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

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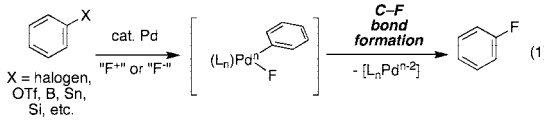
Aryl fluorides are important components of many biologically active molecules, including pharmaceuticals, agrochemicals, and PET imaging agents.[1,2] While a variety of synthetic approaches are available for generating sp^3 C−F bonds,[2] there are relatively few general and practical methods for the 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 of potentially 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. Ar−F bond formation from a Pd(Ar)(F) species, as shown in eq 1, would be a key step in these processes. Analogous Ar−X (X

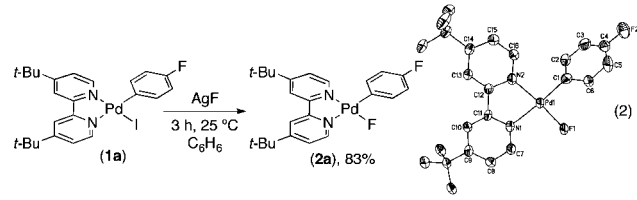


= Cl, Br, I) bond-forming reactions from $Pd^{II}(Ar)(X)$ complexes are well-precedented;[5,6] however, achieving Ar−F coupling from $Pd^{II}(Ar)(F)$ adducts has proven to be extremely challenging. Instead, these Pd^{II} complexes are prone to a variety of side reactions,[4,7] and aryl fluorides have only been obtained in low yields with a highly activated *p*-NO_2-substituted aryl group.[7]

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 of these 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 toward 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] On the basis of 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.

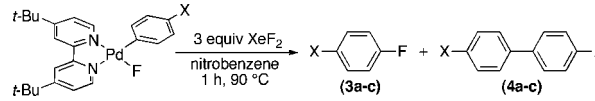
The Pd^{II} precursor (*t*-Bu-bpy)Pd^{II}(*p*-FC_6H_4)(F) (**2a**) was prepared by sonication of (*t*-Bu-bpy)Pd^{II}(*p*-FC_6H_4)(I) (**1a**) with AgF (eq 2).[14a]



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 and 8.74 ppm, respectively. X-ray crystallographic analysis provided further confirmation of the structure of **2a** (eq 2).[14b]

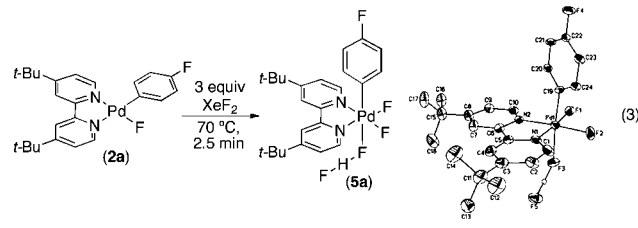
We next examined the reactivity of **2a** with electrophilic fluorinating reagents. Gratifyingly, the combination of **2a** with 3 equiv of XeF_2 in nitrobenzene at 90 °C for 1 h afforded 1,4-difluorobenzene (**3a**) in 57% yield (Table 1, entry 1). Notably, the biaryl species **4a** was also generated 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 electron-donating (**2c**) substituents on the Ar rings also reacted with XeF_2 to afford aryl fluorides (**3b** and **3c**) in yields comparable to that for **2a** (Table 1).[15,16]

Table 1. C−F Bond Formation with Electronically Diverse Ar Groups



entry	X	complex	% **3**	% **4**
1	F	**2a**	57	7
2	CF_3	**2b**	60	3
3	OMe	**2c**	45	6

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** (eq 3), 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 ppm (Pd**F**), respectively. When this solution

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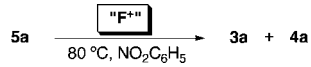
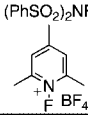
was cooled to −70 °C, a fourth resonance was observed as a doublet of doublets at −177.6 ppm; furthermore, the Pd−F peaks sharpened considerably and appeared as a multiplet (−204.5 ppm) and a doublet (−256.9 ppm). This spectroscopic data, along with a doublet of doublets at 12.7 ppm in the low-temperature ^{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 monoaryl Pd^{IV} species in which the σ-aryl ligand is not stabilized by a chelating ortho substituent.[19]

We next investigated the reactivity of **5a** toward 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 from **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 may be facilitated in this system because the σ-aryl group is not stabilized by a chelating moiety.[9c,21]

Table 2. C−F Bond-Forming Reactions of **5a**



entry	"F$^+$"	3a	4a
1	none	trace	35%
2	XeF_2	92%	4%
3	$(PhSO_2)_2NF$	83%	<1%
4		50%	2%

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. In view of this, we next investigated the thermolysis of **5a** in the presence of XeF_2, *N*-fluorosulfanamide, and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate. We were delighted to find that under these conditions, the ArF 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 from **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 reactivities 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.

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

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(15) The stoichiometric fluorination described in ref 9b shows a 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 a significant increase in the formation of **4a** (75%).
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(20) The poor mass balance may be due to the formation of one or more inorganic byproducts, and efforts are underway to separate/characterize these species.
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(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 a precedent, see ref 17a), which in turn leads to C−F bond-forming reductive elimination from Pd^{IV}. Studies to gain further mechanistic insights into this oxidant-promoted C−F coupling process are ongoing.

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