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Pd-Catalyzed Direct Arylation of Polyfluoroarenes on Water under Mild Conditions Using PPh_3 Ligand

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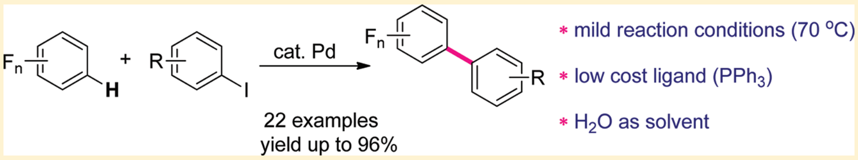
Ⓢ *Supporting Information*

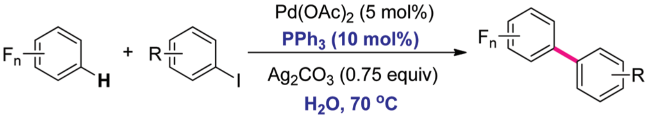


ABSTRACT: We report a Pd-catalyzed direct arylation of polyfluoroarenes with aryl iodides. The advantages of this reaction are its high reaction efficiency, excellent functional group compatibility, mild reaction conditions (70 °C), inexpensive PPh_3 ligand, and use of pure water as reaction medium. The usefulness of this reaction has also been demonstrated by rapid preparation of highly functionalized polyfluoroarenes via iterative Pd-catalyzed C−H bond functionalization.

Biaryls containing polyfluoroarene structural moieties are interesting compounds in materials and life sciences.[1] In particular, such fluorinated compounds play an important role as active materials in electronic devices, such as organic light-emitting diodes (OLEDs) and field-effect transistors (FETs).[1d] Compared to the nonfluorinated counterparts, owing to its strong electron-withdrawing effect, the polyfluorinated aryl group can significantly enhance the photoluminescence efficiency, minimize the self-quenching behavior, and lower the HOMO and LUMO energy levels.[1d] Hence, it is of great synthetic interest to develop an efficient reactions to access these useful compounds. In the past few years, significant progress has been made in the transition-metal-catalyzed direct formation of C−C bonds between polyfluoroarenes and arylhalides/arenes.[2] As an alternative C−C bond-forming strategy, this direct arylation of C−H bonds[3] represents a more efficient access to the polyfluoroaryl-aryls. These reactions are straightforward and attractive; however, the majority of these reactions occur at very high temperature (often above 80 °C) or employ expensive electron-rich bulky phosphine ligand,[2] which restricts their widespread synthetic applications, in particular in large-scale processes. Consequently, to overcome these drawbacks, it is still highly desirable to develop efficient mild reactions by using low cost and readily available ligands.

Recently, from the economical and environmental point of view, the use of water as solvent has attracted much interests because of its innate advantages, such as low cost, ready availability, nontoxicity, and nonflammability.[4] Moreover, the use of water as solvent can also potentially improve reactivities and selectivities, simplify the workup procedures, and allow mild conditions.[4,5] Despite the advantages that water possess, the transition-metal-catalyzed direct arylation of polyfluoroarenes by using pure water as reaction medium without the addition of any organic cosolvents has not been reported.[6] As a part of our ongoing research,[7,2e] herein we demonstrated our results on the Pd-catalyzed direct arylation of polyfluoroarenes with aryl iodides, which featured its high reaction efficiency, excellent functional group compatibility, mild reaction conditions (70 °C), inexpensive PPh_3 ligand, and use of pure water as reaction medium (Scheme 1).

Scheme 1. Pd-Catalyzed Direct Arylation of Polyfluoroarenes with Aryl Iodides



We began this study by choosing pentafluorobenzene **1** and 1-iodo-4-methylbenzene **2a** as model substrates (Table 1). Initially, a $Pd(OAc)_2/PPh_3$ catalytic system, which was successfully used in our previous work on the direct benzylation and allylation of polyfluoroarenes,[7b,d] was investigated. However, when the reaction was carried out with $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), and K_2CO_3 (2.0 equiv) in H_2O at 80 °C, no desired product **3a** was afforded (Table 1, entry 1). Given that silver salts are commonly employed to abstract halide anions from transition-metal complexes, thus rendering them more electrophilic and facilitating the catalytic cycle,[8] Ag_2CO_3 (0.5 equiv) in conjunction with K_2CO_3 (2.0 equiv) was examined, providing **3a** in 89% yield (Table 1, entry 2). A comparable yield was also obtained by sole use of Ag_2CO_3 (Table 1, entry 3), indicating the essential roles of the silver salt, which may function as both a base and halide scavenger in the palladium catalytic cycle. However, the exact mechanism of

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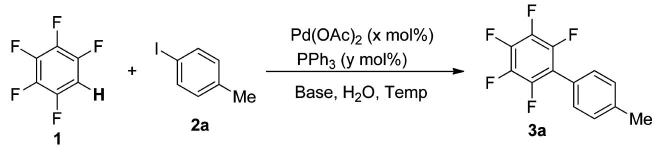
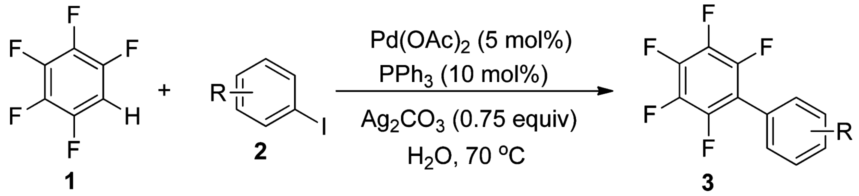
Table 1. Optimization of Pd-Catalyzed Direct Arylation of Pentafluorobenzene 1 with 1-Iodo-4-methylbenzene 2a[a]

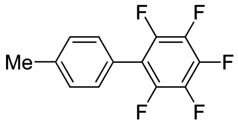


entry	**1** (equiv)	**2a** (equiv)	*x*	*y*	base (equiv)	temp (°C)	time (h)	yield (%)[b]
1	3.0	1	10	20	K_2CO_3 (2.0)	80	10	NR
2	3.0	1	10	20	K_2CO_3 (2.0) Ag_2CO_3 (0.5)	80	10	89
3	3.0	1	10	20	Ag_2CO_3 (1.0)	80	10	90
4	3.0	1	5	10	Ag_2CO_3 (1.0)	80	10	80
5	3.0	1	5	10	Ag_2CO_3 (0.75)	70	10	78
6	2.0	1	5	10	Ag_2CO_3 (0.75)	70	10	82
7	1.5	1	5	10	Ag_2CO_3 (0.75)	70	16	86
8	1.5	1	5	10	Ag_2CO_3 (0.75)	70	24	90
9	1.5	1	5	10	Ag_2CO_3 (0.75)	50	24	74
10	1.5	1	5		Ag_2CO_3 (0.75)	70	24	NR
11	1.5	1		10	Ag_2CO_3 (0.75)	70	24	NR

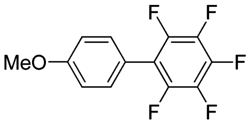
[a] Reaction conditions (unless otherwise specified): **1** (0.9 mmol), H_2O (2.5 mL). [b] Isolated yield.

Table 2. Pd-Catalyzed Direct Arylation of Pentafluorobenzene 1 with Aryl Iodides 2[a]

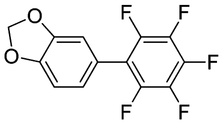




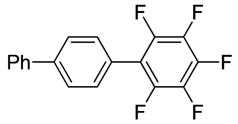
3a, 90%



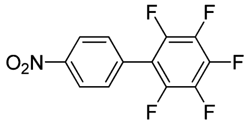
3b, 91%



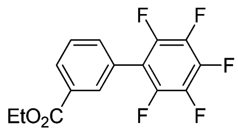
3c, 88%



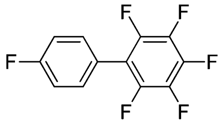
3d, 82%



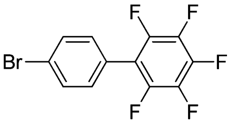
3e, 91%



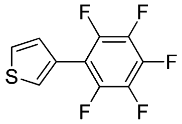
3f, 96%



3g, 73%



3h, 83%



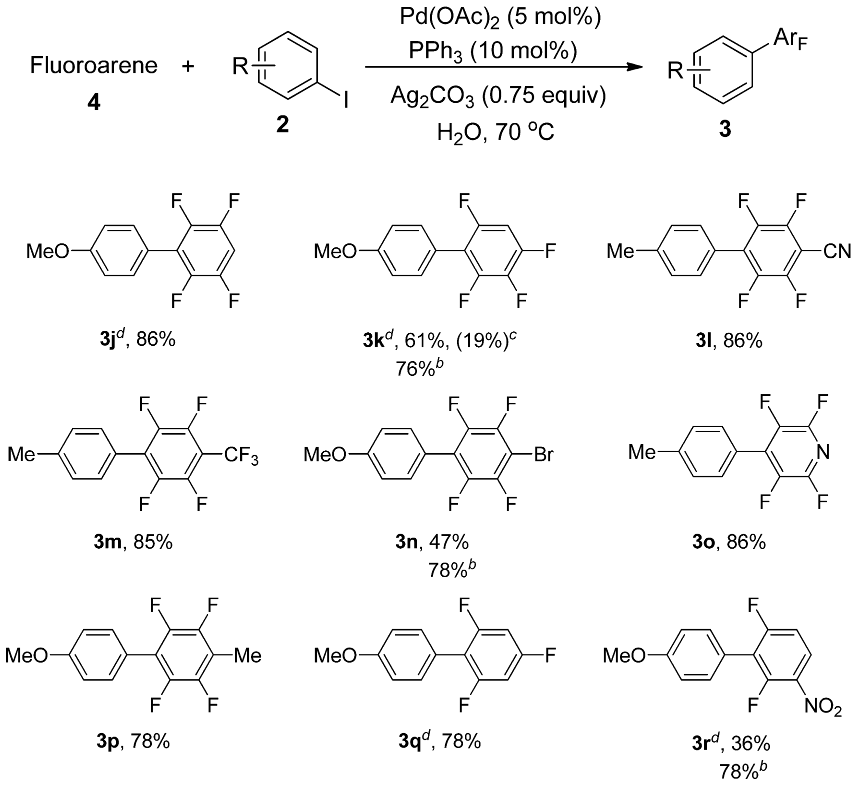
3i, 40%
70%[b]

[a] Reaction conditions (unless otherwise specified): **1** (1.5 equiv), **2** (0.9 mmol), H_2O (2.5 mL), 70 °C, 24 h. All reported yields are isolated yields. [b] Reaction run in DMF.

the silver salt in the catalytic cycle is unclear at this stage. Further optimizing the reaction conditions, we found that 90% yield of **3a** still could be provided by reducing the $Pd(OAc)_2$ loading to 5 mol % with utilization of 1.5 equiv of **1** and 0.75 equiv of Ag_2CO_3 at 70 °C for 24 h (Table 1, entry 8). A decreased yield (74%) was observed when the reaction temperature was decreased to 50 °C (Table 1, entry 9). The absence of PPh_3 or $Pd(OAc)_2$ did not furnish **3a**, demonstrating the pivotal role of the Pd-catalyst in the catalytic cycle (Table 1, entries 11 and 12).

A variety of pentafluorophenyl-aryls were generated by the present method, and good to high yields were obtained (Table 2). Substrates bearing electron-rich or electron-withdrawing groups furnished the corresponding products smoothly. Typical functional groups, such as ester and nitro, are also tolerated by the reaction conditions (**3e**–**f**). Importantly, the successful formation of **3h** with intact bromide provides a good

Table 3. Pd-Catalyzed Direct Arylation of Fluoroarene 4 with Aryl Iodides 2[a]



3j[d], 86%

3k[d], 61%, (19%)[c]
76%[b]

3l, 86%

3m, 85%

3n, 47%
78%[b]

3o, 86%

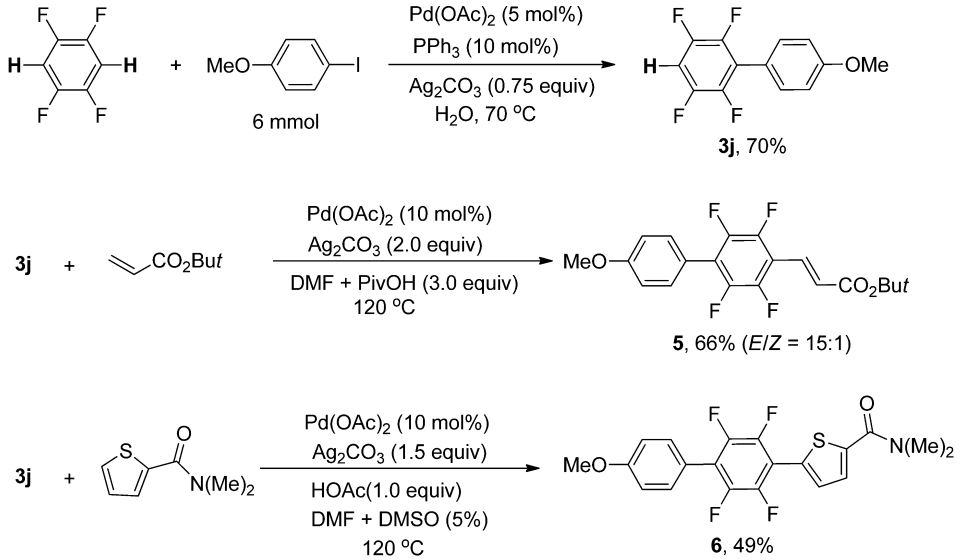
3p, 78%

3q[d], 78%

3r[d], 36%
78%[b]

[a] Reaction conditions (unless otherwise specified): **4** (1.5 equiv), **2** (0.9 mmol), H_2O (2.5 mL), 70 °C, 24 h. All reported yields are isolated yields. [b] Reaction run in DMF. [c] Yield of diarylated product. [d] **4** (4.0 equiv), **2** (0.6 mmol), H_2O (2.5 mL), 70 °C, 24 h.

Scheme 2. Iterative Pd-Catalyzed C−H Bond Functionalization



3j, 70%

5, 66% (*E*/*Z* = 15:1)

6, 49%

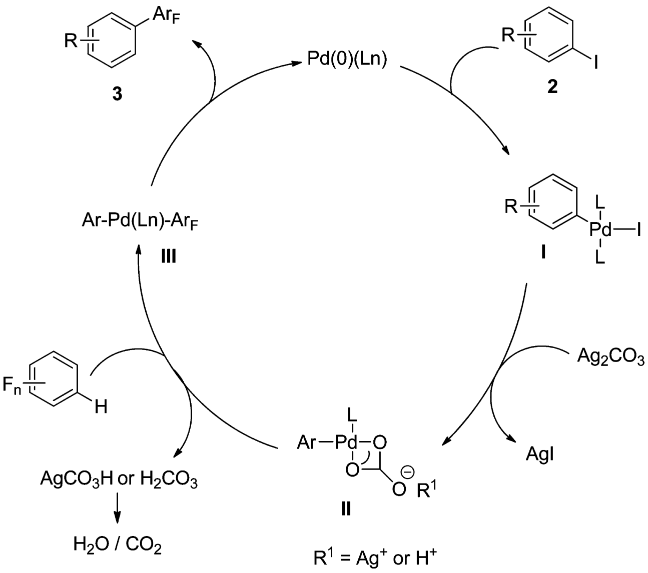
opportunity for further formation of carbon−carbon or carbon−heteroatom bonds by transition-metal-catalyzed coupling and other reactions (**3h**). For example, compound **3h** has been directly introduced into DNA to study the hydrophobic, aromatic pairs that are orthogonal to the natural base-pair in their recognition properties.[9] For 3-thiophenyl substituted **3i**, only a reasonable yield was afforded due to the formation of byproduct and lack of consumption of starting material. To address this issue, DMF was employed, providing **3i** in 70% yield (**3i**).

To further ascertain the scope of this methodology, a variety of fluoroarenes **4** with aryl iodides were investigated (Table 3). For substrates bearing 3 or 4 fluorine atoms contain more than one reaction site, moderate to good yields of monoaryl substituted products were still observed (Table 3, **3j**−**k**, **3q**). Although 2,4-difluoro-1-nitrobenzene furnished **3r** in low yield under standard conditions, the utility of DMF could improve the yield to 78% with a good regioselectivity (Table 3, **3r**). Again useful functional groups showed good tolerance to the reaction conditions (Table 3, **3l**, **3n**, **3o**, and **3r**).

The usefulness of this protocol can also be featured by rapid preparation of highly functionalized polyfluoroarenes via iterative Pd-catalyzed C−H bond functionalization. As shown in Scheme 2, after selective Pd-catalyzed direct C−H bond arylation of 1,2,4,5-tetrafluorobenzene, the resulting compound **3j** was directly alkenylated by Pd-catalyzed oxidative olefination[7a] to furnish a large conjugated system **5** in a highly efficient manner. It should be mentioned that the gram-scale reaction of **2b** still provided good yield. Similarly, a thiophene substituted polyfluoroarene **6** can also be obtained by Pd-catalyzed dehydrogenative cross-coupling.[2e] This strategy provides an efficient protocol to access diversified polyfluoroarene-thiophene structure, a class of important fluorinated compounds in electronic devices.

Although the exact mechanism of the reaction is still not clear, on the basis of the results reported by others,[2a,b,10,11] a plausible mechanism is proposed and shown in Scheme 3. An oxidative addition of aryl iodides **2** to a zero valent Pd species is envisioned to take place as an initial step leading to a Pd-aryl intermediate **I**. After the silver salt abstracts iodide ligand from the palladium(II) complex **I**, a palladium complex **II** would be generated. Complex **II** subsequently goes through the concerted metalation-deprotonation (CMD) process[11] to form **III**. As the final step of the catalytic cycle, reductive elimination of **III** produces polyfluoaryl-aryls upon the regeneration of Pd(0) species.

Scheme 3. Plausible Mechanism of the Pd-Catalyzed Direct Benzylation of Polyfluoroarenes



In conclusion, we have developed a mild reaction (70 °C) for Pd-catalyzed direct arylation of polyfluoroarenes with aryl iodides. The reaction makes use of inexpensive PPh_3 as ligand and pure water as reaction medium and affords high yields and excellent functional group compatibility, which provides a convenient protocol for the preparation of polyfluoaryl-aryls of interest in functional materials and life science.

■ EXPERIMENTAL SECTION

General Procedure for Pd-Catalyzed Direct Arylation of Polyfluoroarenes with Aryl Iodides on Water. To a septum-capped 25 mL Schlenk tube were added $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3 (0.75 equiv), and aryl iodide (0.9 mmol, 1.0 equiv) under N_2, followed by fluoroarene (1.5 equiv). After stirring for 1 min, deionized water (2.5 mL) was added, and the reaction mixture was warmed to 70 °C (oil bath) and stirred for 24 h. The reaction was cooled to room temperature, and EtOAc (80 mL) and water (40 mL) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (40 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography to give desired product.

General Procedure for Pd-Catalyzed Direct Arylation of Polyfluoroarenes with Aryl Iodides in DMF. To a septum-capped 25 mL Schlenk tube were added $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3 (0.75 equiv), and aryl iodide (0.9 mmol, 1.0 equiv) under N_2, followed by fluoroarene (1.5 equiv) and DMF (2.5 mL). The reaction mixture was warmed to 70 °C (oil bath) and stirred for 24 h. The reaction was cooled to room temperature, and EtOAc (80 mL) and water (40 mL) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (40 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography to give desired product.

2,3,4,5,6-Pentafluoro-4′-methyl-1,1′-biphenyl (3a). The product (209 mg, 90% yield) as a white solid (111−113 °C) was purified with silica gel chromatography (petroleum ether). This compound is known. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 4H), 2.42 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.8 (dd, J = 22.4, 8.0 Hz, 2F), −157.7 (t, J = 20.3 Hz, 1F), −163.8 (td, J = 22.4, 8.0 Hz, 2F). [lit.[2a] ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 4H), 2.42 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −164.6 to −164.3 (m, 2F), −158.1 (t, J = 21.0 Hz, 1F), −145.4 (dd, J = 23.0, 7.6 Hz, 2F)]; MS (EI) m/z (%) 258 (M^+, 100), 237.

2,3,4,5,6-Pentafluoro-4′-methoxy-1,1′-biphenyl (3b). The product (224 mg, 91% yield) as a white solid (114−116 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known.^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 7.2 Hz, 2H), 7.02 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.4 (dd, J = 22.8, 8.0 Hz, 2F), −156.3 (t, J = 21.4 Hz, 1F), - 162.3 (td, J = 22.9, 9.0 Hz, 2F). [lit.[2a] ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.38 (m, 2H), 6.98−7.04 (m, 2H), 3.86 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −145.7 (dd, J = 23.0, 7.6 Hz, 2F), −158.5 (t, J = 21.0 Hz, 1F), −164.7 to −164.3 (m, 2F)]; MS (EI) m/z (%) 274 (M^+, 100), 231.

5-(Perfluorophenyl)benzo[*d*][1,3]dioxole (3c). The product (228 mg, 88% yield) as a white solid (95−98 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^1H NMR (300 MHz, $CDCl_3$) δ 6.95−6.88 (m, 3H), 6.05 (s, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.6 (m, 2F), −156.3 (t, J = 19.7, 1F), −162.6 (m, 2F). [lit.[12] ^1H NMR (400 MHz, $CDCl_3$) δ 6.95−6.88 (m, 3H), 6.04 (s, 2H). ^{19}F NMR (377 MHz, $CDCl_3$) δ −143.2 (dd, J = 23.4, 8.3 Hz, 2F, 2F), −156.0 (t, J = 20.7, 1F), −162.3 (m, 2F)]; MS (EI) m/z (%) 288 (M^+), 248 (100).

2,3,4,5,6-Pentafluoro-1,1′:4′,1″-terphenyl (3d). The product (236 mg, 82% yield) as a white solid (186−188 °C) was purified with silica gel chromatography (petroleum ether). This compound is known. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.53−7.42 (m, 4H), 7.40−7.37 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.6 (dd, J = 22.5, 8.0 Hz, 2F), −157.2 (t, J = 20.4 Hz, 1F), −163.4 (td, J = 22.5, 8.1 Hz, 2F). [lit.[12,13] ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.74 (m, 2H), 7.64−7.66 (m, 2H), 7.52−7.46 (m, 4H), 7.42−7.38 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ −143.1 (dd, J = 23.0, 8.3 Hz, 2F), −155.5 (t, J = 20.7 Hz, 1F), −162.2 (m, 2F)]; MS (EI) m/z (%) 320 (M^+, 100).

2,3,4,5,6-Pentafluoro-4′-nitro-1,1′-biphenyl (3e). The product (237 mg, 91% yield) as a yellow solid (86−88 °C) was purified with silica gel chromatography (petroleum ether/EtOAc = 50:1). This compound is known. ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −142.3 (dd, J = 22.2, 7.8 Hz, 2F), −152.3 (t, J = 20.8 Hz, 1F), −160.5 (m, 2F). [lit.[14] ^1H NMR (300 MHz, $CDCl_3$) δ 8.35−8.39 (m, 2H), 7.61−7.66 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −143.7 (dd, J =

21.2, 8.9 Hz, 2F), −153.6 (t, *J* = 20.9 Hz, 1F), −161.9 (m, 2F)]; MS (EI) *m/z* (%) 289 (M$^+$, 100), 242, 231, 224, 193.

Ethyl 2′,3′,4′,5′,6′-Pentafluoro-[1,1′-biphenyl]-3-carboxylate (3f). The product (273 mg, 96% yield) as a light green solid (54−56 °C) was purified with silica gel chromatography (petroleum ether/EtOAc = 50:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.17−8.12 (m, 2H), 7.61−7.59 (m, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −142.5 (dd, *J* = 22.5, 7.9 Hz, 2F), −154.2 (t, *J* = 20.9 Hz, 1F), −161.3 (td, *J* = 22.5, 8.0 Hz, 2F). ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.7, 144.1 (dm, *J* = 247.2 Hz), 140.6 (dm, *J* = 253.2 Hz), 137.8 (dm, *J* = 251.5 Hz), 134.3, 131.2, 130.3, 128.8, 126.7, 115.0 (m), 61.2, 14.2. IR (thin film) ν_{max} 1716 cm^{-1}. MS (EI) *m/z* (%) 316 (M$^+$), 288, 271 (100). Anal. Calcd. for $C_{15}H_9F_5O_2$: C, 56.97; H, 2.87; Found: C, 56.82; H, 2.82.

2,3,4,4′,5,6-Hexafluoro-1,1′-biphenyl (3g). The product (172 mg, 73% yield) as a white solid (112−114 °C) was purified with silica gel chromatography (petroleum ether). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (m, 2H), 7.22 (m, 2H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −111.7 (s, 1F), −143.7 (dd, *J* = 22.5 Hz, 7.9 Hz, 2F), −155.5 (t, *J* = 20.0 Hz, 1F), −162.3 (td, *J* = 22.5, 7.9 Hz, 2F). [lit.[2c] ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36−7.45 (m, 2H), 7.14−7.24 (m, 2H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −113.3 (s, 1F), −142.1 (dd, *J* = 23.0 Hz, 7.6 Hz, 2F), −157.2 (t, *J* = 21.0 Hz, 1F), −163.8 to −164.1 (m, 2F)]; MS (EI) *m/z* (%) 262 (M$^+$, 100), 242.

4′-Bromo-2,3,4,5,6-pentafluoro-1,1′-biphenyl (3h). The product (241 mg, 83% yield) as a white solid (81−83 °C) was purified with silica gel chromatography (petroleum ether). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −143.51 (dd, *J* = 22.3, 7.7 Hz, 2F), −154.99 (t, *J* = 21.1 Hz, 1F), −162.0 (td, *J* = 22.3, 8.7 Hz, 2F). [lit.[9] ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −143.52 (m, 2F), −155.09 (m, 1F), −162.54 (m, 2F)]; MS (EI) *m/z* (%) 324, 322 (M$^+$, 100), 242.

3-(Perfluorophenyl)thiophene (3i). The product (Standard conditions: 90 mg, 40% yield; using DMF as solvent: 158 mg, 70% yield) as a white solid (41−43 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (s, 1H), 7.47 (m, 1H), 7.36 (m, 1H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −142.4 (dd, *J* = 22.3, 7.4 Hz, 2F), −156.6 (t, *J* = 21.0 Hz, 1F), −162.6 (td, *J* = 22.3, 7.8 Hz, 2F). [lit.[2c] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (s, 1H), 7.44−7.46 (m, 1H), 7.35−7.36 (m, 1H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −142.0 (dd, *J* = 22.2, 7.9 Hz, 2F), −156.4 (t, *J* = 20.7 Hz, 1F), −162.5 (m, 2F)]; MS (EI) *m/z* (%) 250 (M$^+$, 100).

2,3,5,6-Tetrafluoro-4′-methoxy-1,1′-biphenyl (3j). 4.0 equiv of fluoroarene was used. The product (132 mg, 86% yield) as a white solid (97−100 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40 (s, 2H), 7.01 (m, 3H), 3.86 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −140.1 (m, 2F), −144.5 (m, 2F). [lit.[12] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39−7.42 (m, 2H), 6.98−7.06 (m, 3H), 3.87 (s, 3H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −139.5 (dd, *J* = 13.2, 23.0 Hz, 2F), −144.3 (dd, *J* = 23.0, 13.6 Hz, 2F)]; MS (EI) *m/z* (%) 256 (M$^+$, 100), 213.

2,3,4,6-Tetrafluoro-4′-methoxy-1,1′-biphenyl (3k). 4.0 equiv of fluoroarene was used. The product (Standard conditions: 94 mg, 61% yield; using DMF as solvent: 117 mg, 76% yield) as a white solid (72−74 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.85 (m, 1H), 3.86 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −118.9 (t, *J* = 9.8 Hz, 1F), −134.5 (m, 1F), −136.2 (d, *J* = 22.5 Hz, 1F), −165.3 (m, 1F). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 159.8, 154.2 (dm, *J* = 246.1 Hz), 149.4 (dm, *J* = 248.7 Hz), 148.9 (dm, *J* = 247.8 Hz), 137.5 (dm, *J* = 252.7 Hz), 131.3, 119.5, 115.6 (m), 113.9, 100.7 (m), 55.2. IR (thin film) ν_{max} 1507 cm^{-1}. MS (EI) *m/z* (%) 256 (M$^+$, 100), 241, 213. HRMS calcd for $C_{13}H_8F_4O$: 256.0511; Found: 256.0508.

2,3,5,6-Tetrafluoro-4′-methyl-[1,1′-biphenyl]-4-carbonitrile (3l). The product (205 mg, 86% yield) as a white solid (150−152 °C) was purified with silica gel chromatography (petroleum ether/EtOAc = 50:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (s, 4H), 2.44 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −134.7 (m, 2F), −141.34 (m, 2F). ^{13}C NMR (100 MHz, CDCl$_3$) δ 147.5 (dm, *J* = 260.5 Hz), 143.8 (dm, *J* = 249.0 Hz), 140.8, 129.8, 129.6, 127.3 (t, *J* = 16.5 Hz), 122.7, 107.6, 92.4 (m), 21.4. IR (thin film) ν_{max} 2247, 1485 cm^{-1}. MS (EI) *m/z* (%) 265 (M$^+$, 100), 244. HRMS: calcd for $C_{14}H_7F_4N$ 265.0514, found 265.0514.

2,3,5,6-Tetrafluoro-4′-methyl-4-(trifluoromethyl)-1,1′-biphenyl (3m). The product (236 mg, 85% yield) as a white solid (111−114 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43−7.36 (m, 4H), 2.48 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −56.4 (m, 3F), −141.2 (m, 2F), −141.9 (m, 2F). [lit.[15] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (m, 4H), 2.49 (s, 3H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −56.17 (t, *J* = 21.5 Hz, 3F), −140.96 (m, 2F), −141.68 (m, 2F)]; MS (EI) *m/z* (%) 308 (M$^+$, 100), 219.

4-Bromo-2,3,5,6-tetrafluoro-4′-methoxy-1,1′-biphenyl (3n). The product (standard conditions: 142 mg, 47% yield; using DMF as solvent: 236 mg, 78% yield) as a white solid (117−119 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −133.6 (m, 2F), −142.1 (dd, *J* = 22.6, 9.0 Hz, 2F). ^{13}C NMR (100 MHz, CDCl$_3$) δ 160.3, 145.3 (dm, *J* = 246.1 Hz), 144.1 (dm, *J* = 248.0 Hz), 131.3, 120.0 (t, *J* = 16.6 Hz), 118.9, 114.2, 97.9 (t, *J* = 22.5 Hz.), 55.3. IR (thin film) ν_{max} 1479 cm^{-1}. MS (EI) *m/z* (%) 336, 334 (M$^+$, 100), 292, 291. Anal. Calcd for $C_{13}H_7BrF_4O$: C, 46.60; H,2.11. Found: C, 46.93; H, 2.15.

2,3,5,6-Tetrafluoro-4-(p-tolyl)pyridine (3o). The product (186 mg, 86% yield) as a white solid (94−96 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 2.44 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −91.4 (m, 2F), −145.7 (m, 2F). [lit.[2c] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −96.1 to −96.3 (m, 2F), −150.3−150.5 (m, 2F)]; MS (EI) *m/z* (%) 241 (M$^+$, 100), 220.

2,3,5,6-Tetrafluoro-4′-methoxy-4-methyl-1,1′-biphenyl (3p). The product (189 mg, 78% yield) as a white solid (116−118 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 3.86 (s, 3H), 2.31 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −144.8 (dd, *J* = 22.8 Hz, 10.1 Hz, 2F), −146.4 (dd, *J* = 22.8, 13.8 Hz, 2F). [lit.[12] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.31 (t, *J* = 2.0 Hz, 3H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −144.4 (dd, *J* = 22.6 Hz, 12.8 Hz, 2F), −146.0 (dd, *J* = 22.2, 12.4 Hz, 2F)]; MS (EI) *m/z* (%) 270 (M$^+$, 100), 255, 227.

2,4,6-Trifluoro-4′-methoxy-1,1′-bipheny (3q). Four equivalents of fluoroarene was used. The product (113 mg, 78% yield) as a white solid (94−96 °C) was purified with silica gel chromatography (petroleum ether/diethyl ether = 100:1). This compound is known. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.75 (t, *J* = 8.1 Hz, 2H). 3.86 (s, 3H). ^{19}F NMR (282 MHz, CDCl$_3$) δ −110.4 (m, 1F), −112.1 (m, 2F). [lit.[12] ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.74 (t, *J* = 8.4 Hz, 2H). 3.85 (s, 3H). ^{19}F NMR (377 MHz, CDCl$_3$) δ −109.9 (t, *J* = 5.6 Hz, 1F), −111.6 (d, *J* = 5.6 Hz, 2F)]; MS (EI) *m/z* (%) 238 (M$^+$, 100), 223, 195.

2,6-Difluoro-4′-methoxy-3-nitro-1,1′-biphenyl (3r). Four equivalents of fluoroarene was used. The product (standard conditions: 57 mg, 36% yield; using DMF as solvent: 123 mg, 78% yield) as a light green solid (96−98 °C) was purified with silica gel chromatography (petroleum ether/EtOAc = 50:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.08 (m, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.11 (t, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H) . ^{19}F NMR (282 MHz, CDCl$_3$) δ −101.9 (m, 1F), −116.4 (dd, *J* = 15.0, 8.2 Hz, 1F). ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.8 (dd, *J* = 257.0, 6.1 Hz), 160.2, 153.9 (dd, *J* = 264.2, 7.9 Hz), 134.8, 131.5, 125.5 (d, *J* = 11.1 Hz), 120.8 (t, *J*

= 18.2 Hz), 118.8, 114.1, 112.0 (dd, *J* = 25.2, 4.1 Hz), 55.3. IR (thin film) ν_{max} 1519 cm^{-1}. MS (EI) *m*/*z* (%) 265 (M$^+$, 100), 219, 175. HRMS calcd for $C_{13}H_9F_2NO_3$ 265.0550, found 265.0552. Anal. Calcd for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.42. Found: C, 58.86; H, 3.42.

(*E*)-*tert*-Butyl 3-(2,3,5,6-tetrafluoro-4′-methoxy-[1,1′-biphenyl]-4-yl)acrylate (5). To a septum-capped 25 mL sealed tube were added Pd(OAc)$_2$ (10 mol %), **3j** (0.3 mmol), and Ag_2CO_3 (2.0 equiv) under N_2, followed by alkene (2.0 equiv), PivOH (3.0 equiv), and DMF (2.0 mL). The reaction mixture was warmed to 120 °C (oil bath) and stirred for 10 h. The reaction was cooled to room temperature, and EtOAc (80 mL) and water (40 mL) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (40 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 50:1) to give **5** (76 mg, 66% yield, *E*/*Z* = 15:1, determined by ^{19}F NMR) as a yellow-green solid. Mp 247−249 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.5 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 16.5 Hz, 1H), 3.87 (s, 3H), 1.56 (s, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −140.6 (dd, *J* = 20.8, 11.5 Hz, 2F), −144.3 (dd, *J* = 21.2, 12.2 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 160.3, 145.6 (dm, *J* = 247.6 Hz), 143.9 (dm, *J* = 244.2 Hz), 131.4, 128.2, 127.8 (t, *J* = 8.6 Hz), 119.0, 114.1, 114.0, 112.7(m), 81.2, 55.3, 28.0. IR (thin film) ν_{max} 1716, 1480 cm^{-1}. MS (EI) *m*/*z* (%) 382 (M$^+$), 326 (100), 309. HRMS calcd for $C_{20}H_{18}F_4O_3$ 382.1192, found 382.1188.

***N*,*N*-Dimethyl-5-(2,3,5,6-tetrafluoro-4′-methoxy-[1,1′-biphenyl]-4-yl)thiophene-2-carboxamide (6).** To a septum-capped 25 mL sealed tube were added Pd(OAc)$_2$ (10 mol %), **3j** (2.0 equiv), *N*,*N*-dimethylthiophene-2-carboxamide (0.3 mmol) and Ag_2CO_3 (1.5 equiv) under N_2, followed by DMSO (0.1 mL) and DMF (1.9 mL). The reaction mixture was warmed to 120 °C (oil bath) and stirred for 10 h. The reaction was cooled to room temperature, and EtOAc (80 mL) and water (40 mL) were added. The organic layer was separated, and the aqueous phase was extracted with EtOAc (40 mL × 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (petroleum ether/EtOAc = 50:1) to give desired product (60 mg, 49% yield) as a yellow-green solid. Mp 155−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 3.6 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.42 (d, J = 3.6 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.23 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −140.0 (dd, *J* = 21.6, 11.0 Hz, 2F), −144.1 (dd, *J* = 21.6, 11.3 Hz, 2F). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.3, 144.3 (dm, *J* = 244.7 Hz), 143.8 (dm, *J* = 248.9 Hz), 139.9 (t, *J* = 3.9 Hz), 131.4, 131.1, 129.5 (t, *J* = 5.9 Hz), 129.1, 119.4 (t, *J* = 16.4 Hz), 119.2, 114.2, 111.9 (t, *J* = 14.6 Hz), 55.3. IR (thin film) ν_{max} 1599, 1468 cm^{-1}. MS (EI) *m*/*z* (%) 409 (M$^+$), 365 (100), 293. HRMS calcd for $C_{20}H_{15}F_4NSO_2$ 409.0760, found 409.0764.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews, see: (a) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (b) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

(2) For selected recent papers, see: (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. (f) Wei, Y.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 3346. (g) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377. (h) Li, H.; Liu, J.; Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2011**, *13*, 276.

(3) For selected recent reviews related to C−H bond activation, see: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Daugulis, O.; Zaitzev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(4) For selected recent reviews, see: (a) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (b) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725. (c) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302.

(5) For selected recent papers related to Pd-catalyzed direct arylation of heteroarenes/arenes using water as solvent under mild conditions, see: (a) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (c) Ohnmacht, S. A.; Patrizia, M.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, *10*, 1241. (d) Ohnmacht, S. A.; Culshaw, A. J.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 224. (e) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781.

(6) A Pd-catalyzed direct arylation of polyfluoroarenes at room temperature using expensive electron-rich bulky phosphine ligand in a water mixed solvent system (EtOAc/water = 2.5:1) has been reported recently; see: René, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116.

(7) (a) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506. (b) Fan, S.; Chen, F.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5918. (c) Fan, S.; Yang, J.; Zhang, X. *Org. Lett.* **2011**, *13*, 4374. (d) Fan, S.; He, C.-Y.; Zhang, X. *Chem. Commun.* **2010**, *46*, 4926. (e) Chen, F.; Zhang, X. *Chem. Lett.* **2011**, *40*, 978. (f) He, C.-Y.; Min, Q.-Q.; Zhang, X. *Organometallics* **2012**, DOI: 10.1021/om200873j.

(8) For examples of cationic Pd(II) complexes generated by Ag(I) abstraction of the iodide ligand, see: (a) Grove, D. M.; van Koten, G.; Louwen, J. N.; Noltes, J. G.; Spec, A. L. *J. Am. Chem. Soc.* **1982**, *104*, 6609. (b) Liston, D. J.; Lee, Y. J.; Scheidt, W. R.; Reed, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 6643. (c) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1995**, *60*, 1013. (d) Albano, V. G.; Di Serio, M.; Monari, M.; Orabona, I.; Panunzi, A.; Ruffo, F. *Inorg. Chem.* **2002**, *41*, 2672.

(9) Zahn, A.; Brotschi, C.; Leumann, C. J. *Chem.—Eur. J.* **2005**, *11*, 2125.

(10) Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. *J. Am. Chem. Soc.* **2011**, *133*, 16338.

(11) For a review, see: Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(12) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350.

(13) Birchall, J. M.; Evans, L. R.; Haszeldine, R. N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1715.

(14) Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

(15) Schaub, T; Backes, M; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964.