Synthesis and Reactivity of a Mono-σ-Aryl Palladium(IV) Fluoride Complex

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Abstract
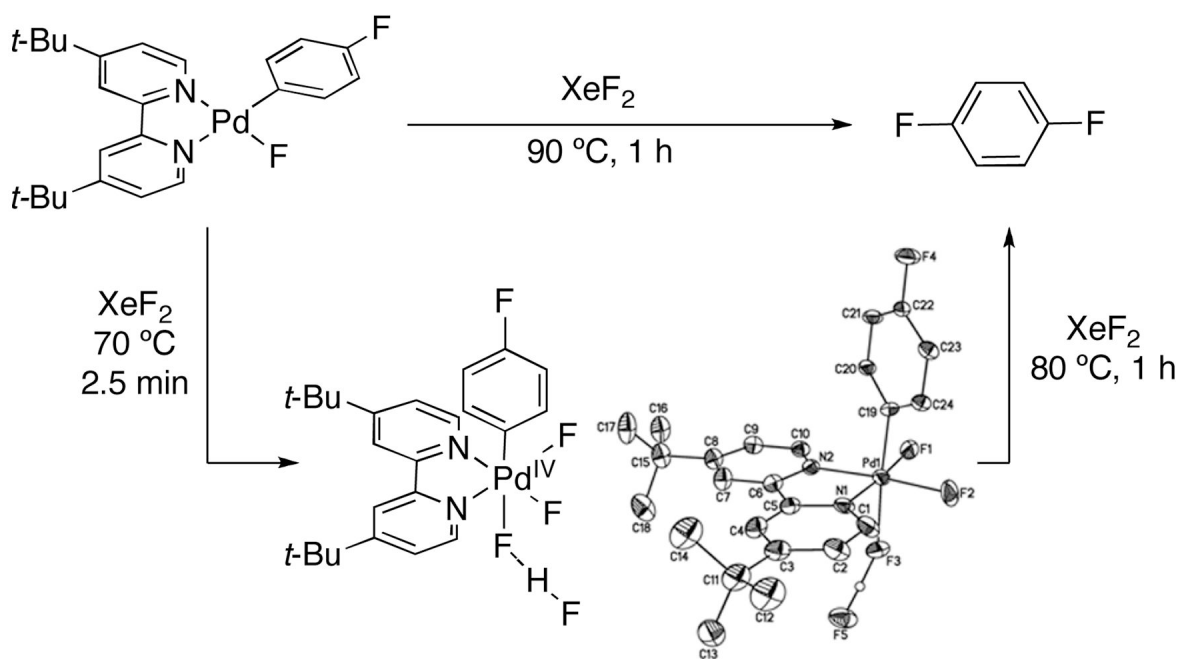
This communication describes the rational design and synthesis of a remarkably stable Pd^{IV} mono-aryl fluoride complex $(t\text{-Bu-bpy})Pd^{IV}(p\text{-FC}_6H_4)(F)_2(FHF)$ (t-Bu-bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine). This and related complexes undergo Ar-F bond formation in the presence of "F^+" sources. This work serves as a foundation for the development of a $Pd^{II/IV}$ catalyzed coupling reactions to form aryl fluorides.

Aryl fluorides are important components of many biologically active molecules, including pharmaceuticals, agrochemicals, and PET imaging agents.[1,2] While a variety of synthetic approaches are available for generating sp[3] C–F bonds,[2] there are relatively few general and practical methods for the formation of aryl fluorides.[2–4] To date, the most common routes to these molecules involve fluorination of aryl diazonium salts (the Balz-Schiemann reaction) [3a] and other nucleophilic aromatic substitution reactions with F^-.[3b,4] However, these transformations have significant limitations (*e.g.*, modest scope, the requirement for potentially

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explosive reagents, low yields, and long reaction times), and new synthetic methods are of great current interest.

An attractive approach to address this challenge would be the development of a Pd-catalyzed coupling reaction to produce aryl fluorides. As shown in eq 1, Ar–F bond-formation from a Pd(Ar)(F) species would be a key step in these processes. Analogous Ar–X (X = Cl, Br, and I) bond-forming reactions at Pd^{II}(Ar)(X) complexes are well-precedented;[5,6] however, achieving Ar–F coupling from Pd^{II}(Ar)(F) adducts has proven extremely challenging. Instead, these Pd^{II} complexes are prone to a variety of side reactions,[4,7] and aryl fluorides have only been obtained in low yields with a highly activated p-NO_2-substituted aryl group.[7]

(1)
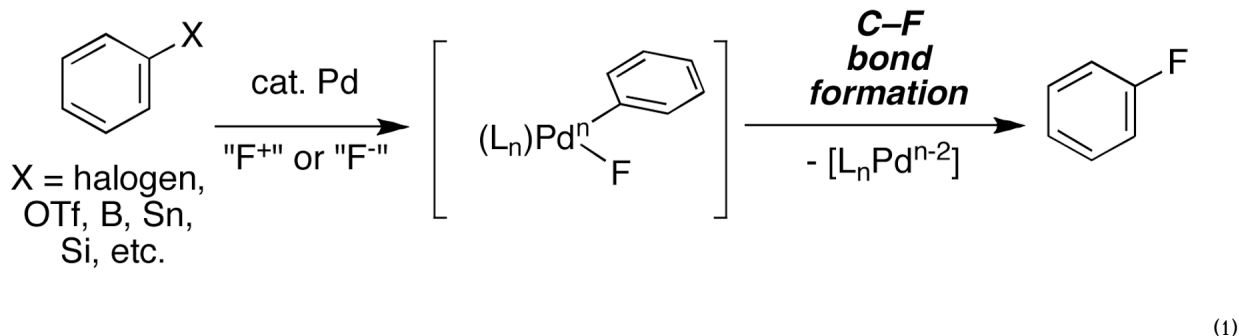
In contrast, several recent reports have shown that aryl fluorides can be formed by reacting Pd^{II}–Ar complexes with electrophilic fluorinating reagents.[8,9] For example, in 2006, our group demonstrated the Pd^{II}-catalyzed ligand-directed fluorination of Ar–H bonds with N-fluoropyridinium reagents.[8] Subsequently, stoichiometric reactions of Pd^{II} σ-aryl species with N-fluoropyridinium salts were shown to afford modest yields of aryl fluorides,[9a] and a related stoichiometric reaction with Selectfluor was recently optimized.[9b] In all cases, mechanisms involving C–F bond formation from transient Pd^{IV}(Ar)(F) intermediates were suggested; however, until a recent report by Ritter,[9c] little evidence was available to support these proposals.[10,11] We report herein on the design, synthesis, and reactivity of an isolable Pd^{IV}(Ar)(F) complex. This work provides a basis for the development of new $Pd^{II/IV}$-catalyzed Ar–F coupling reactions.

Our goal was to design an observable Pd^{IV}(Ar)(F) species in order to study its reactivity towards Ar–F bond-formation. Prior work suggested that such a Pd^{IV} complex should be stabilized by rigid bidentate sp^2 N-donor ligands such as 2,2′-bipyridine (bpy).[11,12] We also reasoned that multiple fluoride ligands would enhance the stability of the desired intermediate, as PdF_4 was one of the first reported compounds with Pd in the +4 oxidation state.[13] Based on these considerations, (t-Bu-bpy)Pd^{IV}(Ar)$(F)_3$ (t-Bu-bpy = 4,4′-di-t-butyl- 2,2′-bipyridine) was identified as our synthetic target.

The Pd^{II} precursor (t-Bu-bpy)Pd^{II}(p-FC_6H_4)(F) (**2a**) was prepared by sonication of (t-Bu-bpy) Pd^{II}(p-FC_6H_4)(I) (**1a**) with AgF (eq 2).[14a] Analysis of **2a** by ^{19}F NMR spectroscopy showed a characteristic broad resonance at −340.7 ppm (Pd**F**) as well as a peak at −122.9 ppm (Ar**F**) in a 1 : 1 ratio. The ^1H NMR spectrum of **2a** contained signals indicative of an unsymmetrical square planar Pd^{II} complex, with the 6- and 6'-protons of the t-Bu-bpy ligand appearing at 8.08 ppm and 8.74 ppm, respectively. X-ray crystallographic analysis provided further confirmation of the structure of **2a** (eq. 2).[14b]

(2)
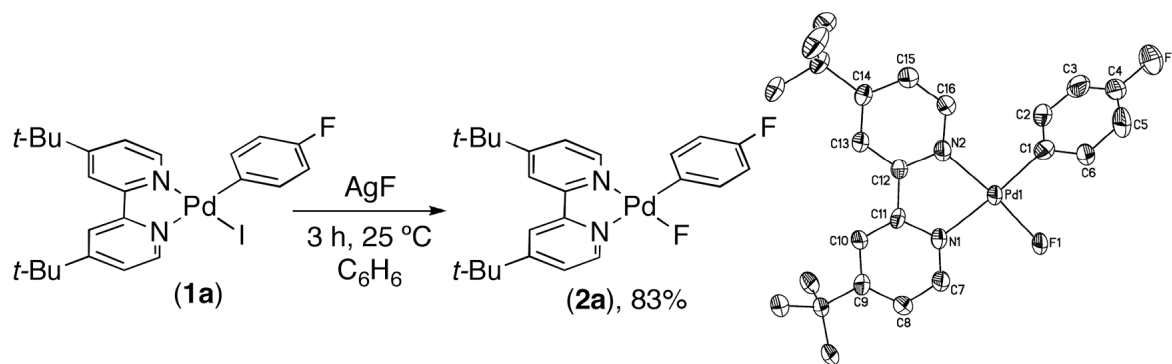
We next examined the reactivity of **2a** with electrophillic fluorinating reagents. Gratifyingly, the combination of **2a** with 3 equiv of XeF_2 in nitrobenzene at 90 °C for 1 h afforded 1,4-difluorobenzene, **3a**, in 57% yield (Table 1, entry 1). Notably, the biaryl species **4a** was also generated as a minor side product (7% yield). This C–F bond-forming reaction also proceeded efficiently with electronically diverse Ar groups. For example, $Pd^{II}(Ar)(F)$ complexes containing electron withdrawing (**2b**) and donating (**2c**) substituents on the Ar rings also reacted with XeF_2 to afford aryl fluorides (**3b** and **3c**) in comparable yields to **2a** (Table 1).[15,16]

The fluorination of **2a** was monitored at lower temperatures in an effort to observe a reactive intermediate. We were delighted to find that stirring **2a** with XeF_2 at 70 °C for 2.5 min afforded a new organometallic species (**5a**), which was isolated in 38% yield by recrystallization from THF/pentanes. The ^{19}F NMR spectrum of **5a** at 25 °C showed three broad resonances in a 1 : 1 : 2 ratio at −117.2 (Ar**F**), −206.3 (Pd**F**), and −257.4 (Pd**F**) ppm, respectively. When this solution was cooled to −70 °C, a fourth resonance was observed as a doublet of doublets at −177.6 ppm; furthermore, the Pd–F peaks sharpened considerably and appeared as a multiplet (−204.4 ppm) and a doublet (−256.9 ppm). This spectroscopic data, along with a doublet of doublets at 12.7 ppm in the low temperature ^{1}H NMR spectrum, is consistent with the formulation of **5a** as (t-Bu-bpy)$Pd^{IV}(Ar)(F)_2$(FHF).[17] This structure was confirmed by X-ray crystallography (eq. 3). The HF in this system is likely due to the reaction of XeF_2 with adventitious water.[18] Notably, this is the first reported example of a Pd^{IV} bifluoride. In addition, **5a** is, to our knowledge, the only isolable mono-aryl Pd^{IV} species where the σ-aryl ligand is not stabilized by a chelating *ortho*-substituent.[19]
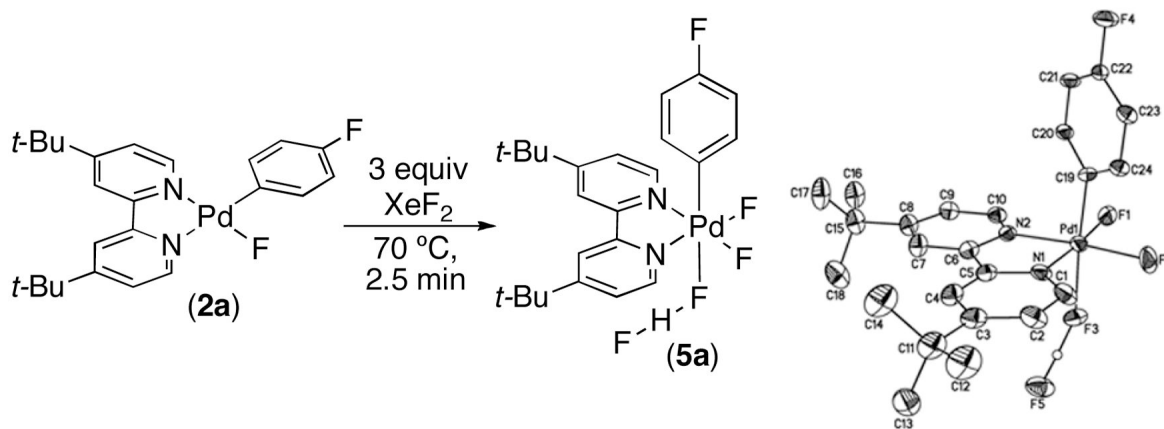
(3)

We next investigated the reactivity of **5a** towards Ar–F bond-forming reductive elimination. Intriguingly, heating this complex at 80 °C for 1 h in nitrobenzene led to only traces of aryl fluoride **3a**. Instead, significant quantities (35%) of biaryl **4a** were observed (Table 2, entry 1).[20] This is in surprising contrast to a related Pd[IV] aryl fluoride, which underwent quantitative C–F bond-forming reductive elimination upon thermolysis.[9c] This result suggests that direct C–F coupling at **5a** is slow relative to σ-aryl exchange between Pd centers (which is the likely pathway to Ar–Ar coupling).[21] The aryl exchange process is likely facilitated in this system because the σ-aryl group is not stabilized by a chelating group.[9c,21]

We noted that the stoichiometric reaction in Table 1 (as well as any catalytic C–F bond-forming reaction of this type) involves an excess of electrophilic fluorinating reagent relative to the Pd[IV](Ar)(F) intermediate. As such, we next investigated the thermolysis of **5a** in the presence of XeF_2, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, and *N*-fluorosulfanamide. We were delighted to find that under these conditions, the C–F coupled product **3a** was obtained in good to excellent yield, along with only traces (<5%) of **4a** (Table 2). While the mechanism of these transformations remains under investigation,[22] this result serves as a model for Ar–F formation from Pd[IV] σ-aryl species in catalytic reactions.

The results presented herein are remarkable for several reasons. First, the facile formation of **5a** suggests that the intermediacy of such Pd[IV] bifluoride species should be considered in catalytic C–F coupling processes, particularly where water has not been rigorously excluded. Second, the fact that the σ-aryl ligand of **5a** is not stabilized as part of a chelate makes this complex directly relevant to the development of Pd-catalyzed coupling reactions to form electronically diverse simple aryl fluorides. Third, the oxidant-promoted C–F coupling at **5a** demonstrates the viability of this step in stoichiometric[9] and catalytic[8] oxidative fluorination reactions. The observed stability of **5a** at room temperature also suggests that Ar–F formation may be turnover-limiting in Pd[II/IV]-catalyzed fluorinations. Finally, the similar reactivity of electron rich and electron deficient Pd–Ar species provides further precedent for the generality of these transformations.[9b]

In conclusion, this communication describes the synthesis of a stable Pd[IV](Ar)(F)$_2$(FHF) complex that undergoes Ar–F bond formation in the presence of "F$^+$" sources. This work serves as a foundation for the development of Pd[II/IV]-catalyzed couplings between electrophilic

fluorinating reagents and aryl stannanes, boronic acids, and/or silanes. The development of such transformations is currently ongoing in our laboratory and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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15. The stoichiometric fluorination described in ref. 9b shows similar tolerance of electronically diverse σ-aryl groups and comparable/slightly higher yields.

16. Nearly identical yields of **3a** and **4a** were obtained when 1 equiv of H_2O was added to the reaction of **2a** with XeF_2. However, the addition of 5 equiv of H_2O led to an erosion of the yield of **3a** (to 3%) and significant increase in the formation of **4a** (75%).

17. Select examples of metal FHF complexes: (a)Jasim NA, Perutz RN. J. Am. Chem. Soc 2000;122:8685. (b)Roe DC, Marshall WJ, Davidson F, Soper PD, Grushin VV. Organometallics 2000;19:4575..

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20. The poor mass balance may be due to the formation of one or more inorganic by-products, and efforts are underway to separate/characterize these species.

21. For examples of related processes at Pd[II], see: (a)Grushin VV, Marshall WJ. J. Am. Chem. Soc 2006;128:4632. [PubMed: 16594700] (b)Cardenas DJ, Martin-Matute B, Echavarren AM. J. Am. Chem. Soc 2006;128:5033. [PubMed: 16608337].

22. *N*-Bromosuccinimide also reacted with **5a** to afford **3a** in >95% yield, suggesting that the oxidant does not serve as the source of fluorine in the organic product. We speculate that electrophilic oxidants may react with the FHF ligand (for precedent, see ref. 17a), which in turn leads to C–F bond-forming reductive elimination from Pd[IV]. Studies are ongoing to gain further mechanistic insights into this oxidant-promoted C–F coupling process.
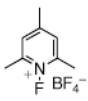
Table 1

C–F Bond Formation with Electronically Diverse Ar Groups
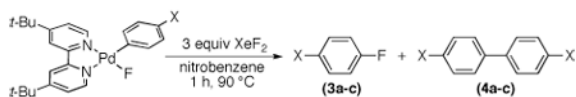
entry	X	complex	%3	%4
1	F	**2a**	57	7
2	CF₃	**2b**	60	3
3	OMe	**2c**	45	6

Table 2

C–F Bond-Forming Reactions of **5a**.
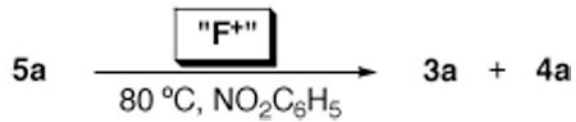
entry	"F$^+$"	3a	4a
1	none	trace	35%
2	XeF$_2$	92%	4%
3	(PhSO$_2$)$_2$NF	83%	<1%
4		50%	2%