Difluoroalkylation

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Palladium-Catalyzed Difluoroalkylation of Aryl Boronic Acids: A New Method for the Synthesis of Aryldifluoromethylated Phosphonates and Carboxylic Acid Derivatives**

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Abstract: *The palladium-catalyzed difluoroalkylation of aryl boronic acids with bromodifluoromethylphosphonate, bromodifluoroacetate, and further derivatives has been developed. This method provides a facile and useful access to a series of functionalized difluoromethylated arenes ($ArCF_2PO(OEt)_2$, $ArCF_2CO_2Et$, and $ArCF_2CONR^1R^2$) that have important applications in drug discovery and development. Preliminary mechanistic studies reveal that a single electron transfer (SET) pathway may be involved in the catalytic cycle.*

Functionalized difluoromethylated arenes are an important structural motif that is found in many biologically active compounds and functional materials.[1] In particular, because of the unique properties of the difluoromethylene group (CF_2), which can function as a bioisostere for an oxygen atom or a carbonyl group,[2] aryldifluoromethylated phosphonates and carboxylic acid derivatives have important applications in drug discovery and development.[3] For example, the difluoromethylene group has been used as an isopolar and isosteric substitute for oxygen atoms in the context of protein tyrosine phosphatase (PTP) inhibitors,[3b–c,4] and it has been used for the modification of biologically active compounds. Furthermore, the synthetic usefulness of these functionalized fluorinated moieties ($CF_2PO(OEt)_2$, CF_2CO_2Et, CF_2CONHR) provides a good platform for downstream transformations. Consequently, to meet the increasing demand for these materials in the life sciences and materials science, it is of great interest to develop synthetic methods for the preparation of such valuable structural motifs.

Although significant advances have been made in the preparation of trifluoromethylated arenes,[5] efficient and general methods for the synthesis of difluoromethylated aromatic compounds are less explored.[6] Generally, aryldifluoromethylated phosphonates and carboxylic acid derivatives can be accessed by difluorination of a carbonyl moiety with aminosulfur trifluorides, such as diethylaminosulfur trifluoride (DAST) or Deoxofluor,[7] and copper-mediated cross-couplings of halodifluoromethylated reagents ($BrCF_2PO(OEt)_2$, XCF_2CO_2Et) with aryl metal species or aryl halides.[8] However, these methods are incompatible with many important functional groups or use a large excess of copper or toxic cadmium precursors.[8] In this context, the transition-metal-catalyzed introduction of the difluoromethylene moiety onto arenes would be an attractive alternative. However, such a transformation has remained a significant challenge because of the instability of the difluoroalkylation reagents, which results in the formation of protonated side products or dimeric decomposition.[9] To date, only a few examples have been reported in this area;[10] their application is limited by a requirement either for electron-deficient aryl iodides or for moisture-sensitive organometallic reagents, which significantly restricted their wide usage in synthesis. Furthermore, the catalytic systems that have been developed for the preparation of aryldifluoroacetates and their derivatives[10a,b] or aryldifluoromethylphosphonates[10c] are incompatible with each other. Hence, it is highly desirable to develop new strategies and a general catalyst to address these issues. As part of systematic study on transition-metal-catalyzed reactions for the direct introduction of fluorinated moieties into organic molecules,[11] we herein describe the first example of a palladium-catalyzed difluoroalkylation of aryl boronic acids with readily and commercially available bromodifluoromethylphosphonate, bromodifluoroacetate, and their derivatives. This new method proceeds under mild reaction conditions and provides a variety of aryldifluoromethylated phosphonates and carboxylic acid derivatives with high efficiency and excellent functional-group compatibility. Furthermore, a preliminary mechanistic study is also presented.

Initially, the palladium-catalyzed reaction between phenyl bromide (**1**) and difluoro(trimethylsilyl)methylphosphonate **2** was investigated to access phenyldifluoromethylphosphonate **3a** (Scheme 1a). However, we immediately found that it was difficult to obtain **3a** with this strategy

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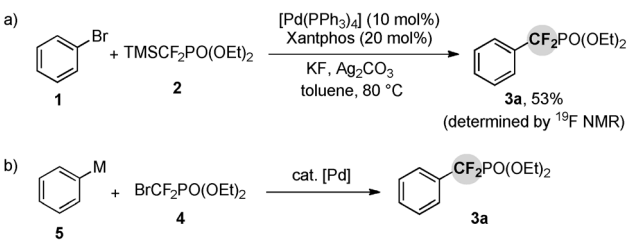
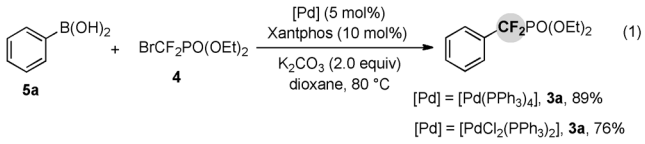


Scheme 1. Strategies for the preparation of aryldifluoromethylphosphonates **3**.

because of the formation of the protonated compound $HCF_2PO(OEt)_2$ and other unidentified byproducts. After extensive investigations, **3a** was still only obtained in moderate yield (53%, determined by ^{19}F NMR spectroscopy) when phenyl bromide **1** was treated with **2** and the $[Pd(PPh_3)_4]$/Xantphos (Pd/L = 1:2) catalytic system in toluene at 80 °C.[12] To further improve the reaction efficiency, we envisioned that if the oxidative addition of the C–Br bond of compound **4** to $[Pd^0]$ was feasible, then the utilization of the moisture-stable and commercially available bromodifluoromethylphosphonate **4** as a coupling partner would benefit the reaction. With this alternative strategy, protonation can be suppressed (Scheme 1b). To the best of our knowledge, such a palladium-catalyzed process has not been reported thus far. Even though transition-metal-catalyzed reactions between aryl metal species and alkyl halides are well established,[13] similar fluoroalkylation processes of aryl metal species with fluoroalkyl halides (R_f–X) that are catalyzed by transition metals have remained underdeveloped, and represent an ongoing challenge.[10b,14]

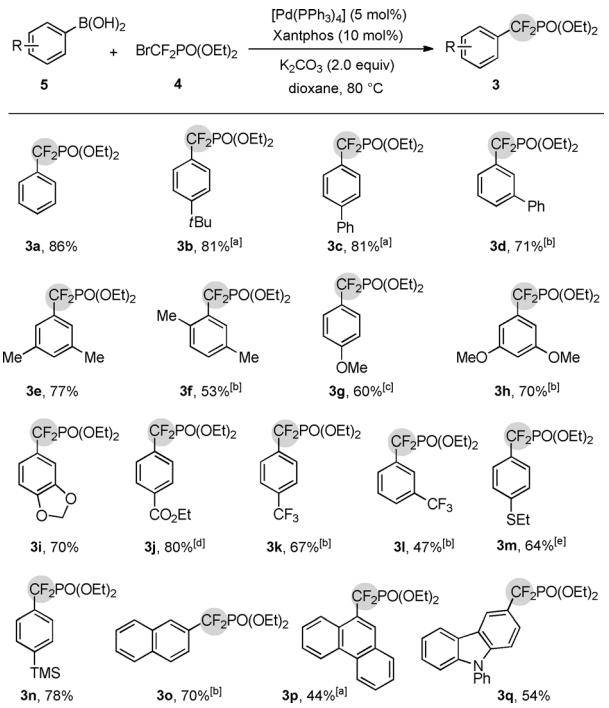
On the basis of the above hypothesis, air-stable phenylboronic acid (**5a**) was chosen as the coupling partner [Eq. (1)]. To our delight, under modified reaction conditions



(1)

(Scheme 1a), **3a** was afforded in 16% yield by using the $[Pd(PPh_3)_4]$/Xantphos/K_2CO_3 catalytic system in toluene at 80 °C (for details, see the Supporting Information). Encouraged by this result, several reaction parameters were investigated to further improve the reaction efficiency (for details, see Supporting Information). The nature of the ligand, the base, and the solvent were critical to the reaction efficiency, and the use of the bidentate ligand Xantphos, K_2CO_3, and dioxane was found to provide the most efficient reaction, providing **3a** in 89% yield, as determined by ^{19}F NMR spectroscopy [Eq. (1)]. Any changes in these three factors led to a low reaction efficiency or no conversion. Among the tested palladium sources, $[PdCl_2(PPh_3)_2]$ was also a suitable pre-catalyst, providing **3a** in good yield (76%, determined by ^{19}F NMR spectroscopy, Eq. (1)).

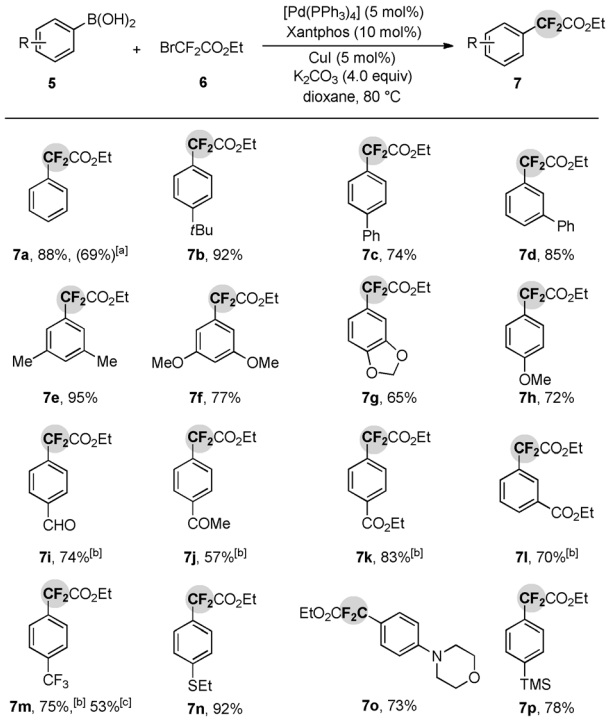
To demonstrate the substrate scope of this method, reactions with a variety of aryl boronic acids were examined (Scheme 2). In many cases, $[PdCl_2(PPh_3)_2]$ was superior to $[Pd(PPh_3)_4]$, providing a wide range of aryldifluoromethylphosphonates **3** with high efficiency. Generally, electron-rich aryl boronic acids **5** provided the corresponding difluoromethylated phosphonates in high yields (**3b–e**, **3g–i**). This is in sharp contrast to previous results, in which the reactions of aromatic derivatives that bear an electron-donating group proceeded with low reaction efficiency.[8e,10c] Electron-deficient substrates **5** were also smoothly transformed when 3 Å molecular sieves (MS) were employed as an additive (**3j–l**). Interestingly, addition of these molecular sieves also had



Scheme 2. Palladium-catalyzed phosphonyldifluoromethylation of aryl boronic acids **5** with bromodifluoromethylphosphonate **4**. Reaction conditions (unless otherwise specified): **5** (0.3 mmol), **4** (2.0 equiv), dioxane (2 mL), 24 h. Yields of isolated products are given. [a] $[PdCl_2(PPh_3)_2]$ (5 mol%). [b] $[PdCl_2(PPh_3)_2]$ (10 mol%), Xantphos (20 mol%), molecular sieves (3 Å). [c] $[PdCl_2(PPh_3)_2]$ (7.5 mol%), Xantphos (15 mol%). [d] Molecular sieves (3 Å) were added. [e] $[PdCl_2(PPh_3)_2]$ (10 mol%), Xantphos (20 mol%).

a beneficial effect on some other substrates (**3d**, **3f**, **3h**, and **3o**). However, their role in the present reaction remains elusive. Importantly, versatile functional groups (ester, thioether, trimethylsilyl) were tolerated rather well (**3j**, **3m**, **3n**). It is noteworthy that the difluoromethylated phosphonate **3o**, a protected protein phosphatase inhibitor,[15] was obtained with high efficiency. Sterically hindered aromatic boronic acids **5f** and **5p** were also suitable substrates, providing compounds **3f** and **3p** in synthetically useful yields. Furthermore, a carbazole-derived boronic acid could also be converted into the corresponding difluoromethylated product in moderate yield (**3q**). However, vinyl-substituted aryl boronic acids and vinyl boronic acids all failed to provide the desired products.

After the generality of this catalytic system had been demonstrated, the preparation of aryldifluoroacetates **7** by the present strategy was also explored (Scheme 3). To our delight, in the presence of a catalytic amount of CuI (5 mol%) as a co-promoter,[16] a large variety of difluoroacetate derivatives **7** could be generated with this method by employing bromodifluoroacetate (**6**) as the coupling partner. Both electron-rich and electron-deficient aryl boronic acids **5** furnished the corresponding difluoroacetates in high efficiency. Many versatile functional groups, such as aldehyde, ketone, ester, thioether, amine, or silyl moieties, were all tolerated under the reaction conditions (**7i–l**, **7n–p**), which highlights the advantages of the present reaction. It should be

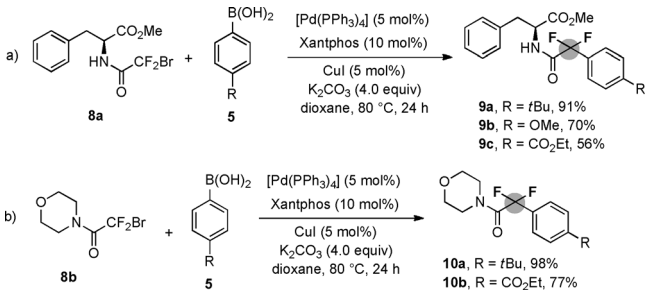


Scheme 3. Palladium-catalyzed difluoroacetylation of aryl boronic acids **5** with bromodifluoroacetate (**6**). Reaction conditions (unless otherwise specified): **5** (0.3 mmol), **6** (2.0 equiv), dioxane (2 mL), 24 h. Yields of isolated products are given. [a] Reaction carried out on a 1 g scale. [b] Molecular sieves (3 Å) were used. [c] *p*-$CF_3C_6H_4$–Bpin was used.

pointed out that the pinacol ester of an aryl boronic acid was also a suitable substrate, and **7m** was provided in moderate yield under the present reaction conditions when *p*-CF_3Ph–Bpin was used as a coupling partner (pin = pinacolato). The difluoroacetate **7a** could also be synthesized on a 1 g scale and was obtained in good yield (69%).

It was also possible to prepare aryldifluoroacetamides **9** and **10** from bromodifluoroamides **8**. The phenylalanine derivative bromodifluoroamide **8a** afforded **9a–c** in moderate to high yields (Scheme 4a). This is noteworthy as it has been demonstrated that fluorinated amino acids and their derivatives have important applications in the design of biologically active peptides and protein engineering.[17] Thus, this method provides a facile and convenient access to such valuable building blocks. Furthermore, compound **8b** was also a suitable substrate, leading to aryldifluoroacetamides **10** with high efficiency (Scheme 4b).

The importance and utility of this method is illustrated by its application to the late-stage synthesis of biologically active compounds for drug discovery and development. A protected protein phosphotyrosine phosphatase (PTPase) inhibitor[18] was obtained in synthetically useful

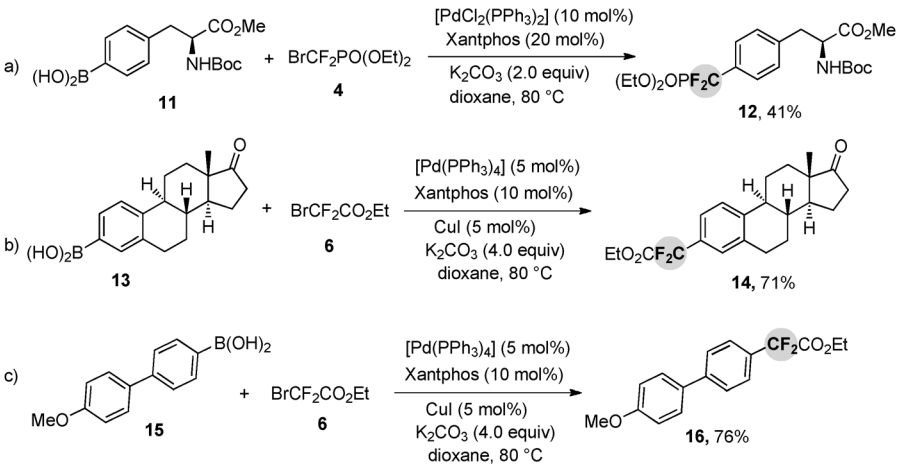


Scheme 4. Palladium-catalyzed cross-coupling of aryl boronic acids **5** with bromodifluoroacetamides **8**.

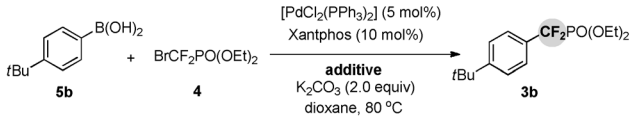
yield by the reaction of bromodifluoromethylphosphonate **4** with aryl boronic acid **11**, which is derived from tyrosine (Scheme 5a). This method was also applicable to the synthesis of the difluoroacetylated natural product estrone **14** (Scheme 5b). Furthermore, a key intermediate for the liver X-receptor modulator **16**[19] was also efficiently synthesized (Scheme 5c).

It has previously been shown that a [Pd^0] complex can initiate the generation of radicals from fluoroalkyl halides through single electron transfer (SET).[20] To identify whether a radical pathway is involved in the catalytic cycle, several radical-inhibition experiments were conducted (Scheme 6). Addition of the ET scavenger 1,4-dinitrobenzene[14b,d] or the radical inhibitor hydroquinone to the reaction mixture of **5b** and **4** in the presence of [$PdCl_2(PPh_3)_2$] (5 mol%), Xantphos (10 mol%), and K_2CO_3 led to a significant decrease of the reaction efficiency. Thus, these preliminary studies suggest that a SET pathway that proceeds via a difluoromethylene-phosphonate radical may be involved in the catalytic cycle.[21]

In conclusion, we have disclosed a first example of a palladium-catalyzed difluoroalkylation of aryl boronic acids with bromodifluoromethylated phosphonates and carboxylic acid derivatives. The bidentate ligand Xantphos is critical for the reaction efficiency. Application of this method led to biologically active compounds in good yields. As this method features several advantages, such as broad substrate scope, high efficiency, excellent functional-group compatibility, and synthetic simplicity, we believe that it should not only



Scheme 5. Synthesis of biologically active compounds.



Additive	3b, yield [%]
None	81
1,4-dinitrobenzene (0.2 equiv)	11
hydroquinone (0.2 equiv)	25

Scheme 6. Inhibition experiments for the palladium-catalyzed cross-coupling of **5b** with **4**.

be useful for drug discovery and development, but also prompt further research in the area of transition-metal-catalyzed difluoroalkylation reactions and related chemistry. Preliminary mechanistic studies reveal that a SET pathway may be involved in the catalytic cycle for the generation of aryldifluoromethylphosphonates. Further studies to determine the exact mechanism of this process and to develop derivative reactions are underway in our laboratory and will be reported in due course.

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[16] In the absence of the Pd catalyst, product **7a** was not formed; however, in the absence of CuI, **7a** was still obtained in 53% yield as determined by ^{19}F NMR spectroscopy, which indicates that CuI may act as a co-catalyst for this reaction (for details, see the Supporting Information, Table S2). For a report on the use of

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[21] A plausible mechanism for the palladium-catalyzed cross-coupling of aryl boronic acids **5** with bromodifluoromethylphosphate (**4**) is proposed in the Supporting Information.

