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# Heteroaryldifluoromethylation of Organoborons Catalyzed by Palladium: Facile Access to Aryl(Heteroaryl)difluoromethanes

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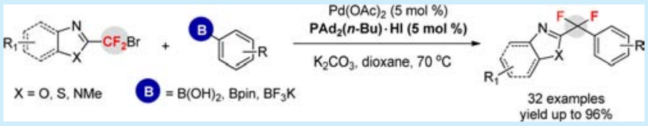
Supporting Information

**ABSTRACT:** A first example of Pd-catalyzed heteroaryldifluoromethylation of organoborons with bromodifluoromethylated heteroarenes has been described. The use of phosphine ligand $PAd_2(n\text{-Bu})\cdot HI$ is critical for the reaction efficiency. With use of this ligand, a wide range of aryl(heteroaryl)difluoromethanes were obtained with high efficiency. The notable features of this reaction are its broad substrate scope and excellent functional group compatibility, thus providing a facile protocol for application in drug discovery and development.



Benzoxazole, benzothiazole, and their derivatives are a class of prominent structural motifs found in numerous pharmaceuticals and agrochemicals.[1] Conceptually, introduction of a difluoromethylene group ($CF_2$) or a functionalized difluoromethylated group ($CF_2R$) onto such heteroarene motifs could lead to the discovery of some interesting bioactive molecules. This is because the $CF_2$ group[2] can functionalize as a bioisostere of the oxygen or a carbonyl group,[3] and can dramatically improve the metabolic stability and change physiochemical properties of biologically active molecules.[4] Traditionally, the $CF_2$ group can be generated by reaction of carbonyl groups with aminosulfur trifluorides.[5] However, the drawbacks of these reactions, such as important functional group incompatibility and use of expensive and toxic fluorinated reagents, significantly limit their widespread synthetic applications. In this context, the use of readily available difluoromethylated sources as starting materials for further transformations would be an attractive alternative.[6] Recently, bromodifluoromethylated benzoxazole, benzothiazoles, and their derivatives have emerged as one of the useful difluoromethylated building blocks for the preparation of fluorinated heteroarene derivatives.[7] However, most of the reported examples are limited to the nucleophilic heteroaryldifluoromethylation of electrophiles, such as aldehydes.[7a,b] To date, due to the lack of general and efficient strategies, there are rare examples of using bromodifluoromethylated heteroarene as electrophiles for carbon−carbon bond formation,[8] and the use of transition-metal-catalyzed cross-coupling processes to construct $Ar-CF_2HetAr$ systems remains challenging.[9] Hence, it is of great interest to develop new strategies and efficient methods to prepare such important fluorinated structures.

Very recently, we developed an efficient method for direct difluoroalkylation of arenes through a palladium-catalyzed process that linked difluoroalkyl halides ($R_f$-Br, $R_f = CF_2P(O)(OEt)_2$, $CF_2CO_2Et$) and arylboronic acids, which represents an efficient strategy to access fluorinated arenes.[9c] Inspired by this preliminary study, herein we describe the first example of palladium-catalyzed heteroaryldifluoromethylation of organoborons with bromodifluoromethylated benzoxazole, (benzo)thiazoles, and benzoimidazole in the presence of phosphine ligand, $PAd_2(n\text{-Bu})\cdot HI$ that has been rarely utilized for fluoroalkylation.[10] The reaction proceeds under mild reaction conditions with excellent functional group compatibility, and is applicable to a wide range of organoborons, including arylboronic acids, boronates, and potassium trifluoroborate salts, thus providing a facile access to a series of aryl(heteroaryl)difluoromethanes. An especially significant feature of this protocol is the successful heteroaryldifluoromethylation of bioactive compounds, thus providing a useful protocol for drug discovery and development.

We began this study by choosing 2-(bromodifluoromethyl)benzo[*d*]oxazole **1a**[7b,e] and phenyl boronic acid **2a** as model substrates (Table 1). Initially, the reaction was tested with 5 mol % of $Pd(OAc)_2$ and a range of phosphines in the presence of $K_2CO_3$ (2.0 equiv) in dioxane at 80 °C (Table 1, entries 1−10). It was found that the reaction was very sensitive to the phosphine ligands, good yield (64% determined by $^{19}F$ NMR) of **3a** was obtained when bidentate ligand XantPhos (5 mol %) was used (Table 1, entry 9). This finding is in accordance with our previous results, in which only XantPhos that bound Pd with a large bite angle showed good reactivity.[9c,11] To our delight, however, the bulky ligand cataCXium HI [$PAd_2(n\text{-Bu})\cdot HI$][10] provided **3a** in even much higher yield (95% determined by $^{19}F$ NMR, Table 1, entry 10). We assumed that this is attributed to the formation of an active T-shaped palladium complex $(Ph)(CF_2HetAr)Pd[PAd_2(n\text{-Bu})]$ that benefits the reductive elimination.[12] But the extremely sterically hindered ligand BrettPhos[13] failed to afford the desired product (Table 1, entry 8). Similar negative results were also found by using other phosphine ligands (Table 1, entries 1−7). The choice of solvent is also critical for the reaction efficiency (for details, see

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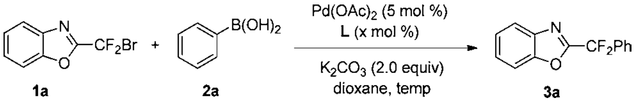
Table 1. Representative Results for Optimization of Pd-Catalyzed Cross-Coupling between **1a** and **2a**[a]



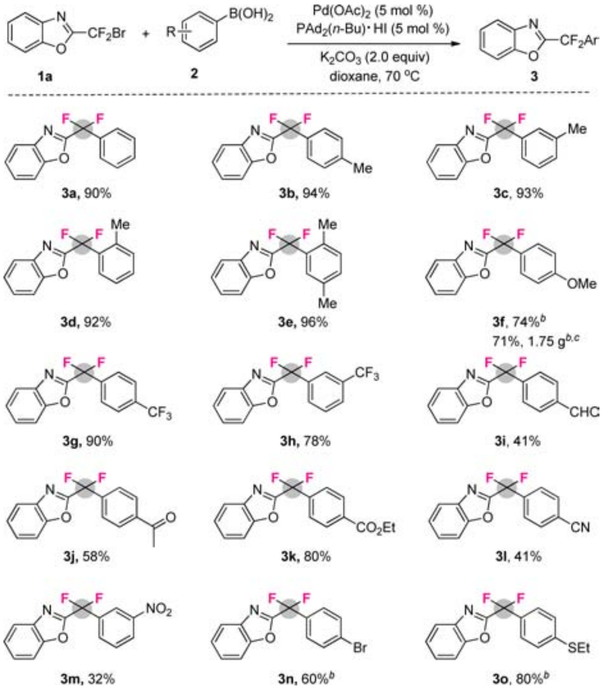
| entry | L (*x*) | temp (°C) | yield (%)[b] |
|---|---|---|---|
| 1 | $PPh_3$ (10) | 80 | ND |
| 2 | $PCy_3 \cdot HBF_4$ (10) | 80 | ND |
| 3 | P*t*-$Bu_3 \cdot HBF_4$ (10) | 80 | ND |
| 4 | DavePhos (10) | 80 | trace |
| 5 | RuPhos (10) | 80 | trace |
| 6 | XPhos (10) | 80 | trace |
| 7 | SPhos (10) | 80 | trace |
| 8 | BrettPhos (10) | 80 | NR |
| 9 | XantPhos (5) | 80 | 64 |
| 10 | $PAd_2$(*n*-Bu)·HI (10) | 80 | 95 |
| 11 | $PAd_2$(*n*-Bu)·HI (10) | 70 | 95 (90) |
| 12 | $PAd_2$(*n*-Bu)·HI (10) | 60 | 90 |
| 13 | $PAd_2$(*n*-Bu)·HI (7.5) | 70 | 95 (90) |
| 14 | $PAd_2$(*n*-Bu)·HI (5) | 70 | 92 (90) |
| 15[c] | $PAd_2$(*n*-Bu)·HI (5) | 70 | NR |
| 16 | none | 70 | NR |

[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol), **2a** (1.5 equiv), dioxane (2 mL), 7 h. [b] NMR yield determined by $^{19}F$ NMR using fluorobenzene as an internal standard (isolated yield in parentheses). [c] Reaction run in the absence of $Pd(OAc)_2$.

Supporting Information). Dioxane is the optimum reaction media. The nonpolar solvent toluene also furnished **3a** in high yield (85% determined by $^{19}F$ NMR). But other solvents, such as DMF and DMSO, led to no product. Finally, the optimal reaction conditions were identified by decreasing the loading amount of $PAd_2$(*n*-Bu)·HI to 5 mol % with utilization of $Pd(OAc)_2$ (5 mol %), $K_2CO_3$ (2.0 equiv) in dioxane at 70 °C (Table 1, entry 14). The use of 1/1 ratio of Pd/$PAd_2$(*n*-Bu)·HI also suggested that a heteroaryldifluoromethylpalladium bromide dimer {$(HetArCF_2)Pd(Br)[PAd_2(n\text{-}Bu)]$}$_2$ formed from the oxidative addition of $RCF_2$−Br bond to $Pd(0)L_n$ was generated during the reaction.[12] Yet the absence of palladium catalyst or phosphine ligand resulted in no product, thus demonstrating the essential roles of both palladium and phosphine ligand for the catalytic cycle (Table 1, entries 15 and 16).

To demonstrate the substrate scope of this method, a variety of arylboronic acids were examined (Scheme 1). Overall, moderate to high yields of **3** were obtained through the present Pd-catalyzed cross-coupling process between **1a** and arylboronic acids **2**, in which aromatic boronic acids bearing electron-rich groups furnished their corresponding products in higher yields than those substrates bearing electron-deficient groups. A variety of versatile functional groups, including base or nucleophile sensitive functional groups, such as formyl, enolizable ketone, alkoxycarbonyl, cyano, nitro, and thioether, were compatible with the reaction (**3i**−**3m** and **3o**). Most remarkably, bromide was also tolerated quite well (**3n**). But in this case, the utilization of $Pd(PPh_3)_4$ (5 mol %) and XantPhos (5 mol %) instead of $Pd(OAc)_2$ (5 mol %) and $PAd_2$(*n*-Bu)·HI showed good activity (**3n**). Thus, this palladium-catalyzed process provide a good platform for downstream transformations. In addition, the sterically hindered substrates **2d** and **2e** did not interfere with the reaction efficiency, providing **3d** and **3e** respectively, in high yields. A gram scale synthesis of **3f** was also performed without affecting the reaction efficiency, thus demonstrating the good reliability of the present reaction (**3f**).

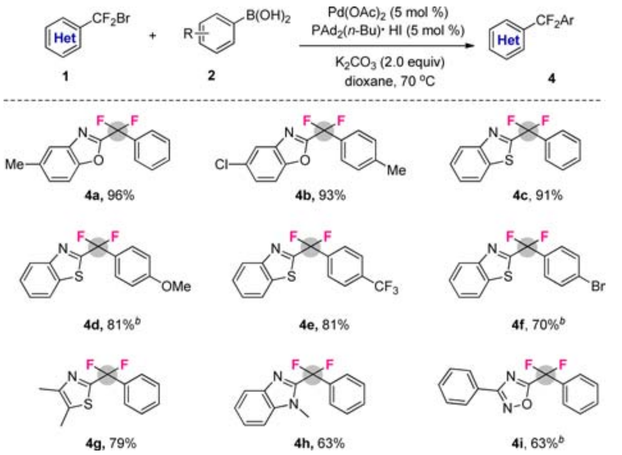
Scheme 1. Pd-Catalyzed Cross-Coupling between **1a** and Aryl Boronic Acids[a]



[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **2** (1.5 equiv), dioxane (3.5 mL), 7 h. [b] $Pd(PPh_3)_4$ (5 mol %), XantPhos (5 mol %). [c] Reaction carried out on a gram scale.

The reaction was not restricted to 2-(bromodifluoromethyl)-benzo[*d*]oxazole **1a**, as other heteroaryldifluoromethyl bromides were also suitable substrates (Scheme 2). Benzoxazole bearing a methyl or a chloride group underwent the reaction smoothly (**4a** and **4b**). The bromodifluoromethylated

Scheme 2. Pd-Catalyzed Cross-Coupling between Heteroaryldifluoromethyl Bromides **1** and Aryl Boronic Acids[a]

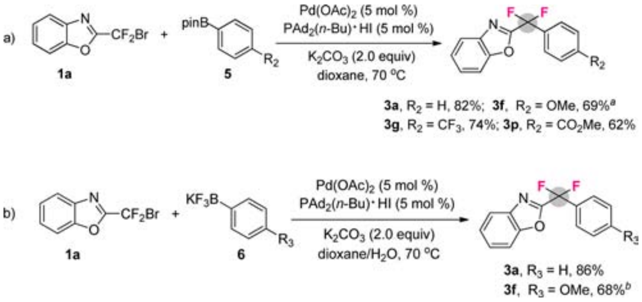


[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol), **2** (1.5 equiv), dioxane (3.5 mL), 7 h. [b] $Pd(PPh_3)_4$ (5 mol %), XantPhos (5 mol %).

benzothiazole, thiazole, and benzoimidazole were also applicable to the present cross-coupling reactions, providing their corresponding products with high efficiency (**4c**−**h**). Notably, oxadiazole substituted difluoromethyl bromide was also a competent coupling partner, with a good yield being obtained (**4i**).

The heteroaryldifluoromethylation of arylboronic acids can also be extended to aryl boronates **5** (Scheme 3a). This is noteworthy, as the aromatic pinacol ester can be easily accessed through Ir-catalyzed C−H borylation.[14] Thus, this transformation provides a good opportunity for direct fluorination of biologically active molecules for drug discovery and development. What is more, aryl potassium trifluoroborate salt **6** also underwent smooth reaction, thus highlighting the good generality of the present reaction (Scheme 3b).

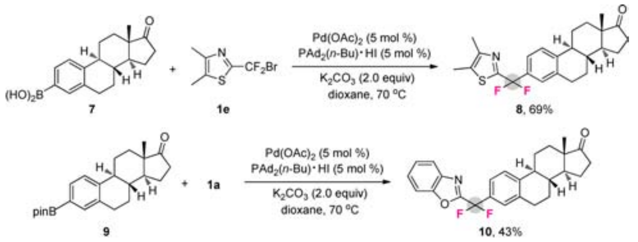
**Scheme 3. Heteroaryldifluoromethylation of Organoborates and Potassium Trifluoroborate Salts**



[a] **1a** (0.5 mmol), **5** (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), XantPhos (5 mol %), $K_2CO_3$ (2.0 equiv), dioxane (3.5 mL), 7 h. [b] **1a** (0.5 mmol), **6** (1.5 equiv), $Pd(PPh_3)_4$ (5 mol %), XantPhos (5 mol %), $K_2CO_3$ (2.0 equiv), dioxane (3.5 mL), $H_2O$ (100 $\mu$L) 7 h.

The utility of this reaction can also be demonstrated by heteroaryldifluoromethylation of biologically active molecules. As shown in Scheme 4, treatment of the estrone-derived arylboronic acid **7** with bromodifluoromethylated thiazole **1e** afforded heteroaryl difluoromethylated compound **8** with high efficiency. Although the reaction of arylboronate **9** with **1a** furnished its difluoroalkylated estrone **10** in a reasonable yield, the success of this transformation provides the possibility for sequential C−H borylation/heteroaryldifluoromethylation of biologically active molecules.

**Scheme 4. Heteroaryldifluoromethylation of Biologically Active Molecules**



In conclusion, we have disclosed the first example of Pd-catalyzed heteroaryldifluoromethylation of organoborons with bromodifluoromethylated heteroarenes. The reaction allowed heteroaryldifluoromethylation of a wide range of organoborons, including arylboronic acids, boronates, and potassium trifluoroborate salts under mild reaction conditions. Application of the method led to difluoroalkylated, biologically active molecules with high efficiency, thus providing a facile route for application in drug discovery and development. The phosphine ligand $PAd_2$(*n*-Bu)·HI used in this study has been rarely utilized for fluoroalkylation, but showed good activity, offering a new opportunity for further study in other derived fluoroalkylation reactions. Further studies to uncover the mechanism as well as other derivative reactions are now in progress in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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