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Access to Difluoromethylated Arenes by Pd-Catalyzed Reaction of Arylboronic Acids with Bromodifluoroacetate

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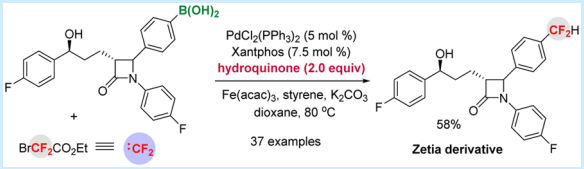
Supporting Information

ABSTRACT: An unprecedented example of Pd-catalyzed difluoromethylation of aryl boronic acids with bromodifluoroacetate is described. The reaction proceeds under mild reaction conditions with hydroquinone and $Fe(acac)_3$ as additives. Preliminary mechanistic studies reveal that a difluorocarbene pathway is involved in the reaction, which is unusual compared to the most traditional approaches. This reaction has advantages of high efficiency and excellent functional group compatibility, even toward bromide and hydroxy group, thus providing a useful protocol for drug discovery and development.

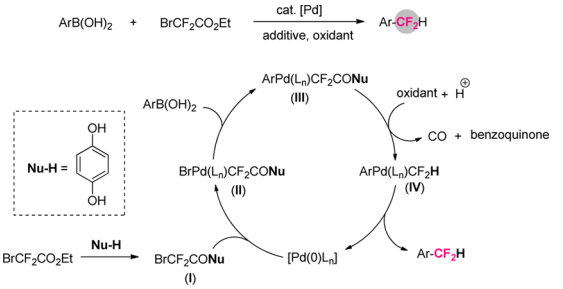


The demand for discovery of new bioactive compounds and advanced functional materials has triggered considerable efforts in the introduction of fluorinated functional groups into organic molecules.[1] It has become an intensive topic of organosynthetic chemistry. Among the organofluorinated compounds, difluoromethylated arenes constitute a type of distinct compound because of the unique properties of the difluoromethyl group (CF_2H)[2] and important applications of difluoromethylated arenes in pharmaceuticals and agrochemicals.[3] To date, however, compared to trifluoromethylation of arenes,[4] strategies for the introduction of CF_2H into an aromatic ring remain limited and have been less explored.[5] Although CF_2H can be prepared through deoxyfluorination of aldehydes with SF_4 or dialkylaminosulfur trifluorides (i.e., DAST or DeoxoFluor),[6] these reactions suffer from important functional group incompatibility and the need for expensive and/or toxic fluorinated reagents.

Recently, some new strategies for the use of difluoroalkylated reagents as fluorine sources to access such a fluorinated structural motif have been developed.[7−10] Despite the importance of these methods, the development of new strategies and efficient methods to access difluoromethylated arenes remains a requirement for drug discovery and development. We envisioned that the transition-metal-catalyzed difluoromethylation of aryl metals with electrophilic difluoromethylated reagents, such as difluoroalkyl halides, would be an attractive alternative. To date, however, such a transformation is a longstanding challenge and has not been reported because some difluoromethyl transition-metal complexes are unstable.[11] To the best of our knowledge, the palladium complex $[HCF_2Pd(L_n)X]$ (X = halides) has not been documented thus far. As part of a systematic study on the transition-metal-catalyzed direct introduction of fluorinated functional groups into organic molecules,[12] we herein disclose an unprecedented example of Pd-catalyzed difluoromethylation of arylboronic acids with low-cost ethyl bromodifluoroacetate.[13] Preliminary mechanistic studies reveal that a difluorocarbene pathway is involved in the reaction, which is unusual compared to the traditional reactions.

We began our studies on the basis of the hypothesis that if an active species **I** could be generated in situ by the reaction of ethyl bromodifluoroacetate **2** with a nucleophile **Nu-H** (i.e., hydroquinone) the formation of difluoromethylated arenes would be possible through the catalytic cycle illustrated in Scheme 1.

Scheme 1. Hypothesis for Pd-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoroacetate



We envisioned that once the intermediate **I** was formed, the oxidative addition of the C−Br bond to $Pd(0)L_n$ would produce the palladium complex **II**, which would subsequently deliver an active palladium complex **III** via transmetalation. The key step to realize the hypothesized reaction is to generate the key intermediate $[ArPd(L_n)CF_2H]$ **IV**. We considered that with the aid of an oxidant, if the −CO**Nu** group (Nu = OPh-*p*-OH) of the complex **III** could be removed through a redox pathway to release CO and benzoquinone, the formation of **IV** would be possible; as a result, the reductive elimination of **IV** would give

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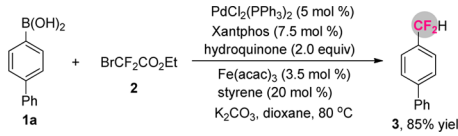
Org. Lett. XXXX, XXX, XXX−XXX

the difluoromethylated arenes and regenerate Pd(0)L_n simultaneously.

Accordingly, our initial studies focused on the Pd-catalyzed cross-coupling of bromodifluoroacetate **2** with arylboronic acid **1a** in the presence of hydroquinone[14] and a variety of oxidants (for details, see Tables S1−S8 in the Supporting Information). After extensive efforts, we found that an optimal yield of **3** (85% upon isolation) could be obtained with utilization of $PdCl_2(PPh_3)_2$ (5 mol %), Xantphos (7.5 mol %), hydroquinone (2.0 equiv), $Fe(acac)_3$ (3.5 mol %), and styrene (20 mol %) in dioxane at 80 °C (eq 1). Styrene is used because of its beneficial



(1)

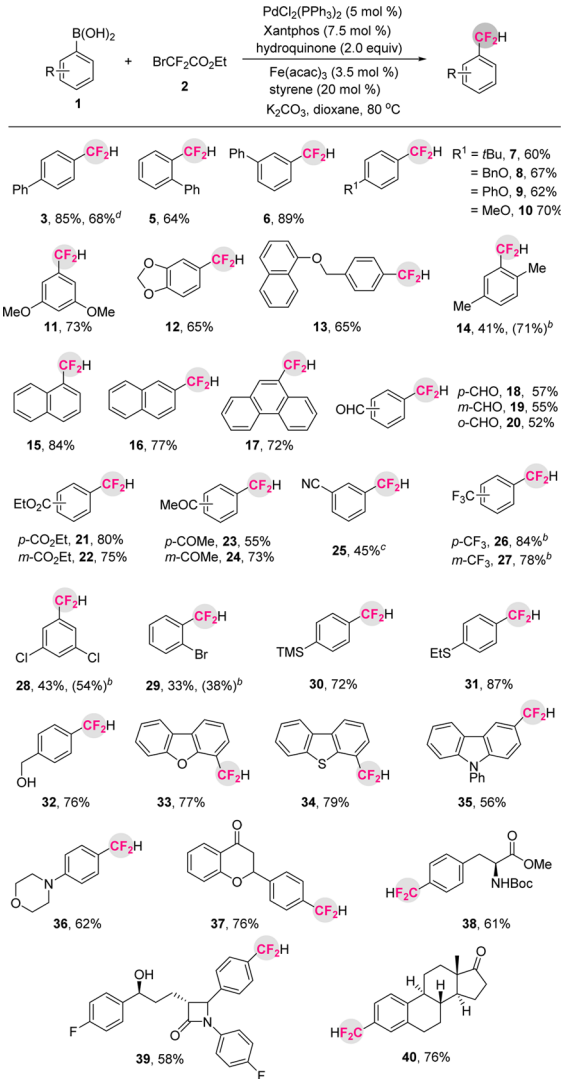
effect on the reaction efficiency. We reasoned that this is probably because styrene can coordinate with iron species and improve the reactivity of the iron complexes.[15,16] Any absence of other reaction factors, such as hydroquinone, $Fe(acac)_3$, and styrene, all led to no or lower yields of **3** (see Table S8 in the Supporting Information). No product **3** was observed without the palladium or Xantphos, thus demonstrating that the Pd/Xantphos do play an essential role to promote the reaction.

A wide range of arylboronic acids could be difluoromethylated with **2** through this method (Scheme 2). Many versatile functional groups, including base or nucleophile-sensitive moieties, such as formyl, alkoxycarbonyl, enolizable ketone, cyano, siyl, thioether, and amine, were tolerated quite well (**18**−**25**, **30**, **31**, and **36**). Most remarkably, chloride, bromide, and free hydroxy group containing aryl boronic acids are also suitable substrates (**28**, **29**, and **32**). This is in sharp contrast to previous results,[7,9,10c] in which aryl halides and/or free proton-containing substrates were incompatible with their reaction conditions. Furthermore, heteroaromatic rings, such as dibenzo[*b*,*d*]furan and -thiophene, and carbazole-derived boronic acids all underwent difluoromethylation smoothly (**33**−**35**). However, pyridine-containing boronic acids were not suitable substrates. Additionally, the difluoromethylated arene **3** could also be synthesized on a 1 g scale with good yield (68%).

The utility of this method can also be demonstrated by late-stage difluoromethylation of different bioactive molecules (**37**−**40**). As shown in Scheme 2, good yields were obtained when the flavanone and estrone derived arylboronic acids were employed (**37** and **40**). The difluoromethylation of tyrosine-derived arylboronic acid also proceeded smoothly with 61% yield (**38**). The most significant example is the direct difluoromethylation of Zetia, a drug famous for the treatment of high blood cholesterol, without protecting the free hydroxy group (**39**), thus providing an useful tool for the medicinal chemistry.

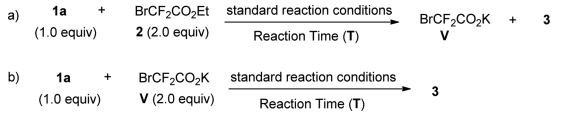
To probe the reaction mechanism illustrated in Scheme 1, we conducted a kinetic study of the reaction of **1a** with **2** (Scheme 3a), and the yield of **3** was plotted against time (Figure 1b, black line). It was found that a new species $BrCF_2CO_2K$ (**V**) instead of 4-hydroxylphenyl difluoroacetate ($BrCF_2O_2Ph$-*p*OH, **I**) was generated at the beginning of the reaction and the production of **3** at initial stage required formation of a large amount of **V** (Figure 1a, black line), thus indicating the critical role of **V** in promotion of the reaction. This finding was further confirmed by the kinetic study of the reaction of **V** with arylboronic acid **1a** under standard reaction conditions, in which a similar kinetic profile was also observed (Scheme 3b, Figure 1b, red line).

Scheme 2. Pd-Catalyzed Difluoromethylation of Arylboronic Acids 1 with Bromodifluoroacetate 2[a]



[a]Reaction conditions (unless otherwise specified): **1** (0.3 mmol), **2** (2.0 equiv), K_2CO_3 (4.0 equiv), dioxane (2.5 mL) for 24 h. All reported yields are isolated yields. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard. [c]**1** (0.6 mmol) and dioxane (3.0 mL). [d]Reaction carried out on a gram scale.

Scheme 3. Cross-Coupling of 1a with 2 or V



Additionally, the ^{19}F NMR and GC−MS analysis of the reaction showed no **I** was formed during the reaction process. Thus, these results imply that the hypothesized mechanism illustrated in Scheme 1 is less likely.

To rule out the possibility that the formation of difluoromethylated arenes arises from the decarboxylation of difluoroacetylated arene, the reaction of compound **4** or **4′** with hydroquinone under standard reaction conditions was conducted (eq 2). However, no difluoromethylated arene **3** was observed during the reaction, thus clearly indicating that an intriguing mechanism is involved in the reaction.

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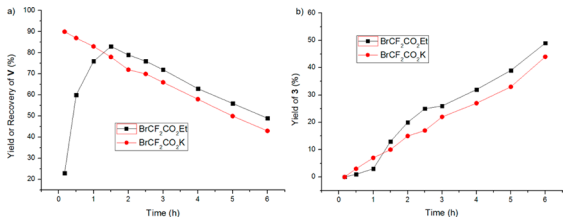
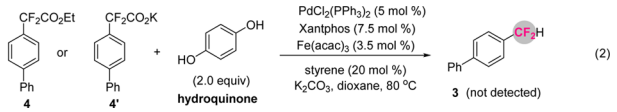
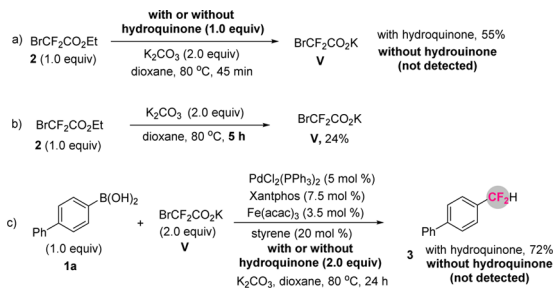


Figure 1. (a) Yield (black line) or recovery of **V** (red line) and (b) yield of **3** with $BrCF_2CO_2Et$ (black line) or $BrCF_2CO_2K$ (red line) as a starting material.



To further understand the role of hydroquinone, several experiments were performed (Scheme 4). It was found that when

Scheme 4. Roles of Hydroquinone for the Reaction

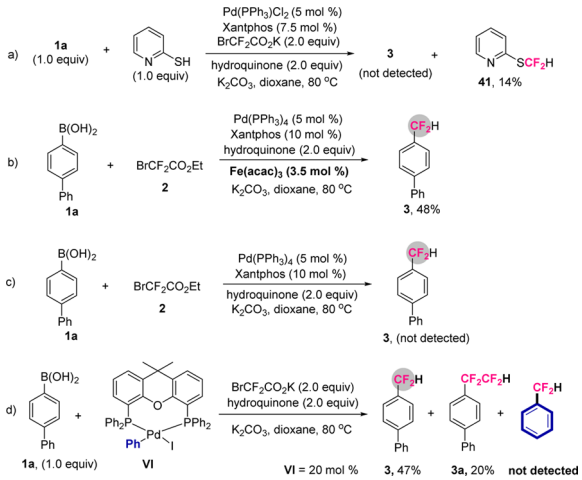


bromodifluoroacetate **2** was treated with K_2CO_3 (2.0 equiv) in the presence of hydroquinone, 55% yield of **V** (determined by ^{19}F NMR) was formed after the reaction was stirred for only 45 min (Scheme 4a). However, the absence of hydroquinone led to no **V** (Scheme 4a), while prolonging the reaction time to 5 h could afford **V** in 24% yield (determined by ^{19}F NMR, Scheme 4b). Thus, these results clearly demonstrate that the hydroquinone has a beneficial effect on the formation of **V**, but it is not essential. On the contrary, the hydroquinone plays an essential role for the generation of difluoromethylated arenes, as no product **3** was observed in the absence of hydroquinone (Scheme 4c). In addition, the comparison of reaction of **1a** with **2** or **V** in the presence of hydroquinone with or without $Fe(acac)_3$ (Schemes S4 and S5 and Figures S2 and S3 in the Supporting Information) reveals that the iron species is not essential for the reaction, but it can facilitate the transformation of **V** into final product **3**.

It has been demonstrated that $BrCF_2CO_2K$ can serve as a precursor of difluorocarbene.[17] This inspired us to surmise that a difluorocarbene may be generated in situ from **V** and a palladium catalytic cycle via a difluorocarbene pathway may be involved in the reaction. To identify whether a difluorocarbene is involved in the reaction, a difluorocarbene scavenger pyridine-2-thiol[18] was added to the reaction by using **V** as a coupling partner (Scheme 5a). It was found that the difluoromethylthiopyridine **41** instead of **3** was produced, thus indicating that a difluorocarbene is involved in the reaction.

In addition, given the fact that a 48% yield of **3** could be provided when **1a** was treated with **2** in the presence of $Pd(PPh_3)_4$ (5 mol %), hydroquinone and $Fe(acac)_3$ (Scheme 5b), but no **3** was produced in the absence of $Fe(acac)_3$ or other

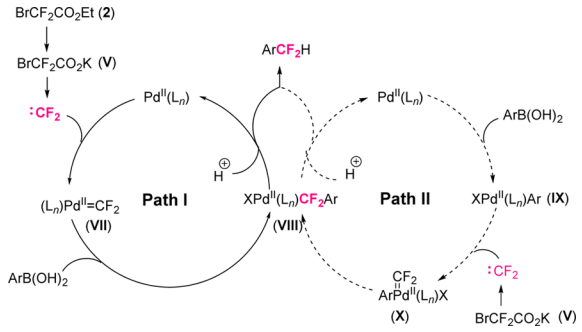
Scheme 5. Mechanistic Studies



oxidants (Scheme 5c), we envisioned that probably only the Pd^{II} species was involved for the formation of difluoromethylated arenes. This was further confirmed by the X-ray photoelectron spectroscopy (XPS) analysis of the reaction, in which only Pd^{II} was found (Scheme S9 and Figure S4, Supporting Information). What is more, when we used a catalytic amount of palladium complex [PhPd(Xantphos)I] **VI** (20 mol %) as a catalyst, compound **3** (47% yield) was indeed generated (Scheme 5d). However, it is worthy to note that no difluoromethylbenzene was generated during the reaction process, even when 50 mol % of **VI** was used (for details, see Scheme S7b , Supporting Information). Thus, these results clearly indicate that the aryl group of the difluoromethylated arene does not derive from [ArPd(Xantphos)X]. In the meantime, a difluorocarbon elongated tetrafluoroethylated **3a** was produced in 20% yield (Scheme 5d). These findings confirm that a difluorocarbene species is involved in the reaction, as it has been demonstrated that an elongated difluorocarbon can be produced by the insertion of a difluorocarbene into fluoroalkylmetal species.[19]

Therefore, on the basis of above results, the hypothesized mechanism illustrated in Scheme 1 can be ruled out, and a plausible mechanism through a the Pd^{II}-involved difluorocarbene pathway is proposed (Scheme 6). The reaction was initiated by

Scheme 6. Proposed Reaction Mechanism



the reaction of $Pd^{II}(L_n)$ with difluorocarbene which was generated in situ from **V** (path I). Subsequently, the resulting palladium(II) difluorocarbene species (**VII**) was trapped by arylboronic acid to produce the key intermediate [$XPd^{II}(L_n)$-CF_2Ar] (**VIII**). Finally, protonolysis of **VIII** afforded difluoromethylated arenes and regenerate $Pd^{II}(L_n)$ simultaneously. In

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Org. Lett. XXXX, XXX, XXX−XXX

the overall catalytic cycle, the hydroquinone is essential for promotion of the reaction. However, the exact role of hydroquinone remains elusive at this stage. As for the role of $Fe(acac)_3$ in the overall catalytic cycle, one possibility is that a Fe-based difluorocarbene species[20] may be generated in the reaction, which is being subsequently transferred onto Pd to produce **VII**. What is more, taking into account the fact that the aryl group of difluoromethylated arene does not derive from the palladium complex $[ArPd(L_n)X]$ (**IX**), the proposed mechanism illustrated in path II[21] for the current reaction can be excluded.

In conclusion, we have demonstrated an unprecedented example of Pd-catalyzed difluoromethylation of arylboronic acids with low-cost ethyl bromodifluoroacetate. The significant features of this reaction are its high efficiency, broad substrate scope, and excellent functional group compatibility, even toward bromide and hydroxyl groups. Applications of the reaction led to difluoromethylated biologically relevant molecules with high efficiency, thus providing a useful protocol for drug discovery and development. Preliminary mechanistic studies reveal that a palladium catalytic cycle via a difluorocarbene pathway is involved in the reaction. To the best of our knowledge, this is the first example of a transition-metal-catalyzed carbon−difluorocarbon single bond ($C-CF_2$) formation via a difluorocarbene pathway. We believe that it will not only prompt the research in the field of transition-metal difluorocarbene chemistry but also be useful for related chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Informationis also is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03206.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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