The Evolution of Pd⁰/PdⅡ-Catalyzed Aromatic Fluorination

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CONPECTUS: 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 Pd⁰/PdⅡ 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 "premodi" 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 N₂-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 deuterium 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 compounds³ have consistently found their place among top-selling pharmaceuticals⁴,⁵ 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 reaction⁸ 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, Pd⁰/PdⅡ catalysis has proven to be pivotal in the practical and general formation of Ar–Z bonds (Z = C, N, O).¹⁴,¹⁵ Experimental¹⁶ and computational¹⁷ 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 L₃PdⅡ(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.
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 = NO2) was heated in the presence of excess t-BuXPhos (L1), a 10% yield of p-fluoronitrobenzene was produced (Figure 2).17 Further investigation into this result questioned whether this process occurs through C−F reductive elimination or simply by an SNAr process, as the thermal decomposition of complexes containing aryl groups that do not stabilize Meisenheimer intermediates (1 with R = H, CH3, CH3O) 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 PdII(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 L2Pd(Ar)X complexes (L2 = BrettPhos; X = Br, Cl) were monomeric20 and hypothesized that the analogous L2Pd(Ar)F complexes would be as well. Thus, L2Pd(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 L2Pd(Ar)F (Ar = 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

| Aryl Triflate | Product | Temp (°C) | Yields (%) |
|--------------|---------|-----------|------------|
| 5a           | F       | 90        | 77%        |
| 5b           | F       | 80        | 82%        |
| 5c           | F       | 100       | 77%        |
| 5d           | F       | 110       | 84%        |
| 5e           | F       | 130       | 57%        |
| 5f           | F       | 90        | 63%        |
| 5g           | F       | 80        | 82%        |
| 5h           | F       | 100       | 73%        |
| 5i           | F       | 110       | 80%        |
| 5j           | F       | 130       | 90%        |
| 5k           | F       | 90        | 83%        |
| 5l           | F       | 100       | 83%        |
| 5m           | F       | 80        | 83%        |

*Isolated yields are shown. Values in parentheses indicate the amounts of reduction products (ArH) formed (n/o = not observed).

*Cyclohexane was used as the reaction solvent.
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

To gain a better understanding of the overall catalytic process and potentially expand the substrate scope of this transformation, L3Pd(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 CD2Cl2 for 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 CD2Cl2 re-establishes the equilibrium with 6a (K_{eq} = 5.71 ± 0.10, CD2Cl2).

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-d8) (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 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 aryl fluoride present in the reaction mixture, resulting in re-aromatization, 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 arylation 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.
general, we have never observed the dearomatative 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 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

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

Table 2. Effect of Para Substituents on Regioisomer Formation

| Yields | R     | X     | Temp | Pd–F | a (%) | b (%) |
|--------|-------|-------|------|------|-------|-------|
| 17a    | Ph    | 70%   | 150 °C | 80%   | 0%    | 100%  |
| 17b    | Ph    | 76%   | 150 °C | 88%   | 0%    | 100%  |
| 17c    | Ph    | 37%   | 150 °C | 98%   | 0%    | 100%  |
| 17d    | F     | 54%   | 150 °C | 98%   | 0%    | 100%  |
| 17e    | F     | 80%   | 150 °C | 98%   | 0%    | 100%  |

“Yields were determined by 19F NMR spectroscopy.”

Figure 11. Proposed mechanism for regioisomer formation from meta-substituted aryl triflates.
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 with HF and eventually lead to a meta-substituted aryl fluoride regioisomer (pathway B; Figure 12). When the reaction is carried out in the presence of t-BuOD, no deuterium incorporation into the product is observed.

Table 3. Effect of Meta Substituents on Regioisomer Formation*

| R         | Yield | R         | Yield |
|-----------|-------|-----------|-------|
| OTu       | 73%   | OTu       | 75%   |
| p-CF3     | 91%   | p-CF3     | 80%   |
| CN        | 72%   | CN        | 60%   |
| NO2       | 73%   | NO2       | 59%   |
| Me        | 76%   | Me        | 57%   |
| OMe       | 75%   | OMe       | 55%   |

*Yields were determined by 19F NMR spectroscopy.

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

Table 4. Effect of Ortho Substituents on Regioisomer Formation*

| R         | Yield | R         | Yield |
|-----------|-------|-----------|-------|
| OTu       | 60%   | OTu       | 52%   |
| p-CF3     | 75%   | p-CF3     | 76%   |
| CN        | 76%   | CN        | 76%   |
| NO2       | 75%   | NO2       | 79%   |

*Yield determined by 19F NMR.

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

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

*Yields were determined by 19F NMR spectroscopy. The corresponding ArCl was detected by GC analysis.

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). 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 observed for the L4-supported catalyst presumably arises from a higher rate of C–F reductive elimination provided by the larger adamantyl substituents on phosphorus. 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 S, entry 3) and the application of stable sources of Pd(0) such as Pd(dbab)2 (Table S, entry 4) and Pd(dba)2 (Table S, entry 5), provide diminished yields of the desired product, likely because of inhibition by the dba ligand. 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). 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 S, entry 6). The limitations associated with these various sources...
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. The new precatalyst (P2) is prepared by simply mixing equivalent amounts of ligand L4 and [COD·Pd(CH2TMS)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 N2 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 triflates derived from biologically active/naturally occurring phenols to the corresponding (hetero)aryl fluorides (21a−j).

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

| R       | X            | Yield | 19F ppm | Solvent | Temp. | t (h) |
|---------|--------------|-------|---------|---------|-------|-------|
| 22a     | Br           | 85%   | 90.8    | 2%      | 90°C  | 1 h   |
| 22b     | Br           | 87%   | 90.8    | 2%      | 90°C  | 1 h   |
| 22c     | Br           | 92%   | 90.8    | 2%      | 90°C  | 1 h   |
| 22d     | Br           | 92%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22e     | Br           | 93%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22f     | Br           | 92%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22g     | Br           | 92%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22h     | Br           | 90%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22i     | Br           | 90%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22j     | Br           | 90%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22k     | Br           | 90%   | 90.8    | 2%      | 90°C  | 3 h   |
| 22l     | Br           | 90%   | 90.8    | 2%      | 90°C  | 3 h   |

**Fluorination of (Hetero)aryl Bromides**

Even with the development of P2, the fluorination of unactivated aryl bromides remained challenging. 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 arene (ArH) product (22a−i, Table 7).

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).
Glove-Box-Free Fluorination\textsuperscript{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 (P\textsubscript{2}, 2 mol %) necessary for the Pd-catalyzed fluorination of aryl triflates (1 mmol) (Figure 15a)\textsuperscript{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 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 P\textsubscript{3} (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).

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

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**Figure 14.** (a) Structure of HGPhos (L\textsubscript{5}) and the synthesis of P\textsubscript{3}. (b) Pd-catalyzed fluorination of heterocyclic aryl bromides using P\textsubscript{3}. Isolated yields are reported. *Yield determined by \textsuperscript{19}F NMR spectroscopy.* \textsuperscript{a}TBME was used as the reaction solvent.

**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.
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 [(L6Pd)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 (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 correspond-

**Table 9. Regioselective Fluorination Using P4**

| Entry | Substrate | Reaction Conditions | Yield | Regioselectivity | Remarks |
|-------|-----------|---------------------|-------|-----------------|---------|
| 25a   | 4(OTf)   | 95% (X = OTf), 24 h  | 94%   | 95%:95%         |         |
| 25b   | 4(Br)    | 95% (X = Br), 24 h   | 95%   | 95%:95%         |         |
| 25c   | 4(OTf)   | 95% (X = OTf), 24 h  | 95%   | 95%:95%         |         |
| 25d   | 4(Br)    | 95% (X = Br), 24 h   | 95%   | 95%:95%         |         |
| 25e   | 4(OTf)   | 95% (X = OTf), 24 h  | 95%   | 95%:95%         |         |
| 25f   | 4(Br)    | 95% (X = Br), 24 h   | 95%   | 95%:95%         |         |
| 25g   | 4(OTf)   | 95% (X = OTf), 24 h  | 95%   | 95%:95%         |         |
| 25h   | 4(Br)    | 95% (X = Br), 24 h   | 95%   | 95%:95%         |         |

Isolated yields are shown. *Yield determined by 19F NMR spectroscopy. The regioisomer was not detected by 19F NMR spectroscopy.

**Table 8. Temperature Dependence of Regioisomer Formation**

| Entry | Temperature (°C) | % Yield, X=OTf | % Yield, X=Br |
|-------|------------------|----------------|--------------|
| 1     | 110              | 76% A, 9% B    | 74% A, 18% B |
| 2     | 90               | 20% A, 1% B (35)| 73% A, 15% B |
| 3     | 90               | 89% A, 3% B    | 86% A, 6% B  |
| 4     | 90               | 87% A, 1% B    | 84% A, 5% B  |
| 5     | 80               | 81% A, 6% B    | 87% A, 5% B  |

*Yields were determined by 19F NMR spectroscopy. Values in parentheses indicate % conversion of the starting material. The reaction time was 48 h.

A ligand incorporating the proposed features, AlPhos (L6), and the corresponding Pd(0) precatalyst [(L6Pd)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 (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 correspond-
Studies toward the Fluorination of Five-Membered Heterocycles

Five-membered heterocycles are a common structural element found in pharmaceuticals, but the preparation of their fluorinated analogues remains a significant challenge. 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. 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 ($\Delta G^\ddagger$) 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). 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.

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Notes

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

**Biographies**

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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 Ulysse Medal (2014), the William H. Nichols Award (2016), and the Nagoya Gold Medal Lecture Award (to be received in 2017).

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