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

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. Nonetheless, accessing them remains a significant challenge. 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 and Yandulov 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. In 2009, we reported that a catalyst based on the biaryl phosphine ligand tBuBrettPhos (1) can effect the conversion of aryl triflates to the corresponding aryl fluorides using CsF (Figure 1). 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).

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. Importantly, we have found that complex 7a (bearing 3'-arylated ligand 6a) consistently generates regioisomerically pure 4-(nBu)PhF (3a) when heated, albeit in low (15−20%) yield (Figure 2). Intriguingly, attempting to increase the yield by adding 4-(nBu)PhOTf (3-OTf) to trap the L·Pd(0) species formed after reductive elimination led to regioisomeric mixtures of 3a and 3b (Figure 2). Together, these results confirm that (a) potential catalytic intermediate 7a does not generate significant quantities of regioisomeric 3-
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. Because regioisomer formation is not observed in the absence of catalyst, we consider this pathway to be unlikely. 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 intermediate such as 10 (Figure 3). The basic fluoride source could be either CsF or a second molecules of 7, as suggested by our previous stoichiometric experiments. The nonselective reaction of 10 with HF would provide regioisomeric L-Pd(aryl)F complexes 7 and 7, 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, suggesting that scission of the C–H bond adjacent to the trflate group occurs before or during the regioselectivity-determining step.

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 tBuOD was added to the catalytic fluorination of 3-OTf, 20% deuterium labeling of the aryl fluoride products was detected by GC/MS. In addition to the normally observed 19F 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 via diazonium salt, which was not isolated. Negishi coupling of 13 with tBuZnCl in the presence of XantPhos-based 2-aminophenyl mesylate precatalyst gave 14, which could be converted to 3c by lithium–halogen exchange with

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**RESULTS AND DISCUSSION**

**Evidence for Pd-Aryne Intermediate.** The most straightforward mechanism for regioisomer formation in this
BuLi followed by quenching with CD$_3$OD 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 only to 3a, are directly competing processes during the catalytic fluorination of 3-OTf.

**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 1-fluoronaphthalene (16e) 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 tBuOD 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], 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. Thus, the rate law for the desired cross-coupling process (at least in this case) follows rate = k[Pd][CsF]$(n > 0)$. 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(aryl)OTf species (L = 1 or 6), and either
transmetalation or reductive elimination is the rate-determining step of the catalytic cycle.\textsuperscript{26}

The fluorination of 3-OTf shows many of the same features as those of 16-OTf (Figure 6). We have previously shown that the reaction is zeroth order in aryl triflate.\textsuperscript{26} Indeed, the growth of both products over time is linear (Figure 6A), with the relative rates for their formation \((k_{3a, nBu}/k_{3b, nBu} = 1.67 \pm 0.34)\) approximately equal to the final observed regioselectivity \((3a/3b \approx 1.7:1)\). 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] \((k_{3a, Pd}/k_{3b, Pd} = 1.71 \pm 0.18, \text{Figure } 6B)\) as that for the reaction of 16-OTf \((k_{3a, Pd}/k_{3b, Pd} = 1.82 \pm 0.18, \text{Figure } 5B)\). 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 arylene on catalyst or ligand loading.

Similar to the results previously reported for the fluorination of 16-OTf,\textsuperscript{24} the Pd-catalyzed fluorination of 3-OTf displays a small but statistically significant positive order in [CsF] \((k_{3, \text{equiv CsF}}/k_{3, \text{equiv CsF}} = 1.24 \pm 0.09, \text{Figure } 6B)\). 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 \(^{19}\text{F}\) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

![Figure 6](https://example.com/figure6.png)
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

**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[Pd][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. 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[Pd]^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(aryl) intermediate, acting as the base responsible for ortho-deprotonation of 9a.33 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 CsHF₂. 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 oligomerization in 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(aryl)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 trflate substitution patterns on the formation and behavior of 10 (Table 2). For each substrate, two Pd-catalyzed fluorinations were conducted: one without tBuOD added to determine the combined yield (a + b)17 and regioselectivity (a/b) of the reaction and one with tBuOD 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

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

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 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
increased regioselectivity in cyclohexane are (1) less of Pd-aryne 10 is forming in cyclohexane or (2) forms to an equal degree in both solvents but is converted into non-fluorine-containing side products, such as aryne-derived trimers 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...
aryl-fluorination of meta-substituted aryl triflates is a complex process. The reaction of meta-substituted substrates with fluorinating agents can lead to the formation of ortho-substituted products, as well as para-substituted products. The regioselectivity of the fluorination reaction is influenced by the nature of the substituents on the aromatic ring.

Table 3. Deuterium Labeling Results with Cyclohexane as Solvent

| Substrate | R        | Combined % Yield (a + b)a | Parameter (a:b)a | % Db | % AryneC |
|-----------|----------|---------------------------|------------------|------|---------|
| 3-OTf     | nBu      | 60                        | 5:7:1            | 15 ± 1 | 33 ± 3  |
| 19-OTf    | Ph       | 79                        | 12:1             | 4 ± 1 | 7–12%   |

a On a 0.2 mmol scale; reactions without tBuOD added. b 19F 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.

Table 4. Effect of Meta Substituents on the Outcome of Fluorination

| Substrate | R        | Combined % Yield (b + a) | Meta:Para (b:a) |
|-----------|----------|--------------------------|-----------------|
| 23-OTf    | nBu      | 73                       | 14:1            |
| 24-OTf    | tBu      | 76                       | 16:1            |
| 25-OTf    | CO2Et    | 72                       | 11:1            |
| 26-OTf    | CN       | 76                       | 16:1            |
| 27-OTf    | NO2      | 75                       | 12:1            |
| 28-OTf    | OMe      | 60                       | >99:1           |
| 29-OTf    | NMe2     | 59                       | >99:1           |

a On a 0.2 mmol scale; reactions without tBuOD added. 19F NMR yields.

The reaction of meta-substituted aryl triflates with fluorinating agents is a complex process, and the regioselectivity of the fluorination reaction is influenced by the nature of the substituents on the aromatic ring. The presence of ortho-substituted products in these cases confirms that Pathway B (Figure 8) is not operative. The absence of para-substituted products in these cases confirms that Pathway C (Figure 8) is not operative.
laboratory. We note that, similar to the results in Table 3, the fluorinations of \textbf{24-OTf (R = tBu)} and \textbf{25-OTf (R = CO₂Et)} could be carried out in cyclohexane to cleanly provide \textbf{24b} and \textbf{25b}, respectively, in high yield, with no evidence of regioisomer formation or deuterium incorporation in the presence of tBuOD (Figure 9).\textsuperscript{7}

\begin{center}
\begin{tabular}{c}
\textbf{24-OTf (R = tBu)}
\hline
\textbf{3 equiv CsF} & 2.5\% [cinnamyl]PdCl₂ \hline
7.5\% 1 & 1 equiv tBuOD \\
130° C, 12 h & \\
\textbf{24b} 81\% & \\
\textbf{25b} 73\% \\
\end{tabular}
\end{center}

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

\textbf{Ortho Substituent Effects.} In the case of ortho-substituted substrates, only one Pd-aryne intermediate, \textbf{10‘} (Figure 10), could conceivably form by competitive ortho-deprotonation of L-Pd(Ar)OTf complex \textbf{9*} (Pathway B, Figure 10) during the desired cross-coupling process (Pathway A, Figure 10). However, as for the fluorination of \textbf{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).\textsuperscript{7,24} Indeed, substrates bearing ortho-alkoxy (\textbf{30-OTf}) and alkyl (\textbf{31-OTf}) substituents proceed cleanly to the desired ortho-substituted aryl fluorides without deuterium labeling in the presence of tBuOD (Table 5). Even ortho-substituted substrates bearing an electron-withdrawing group in the meta position (\textbf{32-OTf}) or an electron-donating group in the para position (\textbf{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 \textbf{3-OTf} (Figure 5) and \textbf{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-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.\textsuperscript{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 without allowing for ortho-deprotonation of \textbf{9*}.\textsuperscript{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 tBu groups of the phosphine ligand, \textbf{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 toward the tBu groups would be highly disfavored (B, Figure 11). This conformation would leave the only proton ortho to the Pd center (H\textsuperscript{*}, 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 \textbf{10‘} compared to \textbf{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.

\begin{center}
\textbf{Table 5.} Fluorinations of Ortho-Substituted Aryl Triflates\textsuperscript{17}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{R} & \textbf{Cy} & \textbf{OMe} & \textbf{Cy} & \textbf{Me} & \textbf{NO₂} \\
\hline
\textbf{80\%} & 16e & 52\% & 30e & 75\% & 31e & 76\% & 32e & 79\% & 33e \\
\end{tabular}
\end{center}

\textbf{Figure 11.} Shielding effect of tBu groups on the ligand could decelerate ortho-deprotonation of preferred conformer A of \textbf{9*}; conformer B is disfavored due to steric interactions between R on the aryl group and the tBu groups on the ligand.
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 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 Pd-aryne intermediate (Figure 3). The substrate classes for which regioisomer formation remains a significant challenge are those bearing certain electron-donating or -withdrawing groups in the meta position, with no other substituents present.

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.

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(10) Attempted trapping of the L-Pd(0) species with other agents such as diphenylacetylene, 1,5-cyclooctadiene, or 4-(OMe)PhF did not lead 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) Retthall, M.; Edwards, A. J.; Rae, A. D.; Willis, A. C.; Bennett, M. A.; Winger, 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) Martinez-Prieto, L. M.; Melero, C.; del Río, D.; Palma, P.; Cámara, J.; Álvarez, E. Organometallics 2012, 31, 1425. (b) Breyer, D.; Braun, T.; Kläring, P. Organometallics 2012, 31, 1417.
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(15) An alternative possibility is that 10 reacts with HF directly to produce the ary 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) dissociation of the Pd center to form a free arene 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.; Gutiérrez, E.; Castedo, L. Angew. Chem., Int. Ed. 1998, 37, 2659.

(17) The addition of bBuOD 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 bBuOD. See Supporting Information Table S1.

(19) To confirm that the presence of bBuOD does not induce formation of 10a and that free H/DF forms in situ as a result of reformation, we also carried out a crossover experiment by submitting C6D5OTf and 4-(bBuO)PhOTf to the reaction conditions observed. Deuterium incorporation into the nBu-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'-trisopropylbiphenyl), CPhos (2-dicyclohexylphosphino-2',6'-bis(N,N-dimethylylamo) biphenyl), PPh3, and dppe (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.; Tsuturani, 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 (% arene) was similar regardless of whether [[(cinnamyl)PdCl2]2/1, Pd2(dba)/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 diadamantyl congener of 1, AdBrettPhos (1'), also show evidence of deuterium incorporation in the presence of bBuOD, with slightly lower regioselectivity and higher % arene 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. Organometallics 1998, 17, 1774.

(24) Noe, T.; Mainone, 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 transmetallation 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 transmetallation, 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 19F 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 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 (δ = −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 pKa 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 bBuOD are added to the fluorination of 3-OTf, doubly deuterated products can be observed by GC/MS and 19F NMR. However, the yields of these reactions are significantly lower than the standard catalytic fluorination of 3, so it is likely that bBuOD 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 multiple deuterated products were observed in the product mixture resulting from the fluorination of 2-OTf in the presence of bBuOD, 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 19F 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 transmetallation 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-(bBuO)PhBr with [[1'-Pd(1,5-cyclooctadiene)] as the precatalyst results in formation of both 3a and 3b; likewise, addition of bBuOD 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.