

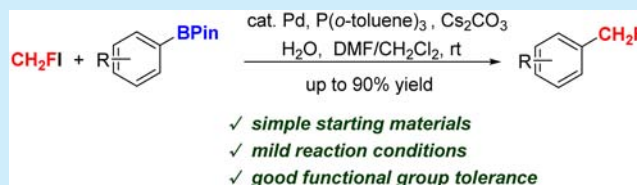
Palladium-Catalyzed Monofluoromethylation of Arylboronic Esters with Fluoromethyl Iodide

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S Supporting Information

ABSTRACT: The first palladium-catalyzed direct monofluoromethylation of arylboronic esters to produce monofluoromethyl arenes is reported. The reaction is typically carried out at room temperature within 4 h and has a good functional group tolerance. The monofluoromethylating agent, CH₂FI, was readily prepared via a halogen-exchange process.

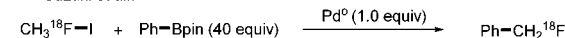


Recent years have witnessed rapidly increasing demand for organofluorine compounds. Properties of organic molecules, such as lipophilicity, metabolic stability, and bioavailability, can be significantly altered by the introduction of fluorinated moieties.¹ Therefore, organofluorine compounds have become regular candidates for agrochemicals and pharmaceuticals.² In contrast to the prosperous progress of the transition-metal-catalyzed tri-³ and difluoromethylation⁴ of arenes during the past years, the incorporation of the monofluoromethyl (CH₂F) group into arenes has been studied to a much lesser extent.⁵ Conventionally, monofluoromethyl arenes (benzylic fluorides) are prepared via nucleophilic fluorination of benzylic alcohols, their derivatives, and benzylic halides.⁶ Although this well- and long-known fluorination method is efficient and convenient for the preparation of many benzylic fluorides, it is not suitable for the late-stage monofluoromethylation of complex molecules due to the limited availability of the corresponding benzylic precursors.⁷ Considering that many biologically active molecules, such as afloqulone, fluticasone propionate, and the anesthetic sevoflurane, contain the CH₂F group as the crucial motif,⁸ the modification of complex molecules with the CH₂F group is potentially useful to improve their bioactivities. However, following Olah's report on monofluoromethylation of arenes with fluoromethanol,⁹ it is only in 2009 that the Suzuki group reported the second example of direct monofluoromethylation of arenes.¹⁰ In Suzuki's report, a large excess amount of pinacolphenylboronate (40 equiv) was treated with [¹⁸F]CH₂FI as the limiting reactant using a stoichiometric amount of palladium and the yield was modest (57%, Scheme 1).¹⁰ As an alternative, indirect monofluoromethylation of arenes assisted by removable activation groups have also appeared in recent years.^{11,12} In 2013, our group reported a copper-catalyzed debenzoylative monofluoromethylation of aryl iodides using fluoromethyl 2-pyridyl sulfone reagents.^{12a,b} More recently, Wang and co-workers reported the nickel-catalyzed monofluoromethylation of arylboronic acids, using fluoromethylating agents bearing either a phenylsulfonyl or ethoxycarbonyl

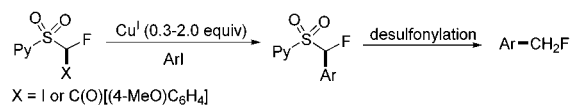
Scheme 1. Transition-Metal-Participated Cross-Coupling Monofluoromethylation Reactions

previous work:

Suzuki et al.:



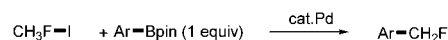
Hu et al.:



Wang et al.:



this work: catalyzed by Pd



moiety.^{12c} However, the reaction conditions of the cross-coupling step were relatively harsh, and the demand for Na(Hg) amalgam for reductive desulfonylation may limit the compatibility of the substrates.^{12c} Herein, we report a facile synthesis of CH₂FI and its use in the first example of palladium-catalyzed direct monofluoromethylation of the arylboronic esters.

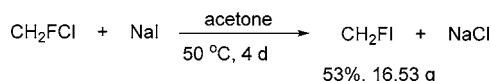
We surmised that a palladium-catalyzed monofluoromethylation using fluoromethyl iodide (CH₂FI) and boronate esters could be realized under carefully optimized reaction conditions. However, there are only a few methods to prepare CH₂FI, which use highly toxic reagents (such as HgF₂), and the purification is usually difficult.¹³ We commenced our study with a halogen-exchange process (Finkelstein reaction)¹⁴ to prepare

Received: May 10, 2015

Published: May 29, 2015

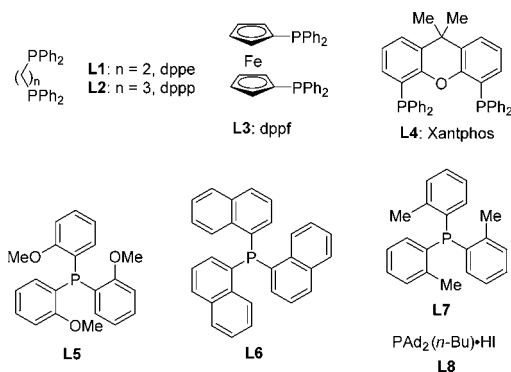
CH₂FI. We chose acetone (200 mL) as the solvent and NaI as the iodination reagent (390 mmol) to exchange the chlorine atom of CH₂FCl (195 mmol) with iodine. After purification, we obtained CH₂FI in 53% isolated yield (Scheme 2).

Scheme 2. Novel Method to Prepare CH₂FI Reagent



Having CH₂FI in hand, we chose air-stable biphenylboronic ester (**2a**) as model substrate to survey reaction conditions. In the presence of a catalytic amount of [Pd₂(dba)₃] (5 mol %) in DMF at 50 °C, with K₂CO₃ as the base and tris(*o*-tolyl)phosphine (L7, Scheme 3) as the ligand, the desired

Scheme 3. Various Ligands Used in Pd-Catalyzed Cross-Coupling Reactions



monofluoromethylated product **3a** was obtained in 20% yield (Table 1, entry 1). Thereafter, a survey of bases (see Table S1 in the Supporting Information) was conducted, which indicated that Cs₂CO₃ showed better activity (Table 1, entry 2). Similar to many other Suzuki cross-coupling reactions, the addition of water plays an important role in our reaction. With 1 equiv of water added, the yield increased to 57% (Table 1, entry 4). Finally, the optimal yield of **3a** (74%) was obtained when the reaction was carried out with CH₂Cl₂ and DMF as cosolvent (Table 1, entry 6; for details of the survey of solvents, see Tables S2 in the Supporting Information).

Using the optimized reaction conditions (Table 1, entry 6) as standard, we next investigated the influence of the ligands and palladium source. The nature of the phosphine ligand has a strong influence on the reaction outcome (Table 1, entries 6–13). Flexible bidentate phosphine ligands (L1 and L2) and rigid bidentate phosphine ligand dppf (L3)¹⁵ were ineffective in the current reaction (Table 1, entries 7–9). XantPhos (L4), a bidentate phosphine ligand with a wide bite angle,¹⁶ was found to be ineffective as well (Table 1, entry 10). The dialkylbiaryl phosphine ligands developed by Buchwald and co-workers¹⁷ were also examined, but neither of them gave a high yield (see Table S3 in the Supporting Information). Other meta or para substituted triarylphosphine ligands gave only a trace amount of the desired product (see Table S3 in the Supporting Information), which indicates that the steric nature (rather than the electronic effect) plays an important role in this reaction. The tris(2-methoxyphenyl)phosphine (L5) and tri(1-naphthyl)phosphine (L6) performed almost as effectively as tri(*o*-tolyl)phosphine (L7) (Table 1, entries 6 and 11–12).

Table 1. Survey of Reaction Conditions^a

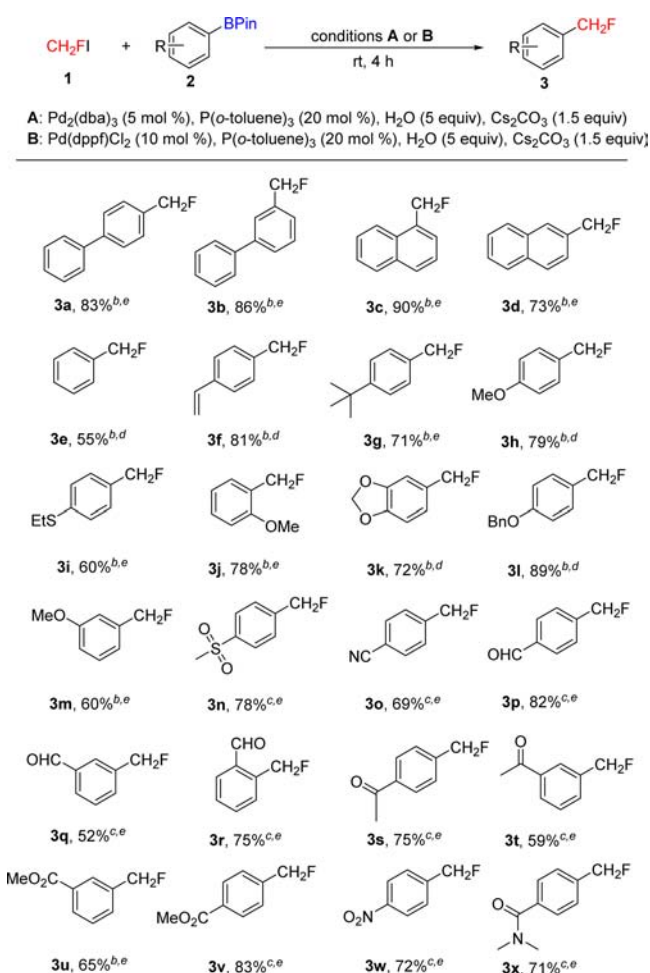
entry	ligand	[Pd]	base	H ₂ O (equiv)	yield (%) ^b
1 ^c	L7	Pd ₂ (dba) ₃	K ₂ CO ₃	–	20
2 ^c	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	–	22
3 ^c	L7	Pd ₂ (dba) ₃	K ₂ CO ₃	1.0	15
4 ^c	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	57
5 ^d	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	64
6	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	74
7 ^e	L1	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	0
8 ^e	L2	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	0
9 ^e	L3	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	0
10 ^e	L4	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	0
11	L5	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	58
12	L6	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	66
13 ^e	L8	Pd ₂ (dba) ₃	Cs ₂ CO ₃	1.0	73
14 ^f	L7	Pd(dppf)Cl ₂	Cs ₂ CO ₃	1.0	68
15 ^f	L7	Pd(OAc) ₂	Cs ₂ CO ₃	1.0	46
16 ^f	L7	Pd(PPh ₃) ₄	Cs ₂ CO ₃	1.0	39
17	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	5.0	83
18 ^g	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	5.0	87
19 ^h	L7	Pd ₂ (dba) ₃	Cs ₂ CO ₃	5.0	85 (83)

^aReaction conditions (unless otherwise noted): **2a** (0.15 mmol, 1.0 equiv), CH₂FI (1.1 equiv), [Pd] (5 mol %), ligand (20 mol %), base (1.5 equiv), DMF/CH₂Cl₂ = 1:1 (1 mL in total), 50 °C, 3 h.

^bDetermined by ¹⁹F NMR spectroscopy using benzotrifluoride as an internal standard, and yield within parentheses is that of the isolated product. ^cDMF (1 mL). ^dCH₂Cl₂ (1 mL). ^eLigand (10 mol %) was used. ^f10 mol % [Pd] was used. ^g**2a** (0.15 mmol, 1.0 equiv), room temperature, 4 h. ^h**2a** (0.50 mmol, 1.0 equiv), room temperature, 4 h.

The phosphine ligand PAD₂(*n*-Bu)-HI (L8), which was used by the Zhang group in their heteroaryldifluoromethylation reaction recently,¹⁸ also worked well in our reaction (Table 1, entry 13). Considering the cost efficiency, we finally chose tri(*o*-tolyl)phosphine as the supporting ligand. A survey of palladium sources showed that Pd₂(dba)₃ was optimal, followed by Pd(dppf)Cl₂, giving a 68% yield (Table 1, entry 14; for details, see Table S4 in the Supporting Information). Increasing the amount of CH₂FI did not improve the product yield (see Table S8 in the Supporting Information). Adjusting the amount of added water to 5 equiv improved the yield to 83% (Table 1, entry 17; for details, see Table S5 in the Supporting Information). Finally, we decreased the reaction temperature to room temperature and prolonged the reaction time to 4 h, and the 4-fluoromethyl-1,1'-biphenyl (**3a**) was isolated in 83% yield (Table 1, entry 19).

With the optimized reaction conditions (Table 1, entry 19) as standard, we examined the scope of this palladium-catalyzed monofluoromethylation of arylboronic pinacole esters (**2**). As shown in Scheme 4, both electron-neutral and electron-rich aryl boronates are compatible with this reaction, giving the corresponding products in high yields. According to the previous study,^{4h} the benzylic fluorides of anisyl and phenolic substrates are not stable because of their highly electron-rich properties. During our study, we also found the electron-rich products, such as **3h** and **3l**, decomposed during the purification process. In contrast to electron-rich and electron-neutral substrates, the reactions of electron-deficient aryl boronate esters gave low yields, with the homocoupling

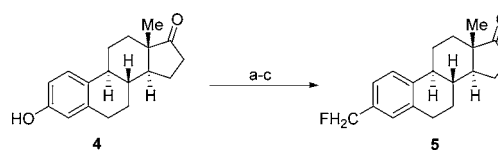
Scheme 4. Monofluoromethylation of Arylboronate Esters^a

^aReaction conditions (unless otherwise noted): **2** (0.5 mmol, 1.0 equiv), CH_2FI (1.1 equiv), $\text{P}(o\text{-toluene})_3$ (20 mol %), Cs_2CO_3 (1.5 equiv), $\text{DMF}/\text{CH}_2\text{Cl}_2 = 1:1$ (3 mL in total), room temperature, 4 h. ^bFor conditions A: $\text{Pd}_2(\text{dba})_3$ (5 mol %). ^cFor conditions B: $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mol %). ^dDetermined by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard. ^eYield of the isolated product.

product being formed as major byproducts when we used $\text{Pd}_2(\text{dba})_3$ as the catalyst. To our delight, changing the palladium catalyst from $\text{Pd}_2(\text{dba})_3$ (5 mol %) to $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mol %) significantly improved the product yields. Therefore, various boronic esters containing an electron-withdrawing group, such as sulfonyl (**3n**), cyano (**3o**), acetyl (**3t**), ester (**3u**), nitro (**3w**), and amides (**3x**), afforded the desired products in good yields (Scheme 4).

To demonstrate further the synthetic application of our monofluoromethylation protocol, we applied this method to the late-stage monofluoromethylation of biologically active compounds. Estrone-derived arylboronate ester was prepared in two steps from estrone by a palladium-catalyzed borylation reaction of the corresponding triflate.¹⁹ We carried out the monofluoromethylation under the optimized reaction conditions, and 3-monofluoromethyl-3-dehydroxyestrone (**5**) was obtained in 73% yield (Scheme 5).

In conclusion, we have described a new preparation of fluoromethyl iodide (CH_2FI) and its use in the first palladium-catalyzed direct monofluoromethylation of arylboronic esters.

Scheme 5. Monofluoromethylation of Biologically Active Estrone (**4**)^a

^a(a) TF_2O (1.1 equiv), DIPEA (1.1 equiv), 87%; (b) $[\text{Pd}(\text{dppf})\text{Cl}_2]$ (4 mol %), $(\text{Bpin})_2$ (2.0 equiv), KOAc (3.0 equiv), 69%; (c) $[\text{Pd}_2(\text{dba})_3]$ (5 mol %), $\text{P}(o\text{-toluene})_3$ (20 mol %), CH_2FI (1.1 equiv), Cs_2CO_3 (1.5 equiv), 73%.

Under mild conditions, both electron-rich and electron-deficient arylboronic esters could be monofluoromethylated in good yields. It can be easily anticipated that aryl halides and phenols are promising substrates for borylation and subsequent monofluoromethylation reactions. We also demonstrated the late-stage monofluoromethylation of a biologically active molecule using our monofluoro-methylation protocol (Scheme 5). Considering the mild conditions of this method and the high potential of monofluoromethyl-containing compounds as biologically active agents, this protocol promises to find more applications in the life-science-related fields. Further exploitation of CH_2FI -based chemistry is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01361.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2015CB931900, 2012CB821600), the National Natural Science Foundation of China (21372246, 21421002, 21402227), Shanghai City (13QH1402400 and 15XD1504400), and the Chinese Academy of Sciences.

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