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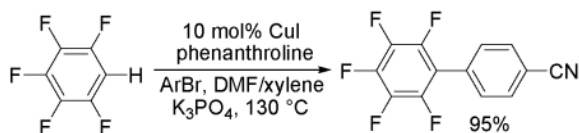
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## Copper-Catalyzed Arylation and Alkenylation of Polyfluoroarene C-H Bonds

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### Abstract



An efficient, copper-catalyzed method for the arylation, alkenylation, and benzylation of polyfluoroarenes has been developed. Arenes containing two or more fluorine substituents on the aromatic ring can be efficiently functionalized. The best results are obtained by using a combination of copper iodide catalyst, phenanthroline ligand, aryl bromide or aryl iodide coupling partner and DMF or DMF/xylene mixed solvent.

Many directing-group containing arenes can now be arylated or alkylated under palladium, rhodium, or ruthenium catalysis.<sup>1</sup> Even arenes lacking traditional directing groups can be functionalized representing the most atom-efficient method for creation of aryl-aryl bonds.<sup>2</sup> However, in this case, regioselectivity issues often are unsolved. An exception can be found in recent elegant work by Fagnou who showed that polyfluorobenzene C-H bonds can be arylated under palladium catalysis.<sup>3</sup> The regioselectivity is imparted by the acidification of *ortho*-C-H bonds by fluorine substituents. While palladium catalysts can be replaced by copper in many coupling processes,<sup>4</sup> use of this cheaper and more convenient alternative in C-H activation reactions is not common.<sup>5</sup> Fluorinated polyaryls are important in medicinal chemistry and direct methods for synthesis of these compounds may allow the development of more efficient pathways to pharmaceuticals.<sup>6</sup> We report here a general method for the copper-catalyzed arylation and alkenylation of polyfluorobenzene C-H bonds.

We have recently shown that palladium catalyst can be replaced by copper in the arylation of electron-rich and electron-poor heterocycles.<sup>7</sup> The reaction mechanism presumably includes a deprotonation of an acidic heterocycle followed by lithium/copper transmetalation and reaction of the organocopper species with aryl iodide. It is reasonable to assume that relatively acidic polyfluorobenzenes<sup>8</sup> can be arylated if a proper combination of base, solvent, and copper catalyst is used. A brief optimization of reaction conditions was carried out. For pentafluorobenzene arylation by aryl bromides, the best results were obtained in mixed DMF/xylene solvent (1:1) and by employing phenanthroline ligand. Lower conversions were observed in DMF. Pentafluorobenzene can be arylated by both aryl bromides and aryl iodides. For other, less reactive substrates, the reaction with aryl iodide in DMF solvent results in higher yields. In most cases, potassium phosphate base affords the best results. Less acidic fluorobenzenes that contain fewer than three fluorines in the molecule can be arylated by employing lithium *tert*-butoxide base. The reaction scope with respect to aryl halide is

presented in Table 1. Both electron-rich (Entries 1–5) and electron-poor (Entries 6–9) aryl halides are reactive. Functional groups, including ester (Entry 8) and cyano (Entry 9) are tolerated. Pyridyl (Entries 10 and 11) and electron-rich thienyl (Entry 12) bromides can be employed for the arylation. If a 5.7/1 E/Z mixture of  $\beta$ -bromostyrene was used in alkenylation of pentafluorobenzene, a 5.7/1 E/Z ratio of pentafluorostilbene was obtained (analysis of crude reaction mixture; 77% E and 12% Z isolated, Entry 13). Substantial steric hindrance is tolerated on the aryl halide (Entries 2 and 3). Mesitylation requires the use of aryl iodide to obtain high yield. Mesityl bromide afforded only 20% isolated yield of the coupling product. Pentafluorobenzene is benzylated in fair yield (Entry 14). A side reaction between benzyl bromide and DMF solvent is responsible for the reduced yield. On a 10 mmol scale yield is almost the same as on 1 mmol scale (88% vs. 91%, Entry 1).

The scope with respect to fluoroarene is presented in Table 2. Two of the three tetrafluorobenzenes can be arylated in good yields (Entries 1–2). The arylation of 1,2,3,4-tetrafluorobenzene affords only a low yield of the cross-coupling product (Entry 3). 1,3,5-Trifluoro- and 1,3-difluorobenzenes are reactive; however, for the arylation of less acidic difluorobenzene a stronger base, LiOtBu, is necessary. Fluorinated pyridines can also be arylated (Entries 6 and 7). Again, for the less fluorinated 3-fluoropyridine use of LiOtBu base is necessary. Fluorobenzene was unreactive under any conditions tried. As observed by Fagnou,<sup>3</sup> the most acidic C-H bonds, those flanked by two C-F bonds, are efficiently arylated.

It is known that pentafluorophenylcopper reacts with electrophiles, including aryl iodides, producing coupling products in high yield.<sup>9</sup> It has also been reported that pentafluorobenzene reacts with aryl iodides in the presence of stoichiometric copper (I) oxide producing pentafluorobiaryls in moderate yields.<sup>10</sup> In light of this, it is reasonable to assume that the catalytic reaction also proceeds by base-promoted formation of fluoroarylcopper followed by the reaction of the copper species with aryl halide affording the coupling product (Scheme 1).<sup>11</sup> If less acidic fluoroaryl is used, a stronger base is required to form the arylcopper species.

In conclusion, we have developed an efficient, copper-catalyzed method for the arylation, alkenylation, and benzylation of polyfluoroarenes. Arenes containing two or more fluorine substituents on the aromatic ring can be efficiently functionalized. The best results are obtained by using a combination of copper iodide catalyst, phenanthroline ligand, aryl bromide or aryl iodide coupling partner and DMF or DMF/xylene mixed solvent.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

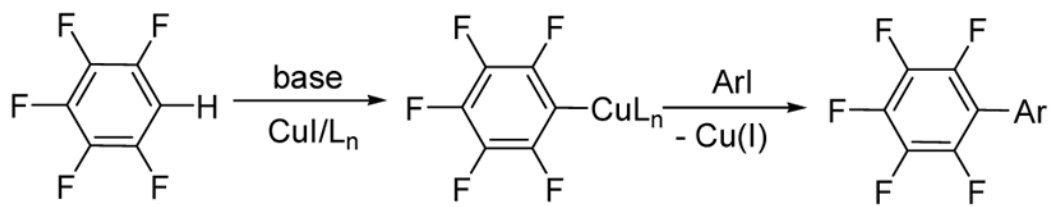
## Acknowledgements

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  11. Arylation of the mixture of pentafluorobenzene and 1,2,4,5-tetra-fluorobenzene under usual reaction conditions resulted in preferential arylation of pentafluorobenzene (2/1). Additionally, it was shown that base-promoted H/D exchange in polyfluoroarenes occurs with the same efficiency both in the presence or absence of CuI. See Supporting information for details.



**Scheme 1.**  
Mechanistic considerations.

Table 1

Arylation scope with respect to halides<sup>a</sup>

Entry	Halide	Product	Yield, %
1	4-MeC <sub>6</sub> H <sub>4</sub> Br		91 88 <sup>b</sup>
2	2-MeC <sub>6</sub> H <sub>4</sub> Br		87
3	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> I		87 20 <sup>c</sup>
4	4-MeOC <sub>6</sub> H <sub>4</sub> Br		88
5	1-Bromonaphthalene		68
6	4-FC <sub>6</sub> H <sub>4</sub> Br		92
7	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Br		88
8	4-EtO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> Br		90
9	4-NCC <sub>6</sub> H <sub>4</sub> Br		95
10	2-Bromopyridine		90
11	3-Bromopyridine		86
12	2-Bromothiophene		92
13 <sup>d</sup>	β-Bromostyrene		77% <sup>e</sup> 12% <sup>f</sup>
14	Benzyl bromide		31%

<sup>a</sup>Substrate (1.5 equiv), aryl halide (1 equiv), base (2 equiv). Yields are isolated yields<sup>b</sup>Ten mmol scale reaction<sup>c</sup>Mesityl bromide used<sup>d</sup>E/Z Mixture (5.7/1) of bromoalkene used

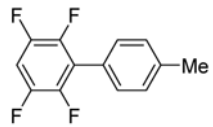
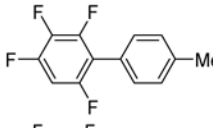
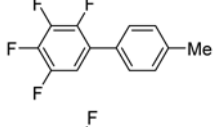
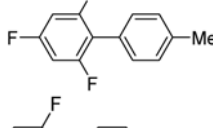
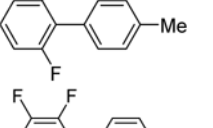
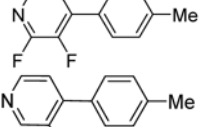
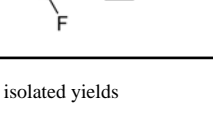
<sup>e</sup>Yield of E-isomer.

<sup>f</sup>Yield of Z-isomer

Table 2

Arylation scope with respect to fluoroarenes<sup>a</sup>

Fluoroarene  $\xrightarrow[\text{DMF, } K_3PO_4, 130-140\text{ }^\circ C]{10\text{ mol\% CuI, phenanthroline, 4-iodotoluene}}$  Me-C<sub>6</sub>H<sub>4</sub>-Ar<sub>F</sub>

Entry	Fluoroarene	Product	Yield, %
1	1,2,4,5-Tetrafluorobenzene		77 <sup>b</sup>
2	1,2,3,5-Tetrafluorobenzene		73 <sup>c</sup>
3	1,2,3,4-Tetrafluorobenzene		10
4	1,3,5-Trifluorobenzene		68
5 <sup>d</sup>	1,3-Difluorobenzene		81
6	2,3,5,6-Tetrafluoropyridine		91
7 <sup>d</sup>	3-Fluoropyridine		40

<sup>a</sup>Substrate (2–3 equiv), aryl halide (1 equiv), base (2–2.5 equiv). Yields are isolated yields<sup>b</sup>Diarylation product (15%) also isolated<sup>c</sup>Diarylation product (17%) also isolated<sup>d</sup>Lithium *t*-butoxide base