Direct Pd-catalyzed benzylation of highly electron-deficient perfluoroarenes†‡

Shilu Fan, Chun-Yang He and Xingang Zhang*

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An efficient and practical method to a wide range of perfluorinated unsymmetrical diarylmethanes with good to excellent yields and high regioselectivities has been developed by Pd-catalyzed direct benzylation of highly electron-deficient perfluoroarenes; excellent compatibility of functional groups has also been established.

Diarylmethanes have recently received great synthetic interests due to the presence of such a motif in a range of biologically active compounds[1] and supramolecular structures.[2] The most widely used approaches to this functional group array rely on cross-couplings of a stoichiometric amount of organometallic aryl with electrophiles (aldehydes or benzyl halides).[3] However, this "prefunctionalization" process suffers from the requirement of additional steps for preparation of organometallic reagents and the incompatibility of functional groups. In this regard, direct benzylation of arenes and heteroarenes have been successfully developed recently.[4] These impressive metal-catalyzed direct C–H functionalizations provide a more effective and straightforward method to this class of compounds since the preactivation step of arenes can be avoided. However, unlike the direct benzylation of electron-rich arenes, reactions of highly electron-deficient perfluoroarenes remain a synthetic challenge. The main reason is that the pentafluorophenyl metals (C_6F_5-M) bond is particularly strong and hard to utilize due to its ionic character,[5] as a result the metal catalyzed cross-couplings of C_6F_5-M with aliphatic halides lead to undesired products.[6] Therefore, to develop an effective methodology for the direct benzylation of electron-deficient perfluoroarenes to meet these challenges is of great importance.

On the other hand, perfluoroarenes constitute a distinct class of fluorinated compounds due to their importance in materials and life science.[7] However, comparing to C–C bond formation between perfluorinated aromatic rings and arenes,[8] only a few cross-coupling methods (including C–H functionalization[8d] and traditional cross-coupling methods[6]) for connecting perfluoroarenes with alkyl (Csp^3) side chains have been reported so far. Thus, development of effective transition metal catalyzed reactions for installing various fluorinated aryl groups onto organic structures is highly desirable. Very recently, we successfully developed a straightforward method for direct olefination of perfluoroarenes by using a Pd catalyst.[9] To continue our research, herein, we disclosed an efficient and practical Pd-catalyzed protocol for Csp^2-Csp^3 direct benzylation of perfluoroarenes.

We began our studies of direct benzylation of pentafluorobenzene **1** by choosing benzyl chloride **2a** as substrate because it is inexpensive, readily available and reluctant to the reductive dehalogenation when compared to the bromo and iodo counterparts (Table 1). Although, initially, a negative result was provided when the reaction was carried out with **1** (2.0 equiv), **2a** (1.0 equiv.) and K_2CO_3 (1.2 equiv.) in the presence of $Pd(OAc)_2$ (10 mol%) at 135 °C for 24 h in the absence of a ligand (Table 1, entry 1), we were pleased to observe the formation of desired product **3a** when 20 mol% of bulky biaryldialkylphosphine **L1** was used, albeit in a low yield (30%) (Table 1, entry 2). With this preliminary result in hand, different bases were examined and Cs_2CO_3 was found to be the optimum base, providing **3a** in 80% yield (Table 1, entry 6). Other bases, such as K_3PO_4, KOAc, and Na_2CO_3 proved to be ineffective (Table 1, entries 3–5). The reaction was found to be sensitive to the reaction temperature and the nature of solvents (Table 1, entries 7–12). A lower reaction temperature (120 °C) or employing polar solvents (such as DMF, DMI, NMP) led to a much lower yield than the reaction run at 140 °C in toluene (Table 1, entry 8).

It has been demonstrated that besides trialkylphosphine and biphenyldialkylphosphine, less reactive triarylphosphine ligands may also accelerate the oxidative addition of aliphatic carbon-halogen bonds to low-valent palladium.[10] Thus, from the viewpoint of synthetic convenience and cost effectiveness, we examined the reactivity of PPh_3 in the catalytic benzylation of pentafluorobenzene. To our delight, 89% isolated yield of **3a** was afforded (Table 1, entry 16). Other ligands such as tricyclohexylphosphine, bidentate ligand, dppf, and P(o-Tol)$_3$ were less effective than PPh_3 (Table 1, entries 13–15). Further investigation of the reaction time showed that the best yield (92%) could be obtained by shortening the reaction time to 12 h (Table 1, entry 17). An attempt to decrease the $Pd(OAc)_2$ to 5 mol% resulted in the yield dramatically dropping to 53% (Table 1, entry 19). As expected, employment of benzyl bromide led to a moderate yield (Table 1, entry 18), indicative of the essentiality of benzyl chlorides to the direct benzylation of pentafluorobenzene **1**.

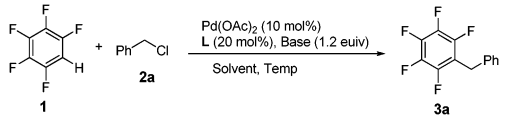
Under the optimum reaction conditions (Table 1, entry 17), the substrate scope of the direct benzylation of pentafluorobenzene **1** was tested and the representative results were illustrated in Table 2. Generally, the reaction efficiency depends on the nature of the substituents on the benzylchlorides. Substrates bearing an electron-donating group furnished the reaction smoothly in good yields (**3b–d**), while for

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. E-mail: xgzhang@mail.sioc.ac.cn; Fax: (+86)-21-6416-6128; Tel: (+86)-21-5492-5333

† In memory of Professor Keith Fagnou.

‡ Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data for all new compounds. See DOI: 10.1039/c0cc00598c

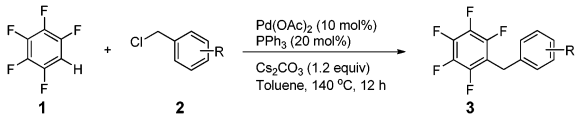
Table 1 Selected results for optimization of direct benzylation of pentafluorobenzene **1**[a]

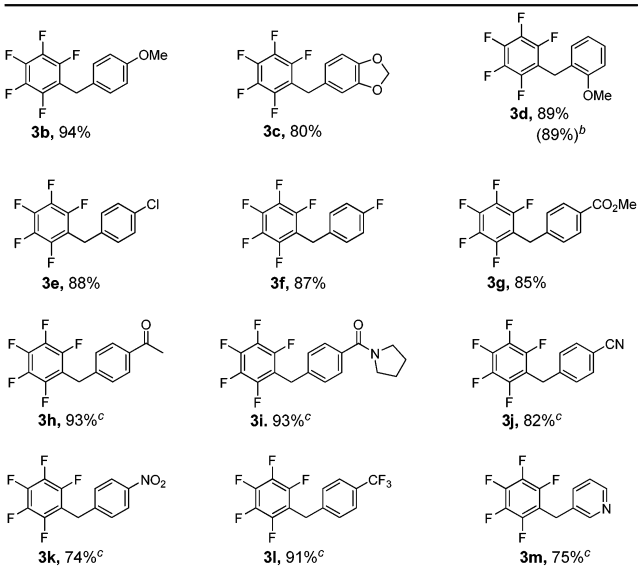


Entry	L	Base	Solvent	T/°C	Yield (%)[b]
1	None	K_2CO_3	Toluene	135	5
2	L1	K_2CO_3	Toluene	135	30
3	L1	K_3PO_4	Toluene	135	13
4	L1	KOAc	Toluene	135	23
5	L1	Na_2CO_3	Toluene	135	8
6	L1	Cs_2CO_3	Toluene	135	80
7	L1	Cs_2CO_3	Toluene	120	53
8	L1	Cs_2CO_3	Toluene	140	95 (87)
9	L1	Cs_2CO_3	Xylene	140	70
10	L1	Cs_2CO_3	DMF	140	8
11	L1	Cs_2CO_3	DMI	140	14
12	L1	Cs_2CO_3	NMP	140	41
13	$PCy_3.HBF_4$	Cs_2CO_3	Toluene	140	57
14	dppf	Cs_2CO_3	Toluene	140	63
15	P(o-Tol)$_3$	Cs_2CO_3	Toluene	140	46
16	PPh_3	Cs_2CO_3	Toluene	140	100 (89)
17[c]	PPh_3	Cs_2CO_3	Toluene	140	100 (92)
18[d]	PPh_3	Cs_2CO_3	Toluene	140	56
19[e]	PPh_3	Cs_2CO_3	Toluene	140	53

[a] Conditions: **1** (0.4 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L** (20 mol%), Base (1.2 equiv.), in solvent (1 mL), 24 h. **L1**: biphenyl-2-yldi-*tert*-butylphosphine. [b] NMR yield determined by ^{19}F NMR using fluorobenzene as internal standard and number in parentheses is isolated yield. [c] Reaction run for 12 h. [d] Using benzylbromide. [e] Using 5 mol% $Pd(OAc)_2$ and reaction run for 36 h.

Table 2 Pd-catalyzed direct benzylation of pentafluorobenzene **1** with various benzylchlorides **2**[a]





[a] Conditions: **1** (1.2 mmol, 2.0 equiv.), **2** (0.6 mmol, 1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (1.2 equiv.), toluene (2.5 mL), 140 °C, 12 h. [b] 1 gram scale reaction. [c] Using 1.2 equiv. of PivOH and 2.4 equiv. of Cs_2CO_3.

electron-withdrawing substituted benzylchlorides (**3h–m**), unsatisfied yields were afforded (see ESI Table S1‡). For further improvement of the reaction efficiency, we found that good to excellent yields were provided by employment of 1.2 equiv. of pivalic acid (PivOH).[9,11] It is noteworthy that versatile functional groups such as ester, methyl ketone, amide, nitro, nitrile and heterocycle, pyridine are compatible to the reaction conditions, providing opportunities for further functionalization without the need for protection/deprotection sequences. Importantly, product **3e** also revealed an excellent chemical selectivity at benzyl chloride over aryl chloride. A 1-*g*-scale synthesis of **3d** was also performed without difficulty (89%), indicating the good reliability of this process.

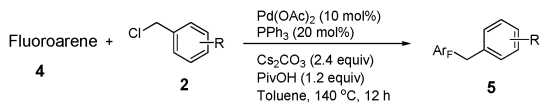
The substrate scope of fluoroarene is not restricted to pentafluoroarene **1**, variations of fluoroarenes **4** containing 2–4 fluorines were also tested (Table 3). Generally, moderate to high yields with high regioselectivities of desired products **5** were afforded under the standard conditions with 1.2 equiv. of PivOH as additive. In particular, when 1,2,4,5-tetrafluoro-3-methoxybenzene was examined, both electron-withdrawing and electron-donating substituents on the aromatic ring of the benzyl chlorides provided **5e** and **5f** in excellent yields (94%–98%). Substrates bearing functional groups, such as ester, nitrile and pyridine, all showed good tolerance to the reaction conditions. It should be pointed out that although substrates bearing 2–3 fluorines contain more than one reaction site, moderate to good yields of mono-benzylated products with high regioselectivities were still observed and the most acidic C–H bond located between two fluorines is the primary reaction site (**5k**). The low reactivity of difluoroarenes is probably due to the low acidity of the C–H bond to be activated.[12]

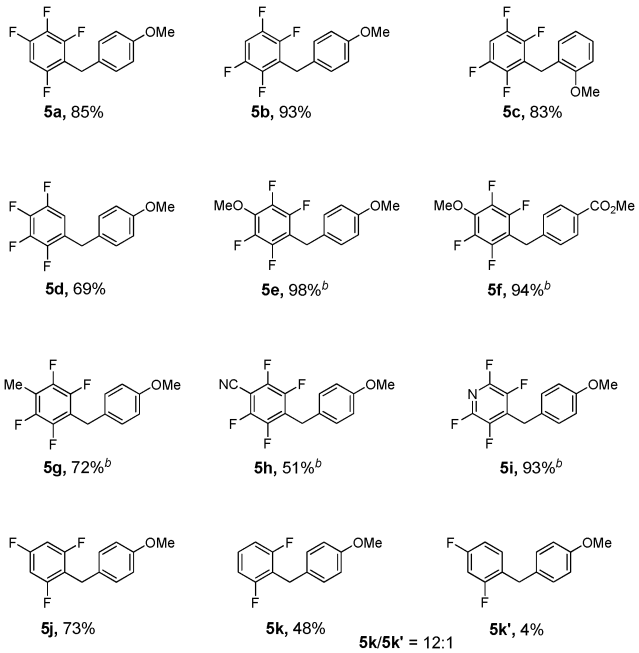
It was also possible to direct benzylation of alkenylated fluoroarene **4l** that was prepared *via* Pd-catalyzed oxidative olefination of 1,2,4,5-tetrafluorobenzene (Scheme 1).[9] The α,β-unsaturated ester was compatible with the reaction system, featuring the utility of this method compared to traditional techniques, thus allowing to access highly functionalized perfluorinated unsymmetrical diarylmethanes by a catalytic method.

Although the exact mechanism of the reaction is still not clear, on the basis of the results reported by others,[8b,13] a plausible mechanism is proposed and shown in Scheme 2. An oxidative addition of benzylchlorides **2** to a zero valent Pd species is envisioned to take place as an initial step leading to a Pd-benzyl intermediate **I**. **I** subsequently goes through the concerted metalation-deprotonation (CMD) process to form **II**.[8b,13] As the final step of the catalytic cycle, reductive elimination of **II** produces perfluorinated unsymmetrical diarylmethanes upon the regeneration of Pd(0) species.

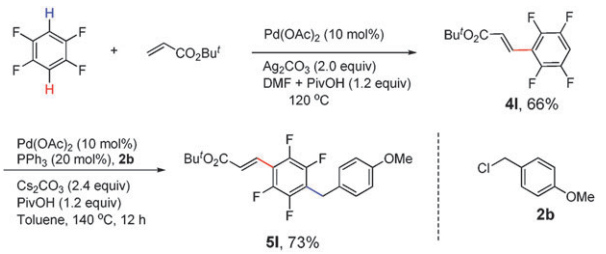
In conclusion, we developed an efficient and practical, $Pd(OAc)_2/PPh_3$ catalyzed system for direct benzylation of highly-electron deficient perfluoroarenes. The reaction affords high yields, good *chemo*- and *regio*-selectivity, and excellent functional group compatibility. Hence, it is a concise and operationally simple method to perfluorinated unsymmetrical diarylmethanes of interest in both life and materials science.

Table 3 Pd-catalyzed direct benzylation of fluoroarenes **4** with various benzylchlorides **2**[a]





[a] Conditions: **4** (1.8 mmol, 3.0 equiv.), **2** (0.6 mmol, 1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2.4 equiv.), PivOH (1.2 equiv.), toluene (2.5 mL), 140 °C, 12 h. [b] Using 2.0 equiv. of **4**.



Scheme 1 Direct benzylation of alkenylated fluoroarene **4l** with benzylchloride **2b**.

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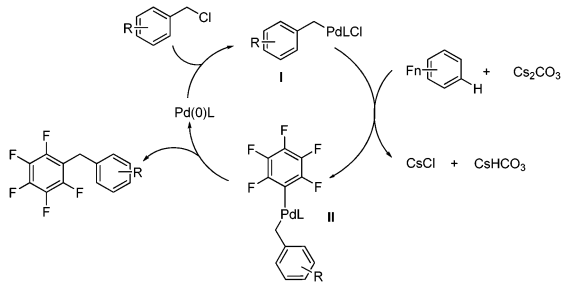

Scheme 2 Plausible mechanism of the Pd-catalyzed direct benzylation of perfluoroarenes.

