Catalytic C–F Activation

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Palladium-Catalyzed *Ortho*-Selective C–F Activation of Polyfluoroarenes with Triethylsilane: A Facile Access to Partially Fluorinated Aromatics**

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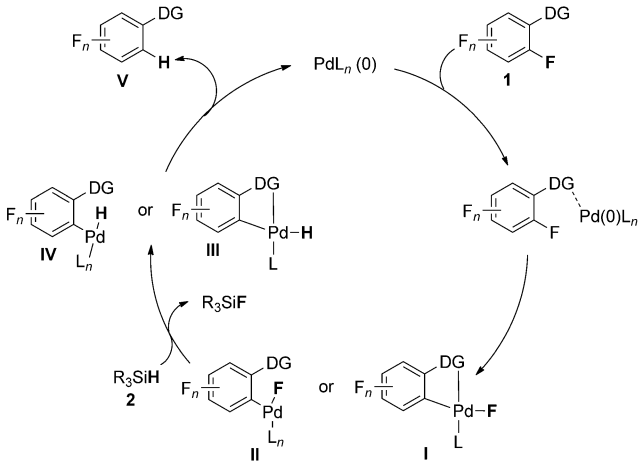
Owing to the unique characteristics of fluorine that often lead to profound changes in physical, chemical, and biological properties of organic molecules when it is incorporated,[1] partially fluorinated aromatics play an important role in life and materials sciences.[2] However, synthetic access to these fluorinated compounds is difficulties[3] and there is only limited commercial availability of fluoroaromatic sources. One attractive approach to partially fluorinated aromatics is selective substitution of polyfluoroarenes through C–F bond activation, as polyfluoroarenes are more readily available and cheaper than their mixed halo or organometallic counterparts. In the past few years, important progress has been made in this field,[4] and the reduction of C–F bonds (hydrodefluorination, HDF) in polyfluoroarenes has become a useful approach to access partially fluorinated aromatics that are difficult to obtain otherwise.[5] However, compared to some aromatic nucleophilic substitution (S_NAr) reactions of polyfluoroarenes that can regioselectively lead to substituted polyfluoroarenes with strong nucleophiles,[4d] the transition-metal-catalyzed chemo- and regioselective transformations of C–F bonds remain a challenge owing to the robustness of the C–F bond and difficulty in adjusting reaction selectivity of different C–F bonds on an aromatic ring.[6] Although examples of selective transition-metal-catalyzed HDF of polyfluoroarenes have been reported, most of them focus on the mechanistic understanding of the HDF cycle.[7,8] In particular, for the palladium-catalyzed HDF reaction, only hydrodefluorination of pentafluoropyridine at the *para* position has been reported to date, in which palladium fluoro or palladium hydrido complexes were used as precatalysts.[9] Therefore, developing a new simple catalytic system with broad substrate scope and high regioselectivity for widespread synthetic applications is appealing.

Azine/diazine (e.g., pyridine, quinoline, quinoxaline) substituted fluorinated aromatics bearing a hydride *ortho* to the heteroaryl group are an important structural motif in light-emitting devices[10] and photocatalysts.[11] However, the limited synthetic methods and commercial availability of fluoroaryl patterns significantly limits the structural and functional diversity of this structural motif in further applications. Continuing our study in palladium-catalyzed polyfluoroarene chemistry,[12] herein, we describe the first example of palladium-catalyzed, chelation-assisted *ortho*-selective C–F activation of polyfluoroarenes with triethylsilane, in which N-containing heterocycles were employed as directing groups. This method provides a useful and facile access to a wide range of azine/diazine substituted fluoroaromatics that are difficult to synthesize otherwise.

We began this study on the basis of the hypothesis that with the aid of a directing group, such as N-containing heterocycles, *ortho* to the fluorine to chelate and direct delivery of palladium catalyst, the oxidative addition of the C–F bond to Pd^0 would be facilitated.[13] Subsequently, the Pd-catalyzed *ortho*-selective hydrodefluorination of polyfluoroarenes would be possible in the presence of a reductant, such as silane (Scheme 1). The formation of thermostable Si–F[14] bond between the newly formed Pd–F complex (**I** or **II**) and silane **2** would be a driving force to promote the generation of palladium hydrido complex (**III** or **IV**) that would release *ortho* hydrodefluorinated aromatics **V** after reductive elimination.



Scheme 1. Mechanism for the palladium-catalyzed, chelation-assisted *ortho*-selective C–F activation of polyfluoroarenes with silane. DG = directing group

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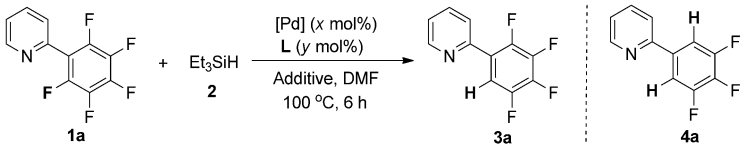
Accordingly, 2-(perfluorophenyl)pyridine **1a** was chose as the model substrate for this study, as the resulting hydrodefluorinated product **3a** is an important structural motif in photoelectronic materials and compound **1a** can be easily accessed by the reaction of cheap and commercially available pentafluorobenzene with 2-bromopyridine.[3b,c] Initially, the reaction of **1a** with triethylsilane **2** was investigated in the presence of $[Pd(PPh_3)_4]$ (10 mol%) in DMF at 100°C, providing **3a** in 11% yield along with 89% starting material **1a** (Table 1, entry 1). Because the base can be functionalized as an activator for the silicon-based cross-coupling reaction,[15] we envisioned that the addition of Cs_2CO_3 may activate triethylsilane **2** and aid the F–H exchange between the newly formed Pd–F complex (**I** or **II**) and Et_3SiH. As a result the conversion of **1a** into the desired product **3a** would be promoted. To our delight, the yield was improved to 34% albeit significant formation of by-product (43% of hydrodefluorinated product at the *para* position was observed) when using Cs_2CO_3 (Table 1, entry 2). The side reactions can be inhibited by switching Cs_2CO_3 to a weaker base, such as Na_2CO_3 (Table 1, entry 3). To further improve the reaction efficiency, a series of reaction parameters, such as different Pd salts, phosphane ligands, solvents, bases, and reaction temperature were examined (Table 1, entries 5–12) (for details see Supporting Information). It turned out that $[\{PdCl(C_3H_5)\}_2]$ showed the best catalytic effect (Table 1, entry 6) (for details see Supporting Information). Among the tested ligands, bidentate ligands dppe and dppb benefited the reaction (Table 1, entries 10 and 12), but a 13% yield of di-hydrodefluorinated product **4a** was observed for dppe (Table 1, entry 10), suggesting that the catalytic system with dppe is more reactive for di-hydrodefluorination. The reaction was also found to be sensitive to the solvents and bases. DMF and Na_2CO_3 were the optimum ones. Other solvents or bases were less or not effective (for details see Supporting Information). Finally, an optimum yield of isolated product (91%) was obtained with utilization of $[\{PdCl(C_3H_5)\}_2]$ (2.5 mol%), dppb (5 mol%), and Na_2CO_3 (0.2 equiv) in DMF at 90°C (Table 1, entry 15). Without Pd catalyst or phosphane ligand no desired product was obtained, thus demonstrating that a Pd-(0/II) catalytic cycle is involved in the reaction (Table 1, entries 17, 18). Additionally, the di-hydrodefluorinated **4a** can also be obtained in good yield (77%) by using $[\{PdCl(C_3H_5)\}_2]$ (3.75 mol%), dppe (7.5 mol%), and Et_3SiH (2.5 equiv) at 120°C (Table 1, entry 19).

Table 1: Palladium-catalyzed *ortho*-selective C–F activation of 2-(perfluorophenyl)-pyridine **1a** with triethylsilane.[a]



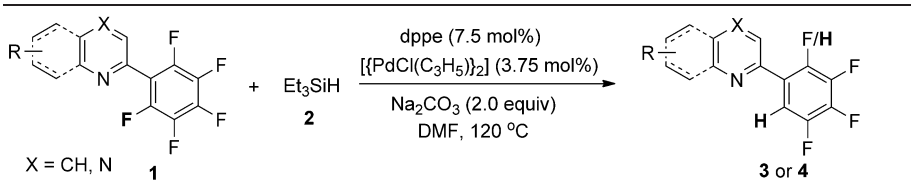
Entry	Pd complex, *x* [mol%]	L, *y* [mol%]	additive [equiv]	**3a** Yield [%][b]
1	$[Pd(PPh_3)_4]$, 10	–	–	11
2	$[Pd(PPh_3)_4]$, 10	–	Cs_2CO_3 [2.0]	34
3	$[Pd(PPh_3)_4]$, 10	–	Na_2CO_3 [2.0]	32
4	$[Pd(PPh_3)_4]$, 10	–	$NaHCO_3$[2.0]	24
5	$[Pd(PPh_3)_4]$, 10	**L1**, 20	Na_2CO_3 [2.0]	75
6	$[\{PdCl(C_3H_5)\}_2]$, 5	**L1**, 20	Na_2CO_3 [2.0]	89
7	$[\{PdCl(C_3H_5)\}_2]$, 2.5	**L1**, 10	Na_2CO_3 [2.0]	66
8	$[\{PdCl(C_3H_5)\}_2]$, 2.5	SPhos, 10	Na_2CO_3 [2.0]	14
9	$[\{PdCl(C_3H_5)\}_2]$, 2.5	XPhos, 10	Na_2CO_3 [2.0]	6
10	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppe, 5	Na_2CO_3 [2.0]	73[c]
11	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppp, 5	Na_2CO_3 [2.0]	68[e]
12	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppb, 5	Na_2CO_3 [2.0]	87 (69)[f]
13[d]	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppb, 5	Na_2CO_3 [2.0]	90 (81)[f]
14[d]	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppb, 5	Na_2CO_3 [1.0]	89[f]
15[d]	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppb, 5	Na_2CO_3 [0.2]	99 (91)[e]
16[d]	$[\{PdCl(C_3H_5)\}_2]$, 2.5	dppb, 5	–	63[e]
17[d]	$[\{PdCl(C_3H_5)\}_2]$, 2.5	–	Na_2CO_3 [0.2]	NR
18[d]	–	dppb, 5	Na_2CO_3 [0.2]	NR
19	$[\{PdCl(C_3H_5)\}_2]$, 3.75	dppe, 7.5	Na_2CO_3 [2.0]	(13)[g]

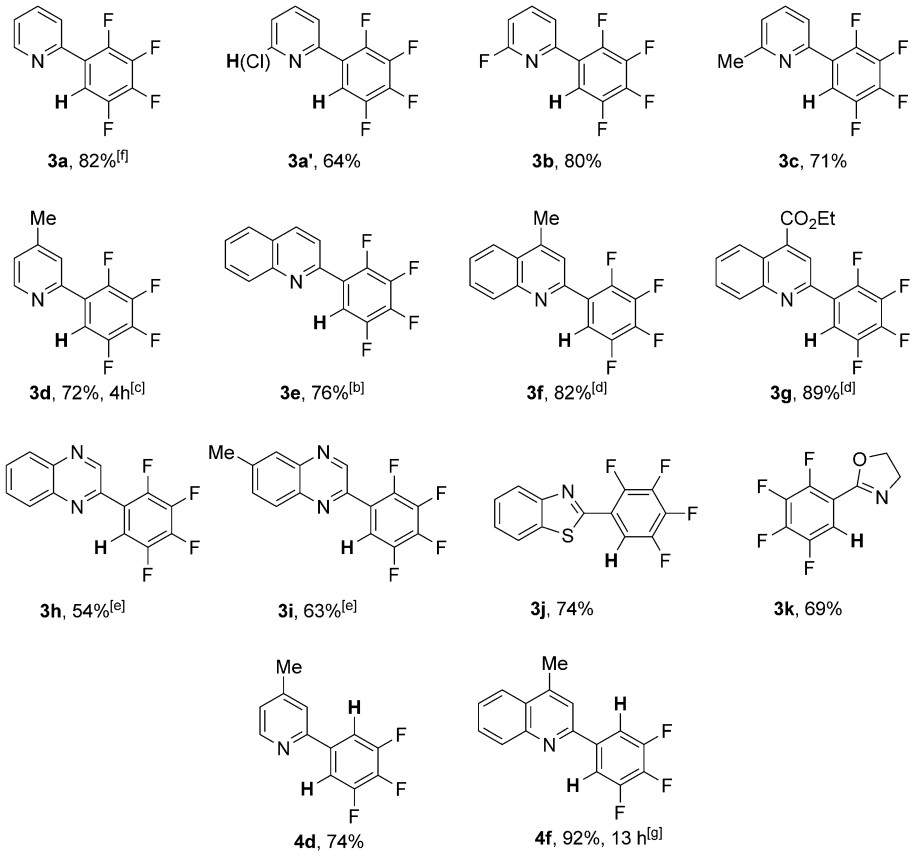
[a] Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), Et_3SiH (2.0 equiv), DMF (1.0 mL). **L1**, P(biphenyl-2-yl)Cy_2. [b] NMR yield determined by ^{19}F NMR using fluorobenzene as internal standard, yield of isolated product is in parenthesis. [c] 13% yield of **4a** was observed. [d] Reaction conducted at 90°C. [e] No **4a** was observed. [f] Less than 5% of **4a** were observed. [g] Using 2.5 equiv of Et_3SiH, and reaction conducted at 120°C for 8 h. 77% yield of **4a** was isolated.

To explore the substrate scope of this method, a variety of N-containing heterocyclic pentafluorobenzenes **1**[16] were investigated. We found that the optimum reaction conditions for **1a** were not always ideal for other substrates owing to their relatively "inertness". Accordingly, on the basis of the above results (Table 1, entries 10 and 19), a more reactive catalytic system using $[\{PdCl(C_3H_5)\}_2]$ (3.75 mol%), dppe (7.5 mol%), Na_2CO_3 (2.0 equiv),[17] and Et_3SiH (2.0 equiv) was identified, which allowed hydrodefluorination of a wide range of N-heterocyclic-substituted pentafluorobenzenes **1** in high efficiency and *ortho* selectivity (Table 2).

Substrates bearing functionalized pyridyl or quinolinyl groups underwent the reaction smoothly (Table 2, **3a**–**3g**). In particular, the ester group, which is useful during the downstream transformations, was stable under the reaction conditions (Table 2, **3g**). Good *chemo*- and *regio*-selectivity was observed for **3b** in which the *ortho* C–F bond on the pyridine ring was intact (Table 2, **3b**), while a reduction of C–Cl bond was observed for 2-chloro pyridyl pentafluorobenzene, demonstrating the higher bond dissociation energies of the C–F bond than the C–Cl bond (Table 2, **3a′**). It should be pointed out that benzothiazole and oxazoline functionalities were also applicable (Table 2, **3j** and **3k**), thus providing an efficient way to diverse structures for further applications. However, for 2-quinaxolinyl-substituted substrates, using $[Pd(PPh_3)_4]$ instead of $[\{PdCl(C_3H_5)\}_2]$ furnished the corresponding products more effective with moderate to good yields (Table 2, **3h** and **3i**). The usefulness of this method is also shown by facile access of **3a** in a 1-gram scale synthesis, thus indicating the good reliability of the process (Table 2, **3a**). To further demonstrate the versatility of this method, the di-hydrodefluorinated products **4d** and **4f** can also be obtained from **1d** and **1f**, respectively, in high efficiency (Table 2, **4d** and **4f**). Thus, through this strategy,

Table 2: Palladium-catalyzed *ortho*-selective C–F activation of N-containing-heterocycle pentafluorobenzenes **1** with triethylsilane.[a]





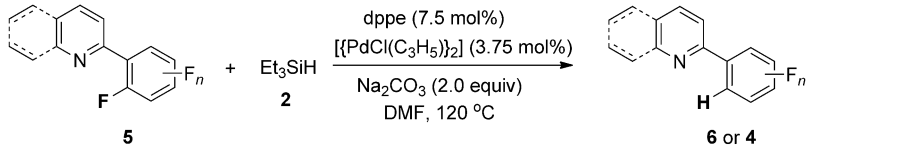
[a] Reaction conditions (unless otherwise specified): **1** (0.4 mmol), Et_3SiH (2.0 equiv), DMF (2.0 mL), 8 h. All reported reaction yields are of isolated products. [b] Using 2.5 mol% [{PdCl(C_3H_5)}$_2$], 5 mol% dppb, 0.2 equiv of Na_2CO_3, 90°C, 8 h. [c] Reaction conducted at 90°C. [d] Using 1.5 equiv of Et_3SiH and reaction run for 3–4 h. [e] Using 10 mol% [$Pd(PPh_3)_4$] and reaction conducted at 120°C for 13 h. [f] 1 gram scale reaction using 2.5 mol% [{PdCl(C_3H_5)}$_2$], 5 mol% dppb, and 0.2 equiv of Na_2CO_3 at 90°C. [g] Using 2.5 equiv of Et_3SiH.

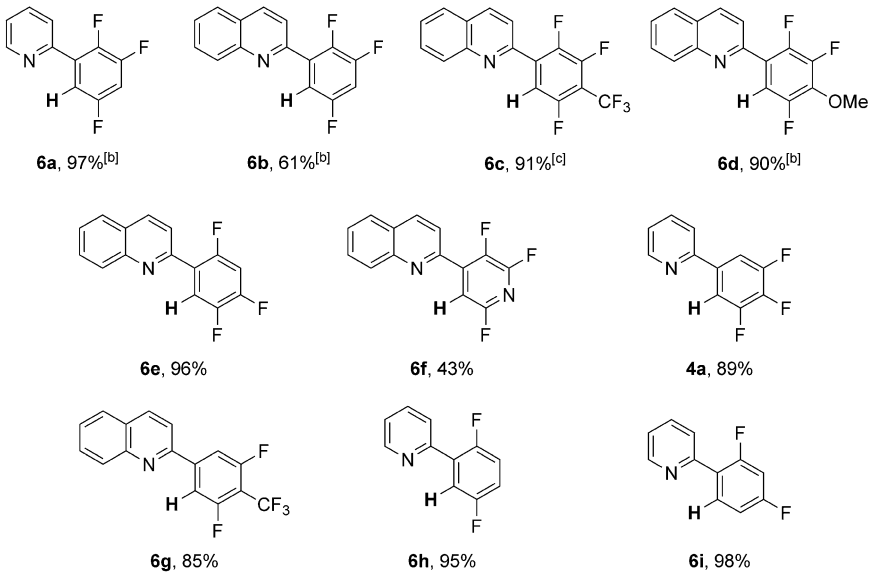
a series of partially fluorinated arenes, which are difficult to prepare otherwise, can be rapid access from simple and readily available starting materials.

The hydrodefluorination of various fluoroarenes **5**[16] containing 3–4 fluorine atoms with Et_3SiH were also tested and representative results are illustrated in Table 3.Generally, compared to pentafluorobenzene derivatives **1**, higher yields were obtained for substrates **5**. Importantly, even for trifluorobenzene derivatives **5h** and **5i**, almost quantitative yields of the corresponding products **6h** and **6i** were obtained (Table 3, **6h** and **6i**), providing a highly efficient way to access these important structural motifs for photoelectronic materials.[10,11] Fluorinated pyridine was also a suitable substrate with reasonable yield obtained (Table 3, **6f**). It was noteworthy that unsymmetrical tetrafluorobenzene derivative **5e** exclusively afforded **6e**. The isomer generated from the reduction of the other C–F bond *ortho* to the quinolinyl group was not observed (Table 3, **6e**). This result may be attributed to the electron-withdrawing effect of an additional fluorine atom attached to C-3, which activates the C–F bond at the 2-position so that oxidative addition of Pd^0 to the C–F bond occurs preferentially at this site. The X-ray crystallographic analysis of **6e** further confirmed its structure.[18] It was also possible to efficiently generate di-hydrodefluorinated products by a sequential C–F bond activation strategy. For example, partially fluorinated aromatics **4a** and **6g** were efficiently synthesized from compounds **3a** and **6c**, respectively (Table 3, **4a** and **6g**).

In an attempt to understand the proposed mechanism illustrated in Scheme 1, the following experiments were performed (Scheme 2). Unexpectedly, when the reaction of **1e** with [{PdCl(C_3H_5)}$_2$] (0.5 equiv) and dppe (1.0 equiv) in the presence of Et_3SiH and Na_2CO_3 was conducted at room temperature, formation of the Pd–Cl complex **II-2** instead of Pd–F complex **II-1** or **I** (see Scheme 1) was observed (Scheme 2a). Further investigation revealed that only trace amount of desired product **3e** was observed under catalytic reaction conditions (Scheme 2b). These findings indicated that an active Pd^0 species was generated in the reaction, which facilitated the oxidative addition of the C–F bond to Pd^0. As to the formation of **II-2**, we reasoned that when [{PdCl(C_3H_5)}$_2$] was treated with Et_3SiH and dppe, besides the formation of Pd^0 species, Et_3SiCl was also generated.[19] Subsequently, Et_3SiCl reacted with Pd–F complex **II-1** generated by the oxidative addition of C–F to Pd^0 to provide Pd–Cl complex **II-2** (Scheme 2c).[9a] The structure of **II-2** was confirmed by X-ray crystallographic analysis (see Supporting Information Figure S2).[18] Subjecting of a solution of **II-2** in DMF, in the presence of Et_3SiH and Na_2CO_3, to heating at 90°C indeed afforded the final product **3e** (Scheme 2d). Thus, these results demonstrate that the catalytic cycle involves the N-containing directing group chelation-assisted *ortho*-selective oxidative addition of the C–F bond to Pd^0 and reductive elimination of the hydrodefluorinated products.

Table 3: Palladium-catalyzed *ortho*-selective C–F activation of N-containing-heterocycle fluoroarenes **5** with triethylsilane.[a]

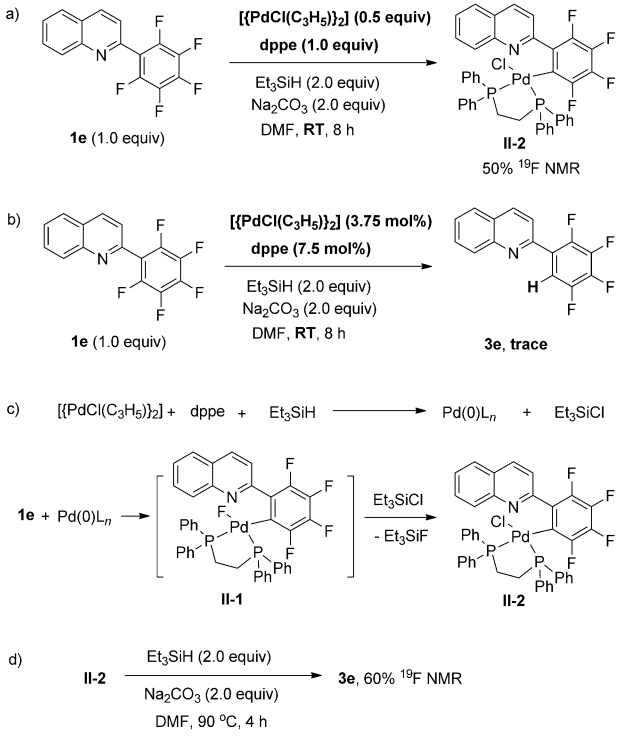




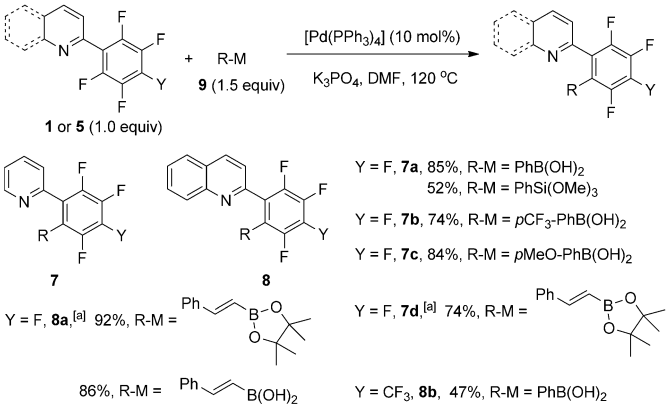
[a] Reaction conditions (unless otherwise specified): **1** (0.4 mmol), Et_3SiH (2.0 equiv), DMF (2.0 mL), 8–13 h. All reported reaction yields are of isolated product. [b] Reaction conducted at 90 °C. [c] Using 2.5 mol% $[\{PdCl(C_3H_5)\}_2]$, 5 mol% dppb, 0.2 equiv of Na_2CO_3 at 90 °C, 6 h.

To illustrate the potential applications of this method, the construction of C–C bond by C–F bond activation has also been examined.[20] As shown in Scheme 3, compounds **7** and **8** can be easily prepared by palladium-catalyzed cross-coupling of **1** or **5** with various aryl and alkenyl species including boronic acids, borates and silanes.

In conclusion, we have developed an efficient and versatile method for preparation of partially fluorinated aromatics by Pd-catalyzed, chelation-assisted, *ortho*-selective C–F bond activation of N-heterocycle-substituted polyfluoroarenes with Et_3SiH. Additionally, this method can also be extended to C–C bond formation by C–F bond activation. The simple catalytic system, broad substrate scope, operational simplicity, high reaction efficiency, and excellent regioselectivity of this route make it a useful method to access a series of interesting azine/dizine-substituted fluoroarenes for drug discovery and photoelectronic devices. Further studies to uncover the detailed mechanism as well as other derivative reactions are now in progress.



Scheme 2. Experiments for mechanistic studies.



Scheme 3. Synthesis of compounds **7** and **8** by C–F bond activation. [a] $[PdCl_2(dppf)]$ (5 mol%), X-phos (10 mol%), K_2CO_3 (1.0–2.0 equiv), DMF, 100 °C. X-phos, dicyclohexyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine.

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[16] Compounds **1** and **5** can be easily prepared through transition-metal-catalyzed cross-coupling of commercially available polyfluoroarenes with heteroaryl halides or tosylates, see Refs. [3c] and [12d].

[17] Using less than 2.0 equiv of Na_2CO_3 led to lower yields.

[18] CCDC 915389 (**6e**), 918117 (**II-2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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