ACCOUNTS of chemical research

Article

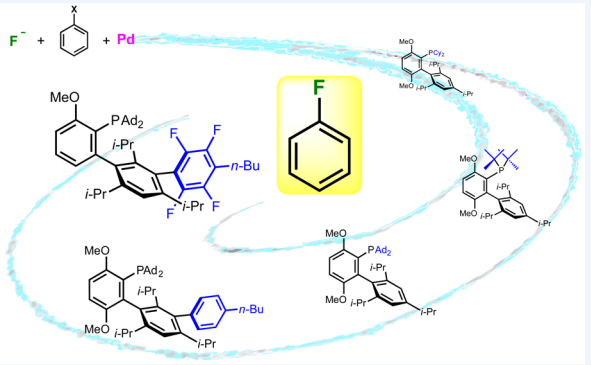
pubs.acs.org/accounts

The Evolution of Pd^0/Pd^{II}-Catalyzed Aromatic Fluorination

Aaron C. Sather and Stephen L. Buchwald*

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

CONSPECTUS: Aromatic fluorides are prevalent in both agrochemical and pharmaceutical agents. However, methods for their rapid and general preparation from widely available starting materials are limited. Traditional approaches such as the Balz–Schiemann and Halex reactions require harsh conditions that limit functional group tolerance and substrate scope. The use of transition metals to affect C–F bond formation has provided some useful alternatives, but a broadly applicable method remains elusive. In contrast to the widespread use of Pd^0/Pd^{II} catalysis for aryl–Z bond formation (Z = C, N, O), the analogous C–F cross-coupling process was unknown until fairly recently. In large part, this is due to the challenging Ar–F reductive elimination from Pd(II) intermediates. We have discovered that certain biaryl monophosphine ligands are uniquely capable of promoting this transformation. In this Account, we describe the discovery and development of a Pd-catalyzed C–F cross-coupling process and the systematic developments that made this once hypothetical reaction possible.



Key to these developments was the discovery of an unusual in situ ligand modification process in which a molecule of substrate is incorporated into the ligand scaffold and the identity of the modifying group is crucial to the outcome of the reaction. This prompted the synthesis of a variety of "premodified" ligands and the identification of one that led to an expanded substrate scope, including (hetero)aryl triflates and bromides. Contemporaneously, a new Pd(0) precatalyst was also discovered that avoids the need to reduce Pd(II) in situ, a process that was often inefficient and led to the formation of byproducts.

The use of inexpensive but hygroscopic sources of fluoride necessitates a reaction setup inside of a N_2-filled glovebox, limiting the practicality of the method. Thus, a preformed wax capsule was designed to isolate the catalyst and reagents from the atmosphere and permit benchtop storage and setup. This new technology thus removes the requirement to employ a glovebox for the aromatic fluorination process and other air-sensitive protocols.

In every catalyst system that we have studied to date, we observed the formation of regioisomeric fluoride side products. Through deuterium labeling studies it was found that they likely arise from a deprotonation event resulting in the formation of HF and a Pd–benzyne intermediate. Through an investigation of the mechanism of this undesired pathway, a new ligand was designed that substantially reduces the formation of the aryl fluoride regioisomer and even allows room-temperature Ar–F reductive elimination from a Pd(II) intermediate.

INTRODUCTION

Largely as a result of their unique biological properties,[1,2] organofluorine compounds[3] have consistently found their place among top-selling pharmaceuticals[4,5] and agrochemicals.[6] In particular, substituting a hydrogen atom of an aromatic ring with fluorine can retard oxidative metabolic pathways,[7] thereby effectively increasing the lifetime of an administered therapeutic. However, mild and general synthetic methods for the preparation of aromatic fluorides are lacking, and traditional methods used to generate them, such as the Balz–Schiemann reaction[8] and the Halex process,[9] typically require harsh conditions, curtailing functional group compatibility and requiring fluorine installation at an early stage in the synthesis. Since the advent of these transformations, significant progress has been made toward the synthesis of aryl fluorides, and transition metals are often employed to enable the challenging C–F bond formation.[10,11] In regard to palladium catalysis, reactive electrophilic fluorine sources ("F^+") have been used to oxidize the metal center to Pd(III) or Pd(IV) to facilitate C–F bond formation by way of a more favorable reductive elimination.[12,13]

In contrast, Pd^0/Pd^{II} catalysis has proven to be pivotal in the practical and general formation of Ar–Z bonds (Z = C, N, O).[14,15] Experimental[16] and computational[17] studies have identified several challenges to the realization of the analogous C–F cross-coupling (Figure 1a). For instance, when simple triaryl phosphines are employed as the supporting ligands, the resulting $L_nPd^{II}(Ar)F$ complexes have been shown to exist as stable fluorine-bridged dimers, which do not readily dissociate into the three-coordinate "T-shaped" complexes that are presumed to be essential for productive C–F reductive elimination (Figure 1b).[17] Furthermore, thermal decomposition of these complexes does not afford the desired aryl fluoride

Received: May 23, 2016
Published: September 22, 2016

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146–2157

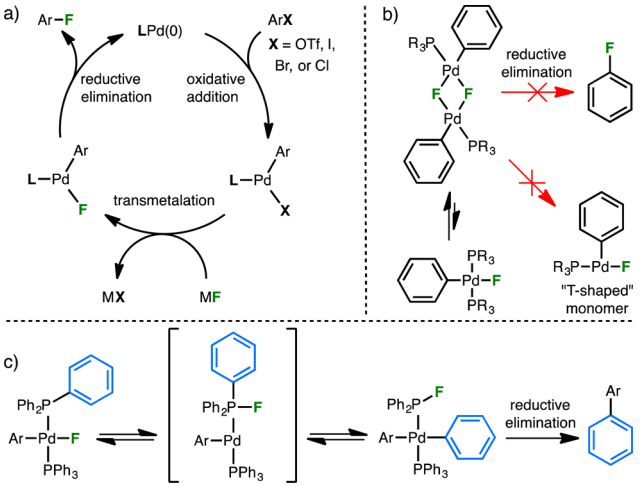


Figure 1. (a) Proposed Pd^0/Pd^{II} catalytic cycle for aryl fluorination. (b) Challenges associated with Pd-catalyzed cross-coupling. (c) Decomposition pathway observed in the thermal decomposition of $L_2Pd(Ar)F$ complexes.

product. Instead, a rearrangement occurs, resulting in the formation of biphenyl and new compounds with a P–F bond as well as other decomposition products (Figure 1c).

It was reported, however, that when a solution of the dimeric Pd(II) fluoride complex **1** (R = NO_2) was heated in the presence of excess *t*-BuXPhos (**L1**), a 10% yield of *p*-fluoronitrobenzene was produced (Figure 2).[17] Further

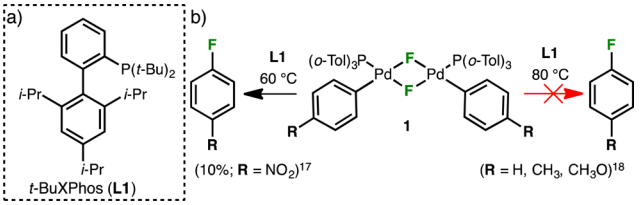


Figure 2. Thermal decomposition of **1** in the presence of **L1**.

investigation into this result questioned whether this process occurs through C–F reductive elimination or simply by an S_NAr process, as the thermal decomposition of complexes containing aryl groups that do not stabilize Meisenheimer intermediates (**1** with R = H, CH_3, CH_3O) did not result in the formation of aryl fluoride even in the presence of excess **L1**.[18] Nevertheless, these studies highlight the fundamental difficulties of C–F reductive elimination from phosphine-ligated $LPd^{II}(Ar)F$ complexes.

Pd-CATALYZED FLUORINATION: DISCOVERY

We were intrigued by the difficulty of C–F reductive elimination and the prospect of developing a Pd-catalyzed aryl fluorination reaction based on this process. This possibility was intermittently investigated for several years prior to our preliminary success,[19] and we renewed our efforts when single-crystal X-ray analysis and NMR experiments revealed that **L2**Pd(Ar)X complexes (**L2** = BrettPhos; X = Br, Cl) were monomeric[20] and hypothesized that the analogous **L2**Pd(Ar)F complexes would be as well. Thus, **L2**Pd(Ar)F complexes were prepared to determine their structure and whether **L2** would be effective for promoting C–F reductive elimination (Figure 3). As shown in Figure 3a, the crystal structure of **L2**Pd(Ar)F (Ar

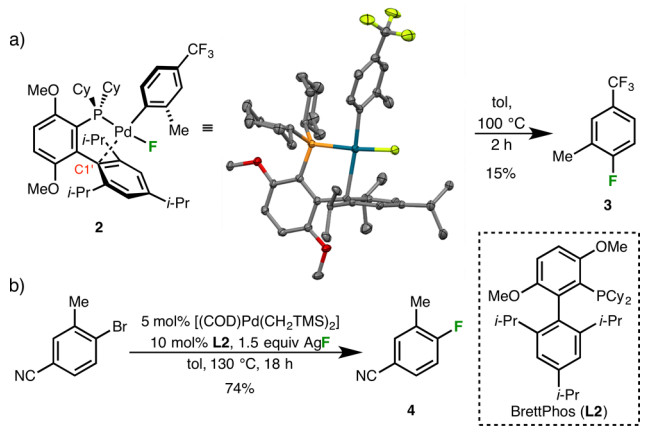
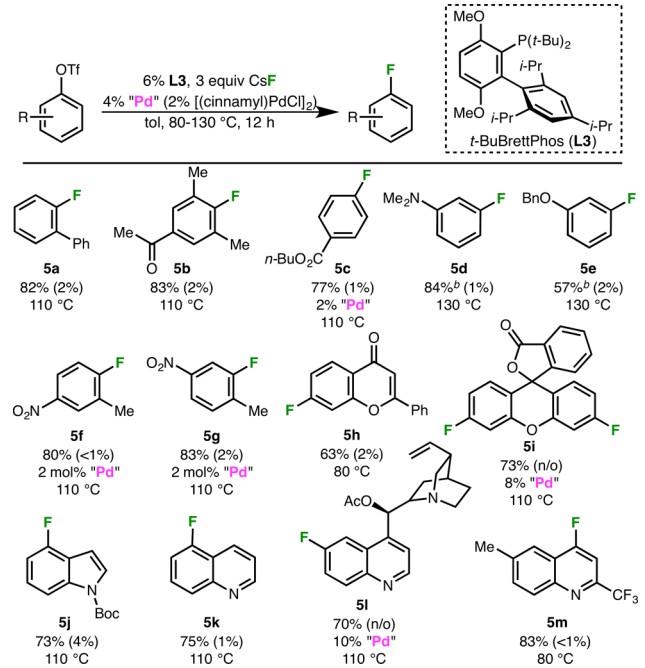


Figure 3. (a) X-ray crystal structure of **2** and C–F reductive elimination from **2**. (b) Catalytic fluorination using **L2**.

= 4-trifluoro-2-methylphenyl) confirmed the monomeric nature of the complex. Presumably the bulky biaryl monophosphine ligand **L2** enforces the T-shaped geometry by disfavoring dimerization through steric repulsion. Thermolysis of **2** provided **3** in 15% yield, providing the first example of C–F reductive elimination from an isolated Pd(II) complex. Additionally, **L2** enabled the catalytic fluorination of 4-bromo-3-methylbenzonitrile to afford **4** in 74% yield (Figure 3b). However, at this stage of development, the scope of aryl bromides was limited, and only electron-poor substrates with ortho substituents were efficiently transformed to the desired C–F coupled products.

By the use of CsF, a more sterically demanding ligand (*t*-BuBrettPhos (**L3**)), and $[(cinnamyl)PdCl]_2$, a variety of aryl triflates were transformed into the corresponding fluorinated arene products (**5a–m**; Table 1). This methodology could be

Table 1. Pd-Catalyzed Fluorination of Aryl Triflates[a]



[a]Isolated yields are shown. Values in parentheses indicate the amounts of reduction products (ArH) formed (n/o = not observed). [b]Cyclohexane was used as the reaction solvent.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146–2157

applied to a variety of heterocyclic substrates, highlighting the potential to prepare pharmaceutically relevant compounds with this transformation, although electron-rich aryl triflates required higher temperatures (130 °C) and catalyst loadings to achieve full conversion. In some instances, regioisomeric aryl fluoride products were formed. The mechanism of this side reaction was investigated and will be discussed in detail (vide infra). Additionally, the reaction is sensitive to water, and the hygroscopic CsF must be handled in a nitrogen-filled glovebox. Though the reaction components are sensitive, the method was later successfully adapted to a continuous-flow process using a CsF packed bed reactor.[21]

IN SITU CATALYST MODIFICATION[22,23]

To gain a better understanding of the overall catalytic process and potentially expand the substrate scope of this transformation, **L3**Pd^{II}(Ar)F complexes were sought to further investigate the stoichiometric C−F reductive elimination process. Oxidative addition complex **6a** was isolated as a bright-yellow solid that precipitated from the reaction mixture (Figure 4a). However, when **6a** was dissolved in CD_2Cl_2 for

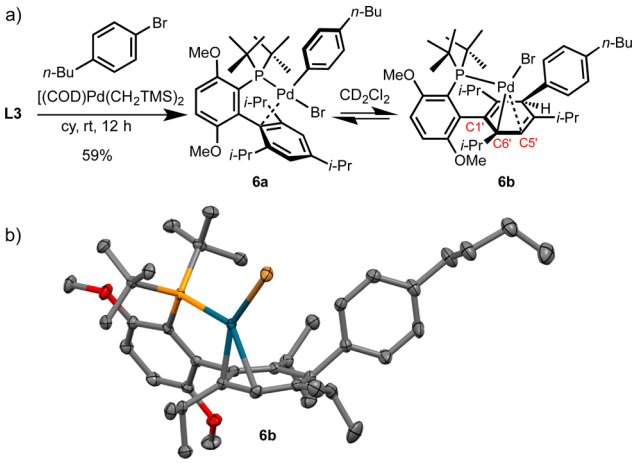


Figure 4. (a) Synthesis of **6a** and the dearomative rearrangement of **6a** to **6b**. (b) X-ray crystal structure of **6b**.

characterization, the initial yellow solution became dark red as a new complex was formed, eventually establishing an approximately 6:1 equilibrium mixture with the starting material. Single crystals of the major component were isolated, and X-ray diffraction revealed the structure of dearomatized Pd(II) bromide complex **6b** (Figure 4b). Complex **6b** is air-stable and thermally robust, although dissolution in CD_2Cl_2 re-establishes the equilibrium with **6a** (K_{eq} = 5.71 ± 0.10, CD_2Cl_2).

As expected, the structure of the ligand directly impacts the rearrangement process. For instance, compared with oxidative addition complexes bearing **L3**, the smaller cyclohexyl groups of **L2** provide complexes that no longer undergo dearomatization, as **7a** did not rearrange to **7b** even after 10 days in solution (Figure 5a). In contrast, the **L4**-based complex **8a**, boasting bulky adamantyl substituents at phosphorus, behaves in a similar manner as **6a**, establishing an equilibrium that favors the rearranged complex **8b** (K_{eq} = 9.00 ± 0.16, THF-d_8) (Figure 5b). Thus, as is true for reductive elimination, a probable driving force for the observed rearrangement is the relief of unfavorable steric interactions between the bulky

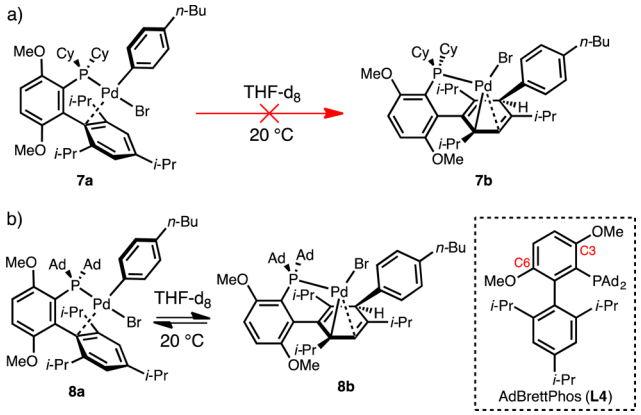


Figure 5. (a) **L2**-supported oxidative addition complex **7a** does not undergo rearrangement to **7b**. (b) Dearomative rearrangement of **8a** to **8b**.

groups on phosphorus and the Pd-bound aryl group. Additionally, it should be noted that while substituents at C3 promote rearrangement, groups at C6 retard this process, further exemplifying that the dearomative isomerization of these Pd(II) oxidative addition complexes intimately relies on the identity of the biaryl monophosphine ligands that support them.

Under catalytic conditions, the dearomatized complex undergoes subsequent deprotonation by the highly basic anhydrous fluoride present in the reaction mixture, resulting in rearomatization, reduction to Pd(0), and incorporation of the aryl electrophile into the ligand scaffold. Thus, the overall consequence of the rearrangement is the in situ formation of a new ligand whose competence in further aryl fluorination is dependent on the substrate employed.

To further investigate the ligands/complexes arising from the rearrangement/arylation process, **10** was prepared by treating an equilibrating mixture of **6a** and **6b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence 4-(*n*-Bu)PhBr (Figure 6). As opposed to the parent complex **6a**, **10** is remarkably stable and can be heated to 100 °C without undergoing further rearrangement or decomposition. In

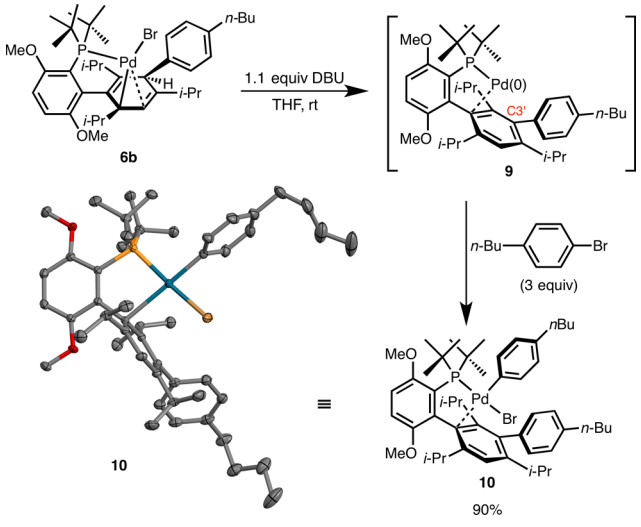


Figure 6. Rearomatization of **6b** followed by trapping with 4-(*n*-Bu)PhBr to yield complex **10**. The X-ray crystal structure of **10** is also shown.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

general, we have never observed the dearomative isomerization of complexes that already contain substitution at the 3′ position.

Arylated LPd(Ar)F complex **11** was prepared to investigate its reactivity toward C−F bond formation (Figure 7). When **11**

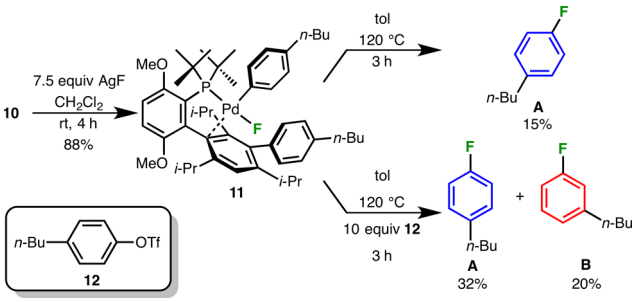


Figure 7. Synthesis and reactivity of LPd(Ar)F complex **11**.

was heated in toluene, 4-(*n*-Bu)PhF (**A**) was formed in 15% yield, demonstrating that reductive elimination produces a single regioisomer. However, when **11** was heated in the presence of 4-(*n*-Bu)PhOTf (**12**), which serves as a trapping agent for the L·Pd(0) species formed after reductive elimination, regioisomers **A** and **B** were obtained as a 1.6:1 mixture, suggesting that a Pd-bound fluoride species is involved in the formation of the undesired regioisomer **B**.

FORMATION OF REGIOISOMERIC ARYL FLUORIDES[24]

As we originally noted, the Pd-catalyzed fluorination of aryl triflates produces mixtures of regioisomeric aryl fluoride products for certain classes of substrates. Control experiments implicate the involvement of catalytic intermediates in this process, as regioisomer formation does not occur in the absence of catalyst and the observed regioisomeric ratio of fluorinated products differs significantly from those produced from a discrete benzyne intermediate.[25] Additionally, a higher degree of regioselectivity is observed for 2,6-dideuterated aryl triflates compared with the protio analogues, suggesting that ortho C−H(D) bond scission occurs before or in conjunction with the irreversible regioisomer-forming step.[19,24] These observations led to the proposal of a Pd−aryne intermediate (**13**) that results from ortho-deprotonation of **14** or **15** by an external basic fluoride species (CsF or **14**) (Figure 8). Recombination of **13** with the liberated molecule of HF would give rise to regioisomeric LPd(Ar)F complexes **14** and **14′**, which

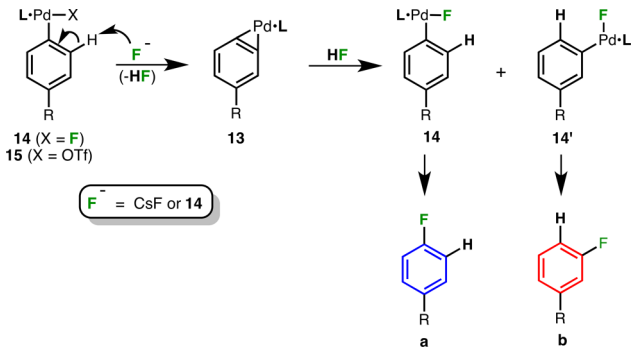


Figure 8. Proposed mechanism for the formation of regioisomeric aryl fluorides from para-substituted aryl triflates.

following reductive elimination would produce regioisomeric aryl fluorides **a** and **b**, respectively.

The addition of a deuterium source was used as a means to probe the formation of **13**. In the presence of *t*-BuOD, HF exchanges with *t*-BuOD to give DF before recombining with **13**, resulting in a mixture of deuterated and nondeuterated aryl fluoride products (Figure 9). This distribution of aryl fluoride

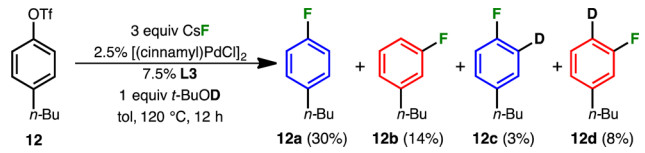


Figure 9. Addition of *t*-BuOD to the Pd-catalyzed fluorination of **12** gives a mixture of aryl fluorides (**12a−d**).

products provides evidence that the formation of Pd−aryne **13** and C−F cross-coupling processes directly compete during Pd-catalyzed fluorination.

Kinetic experiments using **L3** indicated that the resting state of the catalyst during the catalytic fluorination reaction is likely an LPdArOTf species, and it was postulated that transmetalation is the rate-determining step of the catalytic cycle (Figure 1a).[24] Thus, the major species undergoing ortho-deprotonation is likely the LPd(Ar)OTf complex (**15**), as it is present in higher concentrations than LPd(Ar)F (**14**). Since the regiochemical outcome of the reaction is unaffected by the catalyst loading, it is probable that regioisomer formation and cross-coupling have the same rate dependence on [Pd]. Therefore, rate-limiting ortho-deprotonation requiring the reaction between two Pd complexes (**14** and **15**) is unlikely, as increasing the catalyst loading would accelerate the rate of ortho-deprotonation compared with cross-coupling. This result is consistent with CsF (which is present in excess under conditions relevant to the catalytic reaction) behaving as a base to form **13**. However, in view of the previously mentioned stoichiometric experiments involving **11** (Figure 7), we cannot completely discount the possibility that a small amount of Pd−aryne intermediate **13** may arise from reaction of **14** with **15** in the catalytic reaction. The overall mechanistic picture for the formation of regioisomers is shown in Figure 10.

An array of para-substituted aryl triflates were subjected to our Pd-catalyzed fluorination protocol to determine the effect of the electronic properties of the substituents on regioisomer formation. As shown in Table 2, substrates with electron-donating groups provide the lowest levels of regioselectivity (**17a−c**) and those containing strongly electron-withdrawing groups react cleanly to afford the desired aryl fluorides (**17d** and **17e**). The para electron-donating substituents likely lower the rate of transmetalation relative to the competitive ortho-deprotonation process, resulting in the poor regioselectivities observed for this class of substrate. It was also found that regioisomer formation could be suppressed (but not completely eliminated) by performing the reaction in cyclohexane in place of toluene. We have no clear-cut explanation for this solvent effect, but it may be due to a decrease in solubility of CsF in cyclohexane.

In addition to undergoing reductive elimination (pathway A; Figure 11), the LPd(Ar)OTf complexes of meta-substituted aryl triflates have the opportunity to form two nonequivalent Pd−aryne intermediates, which differ by the site of ortho-deprotonation. Deprotonation para to R would yield the same

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

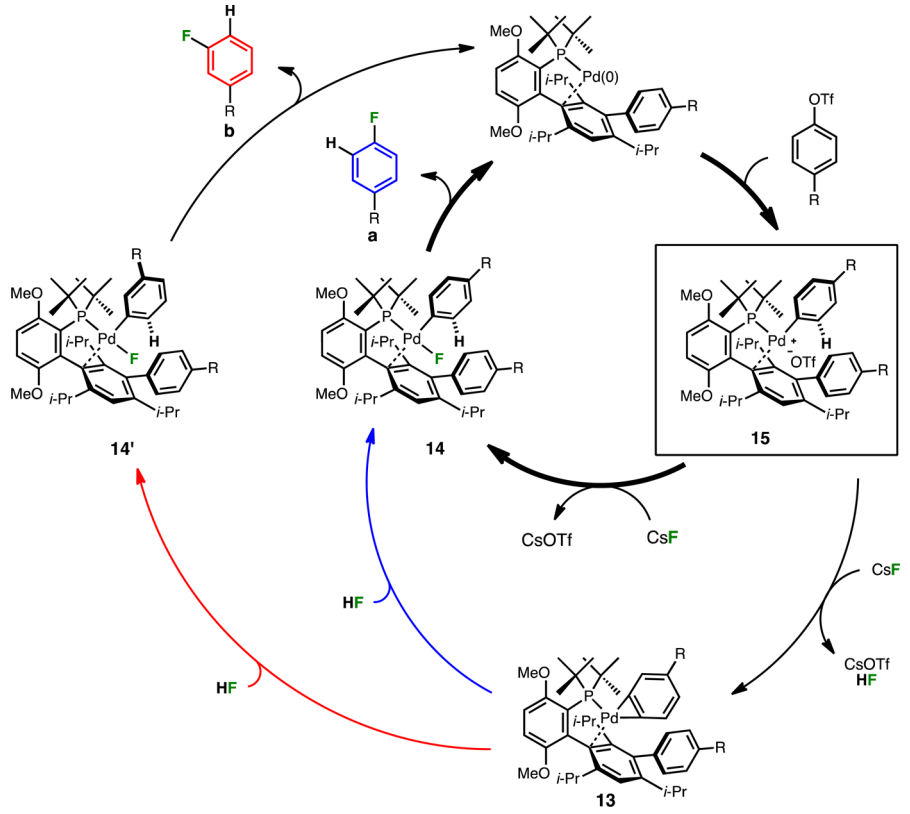
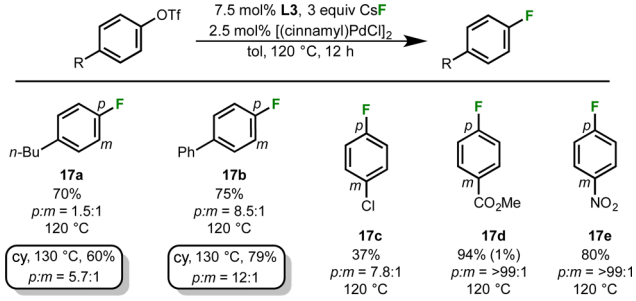


Figure 10. Proposed mechanism for the formation of regioisomeric aryl fluorides **a** and **b**.

Table 2. Effect of Para Substituents on Regioisomer Formation[a]



[a]Yields were determined by ^{19}F NMR spectroscopy.

Pd−aryne intermediate **13** as observed for the corresponding para-substituted aryl triflate (pathway B; Figure 11). Thus, recombination of **13** with HF would give rise to complexes **14′** and **14** and eventually lead to the desired (**b**) and undesired (**a**) aryl fluorides, respectively. Following a similar sequence, deprotonation ortho to both R and the Pd center would successively provide Pd−aryne intermediate **13′**, complexes **14′** and **14″**, and finally a mixture of the desired (**b**) and undesired (**c**) regioisomers resulting from C−F reductive elimination (pathway C; Figure 11). However, throughout our studies, ortho-substituted aryl fluoride products (**c**) arising from an intermediate such as **14″** were never observed.

As shown in Table 3, a series of meta-substituted aryl triflates provided detectable amounts of the undesired para re-

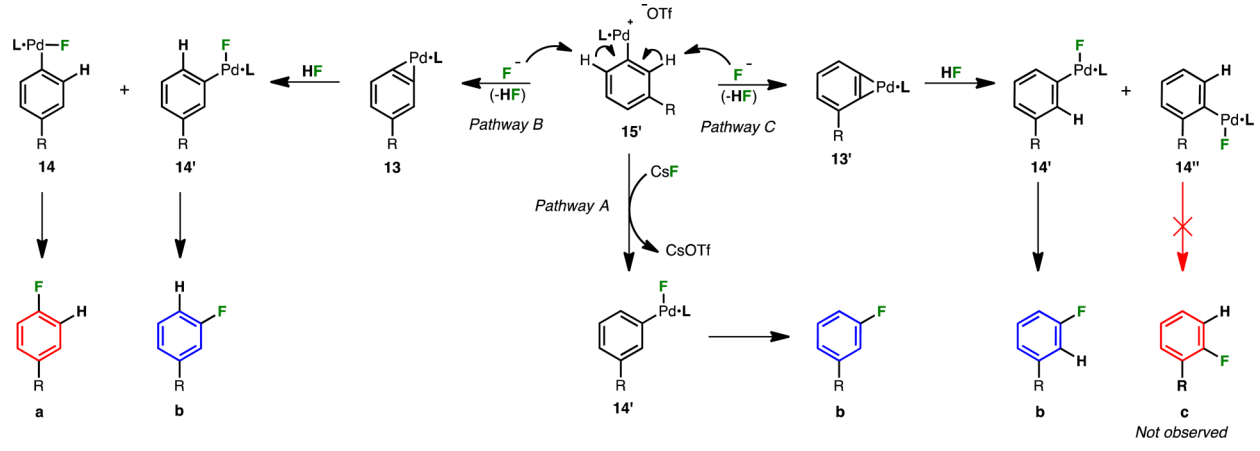
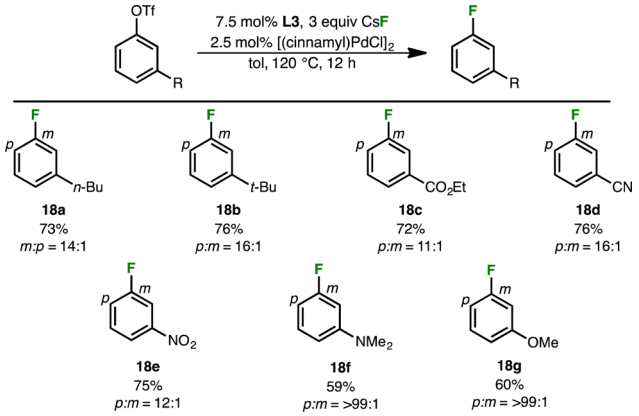


Figure 11. Proposed mechanism for regioisomer formation from meta-substituted aryl triflates.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

Table 3. Effect of Meta Substituents on Regioisomer Formation[a]



[a]Yields were determined by ^{19}F NMR spectroscopy.

gioisomers (**18a–e**), which is consistent with the formation of **13** (pathway B; Figure 11). Substrates with strongly electron-donating meta substituents, however, provide aryl fluoride products (**18f** and **18g**) without the formation of the undesired regioisomer.

Ortho-substituted aryl triflates can potentially form a single Pd–aryne intermediate (**13′**) via ortho-deprotonation of oxidative complex **15″** (Figure 12), which would recombine

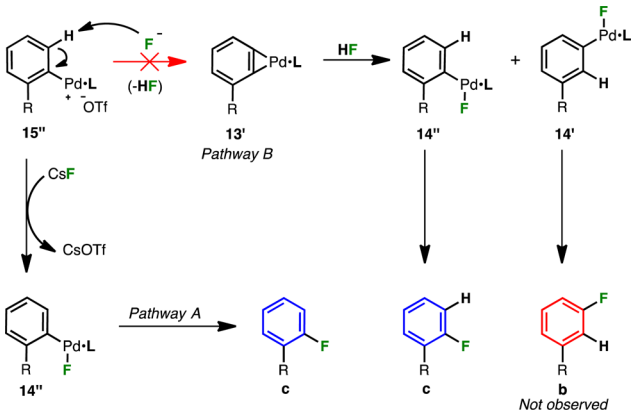


Figure 12. Proposed mechanism for regioisomer formation from ortho-substituted aryl triflates.

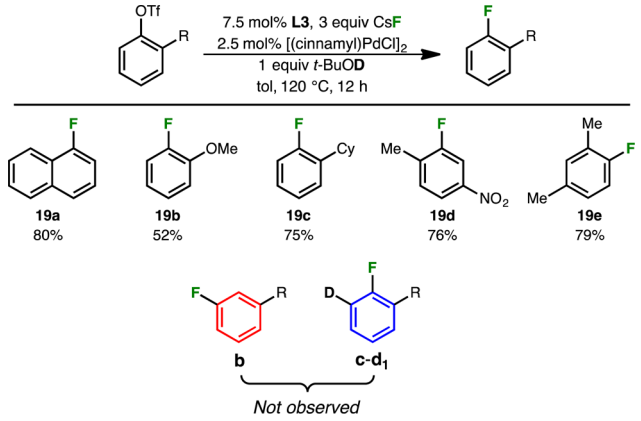
with HF and eventually lead to a meta-substituted aryl fluoride regioisomer (pathway B; Figure 12). However, *o*-aryl triflates react cleanly to form the desired isomer (**19a–e**; Table 4). When the reaction is carried out in the presence of *t*-BuOD, no deuterium incorporation into the product is observed.

■ Pd-CATALYZED FLUORINATION: DEVELOPMENTS

Improved Catalyst System

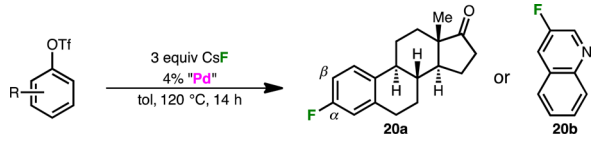
Our original combination of **L3** and [(cinnamyl)PdCl]$_2$ proved effective for the catalytic fluorination of a variety of aryl triflates. However, poor reactivity was observed for electron-rich and heteroaryl substrates, such as the triflates of estrone and 3-quinolinol (Table 5, entry 1).[26] It was found, however, that a catalyst system based on AdBrettPhos (**L4**) is capable of effectively transforming these more challenging substrates (Table 5, entry 2), although to some degree the formation of regioisomeric aryl fluorides persists. The enhanced reactivity

Table 4. Effect of Ortho Substituents on Regioisomer Formation[a]



[a]Yield determined by ^{19}F NMR.

Table 5. Fluorination Using Various Sources of Pd Supported by L3 or L4[a]



entry	Pd source	ligand (L:Pd = 1.5:1)	% yield (**20a**)	% yield (**20b**)
1	[(cinnamyl)PdCl]$_2$	**L3**	< 20%	30%[b]
2	[(cinnamyl)PdCl]$_2$	**L4**	75% (α:β = 8:1)[b]	70%[b]
3	Pd(OAc)$_2$	**L4**	0%	0%
4	Pd$_2$(dba)$_3$	**L4**	58% (α:β = 7:1)	0%
5	Pd(dba)$_2$	**L4**	73% (α:β = 5:1)	47%
6	**P1**	-	35%	50%
7	**P2**	-	72% (α:β = 13:1)	70%

[a]Yields were determined by ^{19}F NMR spectroscopy. [b]The corresponding ArCl was detected by GC analysis.

observed for the **L4**-supported catalyst presumably arises from an increased rate of C–F reductive elimination provided by the larger adamantyl substituents on phosphorus.[27] Although this improvement in reactivity is significant, the typical Pd(II) species employed must be reduced in situ, which can introduce undesirable reactants into the reaction mixture. For instance, upon activation of [(cinnamyl)PdCl]$_2$, chloride ion is released, which leads to the formation of a small amount of aryl chloride that is difficult to separate from the desired aryl fluoride product. Furthermore, the use of Pd(OAc)$_2$ is ineffective (Table 5, entry 3) and the application of stable sources of Pd(0) such as Pd$_2$(dba)$_3$ (Table 5, entry 4) and Pd(dba)$_2$ (Table 5, entry 5), provide diminished yields of the desired product, likely because of inhibition by the dba ligand.[28] In addition to these drawbacks, the use of an excess of ligand is required when these Pd sources are employed.

Our laboratory has developed a set of preligated Pd(II) precatalysts that activate cleanly to form the corresponding L·Pd(0) species in the presence of base without the need for additional ligand (Figure 13a).[29] Unfortunately, the use of our third-generation precatalyst (**P1**) in the C–F bond-forming reaction generates an equivalent of carbazole and HF, both of which adversely affect the Pd-catalyzed fluorination (Table 5, entry 6). The limitations associated with these various sources

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146–2157

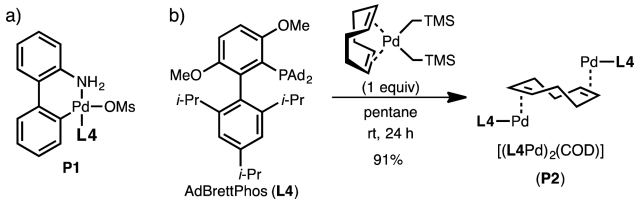
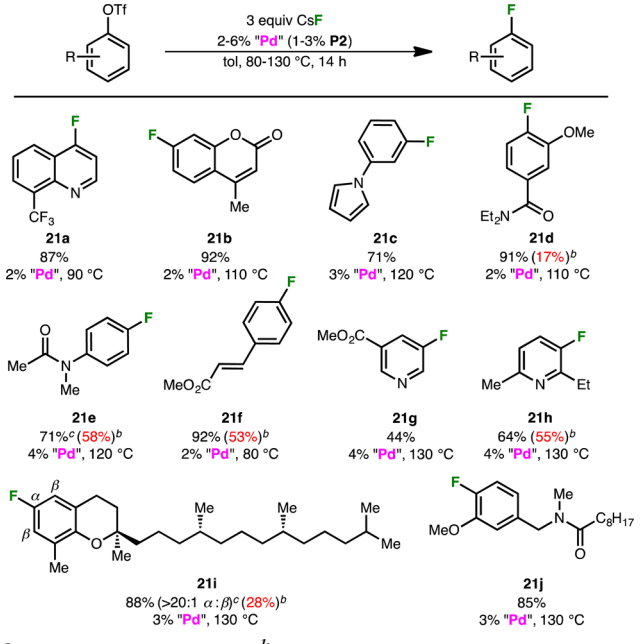


Figure 13. (a) Structure of **L4**-based precatalyst **P1**. (b) Synthesis of **L4**-supported Pd(0) precatalyst **P2**.

of Pd were overcome by using a 1,5-cyclooctadiene (COD)-based Pd(0) precatalyst that was serendipitously discovered during our investigations of Pd(II) oxidative addition complexes.[30] The new precatalyst (**P2**) is prepared by simply mixing equivalent amounts of ligand **L4** and [COD·Pd-$(CH_2TMS)_2$] in pentane at room temperature (Figure 13b). Indeed, **P2** possessed the desired reactivity, as both estrone triflate and 3-quinolinyl triflate were converted to the corresponding aryl fluorides in yields comparable to those obtained using $[(cinnamyl)PdCl]_2$ without the formation of aryl chloride byproducts (Table 5, entry 7). **P2** has a half-life of approximately 3 days when left open to air, but it is indefinitely stable when stored under N_2 in a benchtop desiccator or inside of a nitrogen-filled glovebox.

As shown in Table 6, the use of **P2** enables the effective transformation of several heteroaryl triflates and a variety of aryl

Table 6. Fluorination of (Hetero)aryl Triflates and Aryl Triflates Derived from Biologically Active Phenols[a]



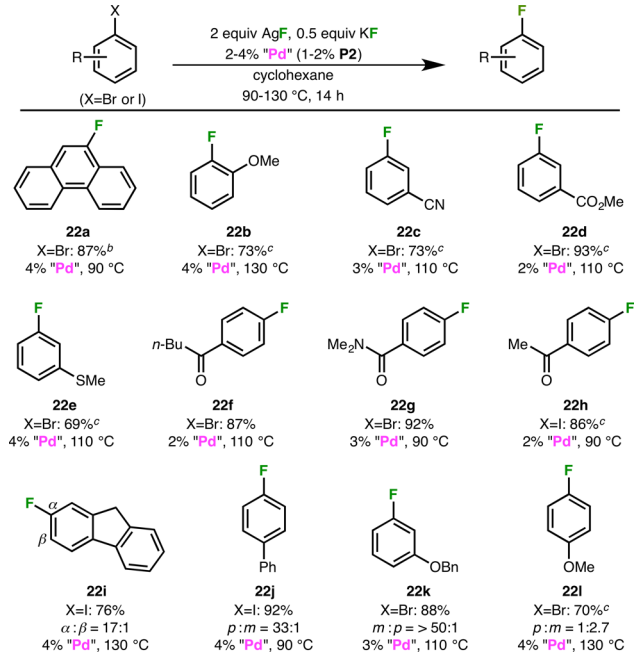
[a]Isolated yields are shown. [b]Yield when the reaction was conducted under the same conditions using $[(cinnamyl)PdCl]_2$/**L4** (Pd/**L4** = 1:1.5) instead of **P2**. The corresponding ArCl was detected by GC analysis. [c]Cyclohexane was used as the reaction solvent.

triflates derived from biologically active/naturally occurring phenols to the corresponding (hetero)aryl fluorides (**21a–j**). Additionally, compared with $[(cinnamyl)PdCl]_2$, **P2** provides significantly increased yields of the aryl fluoride in several instances (**21d–f** and **21h–j**), demonstrating the superiority of the new catalyst system.

Fluorination of (Hetero)aryl Bromides

Even with the development of **P2**, the fluorination of unactivated aryl bromides remained challenging.[31] In light of the dearomative ligand rearrangement process, it was postulated that a substoichiometric amount of base might be required to promote the in situ ligand modification and the generation of the active catalyst (vide supra). Indeed, 0.5 equiv of either KF or CsF must be used in conjunction with AgF to effectively promote the desired C–F cross-coupling, but KF is preferred because it is less expensive and hygroscopic than CsF. With these conditions, a variety of aryl bromides and iodides were successfully fluorinated in good yields with minimal formation of reduced arene (ArH) product (**22a–l**; Table 7).

Table 7. Pd-Catalyzed Fluorination of Aryl Halides Using P2[a]



[a]Isolated yields are shown. [b]Toluene was used as the reaction solvent. [c]Yield determined by ^{19}F NMR spectroscopy.

Although the reactions were performed in cyclohexane, regioisomeric aryl fluoride products were observed in a few cases (**22i–l**), with the formation of the undesired isomer favored for **22l**.

While beneficial, the addition of the fluoride base alone was insufficient to achieve satisfactory yields for the fluorination of heteroaryl bromides. It was postulated that when heteroaryl bromides were used as substrates, either the ligand modification process was inefficient or the resulting modified ligand performed poorly in the desired reaction. This modification process was avoided altogether by synthesizing a "premodified" ligand, HGPhos (**L5**), which was converted to the corresponding COD-based Pd(0) precatalyst **P3** (Figure 14a). However, high yields of aryl fluoride were obtained only when KF was included, suggesting that the role of KF is more complicated than originally postulated. Nevertheless, **P3** enabled the preparation of an array of heteroaryl fluorides (**23a–k**; Figure 14b).

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146–2157

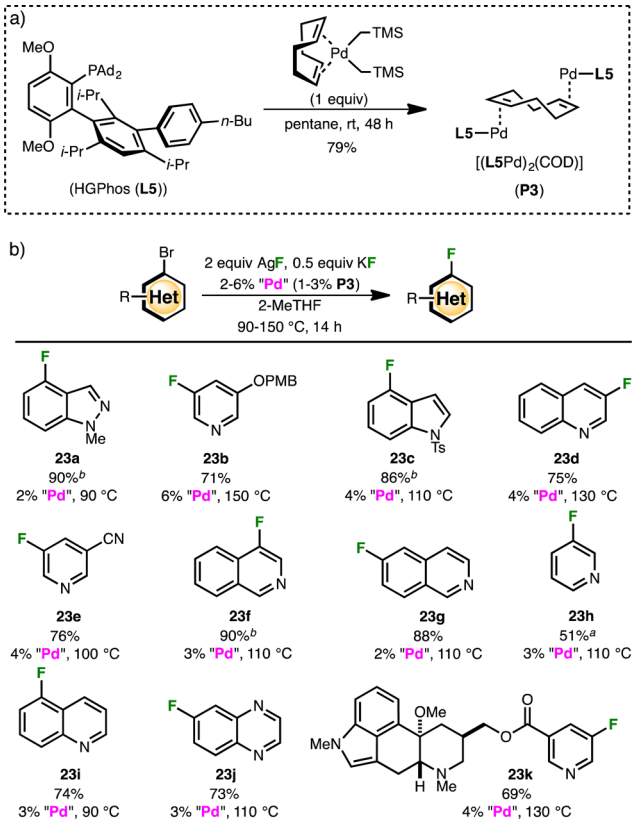


Figure 14. (a) Structure of HGPhos (**L5**) and the synthesis of **P3**. (b) Pd-catalyzed fluorination of heterocyclic aryl bromides using **P3**. Isolated yields are reported. [a]Yield determined by ^{19}F NMR spectroscopy. [b]TBME was used as the reaction solvent.

Glove-Box-Free Fluorination[32]

As described in the experimental procedures, the reactions discussed thus far had to be set up in a nitrogen-filled glovebox because of the hygroscopicity of the CsF or AgF employed and the reaction's characteristic sensitivity to water. As many laboratories lack access to a glovebox and the use of one is inconvenient at best, this requirement greatly limits the practicality of the transformation, which ultimately determines whether a method is adopted for routine use. The need to use a glovebox was successfully eliminated by the development of single-use paraffin wax capsules (melting point 58−62 °C) filled with the reagent (CsF, 3 equiv) and catalyst (**P2**, 2 mol %) necessary for the Pd-catalyzed fluorination of aryl triflates (1 mmol) (Figure 15a).[32,33] In this way, the sensitive materials are isolated from the atmosphere within the capsule, rendering the contents bench-stable. By the use of these capsules, a variety of aryl and heteroaryl triflates were conveniently converted to the corresponding aryl fluorides (**21a**−**f**) without relying on a glovebox (Figure 15b). Notably, the product yields realized with the wax capsules were undiminished compared to those obtained with the aid of a glovebox.

The wax capsule technology could also be applied to the catalytic conversion of (hetero)aryl bromides. By the use of wax capsules containing AgF (2 equiv), KF (0.5 equiv), and **P3** (2 mol %), a range of (hetero)aryl bromides (1 mmol) were smoothly fluorinated (**23a** and **24a**−**e**), again without the use of a glovebox (Figure 16).

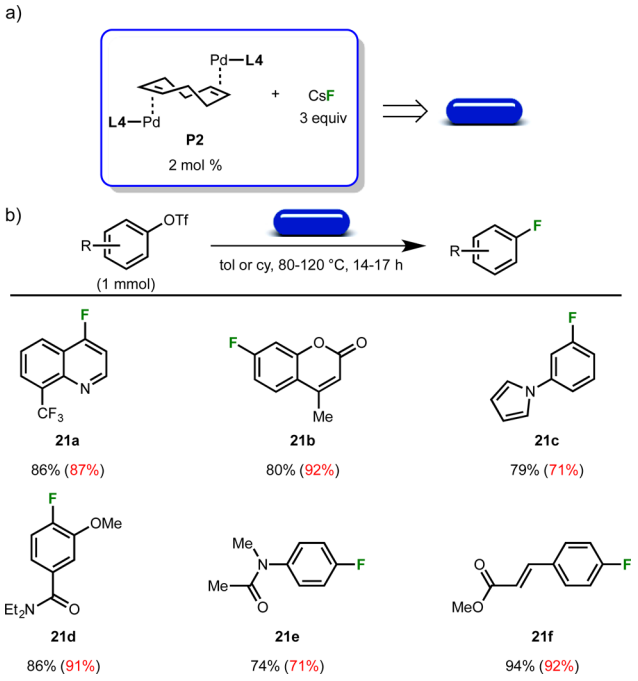


Figure 15. (a) Contents of the wax capsules for the Pd-catalyzed fluorination of aryl triflates. (b) Glove-box-free fluorination of aryl triflates. Isolated yields are reported. Values in parentheses are isolated yields obtained using a glovebox to set up the reactions.

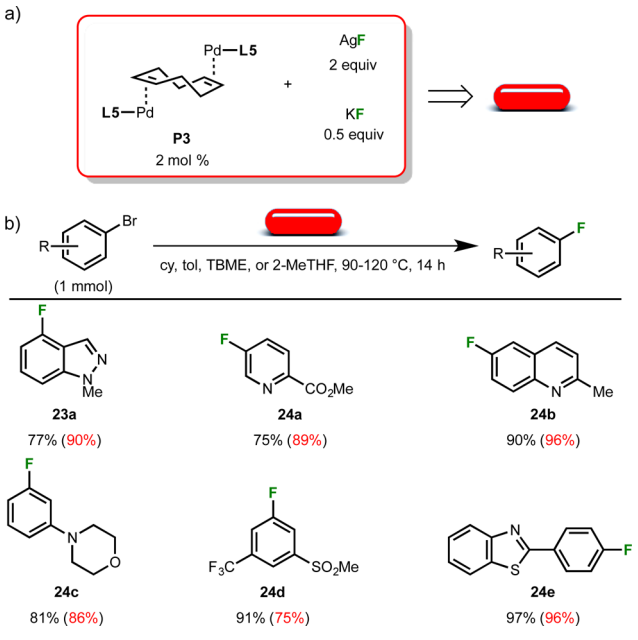


Figure 16. (a) Contents of the wax capsules for the Pd-catalyzed fluorination of aryl bromides. (b) Glove-box-free fluorination of aryl bromides. Isolated yields are reported. Values in parentheses are isolated yields obtained using a glovebox to set up the reactions.

Regioselective and Room-Temperature Fluorination

As described earlier, the formation of regioisomeric aryl fluoride products occurs for a few classes of substrates (vide supra) and elevated reaction temperatures are required in all cases to achieve full conversion of the starting material. These issues are attributed to a process that competes with transmetalation and the challenging C−F reductive elimination from Pd(II) complexes. It was hypothesized that incorporating an

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

electron-deficient substituent at C3′ of the ligand would diminish donation of electron density from C1′ to the Pd(II) center, resulting in a metal center with more three-coordinate character, thus facilitating reductive elimination.[34,35]

A ligand incorporating the proposed features, AlPhos (**L6**), and the corresponding Pd(0) precatalyst [(**L6**Pd)$_2$·COD] (**P4**) were prepared on a multigram scale and are commercially available (Figure 17).[36,37] The effectiveness of the **L6**-supported catalyst in suppressing the formation of regioisomeric aryl fluoride byproducts was evaluated using 4-(*n*-Bu)PhX (X = OTf, Br) as model substrates (Table 8). For comparison, **L5** was assessed under identical reaction conditions alongside **L6**. As shown in Table 8, the **L5**-based catalyst system produced substantial amounts of the regioisomeric aryl fluoride (**B**) with either aryl electrophile (Table 8, entry 1). Lowering the reaction temperature resulted in either incomplete conversion (X = OTf) or little change in yield or selectivity (X = Br) (Table 8, entry 2). In contrast, the **L6**-supported catalyst exhibited superior reactivity, and its use resulted in the full conversion of the starting materials at lower temperatures, revealing a temperature dependence of the formation of **B** (Table 8, entries 3–5, X = OTf) and allowing the desired regioisomer to be prepared in pure form. While the use of **L6** diminishes the amount of **B** formed (X = Br), a similar temperature dependence was not observed.

The ability of the **L6**-supported catalyst to suppress regioisomer formation was similarly extended to a number of previously problematic substrates (Table 9). The corresponding aryl fluorides (**25a–h**, **17b**, and **18e**) were prepared in high yields with excellent levels of regioselectivity (>100:1) and with minimal formation of reduction products (ArH was observed only for **25a** (0.75%), **25e** (0.64%), and **22l** (0.52%)). When 4-bromoanisole was used as the substrate, the use of **L5** favored the formation of the undesired regioisomer (1:2.7) (**22l**; Table 7). When **L6** was employed, the regioselectivity was reversed (2.2:1) and the overall yield was improved (**22l**; Table 9). Surprisingly, a sample of **P4** retained its full catalytic activity after storage on the benchtop in an air atmosphere for 1 week.

As a testament to the enhanced reactivity of the **L6**-based catalyst system, a variety of activated (hetero)aromatic triflates were converted to the corresponding aryl fluorides (**26a–m**) in high yields at room temperature (Table 10), demonstrating catalytic C–F reductive elimination under ambient conditions for the first time.

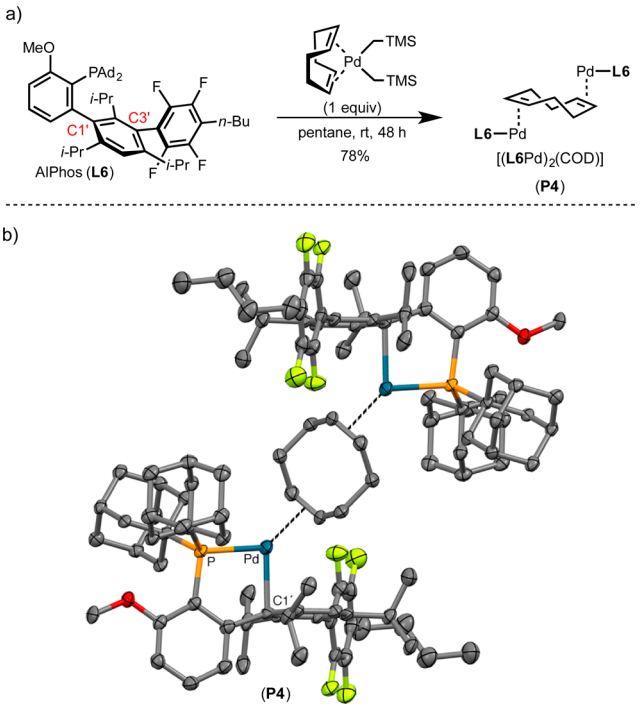
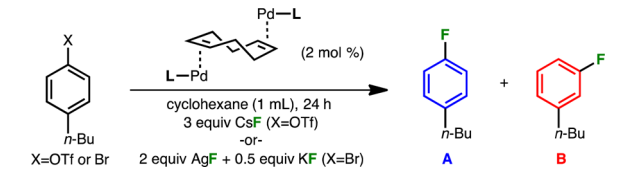


Figure 17. (a) Structure of AlPhos (**L6**) and the synthesis of [(**L6**Pd)$_2$·COD] (**P4**). (b) Crystal structure of **P4**.

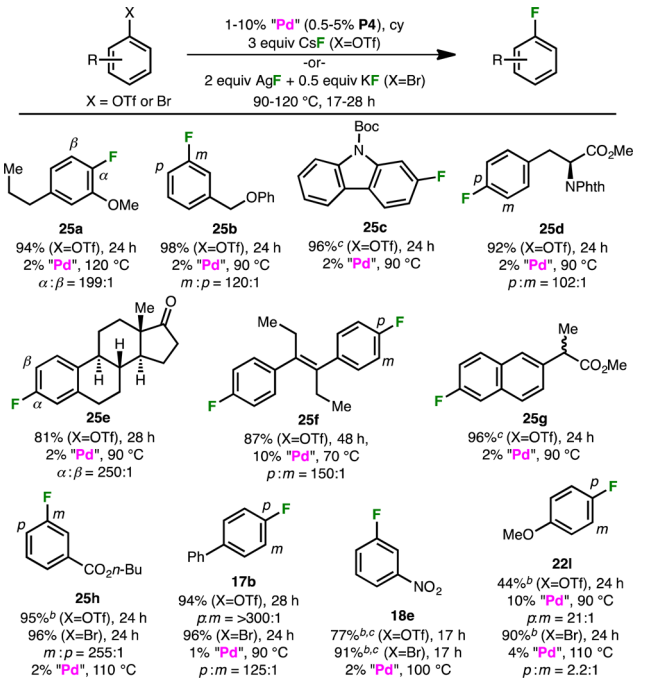
Table 8. Temperature Dependence of Regioisomer Formation[a]



entry	L	temp (°C)	% yield, X=OTf	% yield, X=Br
1	**L5**	110	76% **A**, 9% **B**	74% **A**, 18% **B**
2	**L5**	90	20% **A**, 1% **B** (35)	73% **A**, 15% **B**
3	**L6**	110	89% **A**, 3% **B**	86% **A**, 6% **B**
4	**L6**	90	87% **A**, 1% **B**	84% **A**, 5% **B**
5[b]	**L6**	80	81% **A**, -- **B**	87% **A**, 5% **B**

[a]Yields were determined by ^{19}F NMR spectroscopy. Values in parentheses indicate % conversion of the starting material. [b]The reaction time was 48 h.

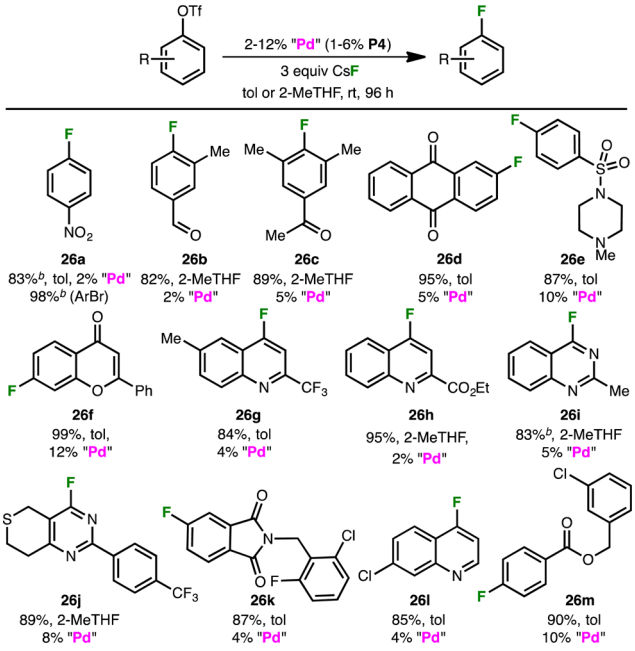
Table 9. Regioselective Fluorination Using P4[a]



[a]Isolated yields are shown. [b]Yield determined by ^{19}F NMR spectroscopy. [c]The regioisomer was not detected by ^{19}F NMR spectroscopy.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146–2157

Table 10. Room-Temperature Fluorination of Aryl Triflates[a]



[a]Isolated yields are shown. [b]Yield determined by ^{19}F NMR spectroscopy.

Studies toward the Fluorination of Five-Membered Heterocycles

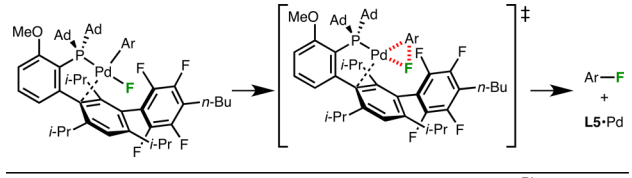
Five-membered heterocycles are a common structural element found in pharmaceuticals,[38] but the preparation of their fluorinated analogues remains a significant challenge.[39] Compared with their six-membered counterparts, reductive elimination involving five-membered heterocycles is considerably more difficult because of their smaller size and augmented electron richness.[40,41] It was reasoned, however, that the enhanced ability of the **L6**-supported catalyst to facilitate reductive elimination would be well-suited to this challenge. Thus, we aimed to extend our Pd-catalyzed fluorination methodology to include five-membered heteroaryl triflates and/or halides. Computational studies of thiophene-based Pd(II)F model complexes confirmed the expected increase in barrier to reductive elimination (**27** compared with **28**; Table 11) although incorporation of an *o*-phenyl substituent onto the thiophene ring (**29**) resulted in a significant decrease.[39]

In accord with the calculations, a variety of phenyl-substituted bromothiophenes were subjected to our Pd-catalyzed fluorination conditions (Table 12).[39] The scope of this transformation is limited to a very particular class of substrate, and in general, only thiophene derivatives containing both a phenyl substituent and an appropriate electron-withdrawing group were fluorinated in synthetically useful yields under the reaction conditions (**30a**−**e**). In some cases, a fluorinated byproduct was formed, which was presumed (but not proven) to be the regioisomer of the desired product.

■ CONCLUSIONS AND FUTURE PERSPECTIVES

Since its initial discovery, the Pd-catalyzed fluorination of aryl electrophiles has seen a series of key advances. Central to this improvement has been the design and development of new biaryl monophosphine ligands capable of facilitating C−F reductive elimination from Pd(II) metal centers. Also crucial to our success were the serendipitous discovery of a stable Pd(0) precatalyst and the in situ ligand modification process, which provided us with an avenue to explore improvements in the ligand scaffold. Thus, by expanding upon these findings, a process once considered impossible can now be realized, in some cases, at room temperature. While these advances are notable, the development of a practical and truly general method for C−F bond formation continues to motivate our research in this area. At present, (hetero)aryl (pseudo)halides containing protic functional groups, (hetero)aryl chlorides, and five-membered heteroaryl (pseudo)halides are not viable substrates, and the work presented here will serve as the foundation for future developments in these areas.

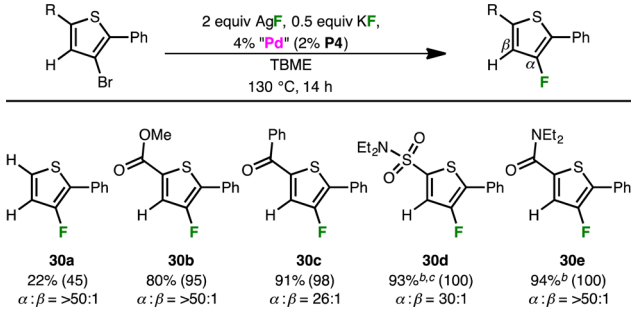
Table 11. Computationally Determined Barriers to Reductive Elimination for L6·Pd(Ar)F Complexes 27−29[a]



Ar =			
complex	**27**	**28**	**29**
ΔG‡ (kcal/mol)	20.7	25.9	22.8

[a]Energies were calculated at the M06/6-311+G(d,p)-SDD/SMD (toluene) level of theory with geometries optimized at the B3LYP/6-31G(d) level. $\Delta G^{\ddagger}$ values were determined at 25 °C.

Table 12. Pd-Catalyzed Fluorination of 2-Substituted 3-Bromothiophenes[a]



[a]Yields determined by ^{19}F NMR spectroscopy are shown. Values in parentheses indicate % conversion of the starting material. [b]Isolated yield. [c]Toluene was used as the reaction solvent.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sbuchwal@mit.edu.

Funding

We thank the National Institutes of Health (NIH) for financial support of this research (R01GM46059). A.C.S. thanks the NIH for a postdoctoral fellowship (1F32GM108092-01A1).

Notes

Disclaimer: the content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The authors declare the following competing financial interest(s): MIT has obtained patents on the ligands/

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

precatalysts described in this Account, from which S.L.B. and former/current coworkers receive royalty payments.

Biographies

Aaron C. Sather was born in Seattle, Washington. He received his B.Sc. from the University of Oregon, where he worked on arsenic remediation and anion recognition with Prof. Darren W. Johnson. He then moved to The Scripps Research Institute (TSRI) to study organic chemistry and molecular recognition under the guidance of Prof. Julius Rebek, Jr. Upon earning his Ph.D. from TSRI, he began work at MIT in the laboratories of Prof. Stephen L. Buchwald, where he is currently an NIH Postdoctoral Fellow.

Stephen L. Buchwald is the Camille Dreyfus Professor and Associate Head of Chemistry at MIT. He has received a number of honors. Recent ones include the BBVA Frontiers in Knowledge Award in Basic Sciences (2014), the Linus Pauling Medal (2014), the Ulysses Medal (2014), the William H. Nichols Award (2016), and the Nagoya Gold Medal Lecture Award (to be received in 2017).

■ ACKNOWLEDGMENTS

We thank Drs. Yiming Wang and Michael Pirnot for assistance with the preparation of this Account.

■ REFERENCES

(1) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359.
(2) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369.
(3) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C-F bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.
(4) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506.
(5) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II−III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422−518.
(6) Jeschke, P. The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection. *ChemBioChem* **2004**, *5*, 570−589.
(7) Kaufman, S. The enzymic conversion of 4-fluorophenylalanine to tyrosine. *Biochim. Biophys. Acta* **1961**, *51*, 619−621.
(8) Balz, G.; Schiemann, G. Aromatic Fluorine Compounds, I.: A new Method for Their Preparation. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1186−1190.
(9) Finger, G. C.; Kruse, C. W. Aromatic Fluorine Compounds. VII. Replacement of Aromatic -Cl and -NO_2 Groups by -F. *J. Am. Chem. Soc.* **1956**, *78*, 6034−6037.
(10) Campbell, M. G.; Ritter, T. Modern Carbon−Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115*, 612−633.
(11) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174.
(12) Engle, K. M.; Mei, T. S.; Wang, X.; Yu, J. Q. Bystanding F+ Oxidants Enable Selective Reductive Elimination from High-Valent Metal Centers in Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478−1491.
(13) Mazzotti, A. R.; Campbell, M. G.; Tang, P.; Murphy, J. M.; Ritter, T. Palladium(III)-Catalyzed Fluorination of Arylboronic Acid Derivatives. *J. Am. Chem. Soc.* **2013**, *135*, 14012−14015.
(14) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
(15) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
(16) Grushin, V. V. The Organometallic Fluorine Chemistry of Palladium and Rhodium: Studies toward Aromatic Fluorination. *Acc. Chem. Res.* **2010**, *43*, 160−171.
(17) Yandulov, D. V.; Tran, N. T. Aryl-Fluoride Reductive Elimination from Pd(II): Feasibility Assessment from Theory and Experiment. *J. Am. Chem. Soc.* **2007**, *129*, 1342−1358.
(18) Grushin, V. V.; Marshall, W. J. Ar−F Reductive Elimination from Palladium(II) Revisited. *Organometallics* **2007**, *26*, 4997−5002.
(19) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. Formation of ArF from LPdAr(F): Catalytic Conversion of Aryl Triflates to Aryl Fluorides. *Science* **2009**, *325*, 1661−1664.
(20) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. A Highly Active Catalyst for Pd-Catalyzed Amination Reactions: Cross-Coupling Reactions Using Aryl Mesylates and the Highly Selective Monoarylation of Primary Amines Using Aryl Chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 13552−13554.
(21) Noël, T.; Maimone, T. J.; Buchwald, S. L. Accelerating Palladium-Catalyzed C−F Bond Formation: Use of a Microflow Packed-Bed Reactor. *Angew. Chem., Int. Ed.* **2011**, *50*, 8900−8903.
(22) Maimone, T. J.; Milner, P. J.; Kinzel, T.; Zhang, Y.; Takase, M. K.; Buchwald, S. L. Evidence for in Situ Catalyst Modification During the Pd-Catalyzed Conversion of Aryl Triflates to Aryl Fluorides. *J. Am. Chem. Soc.* **2011**, *133*, 18106−18109.
(23) Milner, P. J.; Maimone, T. J.; Su, M.; Chen, J.; Müller, P.; Buchwald, S. L. Investigating the Dearomative Rearrangement of Biaryl Phosphine-Ligated Pd(II) Complexes. *J. Am. Chem. Soc.* **2012**, *134*, 19922−19934.
(24) Milner, P. J.; Kinzel, T.; Zhang, Y.; Buchwald, S. L. Studying regioisomer formation in the Pd-catalyzed fluorination of aryl triflates by deuterium labeling. *J. Am. Chem. Soc.* **2014**, *136*, 15757−15766.
(25) Grushin, V. V.; Marshall, W. J. Fluorination of Nonactivated Haloarenes via Arynes under Mild Conditions, Resulting from Further Studies toward Ar−F Reductive Elimination from Palladium(II). *Organometallics* **2008**, *27*, 4825−4828.
(26) Lee, H. G.; Milner, P. J.; Buchwald, S. L. An Improved Catalyst System for the Pd-Catalyzed Fluorination of (Hetero)Aryl Triflates. *Org. Lett.* **2013**, *15*, 5602−5605.
(27) Su, M.; Buchwald, S. L. A Bulky Biaryl Phosphine Ligand Allows for Palladium-Catalyzed Amidation of Five-Membered Heterocycles as Electrophiles. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710−4713.
(28) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. Identification of the Effective Palladium(0) Catalytic Species Generated in Situ from Mixtures of $Pd(dba)_2$ and Bidentate Phosphine Ligands. Determination of Their Rates and Mechanism in Oxidative Addition. *J. Am. Chem. Soc.* **1997**, *119*, 5176−5185.
(29) Bruno, N. C.; Buchwald, S. L. Synthesis and Application of Palladium Precatalysts that Accommodate Extremely Bulky Di-tert-butylphosphino Biaryl Ligands. *Org. Lett.* **2013**, *15*, 2876−2879.
(30) Lee, H. G.; Milner, P. J.; Colvin, M. T.; Andreas, L.; Buchwald, S. L. Structure and Reactivity of $[(L{\cdot}Pd)_n{\cdot}(1,5\text{-cyclooctadiene})]$ (n = 1−2) Complexes Bearing Biaryl Phosphine Ligands. *Inorg. Chim. Acta* **2014**, *422*, 188−192.
(31) Lee, H. G.; Milner, P. J.; Buchwald, S. L. Pd-Catalyzed Nucleophilic Fluorination of Aryl Bromides. *J. Am. Chem. Soc.* **2014**, *136*, 3792−3795.
(32) Sather, A. C.; Lee, H. G.; Colombe, J. R.; Zhang, A.; Buchwald, S. L. Dosage Delivery of Sensitive Reagents Enables Glove-Box-Free Synthesis. *Nature* **2015**, *524*, 208−211.
(33) Commercialization of these capsules is underway.
(34) Hoffmann, R. Reductive Elimination. In *Frontiers of Chemistry*; Laidler, K. J., Ed.; Pergamon Press: Oxford, U.K., 1982; pp 247−263.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157

(35) Tatsumi, K.; Hoffmann, R.; Yamamoto, A.; Stille, J. K. Reductive Elimination of d^8-Organotransition Metal Complexes. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1857−1867.
(36) Sather, A. C.; Lee, H. G.; De La Rosa, V. Y.; Yang, Y.; Muller, P.; Buchwald, S. L. A Fluorinated Ligand Enables Room-Temperature and Regioselective Pd-Catalyzed Fluorination of Aryl Triflates and Bromides. *J. Am. Chem. Soc.* **2015**, *137*, 13433−13438.
(37) AlPhos (**L6**) and **P4** are available through Sigma-Aldrich (cat. nos. 799718 and 799726) and Strem (cat. nos. 15-2065 and 46-0241).
(38) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257−10274.
(39) Milner, P. J.; Yang, Y.; Buchwald, S. L. In-Depth Assessment of the Palladium-Catalyzed Fluorination of Five-Membered Heteroaryl Bromides. *Organometallics* **2015**, *34*, 4775−4780.
(40) Su, M.; Hoshiya, N.; Buchwald, S. L. Palladium-Catalyzed Amination of Unprotected Five-Membered Heterocyclic Bromides. *Org. Lett.* **2014**, *16*, 832−835.
(41) Hooper, M. W.; Hartwig, J. F. Understanding the Coupling of Heteroaromatic Substrates: Synthesis, Structures, and Reductive Eliminations of Heteroarylpalladium Amido Complexes. *Organometallics* **2003**, *22*, 3394−3403.

DOI: 10.1021/acs.accounts.6b00247
Acc. Chem. Res. 2016, 49, 2146−2157