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 transitionmetal-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.

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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 poly-fluoroarene 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 Pd⁰ 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

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

€ N F	F + Et ₃ SiH - F 2	[Pd] (x mol%) L (y mol%) Additive, DMF 100 °C, 6 h	H F F	
		1 I [3a ;	4a
Entry	Pa complex, x [mol %	j L , γ [moi %]	additive [equiv]	sa rield [%]
1	[Pd(PPh ₃) ₄], 10	-	-	11
2	[Pd(PPh ₃) ₄], 10	-	Cs ₂ CO ₃ [2.0]	34
3	[Pd(PPh ₃) ₄], 10	-	Na ₂ CO ₃ [2.0]	32
4	[Pd(PPh ₃) ₄], 10	-	NaHCO ₃ [2.0]	24
5	[Pd(PPh ₃) ₄], 10	L1 , 20	Na ₂ CO ₃ [2.0]	75
6	[{PdCl(C ₃ H ₅)} ₂], 5	L1, 20	Na ₂ CO ₃ [2.0]	89
7	[{PdCl(C ₃ H ₅)} ₂], 2.5	L1 , 10	Na ₂ CO ₃ [2.0]	66
8	[{PdCl(C ₃ H ₅)} ₂], 2.5	SPhos, 10	Na ₂ CO ₃ [2.0]	14
9	[{PdCl(C ₃ H ₅)} ₂], 2.5	XPhos, 10	Na ₂ CO ₃ [2.0]	6
10	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppe, 5	Na ₂ CO ₃ [2.0]	73 ^[c]
11	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppp, 5	Na ₂ CO ₃ [2.0]	68 ^[e]
12	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppb, 5	Na ₂ CO ₃ [2.0]	87 (69) ^[f]
13 ^[d]	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppb, 5	Na ₂ CO ₃ [2.0]	90 (81) ^[f]
14 ^[d]	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppb, 5	Na ₂ CO ₃ [1.0]	89 ^[f]
15 ^[d]	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppb, 5	Na ₂ CO ₃ [0.2]	99 (91) ^[e]
16 ^[d]	[{PdCl(C ₃ H ₅)} ₂], 2.5	dppb, 5	-	63 ^[e]
17 ^[d]	[{PdCl(C ₃ H ₅)} ₂], 2.5	-	Na ₂ CO ₃ [0.2]	NR
18 ^[d]	-	dppb, 5	Na ₂ CO ₃ [0.2]	NR
19	[{PdCl(C ₃ H ₅)} ₂], 3.75	dppe, 7.5	Na ₂ CO ₃ [2.0]	(13) ^[g]

[a] Reaction conditions (unless otherwise specified): **1a** (0.2 mmol), Et₃SiH (2.0 equiv), DMF (1.0 mL). **L1**, P(biphenyl-2-yl)Cy₂. [b] NMR yield determined by ¹⁹F 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 Et₃SiH, and reaction conducted at 120°C for 8 h. 77% yield of **4a** was isolated.

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 Et₃SiH. 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 Cs₂CO₃ (Table 1, entry 2). The side reactions can be inhibited by switching Cs₂CO₃ to a weaker base, such as Na₂CO₃ (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(C₃H₅)}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-hydro-defluorinated 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 Na₂CO₃ 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 Na₂CO₃ (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 Et₃SiH (2.5 equiv) at 120°C (Table 1, entry 19).

To explore the substrate scope of this method, a variety of N-containing heterocyclic pentafluorobenzenes $\mathbf{1}^{[16]}$ were investigated. We found that the optimum reaction conditions for $\mathbf{1a}$ 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(C₃H₅)}₂] (3.75 mol%), dppe (7.5 mol%), Na₂CO₃ (2.0 equiv),^[17] and Et₃SiH (2.0 equiv) was identified, which allowed hydrodefluorination of a wide range of N-heterocyclicsubstituted pentafluorobenzenes $\mathbf{1}$ 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(PPh₃)₄] instead of [{PdCl(C₃H₅)}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,

sively 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-with-

drawing 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 Pd⁰ to the C-F bond

occurs preferentially at this site.

The X-ray crystallographic analysis of 6e further confirmed its struc-

ture.^[18] It was also possible to efficiently generate di-hydrode-

fluorinated products by a sequential C-F bond activation strategy. For example, partially fluorinated

aromatics 4a and 6g were effi-

ciently synthesized from com-

pounds 3a and 6c, respectively

proposed mechanism illustrated in Scheme 1, the following experi-

 (C_3H_5)]₂] (0.5 equiv) and dppe

(1.0 equiv) in the presence of Et₃SiH and Na₂CO₃ 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 (Sche-

revealed that only trace amount

of desired product 3e was observed

under catalytic reaction conditions

(Scheme 2b). These findings indi-

cated that an active Pd⁰ species was

generated in the reaction, which

Further investigation

were (Scheme 2). Unexpectedly, when the reaction of 1e with [{PdCl-

In an attempt to understand the

performed

(Table 3, 4a and 6g).

ments

me 2 a).

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), Et₃SiH (2.0 equiv), DMF (2.0 mL), 8 h. All reported reaction yields are of isolated products. [b] Using 2.5 mol% [{PdCl(C₃H₅)}₂], 5 mol% dppb, 0.2 equiv of Na2CO3, 90°C, 8 h. [c] Reaction conducted at 90°C. [d] Using 1.5 equiv of Et3SiH and reaction run for 3-4 h. [e] Using 10 mol% [Pd(PPh₃)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 Na₂CO₃ at 90 °C. [g] Using 2.5 equiv of Et₃SiH.

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 $\mathbf{5}^{[16]}$ containing 3-4 fluorine atoms with Et₃SiH 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, 6 f). It was noteworthy that unsymmetrical tetrafluorobenzene derivative 5e exclu-

facilitated the oxidative addition of the C–F bond to Pd⁰. As to the formation of **II-2**, we reasoned that when $[{PdCl(C_3H_5)}_2]$ was treated with Et₃SiH and dppe, besides the formation of Pd⁰ species, Et₃SiCl was also generated.^[19] Subsequently, Et₃SiCl reacted with Pd-F complex II-1 generated by the oxidative addition of C-F to Pd⁰ 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 Et₃SiH and Na₂CO₃, 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 Pd⁰ 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, orthoselective C-F bond activation of Nheterocycle-substituted polyfluoroarenes with Et₃SiH. 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.



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