

# Pd-catalyzed Highly Regio- and Stereocontrolled Direct Alkenylation of Electron-deficient Polyfluoroarenes

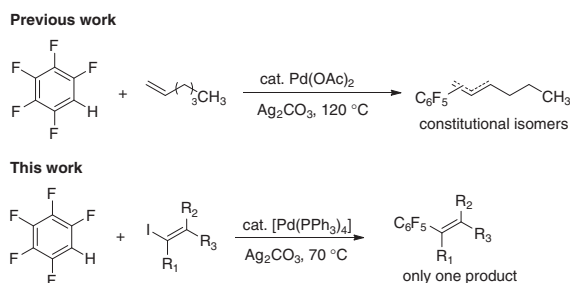
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An effective and reliable method for Pd-catalyzed highly regio- and stereocontrolled direct alkenylation of electron-deficient polyfluoroarenes with alkenyl iodides has been developed. The advantages of this reaction are its high regio- and stereoselectivity, mild reaction temperature (70 °C), and the use of readily available Pd(PPh<sub>3</sub>)<sub>4</sub>. This approach provides a useful access to polyfluoroarylated derivatives of interest in both life and materials science.

Due to the importance of polyfluoroarenes in materials and life science,<sup>1</sup> it is of great synthetic interest to develop efficient methods for the preparation of fluoroarylated compounds. Of the developed methods, the transition-metal-catalyzed direct functionalization of simple polyfluoroarenes is the most attractive approach, because this direct C–H bond functionalization process provides a more effective strategy in terms of atom and step economy.<sup>2</sup> Since the first example of palladium-catalyzed direct arylation of polyfluoroarenes with arylhalides was reported by Fagnou,<sup>3</sup> impressive progress in direct functionalization of polyfluoroarenes has been made.<sup>4</sup> However, many of these efforts mainly focused on the direct arylation of polyfluoroarenes.<sup>4a–4f</sup> Very recently, we successfully developed a straightforward protocol for direct Pd-catalyzed alkenylation of polyfluoroarenes,<sup>5</sup> which represents one of the rare examples of catalytic direct olefination of electron-deficient arenes.<sup>6</sup> Unfortunately, when branched or aliphatic alkenes were investigated in this Fujiwara–Moritani oxidative Heck type reaction, a mixture of constitutional isomers was generated.<sup>5</sup> In fact, this is the most difficult problem in the intermolecular Mizoroki–Heck reaction.<sup>7</sup> To continue our research, we envisioned that the installation of a halogen substituent onto the alkenes would be a reliable strategy to solve this difficult problem. Since these “prefunctionalized” alkenes would direct Pd-catalyst to install polyfluoroarenes at specific position, as a result, a high regio- and stereoselectivity would be obtained (Scheme 1).



**Scheme 1.** Direct alkenylation of electron-deficient polyfluoroarenes.

Herein, we reported an effective method for Pd-catalyzed direct alkenylation of polyfluoroarenes with alkenyl iodides. The advantages of this reaction are high regio- and stereoselectivity, mild reaction temperature (70 °C), and use of readily available Pd(PPh<sub>3</sub>)<sub>4</sub>. This approach provides a useful access to the fluorinated styrenyl products.

We began this study by choosing pentafluorobenzene (**1a**) and (*Z*)-ethyl 3-iodoacrylate (**2a**) as model substrates (Table 1). Initially, from the viewpoint of synthetic convenience and cost effectiveness, a Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> catalytic system, which was successfully used in our previous work on the direct functionalization of polyfluoroarenes,<sup>8</sup> was investigated. However, no desired product **3a** was obtained (Table 1, Entry 1). Considering that silver(I) salts are commonly employed to abstract halide anions from transition-metal complexes thus rendering them more electrophilic and facilitating the catalytic cycle,<sup>3c,9</sup> Ag<sub>2</sub>CO<sub>3</sub> was investigated, and provided compound **3a** in 17% NMR yield (Table 1, Entry 2). We were pleased to observe that switching Pd source from Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> to Pd(PPh<sub>3</sub>)<sub>4</sub> benefited the reaction, and 70% NMR yield of **3a** was afforded when the reaction was carried out with Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %) and Ag<sub>2</sub>CO<sub>3</sub> (0.75 equiv) in DMF at 120 °C (Table 1, Entry 3). AgOAc was also found to be comparable with Ag<sub>2</sub>CO<sub>3</sub>, but some by-products were formed (Table 1, Entry 4). The solvent

**Table 1.** Optimization of Pd-catalyzed regio- and stereocontrolled direct alkenylation of electron-deficient pentafluorobenzene<sup>a</sup>

| Entry | Catalyst (mol %)                                   | Additive (equiv)                       | Solvent | Temp /°C | Yield <sup>b</sup> /% |
|-------|----------------------------------------------------|----------------------------------------|---------|----------|-----------------------|
| 1     | Pd(OAc) <sub>2</sub> (10)<br>PPh <sub>3</sub> (20) | K <sub>2</sub> CO <sub>3</sub> (0.75)  | DMF     | 100      | N.R.                  |
| 2     | Pd(OAc) <sub>2</sub> (10)<br>PPh <sub>3</sub> (20) | Ag <sub>2</sub> CO <sub>3</sub> (0.75) | DMF     | 100      | 17                    |
| 3     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)            | Ag <sub>2</sub> CO <sub>3</sub> (0.75) | DMF     | 120      | 70                    |
| 4     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)            | AgOAc (1.5)                            | DMF     | 120      | 76                    |
| 5     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)            | Ag <sub>2</sub> CO <sub>3</sub> (0.75) | DMSO    | 120      | 83(68)                |
| 6     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)            | Ag <sub>2</sub> CO <sub>3</sub> (0.75) | Dioxane | 120      | 0                     |
| 7     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)             | Ag <sub>2</sub> CO <sub>3</sub> (0.75) | DMSO    | 120      | 86                    |
| 8     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)             | Ag <sub>2</sub> CO <sub>3</sub> (0.5)  | DMSO    | 120      | 86                    |
| 9     | Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)             | Ag <sub>2</sub> CO <sub>3</sub> (0.5)  | DMSO    | 70       | 87(74)                |

<sup>a</sup>Conditions: **1a** (0.9 mmol) and **2a** (0.3 mmol) in solvent (2 mL), 10 h. <sup>b</sup>NMR yield determined by <sup>19</sup>F NMR and number in parentheses is isolated yield.

**Table 2.** Pd-Catalyzed regio- and stereocontrolled direct alkenylation of electron-deficient polyfluoroarenes<sup>a</sup>

| Fluoroarene<br>1 |  | Alkenyl iodide<br>2                                                                                                                   |  | Product<br>3 |                      |
|------------------|--|---------------------------------------------------------------------------------------------------------------------------------------|--|--------------|----------------------|
|                  |  | $\xrightarrow[\text{DMSO, 70 } ^\circ\text{C}]{\text{[Pd(PPh}_3)_4] \text{ (5 mol\%)} \\ \text{Ag}_2\text{CO}_3 \text{ (0.5 equiv)}}$ |  |              |                      |
|                  |  |                                                                                                                                       |  |              | 3a, 74%              |
|                  |  |                                                                                                                                       |  |              | 3b, 79%              |
|                  |  |                                                                                                                                       |  |              | 3c, 76%              |
|                  |  |                                                                                                                                       |  |              | 3d, 66%              |
|                  |  |                                                                                                                                       |  |              | 3e, 66%              |
|                  |  |                                                                                                                                       |  |              | 3f, 41%              |
|                  |  |                                                                                                                                       |  |              | 3g, 70% <sup>b</sup> |
|                  |  |                                                                                                                                       |  |              | 3h, 87%              |
|                  |  |                                                                                                                                       |  |              | 3i, 54%              |
|                  |  |                                                                                                                                       |  |              | 3j, 87%              |
|                  |  |                                                                                                                                       |  |              | 3k, 52%              |
|                  |  |                                                                                                                                       |  |              | 3l, 70%              |

<sup>a</sup>Conditions: **1a** (0.9 mmol) and **2a** (0.3 mmol) in DMSO (2 mL), 10 h. <sup>b</sup>8 equiv of fluoroarene was used.

effect also influenced the reaction efficiency (Table 1, Entries 5 and 6), and DMSO was the optimum reaction medium with 68% isolated yield obtained (Table 1, Entry 6). Further optimization revealed that the reaction could proceed smoothly in good yield (74% isolated yield) with utilization of 5 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> and 0.5 equiv of Ag<sub>2</sub>CO<sub>3</sub> at 70 °C (Table 1, Entry 9).

Under the optimum reaction conditions (Table 1, Entry 9), the substrate scope of the regio- and stereocontrolled direct alkenylation of polyfluoroarenes **1** was tested and the representative results are illustrated in Table 2. The fluorinated styrenyl products could be obtained as a single *Z*- or *E*-isomer through the present reaction. Notably, for the aliphatic alkenyl iodides, especially for the linear aliphatic alkene **2e** (Table 2, **3e**), no constitutional isomers were observed (Table 2, **3d–3f**), which is in sharp contrast to our previous results,<sup>5</sup> thus providing a complementary method to the Fujiwara–Moritani oxidative Heck type reaction. The substrate scope of polyfluoroarene is not restricted to pentafluorobenzene, variations of polyfluoroarenes **1** were also suitable substrates for the reaction (Table 2, **3g–3l**). Generally, the reaction efficiency depends on the nature of the substituents on the fluoroaromatic ring. Substrates bearing an electron-withdrawing group provided higher yields than that of fluoroarenes containing an electron-donating group (Table 2, **3h–3k**). Lewis basic functionality, a pyridyl group, was tolerated, and provided **3l** in good yield (Table 2, **3l**). Importantly, nitrile groups are also compatible to the reaction conditions with 87% yield obtained (Table 2, **3h**), thus providing opportunities for further functionalization. For compounds **3f**, **3i**, and **3k**, due to the low conversion of alkenyl iodide **3f** or formation of by-products **3i** and **3k**, modest yields were provided.

In conclusion, we have developed an effective Pd(PPh<sub>3</sub>)<sub>4</sub>/Ag<sub>2</sub>CO<sub>3</sub>-catalyzed system for regio- and stereocontrolled direct

alkenylation of electron-deficient polyfluoroarenes with alkenyl iodides.<sup>10</sup> The reaction was carried out under mild reaction temperature (70 °C) and afforded good yields and high regio- and stereoselectivity. Hence, it is a useful and reliable method for the preparation of polyfluoroarylated derivatives of interest in both life and materials science.

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