Communication

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Sophie I. Arlow, and John F. Hartwig

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Synthesis, Characterization, and Reactivity of Palladium Fluoroenolate Complexes

Sophie I. Arlow and John F. Hartwig*

Department of Chemistry, University of California, Berkeley, California 94720, United States

Supporting Information Placeholder

ABSTRACT: Cross-coupling reactions of aryl groups with α-fluoro carbonyl compounds catalyzed by palladium complexes have been reported, but palladium fluoroenolate intermediates relevant to such reactions have not been isolated or even detected previously. We report the synthesis, structural characterization, and reactivity of a series of C-bound arylpalladium fluoroenolate complexes ligated by monophosphines and bisphosphines. DPPF-ligated arylpalladium fluoroenolate complexes (DPPF=1,1-bis(diphenylphosphino)-ferrocene) derived from a monofluoroester, a difluoroester, difluoroamides, and difluoroacetonitrile underwent reductive elimination in high yields. Reductive elimination was faster from complexes containing less electron-withdrawing fluoroenolate groups and longer Pd-C(enolate) bond lengths than from complexes containing more electron-withdrawing fluoroenolate groups and shorter Pd-C(enolate) bond lengths. The rates of reductive elimination from these C-bound fluoroenolate complexes were significantly faster than those of the analogous trifluoromethyl complexes.

The importance of fluorinated compounds in pharmaceuticals, agrochemicals, and materials has prompted the development of transition metal-catalyzed methods for the synthesis of fluoroalkyl arenes.[1-6] Palladium-catalyzed coupling reactions for the synthesis of aryldifluoromethyl carboxylic acid derivatives have been reported recently. The α-arylations of α,α-difluoroketones,[7-8] α,α-difluoroesters,[9] and α,α-difluoroacetamides[10] with aryl halides all occur with broad scope. In addition, palladium-catalyzed cross-couplings of arylboronic acids with bromodifluoroacetates and –acetamides ($BrCF_2CO_2Et$, $BrCF_2C(O)NRR'$) have been developed.[11]

The aryl-fluoroalkyl bond could form in these catalytic processes by reductive elimination from an arylpalladium difluoroenolate complex. However, the isolation and reactivity of such complexes have not been reported. Reductive elimination reactions of alkylpalladium complexes containing fluorine atoms on the α-carbon of an alkyl group are significantly slower than those of their non-fluorinated analogs.[12] Reductive elimination reactions to form aryl-fluoroalkyl bonds from isolated fluoroalkyl palladium complexes are rare and are limited to trifluoromethyl,[13-23] pentafluoroethyl,[19, 21] and difluoromethyl[24] compounds.

Previous examples of isolated transition-metal fluoroenolates are limited, and complexes relevant to metal-catalyzed fluoroenolate arylations have not been isolated. Two chloroplatinum difluoroketone complexes have been prepared,[25-26] but no reactions of the isolated complexes were reported, and platinum-catalyzed fluoroenolate arylations are unknown. In 2015, a nickel difluoroketone enolate was prepared by fluoride abstraction from a Ni^0-trifluoroacetophenone complex,[27] but reactions relevant to catalytic coupling between fluoroenolates and aryl groups were not reported.

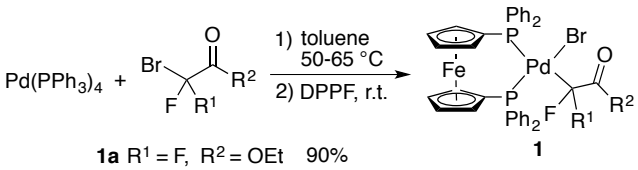
Here, we report the synthesis and structural characterization of a series of phosphine-ligated arylpalladium complexes of C-bound fluorinated enolates. Arylpalladium complexes ligated by DPPF underwent reductive elimination in high yield, allowing an assessment of the effects of the steric and electronic properties of the aryl and enolate ligands on the rates of this reaction. Synthesis of complexes containing various phosphines allowed an assessment of the effect of the ancillary ligands and a direct comparison of reductive elimination from a difluoroenolate complex and an analogous trifluoromethyl complex.

To prepare arylpalladium difluoroenolate complexes, we first synthesized a series of bromopalladium difluoroenolate complexes ligated by DPPF. The complexes were prepared by oxidative addition of a carbon-bromine bond of bromodifluoromethyl and bromofluoromethyl esters and amides to $Pd(PPh_3)_4$, followed by ligand exchange with DPPF. The C-bound difluoroester enolate **1a** was prepared in 90% isolated yield by oxidative addition of ethyl bromodifluoroacetate, followed by ligand exchange of DPPF for PPh_3. A series of palladium monofluoroester (**1b**) and difluoroamide (**1c-e**) complexes ligated by DPPF were prepared in 73-94% yield by analogous routes

involving oxidative addition of the corresponding bromofluorocarbonyl compound (Scheme 1).

The bromopalladium fluoroenolate complexes were characterized by NMR spectroscopy, and the connectivity of complex **1a** was confirmed by single-crystal x-ray diffraction (Figure S1). Like the previously reported platinum[25-26] and nickel[27] difluoroketone enolates, palladium enolate **1a** was C-bound. The carbon-oxygen bond lengths of the difluoroester group in **1a** were consistent with typical values for a C-O double bond and a C-O single bond, supporting the assignment of the complex as an η^1-C-bound enolate.

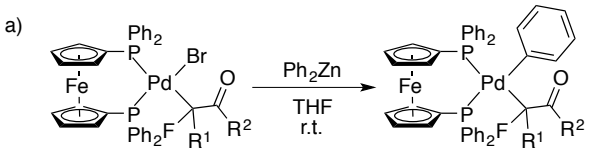
Scheme 1. Synthesis of DPPF-Ligated Bromopalladium Fluoroenolate Complexes



1a R^1 = F, R^2 = OEt 90%
1b R^1 = H, R^2 = OEt 93% **1d** R^1 = F, R^2 = NMe_2 94%
1c R^1 = F, R^2 = N⌒O 83% **1e** R^1 = F, R^2 = NEt_2 73%

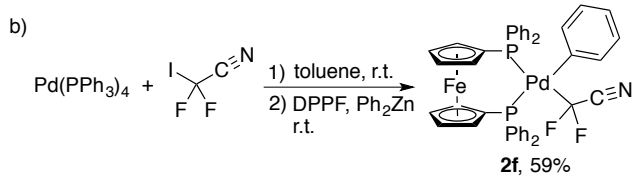
Scheme 2. Synthesis of DPPF-Ligated Arylpalladium Fluoroenolate Complexes

a)



2a R^1 = F, R^2 = OEt 71%
2b R^1 = H, R^2 = OEt 58% **2d** R^1 = F, R^2 = NMe_2 40%
2c R^1 = F, R^2 = N⌒O 83% **2e** R^1 = F, R^2 = NEt_2 37%[a]

b)



[a]Prepared by transmetallation with $PhB(OH)_2$.

Bromopalladium fluoroenolate complexes **1a-e** were converted to the corresponding arylpalladium fluoroenolates by reactions with aryl nucleophiles. The reaction of bromopalladium fluoroenolates **1a-1d** with diphenylzinc occurred rapidly in THF at room temperature to afford the corresponding phenylpalladium fluoroenolate complexes (**2a-d**) in 40-83% isolated yield (Scheme 2a). Complex **2e** was prepared by transmetallation with phenylboronic acid in 37% isolated yield. A modified synthetic route afforded difluorocyanomethyl complex **2f** in 59% isolated yield (Scheme 2b). The ^{19}F NMR spectra of the arylpalladium fluoroenolate complexes consisted of a single fluorine resonance with ^{31}P-^{19}F coupling between fluorine and two inequivalent phosphorus nuclei ($J_{F\text{-}P}$ = 44.0, 37.3 Hz for difluoroester enolate **2a**). The ^{31}P NMR spectra consisted of two triplets of doublets, due to ^{31}P-^{19}F and ^{31}P-^{31}P coupling.

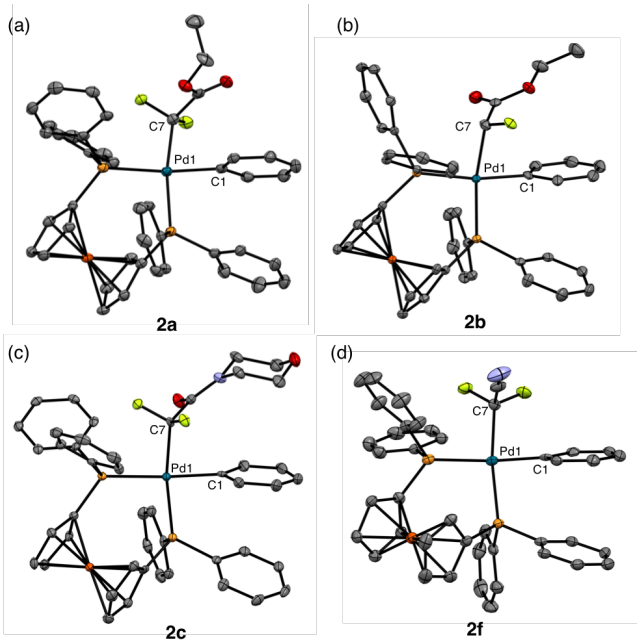
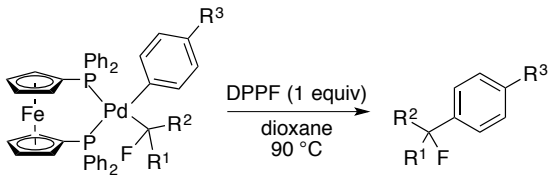


Figure 1. ORTEP diagrams of complexes **2a-c** and **2f**. Selected bond lengths: (a) Pd1-C1, 2.053(3) Å; Pd1-C7, 2.099(3) Å; (b) Pd1-C1, 2.051(2) Å; Pd1-C7, 2.105(3) Å; (c) Pd1-C1, 2.055(5) Å; Pd1-C7, 2.188(3) Å; (d) Pd1-C1, 2.058(3)Å; Pd1-C7, 2.089(3) Å.[28] Ellipsoids are shown at 50% probability, and hydrogen atoms and solvents of crystallization are omitted for clarity.

Table 1. Reductive Elimination from Pd-Fluoroenolate Complexes



entry	complex	R^1	R^2	R^3	yield[a]	$t_{1/2}$ (min)[b]
1	**2a**	F	CO_2Et	H	99%	213
2	**2b**	H	CO_2Et	H	93% (98%)[c]	<5 (83)[c]
3	**2c**	F	C(O)N⌒O	H	98%	42
4	**2d**	F	$C(O)NMe_2$	H	93%	53
5	**2e**	F	$C(O)NEt_2$	H	95%	30
6	**2f**	F	CN	H	92%[d]	845
7	**2g**[e]	F	CO_2Et	OMe	99%	223
8	**2h**[e]	F	CO_2Et	Cl	84%[f]	811

[a]Determined after 24 h by ^{19}F NMR spectroscopy. [b]Determined by monitoring the decay of the Pd complex by ^{19}F NMR spectroscopy. [c]At 50 °C. [d]Yield after 72 h. [e]Prepared by transmetallation between complex **1a** and the corresponding arylboronic acid (see Supporting Information for synthetic details). [f]Yield after 36 h.

The structures of DPPF-ligated arylpalladium fluoroenolate complexes **2a-c** and **2f** were confirmed by single-

crystal, x-ray crystallography (Figure 1). The geometry about the palladium atom is square planar in each complex. The Pd-C(aryl) bond lengths are nearly constant, ranging from 2.051(2)-2.058(3) Å. The enolates are η^1-C-bound in all cases, but the Pd-C(enolate) bond lengths vary over a wide range from 2.089(3)-2.188(3) Å. Among the complexes of difluorinated enolates (**2a**, **2c**, and **2f**), the Pd-C(enolate) bond is shorter for enolates containing more electron-withdrawing groups. The Pd-C(enolate) bond is shortest in difluorocyanomethyl complex **2f** (2.089(3) Å), followed by difluoroester complex **2a** (2.099(3) Å). The Pd-C(enolate) bond is longest in difluoroamide complex **2c** (2.188(3) Å).

Arylpalladium fluoroenolate complexes **2a-e**, containing difluoroester, monofluoroester, and difluoroamide enolates, and complex **2f**, containing a difluorocyanomethyl ligand, underwent reductive elimination to form the corresponding aryl fluorocarbonyl and -nitrile compounds in 92-99% yield (Table 1). The effect of the electronic and steric properties of the enolate was assessed by measuring the rate constants for the reaction of a series of fluoroenolate complexes ligated by DPPF. The rate constants were measured from the decay of the Pd-fluoroenolate complexes by ^{19}F NMR spectroscopy in the presence of 1 equiv of DPPF.[29] These data fit a first-order exponential decay, from which the rate constants and half-lives for reductive elimination were determined.

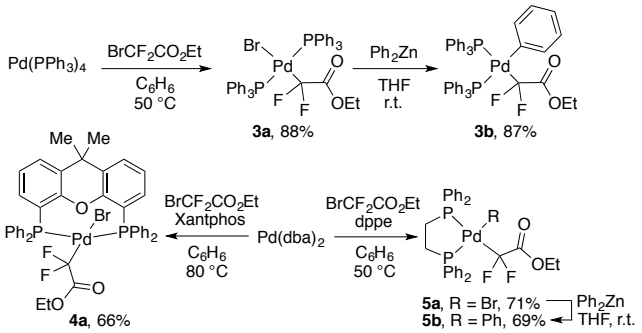
Comparison of these half-lives show that complexes of more electron-rich enolates underwent reductive elimination at lower temperatures and with faster rates than did complexes of more electron-poor enolates. Difluoroamide complex **2c** reacted approximately 4 times faster than difluoroester complex **2a** and approximately 20 times faster than difluoronitrile complex **2f**. The number of fluorine atoms on the α-carbon of the enolate also significantly affected the rate of reductive elimination of the corresponding Pd enolate complex; monofluoroester complex **2b** underwent reductive elimination in 98% yield upon heating at 50 °C, whereas difluoroester complex **2a** reacted to <5% conversion after 24 hours at the same temperature. Overall, the trend in rates of reductive elimination of the palladium fluoroenolate complexes was: monofluoroester > difluoroamide > difluoroester > difluoronitrile. The relationships between these relative rates and the structures of the enolate complexes can be assessed by comparing the data in Table 2 to the structures of the complexes determined by x-ray diffraction (Figure 1). Among the complexes of difluorinated ester (**2a**), amide (**2c**), and nitrile (**2f**) enolates, a correlation between a longer Pd-C(enolate) bond and a faster rate of reductive elimination was observed.

Complexes of more sterically hindered enolates underwent reductive elimination with faster rates than those of less hindered enolates: at 90 °C, the half-life for reaction of dimethylamide complex **2d** was 53 minutes, whereas the half-life for reaction of the analogous diethylamide complex **2e** was 30 minutes. The magnitude of this effect is comparable to that observed for reductive elimination from arylpalladium complexes of non-fluorinated enolates of dimethyl- and diethylamides.[12]

The relative rates of reductive elimination from complexes **2a**, **2g**, and **2h** containing hydrogen, methoxy and chloro substituents on the palladium-bound aryl group were measured (Table 2, entries 1 and 7-8). The half-life for reductive elimination from the more electron-rich *para*-anisylpalladium complex **2g** was nearly identical to that for reductive elimination from the phenylpalladium complex **2a**; the half-life for reaction of *para*-chlorophenyl complex **2h** was longer than that for the reactions of **2a** or **2g**. In previous studies of reductive elimination from arylpalladium cyano complexes[30] and arylpalladium complexes of non-fluorinated ketone enolates,[12] the reactions of *para*-chlorophenyl complexes were slower than those of the parent phenyl complexes, just as observed for complexes **2h** and **2a** of the fluorinated enolates.

Finally, we investigated the effect of the ancillary phosphine ligand on this class of reductive elimination. A series of phosphine-ligated difluoroester complexes were prepared by oxidative addition of a carbon-halogen bond to the Pd^0 precursors $Pd(PPh_3)_4$ or $Pd(dba)_2$. Complex **3a** was isolated from the oxidative addition of ethyl bromodifluoroacetate to $Pd(PPh_3)_4$ in 88% yield. Oxidative addition of ethyl bromodifluoroacetate to $Pd(dba)_2$ in the presence of a chelating bisphosphine afforded difluoroester complexes **4a**, ligated by Xantphos, and **3a**, ligated by DPPE (DPPE=1,2-bis(diphenylphosphino)ethane), in 66 and 71% yield, respectively (Scheme 3). The connectivity of Xantphos complex **4a** was confirmed by x-ray crystallography (Figure S2). Transmetallation with diphenylzinc afforded triphenylphosphine- and DPPE-ligated complexes **3b** and **5b** in 87% and 69% yield, respectively.

Scheme 3. Synthesis of Phosphine-Ligated Palladium Difluoroester Complexes

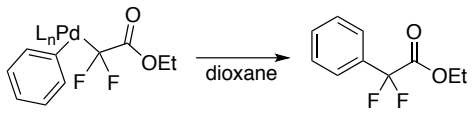


Reductive elimination to form ethyl phenyldifluoroacetate from arylpalladium difluoroester enolate complexes ligated by monophosphines and bisphosphines occurred with rates and yields that depended strongly on the identity of the ancillary ligand (Table 2). Triphenylphosphine-

ligated arylpalladium difluoroester complex **3b** did not undergo reductive elimination in high yield; only 31% yield of ethyl phenyldifluoroacetate was obtained upon heating of **3b** at 90 °C for 24 h, although full consumption of **3b** was observed.

While reductive elimination from difluoroester enolate complex **2a**, ligated by DPPF (bite angle = 99.1°[31]), proceeded in high yield (*vide supra*), the analogous elimination from complex **5b**, ligated by DPPE (bite angle = 85.8°[32]), proceeded in low yield. Complex **5b** required heating at 100 °C for 72 hours for full conversion, and only 25% yield of ethyl phenyldifluoroacetate formed.

Table 2. Reductive Elimination of Arylpalladium Difluoroester Complexes



entry	complex	ligand	temperature	yield[a]
1	**2a**	DPPF	90 °C	97%[b]
2	**3b**	PPh_3	90 °C	31%[b]
3	**4b**[c]	Xantphos	r.t.	94%[d,b]
4	**5b**	DPPE	90 °C	0%[e] (25%)[b,f]

[a]Determined after 24 h by ^{19}F NMR spectroscopy with fluorobenzene as internal standard. [b]Full conversion of the starting material was observed. [c]Formed *in situ* from complex **4a** and Ph_2Zn with THF as solvent. [d]Yield after 30 min. [e]<5% conversion of the starting material was observed. [f]At 100 ºC for 72 h.

The reaction of a Xantphos-ligated difluoroester enolate complex allows a comparison of the rate of reductive elimination from a difluoroenolate to that of reductive elimination from trifluoromethyl compound. Treatment of complex **4a**, ligated by Xantphos (bite angle = 111°[33]), with diphenylzinc formed the corresponding arylpalladium difluoroester enolate **4b**, which was characterized *in situ*. Consistent with the high yields obtained from arylation reactions of difluorocarbonyl compounds catalyzed by palladium and Xantphos[9, 11] and the effect of large bite angles on the rates of reductive elimination, reductive elimination of ethyl phenyldifluoroacetate occurred in 94% yield after just 30 min at room temperature. Reductive elimination from this compound was much faster than reductive elimination of trifluoromethylbenzene from the (Xantphos)Pd(Ph)(CF_3) complex studied by Grushin, which required heating for 3 hours at 80 °C for reductive elimination to occur in high yield.[15]

In conclusion, we report the first examples of isolated fluoroenolate complexes of palladium, as well as the first reductive elimination reactions of isolated fluoroenolate complexes. DPPF-ligated arylpalladium complexes of C-bound fluorinated ester, amide, and nitrile enolates were isolated, characterized, and shown to undergo reductive elimination in high yield upon heating. The combination of structural data and rates of reductive elimination reveal that complexes containing more electron-donating fluoroenolate groups, which have longer Pd–C(enolate) bonds, react significantly faster than those with less electron-donating groups and shorter Pd–C(enolate) bonds. Future work will examine the reactivity of metal fluoroenolate and fluoroalkyl complexes ligated with a range of ancillary ligands, as well as the development of new catalytic reactions involving these classes of complexes.

ASSOCIATED CONTENT

Experimental procedures and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

jhartwig@berkeley.edu

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28. Two molecules of complex **2f** were present in the unit cell. For clarity, only one molecule of **2f** is shown in Figure 1d, and bond lengths for only one molecule of **2f** are provided.

29. Reductive elimination was found to be zero-order in the concentration of added DPPF.

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