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Pd-catalyzed direct arylation of electron-deficient polyfluoroarenes with aryliodine(III) diacetates

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ABSTRACT

A Pd-catalyzed direct arylation of electron-deficient polyfluoroarenes with readily available aryliodine(III) diacetates was developed with moderate to good yields. The process exhibited good functional tolerance with respect to methyl, methoxy, bromo, chloro, trifluoromethyl, cyano, and aldehyde groups. Mechanistic studies revealed this coupling involved in situ generation of aryl iodide from heating-promoted decomposition of aryliodine(III) diacetate, followed by coupling with polyfluoroarenes substrates to afford the desired products.

For environmental and economical attractiveness, transition-metal-catalyzed direct arylation of aromatic C–H bonds has been a powerful tool for straightforward synthesis of valuable biaryl products from a large pool of arenes over the last decades, which usually performs a practical alternative route to the traditional cross-coupling reactions and becomes the focus of many research activities.[1] Of these reactions, electron-deficient polyfluoroarenes are extensively employed in a wide range of areas to prepare corresponding polyfluorobiaryl structural motif, ranging from the elaboration of pharmaceutical chemistry to materials science.[2,3] In this regard, some initial works include the Pd-catalyzed selective C–H bond arylation of electron-deficient polyfluoroarenes with aryl halides to synthesis of fluorobiaryl or heterocycle-containing biaryl molecules,[4] and further effort made by Daugulis led to the development of Cu-catalyzed direct arylation of polyfluoroarenes via C–H bond activation with aryl halides.[5] Su and others established oxidative C–H arylation of polyfluoroarenes with arylboronic acids,[6] organosilicon reagents,[7] and arenediazonium tetrafluoroborates,[8] respectively. However, some of the coupling partners in these reported transformations often suffer from limitations for disadvantage with regard to the use of unstable or hard to prepare organometallic reagents. In addition, elegant works in oxidative cross-coupling of polyfluoroarenes via C–H bond activation with alkenes,[9] alkynes,[10] (hetero)arenes,[11] aromatic carboxylic acids,[12] amines,[13] and sulfoximines[14] has been reported. Among these reported reactions, polyfluorobiaryls can be successfully obtained from new methodologies via oxidative cross-coupling of electron deficient polyfluoroarenes with C–H activation of (hetero)arenes[11] or decarboxylation of aromatic carboxylic acids.[12] In contrast to arylation reactions of polyfluoroaromatic C–H bond with (hetero)arenes or aromatic carboxylic acids as aryl source that have recently been attracted great attentions, nevertheless, to the best of our knowledge, no example of the direct C–H bond functionalization of electron-deficient polyfluoroarenes with aryliodine(III) diacetates as aryl source has been revealed.

Phenyliodine(III) diacetate is one of the most useful hypervalent iodine reagents, Kitamura reported an easy and cheap procedure to synthesize (diacetoxyiodo)arenes by the reaction of arenes with iodine under mild conditions ($Ar\text{-}H + I_2$).[15] Therefore, basing on its readily availability and rich chemistry,[16–18] phenyliodine(III) diacetate is widely used in considerable organic synthesis, it is not only served as a surrogate for oxidant in oxidative transformations,[17] but applied for radical reactions to generate oxygen-centered radicals and carbon-centered radicals with potential utility.[18] Furthermore, although apparent progress has been made on transition-metal-mediated coupling reactions between diaryliodonium salts as the arylation reagent and arene,[19] phenol ester,[20] alkene[21] and various nucleophiles,[22] the employment of aryliodine(III) diacetate as the arylation or acetoxylation reagents in the oxidative transformations also received considerable attentions,[23] for example, efforts made by Mao[23a] and Magedov[23b] have led to the development of palladium-catalyzed arylation of alkenes with aryliodine(III) diacetate; Suna[23c] and others[23d–f] disclosed Pd-catalyzed acetoxylation of (hetero)arenes or olefins with the employment of aryliodine(III) diacetate. Recently, the group of

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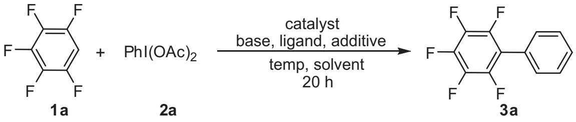
Cheng[24a] and Fairlamb[24b] reported direct arylation of benzoxazole C–H bonds with aryliodine(III) diacetate. With particular interest in the transformation reaction of electron-deficient arene C–H bond, we describe that such an attempt to use ArI(OAc)$_2$ reagents in an oxidative electron-deficient polyfluoroarene C–H bond transformation resulted in the direct arylation reaction of electron-deficient polyfluoroarene with Pd/Ag bimetallic system, and this observation represents a beneficial complement to the well documented versions of direct arylation reaction of electron-deficient polyfluoroarenes.

We initiated our investigation by taking reaction of pentafluorobenzene **1a** with iodobenzene diacetate **2a** as the model reaction for the optimization studies. Table 1 presents some selected results from these optimization studies that showed the effects of the solvent, base, and other factors on the reaction outcome. At first, using a stoichiometric K_3PO_4 as base in the model reaction in DMF solvent, it was found that the catalyst greatly affects reaction efficiency, the reaction of **1a** with **2a** conducted in the presence of 10 mol % Pd(OAc)$_2$ as catalyst under nitrogen atmosphere furnished desired product 2,3,4,5,6-pentafluorobiphenyl **3a** in 54% isolated yield in DMF at 130 °C (entry 3, Table 1), however, either inferior yield (23%) displayed when 20 mol % CuI instead of 10 mol % Pd(OAc)$_2$ or no product was obtained when Pd catalyst was absent (entries 1–2), the results indicated that Pd catalyst has an essential role in the catalytic reaction. Subsequently, a brief survey of the solvents under otherwise identical conditions, including polar and less polar solvents, revealed that better yields could be obtained in polar solvents than that in less polar solvent such as toluene (entries 4–9). Considering DMSO could play an important role and function as a ligand to activate the Pd catalyst and prevent the formation of palladium black,[11c,24b,25] thus, different bases were screened in the model reaction in 5% DMSO/DMF (v/v) mixed solvents (entries 10–14). Among them, K_3PO_4, KOAc, KO^{t}Bu, K_2CO_3, LiO^{t}Bu, and Ag_2CO_3 appeared to be the best choice and had a significant influence on the reaction, delivering **3a** in synthetically useful levels (76% yield) (entry 14). The effect of different loading of Ag_2CO_3 was the next variable evaluated, decreasing the amount of Ag_2CO_3 to 1.5 equiv gave comparable yield (75%), however, further reducing Ag_2CO_3 loading to 1 equiv led to a slightly lower yield (70%) (entries 15 and 16). Varying the ratio of DMSO to DMF in the mixed solvents system led to change in the yield, as a result, replacing 5% DMSO–DMF with 2.5% DMSO–DMF depressed the yield (entry 17). The influence of reaction temperature on the catalytic process was also investigated, studies showed that lowering reaction temperature to 110 °C did not affect the efficiency (74%), whereas unsatisfied yield (64%) was obtained when reaction conducted at 90 °C (entries 18–19). Reaction time also had significant effect on this reaction, and a shorter reaction time did not contribute to increasing the yield (entry 20).

After identifying the factors influencing the reaction outcome, the scope of this protocol with respect to polyfluoroarene was explored by employing the conditions of entry 18 in Table 1. As shown in Table 2, beside the pentafluorobenzene, a broad array of polyfluoroarenes, tetrafluoro-, trifluoro-, and even some polychloroarenes were chemoselectively arylated with (diacetoxyiodo)benzene **2a** under the standard conditions to furnish corresponding products in moderate to good yields. Electron-rich substituents such as methyl and methoxy, electron-deficient substituents such as bromo, trifluoromethyl, cyano, and aldehyde groups all could be quite well tolerated, and it was observed that the reaction was facilitated when a substituent at the *para*-position of tetrafluorobenzene derivative has electron-donating effect or p–pi conjugation effect (**3a–d**), on the contrary, the reaction was undermined when an electron-withdrawing group at the *para*-position of tetrafluorobenzene derivative (**3e–g**). 1,2,3,5-tetrafluorobenzene and 1,2,4,5-tetrafluorobenzene, each of which possesses two potential reaction sites, generated mixtures of mono- and di-substituted arylation products (**3i** and **3i′**, **3j** and **3j′**) in 62% and 57% overall yield, respectively. Interestingly, arylation of pentachlorobenzene was also achieved (**3h**), the low yield suggested that a C–H bond flanked with chlorine atoms was less

Table 1
Selected results of screening the optimal conditions[a]



Entry	Catalyst (mol %)	Base (equiv)	Temp. (°C)	Solvent	Isolated yield (%)
1	–	K_3PO_4 (**2**)	130	DMF	0
2	CuI (**20**)	K_3PO_4 (**2**)	130	DMF	23
3	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	DMF	54
4	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	DMSO	37
5	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	NMP	36
6	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	CH_3CN	24
7	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	THF	20
8	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	Toluene	<5
9	Pd(OAc)$_2$ (**10**)	K_3PO_4 (**2**)	130	5% DMSO–DMF	39
10	Pd(OAc)$_2$ (**10**)	KOAc (**2**)	130	5% DMSO–DMF	43
11	Pd(OAc)$_2$ (**10**)	KO^{t}Bu (**2**)	130	5% DMSO–DMF	40
12	Pd(OAc)$_2$ (**10**)	K_2CO_3 (**2**)	130	5% DMSO–DMF	<5
13	Pd(OAc)$_2$ (**10**)	LiO^{t}Bu (**2**)	130	5% DMSO–DMF	35
14	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**2**)	130	5% DMSO–DMF	76
15	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**1.5**)	130	5% DMSO–DMF	75
16	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**1**)	130	5% DMSO–DMF	70
17	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**1.5**)	130	2.5% DMSO–DMF	69
18	**Pd(OAc)$_2$ (10)**	**Ag_2CO_3 (1.5)**	110	**5% DMSO–DMF**	**74**
19	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**1.5**)	90	5% DMSO–DMF	64
20[b]	Pd(OAc)$_2$ (**10**)	Ag_2CO_3 (**1.5**)	110	5% DMSO–DMF	66

[a] Conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), solvent (2 mL), 20 h.

[b] Reaction run for 10 h.