Tetrahedron Letters 54 (2013) 2833-2836

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history: Received 11 January 2013 Revised 10 March 2013 Accepted 19 March 2013 Available online 27 March 2013

Keywords: Pd-catalyzed Crosscoupling Fluorobiphenyl Simple arenes Decarboxylative

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 arvl 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 crosscouplings. 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 crosscoupling are widely reported for its considerable advantages over traditional organometallical 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 crosscoupling 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 crossing-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, Pd(Cl₂, Pd(CH₃CN)Cl₂, 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, 1,4dioxane, 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	$Pd(TFA)_2$	Ag_2CO_3	DMSO	44
	(10)	(2.0 equiv)	(0.1 mL)	
2	PdCl ₂	Ag_2CO_3	DMSO	5
	(10)	(2.0 equiv)	(0.1 mL)	
3	$Pd(CH_3CN)Cl_2$	Ag_2CO_3	DMSO	53
	(10)	(2.0 equiv)	(0.1 mL)	
4	Pd(PhCN)Cl ₂	Ag_2CO_3	DMSO	0
	(10)	(2.0 equiv)	(0.1 mL)	
5	$Pd(OAc)_2$	Ag_2CO_3	DMSO	88
	(10)	(2.0 equiv)	(0.1 mL)	
6	$Pd(OAc)_2$	Ag_2CO_3	DMF	32
	(10)	(2.0 equiv)	(0.1 mL)	
7	$Pd(OAc)_2$	Ag_2CO_3	1,4-Dioxane	36
	(10)	(2.0 equiv)	(0.1 mL)	
8	$Pd(OAc)_2$	Ag_2CO_3	NMP	34
	(10)	(2.0 equiv)	(0.1 mL)	
9	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	19
	(10)	(2.0 equiv)	(0.1 mL)	
10	$Pd(OAc)_2$	Ag_2CO_3	DMSO	41
	(10)	(2.0 equiv)	(0.1 mL)	
11	$Pd(OAc)_2$	Ag_2CO_3	DMSO	87
	(7.5)	(2.0 equiv)	(0.1 mL)	
12	Pd(OAc) ₂	Ag ₂ CO ₃	DMSO	89
	(5)	(2.0 equiv)	(0.1 mL)	
13	$Pd(OAc)_2$	Ag_2CO_3	DMSO	54
	(2.5)	(2.0 equiv)	(0.1 mL)	

^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



 $^{\rm a}$ 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.

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



Scheme 2. Arylation of pentafluoroarene and pentafluorobenzoic acid with aromatic heterocycle.



Scheme 3. Arylations of pentafluorobenzene with benzene.

product was obtained both using pentafluorobenzene and penta-fluorobenzonic acid in good yield.¹⁴

In order to confirm the possible existence of the silver species facilitated decarboxylative activation step, the electron-deficient pentafluorobenzene **4a** was reacted with benzene under very similar reaction conditions (Scheme 3). Interestingly, using this Pd/Ag bimetallic system, arylations of simple arenes with perfluoroarenes have been achieved by C–H/C–H bond functionalization in 88% yield. On the base of these results, we think that the same silver species existed in these two kinds of reactions.

A mechanism similar to the one proposed by Larrosa^{6a} could be operative here to explain the formation of the decarboxylative coupling products and by-products in two intertwined catalytic cycles (Scheme 4). First, the palladium was inserted into the benzene ring via a reversible electrophilic palladation (I and II) process, which was reported by Van Helden and Sasson.¹⁵ Decarboxylation using metal carbonates was well-established in the literature,¹⁶ so a silver species facilitated decarboxylative activation step (**IV** and **V**). In these processes, **II** and **V** could lead to two by-products **4a** and **VI**. From the direct arylation of perfluoroarenes with simple arenes, 4a could be easily recycled via oxidative arylation process with simple arene to obtain the same product **3f** (Scheme 4, catalytic cycle **A**). Transmetallation of Ar-Pd species **II** with silver species intermediates V would then afford the palladium intermediate III, which could produce the coupled product **3f** through reductive elimination. Finally, oxidation of Pd⁰ to Pd^{II} (I), also performed by the silver salt, completed the arvlation cycle.

In conclusion, we have developed an efficient Pd catalyzed method for the direct decarboxylative C–H arylation that allows the intermolecular coupling of a variety of electron-poor benzoic acids with simple arenes, based on a Pd/Ag bimetallic system.¹⁷ With a low loading of Pd catalyst (5 mol %) and ligand free, the reaction provides the rapid and practical synthesis of perfluorobiphenyls, without any prefunctionalization chemistry being necessary.

Acknowledgements

The authors thank the NSF of Jiangxi Provincial Education Department (GJJ12570) for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 03.086.



Scheme 4. Proposed mechanism.

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- For a recent review, see Ackermann, L; Vicente, R.; Kapdi, A. R. Angew. Chem., Int. Ed. 2009, 48, 9792–9826.
- 17. Typical experimental procedure: To a septum capped 25 mL of sealed tube with a magnetic stirring bar were added Pd(OAc)₂ (5 mol %) and Ag₂CO₃ (164 mg, 0.6 mmol, 2.0 equiv) under air, DMSO (0.10 mL), and perfluorobenzoic acid 1a (0.3 mmol) and *p*-xylene **2a** (0.9 mL) were added subsequently. The sealed tube was screwcapped and heated to 130 °C (oil bath), and stirred for 12 h. After completion, the reaction was cooled to room temperature, then the mixture was diluted with 10 mL water. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified with silica gel chromatography to provide pure product **3a** in 89% yield (white solid). ¹H NMR (400 MHz, CDCl3): δ 7.19–7.26 (m, 2H), 7.02 (s, 1H), 2.37 (s, 3H), 2.15 (s, 3H); ¹³C NMR (100 MHz, CDCl3): δ 145.3–145.2 (m), 142.9–142.8 (m), 142.8–142.7 (m), 139.3–139.0 (m), 136.4–136.3 (m), 135.6, 134.2, 131.1, 130.4, 130.4, 126.6, 115.8–115.4 (m); ¹⁹F NMR (282.4 MHz, CDCl₃): δ –140.7 (dd, *J* = 23.6, 8.6 Hz, 2F), –155.7 (t, *J* = 21.8 Hz, 1F), –162.5–162.4 (m, 2F).