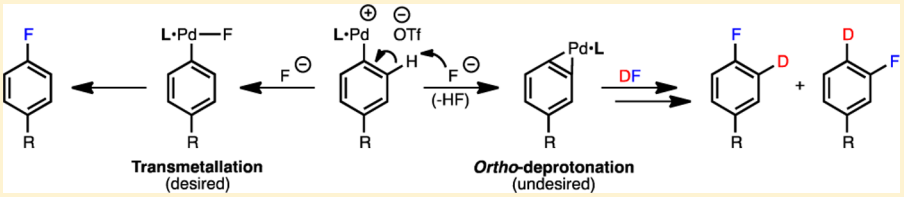
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Studying Regioisomer Formation in the Pd-Catalyzed Fluorination of Aryl Triflates by Deuterium Labeling

Phillip J. Milner, Tom Kinzel, Yong Zhang, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information



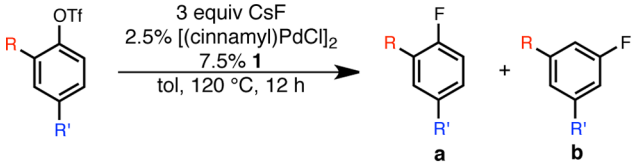
ABSTRACT: Isotopic labeling has been used to determine that a portion of the desired product in the Pd-catalyzed fluorination of electron-rich, non-ortho-substituted aryl triflates results from direct C−F cross-coupling. In some cases, formation of a Pd-aryne intermediate is responsible for producing undesired regioisomers. The generation of the Pd-aryne intermediate occurs primarily via ortho-deprotonation of a L·Pd(Ar)OTf (L = biaryl monophosphine) species by CsF and thus competes directly with the transmetalation step of the catalytic cycle. Deuterium labeling studies were conducted with a variety of aryl triflates.

INTRODUCTION

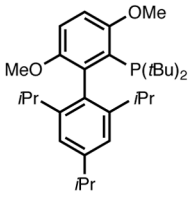
Fluorinated arenes are prevalent in the pharmaceutical and agrochemical industries due to their desirable metabolic properties.[1] Nonetheless, accessing them remains a significant challenge.[2] Although Pd-catalyzed halide exchange of aryl (pseudo)halides with a metal fluoride salt (F^-) would be an efficient route to generate C−F bonds, studies by Grushin[3] and Yandulov[4] revealed that such a reaction would be hampered by a high barrier to reductive elimination from a Pd(II) intermediate and the solvent-dependent nucleophilicity and basicity of metal fluorides. To circumvent these problems, several reactions based on reductive elimination from a Pd(IV) species using electrophilic fluorinating agents (F^+) have been developed.[5] To date, only a few transition metal-mediated nucleophilic aryl fluorination reactions have been reported.[2b,6]

In 2009, we reported that a catalyst based on the biaryl phosphine ligand *t*BuBrettPhos (**1**) can effect the conversion of aryl triflates to the corresponding aryl fluorides using CsF (Figure 1).[7] Surprisingly, the fluorinations of electron-rich substrates lacking ortho substituents, such as **2-OTf** and **3-OTf**, yield regioisomeric products **2b** and **3b** in addition to desired products **2a** and **3a** (Figure 1). In contrast, electron-deficient (**4-OTf**) and ortho-substituted substrates (**5-OTf**) convert cleanly to the desired products **4a** and **5a**, respectively (Figure 1).[7]

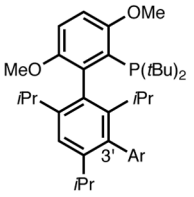
Previous mechanistic investigations of the catalytic fluorination reaction revealed that 3′-arylation of **1** by the substrate, leading to **6**, occurs during the fluorination reaction (Figure 1), although this process appears to be independent of regioisomer formation.[8] Importantly, we have found that complex **7a** (bearing 3′-arylated ligand **6a**) consistently generates regioisomerically pure 4-(*n*Bu)PhF (**3a**) when heated, albeit in low (15−20%) yield (Figure 2).[8b] Intriguingly, attempting to increase the yield by adding 4-(*n*Bu)PhOTf (**3-OTf**) to trap the L·Pd(0) species formed after reductive elimination[9] led to regioisomeric mixtures of **3a** and **3b** (Figure 2).[8b,10] Together, these results confirm that (a) potential catalytic intermediate **7a** does not generate significant quantities of regioisomeric 3-



Substrate	R	R'	% Yield (a + b)	a : b
2-OTf	H	OMe	55	1 : 2.7
3-OTf	H	*n*Bu	70	1.5 : 1
4-OTf	H	CN	80	> 99 : 1
5-OTf	Me	H	80	> 99 : 1



1(*t*BuBrettPhos)



6
6a: Ar = 4-(*n*Bu)Ph

Figure 1. Regioisomer formation in the Pd-catalyzed fluorination of aryl triflates **2**−**5-OTf** and ligands (**1**, **6**) for this process. tol = toluene.

Received: September 4, 2014
Published: October 9, 2014

   dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757−15766

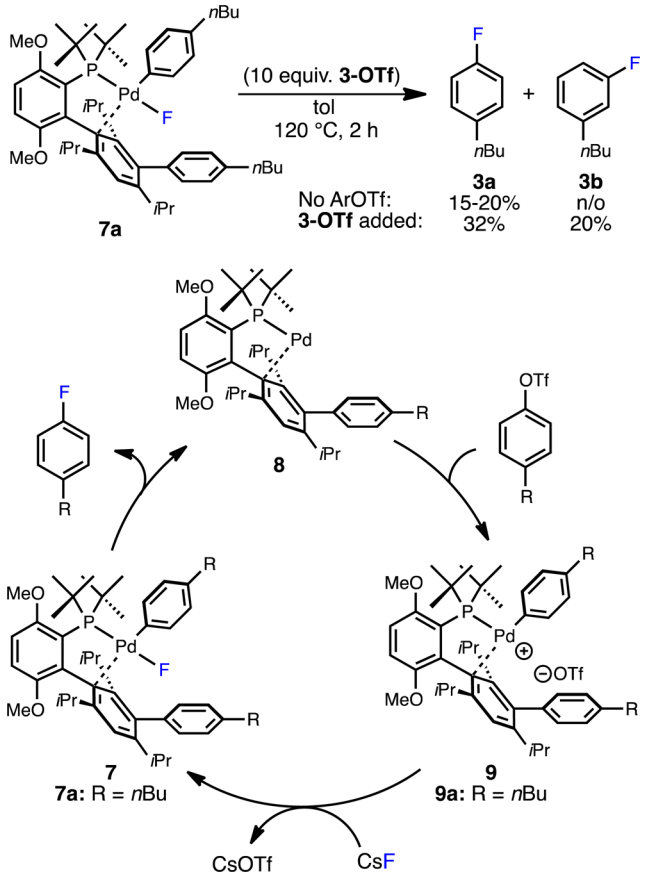


Figure 2. Observed stoichiometric C−F reductive elimination from **7a**, with regioisomer formation observed only in the presence of **3-OTf**.[8b] The proposed catalytic cycle for the formation of aryl fluorides from aryl triflates. n/o = not observed.

(*n*Bu)PhF (**3b**) on its own and (b) regioisomer formation in the catalytic reaction may not require the presence of basic CsF to occur. We propose that the catalytic cycle shown in Figure 2, involving oxidative addition of the aryl triflate to **8** to form **9**, transmetalation with CsF to form **7**, and C−F reductive elimination from **7**, is a feasible pathway to form aryl fluorides from aryl triflates. Thus, in the case of aryl triflates such as **2-OTf** and **3-OTf**, a separate pathway must be occurring to generate the regioisomeric products **2b** and **3b**. In the present work, we provide evidence that the process in Figure 2 occurs to convert **3-OTf** to **3a** and that the analogous pathway is operative during the fluorination of other aryl triflates. However, in cases where regioisomeric mixtures of products are observed, ortho-deprotonation of L·Pd(Ar)OTf intermediates **9** to generate Pd-aryne intermediates, which recombine with HF to ultimately produce regioisomeric mixtures of aryl fluorides, competes with this process. Although our previously reported stoichiometric studies[8b] show that L·Pd(Ar)F complexes are capable of effecting this ortho-deprotonation process as well, the studies presented herein suggest that CsF is the more likely culprit for this process in the catalytic reaction. By selectively deuterating aryl fluoride products generated from Pd-aryne intermediates, we can estimate the contribution of this pathway to the outcome of catalytic fluorination reactions.

RESULTS AND DISCUSSION

Evidence for Pd-Aryne Intermediate. The most straightforward mechanism for regioisomer formation in this reaction involves ortho-deprotonation of the starting material or product(s) by a basic fluoride species without direct involvement of the catalyst. The aryne so generated would lead to both aryl fluoride products by nucleophilic attack of external fluoride at two distinct sites.[11] Because regioisomer formation is not observed in the absence of catalyst, we consider this pathway to be unlikely.[12] A more plausible scenario is ortho-deprotonation of a catalytic intermediate, such as **9** or **7**, by an external basic fluoride species to generate a Pd-aryne[13] intermediate such as **10** (Figure 3). The basic fluoride

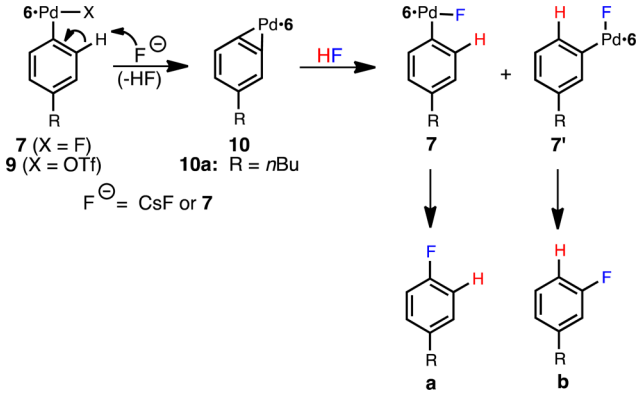


Figure 3. Proposed mechanism of regioisomer formation by deprotonation of **7** or **9** (Figure 2) by CsF or **7** to generate **10**, leading to **7** and **7′**, which then reductively eliminate to form **a** and **b**, respectively.

source could be either CsF or a second molecules of **7**, as suggested by our previous stoichiometric experiments.[8b,14] The nonselective reaction of **10** with HF would provide regioisomeric L·Pd(Ar)F complexes **7** and **7′**,[15] which could, in turn, independently undergo C−F reductive elimination to generate the observed mixture of regioisomeric aryl fluorides **a** and **b**. Consistent with this hypothesis, we have reported that the fluorinations of 2,6-dideuterated aryl triflates show improved regioselectivity compared to that of their non-deuterated analogues,[7] suggesting that scission of the C−H bond adjacent to the triflate group occurs before or during the regioselectivity-determining step.[16]

To investigate the plausibility of this mechanism, we reasoned that the addition of an exchangeable deuterium source to the reaction mixture would form DF in situ, which could recombine with **10** to allow deuterium incorporation into the aryl fluoride products. However, any product resulting from the desired direct C−F reductive elimination pathway outlined in Figure 2 would not show evidence of deuterium incorporation under these conditions. When 1.0 equiv of *t*BuOD was added to the catalytic fluorination of **3-OTf**, 20% deuterium labeling of the aryl fluoride products was detected by GC/MS.[17−19] In addition to the normally observed ^{19}F NMR signals for **3a** (30%) and **3b** (14%) in the product mixture were two new signals for aryl fluoride species **3c** (3%) and **3d** (8%) (Figure 4). The structures of these compounds were confirmed by their independent synthesis using the routes in Scheme 1. Compound **3a** was prepared from **11** by adapting previously reported conditions for the Balz−Schiemann reaction[20] via diazonium salt **12**, which was not isolated. Negishi coupling of **13** with *n*BuZnCl in the presence of XantPhos-based 2-aminobiphenyl mesylate precatalyst **15**[21,22] gave **14**, which could be converted to **3c** by lithium−halogen exchange with

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757−15766

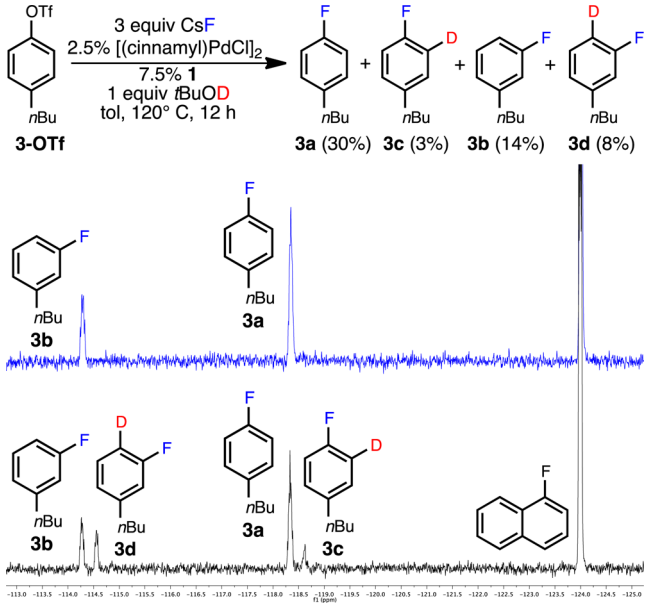
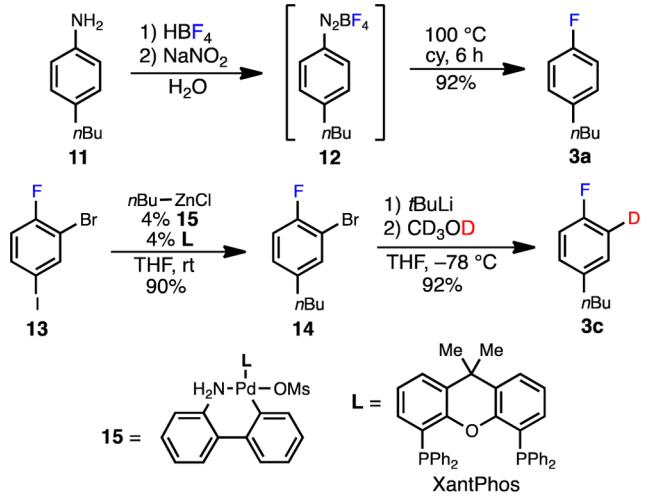


Figure 4. Addition of *t*BuOD to the fluorination of **3-OTf** leads to **3a–d**. The ^{19}F NMR (282 MHz) spectra of the crude product mixture without (top) and with (bottom) *t*BuOD added are shown. An internal reference of 1-fluoronaphthalene is included.

Scheme 1. Preparation of 3a and 3c



*t*BuLi followed by quenching with CD_3OD at −78 °C. Similar routes were used to prepare **3b** and **3d** (not shown, see Supporting Information for details). The presence of **3b** in the product mixture suggests that deuteration of products originating from **10a** was not complete and therefore that some of the desired product **3a** likely comes from **10a** as well. By assuming that the two sites of **10a** are similarly susceptible to deuterium incorporation upon reaction with DF (see Supporting Information for details), we estimate that 5% of the observed **3a** comes from the aryne intermediate **10a** and the other 25% originates from a pathway for which no deuterium labeling or regioisomer formation is possible. In other words, 56% of the aryl fluoride products likely originate from **10a**, and the other 45%, exclusively **3a**, likely comes from the desired C–F cross-coupling pathway outlined in Figure 2. This study provides the first tangible evidence that formation of **10a** (Figure 3), leading to **3a–b**, and C–F cross-coupling (Figure 2), leading only to **3a**, are directly competing processes during the catalytic fluorination of **3-OTf**.[23]

Species Responsible for Pd-Aryne Formation. *Kinetic Profiles of Pd-Catalyzed Fluorinations of 1-Naphthyl and 4-(n-Butyl)phenyl Triflates.* To determine the kinetic parameters of the two pathways occurring during the fluorination of **3-OTf**, it is helpful to compare the Pd-catalyzed fluorinations of 1-naphthyl triflate (**16-OTf**, Figure 5), which proceeds cleanly to

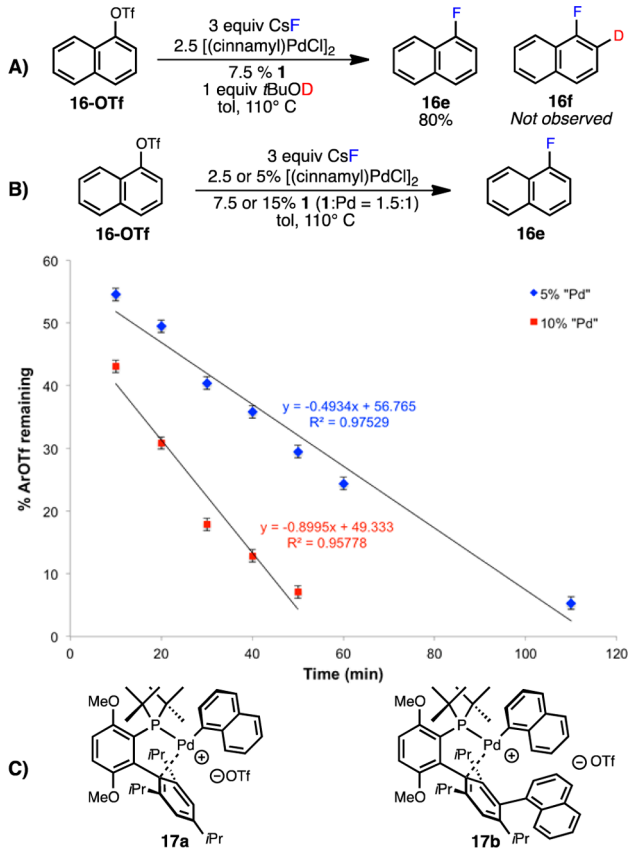


Figure 5. Analysis of the Pd-catalyzed fluorination of **16-OTf**, which proceeds cleanly to **16e**. (A) No deuterium incorporation to form **16f** is observed in the presence of *t*BuOD. (B) Rate of starting material consumption during the fluorination of **16-OTf** with 5% Pd (blue diamonds) or 10% Pd (red squares). Conversions determined by GC analysis. (C) The resting state of the catalyst during the catalytic fluorination reaction is likely **17a** or **17b**.

1-fluoronaphthalene (**16e**)[24] and thus likely by a pathway analogous to that outlined in Figure 2, with that of **3-OTf**, which produces both **3a** and **3b**. Notably, the addition of *t*BuOD to the fluorination of **16-OTf** did not result in deuterium incorporation into the formed 1-fluoronaphthalene **16e**, indicating that competitive Pd-aryne formation is likely not occurring in this case (Figure 5A, see the Ortho Substituent Effects section for discussion). The fluorination of **16-OTf** is zeroth order in [ArOTf],[24] nearly first order in [Pd] ($k_{10\%\ Pd}/k_{5\%\ Pd}$ = 1.82 ± 0.18, Figure 5B), and, as we have previously reported, shows a positive order in CsF.[24,25] Thus, the rate law for the desired cross-coupling process (at least in this case) follows rate = k[Pd][CsF]^n (n > 0). These findings are consistent with L·Pd(1-naphthyl)OTf species **17a** or **17b** (Figure 5C) being the resting state of the catalyst. Thus, for the desired cross-coupling reaction, the resting state of the catalyst is likely a L·Pd(Ar)OTf species (L = **1** or **6**), and either

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757–15766

transmetalation or reductive elimination is the rate-determining step of the catalytic cycle.[26]

The fluorination of **3-OTf** shows many of the same features as those of **16-OTf** (Figure 6). We have previously shown that

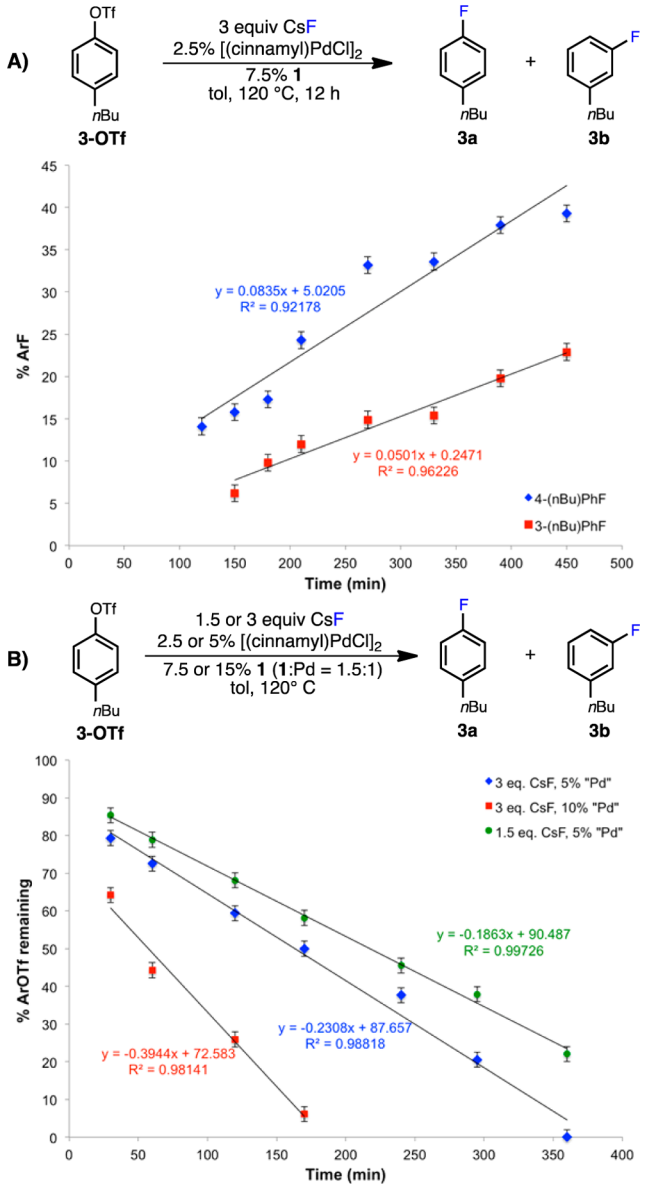


Figure 6. Analysis of the Pd-catalyzed fluorination of **3-OTf**. (A) The growth of **3a** (blue diamonds) and **3b** (red squares) during the catalytic fluorination of **3-OTf**. Yields were determined by ^{19}F NMR (282 MHz). (B) Rate of starting material consumption during the fluorination of **3-OTf** with 3.0 equiv CsF, 5% Pd (blue diamonds); 3.0 equiv CsF, 10% Pd (red squares); and 1.5 equiv CsF, 5% Pd (green circles). Conversions were determined by GC analysis.

the reaction is zeroth order in aryl triflate.[8b] Indeed, the growth of both products over time is linear (Figure 6A), with the relative rates for their formation ($k_{4\text{-}n\text{Bu}}/k_{3\text{-}n\text{Bu}}$ = 1.67 ± 0.34) approximately equal to the final observed regioselectivity (**3a**/**3b** ≈ 1.7:1). This finding is consistent with our hypothesis that formation of the undesired regioisomer **3b** occurs competitively with formation of **3a** and suggests that both products ultimately originate from the same intermediate. In addition, the rate of starting material consumption during the Pd-catalyzed fluorination of **3-OTf** shows a nearly identical dependence on [Pd] ($k_{10\%\ Pd}/k_{5\%\ Pd}$ = 1.71 ± 0.18, Figure 6B) as that for the reaction of **16-OTf** ($k_{10\%\ Pd}/k_{5\%\ Pd}$ = 1.82 ± 0.18, Figure 5B). This finding suggests that the rate dependence on [Pd] of the pathways occurring during the fluorination of **3-OTf** is nearly equal, as otherwise this reaction would show a different rate dependence on [Pd] than the fluorination of **16-OTf** (vide infra). Indeed, when the catalytic fluorination of **3-OTf** was conducted using varying amounts of [(cinnamyl)PdCl]$_2$ (2.50−10.0%) and **1** (3.75−15.0%) while maintaining the 1:1.5 ratio of Pd/**1**, no significant change in the extent of deuterium incorporation was observed (see Supporting Information Table S3a). Likewise, changing the amount of **1** (5.00−10.0%) while holding the quantity of [(cinnamyl)PdCl]$_2$ constant (Supporting Information Table S3b) or conducting the same experiment using varying amounts of **9a** (5.00−10.0%) (Supporting Information Table S3c) showed no significant dependence of regioselectivity or the percent aryne on catalyst or ligand loading.

Similar to the results previously reported for the fluorination of **16-OTf**,[24] the Pd-catalyzed fluorination of **3-OTf** displays a small but statistically significant positive order in [CsF] ($k_{3\text{equiv CsF}}/k_{1.5\text{equiv CsF}}$ = 1.24 ± 0.09, Figure 6B).[27] The observed zeroth order dependence on [ArOTf] but positive order in [CsF] suggests that **9a** is likely the resting state of the catalyst during this reaction. Additionally, low-temperature ^{19}F NMR (470 MHz, −78 °C) studies of the catalytic fluorination reaction of **3-OTf** run to partial conversion (see Supporting Information Figure S2), support that **9a** is the resting state of the catalyst, with **7a** present in too low of a concentration to be reliably observed.[28] From all of the experiments we have conducted to date, we can reliably conclude that (a) the resting state of the catalyst in these reactions is a L·Pd(Ar)OTf species, (b) regioisomer formation and the desired cross-coupling reaction show a similar rate dependence on [Pd], (c) both reactions show a positive, nonlinear dependence on [CsF], and (d) ortho-deprotonation is the rate-determining step of regioisomer formation (vide supra). On the basis of these conclusions, we next investigated which species were directly involved in Pd-aryne formation during the catalytic fluorination of **3-OTf**.

Species Undergoing Ortho-Deprotonation. We initially hypothesized that **9a** is the major species undergoing ortho-deprotonation competitively with transmetalation because (a) **9a** is the resting state of the catalyst and so is present in a much higher concentration than **7a**, (b) the protons in **9a** adjacent to the cationic Pd center should be more acidic than the corresponding protons in **7a**, and (c) in our previously reported stoichiometric reductive elimination experiments with **7a** (Figure 2), regioisomer formation was observed only when **3-OTf** was added to trap the L·Pd(0) species formed after reductive elimination from **7a**.[8b,29] In addition, the lack of multiply deuterated products in the product mixture is consistent with ortho-deprotonation of **9a** instead of **7a**. The deprotonation of **9a** to form **10a** should be irreversible because the reverse process would require three species, namely, **10a**, HF, and CsOTf, to react together in the transition state.[30] Thus, if **7a** (and the corresponding meta-substituted isomer **7a′**) cannot be deprotonated during the catalytic reaction, then only one deuterium incorporation event could take place before formation of the desired aryl fluorides, leading to **3a**−**d**. However, if ortho-deprotonation of **7a** (or **7a′**) in competition with reductive elimination were possible, then multiple

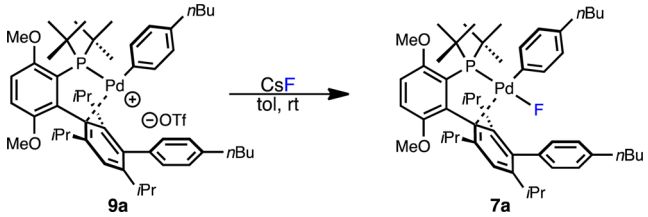
dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757−15766

deuterium atoms could be incorporated into the aryl fluoride products. The lack of multiply deuterated products is consistent with the reaction of **10a** with HF being irreversible. In other words, ortho-deprotonation of **7a** likely does not directly compete with reductive elimination.[31,32]

F⁻ Source Involved in Pd-Aryne Formation. We also investigated whether CsF or **7a** was more likely to be the base responsible for Pd-aryne formation. Although significantly more CsF (~40−60 equiv relative to **9a**) is present than **7a** during the catalytic reaction, our previous stoichiometric studies corroborate that **7a** is capable of deprotonating **9a**.[8b,29] Our kinetic studies with **16-OTf** suggest that the rate law of the desired cross-coupling process is rate = $k[\mathrm{Pd}][\mathrm{CsF}]^n$ ($n > 0$). In addition, the improved regioselectivity observed with 2,6-dideuterated substrates suggests that ortho-deprotonation occurs before or during the rate-limiting step of regioisomer formation.[7] If rate-limiting ortho-deprotonation involved one molecule of **7a** reacting with a molecule of **9a**, then the rate of ortho-deprotonation would follow rate = $k[\mathrm{Pd}]^2$. In this case, the extent of regioisomer formation and percentage of aryne would increase with catalyst loading, as the rate of ortho-deprotonation would be greatly accelerated over that of cross-coupling. However, if ortho-deprotonation involved deprotonation of **9a** by CsF, then the rate of ortho-deprotonation would follow rate = $k[\mathrm{Pd}][\mathrm{CsF}]^m$ ($m > 0$; m and n are not necessarily equal). In this case, increasing the catalyst loading would equally raise the rate of the competing cross-coupling process (Figure 2) and Pd-aryne formation (Figure 3), resulting in no change in regioselectivity at higher catalyst loadings. As we previously showed (Kinetic Profiles of Pd-Catalyzed Fluorinations of 1-Naphthyl and 4-(n-Butyl)phenyl Triflates section), changing the catalyst loading of the Pd-catalyzed fluorination of **3-OTf** does not affect the regioselectivity or percent aryne of the reaction (see Supporting Information Table S3a,c). These results suggest that regioisomer formation and the pathway shown in Figure 2 have the same rate dependence on [Pd]. This result is consistent with CsF, not a L·Pd(Ar)F intermediate, acting as the base responsible for ortho-deprotonation of **9a**.[27] Nonetheless, stoichiometric experiments confirm that **7a** is capable of reacting with **9a** to generate **10a**. Therefore, it is likely only the extremely low concentration of **9a** present during the catalytic reaction that limits its involvement in regioisomer formation. We cannot entirely rule out that a small portion of the **10a** formed during the catalytic reaction comes from ortho-deprotonation of **9a** by **7a**.

We also investigated the stoichiometric reaction between **9a** and CsF to search for evidence of formation of **10a**. When CsF (5 equiv) was added to a solution of **9a** (1 equiv) in toluene, minimal conversion to **7a** was observed, even after 12 h (Table 1, entry 1). This finding is likely due to the poor solubility of CsF in toluene, especially at room temperature. When the CsF/Pd ratio was increased to that found at the beginning of the catalytic reaction (60:1), significant conversion (85%) of **9a** occurred in only 0.5 h, but a lower yield of **7a** than expected (55% yield relative to an internal standard) was observed (Table 1, entry 2). No other fluorine- or phosphorus-containing species could be detected by NMR, as the generated HF was likely rapidly trapped as $CsHF_2$. However, analysis of the reaction mixture by GC/MS showed unidentified high molecular weight compounds to be present. Thus far, our unsuccessful efforts to isolate **10a** (not shown) suggest that it is extremely reactive toward trimerization and oligimerization in

Table 1. Stoichiometric Transmetalation Experiments with 12 and CsF in Toluene



entry	CsF equiv	time (h)	conversion (%)	yield (%)
1	5	12	<10	<10
2	60	0.5	85	55

solution.[16] Thus, the discrepancy in conversion and yield when **9a** is reacted with CsF is indirect evidence that **10a** is forming in situ along with **7a**.[33] On the basis of these findings, the mechanism shown in Figure 7, involving competitive transmetalation (leading ultimately to **a**) and deprotonation (leading ultimately to **a** and **b**) of a L·Pd(Ar)OTf intermediate with CsF, is the most likely scenario for regioisomer formation in the Pd-catalyzed fluorination of aryl triflates.

Para Substituent Effects. We next applied our deuterium labeling protocol to other para-substituted substrates to gain insight into the effect of aryl triflate substitution patterns on the formation and behavior of **10** (Table 2). For each substrate, two Pd-catalyzed fluorinations were conducted: one without *t*BuOD added to determine the combined yield (a + b)[17] and regioselectivity (a/b) of the reaction and one with *t*BuOD added to determine the total deuterium incorporation into the aryl fluoride products (% D) and the estimated fraction of aryl fluoride products originating from **10** (% aryne). In a series of para-substituted aryl triflates (Table 2), deuterium incorporation (% D) and percent aryne steadily decrease as the substituent becomes more electron-withdrawing so that electron-deficient aryl fluorides **4a**, **21a**, and **22a** are formed without any corresponding deuterated or regioisomeric products. The observed reactivity of para-substituted aryl triflates is consistent with the mechanistic scenario presented in Figure 7. This is because catalytic intermediates bearing electron-rich aryl groups would undergo slower transmetalation than those bearing electron-deficient aryl groups, providing a greater opportunity for competitive ortho-deprotonation by CsF (or **7**) to occur. Notably, multiply deuterated products were not observed in the product mixtures for these para-substituted substrates, consistent with our hypothesis that conversion of **10** to **7** is irreversible.[32]

We have previously reported that Pd-catalyzed fluorination reactions conducted in cyclohexane instead of toluene result in improved regioselectivity for formation of the desired product.[7] However, using cyclohexane as the reaction solvent typically requires higher temperatures and/or catalyst loadings, presumably due to the even lower solubility of CsF in cyclohexane compared to toluene.[34] As the results in Table 3 show, for **3-OTf** and **19-OTf** more of the aryl fluoride product **a** originates from the desired cross-coupling process (Figure 2) and less from Pd-aryne **10** (Figure 3), leading to an improved regioselectivity for the desired products **3a** and **19a**, respectively.[35] Notably, the fluorination reactions of substrates with more electron-withdrawing para substituents proceed to a single regioisomer of product in cyclohexane as well as in toluene (not shown). The two most likely explanations for

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757−15766

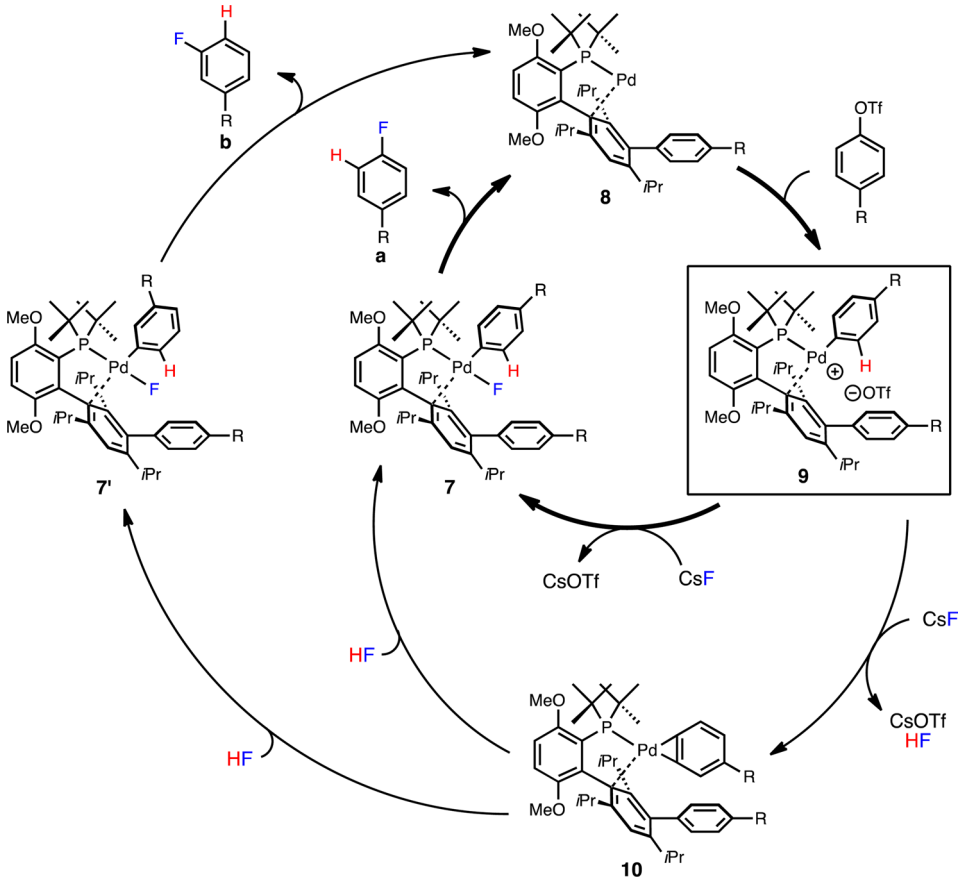
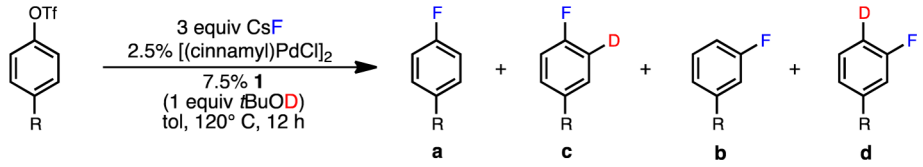


Figure 7. Complex **9** can either undergo transmetalation to yield **7** (Figure 2) and ultimately aryl fluoride **a** or ortho-deprotonation to yield **10** (Figure 3) and ultimately aryl fluorides **a** (from **7**) and **b** (from **7′**) during the catalytic fluorination reaction.

Table 2. Effect of Para-Substituents on Fluorination



substrate	R	combined % yield (a + b)[a,17]	para:meta (a:b)[a]	a:c:b:d[b]	% D[b]	% aryne[b]
3-OTf	*n*Bu	70	1.5:1	30:3:14:8	20 ± 1	56 ± 3
18-OTf	H	61	n/a	51:10	16 ± 1	16–33[c]
19-OTf	Ph	75	8.5:1	66:5:5:5	12 ± 1	25 ± 3
20-OTf	Cl	37	7.8:1	31:2:2:2	11 ± 1	20 ± 3
21-OTf	CO_2Me	94	>99:1	94:n/o:n/o:n/o	<1	<1
4-OTf	CN	80	>99:1	80:n/o:n/o:n/o	<1	<1
22-OTf	NO_2	80	>99:1	80:n/o:n/o:n/o	<1	<1

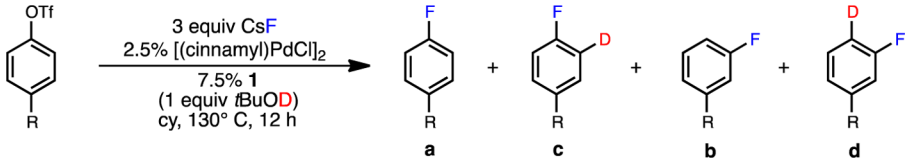
[a]On a 0.2 mmol scale; reactions without *t*BuOD added. ^{19}F NMR yields. [b]On a 0.2 mmol scale; reactions with *t*BuOD added. ^{19}F NMR yields. [c]Estimated range assuming that between 0% of **18a** (16% aryne) and 10% of **18a** (33% aryne) originates from **10**. n/o = not observed.

increased regioselectivity in cyclohexane are (1) less of Pd-aryne **10** is forming in cyclohexane or (2) **10** forms to an equal degree in both solvents but is converted into non-fluorine-containing side products, such as aryne-derived trimers[16] or oligomers, instead of aryl fluoride products, in cyclohexane. Because the overall yields for the reactions in Table 3 are close to those in Table 2 and no increase in potential aryne-derived byproducts occurs in cyclohexane, the second explanation is unlikely. Thus, switching the solvent to cyclohexane likely slows ortho-deprotonation more than it does transmetalation, leading to the observed increase in regioselectivity. The reason for this change remains unclear, although a subtle change in the nature of the reaction occurring between **9** and the surface of CsF nanoparticles is the most likely explanation. Nonetheless, switching to the nonpolar solvent cyclohexane has the general benefit of decreasing the amount of aryl fluorides originating from Pd-aryne **10**.

Meta Substituent Effects. In the case of meta-substituted substrates, the desired C–F cross-coupling process (Pathway A, Figure 8) leads to the meta-substituted product **b**. This pathway could be intercepted at intermediate **9′** by the formation of two Pd-aryne intermediates, either away from R (Pathway B) or

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757–15766

Table 3. Deuterium Labeling Results with Cyclohexane as Solvent



substrate	R	combined % yield (a + b)[a,17]	para:meta (a:b)[a]	a:c:b:d[b]	% D[b]	% aryne[b]
3-OTf	*n*Bu	60	5.7:1	30:2:5:4	15 ± 1	33 ± 3
19-OTf	Ph	79	12:1	64:3:2:n/o	4 ± 1	7−12[c]

[a]On a 0.2 mmol scale; reactions without *t*BuOD added. ^{19}F NMR yields. [b]On a 0.2 mmol scale; reactions with *t*BuOD added. ^{19}F NMR yields. [c]Estimated range assuming that between 0% of **19a** (7% aryne) and 3% of **19a** (12% aryne) originates from **10**. cy = cyclohexane.

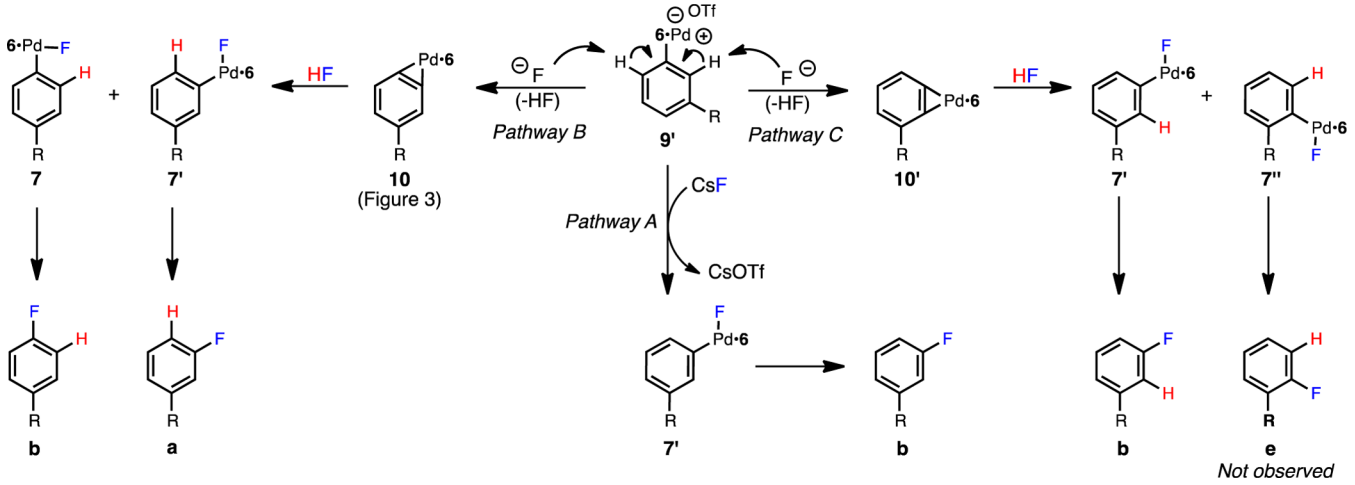
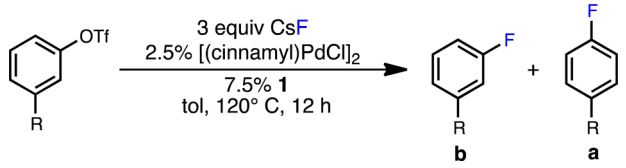


Figure 8. Meta-substituted **9′** can undergo transmetalation to yield **7′** and ultimately aryl fluoride **b** (Pathway A), and/or ortho-deprotonation to yield **10** (Figure 3) and ultimately products **a** and **b** from **7** and **7′**, respectively (Pathway B), and/or ortho-deprotonation to yield **10′** and ultimately aryl fluorides **b** and **e** from **7′** and **7″**, respectively (Pathway C). Ortho-substituted products **e** are not observed.

toward R (Pathway C) (Figure 8). Deprotonation away from R provides **10**, the same intermediate formed by deprotonation of the corresponding para-substituted substrate. Reaction of this intermediate with HF would provide complexes **7′** and **7**, leading to the desired product **b** and the undesired para-substituted regioisomer **a**, respectively. Deprotonation between the Pd center and R would generate Pd-aryne **10′**, which could, in turn, react with HF to form regioisomeric L·Pd(Ar)F complexes **7′** and **7″**. Reductive elimination from **7′** and **7″** would produce **b** and **e**, respectively (Figure 8). Preliminary isotopic labeling studies suggest that for the majority of meta-substituted substrates all three pathways are operative during the catalytic reaction.[36]

Although determination of estimated percent aryne values for reactions of meta-substituted substrates was not possible,[36] we were able to investigate the effect of meta substituents on regioisomer formation (Table 4). Notably, ortho-substituted products **e** resulting from **7″** (Pathway C, Figure 8) were not observed in any case. With alkyl-substituted substrates **23-OTf** (R = *n*Bu) and **24-OTf** (R = *t*Bu), small amounts of para-substituted products **23**−**24a** were observed along with the desired meta-substituted products **23**−**24b**, which is consistent with formation of **10** (Pathway B, Figure 8) during the reaction (Table 4). Substrates bearing electron-withdrawing ester (**25-OTf**), nitrile (**26-OTf**), and nitro (**27-OTf**) groups in the meta position also generate meta-substituted products (**25**−**27b**) with high regioselectivity over para-substituted aryl fluorides (**25**−**27a**) (Table 4).[7] However, the identity of the electron-withdrawing group does not have a significant effect on the yield or extent of regioisomer formation. A different result was observed with OMe (**28-OTf**) or NMe_2 (**29-OTf**) groups in the meta position (**28-OTf**): in both cases, only the desired products **28**−**29b** were observed by ^{19}F NMR (Table 4). The absence of para-substituted products in these cases confirms that Pathway B (Figure 8) is not operative. Studies aimed at understanding the mechanistic intricacies of the Pd-catalyzed fluorination of meta-substituted aryl triflates are ongoing in our

Table 4. Effect of Meta Substituents on the Outcome of Fluorination[a]



substrate	R	combined % yield (b + a)	meta:para (b:a)
23-OTf	*n*Bu	73	14:1
24-OTf	*t*Bu	76	16:1
25-OTf	CO_2Et	72	11:1
26-OTf	CN	76	16:1
27-OTf	NO_2	75	12:1
28-OTf	OMe	60	>99:1
29-OTf	NMe_2	59	>99:1

[a]On a 0.2 mmol scale; reactions without *t*BuOD added. ^{19}F NMR yields.

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757−15766

laboratory. We note that, similar to the results in Table 3, the fluorinations of **24-OTf** (R = *t*Bu) and **25-OTf** (R = CO_2Et) could be carried out in cyclohexane to cleanly provide **24b** and **25b**, respectively, in high yield, with no evidence of regioisomer formation or deuterium incorporation in the presence of *t*BuOD (Figure 9).[7]

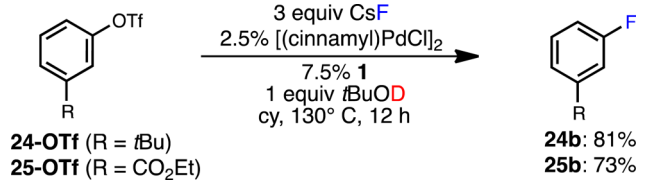


Figure 9. Using cyclohexane as the reaction solvent improves the regioselectivity of the fluorinations of **24**–**25-OTf**. cy = cyclohexane.

Ortho Substituent Effects. In the case of ortho-substituted substrates, only one Pd-aryne intermediate, **10′** (Figure 10),

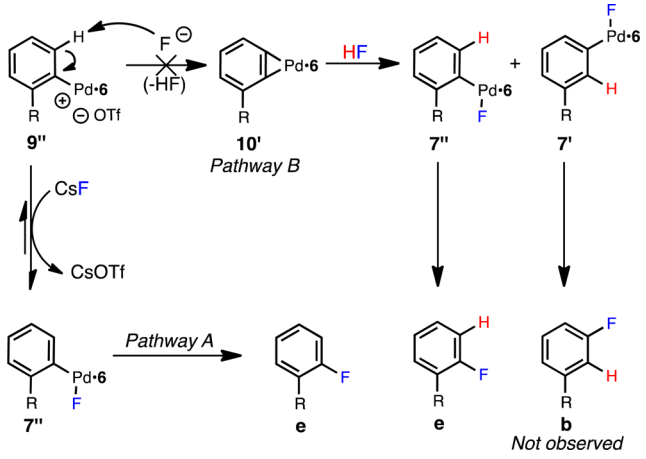
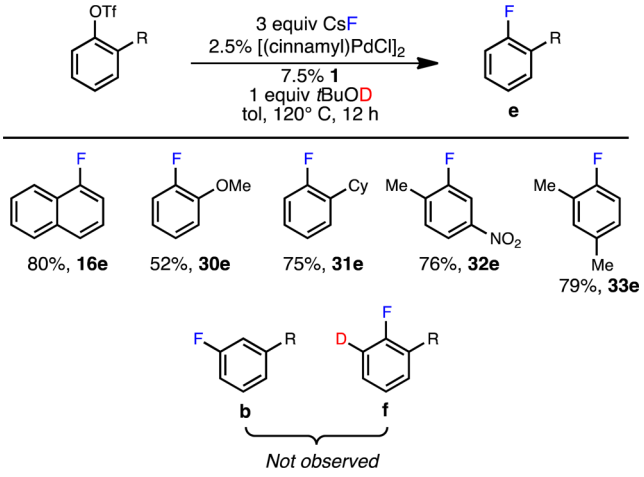


Figure 10. Formation of Pd-aryne **10′** from **9″** (Pathway B) does not occur during the Pd-catalyzed fluorination of ortho-substituted aryl triflates (Pathway A).

could conceivably form by competitive ortho-deprotonation of L·Pd(Ar)OTf complex **9″** (Pathway B, Figure 10) during the desired cross-coupling process (Pathway A, Figure 10). However, as for the fluorination of **16-OTf** (Figure 5), meta-substituted regioisomers do not form during the Pd-catalyzed fluorination of any ortho-substituted aryl triflate tested to date (Table 5).[7,24] Indeed, substrates bearing *ortho*-alkoxy (**30-OTf**) and alkyl (**31-OTf**) substituents proceed cleanly to the desired ortho-substituted aryl fluorides without deuterium labeling in the presence of *t*BuOD (Table 5). Even ortho-substituted substrates bearing an electron-withdrawing group in the meta position (**32-OTf**) or an electron-donating group in the para position (**33-OTf**) do not undergo deuterium labeling or regioisomer formation, confirming that ortho substitution overrules substituent patterns that normally result in regioisomer formation and deuterium incorporation (Tables 2 and 4).

Because we observed that a L·Pd(Ar)OTf species was the resting state of the catalyst in both the fluorinations of **3-OTf** (Figure 5) and **16-OTf** (Figure 6), it is likely not a change in resting state or rate-determining step that explains the lack of regioisomer formation in the latter case. In general, we have observed that the Pd-catalyzed fluorinations of ortho-

Table 5. Fluorinations of Ortho-Substituted Aryl Triflates[17]



substituted substrates are much faster than those of other substrates (compare Figure 5B with Figure 6B). It is well-known that ortho-substituents accelerate the rate of reductive elimination.[37] This could account for the complete regioselectivity of the reactions in Table 5 if reductive elimination is the rate-determining step of Pathway A (Figure 10) and transmetalation is reversible, as the reaction would rapidly funnel toward the desired product **e** without allowing for ortho-deprotonation of **9″**.[38]

An alternative explanation for the complete regioselectivity of the reactions in Table 5 is that, in an effort to minimize steric interactions between the ortho substituent and the *t*Bu groups of the phosphine ligand, **9″** would likely preferentially adopt a conformation with the R group pointing away from the phosphine ligand (**A**, Figure 11), as pointing the R group

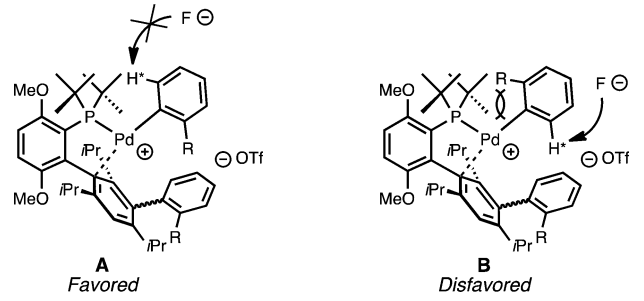


Figure 11. Shielding effect of *t*Bu groups on the ligand could decelerate ortho-deprotonation of preferred conformer **A** of **9″**; conformer **B** is disfavored due to steric intereactions between R on the aryl group and the *t*Bu groups on the ligand.

toward the *t*Bu groups would be highly disfavored (**B**, Figure 11). This conformation would leave the only proton ortho to the Pd center (H*, Figure 11) very close to the bulky phosphine ligand, making deprotonation by CsF difficult.

Similarly, increased steric interactions between the bulky phosphine ligand and R in **10′** compared to **9″** could disfavor formation of this high-energy intermediate and thus decelerate the rate of Pd-aryne formation (Pathway B, Figure 10). In short, ortho-substituted aryl triflates are a general class of substrates that show no evidence of deuterium incorporation, suggesting that competitive formation of a Pd-aryne intermediate is not occurring under catalytic conditions.

dx.doi.org/10.1021/ja509144r | J. Am. Chem. Soc. 2014, 136, 15757–15766

CONCLUSIONS

We have found that deuterium labeling can be used to estimate the amount of Pd-aryne intermediates generated during the catalytic fluorination of a variety of ortho- and para-substituted aryl triflates. Using this method, we have revealed that the transmetalation step of the desired C−F cross-coupling process (Figure 2) likely competes with ortho-deprotonation to form a Pd-aryne intermediate (Figure 3). The substrate classes for which regioisomer formation remains a significant challenge are those bearing electron-donating groups in the para position and those bearing certain electron-donating or -withdrawing groups in the meta position, with no other substituents present. Switching the solvent to cyclohexane can prove to be beneficial in these cases by reducing the extent of products originating from Pd-aryne intermediates.[7] Most importantly, the results herein provide corroborating evidence that the desired C−F cross-coupling pathway outlined in Figure 2 occurs to some degree during the Pd-catalyzed fluorination of all tested aryl triflates. Further work in this area will involve investigating regioisomer formation in the recently reported fluorination of aryl bromides and iodides using AgF,[39] elucidating the behavior of meta-substituted substrates, and designing new catalysts that do not allow for regioisomer formation.

ASSOCIATED CONTENT

Supporting Information

Additional procedural and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

sbuchwal@mit.edu

Notes

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts used in this work from which S.L.B. and former/current coworkers receive royalty payments.

ACKNOWLEDGMENTS

Dedicated to the memory of Gregory L. Hillhouse. We gratefully acknowledge Prof. Thomas J. Maimone (UC Berkeley) for helpful discussions and guidance during this work. We also thank Drs. Hong Geun Lee (MIT) and Aaron Sather (MIT) for assistance with this manuscript. We thank Dr. Mingjuan Su (MIT) for assistance with this manuscript and for carrying out preliminary DFT calculations. Research reported in this publication was supported by the National Institutes of Health under award no. GM46059. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. P.J.M. thanks the National Science Foundation for a predoctoral fellowship (2010094243). P.J.M also thanks Amgen for an educational donation, for which we are grateful. T.K. thanks the Alexander von Humboldt Foundation for a Feodor Lynen postdoctoral fellowship.

REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(2) (a) Liang, T.; Neumann, C.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.

(3) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.

(4) Yandulov, D. V.; Tran, N. T. *J. Am. Chem. Soc.* **2007**, *129*, 1342.

(5) For C−F reductive elimination from Pd(IV) intermediates, see: (a) Pérez-Temprano, M. H.; Racowski, J. M.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 4097. (b) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414. (c) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (d) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (e) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. For additional examples of Pd-mediated electrophilic aryl fluorination reactions, see: (f) Ding, Q.; Ye, C.; Pu, S.; Cao, B. *Tetrahedron* **2014**, *70*, 409. (g) Lou, S.-J.; Xu, D.-Q.; Xia, A.-B.; Wang, Y.-F.; Liu, Y.-K.; Du, X.-H.; Xu, Z.-Y. *Chem. Commun.* **2013**, *49*, 6218. (h) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081. (i) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (j) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993. (k) Hull, K. L.; Anani, W. Q.; Sanford, M.S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. For a reaction proceeding via Pd(III) intermediates in which mixtures of regioisomeric products are observed in certain cases, see: (l) Mazzotti, A.; Campbell, M.; Tang, P.; Murphy, J.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 14012. For a reaction proceeding through ^{18}F-containing Pd(IV) intermediates, see: (m) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.

(6) For Cu-catalyzed or mediated nucleophilic aryl fluorination reactions, see: (a) Mu, X.; Zhang, H.; Chen, P.; Liu, G. *Chem. Sci.* **2014**, *5*, 275. (b) Ye, Y.; Schimler, S. D.; Hanley, P. S.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 16292. (c) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (d) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134. (e) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 10795. (f) Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011**, *133*, 19386. For Cu-mediated nucleophilic fluorination with ^{18}F$^-$, see: (g) Ichiishi, N.; Brooks, A. F.; Topczewski, J. J.; Rodnick, M. E.; Sanford, M. S.; Scott, P. J. H. *Org. Lett.* **2014**, *16*, 3224. For Ni-mediated nucleophilic fluorination with ^{18}F$^-$, see: (h) Lee, E.; Hooker, J. M.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 17456.

(7) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(8) (a) Milner, P. J.; Maimone, T. J.; Su, M.; Chen, J.; Müller, P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 19922. (b) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 18106.

(9) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205.

(10) Attempted trapping of the L·Pd(0) species with other agents such as diphenylacetylene, 1,5-cyclooctadiene, or 4-(*n*Bu)PhCl did not led to an improvement in the yield of **3a**.

(11) Ortho-deprotonation of aryl chlorides and bromides by anhydrous fluoride has been previously reported. See: Grushin, V. V.; Marshall, W. J. *Organometallics* **2008**, *27*, 4825. However, the ratios of products obtained using Grushin's methodology differ greatly from those observed using the Pd-catalyzed fluorination reaction.

(12) To rule out the possibility of deprotonation of the aryl fluoride product by a species generated in situ, we added 4-(OMe)PhF to the catalytic fluorination reaction of **3-OTf**. No isomerization to 3-(OMe)PhF was observed; the added 4-(OMe)PhF was recovered quantitatively.

(13) Retbøll, M.; Edwards, A. J.; Rae, A. D.; Willis, A. C.; Bennett, M. A.; Wenger, E. *J. Am. Chem. Soc.* **2002**, *124*, 8348.

(14) Pd−F compounds are known to be highly basic and nucleophilic sources of F$^-$. See: (a) Martínez-Prieto, L. M.; al Melero, C.; del Río, D.; Palma, P.; Cámpora, J.; Álvarez, E. *Organometallics* **2012**, *31*, 1425. (b) Breyer, D.; Braun, T.; Kläring, P. *Organometallics* **2012**, *31*, 1417.

(c) Grushin, V. V.; Marshall, W. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4476.

(15) An alternative possibility is that **10** reacts with HF directly to produce the aryl fluoride products without the intermediacy of **7** and **7′**. We consider this possibility unlikely because direct reaction of **10** with HF would require either (a) reaction with the p orbitals that are part of the aromatic system or (b) disassociation of the Pd center to form a free aryne species, which then would react with HF. Nonetheless, these possibilities cannot be entirely ruled out.

(16) Additionally, triphenylene was detected in the crude product mixture of the fluorination of phenyl triflate. Pd-catalyzed trimerization of arynes is well-known; see: Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659.

(17) The addition of *t*BuOD also resulted in approximately 15% yield loss due to an increase in the amount of biaryl ether formed by reaction with adventitious water.

(18) Other acidic deuterium sources were also evaluated, but none proved to be superior to *t*BuOD. See Supporting Information Table S1.

(19) To confirm that the presence of *t*BuOD does not induce formation of **10a** and that free H/DF forms in situ as a result of regioisomer formation, we also carried out a crossover experiment by subjecting C_6D_5OTf and 4-(*n*Bu)PhOTf to the reaction conditions together. Deuterium incorporation into the *n*Bu-containing products was observed. See Supporting Information Figure S1.

(20) Matsumoto, J.-i.; Myamoto, T.; Minamida, A.; Nishimura, Y.; Egawa, H.; Nishimura, H. *J. Heterocycl. Chem.* **1984**, *21*, 673.

(21) Several traditional ligands were evaluated for this reaction, including XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl), CPhos (2-dicyclohexylphosphino-2′,6′-bis(*N*,*N*-dimethylamino) biphenyl), PPh_3, and dppf (1,1′-bis(diphenylphosphino)ferrocene), but only a catalyst based on XantPhos provided the desired product free from biaryl byproducts, which were difficult to separate from **14**. For a previous example of the use of XantPhos in Negishi couplings, see: Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, *1*, 31.

(22) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.

(23) It is worth noting that the estimated portion of **3a**,**b** originating from **10** (% aryne) was similar regardless of whether [(cinnamyl)PdCl]$_2$/**1**, $Pd_2(dba)_3$/**1**, or independently prepared **9a** was used as the catalyst source (Supporting Information Table S2). Additionally, reactions conducted using a catalyst derived from the more reactive di-adamantyl congener of **1**, AdBrettPhos (**1′**), also show evidence of deuterium incorporation in the presence of *t*BuOD, with slightly lower regioselectivity and higher % aryne than those carried out with **1**. For the use of **1′** in Pd-catalyzed fluorination, see: Lee, H. G.; Milner, P. J.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 5602.

(24) Noël, T.; Maimone, T. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900.

(25) Determining the exact order in CsF is difficult due to its near insolubility in toluene. In general, Pd-catalyzed fluorination reactions are nonhomogenous and therefore factors such as stirring rate, reaction scale, and average CsF particle size can affect the yields and rates of reactions.

(26) Preliminary computational work carried out in our group suggests that transmetalation is a highly thermodynamically favored step in the catalytic cycle and that the barrier to reductive elimination is lower (<20 kcal/mol) than might be initially expected based on previous work by Yandulov.[4] These preliminary calculations suggest that transmetalation, not reductive elimination, is the rate-determining step of the catalytic cycle shown in Figure 2.

(27) Determining the effect of increasing [CsF] on the rate of the fluorination of **3-OTf** or the extent of Pd-aryne generation is difficult due to its poor solubility in toluene as well as contamination of the CsF with CsOH, which results in lowering of the overall product yield when more CsF is added to the reaction mixture. See Supporting Information Table S4 and the subsequent discussion for details.

(28) An in situ ^{19}F NMR (470 MHz) investigation of the Pd-catalyzed fluorination of **16-OTf** run to partial conversion was also carried out (see Supporting Information Figure S3). The major species observed were **16-OTf**, a 30:1 mixture of two L·Pd(Ar)OTf species (minor, δ −77.3 ppm; major, δ −77.9 ppm), **16e**, and cinnamyl fluoride. Comparison with independently prepared samples of **17a** and **17b** suggests that complete modification of the ligand had not occurred after 15 min of reaction time. Notably, significant quantities of L·Pd(Ar)F species ($\sim\delta$ −210 ppm) were not detected.

(29) Consistently, heating a mixture of **7a** (1.0 equiv) and **9a** (0.5 equiv) led to formation of both **3a** (26%) and **3b** (17%) in a similar ratio (1.5:1) as that from heating **7a** with **3-OTf** (1.6:1) (see Supporting Information for details).

(30) Reversion of **10a** to **9a** could also hypothetically occur by direct reaction of **10a** with triflic acid (HOTf), but given the low pK_a of HOTf (0.3 in DMSO) compared to HF (15 in DMSO) its generation in situ is highly disfavored.

(31) When 4 or more equiv of *t*BuOD are added to the fluorination of **3-OTf**, doubly deuterated products can be observed by GC/MS and ^{19}F NMR. However, the yields of these reactions are significantly lower than the standard catalytic fluorination of **3**, so it is likely that *t*BuOD adversely affects the cross-coupling process at such high concentrations. The presence of hydrogen-bond donors can greatly affect the reactivity of Pd−F complexes; for example, see: Pilon, M. C.; Grushin, V. V. *Organometallics* **1998**, *17*, 1774.

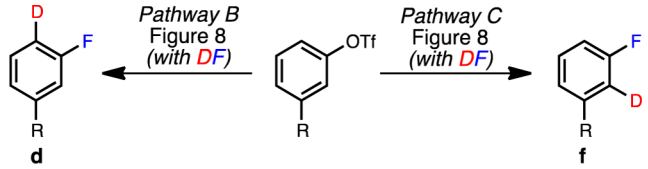
(32) Although multiply deuterated products were observed in the product mixture resulting from the fluorination of **2-OTf** in the presence of *t*BuOD, analysis of this reaction was complicated by the fact that this reaction proceeds almost exclusively through a Pd-aryne intermediate. See Supporting Information Table S5, Figure S4, and the associated discussion for details.

(33) Repeating the reductive elimination of **7a** in the presence of 5.0 equiv of CsF led only to **3a** (7% yield); **3b** was not detected. See Supporting Information for details.

(34) The fluorination of **3-OTf** does not go to full conversion at temperatures below 130 °C in cyclohexane (or below 120 °C in toluene), limiting our ability to examine temperature effects on the regioselectivity of the reaction.

(35) This improvement in regioselectivity is also observed for reactions conducted with **2-OTf**. See Supporting Information Table S5.

(36) Analysis of the ratios of deuterium incorporation was complicated because the desired product can form by all three pathways in Figure 8, with deuterium incorporation possible at two distinct sites to form **d** and/or **f** (see below) by Pathway B or Pathway C, respectively. We have found that we cannot reliably distinguish between **d** and **f** by ^{19}F NMR.



(37) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232.

(38) The effect of ortho substitution on the rate of transmetalation has never, to our knowledge, been thoroughly studied.

(39) Lee, H. G.; Milner, P. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 3792. Preliminary results show that the fluorination of 4-(*n*Bu)PhBr with [(**1′**·Pd)$_2$(1,5-cyclooctadiene)] as the precatalyst results in formation of both **3a** and **3b**; likewise, addition of *t*BuOD to this reaction results in formation of both **3c** and **3d** in addition to **3a** and **3b**. Thus, it is likely that regioisomer formation in the fluorination of aryl bromides proceeds through a similar mechanism.