



Pd-catalyzed decarboxylative cross-coupling of perfluorobenzoic acids with simple arenes

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ABSTRACT

Using a Pd/Ag bimetallic system, arylations of simple arenes with perfluorobenzoic acids have been achieved by decarboxylative C–H bond functionalization, providing the desired cross-coupling products in moderate to good yields. These straightforward protocols provide new and efficient methods for the synthesis of fluorobiphenyl scaffolds under simple and mild conditions.

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Transition-metal-catalyzed decarboxylative coupling is an important and very attractive research point of organic synthesis in recent years.¹ This method avoids the preparation and use of stoichiometric organometallic reagents such as boronic acids and releases gaseous carbon dioxide as the leaving group instead of often toxic or expensive metal salts. Representative examples include the decarboxylative coupling of benzoic acids with aryl halides or triflates with carefully optimized Pd/Cu catalytic systems,² the decarboxylative olefination, and biaryl coupling of aromatic carboxylic acids with Pd/Ag catalytic systems,³ and other recent developments of Pd-catalyzed decarboxylative coupling.⁴ However, the requirement of prefunctionalization of the coupling partners to activate the aromatic C–H bonds, for example, using aryl halides or aryl triflates as the synthetic substrates, limited the application of these kinds of decarboxylative aryl–aryl cross-couplings. To overcome this challenge, cross-coupling of unactivated arenes was developed via direct C–H activation. In that case, a directing group was usually necessary for the high chemo- and regioselectivity of the transformation.⁵ An alternative strategy to avoid installing a directing group for decarboxylative cross-coupling was the use of electron-rich heterocycles,⁶ or intramolecular direct arylation through Pd-catalyzed C–H activation.⁷

As part of our ongoing research on efficient palladium-catalyzed direct cross-coupling reaction,⁸ we aimed at the difficult but highly desirable coupling for the construction of complicated fluorinated

scaffolds,⁹ which have a potential value in the field of material science.¹⁰

Studies on the preparation of polyfluorobiaryls via direct cross-coupling are widely reported for its considerable advantages over traditional organometallic transformation process.^{11,12} Among these current progresses, it is of note that decarboxylative coupling of electron-deficient perfluorobenzoates represented one to polyfluorobiaryls.¹²

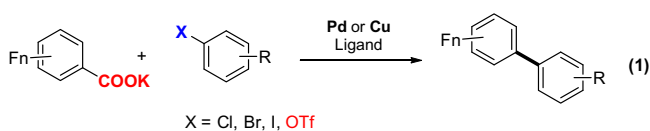
Nevertheless, to the best of our knowledge, the direct cross-coupling of perfluorobenzoic acids with simple arenes instead of aryl halides or triflates is unprecedented to date (Scheme 1, Eq. 1). Herein we describe the first example of direct Pd-catalyzed decarboxylative arylation of perfluorobenzoic acids with simple arenes via C–H bond functionalization (Scheme 1, Eq. 2). With a low loading of Pd catalyst (5 mol %) and ligand free, this direct arylation reaction provides a novel and efficient method for the synthesis of perfluorobiphenyls.

We began our investigation by choosing commercially available perfluorobenzoic acid (**1a**) and *p*-xylene (**2a**) as our initial model substrates. The effect of reaction parameters on the conversion was summarized in Table 1. It was found that the desired decarboxylative cross-coupling product **3a** was provided with a remarkable 88% isolated yield in the presence of the catalytic amount of Pd(OAc)₂ and stoichiometric Ag₂CO₃ at 130 °C in DMSO solution (Table 1, entry 5), whereas, small amounts of by-products **3aa** and **3ab** through homo-coupling and oxidation of arene were detected. Other commonly used palladium sources, such as Pd(TFA)₂, PdCl₂, Pd(CH₃CN)₂, and Pd(PhCN)Cl₂ were less effective

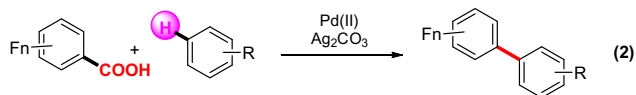
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Direct Arylation with Perfluoroarenes reported by Liu

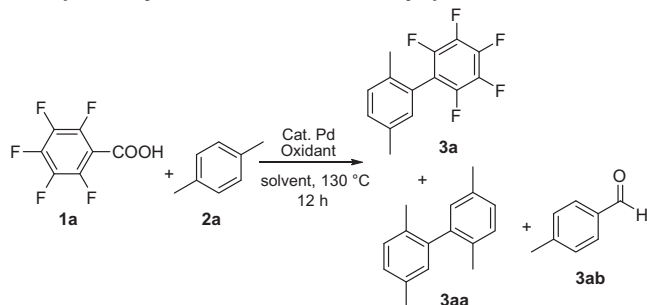


Our work via C-H functionalization



Scheme 1. Decarboxylative arylation of perfluorobenzoic acids.

or completely ineffective (Table 1, entries 1–4). The yields collapsed significantly when the solvent was replaced by DMF, 1,4-dioxane, or NMP (Table 1, entries 6–8). DMSO proved to be the best choice, presumably because of its dual functions, not only as solvent but also as a ligand to activate the Pd catalyst and prevent the formation of palladium black.¹³ In addition, replacement of the oxidant Ag₂CO₃ with Cu(OAc)₂ or AgOAc led to lower reaction

Table 1
Direct arylation of pentafluorobenzoic acid **1a** with *p*-xylene **2a**^a

Entry	Pd (mol %)	Oxidant	Solvent	Yield of 3a ^b (%)
1	Pd(TFA) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	44
2	PdCl ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	5
3	Pd(CH ₃ CN) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	53
4	Pd(PhCN) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	0
5	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	88
6	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMF (0.1 mL)	32
7	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	1,4-Dioxane (0.1 mL)	36
8	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	NMP (0.1 mL)	34
9	Pd(OAc) ₂ (10)	Cu(OAc) ₂ (2.0 equiv)	DMSO (0.1 mL)	19
10	Pd(OAc) ₂ (10)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	41
11	Pd(OAc) ₂ (7.5)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	87
12	Pd(OAc)₂ (5)	Ag₂CO₃ (2.0 equiv)	DMSO (0.1 mL)	89
13	Pd(OAc) ₂ (2.5)	Ag ₂ CO ₃ (2.0 equiv)	DMSO (0.1 mL)	54

^a Reactions were performed in a sealed tube under air with pentafluorobenzoic acid **1a** (0.3 mmol) and *p*-xylene **2a** (0.9 mL).

^b Isolated yield based on pentafluorobenzoic acid.

conversion (Table 1, entries 9 and 10). After further optimization on the catalyst loading of Pd(OAc)₂, the coupling product was obtained without any alteration in yield when the amount of Pd(OAc)₂ was reduced to 5 mol % (Table 1, entries 11–13).

Based on the optimized condition of direct decarboxylative arylation of pentafluorobenzoic acid with simple arenes, we proceeded to explore the scope of the decarboxylative arylation reaction of polyfluorobenzoic acid derivatives with various simple arenes. The results were presented in Table 2. It is intriguing to note that chloride substituent in the substrate was tolerant to the reaction system, despite lack of selectivity affording slightly reduced but acceptable yields of the desired product (Table 2, entry 3). Results of 1,2- and 1,3-disubstituted benzenes indicate that the steric effect dominates the reaction regioselectivity at the preferable less hindered C–H position (Table 2, entries 4 and 5). Less comparably active polyfluorobenzoic acid substrates, even bearing electron-donating group such as MeO – were also sustainable to the decarboxylative arylation reaction under the same condition (Table 2, entries 7–8).

Aromatic heterocycle was also subjected to the reaction (Scheme 2). We are happy to find that the desired cross-coupling

Table 2
Decarboxylative arylation of polyfluorobenzoic acid **3a** with various simple arenes **2**^a

Entry	Polyfluorobenzoic acid	Arene	Product	Yield ^b (%)
1			3a	89
2			3b	70 ^c o:m:p = 1:2:2
3			3c	65 o:m:p = 1:2:2
4			3d	79 2:1 = 6.3:1
5			3e	80 1:2 = 2:2:1
6			3f	82
7			3g	65
8			3h	73

^a Reactions were performed in a sealed tube under air with polyfluorobenzoic acid **1** (0.3 mmol) and simple arenes **2** (0.9 mL).

^b Isolated yield based on polyfluorobenzoic acids.

^c Yield determined as a mixture of isomers, and the ratio of isomers was calculated by GC–MS or/and ¹⁹F NMR.

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