

Short Communication

Direct palladium-catalyzed desulfinitative C–C coupling of polyfluoroarenes with arylsulfinate salts: Water-accelerated reactions

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ABSTRACT

A new approach to the synthesis of fluorinated biaryl compounds from easily available starting materials is described. This protocol is based on the direct palladium-catalyzed desulfinitative cross-coupling of polyfluoroarenes with various arylsulfinate salts via C–H bond activation, accelerated by trace amount of water. The method allows the synthesis of various fluorinated biaryl products in moderate to good yields, and tolerated a variety of functional groups, including alkyl, phenyl, methoxy, fluoro, and chloro groups.

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1. Introduction

Perfluoroarene structures represent a promising class of molecules which have been widely used as pharmaceuticals and functional materials [1–4]. Accordingly, methods able to synthesize such molecules are highly desired [5–11]. Different synthetic strategies utilized in the construction this structural motif have been reported in literature [12–16]. Among the existent protocols, the use of transition metal-catalysis to effect direct functionalization of C–H bonds of polyfluoroarenes must be regarded to be particularly promising because this method offers an effective and straightforward conversion of simple starting materials into more complex molecules by C–C bond formation.

Several metal-catalyzed direct arylation of electron-poor fluorinated arenes have been developed involving coupling either with aryl halides [17–21], aryl triflates [22], arylboronic acids [23], or arenediazonium tetrafluoroborates [24], even with simple arenes [23,25,26]. However, these precedents are still restricted in generality and selectivity: for example, addition of a base or an acid is required for the reactions and in some reactions low regioselectivity is observed. Therefore, further developments of this

transformation, using more robust starting materials under milder reaction conditions are still quite desirable.

Arylsulfinate salts are attractive and useful synthetic reagents in organic chemistry owing to their remarkable stability and ease of reagent handling [27–32]. For example, sodium arenesulfonates have been successfully used as powerful sulfonylation reagents [33–37]. Furthermore, arylsulfinate salts could also serve as one ideal arylating reagents for C–C bond-forming reactions through release of SO₂, despite this transformation is rare [27–29,31].

As part of our ongoing research into synthesis of fluorine-containing compounds [38,39], we were interested in the possibility of developing an efficient, direct palladium-catalyzed C–C coupling of polyfluoroarenes with arylsulfinate salts via desulfinitation. Such a reaction would represent a powerful new and direct C–C bond forming method for the formation of fluorinated polyaryls [40]. Herein we report the details of our preliminary findings.

2. Results and discussion

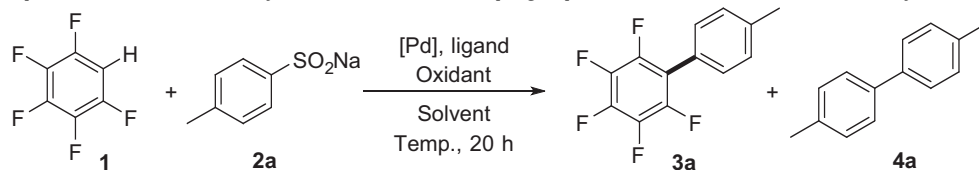
For optimization of the reaction conditions, pentafluorobenzene (**1**) and sodium 4-methylbenzenesulfinate (**2a**) were chosen as model substrates. Different palladium catalysts, ligands, and additives were screened in the transformation of **1** and **2a** into coupling product 1,2,4,5-tetrafluoro-3-(*p*-tolylloxy)benzene (**3a**) in

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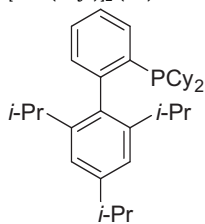
DMF for 20 h (Table 1). After exploring these reaction parameters, we found that the reaction of **1** and **2a**, using [PdCl(allyl)]₂ (20 mol%)/Xphos (20 mol%) as catalyst and Ag₂O (2 equiv) as an additive, in wet DMF (containing 1 vol% of H₂O) at 110 °C for 20 h afforded the desired coupling product **3a** in 72% yield (Table 1, entry 1). However, when the reaction was tested in anhydrous DMF, a predominant amount of the homocoupling product **4a** (74% yield) and only traces of the cross-coupled product **3a** was observed (Table 1, entry 2). This observation suggested that a trace amount of water present in DMF was highly beneficial for the cross-coupling. This acceleration might possibly be a result of formation of a more active catalyst [41,42]. In the absence of [PdCl(allyl)]₂ and Xphos, only 5% yield of cross-coupling product **3a** was observed, which proved that the present reaction is indeed catalyzed by palladium catalyst (Table 1, entry 3). At lower palladium complex loading (10 mol%), traces of **3a** and a significant amount of homocoupling product **4a** (50% yield) could be detected in the crude mixture (Table 1, entry 4). Almost no reaction occurred in the absence of an additive, Ag₂O, after a

reaction time of 20 h (Table 1, entry 5). Furthermore, both 1 equiv and 3 equiv of Ag₂O offered the desired product **3a** in a low yield (Table 1, entries 6 and 7). Therefore, a combination of [PdCl(allyl)]₂ (20 mol%)/Xphos (20 mol%) and Ag₂O (2 equiv) turned out to be essential for obtaining the cross-coupled product **3a** in good yield (Table 1, entry 1). Replacing Ag₂O with other additives such as Ag₂CO₃, AgOAc, AgF, AgNO₃, air, Cu(OTf)₂, and Cu(OAc)₂ resulted in a much lower reaction efficiency (Table 1, entries 8–14). Subsequently, a series of other palladium complexes, including Pd(OAc)₂, Pd(TFA)₂, and Pd₂(dba)₃, were examined, and they exhibited very poor catalytic activity for the reaction (Table 1, entries 15–17). Reactions conducted with other mono- or bidentate phosphine ligands, such as Cy-John-Phos, Mephos, P(Cy)₃, and dppe, unfortunately provided unsatisfactory results (Table 1, entries 18–21). The temperature effects on the reaction were also examined. The cross-couplings were significantly retarded by decreasing the temperature to 80 °C or increasing the temperature to 140 °C (Table 1, entries 22 and 23).

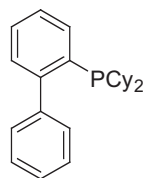
Table 1
Optimization of direct Pd-catalyzed desulfinitative cross-coupling of pentafluorobenzene with sodium 4-methylbenzenesulfonate.^a



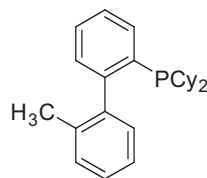
Entry	Pd catalyst (mol %)	Ligand (mol %)	Additive (equiv.)	Solvent ^b	Temp. (°C)	Yield of 3a (%)	Yield of 4a (%) ^c
1	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (2)	DMF	110	72 ^c	2
2	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (2)	Anhydrous DMF	110	4 ^d	74
3	–	–	Ag ₂ O (2)	DMF	110	5 ^d	9
4	[PdCl(allyl)] ₂ (10)	Xphos (20)	Ag ₂ O (2)	DMF	110	2 ^d	50
5	[PdCl(allyl)] ₂ (20)	Xphos (20)	–	DMF	110	3 ^d	5
6	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (1)	DMF	110	30 ^d	19
7	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (3)	DMF	110	47 ^c	14
8	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ CO ₃ (2)	DMF	110	15 ^d	64
9	[PdCl(allyl)] ₂ (20)	Xphos (20)	AgOAc (2)	DMF	110	9 ^d	58
10	[PdCl(allyl)] ₂ (20)	Xphos (20)	AgF (2)	DMF	110	6 ^d	44
11	[PdCl(allyl)] ₂ (20)	Xphos (20)	AgNO ₃ (2)	DMF	110	8 ^d	72
12	[PdCl(allyl)] ₂ (20)	Xphos (20)	Air	DMF	110	10 ^d	32
13	[PdCl(allyl)] ₂ (20)	Xphos (20)	Cu(OTf) ₂ (2)	DMF	110	3 ^d	67
14	[PdCl(allyl)] ₂ (20)	Xphos (20)	Cu(OAc) ₂ (2)	DMF	110	5 ^d	53
15	Pd(OAc) ₂ (20)	Xphos (20)	Ag ₂ O (2)	DMF	110	4 ^d	82
16	Pd(TFA) ₂ (20)	Xphos (20)	Ag ₂ O (2)	DMF	110	6 ^d	78
17	Pd ₂ (dba) ₃ (20)	Xphos (20)	Ag ₂ O (2)	DMF	110	9 ^d	53
18	[PdCl(allyl)] ₂ (20)	Cy-John-Phos (20)	Ag ₂ O (2)	DMF	110	36 ^c	0
19	[PdCl(allyl)] ₂ (20)	Mephos (20)	Ag ₂ O (2)	DMF	110	31 ^c	0
20	[PdCl(allyl)] ₂ (20)	P(Cy) ₃ (20)	Ag ₂ O (2)	DMF	110	58 ^c	0
21	[PdCl(allyl)] ₂ (20)	dppe (20)	Ag ₂ O (2)	DMF	110	44 ^c	0
22	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (2)	DMF	80	2 ^d	12
23	[PdCl(allyl)] ₂ (20)	Xphos (20)	Ag ₂ O (2)	DMF	140	4 ^d	3



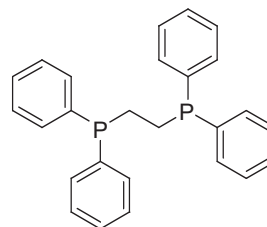
Xphos



Cy-John-Phos



Mephos



dppe

^a Reaction conditions: pentafluorobenzene **1** (0.20 mmol), **2a** (0.10 mmol), solvents (1.0 mL), DMF = *N,N*-dimethylformamide.

^b Containing 1 vol% of H₂O, based on the amount of DMF.

^c Isolated yield.

^d Detected by ¹⁹F NMR.

^e Yields were determined by GC–MS analysis of the crude reaction mixture.

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