In-Depth Assessment of the Palladium-Catalyzed Fluorination of Five-Membered Heteroaryl Bromides

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ABSTRACT: A thorough investigation of the challenging Pd-catalyzed fluorination of five-membered heteroaryl bromides is presented. Crystallographic studies and density functional theory (DFT) calculations suggest that the challenging step of this transformation is C-F reductive elimination of five-membered heteroaryl fluorides from Pd(II) complexes. On the basis of these studies, we have found that various heteroaryl bromides bearing phenyl groups in the ortho position can be effectively fluorinated under catalytic conditions. Highly activated 2-bromoazoles, such as 8-bromocaffeine, are also viable substrates for this reaction.

INTRODUCTION

Five-membered heterocycles are widely prevalent in the pharmaceutical industry. For example, a number of top-selling drugs, including raltegravir (Isentress), sitagliptin (Januvia), atorvastatin (Lipitor), and resperidone (Risperdal), contain at least one five-membered heterocycle (Figure 1, highlighted in blue). The commonality of five-membered heterocycles is due, in part, to their enormous structural diversity and interesting biological and electronic properties. Similarly, (hetero)aryl fluorides are frequently employed in medicinal chemistry due to their enhanced metabolic stability and membrane permeability in comparison to nonfluorinated analogues (Figure 1, highlighted in red). Indeed, all of the drugs shown in Figure 1 contain both a five-membered heterocyclic core and an aryl fluoride.

Considering the independent importance of five-membered heterocycles and aryl fluorides in the pharmaceutical industry, there is a surprising lack of five-membered heteroaryl fluorides that have been prepared and studied for potential biological activity. This is likely due to the limited methods available for the fluorination of five-membered heteroarenes, which include thermal or photochemical Balz–Schiemann reactions, Halex reactions, electrophilic fluorinations of metalated heteroarenes, and direct fluorinations with F2. All of these methods suffer from severe drawbacks in terms of safety, functional group tolerance, generality, and/or formation of complex mixtures of products, which limit their utility. To date, most of the recently developed transition-metal-mediated methods for aryl fluorination have seen limited application to five-membered heteroaryl systems. Thus, there remains a strong need for the development of new methods for the fluorination of five-membered heteroarenes.

We and others have explored the Pd-catalyzed cross-coupling of (hetero)aryl halides with a metal fluoride salt as a simple and general method for the synthesis of (hetero)aryl fluorides. Advances in ligand (L1–L3) and precatalyst (P1–P3, Figure 2B) design have allowed us to convert a variety of nitrogen-containing six-membered heteroaryl triflates and bromides into the corresponding heteroaryl fluorides. Thus, we wondered if this methodology could be extended to the preparation of five-membered heteroaryl fluorides. However, previous stoichiometric and catalytic investigations of cross-coupling reactions involving...
five-membered heteroaryl halides suggest that reductive elimination is significantly more challenging in these reactions in comparison to that with six-membered aryl halides, likely due to the smaller size and increased electron richness of five-membered heteroaryl groups. Considering the already high kinetic barrier for C−F reductive elimination from Pd(II), prior to this work it remained unclear if the reductive elimination of five-membered heteroaryl fluorides was feasible under synthetically relevant conditions. As a second challenge, nitrogen-containing heterocycles can inhibit Pd-catalyzed reactions by coordinating to the Pd center. Herein, we describe catalytic, stoichiometric, and computational studies aimed toward determining if the Pd-catalyzed fluorination of five-membered heteroaryl bromides is a viable transformation with current catalyst systems.

## RESULTS AND DISCUSSION

We began our investigation by attempting the Pd-catalyzed fluorination of an array of five-membered heteroaryl bromides (4−13) under the standard reaction conditions used for the fluorination of six-membered heteroaryl bromides using P1−P3 as precatalysts (Table 1). Unfortunately, the desired product was not observed in any of these reactions (see Table S1 in the Supporting Information for additional examples). In most cases, the starting material was recovered along with trace amounts of the corresponding reduction (Ar−H) product, as judged by GC/MS analysis of the crude reaction mixtures.

![Figure 2.](image-url)

**Figure 2.** (A) Catalytic cycle for the Pd-catalyzed fluorination of aryl halides. (B) Ligands (L1−L3) and precatalysts (P1−P3) for this reaction.

### Table 1. Selected Examples of Unsuccessful Pd-Catalyzed Fluorinations of Five-Membered Heteroaryl Bromides

| HetArBr | 2 eq. AgF | 0.5 eq. KF | 2% P1−3 | HetArF |
|---------|-----------|------------|---------|--------|
| 4a (R = H) | | | | |
| 4b (R = CO2Me) | | | | |
| 5a (R = H) | | | | |
| 5b (R = CO2Me) | | | | |
| 6 (Z = S) | | | | |
| 7 (Z = NSO2Ph) | | | | |
| 8a (R = H) | | | | |
| 8b (R = OPh) | | | | |
| 9a (R = H) | | | | |
| 9b (R = Ph) | | | | |
| 10a (R = SO2Ph) | | | | |
| 10b (R = CPh3) | | | | |
| 10c (R = 4-FFPh) | | | | |
| 11 | | | | |
| 12a (R = H) | | | | |
| 12b (R = CPh3) | | | | |
| 13 | | | | |
| 14 | | | | |

*Reaction conditions: ArBr (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), P1−P3 (2%), solvent (1.0 mL), 130 °C, 14 h. TBME = tert-butyl methyl ether. *Significant decomposition observed by 19F NMR and GC/MS. 1PhSO2F observed by 19F NMR and GC/MS.

Increasing the catalyst loading, reaction temperature, or number of equivalents of AgF/KF did not change the outcome of these reactions. For bromoazoles containing sp2-hybridized nitrogen centers (8−12), catalyst inhibition could account for this observation. Indeed, we have found that the addition of various thiazoles and N-substituted (benz)imidazoles to the otherwise high-yielding Pd-catalyzed fluorination of 4-(nBu)-PhBr inhibits the desired reaction (see Table S2 in the Supporting Information). Herein, we have observed that 1-methyl-1H-pyrazole did not significantly inhibit this reaction, indicating that the unsuccessful fluorinations of 10 and 11 are not necessarily due to catalyst inhibition. Thus, for simple five-membered heteroaryl bromides lacking sp2-hybridized nitrogen centers (e.g., 4−7), as well as bromopyrazoles (10 and 11), at least one of the elementary steps of the catalytic cycle shown in Figure 2 must not be operative under the standard reaction conditions.

On the basis of previous work, we hypothesized that C−F reductive elimination from Pd(II) was the most challenging step in these reactions. We carried out an in-depth study of this transformation in order to improve its efficiency. To this end, we prepared L1-ligated oxidative addition complexes of 2-bromothiophene (13) and 5-acetyl-2-bromothiophene (14) to study their solid-state structures (Figure 3A). Although 13 and 14 proved to be unstable in solution for extended periods of time, single crystals suitable for X-ray diffraction of both complexes could be obtained (Figure 3B).

![Figure 3.](image-url)

**Figure 3.** (A) Synthesis of oxidative addition complexes of five-membered heteroaryl bromides 13 and 14. (B) Solid-state structures of 13 and 14 (ellipsoids shown at 50%). (C) Comparison of the structures of 13 and 14 with that previously reported for 15.
complexes are among the first biaryl monophosphine-ligated oxidative addition complexes of five-membered heteroaryl halides that have been synthesized and characterized. The solid-state structures of 13 and 14 were compared with that of the previously reported complex L1-Pd(4-(CN)Ph)Br (15) to analyze the differences that arise upon replacing a six-membered aryl group with a smaller five-membered heteroaryl group (Figure 3C). Consistent with our previous computational studies, the Ar−Pd−Ar angle is significantly wider in five-membered heteroaryl complexes 13 and 14 (13, 81.48°); 14, 81.21°) than in six-membered aryl complex 15 (79.03°) (Figure 3C). The smaller angle in 15 in comparison to those in 13 and 14 reflects the greater proclivity of this complex to undergo reductive elimination. Notably, only small differences were observed in the Pd−Ar and Pd−ipso bond lengths among these complexes (Figure 3C).

Unfortunately, to date, all attempts to prepare L-Pd(Ar)F complexes bearing five-membered heteroaryl groups have been unsuccessful. Thus, we carried out density functional theory (DFT) calculations to better understand the structure and reactivity of these species (17−19) in comparison to that of the analogous complex bearing a phenyl group (16); the results of these studies are summarized in Table 2 (see the Supporting Information for optimized ground- and transition-state geometries). Consistent with our initial hypothesis, the barrier to reductive elimination for the corresponding 3-thienyl complex 18 was 1.8 kcal/mol lower than for 17, which is also consistent with previous experimental and theoretical findings. Taken together, these crystallographic (Figure 3) and computational (Table 2) studies confirm that C−F reductive elimination of five-membered heteroaryl fluorides is an extremely challenging process and is therefore most likely the rate-limiting step of the Pd-catalyzed fluorinations presented in Table 1.

On the basis of this analysis, we hypothesized that ortho-substituted heteroaryl bromides might be effective substrates for this reaction, due to the known accelerating effect of ortho substituents on reductive elimination. Indeed, DFT calculations confirm that the addition of an phenyl group adjacent to the Pd center (19) decreases the barrier of C−F reductive elimination substantially (21.8 kcal/mol) in comparison to 18 (25.9 kcal/mol). Therefore, we investigated the reactivity of 2-substituted-3-bromothiophenes (Table 3), because bromothiophenes tend to be well-behaved in Pd-catalyzed cross-coupling reactions. Unfortunately, the desired product was not observed with a methyl group in the 2-position (20a, entry 1). The addition of an additional electron-withdrawing group to further promote reductive elimination (20b, entry 2) was still ineffective. However, the corresponding substrate substituted with a bulky phenyl group in the ortho position furnished the desired product 20c, albeit in modest yield (entry 3). This finding represents one of the first transition-metal-catalyzed fluorinations of a five-membered heteroarene. An examination of the solvent and precatalyst employed revealed that tert-butyl methyl ether (TBME) is generally superior to other ethereal (2-MeTHF, cyclohexyl methyl ether, Bu3O) and hydrocarbon (toluene, cyclohexane) solvents and that P3 is consistently superior to P1 and P2 for carrying out this transformation. The incorporation of various electron-withdrawing groups at the S-position of the heteroaryl bromide further improved the yield of the desired product to synthetically useful levels (entries 4−8). Indeed, the presence of an ester (20d), nonenolizable ketone (20e), sulfonamide (20f), or amide (20g) was advantageous at this position, although substrates bearing formyl, acetyl, cyano, and nitro groups underwent significant decomposition during the reaction (see Table S1 in the Supporting Information). It should be noted that isolated products were contaminated with less than 1% of the corresponding reduction product, as judged by GC analysis (see the Supporting Information for details). However, small amounts (<5%) of a second fluorothiophene product, which is likely the regioisomeric product with the fluorine adjacent to the electron-withdrawing group, were detected in the crude reaction mixtures. Consistent with this hypothesis, this side product was not observed during the synthesis of 20h (entry 9), wherein the proposed regioisomer and the desired product are identical compounds. Additionally the use of AlPhos (L3) generally affords better selectivity for the desired product in comparison to HGPSos (L2) (as shown for 20d, entries 4 and 5), which is also the case with six-membered-ring substrates. In all cases except for 20f, the undesired regioisomer could be chromatographically separated from the desired product.

We also investigated whether additional ortho substitution could further promote C−F reductive elimination (entries 10−12). Bromothiophenes bearing additional methyl (20i, entry 10) or phenyl (20j, entry 11) groups adjacent to the bromine atom produced diminished yields in comparison to the corresponding substrate lacking substitution at the 4-position (20h, entry 9). Likewise, the presence of a bulky 1-naphthyl group in the ortho position impeded the formation of 20k (entry 12). The sluggish reactivity of these extremely hindered substrates is likely due to slow oxidative addition of the aryl fluorides.
bromide to the active L3-Pd(0) species. Overall, these studies revealed that only 3-bromothiophenes bearing both phenyl groups in the ortho position and electron-withdrawing groups on the thiophene ring provide synthetically useful yields, which is consistent with our hypothesis that C–F reductive elimination is the challenging process in this transformation.

We next attempted to extend these findings to other five-membered heteroaryl bromides bearing ortho phenyl substituents (Table 4). Consistent with the results highlighted in Table 3 (compare 21b to 20h and 21c to 20c) are consistent with the DFT calculations in Table 2, which show that reductive elimination of 3-thienyl bromides is easier than that of 2-thienyl groups, as well as with literature precedent.17c,d Notably, in the case of 21a, 4% of the corresponding reduction product was isolated along with the desired aryl fluoride.

The fluorinations of ortho-substituted benzo-fused heteroaryl bromides (22 and 23) afforded similar results. Although 3-bromo-2-phenylbenzo[b]thiophene underwent fluorination only sluggishly, furnishing an inseparable mixture of starting material and 22a, the corresponding benzo[b]thiophene underwent clean fluorination to give 22b in high yield. The higher reactivity of benzofurans (22b) in comparison to benzothiophenes (22a) likely reflects the stronger inductive electron-withdrawing effect of the O atom in the benzofuran ring.17c,d,27 Unfortunately, the corresponding 3-bromo-N-sulfonylindole did not undergo fluorination to provide 22c. Consistent with our studies concerning non-benzo-fused bromothiophenes (Tables 3 and 4), the corresponding 2-bromobenzo[b]thiophene bearing an ortho phenyl group provided only a low yield of 23 under the reaction conditions.

We also examined the Pd-catalyzed fluorination of bromoazoles with phenyl groups in the ortho position (24–26, Table 4). Low yields of the desired product were observed with both ortho-substituted 4- (24a,b) and 5-bromothiazoles (25). Thiazoles inhibit the desired reaction, which likely explains the observed decrease in reactivity in comparison to thiophenes (see Table S2 in the Supporting Information). As in previous cases, increasing the catalyst loading did not significantly improve the yield of these reactions. Additionally, none of the desired product was observed with more electron-rich 4-bromo-1H-pyrazoles substituted with a phenyl group in the ortho position (26a,b), regardless of the nitrogen protecting group (for additional examples, see Table S1 in the Supporting Information).

To overcome the generally poor reactivity of bromoazoles, we also attempted the fluorination of electron-deficient 2-bromo-1,3-azoles (Table 5). In these cases, significant formation of side products occurred using TBME as the reaction solvent, and so these reactions were carried out in...
Table 5. Pd-Catalyzed Fluorinations of 2-Bromo-1,3-azoles

| Reagents | Reaction Conditions | Isolated Yield (%) | Notes |
|----------|---------------------|--------------------|-------|
| 27a (R1 = R2 = H): n/o | 0.2 mmol AgF, 0.05 mmol KF, toluene, 130 °C, 14 h | <5% | Yield determined by 19F NMR comparison to an authentic sample. |
| 27b (R1 = Ph, R2 = H): 19% | | | Isolated yield, 0.50 mmol scale. |
| 27c (R1 = Me, R2 = CO2Et): 67% | | | Significant decomposition observed by 19F NMR and GC/MS. |

27a Reaction conditions unless specified otherwise: ArBr (0.10 mmol), AgF (0.20 mmol), KF (0.05 mmol), P3 (2%), toluene (1.0 mL), 130 °C, 14 h. n/o = not observed.

EXPERIMENTAL SECTION

General Procedure for Pd-Catalyzed Fluorination Reactions. In a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube equipped with a stir bar was charged (in this order) with silver fluoride (26 mg, 0.20 mmol, 2.00 equiv), additive (0.05 mmol, 0.50 equiv), P1–P3 (4.0 mg, 2%), aryl bromide (0.10 mmol, 1.00 equiv), and solvent (1.0 mL). The tube was capped, removed from the glovebox, and placed in an oil bath that had been preheated to 130 °C, and the mixture was vigorously stirred for 14 h. (Caution! Perform behind a barrier such as a blast shield!) At this time, the tube was cooled to room temperature, and 1-fluoronaphthalene (20 μL, 1.55 equiv) was added. The reaction mixture was analyzed directly by 19F NMR. Afterward, the reaction mixture was filtered through a silica gel plug, eluted with EtOAc, and analyzed by GC (or GC/MS).

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00631.

Full procedural and spectroscopic data (PDF)
Solid-state structure of 13 (CIF)
Solid-state structure of 14 (CIF)
Cartesian coordinates for the ground-state structures of 16–19 and the corresponding C–F reductive elimination transition-state geometries (XYZ)

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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 coworkers receive royalty payments.

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DEDICATION

Dedicated to the memory of Professor Gregory L. Hillhouse: brilliant chemist, great person and friend.

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