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Evidence for In Situ Catalyst Modification During the Pd-Catalyzed Conversion of Aryl Triflates to Aryl Fluorides

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Abstract

A mechanistic investigation of the Pd-catalyzed conversion of aryl triflates to fluorides is presented. Studies reveal that C—F reductive elimination from an LPd(II)(aryl) fluoride complex (L = *t*-BuBrettPhos (**2**), RockPhos (**3**)) does not occur when the aryl group is electron rich. Evidence is presented that a modified phosphine, generated in-situ, serves as the actual supporting ligand during catalysis with such substrates. A preliminary study of the reactivity of an LPd(II)(aryl) fluoride complex based on this modified ligand is reported.

Owing to their desirable metabolic properties and unique electronic characteristics, aryl fluoride-containing compounds are highly valued in a number of fields.[1] Despite their recognized importance, the construction of aryl C—F bonds still remains quite challenging.[2] A metal-catalyzed coupling of the heavier aryl halides and pseudohalides (X = Cl, Br, I, OTf) with a simple metal fluoride salt would be an ideal route to generate aryl fluorides with respect to waste, simplicity, and generality (Figure 1).

The elegant studies of Grushin[3] and Yandulov[4] have shed considerable light on the challenges associated with developing a Pd-catalyzed nucleophilic fluorination. A difficult C—F reductive elimination step, the formation of stable Pd(II) fluoride-bridged dimers, and myriad fluoride-induced ligand decomposition pathways have cast doubt as to whether accessing the catalytic cycle shown in Figure 1 is possible. To avoid these problems, processes in which C—F reductive elimination occurs from a higher oxidation state metal fluoride, notably Pd(IV), have attracted significant interest.[5] We recently described the catalytic conversion of aryl triflates to aryl fluorides, which we believe operates by a Pd(0)/Pd(II) cycle.[6] Key to the success of this reaction was the use of bulky, monodentate biaryl phosphines—catalysts based on these ligands appear to circumvent many of the aforementioned problems. While C—F reductive elimination was demonstrated from BrettPhos-ligated **1**•Pd(Ar)F complexes,[6] it was only observed when the aryl group was electron deficient and possessed an *ortho* alkyl group, two structural features known to favor reductive elimination (Figure 2).[7] In addition, Pd catalysts based on BrettPhos (**1**) are not active in most fluorination reactions—only catalysts derived from the di-*tert*-butyl-based ligand *t*-BuBrettPhos (**2**) were shown to be capable of transforming a wide range of aryl triflates to their corresponding fluorides. We have now discovered that catalysts based on the structurally similar RockPhos (**3**) also perform well in these fluorination reactions with product yields similar to **2** (*vide infra*).[8]

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SUPPORTING INFORMATION. Procedural, spectral, and X-ray crystallographic (CIF) data. This material is available free of charge via the Internet at http://pubs.acs.org.

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In our previous report, we described the formation of regioisomeric aryl fluoride products whose quantities increased as the arene became more electron rich (Figure 3).[6]

Because the product ratios obtained differ from those reported by a process involving external fluoride attack on a benzyne-type intermediate,[3h] we felt that it was possible that a discrete LPd(II)(Ar) fluoride complex is involved in the fluorination of electron-rich aryl triflates. To address this question, a better understanding of the C—F reductive-elimination process from electron-rich LPd(II)(Ar) fluoride complexes supported by ligands relevant to the catalytic reaction was required.

Herein we report results that cast doubt as to whether **2** (or **3**) serves as the actual supporting ligand in many of these reactions, but suggest that reductive elimination from LPd(Ar)F complexes (with electron-rich aryl groups) is possible and likely occurs as part of the catalytic cycle.

We began by preparing the **3**•Pd(Ar)F complex **5** presumed to be an intermediate in the catalytic fluorination of 4-*n*BuPhOTf. In general, Pd-complexes derived from **3** have proven superior to those originating from **2** in terms of isolation, characterization, and synthetic manipulation. Simply by stirring (COD)Pd(CH_2TMS)$_2$, **3**, and 4-*n*BuPhBr in a minimum quantity of cyclohexane, the desired oxidative-addition complex **4** precipitated as a bright yellow solid in good yield (76%). Complex **4** is the first di-*t*-butylphosphinobiaryl Pd-complex with an OMe group in the 3 position that we have been able to structurally characterize. X-ray crystallographic analysis showed that **4** adopts a *C*-bound conformation in the solid state with a Pd—Br bond length of 2.4663(3) Å. It is worth noting that unlike with **1**, oxidative addition complexes derived from **3** show no signs of an *O*-bound conformation in solution.[9] Halide exchange of **4** with AgF afforded the desired LPd(Ar)F complex **5**.

When complex **5** was heated in toluene, no observable product of C—F reductive elimination was detected, either with or without a variety of additives, despite **5** being fully consumed (Table 1). ^{19}F and ^{31}P NMR analysis of the crude reaction mixtures indicated the absence of aryl fluorides of any kind and no evidence for P—F bond formation.[3] The major fluorine-containing species detected by ^{19}F NMR (δ −136 and −148 ppm) vanished upon the addition of Et_3N, leading us to speculate that a formal loss of HF may have occurred (*vide infra*).

While preparing the analogous *t*-BuBrettPhos-ligated LPd(Ar)Br complex **6**, we observed that the initially-formed bright yellow complex (^{31}P NMR δ 69 ppm) that had precipitated from cyclohexane began to rapidly convert to a new dark red-colored compound (^{31}P NMR: δ 83 ppm) when dissolved in CD_2Cl_2, eventually reaching an approximate 6:1 mixture as determined by ^{1}H NMR (Figure 4).[10] From this mixture, the major component could be crystallized and X-ray analysis identified it as dearomatized Pd(II) bromide complex **7** with Pd—Br and Pd—P bond lengths of 2.511 and 2.298 Å respectively (Figure 5).[11] In complex **7**, the Pd atom is sigma bound to C2 and has an additional interaction with C3, analogous to the one carbon Pd-arene interaction seen in **4** and previously observed.[12] Despite its twisted, dearomatized structure, **7** is air-stable and thermally robust. Dissolving pure crystalline **7** in CD_2Cl_2 re-established a nearly 6:1 mixture of **7:6**; thus, remarkably, these compounds appear to be in equilibrium. Although the origin of the difference in reactivity between **4** and **6** is not yet known,[13] we have observed that complexes based on electron-deficient aryl groups show far less propensity to rearrange than those bearing electron-rich arenes. For example, after 60 hours in CD_2Cl_2, **3**•Pd(Ar)Br (Ar = 4-cyanophenyl) shows no detectable rearrangement and the corresponding complex with **2** shows only ~10% isomerization.

Treating **7** with DBU (1.2 equiv.) and 4-*n*BuPhBr (3 equiv.) in THF led to the clean formation of a new bright yellow compound (^{31}P NMR: δ 71 ppm) that was identified as the oxidative addition complex **8** by X-ray diffraction analysis (Figure 6). Importantly, this demonstrates that if complexes similar to **7** are formed in cross-coupling reactions using **2**, there exists a pathway by which they can return to a LPd(0) state if base is present. In contrast to **6**, **8** could be heated to 100 °C without any detectable decomposition or rearrangement as judged by ^{31}P NMR.

With the reactivity of complexes of **2** and **3** brought to light, we began to probe their relevance to the catalytic fluorination reaction. Performing a C—F bond-forming reaction (utilizing **3** as ligand and 4-*n*BuPhOTf as the substrate) and re-isolating the phosphine present at the end of the reaction gave arylated phosphine **9**, whose structure and connectivity were confirmed by X-ray analysis (Figure 7).[14,15] The very similar chemical shifts (^{31}P NMR) of **9** relative to **3** had allowed it to previously evade our detection.[16] We then compared the performance of **9** relative to **3** as supporting ligand (Figure 8). Using isolated ligand **9** in place of **3** led to an improvement in yield of 13% in the fluorination of 4-*n*BuPhOTf (73% vs. 60%). No further arylation of **9** was detected as judged by ^{31}P NMR of the crude reaction mixture.[17] Thus the yield increase observed is likely due to factors beyond just the inability of **9** to undergo arylation.[18]

To date, the kinetic profile of every fluorination reaction we have studied shows a substantial initial mass loss of ArOTf without the formation of an equivalent amount of ArF. During this stage, ArCl (chloride from the [(cinnamyl)PdCl]$_2$ precursor) and ArOAr are the only other detectable products formed by GC-MS analysis. After this induction period, zeroth-order overall decay of the remaining ArOTf is observed. Using ligand **9,** the initial mass loss of aryl triflate is less and the zeroth-order decay process begins rapidly compared to when **3** is employed (Figure 8).

Upon re-examination of the studies on the stoichiometric reductive elimination of C—F bonds (Table 1), we observed that substantial quantities of ligand **9** were present in the crude reaction mixtures (Figure 9). For example, at the end of the reaction shown in entry 2 (Table 1), there was a ~1:1 mixture of **3** and **9** (^{31}P NMR). In the case where excess aryl bromide was included in the reaction mixture (entry 4, Table 1), **3** had been mostly consumed and two new virtually identical ligands were detected by ^{31}P NMR—**9**, and what we presume to be **10**.[19] Although we were unable to directly observe a rearranged Pd(II) fluoride analogous to **7**, it is now clear that formal net loss of HF had taken place (*vide supra*).

The arylated LPd(Ar)F complex **11** could be readily prepared from **8** and its reactivity was compared to **5** (Table 2). Upon heating **11** in toluene or cyclohexane, 4-*n*BuPhF was formed in yields of 15% and 20%, respectively. Heating **11** in the presence of an excess of PhBr produced primarily PhF (40%) (Table 2, entry 2). Similarly, in the presence of 1-naphthyltriflate, 1-fluoronaphthalene was formed in 75% yield (entry 3). The precise mechanism leading to formal aryl exchange is currently under investigation. Perhaps most relevant to the catalytic reaction was the fate of complex **11** when heated in the presence 4-*n*BuPhOTf (entry 4). A 1.6:1 mixture of 4-*n*BuPhF and 3-*n*BuPhF was produced in 52% combined yield—this is nearly the same ratio of products seen in catalytic reactions employing **2**. This demonstrates that the formation of regioisomeric aryl fluorides in the catalytic reaction does not require the presence of highly basic CsF nor any other additional fluoride source.[20] Notably, if this stoichiometric reaction was conducted in cyclohexane a slightly improved ratio (2:1) of 4-*n*BuPhF to 3-*n*BuPhF was observed. This is similar to the improvements in selectivity in the catalytic reaction that we have seen when utilizing cyclohexane in lieu of toluene.[6] If 4-*n*BuPhBr was used as the additive during the thermolysis (entry 5), very little regioisomer was formed. Finally, inclusion of 4-MeOPhOTf

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led to a 1.7:1 mixture of 4-*n*BuPhF and 3-*n*BuPhF along with small amounts of 3-MeOPhF (7%); interestingly, no 4-MeOPhF could be detected (entry 6). In addition, **11** was found to be catalytically competent in the fluorination of 4-*n*-BuPhOTf with the highest yield we have seen to date for this substrate (Figure 10).

It has not escaped our attention that the ability of ligands **2** and **3** to undergo arylation may play a role in their success (or failure) in other previously reported transformations.[8,21] The findings reported herein also imply both that there is a slightly different catalyst for each individual substrate and that processes using **3** and especially **2** may be more complex than previously assumed.

In conclusion, we have shown that a **3**•Pd(Ar)F complex does not undergo a C—F reductive elimination process in the case where the arene is electron-rich. The observed facile and reversible rearrangement of oxidative addition complex **6** led us to discover the formation of terarylphosphine ligands, which are formed in situ in the fluorination reaction when starting with **2** or **3**.[22] The addition of a third aryl ring to the phosphine ligand confers marked stability to the Pd-complexes subsequently formed—this may be required for C—F bond formation to occur. Although we believe these results are interesting and informative, they do not directly relate to the mechanism of formation of different regioisomers in the catalytic C-F bond-forming process. This is a topic of ongoing investigations in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. Catalysts-based on RockPhos (**3**) have been shown to be excellent in C—O cross coupling involving aliphatic alcohols. See, Wu X, Fors BP, Buchwald SL. Angew Chem Int Ed. 2011 early view. 10.1002/anie.201104361
9. "*O*-bound" refers to binding of the Pd(II) center to the oxygen of the OMe group in the 3 position as opposed to the lower arene (i.e. "*C*-bound"). see: Fors BP, Watson DA, Biscoe MR, Buchwald SL. J Am Chem Soc. 2008; 130:13552–13554. [PubMed: 18798626]
10. Rearrangements of this type are likely a contributing factor to our previously encountered difficulty in isolating and characterizing Pd-complexes derived from **2**.
11. Doyle has recently observed a seemingly similar dearomatization of **1** involving Nickel(0) and an epoxide substrate. The connectivity in their complex is slightly different with respect to the point of lower ring dearomatization. See: Nielsen DK, Doyle AG. Angew Chem Int Ed. 2011; 50:6056–6059.
12. Barder TE, Biscoe MR, Buchwald SL. Organometallics. 2007; 26:2183–2192.
13. After 2 hours at room temperature, a CD_2Cl_2 solution of RockPhos complex **4** showed only ~ 5% of a rearranged compound.
14. *t*-BuBrettPhos (**2**) is quantitatively arylated in the catalytic fluorination reaction. We have been unable however, to isolate arylated **2** in pure form from the crude mixture to resubject it to a catalytic reaction.
15. Since chloride is also present in the catalytic reaction, we cannot rule out at this time that the arylated ligand is formed via the rearrangement of an initially formed LPd(Ar)Cl complex as opposed to a LPd(Ar)F complex.
16. The ^{31}P NMR chemical shift of arylated ligands based on **2** or **3** have characteristic downfield shifts of ~ 1.2 ppm relative to the parent ligand.
17. Spiking the crude reaction mixture with an authentic sample of **9** showed the presence of only **9** by ^{31}P NMR. We assume a doubly arylated ligand would possess a slightly different ^{31}P chemical shift.
18. Arylation of **3** can consume 7.5% of the aryl triflate at maximum, yet the yield increase seen with **11** is 13%. Thus it may be possible that the HF (or HCl) initially formed may serve to destroy additional aryl triflate.
19. The ^{31}P NMR shift of **9** and what we presume to be **10** differ by only 0.04 ppm. LC-MS analysis of the crude mixture the presence of a compound with the mass of **10** (MW = 545).
20. Grushin has shown that fluoride retains considerable basicity even when bound to Pd. See: Grushin VV, Marshall WJ. Angew Chem Int Ed. 2002; 41:4476–4479.
21. a) Fors BP, Dooleweerdt K, Zeng Q, Buchwald SL. Tetrahedron. 2009; 65:6576–6583. [PubMed: 20740063] b) Fors BP, Buchwald SL. J Am Chem Soc. 2010; 131:12898–12899. [PubMed: 19737014] c) Maimone TJ, Buchwald SL. J Am Chem Soc. 2010; 132:9990–9991. [PubMed: 20604520] d) Shen X, Hyde AM, Buchwald SL. J Am Chem Soc. 2010; 132:14076–14078. [PubMed: 20857936] e) Dooleweerdt K, Fors BP, Buchwald SL. Org Lett. 2010; 12:2350–2353. [PubMed: 20420379] f) Breitler S, Oldenhuis NJ, Fors BP, Buchwald SL. Org Lett. 2011; 13:3263–3265.
22. In situ ligand modification has been documented during Pd-catalyzed cross-coupling processes in the past, with Hartwig's Q-phos system being a notable example. See, Shelby Q, Kataoka N, Mann G, Hartwig J. J Am Chem Soc. 2000; 122:10718–10719.

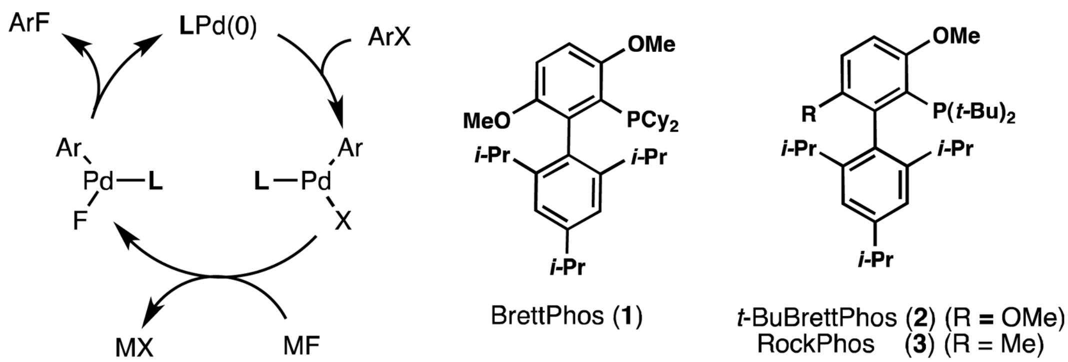
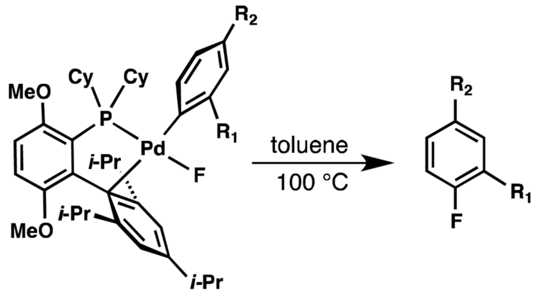


Figure 1.
Presumed mechanism of Pd-catalyzed nucleophilic fluorination and ligands used in this study.



R_1	R_2	Yield (%)
Me	CN	20% (45%)[a]
Me	CF_3	15% (55%)[a]
H	*n*-Bu	0%

[a] Yield in the presence of PhBr

Figure 2.

Previously reported C—F reductive elimination from a Pd(II) fluoride.

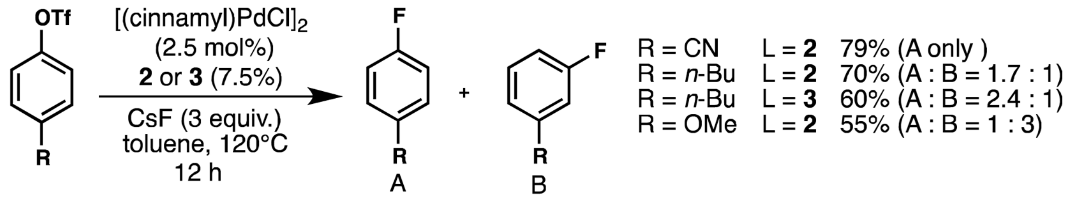
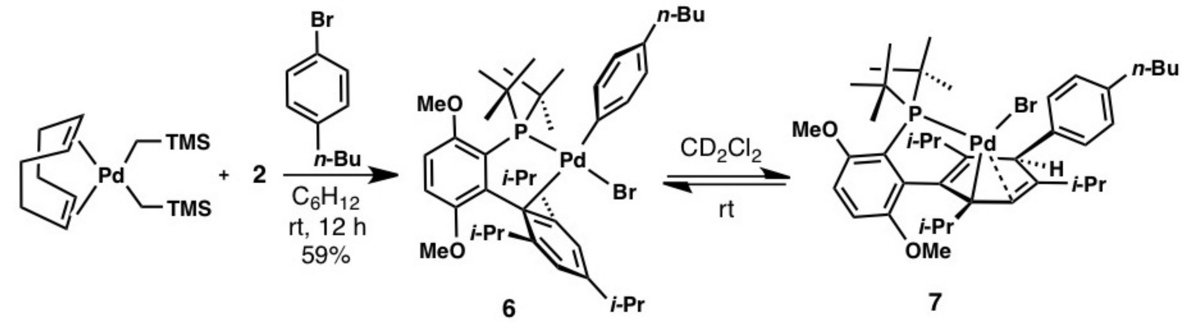


Figure 3.
Regioisomer formation.



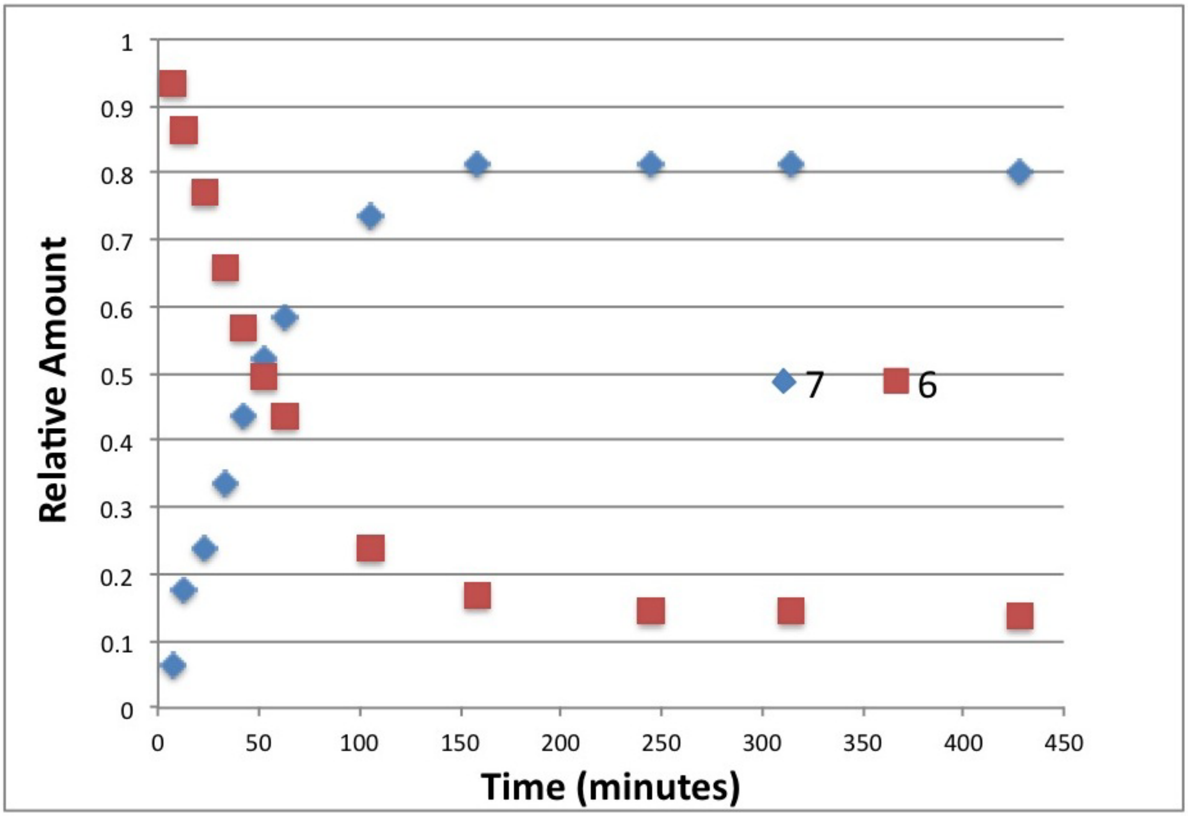


Figure 4.
Synthesis and isomerization of *t*-BuBrettPhos oxidative addition complex **6**.

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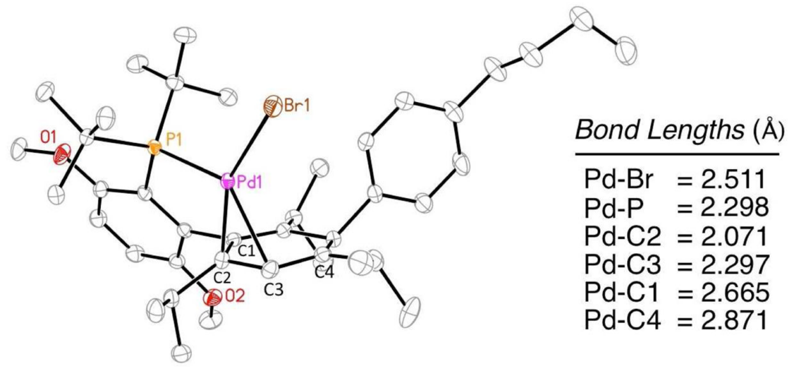

Figure 5.
X-ray structure of **7** and relevant bond lengths (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted).

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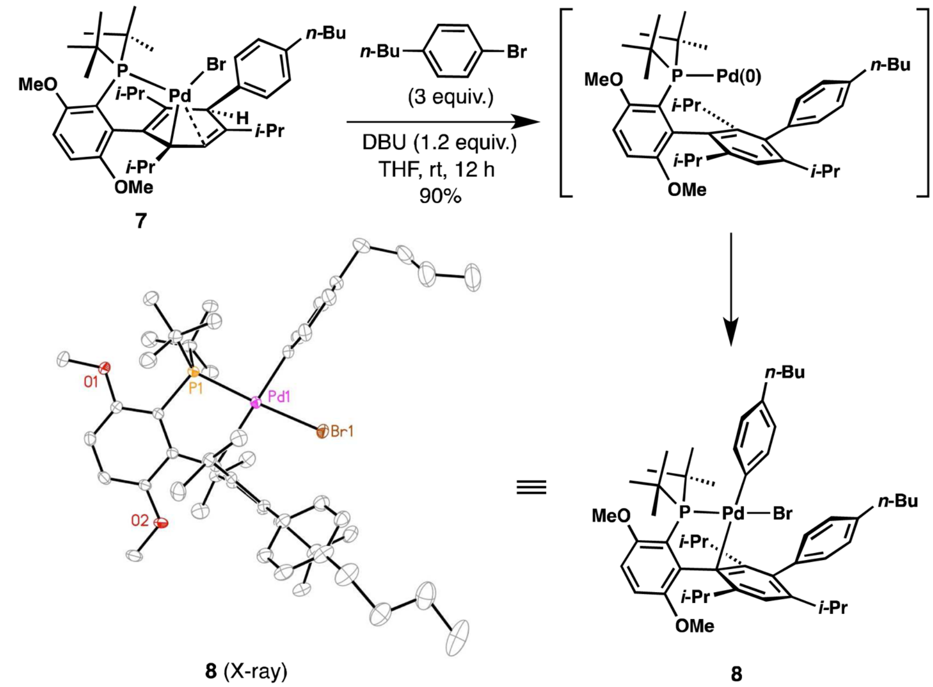


Figure 6.

Rearomatization of **7** with concurrent oxidative addition. (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted).

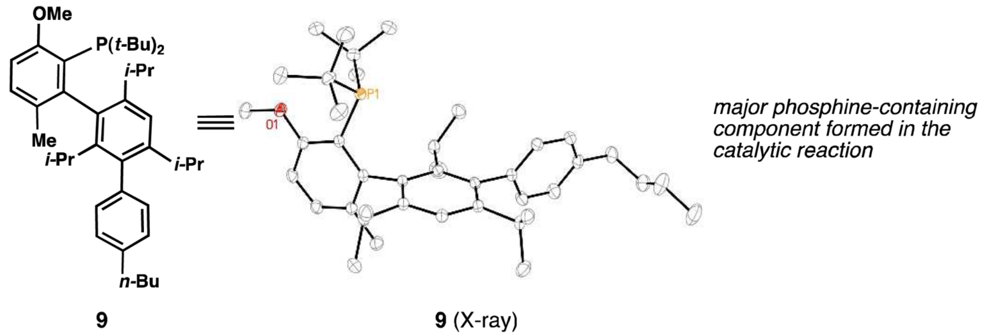
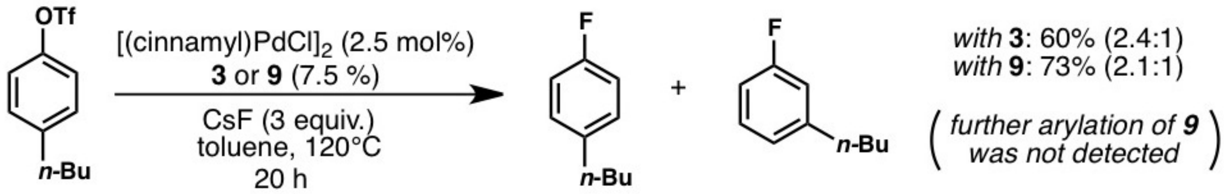


Figure 7.
Arylated RockPhos ligand **9** isolated from the catalytic fluorination reaction.



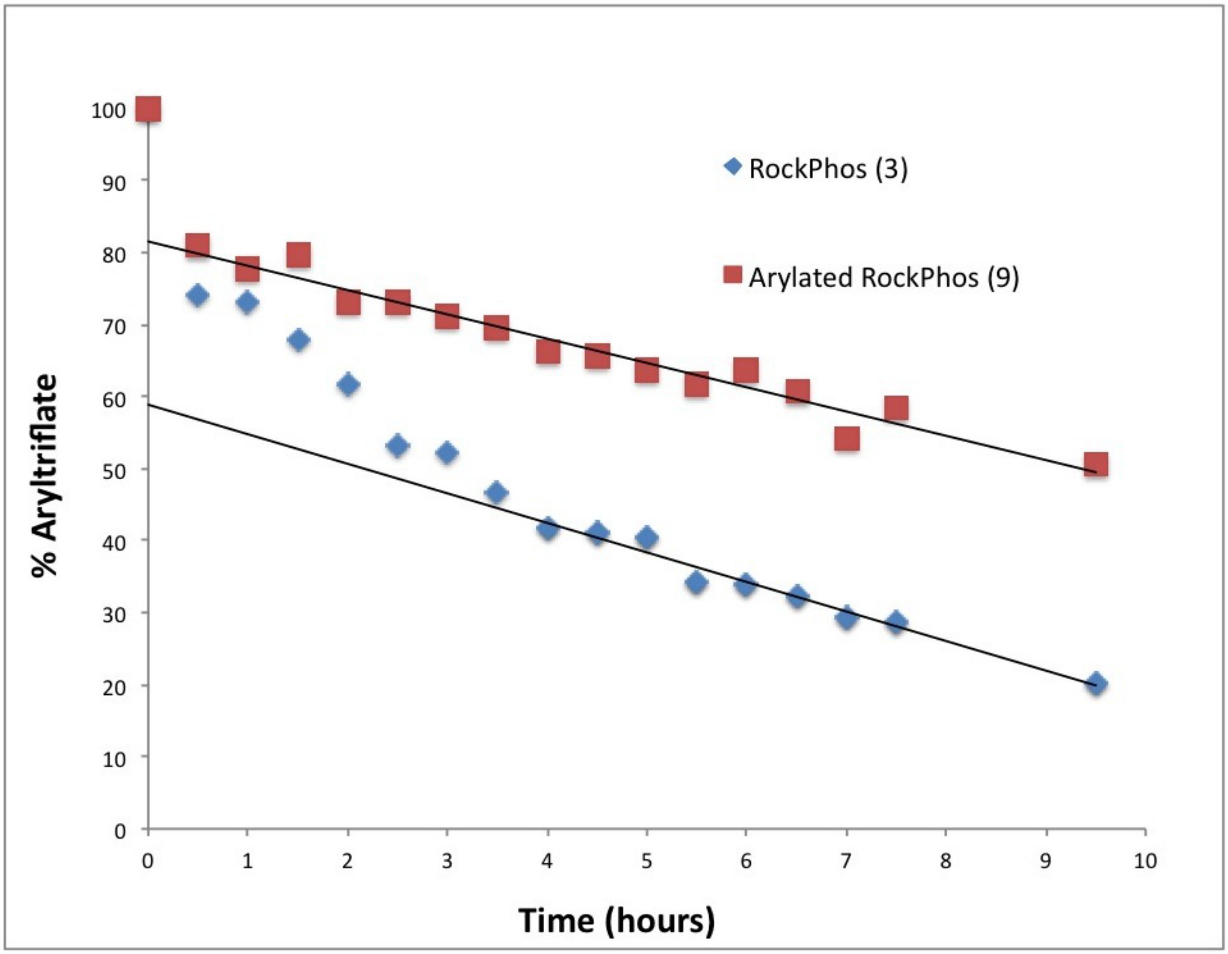


Figure 8.
Comparison of **3** and **9** in the catalytic fluorination reaction of 4-*n*BuPhOTf.

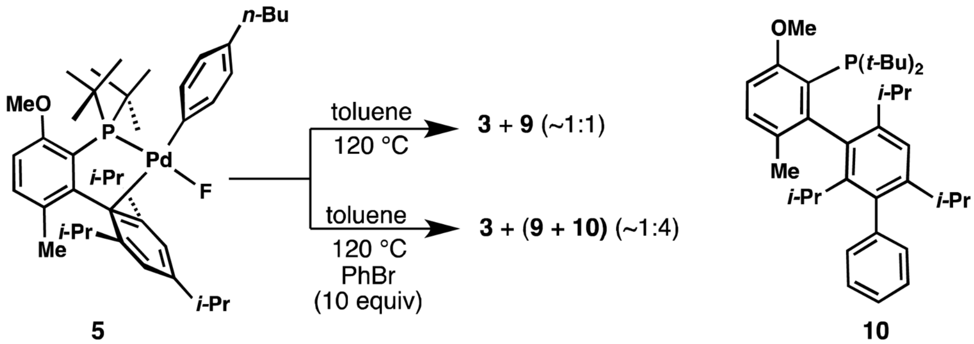


Figure 9.
Fate of the ligand during experiments that failed to give products of C—F reductive elimination.

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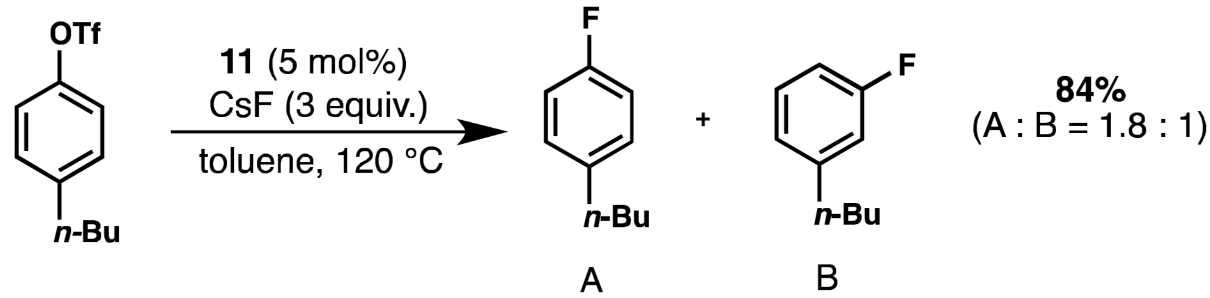
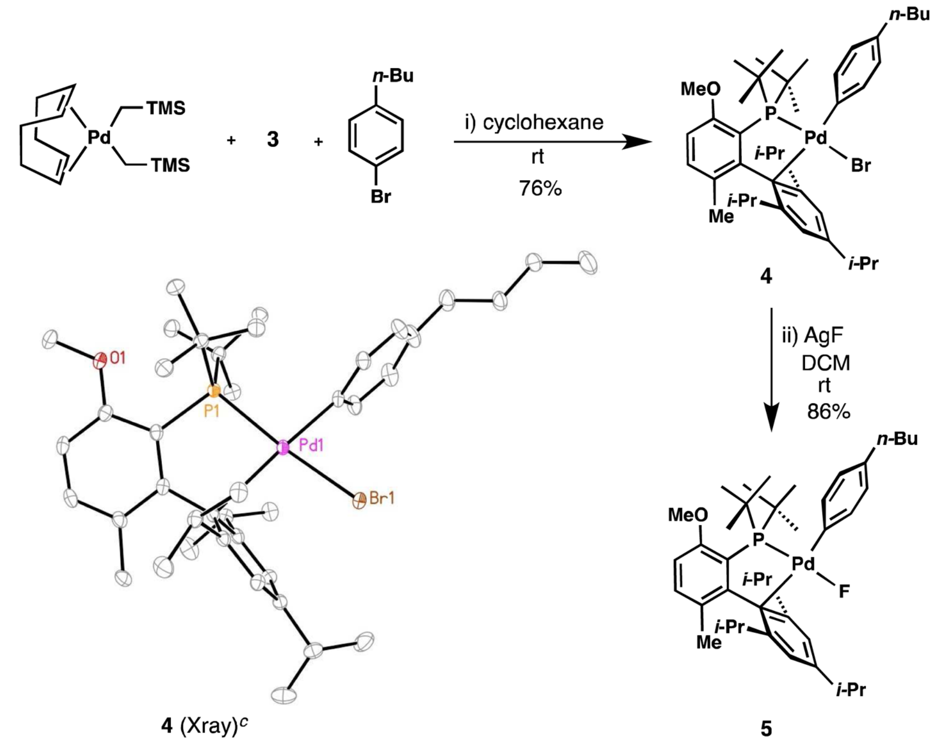


Figure 10.
Catalytic competence of complex **11**.



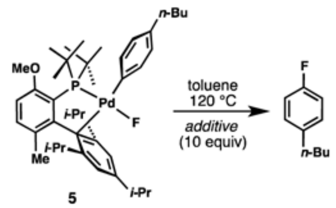
Scheme 1.

Preparation of **3**•Pd(Ar)F complex **5**.[a,b,c]

[a] Reaction conditions: i) (COD)Pd(CH_2TMS)$_2$ (1 equiv.), **3** (1.1 equiv.), 4-*n*BuPhBr (5 equiv.), cyclohexane, 12 h, 76% ii) AgF (7.5 equiv.), DCM, 7 h, 86%. [b] Isolated yields. [c] Thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted.

Table 1

Thermolysis of **3**•Pd(Ar)F complex **5**.

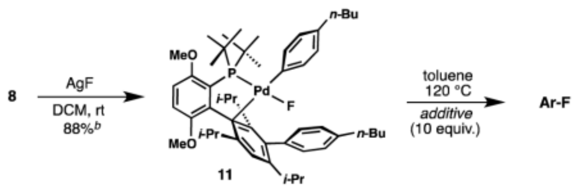


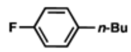
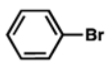
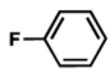
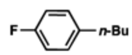
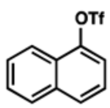
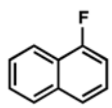
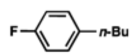
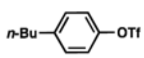
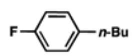
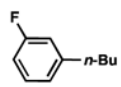
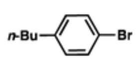
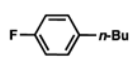
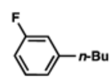
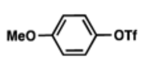
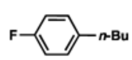
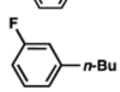
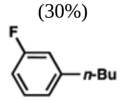
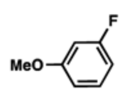
5

Entry	Additive	Yield (%)
1	none	0%
2	**3**	0%
3	PhBr	0%
4	**4**-*n*BuPhOTf	0%

Table 2

Synthesis and reactivity of arylated LPd(Ar)F complex **11**.[a–e]



Entry	Additive (10 equiv)	Ar-F Products (%)[c]	
1	none	 (15%)[d]	
2		 (40%)	 (6%)
3		 (75%)	 (~3%)
4		 (32%)[e]	 (20%)[e]
5		 (24%)	 (3%)
6		  (30%)  (18%)	 (7%)

[a]Reaction conditions: i) AgF (7.5 equiv.), DCM, 4 h, 88%. ii) toluene, additive (10 equiv.), 120 °C, 3h

[b]Isolated yield.

[c]Yields based on **11** and determined by ^{19}F NMR.

[d]Yield in cyclohexane = 20%

[e]Yield in cyclohexane = 40%, selectivity = 2:1.