Organic LETTERS

Letter

pubs.acs.org/OrgLett

Palladium-Catalyzed Domino Heck/Intermolecular C−H Bond Functionalization: Efficient Synthesis of Alkylated Polyfluoroarene Derivatives

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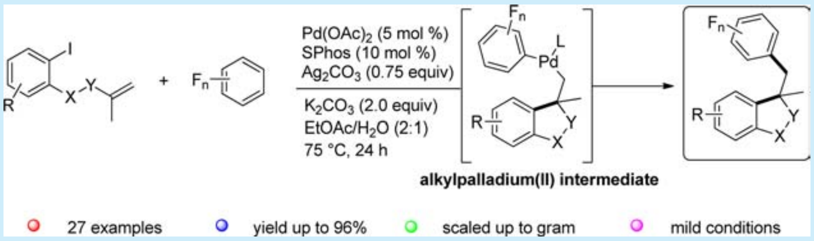
Supporting Information



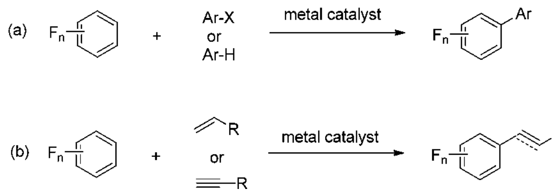
ABSTRACT: An efficient palladium-catalyzed alkylation of electron-deficient polyfluoroarenes is described. The protocol provides a useful and operationally simple access to a broad scope of alkylated polyfluoroarene derivatives in moderate to excellent yields. This also represents the first example of the introduction of a polyfluoroarene structure involving an alkylpalladium(II) intermediate.

The functionalization of polyfluoroarenes has emerged as a chemical transformation of fundamental importance in synthetic organic chemistry because of the widely utilized in the synthesis of complex biologically active natural products and pharmaceuticals as well as in active materials syntheses.[1] To date, numerous approaches for the introduction of polyfluoroarene structures have been developed; however most are focused on the construction of C(sp^2)−C(sp^2) bonds (arylation[2] or alkenylation[3] of polyfluoroarenes). Seminal work by Fagnou utilizing polyfluorobenzenes as the coupling partners to capture the arylpalladium species provided various polyfluorinated biaryls.[4] Subsequently, contributions from the groups of Daugulis,[5] Zhang,[6] Su,[7] Miura,[8] and others[9] greatly enriched the chemistry of polyfluoroarenes in the construction of C(sp^2)−C(sp^2) bonds. In 2009, a copper-catalyzed direct alkynylation of polyfluoroarenes to construct C(sp^2)−C(sp) bonds was presented by Su and co-workers. In the transformation, polyfluoroarenes were deprotonated by the base and then coordinated with the catalyst.[10] Recently, Miura and co-workers further reported the alkynylation of polyfluoroarenes with terminal alkynes under atmospheric conditions.[11]

Despite the significant progress achieved in the functionalization of polyfluoroarenes, the products are mainly limited to polyfluorinated biaryls and polyfluorinated conjugate arenes (Scheme 1). Consequently, introducing alkyl (Csp^3) substituents for installing various polyfluoroaryl groups on organic molecules is particularly desirable.

In 2010, the group of Zhang realized the palladium-catalyzed benzylation and allylation of polyfluoroarenes, respectively (Scheme 2a and 2b).[12] The benzylpalladium[13] and π-allylpalladium[14] intermediates were involved in the two processes, which are relatively stabilized and show high activities compared with σ-alkylpalladium intermediates.[15] On the other hand, electron-deficient arenes present poor reactivities due to the poor coordination capacities with the catalysts. So the reactions of electron-deficient polyfluoroarenes with alkylpalladium intermediates are still a great challenge. Here we describe our development of a palladium catalyzed alkylation of electron-deficient polyfluoroarenes with transient alkylpalladium(II) intermediates based on a domino Heck/intermolecular C−H bond functionalization pathway. This approach provides a highly efficient protocol for the preparation of a wide range of alkylated polyfluoroarene compounds.

Scheme 1. Construction of C(sp^2)−C(sp^2) or C(sp^2)−C(sp) Bonds for Introducing Polyfluoroarene Groups



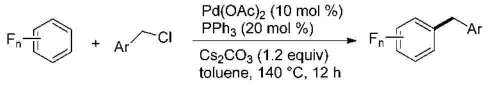
We started our model reaction by investigating aryl iodide **1a** and 1,2,4,5-tetrafluorobenzene **2a** for the optimization of reaction conditions. First, various phosphine ligands were screened in the alkylation reaction. SPhos was better than PPh$_3$, XPhos, Xantphos, and DPEphos, affording the desired product **3a** in 71% yield (Table 1, entries 1−5). We subsequently

Received: February 22, 2016
Published: March 25, 2016

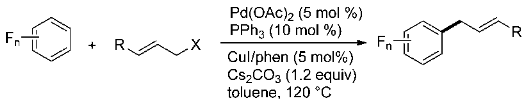
DOI: 10.1021/acs.orglett.6b00447
Org. Lett. 2016, 18, 1784−1787

Scheme 2. C(sp^2)−C(sp^3) Bond-Forming Reactions of Polyfluoroarenes

(a) The benzylation of polyfluoroarenes via benzylpalladium intermediates (**ref 12a**)



(b) The allylation of polyfluoroarenes via π-allylpalladium intermediates (**ref 12b**)



(c) The direct alkylation of polyfluoroarenes via σ-alkylpalladium intermediates (**this work**)

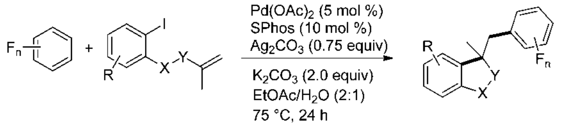
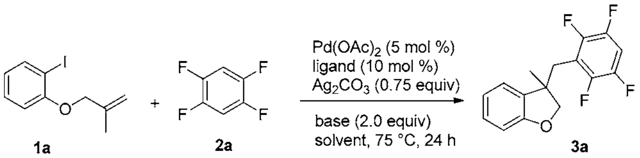


Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

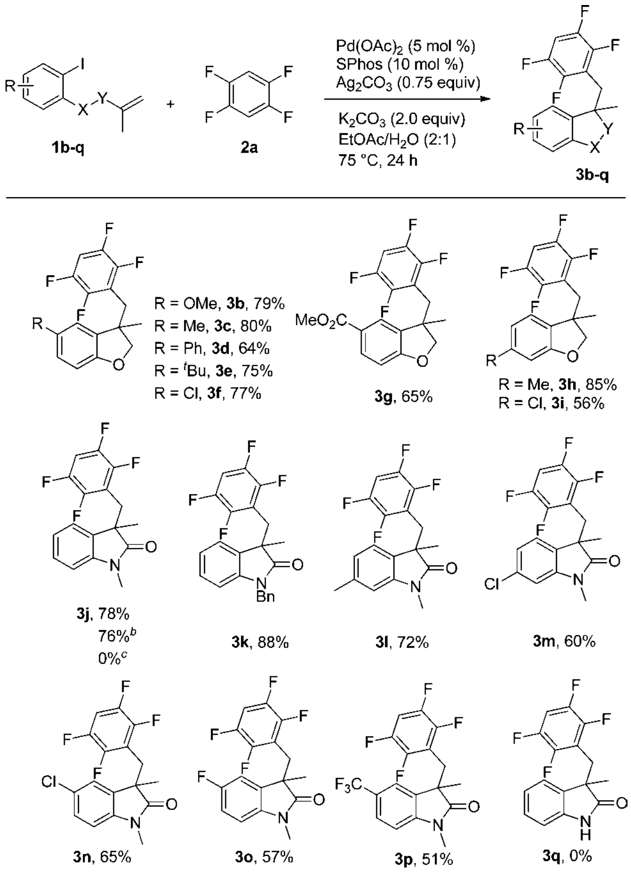
entry	solvent	ligand	base	yield (%)[b]
1	EtOAc	PPh_3	K_2CO_3	<10
2	EtOAc	XPhos	K_2CO_3	18
3	EtOAc	Xantphos	K_2CO_3	35
4	EtOAc	DPEphos	K_2CO_3	30
5	EtOAc	SPhos	K_2CO_3	71
6	EtOAc	SPhos	–	48
7	EtOAc	SPhos	Cs_2CO_3	65
8	EtOAc	SPhos	LiO^tBu	39
9	EtOAc	SPhos	KO^tBu	46
10	EtOAc	SPhos	Et_3N	0
11	EtOAc/H_2O (3:1)	SPhos	K_2CO_3	76
12	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	89
13	EtOAc/H_2O (1:1)	SPhos	K_2CO_3	84
14	EtOAc/H_2O (1:2)	SPhos	K_2CO_3	74
15	H_2O	SPhos	K_2CO_3	21
16[c]	PhMe/H_2O (2:1)	SPhos	K_2CO_3	46
17[c]	MeCN/H_2O (2:1)	SPhos	K_2CO_3	67
18[c]	dioxane/H_2O (2:1)	SPhos	K_2CO_3	54
19[d]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	<10
20[e]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	<10
21[f]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	62
22[g]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	48
23[h]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	67
24[i]	EtOAc/H_2O (2:1)	SPhos	K_2CO_3	56

[a] Reaction conditions unless otherwise noted: **1a** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (0.015 mmol), ligand (0.03 mmol), Ag_2CO_3 (0.225 mmol), base (0.6 mmol), solvent (1.5 mL, 0.2 M), 75 °C, 24 h. [b] Isolated yields. [c] 85 °C. [d] No Ag_2CO_3 added. [e] 25 °C. [f] 60 °C. [g] $Pd(OAc)_2$ (2.5 mol %), SPhos (5 mol %). [h] $Pd(OAc)_2$ (5 mol %), SPhos (5 mol %). [i] **1a**/**2a** (1:1).

found that a base was necessary in this transformation. In its absence, a large drop in yield was observed (entry 6). Compared with Cs_2CO_3, LiO^{t}Bu, KO^{t}Bu, and Et_3N, K_2CO_3 was the best in promoting the reaction (entries 7−10). Next, we examined biphasic conditions[6a,16] and found that the ratio of the two solvent components was crucial for the reaction system. The highest isolated yield (89%) was obtained with the use of a 2:1 mixture of EtOAc and water (entries 11−14). Only a 21% yield was observed by using pure water as the reaction medium (entry 15). Upon switching the solvent from EtOAc to others, such as toluene, MeCN, and dioxane, no improvement in yields could be achieved (entries 16−18). Finally, a control experiment revealed that Ag_2CO_3[17] was essential for the reaction (entry 19). In addition, the lower temperature, lower catalytic loadings, and lower substrate ratio were inferior for the transformation (entries 20−24).

Under the above-mentioned optimized reaction conditions, we then examined the scope of aryl iodides.[18] As shown in Scheme 3, both oxygen- and nitrogen-containing substrates (**1b−p**) all worked well in this reaction, thus affording the corresponding products **3b−p** in moderate to good yields. The substrates with electron-donating substituents on the arenes generally gave slightly higher yields than electron-withdrawing substituents (**3b−i**). Additionally, the reaction of *N*-methyl or *N*-benzyl amides could be incorporated into the final products in 78% and 88% yields, respectively (**3j** and **3k**). Using aryl bromide as the substrate, we also obtained the product **3j** in good yield. However, no product was observed when using aryl triflate as the substrate. Substrates with halogen substituents (Cl and F) at the

Scheme 3. Substrate Scope[a]

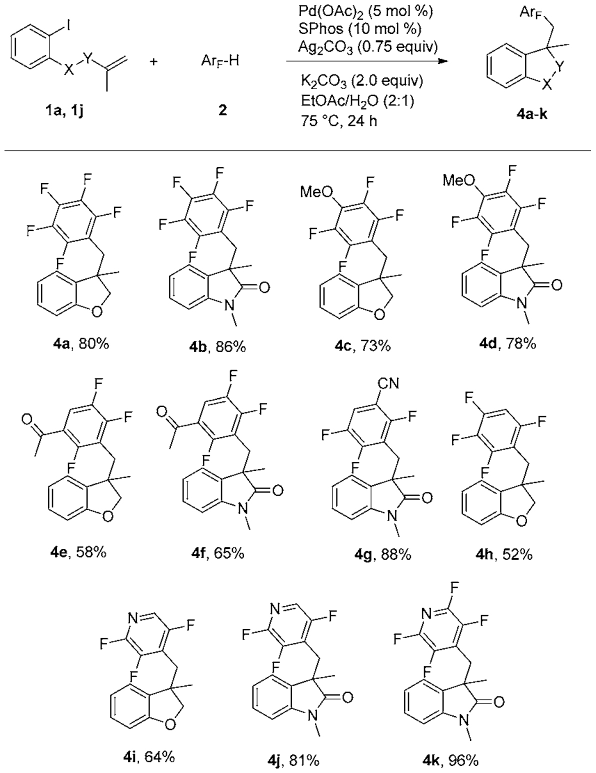


[a] Reaction conditions unless otherwise noted: **1** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (0.015 mmol), SPhos (0.03 mmol), Ag_2CO_3 (0.225 mmol), K_2CO_3 (0.6 mmol), EtOAc/H_2O (1 mL/0.5 mL), 75 °C, 24 h. [b] Aryl bromide as the substrate. [c] Aryl triflate as the substrate. Isolated yields are shown.

different positions could also be converted into the corresponding products in moderate yields (**3m−o**). Notably, a CF_3 group was also tolerated under the reaction conditions, although a relatively low yield (51%) for the product **3p** was obtained. The amide bearing a free N−H bond failed to afford the desired product **3q**.

To ascertain further the scope of this method, a variety of polyfluoroarenes were investigated (Scheme 4). Both 2,3,5,6-tetrafluoroanisole and pentafluorotoluene smoothly underwent direct alkylation, and moderate to good yields were obtained (**4a−d**). The structure of **4a** was also further unambiguously elucidated by X-ray crystallography (see the Supporting Information). Other polyfluorobenzenes, such as those containing keto and cyano groups, also can be alkylated (**4e−g**). However, for 1,2,3,5-tetrafluorobenzene, an unsatisfactory yield was obtained under the standard conditions (**4h**). Gratifyingly, polyfluoropyridines were also suitable substrates and provided the alkylation products in moderate to excellent yields (**4i−k**).

Scheme 4. Substrate Scope with Various Polyfluoroarenes[a]

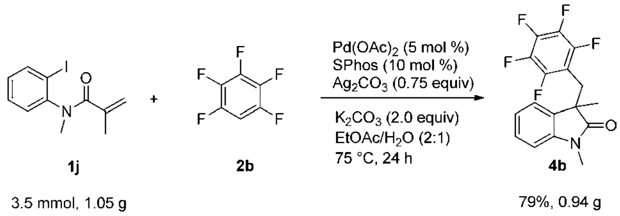


[a] Reaction conditions unless otherwise noted: **1** (0.3 mmol), **2** (0.9 mmol), $Pd(OAc)_2$ (0.015 mmol), SPhos (0.03 mmol), Ag_2CO_3 (0.225 mmol), K_2CO_3 (0.6 mmol), EtOAc/H_2O (1 mL/0.5 mL), 75 °C, 24 h. Isolated yields are shown.

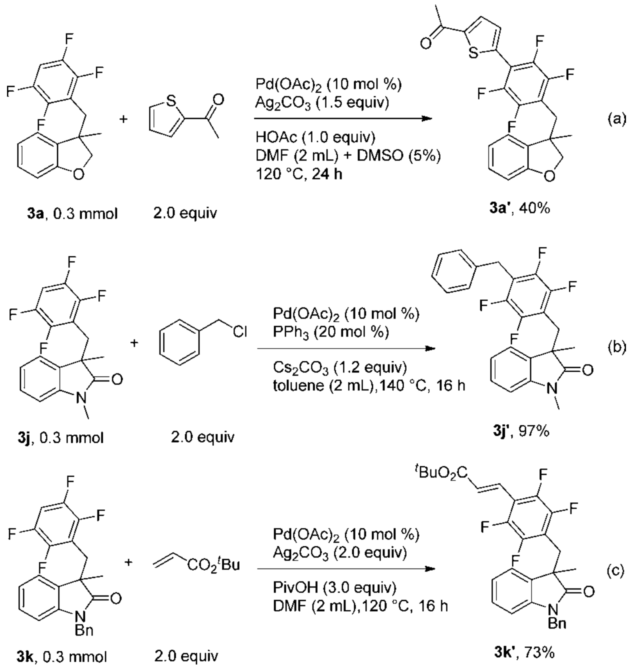
To test the practicality of the new methodology, a gram-scale reaction has been carried out. A reasonable yield of the product **4b** was isolated, which might provide a potential application for this method in industrial production (Scheme 5).

Finally, a series of derivitization experiments were carried out to prepare highly functionalized polyfluoroarenes via Pd-catalyzed C−H bond functionalization. As shown in Scheme 6, a thienyl substituted[6d] polyfluoroarene **3a′** could be obtained in 40% yield by palladium-catalyzed dehydrogenative cross-coupling (Scheme 6a). In addition, the direct benzylation[12a] (Scheme 6b) and alkenylation[6b] (Scheme 6c) of the alkylation products were also achieved in good to excellent yields.

Scheme 5. Scale-Up Experiments

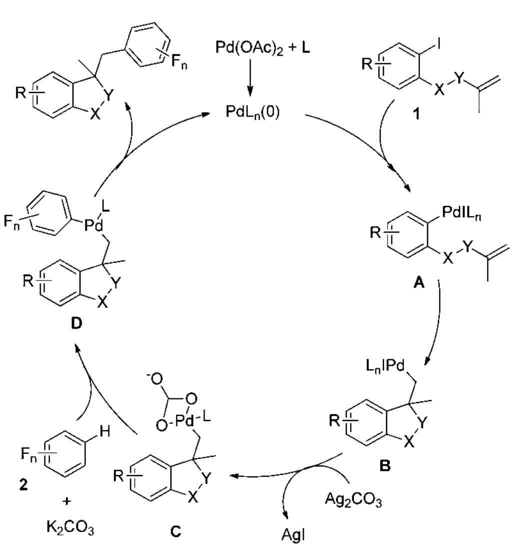


Scheme 6. Derivatization of Products



A catalytic cycle is proposed as depicted in Scheme 7. The in situ formed Pd(0) undergoes oxidative addition with the C−I bond in **1** affording intermediate **A**, which then undergoes an intramolecular Heck-type reaction to form alkylpalladium

Scheme 7. Proposed Reaction Mechanism



intermediate **B**.[19] Next, the silver salt abstracts iodide from **B**, thereby generating a palladium intermediate **C**. Subsequently, **C** goes through the concerted metalation−deprotonation[20] process to form **D**. Finally, reductive elimination of **D** produces an alkylated polyfluoroarene product and regenerates the Pd(0) species.

In conclusion, we have developed the first palladium-catalyzed domino Heck reaction/direct alkylation reaction of electron-deficient polyfluoroarenes, thus affording the alkylated polyfluoroarene products in moderate to excellent yields under mild conditions. This reaction represents a convenient, operationally simple, and useful protocol for the preparation of alkyl substituted polyfluoroarene derivatives. Efforts toward expanding the reaction scope (e.g., other electron-deficient arenes) and detailed mechanistic studies are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00447.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)
X-ray data for **3k** (CIF)
X-ray data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (NSF21272101, NSF21472073, NSF21472074, and NSF21302076), the Program for Changjiang Scholars and Innovative Research Team in University (IRT1138 and IRT15R28).

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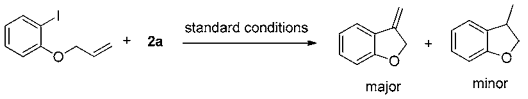
(18) When using monosubstituted olefin as the substrate, no desired product was obtained and the *β*-hydride elimination product was the major product:



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