Paper in Celebration for the 2010 Nobel Prize in Chemistry

doi:10.1246/cl.2011.978

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

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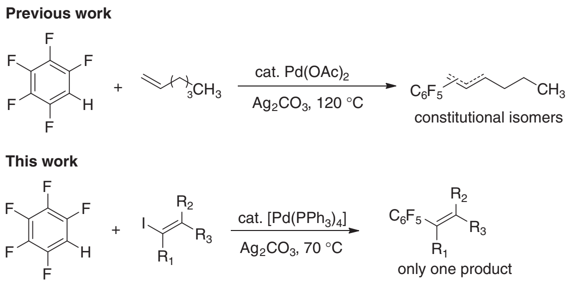
(Received May 30, 2011; CL-110453; E-mail: xgzhang@mail.sioc.ac.cn)

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 $Pd(PPh_3)_4$. 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,[1] 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.[2] Since the first example of palladium-catalyzed direct arylation of polyfluoroarenes with arylhalides was reported by Fagnou,[3] impressive progress in direct functionalization of polyfluoroarenes has been made.[4] However, many of these efforts mainly focused on the direct arylation of polyfluoroarenes.[4a–4f] Very recently, we successfully developed a straightforward protocol for direct Pd-catalyzed alkenylation of polyfluoroarenes,[5] which represents one of the rare examples of catalytic direct olefination of electron-deficient arenes.[6] Unfortunately, when branched or aliphatic alkenes were investigated in this Fujiwara–Moritani oxidative Heck type reaction, a mixture of constitutional isomers was generated.[5] In fact, this is the most difficult problem in the intermolecular Mizoroki–Heck reaction.[7] 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).

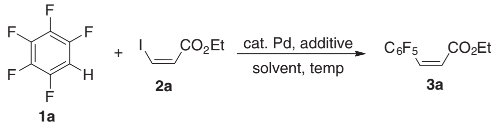


Scheme 1. Direct alkenylation of electron-deficient polyfluoroarenes.

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 $Pd(PPh_3)_4$. 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 $Pd(OAc)_2/PPh_3$ catalytic system, which was successfully used in our previous work on the direct functionalization of polyfluoroarenes,[8] 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,[3c,9] Ag_2CO_3 was investigated, and provided compound **3a** in 17% NMR yield (Table 1, Entry 2). We were pleased to observe that switching Pd source from $Pd(OAc)_2/PPh_3$ to $Pd(PPh_3)_4$ benefited the reaction, and 70% NMR yield of **3a** was afforded when the reaction was carried out with $Pd(PPh_3)_4$ (10 mol %) and Ag_2CO_3 (0.75 equiv) in DMF at 120 °C (Table 1, Entry 3). AgOAc was also found to be comparable with Ag_2CO_3, but some by-products were formed (Table 1, Entry 4). The solvent

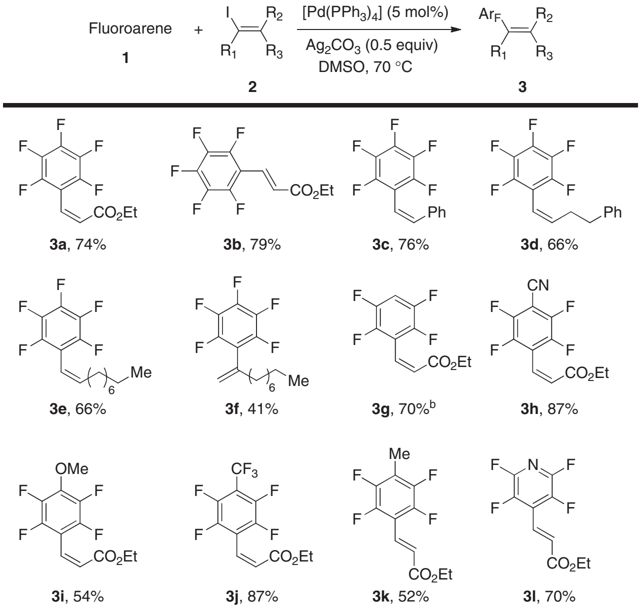
Table 1. Optimization of Pd-catalyzed regio- and stereocontrolled direct alkenylation of electron-deficient pentafluorobenzene[a]



Entry	Catalyst (mol %)	Additvie (equiv)	Solvent	Temp /°C	Yield[b] /%
1	$Pd(OAc)_2$ (10) PPh_3 (20)	K_2CO_3 (0.75)	DMF	100	N.R.
2	$Pd(OAc)_2$ (10) PPh_3 (20)	Ag_2CO_3 (0.75)	DMF	100	17
3	$Pd(PPh_3)_4$ (10)	Ag_2CO_3 (0.75)	DMF	120	70
4	$Pd(PPh_3)_4$ (10)	AgOAc (1.5)	DMF	120	76
5	$Pd(PPh_3)_4$ (10)	Ag_2CO_3 (0.75)	DMSO	120	83(68)
6	$Pd(PPh_3)_4$ (10)	Ag_2CO_3 (0.75)	Dioxane	120	0
7	$Pd(PPh_3)_4$ (5)	Ag_2CO_3 (0.75)	DMSO	120	86
8	$Pd(PPh_3)_4$ (5)	Ag_2CO_3 (0.5)	DMSO	120	86
9	$Pd(PPh_3)_4$ (5)	Ag_2CO_3 (0.5)	DMSO	70	87(74)

[a]Conditions: **1a** (0.9 mmol) and **2a** (0.3 mmol) in solvent (2 mL), 10 h. [b]NMR yield determined by ^{19}F NMR and number in parentheses is isolated yield.

Table 2. Pd-Catalyzed regio- and stereocontrolled direct alkenylation of electron-deficient polyfluoroarenes[a]



3a, 74%; **3b**, 79%; **3c**, 76%; **3d**, 66%

3e, 66%; **3f**, 41%; **3g**, 70%[b]; **3h**, 87%

3i, 54%; **3j**, 87%; **3k**, 52%; **3l**, 70%

[a]Conditions: **1a** (0.9 mmol) and **2a** (0.3 mmol) in DMSO (2 mL), 10 h. [b]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 % $Pd(PPh_3)_4$ and 0.5 equiv of Ag_2CO_3 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,[5] 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 $Pd(PPh_3)_4$/Ag_2CO_3-catalyzed system for regio- and stereocontrolled direct alkenylation of electron-deficient polyfluoroarenes with alkenyl iodides.[10] 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.

The NSFC (Nos. 20902100 and 20832008), the Shanghai Rising-Star Program (No. 09QA1406900), and SIOC are warmly acknowledged for funding this work.

This paper is in celebration of the 2010 Nobel Prize awarded to Professors Richard F. Heck, Akira Suzuki, and Ei-ichi Negishi.

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