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Highly Selective *gem*-Difluoroallylation of Organoborons with Bromodifluoromethylated Alkenes Catalyzed by Palladium

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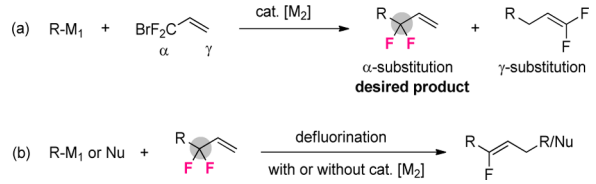
Supporting Information

ABSTRACT: A first example of Pd-catalyzed *gem*-difluoroallylation of organoborons using 3-bromo-3,3-difluoropropene (BDFP) in high efficiency with high α/γ-substitution regioselectivity has been developed. The reaction can also be extended to substituted BDFPs and has advantages of low catalyst loading (0.8 to 0.01 mol %), broad substrate scope, and excellent functional group compatibility, thus providing a facile route for practical application in drug discovery and development.

The importance of fluorinated compounds in agrochemicals, pharmaceuticals, and materials science[1] has triggered an explosion of research efforts in developing new and efficient methods to introduce fluorinated functional groups into organic molecules. Over the past few years, although considerable progresses have been achieved in fluorination and trifluoromethylation of organic substrates,[2] to date, strategies for introduction of a difluoromethylene (CF_2) group into organic molecules have been less explored[3] despite the unique properties and important biological activity of compounds containing CF_2.[4] For instance, CF_2 is usually considered as a bioisostere of the oxygen or a carbonyl group,[5] which leads to increased dipole moments, enhanced acidity of its neighboring group, and conformational changes.[6] In particular, the introduction of a CF_2 onto the aromatic rings can dramatically improve the metabolic stability and oral bioavailability of biological active compounds.[7] Generally, such a structural moiety is achieved by conversion of carbonyl group with DAST or deoxofluor.[8] But the intrinsic limitations of this method, such as the important functional groups incompatibility and the use of expensive and toxic fluorinated reagents, significantly restrict its widespread synthetic applications. To address these issues, one alternative approach is to directly introduce a functionalized CF_2 group into the organic molecules catalyzed by transition metal. However, these difluoroalkylation processes still remain challenging, and only a handful of examples have been developed so far.[9,10]

As part of ongoing study in transition-metal-catalyzed reactions for introduction of fluorinated functional groups into organic molecules,[11] herein we demonstrate the feasibility of Pd-catalyzed *gem*-difluoroallylation. The *gem*-difluoroallyl group ($CF_2CH{=}CH_2$) is extremely appealing due to the versatile synthetic utility of the carbon=carbon double bond. However, synthetically useful methods to access such valuable structures are rare.[12] We chose 3-bromo-3,3-difluoropropene (BDFP) as the starting reagent for *gem*-difluoroallylation because it is readily and commercially available,[13] and a transition-metal-catalyzed cross-coupling between the low cost BDFP and widely available organometallics would thus provide a cost-efficient access to *gem*-difluoroallylated structures that can be applied in the synthesis of bioactive compounds. In this study, we focused our research on addressing three crucial issues: (1) regiochemical selectivity, i.e., α- vs γ-substitution (Scheme 1a); (2) efficient catalytic system

Scheme 1. Transition-Metal-Catalyzed Cross-Coupling Between 3-Bromo-3,3-difluoropropene and Organometallics



that can suppress undesired defluorination side reaction resulted from *gem*-difluoroallylated products[14] (Scheme 1b); and (3) efficient and practical processes with broad substrate scope. As a result, we disclose the first example of highly selective Pd-catalyzed *gem*-difluoroallylation of organoborons with BDFP. The reaction can also be extended to substituted BDFPs. The notable advantages of this reaction are its high efficiency and regioselectivity (α/γ up to >37:1), low catalyst loading (0.8 to 0.01 mol % Pd), applicability for large scale production (10 g), broad substrate scope, and excellent functional group compatibility.

We began our study with the reaction of air stable (4-(*tert*-butyl)phenyl)boronic acid **1a** and BDFP **2** in the presence of Pd-catalyst (Table 1). After screening the reaction conditions, we found a 77% yield of a mixture of **3a** and **4a** with α-substitution **3a** as major product (**3a**/**4a** = 6.2:1) was obtained when the reaction was carried out with **1a** (1 mmol), **2** (2 equiv), Cs_2CO_3 (1.5 equiv), $Pd(OAc)_2$ (5 mol %), and PPh_3 (10 mol %) in dioxane at 80 °C (Table 1, entry 1). Notably, no defluorination of **3a** was observed under these reaction conditions. This is in sharp contrast to previous results, in which the defluorination of *gem*-difluoroallylated compounds frequently occurred.[14] The reaction was also found very sensitive to the bases (Table 1, entries 2−5) and solvents. K_2CO_3 and dioxane were the optimal choice. Other bases and solvents led to either lower yields or poor regioselectivities. No product was obtained when polar solvents,

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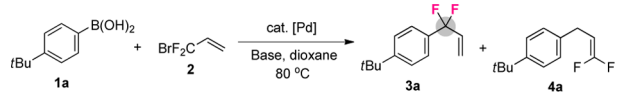
Table 1. Representative Results for Optimization of Pd-Catalyzed Cross-Coupling between 1a and 2[a]



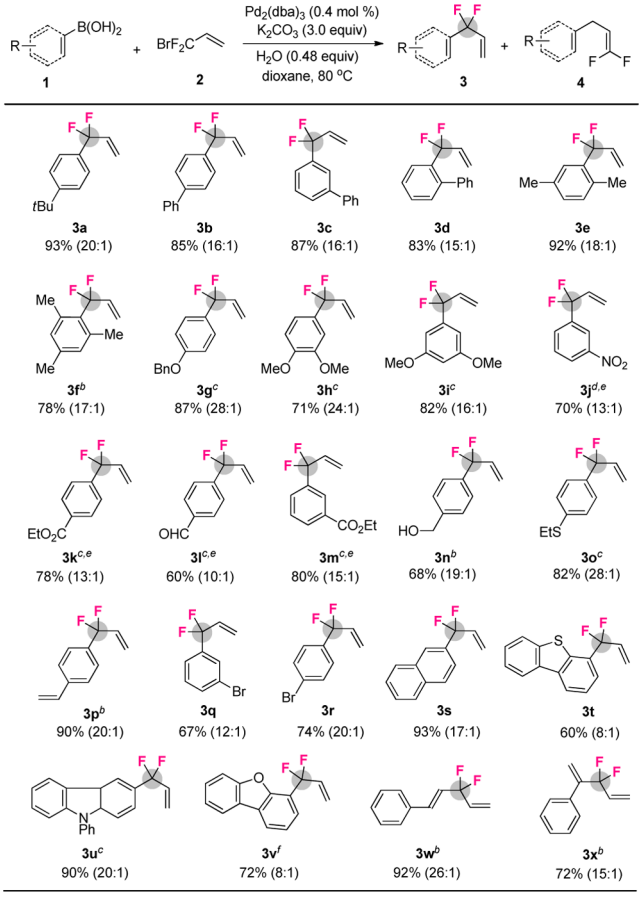
entry	[Pd] (mol %)	base (equiv)	3a + 4a yield (%), 3a/4a[b]
1[c]	$Pd(OAc)_2$ (5)	Cs_2CO_3 (1.5)	77, 6.2:1
2[c]	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	78, 6.4:1
3[c]	$Pd(OAc)_2$ (5)	Na_2CO_3 (1.5)	26, 5.9:1
4[c]	$Pd(OAc)_2$ (5)	KOAc (1.5)	11, only **3a**
5[c]	$Pd(OAc)_2$ (5)	K_3PO_4 (1.5)	28, 5.9:1
6	$Pd(PPh_3)_4$ (5)	K_2CO_3 (1.5)	75, 3.2:1
7	$Pd(PPh_3)_4$ (0.4)	K_2CO_3 (1.5)	97, 9.4:1
8	$Pd(PPh_3)_4$ (0.2)	K_2CO_3 (1.5)	94, 10:1
9	$Pd_2(dba)_3$ (0.4)	K_2CO_3 (1.5)	89, 20:1
10[d]	$Pd_2(dba)_3$ (0.1)	K_2CO_3 (1.5)	77, 20:1
11[d]	$Pd_2(dba)_3$ (0.05)	K_2CO_3 (1.5)	73, 20:1
12[e]	$Pd_2(dba)_3$ (0.4)	K_2CO_3 (3.0)	92 (93), 20:1

[a]Reaction conditions (unless otherwise specified): **1a** (1.0 mmol, 1.0 equiv), **2** (1.5 equiv), dioxane (5 mL), 80 °C, 24 h under N_2. [b]Determined by ^{19}F NMR using trifluoromethylbenzene as internal standard, and number in parentheses is isolated yield. The ratio of **3a**/**4a** was determined by ^{19}F NMR before working up. [c]Using 2.0 equiv of **2**, 10 mol % PPh_3. [d]Using 1.2 equiv of **2**. [e]Using 0.48 equiv of H_2O, and reaction was conducted under air.

such as DMF, DMSO, and CH_3CN, were used due to the formation of uncertain byproducts from BDFP (see Supporting Information (SI)). To our delight, a low catalyst loading of $Pd(PPh_3)_4$ (0.2 mol %) showed a beneficial effect on both reaction efficiency and regioselectivity (94% yield, **3a**/**4a** = 10:1) (Table 1, entry 8). Switching $Pd(PPh_3)_4$ to $Pd_2(dba)_3$ dramatically increased the α/γ (**3a**/**4a**) regioselectivity (**3a**/**4a** = 20:1) (Table 1, entry 9). Importantly, even the amount of catalyst loading was reduced to 0.05 mol % in combination of 1.2 equiv of **2**, high yield of **3a** was still afforded while maintaining high levels of regioselectivity (Table 1, entry 11). Finally, the optimal reaction conditions were identified by increasing the amount of K_2CO_3 to 3.0 equiv with utilization of 0.48 equiv of H_2O (Table 1, entry 12), providing **3a** in high yield with excellent regioselectivity (**3a**/**4a** = 20:1) (for details see SI). It is noteworthy that this reaction could be successfully conducted under air in wet solvent, thus featuring an operational simplicity advantage of the present process. It should be mentioned that even BDFP **2** was treated with 2.5 equiv of **1a** under optimized reaction conditions (Table 1, entry 12), only 5% yield (determined by ^{19}F NMR) of defluorinated side product fluoroolefin was observed, and 90% yield of desired product **3a** still could be obtained with high α/γ regioselectivity (**3a**/**4a** > 20:1) (for details see SI).

To ascertain the substrate scope of this method, a wide range of aryl boronic acids was then examined (Table 2). Generally, aromatic boronic acids bearing either electron-rich or electron-deficient substituents all led to **3** in high yields with high to excellent α/γ regioselectivities (**3a**−**m**). Importantly, in many cases the $Pd_2(dba)_3$ loading can be reduced to 0.2 mol % without compromising the reaction efficiency and α/γ regioselectivities (**3g**−**i**, **3k**−**m**). However, in the case of 3-nitrophenyl boronic acid, a dramatically decreased yield (44% determined by ^{19}F NMR) of **3j** was observed. Further improvement of the reaction efficiency by employing $Pd(PPh_3)_4$ (0.4 mol %) in conjunction with catalytic amount of CuI (6 mol %) provided **3j** in good yield

Table 2. *gem*-Difluoroallylation of Organoboronic Acids 1 with 2[a]



[a]Reaction conditions (unless otherwise specified): **1** (1 mmol), **2** (1.5 mmol), dioxane (5 mL) under air for 24 h. All reported yields are combined isolated yields of **3** and **4**. The ratio of **3**/**4** in parentheses was determined by ^{19}F NMR before working up. [b]1.5 mmol of **1** and 1.0 mmol of **2** were used. [c]0.2 mol % of $Pd_2(dba)_3$ was used. [d]0.4 mol % of $Pd(PPh_3)_4$ and 6 mol % of CuI were used. [e]2.0 mmol of **2** and 2.0 mmol of K_2CO_3 were used. [f]0.2 mol % of $Pd(PPh_3)_4$ was used.

(70%) with high regioselectivity (**3j**/**4j** = 13:1). The steric effect of the aromatic boronic acids did not interfere with the reaction. The phenyl substituent at the *para*, *meta*, and *ortho* position of the phenyl boronic acid afforded the corresponding products **3** in high efficiency with high α/γ regioselectivity (**3b**−**d**). Notably, even sterically hindered mesitylboronic acid previously demonstrated to be a challenging substrate for fluoroalkylation was also a competent coupling partner (**3f**), thus demonstrating the generality of the present reaction.

A variety of versatile functional groups (nitro, ester, aldehyde, alcohol, thioether, and vinyl) were quite well-tolerated (**3j**−**p**). Most remarkably, the successfully selective formation of **3q**−**r** with intact bromide provided a good platform for further functionalization. Heteroaromatic rings are a prominent structural motif found in numerous pharmaceuticals and agrochemicals. Boronic acids derived from dibenzo[*b*,*d*]-thiophene, carbazole, and dibenzo[*b*,*d*]furan all underwent *gem*-difluoroallylation smoothly (**3t**−**v**). Most importantly, N-containing heterocycle carbazole furnished its *gem*-difluoroallylated product **3u** in 90% yield with high regioselectivity (**3u**/**4u** = 20:1). However, pyridine-containing boronic acids were not suitable substrates. Furthermore, the reaction was not restricted

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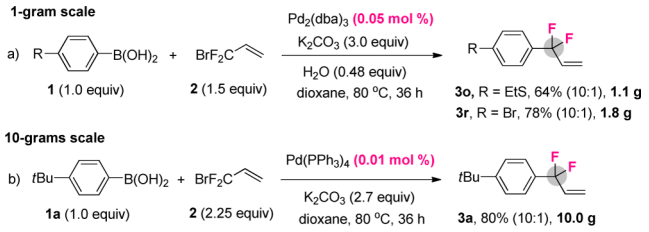
to the (hetero)aryl boronic acids, vinyl boronic acids were also suitable substrates and provided linear and branched *gem*-difluoromethylenated dienes in high efficiency with high to excellent α/γ regioselectivities (**3w–x**).

In spite of substantial progress in fluoroalkylation of organic molecules, efficient method that enables low catalyst loading to practically synthesize fluorinated compounds has received rare attention. In this context, gram-scale synthesis of *gem*-difluoroallylated arenes **3** with utilization of 0.1 to 0.01 mol % of Pd catalyst was conducted to demonstrate the synthetic utility of the protocol further (Scheme 2). As shown in Scheme 2a, gram-scale synthesis of **3o** and **3r** in the presence of 0.05 mol % $Pd_2(dba)_3$ proceeded smoothly with high α/γ regioselectivity, thus offering a reliable and practical access to highly functionalized difluoromethylenated structure. Most excitingly, a 10 g-scale reaction with Pd-catalyst loading as low as 0.01 mol % afforded **3a** in 80% yield with high regioselectivity (α/γ = 10:1) (Scheme 2b). To the best of our knowledge, this is the first example of transition-metal-catalyzed fluoroalkylation of organic molecules by using as low as 0.01 mol % catalyst in a practical manner.

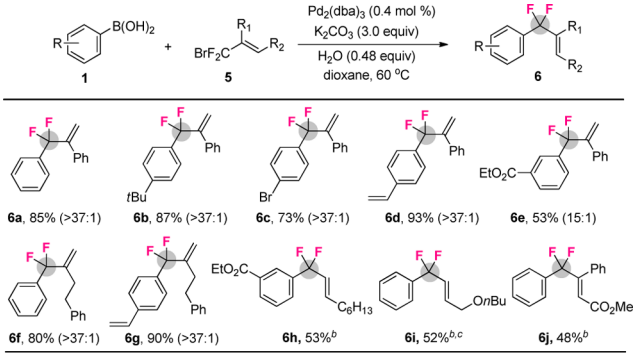
Scheme 2. Gram-Scale Synthesis of *gem*-Difluoroallylated Arenes with Low Catalyst Loading[a]



[a]All reported yields are combined isolated yields of **3** and **4**, and the number in parentheses is the ratio of **3**/**4**.

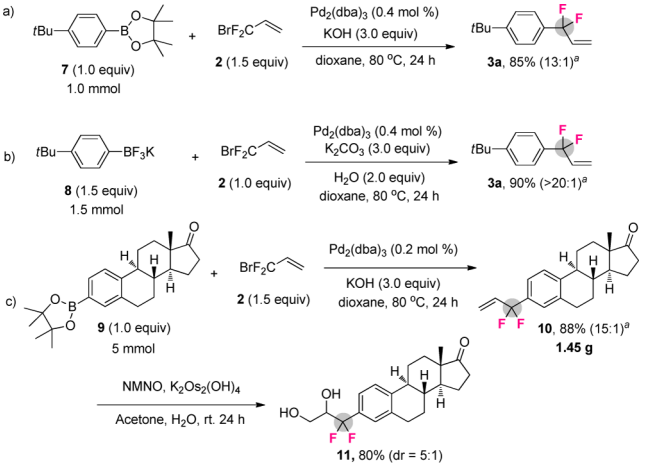
The substituted BDFPs[15] were also applicable to the reaction. As shown in Table 3, branched BDFP derivatives including phenyl and alkyl-substituted substrates underwent the *gem*-difluoroallylation in high efficiency with excellent α/γ regioselectivity (**6a–g**). Again, important functional groups were compatible with the reaction conditions (**6c–e**, **6g**). It was found that the linear substituted BDFPs were more reactive than BDFP and resulted in some undesired defluorinated compounds and other uncertain byproducts. To our delight, decreasing the reaction temperature and using $Pd(PPh_3)_4$ (0.4 mol %) as a catalyst could afford *gem*-difluoallylated products in moderate yields (**6h–i**). Importantly, no branched products (γ-substitution) were observed during the reaction. We reasoned that this is probably due to the steric effect of the substituents. It should be pointed out that bisubstituted BDFP was also a suitable substrate, providing **6j** in synthetically useful yield. This is noteworthy, as it is difficult to prepare such fluorinated molecule otherwise.

Table 3. *gem*-Difluoroallylation of Organoboronic Acids 1 with Substituted BDFPs 5[a]



[a]Reaction conditions (unless otherwise specified): **1** (1.3 mmol), **5** (1.0 mmol), dioxane (5 mL) under air for 10 h. All reported yields are combined isolated yields, the number in parentheses is the ratio of α/γ. [b]0.4 mol % of $Pd(PPh_3)_4$ and 3.0 mmol of KOH were used. [c]1.0 mmol of **1** and 1.3 mmol of **5** were used.

Scheme 3. *gem*-Difluoroallylation of Organoborates and Potassium Trifluoroborate Salt[a]



[a]Combined isolated yield of α and γ substitutions, and the number in parentheses is the ratio of α/γ.

α/γ regioselectivity (**3a**/**4a** = 13:1) was obtained by reaction of arylborate **7** with BDFP **2** (Scheme 3a). Furthermore, aryl potassium trifluoroborate salt **8** also underwent the reaction smoothly in high yield (90%) with excellent regioselectivity (**3a**/**4a** > 20:1) (Scheme 3b) (for details see SI). However, the Burke's MIDA esters afforded poor yields.

The usefulness of this protocol can also be featured by the late-stage *gem*-difluoroallylation of bioactive natural product. This offered a unique and highly valuable opportunity for drug discovery and development, because the unique structure of *gem*-difluoroallyl group not only provides a platform to use CF_2 as a bioisostere of the oxygen or a carbonyl group[5] but also makes it possible to further modify the bioactive compounds through transformation of double bond. As shown in Scheme 3c, treatment of arylborate **9** derived from estrone with BDFP on a gram-scale afforded *gem*-difluoroallylated compound **10** in 88% yield with high regioselectivity (α/γ = 15:1). Subsequently, dihydroxylation of **10** afforded modified bioactive compound **11** in high efficiency. While previous preparation of aryl *gem*-difluorodiols required electrochemical fluorination, and only low yield of desired product was provided,[16] thus highlighting the advantages of the present process. In addition, the successful use of aromatic pinacol esters as the coupling partners also provides the possibility for sequential C–H borylation/*gem*-difluoroallylation reactions. This is because aromatic pinacol esters are readily available through Ir-catalyzed C–H borylation.[17]

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In conclusion, we have demonstrated a first example of Pd-catalyzed *gem*-difluoroallylation of organoborons with BDFP. The reaction allowed *gem*-difluoroallylation of a wide range of organoborons including (hetero)aryl and vinyl boronic acids, borates, and potassium trifluoroborate salt with low catalyst loading under mild and operationally simple conditions. This reaction can also be extended to substituted BDFPs. Application of the method led to modified fluorinated bioactive compounds in a highly efficient and practical manner. Because of the unique structure of *gem*-difluoroallyl group and the advantages of this protocol, such as practicality with low catalyst loading, high regioselectivity, and excellent functional group compatibility, we believed that this protocol should be useful for drug discovery and development. 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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