³)−F bond-forming reductive elimination from a high-valent Pt center as a key step; however, no intermediates were isolated in either of these transformations. Our goal was to design a system with which we could access Pd[IV] alkyl fluoride complexes and directly study their reactivity toward C−F bond-forming reductive elimination. We report herein the first direct observation and study of this important transformation from a Group 10 metal center.[10,11]

We targeted the cyclometalated bipyridine–Pd[II] complex 1[12] as a precursor to stable Pd[IV] alkyl fluoride adducts. The oxidation of 1 with NFTPT (N-fluoro-2,4,6-trimethylpyridinium triflate)[13] afforded the Pd[IV] complex 2 in 94% yield (Scheme 1). The triflate ligand of 2 was highly labile and

could be displaced by pyridine or water to generate cationic products 3 and 4, respectively. An analogue of 3 with a BF_4^- counterion (3-BF₄) was also prepared by oxidation of 1 with N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate
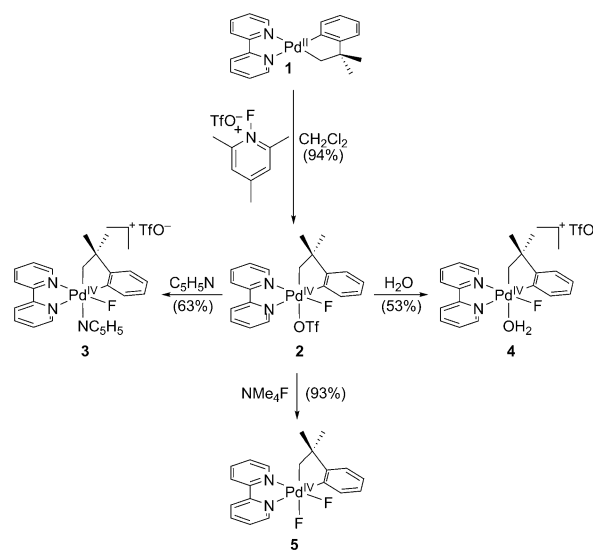
Scheme 1. Synthesis of Pd[IV] fluoride complexes 2–5. TfO = trifluoromethanesulfonate.

(NFTPB) in the presence of pyridine. The Pd[IV] complexes 2–4 were all formed as a single detectable stereoisomer (established by ¹H NMR spectroscopic analysis). Notably, unlike most other palladium–fluoride complexes,[14] 2–4 are not sensitive to water. They were routinely synthesized under ambient conditions and could be stored on the bench top for several hours (and in a freezer at −35°C for several weeks) without noticeable decomposition. The fluoride ligand of 2–4 appears as a sharp doublet at −336.17 ppm ($J = 15$ Hz) in the ¹⁹F NMR spectrum. In all cases, the fluoride is coupled to one of the α hydrogen atoms of the σ alkyl ligand (coupling to the other α hydrogen atom is not observed, presumably because of the small magnitude of this second coupling constant). The sharpness of this ¹⁹F NMR signal and the insensitivity of the complex to adventitious moisture both suggest that there are no interactions of the fluoride ligand with H_2O in solution.[14]

X-ray quality crystals of 4 were obtained by slow diffusion of pentane into a solution of 3 in wet acetone at −35°C. The crystal structure of 4 shows that the σ alkyl group of the cyclometalated ligand is trans to the labile H_2O ligand, whereas the σ aryl and fluoride ligands are trans to the bipyridine unit (Figure 1).

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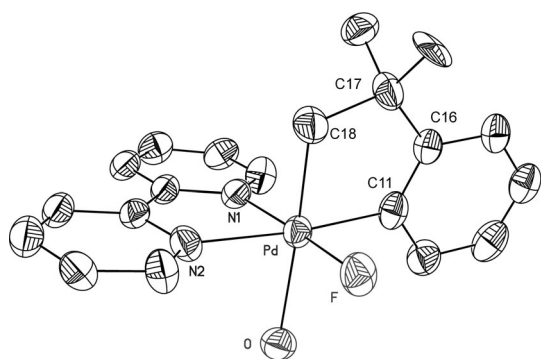E-mail: mssanfor@umich.edu

Figure 1. ORTEP drawing of complex **4**.[27] Thermal ellipsoids are drawn at 50% probability, and hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: Pd–F 1.979(5), Pd–C11 2.008(9), Pd–N1 2.015(7), Pd–C18 2.025(9), Pd–N2 2.151(8), Pd–O 2.229(6), C11–C16 1.383(13), C17–C18 1.522(13). Selected bond angles [°]: F-Pd-C11 85.9(3), F-Pd-N1 175.8(3), C11-Pd-N1 98.3(3), F-Pd-C18 89.2(3), F-Pd-N2 96.1(2), F-Pd-O 90.1(2), C11-Pd-O 100.6(3), N1-Pd-O 89.8(2).

The triflate ligand of **2** could also be readily replaced with fluoride. For example, the treatment of **1** with NFTPT for 15 minutes followed by the addition of 1.6 equivalents of NMe_4F afforded the difluoride complex **5** in 93% yield (Scheme 1). The ^{19}F NMR spectrum of **5** shows two distinct fluorine resonances, a doublet at −201.42 ppm and a doublet of doublets at −336.73 ppm. Complex **5** could also be prepared in high yield by the direct reaction of Pd^{IV} triflate complex **2** with 1.6 equivalents of NMe_4F.

Difluoride Pd^{IV} complex **5** had very different properties than **2**–**4**. Complex **5** was extremely sensitive to water, and attempts to synthesize **5** without rigorous exclusion of moisture resulted in the formation of mixtures of unidentified products. Given the strong trans influence of the σ alkyl ligand, the trans-fluoride of **5** is likely labile and highly susceptible to H-bonding interactions with H_2O.

We next sought to study the reactivity of these Pd^{IV} fluoride complexes toward C−F bond-forming reductive elimination. There are several potential challenges to consider for these transformations. First, **2**–**5** all contain both σ aryl and σ alkyl ligands; thus, it was not clear whether selectivity could be achieved in the reductive elimination processes. Second, C(sp³)−heteroatom bond-forming reductive eliminations from Pd^{IV} complexes generally proceed by outer-sphere mechanisms that involve an S_N2-type attack of a nucleophile on the σ alkyl ligand.[15] However, it is well-known in organic chemistry that fluoride is a poor nucleophile for S_N2 reactions,[16] thus suggesting that such a pathway might not be viable in these systems. In addition, the high degree of β substitution at the C(sp³)−Pd bond in **2**–**5** was expected to further disfavor S_N2-type processes.

We were pleased to find that, despite these potential challenges, both **3** and **5** underwent clean C−F bond-forming reductive elimination at 80°C. Heating **3** for 30 minutes at 80°C produced **6** in 93% yield (Scheme 2a); **3**-BF_4 showed similar reactivity and gave **6**-BF_4 in 58% yield. Similarly, **5** was converted cleanly to **7** upon heating at 80°C for 15 minutes (Scheme 2b).[17] These are the first examples of a non-allylic C(sp³)−F bond-forming reductive elimination
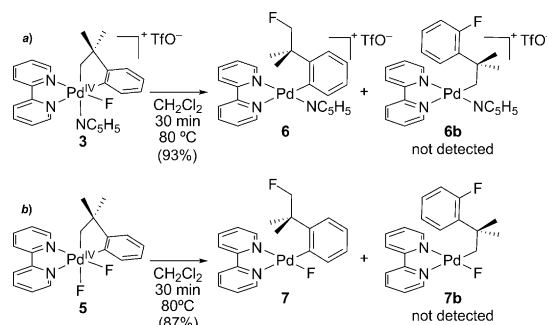
Scheme 2. C(sp³)−F bond-forming reductive elimination from **3** and **5**.

from a palladium center.[10] Remarkably, the reactions were both highly selective for C(sp³)−F coupling, and the analogous aryl fluorides **6b** and **7b** were not detected under any conditions examined. This is a reversal of the "normal" selectivity of reductive elimination (for example, at Pd^{II} and most other metal centers C(sp²) ligands are typically much more reactive toward reductive elimination than their non-allylic C(sp³) analogues).[18] This result highlights an important and complementary feature of Pd^{IV}-mediated fluorinations[4–6] compared to analogous transformations at Pd^{II} centers.[2]

Stacked ^{19}F NMR spectra for the conversion of **3**-BF_4 to **6**-BF_4 are shown in Figure 2. The disappearance of starting material proceeded with clean first order kinetics ($k = 3.5 \times$
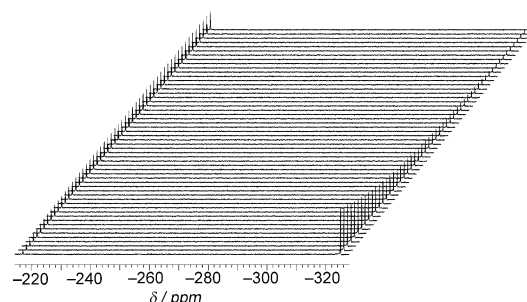

Figure 2. Stacked ^{19}F NMR spectra of reductive elimination from **3**-BF_4.

10^{-4} s^{-1} at 45°C), and no intermediates were detected by ^{19}F NMR spectroscopy. The rate of C−F bond-forming reductive elimination from **3**-BF_4 slowed dramatically upon the addition of pyridine. For example, in the absence of added pyridine, reductive elimination was complete after 30 minutes at 80°C.[19] In contrast, under analogous conditions but with 50 equivalents of added pyridine, no reaction was observed. A quantitative study of k_{obs} versus concentration of pyridine is shown in Figure 3. An excellent linear fit was observed for a plot of k_{obs} versus $1/[C_5D_5N]$.

On the basis of these studies, we propose that C(sp³)−F bond-forming reductive elimination proceeds by the mechanism shown in Scheme 3. The inverse first-order dependence on the concentration of pyridine implicates dissociation of the pyridine ligand prior to the rate-determining step. Following this dissociation, C−F coupling could potentially occur either
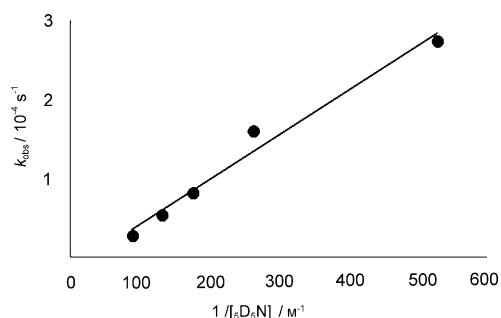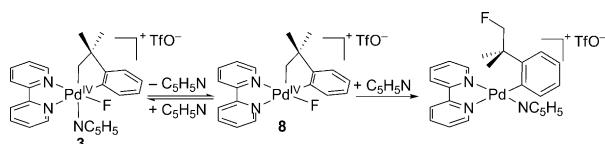
Figure 3. Plot of k_{obs} versus $1/[C_5D_5N]$ for reductive elimination from **3**-BF$_4$ to form **6**-BF$_4$ in CD$_2$Cl$_2$ at 45°C. $y = (5.65 \times 10^{-7})x - 1.39 \times 10^{-5}$; $R^2 = 0.979$.

Scheme 3. Proposed reaction pathway for complex **3**.

by direct reductive elimination from **8** (shown in Scheme 3) or by dissociation of fluoride from **8** to generate a Pd^{IV} dication followed by S$_N$2-type attack of F$^-$ on the σ alkyl ligand. While we cannot definitively distinguish these possibilities at this time, we favor the direct reductive elimination pathway for several reasons. First, as discussed above, fluoride is generally a poor nucleophile for S$_N$2 reactions, and S$_N$2 reactions are typically slow in systems with high degrees of β substitution.[16] Second, dissociation of fluoride to generate a $14e^-$ dicationic Pd^{IV} species is expected to be unfavorable, particularly in the relatively non-polar solvent CH$_2$Cl$_2$.[20] Third, stereochemical studies have implicated direct C(sp^3)–F bond-forming reductive elimination (with retention of configuration at carbon) at related Pt^{IV} and Au^{III} centers.[9,10] For example, Gagne demonstrated retention in the C–F coupling reaction shown in Scheme 4, and consequently proposed a reaction pathway that involves direct reductive elimination from the transient Pt^{IV} intermediate **9**.[9]
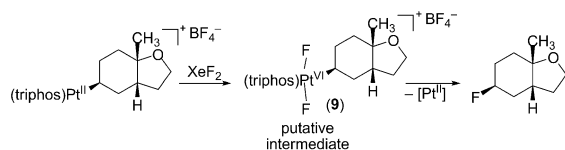

Scheme 4. C(sp^3)–F bond formation proceeds with retention of stereochemistry from putative Pt^{IV} intermediates (triphos = bis(2-diphenylphosphinoethyl)phenylphosphine).

A final series of studies were conducted to evaluate the mechanism (Scheme 3) by using DFT calculations. In particular, we sought to gain insights into the origin of the preference to form C(sp^3)–F over C(sp^2)–F bonds in this system. The calculations were conducted in Gaussian 09[21] using the M06 functional[22] and CEP-31G basis set[23,24] with the SMD solvent correction[25] (parameters were selected based on benchmarks from previous work in our group on

related transformations).[13b] We first compared proposed intermediate **8** to isomeric complex **8**-I (which contains the C(sp^2) of the cyclometalated ligand at the axial position and the C(sp^3) at the equatorial position). The optimized geometries of both complexes are approximately square-pyramidal, and **8** is the lower-energy structure (ΔH_{298} lowered by 3.2 kcal mol^{-1}).

Transition states for both C(sp^3)–F and C(sp^2)–F bond-forming reductive elimination were optimized from **8** and **8**-I. In both cases, low-energy transition states for C(sp^3)–F coupling were found; for example, $\Delta H^{\ddagger}_{298}$ from **8** is 15.2 kcal mol^{-1} (Scheme 5). The C(sp^3)–F coupling was kinetically
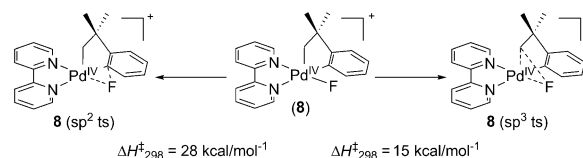
Scheme 5. Calculated energies for C(sp^3)–F versus C(sp^2)–F bond-forming reductive elimination from **8** (ts = transition state).

favored for both complexes ($\Delta\Delta H^{\ddagger}_{298}$ was 12.7 and 5.8 kcal mol^{-1} for **8** and **8**-I, respectively).[26] These results strongly suggest that the observed chemoselectivity is not a consequence of the geometry of **8** (which contains the C(sp^3) ligand at the axial position). Instead, they indicate that this selectivity reflects an inherent preference of this Pd^{IV} center.

In conclusion, we have demonstrated the synthesis of a series of Pd^{IV} fluoride complexes, including several (**2–4**) that are remarkably insensitive to water. We have also reported the first example of a C(sp^3)–F bond formation from a palladium center. This reaction proceeds with high selectivity for C(sp^3)–F bond formation despite the potential for competing C(sp^2)–F coupling. Preliminary studies are consistent with a mechanism that involves direct C–F bond formation rather than S$_N$2-type attack on the Pd^{IV}–alkyl bond. We anticipate that further investigations of this system and related ones will initiate the development of new Pd$^{II/IV}$-catalyzed alkane/alkene fluorination processes.

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[17] Thermolysis of complexes **2** and **4** gave complex and intractable mixtures of products. We hypothesize that this result may be due to decomposition of the initially formed reductive elimination products (analogues of **6** and **7**), because these Pd^{II} species would contain highly labile H_2O and/or OTf ligands.

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[19] Reductive elimination from **5** is inhibited by added NMe_4F. For example, k was $5.75 \times 10^{-4} \, s^{-1}$ without added NMe_4F and $3.26 \times 10^{-4} \, s^{-1}$ in the presence of 2.4 equivalents of NMe_4F. This result is consistent with reductive elimination from **5** proceeding by an analogous pathway to that proposed for **3**.

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[26] We were unable to optimize a unique transition state corresponding to $C(sp^3)$–F coupling from **8**-I. All attempts resulted in the same transition state structure found for **8**.

[27] CCDC 852596 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.