Angewandte Chemie

Deutsche Ausgabe: DOI: 10.1002/ange.201500124
Internationale Ausgabe: DOI: 10.1002/anie.201500124

C−F Activation

Rhodium-Catalyzed *ortho*-Selective C−F Bond Borylation of Polyfluoroarenes with Bpin−Bpin**

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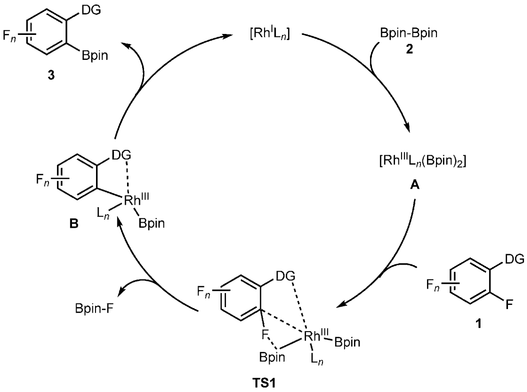
***Abstract:** An ortho-selective C−F bond borylation between N-heterocycle-substituted polyfluoroarenes and Bpin-Bpin with simple and commercially available $[Rh(cod)_2]BF_4$ as a catalyst is now reported. The reaction proceeds under mild reaction conditions with high efficiency and broad substrate scope, even toward monofluoroarene, thus providing a facile access to a wide range of borylated fluoroarenes that are useful for photoelectronic materials. Preliminary mechanistic studies reveal that a $Rh^{III/V}$ catalytic cycle via a key intermediate rhodium(III) hydride complex $[(H)Rh^{III}L_n(Bpin)]$ may be involved in the reaction.*

Fluorinated compounds play an important role in life and material sciences due to the unique properties of fluorine atom and/or C−F bond.[1] Over the past few years, there have been substantial efforts on developing new methods to access such valuable compounds.[2] Among the developed methods, selective C−F bond activation catalyzed by transition metals has emerged as a striking approach,[3] because it paves a new way to prepare a number of fluorinated molecules that are difficult to synthesize by conventional methods. On the other hand, the degradation of environmentally persistent fluorinated molecules has also stimulated fundamental research in understanding C−F bond activation. Recently, significant advances have been made in this area, but most of the reactions mainly focus on hydrodefluorination.[4,5] Although examples of the construction of the C−C bond by transition-metal-catalyzed C−F bond activation have been reported,[6] the selective replacement of fluorine with a versatile functional group to access highly valuable fluorinated molecules is very limited. In particular, the transition-metal-catalyzed selective C−F bond borylation has been scarcely studied,[7] and remains challenging because of the robustness of the C−F bond and difficulty in controlling the selective activation of the C−F bond in perfluorinated and polyfluorinated molecules.

As part of an ongoing study on transition-metal-catalyzed polyfluoroarene chemistry,[8] herein we demonstrate the feasibility of the rhodium-catalyzed selective C−F bond borylation of polyfluoroarenes. Partially fluorinated aromatics constitute a distinct class of compounds in life and materials science.[9] However, synthetic access to such a structural motif is difficult,[10] and there is only limited commercial availability of fluoroaromatic sources. In this study, we focused our research on addressing three crucial issues: 1) regiochemical selectivity of C−F bond borylation; 2) a simple and efficient catalytic system that enables the use of a commercially available catalyst with broad substrate scope; 3) mechanistic insight into the Rh-catalyzed C−F bond borylation. As a result, we disclose the first example of *ortho*-selective C−F bond borylation of polyfluoroarenes with simple and commercially available $[Rh(cod)_2]BF_4$ as a catalyst. Preliminary mechanistic studies revealed that a $Rh^{III/V}$ catalytic cycle may be involved in the reaction, thus providing us with a new view to understand C−F bond activation.

We began our study based on the fact that the formation of the B−F bond is thermodynamically favorable.[11] Therefore, if a rhodium boryl complex $[Rh^{III}L_n(Bpin)_2]$ **A** (Scheme 1), which was generated in situ between rhodium catalyst $[Rh^{I}L_n]$ and Bpin-Bpin, chelates with a directing group, such as N-containing heteroaromatics, the *ortho*-selective C−F bond borylation would be possible after reductive elimination of key intermediate **B**.

Accordingly, our initial study focused on the reaction of 2-(perfluorophenyl)pyridine **1a**[12] with bis(pinacolato)diboron (Bpin-Bpin, **2**) in the presence of different simple and commercially available [Rh^{I}] catalysts (Table 1, entries 1–5). To our delight, 66% yield (determined by ^{19}F NMR spectroscopy) of **3a** was obtained when the reaction was carried out with **1a** (1.0 equiv), **2** (2.0 equiv), $[Rh(cod)_2]BF_4$ (5 mol%), KOAc (2.0 equiv) in toluene at 120°C for 12 h (Table 1, entry 4). Other [Rh^{I}] catalysts also showed activity, but led to



Scheme 1. Hypothesis for Rh-catalyzed *ortho*-selective C−F bond borylation.

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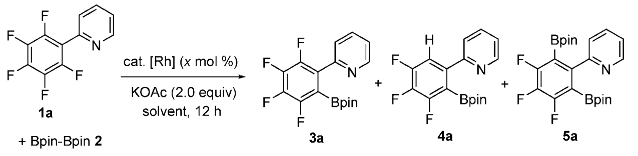
[**] This work was financially supported by the National Basic Research Program of China (973 Program) (Nos. 2012CB821600 and 2015CB931900), the NSFC (21425208, 21421002, 21172242, and 21332010), and SIOC.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500124.

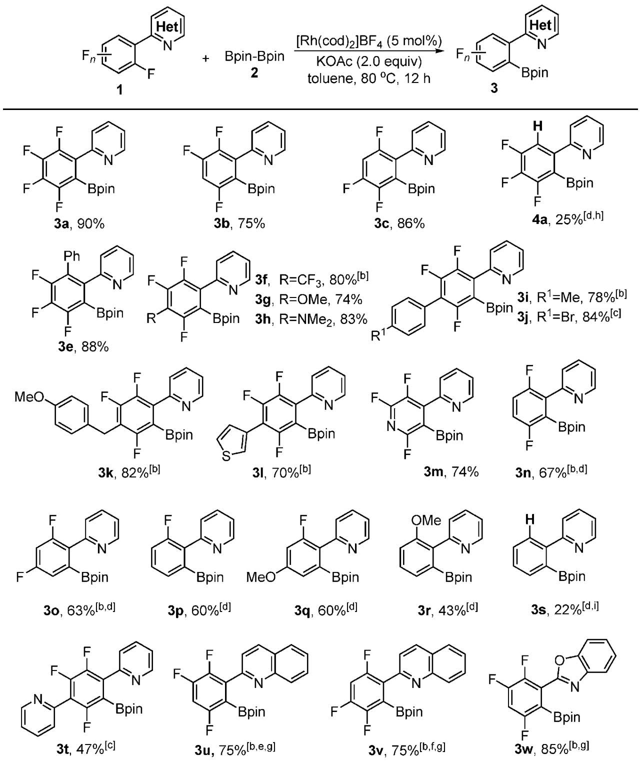
Table 1: Representative results for optimization of Rh-catalyzed C−F bond borylation of 2-(perfluorophenyl)-pyridine **1a**.[a]



Entry	[Rh] (*x*)	*T* [°C]	Solvent	Yield of **3a** [%][b]
1	Rh(PPh$_3$)$_3$Cl (5)	120	toluene	15
2	Rh(CO)(PPh$_3$)$_3$Cl (5)	120	toluene	10
3	[Rh(cod)Cl]$_2$ (2.5)	120	toluene	45
4	[Rh(cod)$_2$]BF$_4$ (5)	120	toluene	66
5	[Rh(cod)OH]$_2$ (2.5)	120	toluene	60
6	[Rh(cod)$_2$]BF$_4$ (5)	80	toluene	93 (90)

[a] Reaction conditions (unless specified otherwise): **1a** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), solvent (1.5 mL). [b] Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard and number in parenthesis is the yield of the isolated product.

Table 2: Rh-catalyzed *ortho*-selective C−F bond borylation of polyfluoroarenes.[a]



[a] Reaction conditions (unless specified otherwise): **1** (0.4 mmol), Bpin-Bpin (2.0 equiv), toluene (2 mL), 12 h. All reported yields are those of isolated products. [b] Reaction run in dioxane (2 mL). [c] Reaction run for 24 h. [d] Reaction run at 120 °C for 14 h. [e] Reaction run at room temperature. [f] Reaction run at 40 °C. [g] The yield was determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [h] 45 % yield of C−H bond borylated product **3a** was formed. [i] 10 % yield of C−H bond borylated product **3p** was formed.

lower yields. It should be mentioned that the borylation occurred only *ortho* to the pyridyl group. However, some *ortho* hydrodefluorinated polyfluoroarene **4a** and diborylated product **5a** were formed in the meanwhile. Decreasing the reaction temperature benefited the reaction efficiency, and an optimal yield (90 % upon isolation) was obtained when the reaction was performed at 80 °C (Table 1, entry 6). It was also found that the choice of solvent and base were crucial for the reaction efficiency, toluene and KOAc are the best choice (for details, see the Supporting Information, SI).

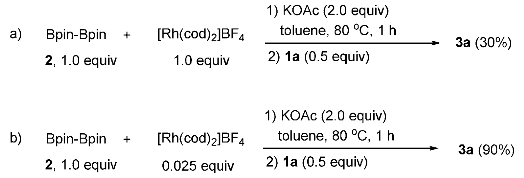
Upon the identification of viable reaction conditions, a variety of pyridyl-containing polyfluoroarenes were employed as substrates in this transformation (Table 2). Substrates bearing four fluorine atoms all underwent the reactions smoothly, providing corresponding borylated products with high efficiency (**3b**–**3m**). It should be mentioned that the active C−H bond *para* or *meta* to the pyridyl group did not interfere with the regioselectivity, as no C−H bond borylations were observed (**3b** and **3c**). However, in the case of tetrafluoroarene **1d** bearing a C−H bond *ortho* to the pyridyl group, both C−H and C−F bond borylations were observed (**4a**).[13] Notably, an unsymmetrical tetrafluorobenzene derivative exclusively produced **3c** in high yield (86 %). This may be ascribed to the electron-withdrawing effect of an additional fluorine atom attached at the C3 position, which activates the C−F bond at the C2 position. Thiophene-containing tetrafluoroarene, an important structural motif for electronic materials,[9a,b] is also a competent coupling partner (**3l**), thus providing an efficient way to such a functionalized structure for further applications.

To demonstrate the generality of this catalytic system, the fluoroarenes bearing 3–2 fluorine atoms were also examined (**3n**–**3q**). Although a relative inertness of these substrates was observed, increasing the reaction temperature to 120 °C still furnished their corresponding products in good yields. Even the monofluoroarene substituted with an electron-rich group also underwent the reaction smoothly and produced a synthetically useful yield of **3r**. However, 2-(2-fluorophenyl)pyridine **1s** led to a low yield of **3s**. Interestingly, 2,2′-(perfluoro-1,4-phenylene)dipyridine did not afford the diborylated product; instead, the monoborylated fluoroarene **3t** was obtained in 47 % yield. The reaction is not restricted to pyridyl-containing fluoroarenes, because a quinolinyl and benzooxazole moiety were also applicable, providing the corresponding products in good yields (**3u**–**3w**).

To illustrate the potential applications of this method, the transformation of **3a** was conducted.[14] As shown in Scheme 2, the organometallic iridium fluorinated complexes used for the photoelectronic materials, such as light-emitting devices and photocatalysts,[1d,15] could be easily prepared from compound **3**. For example, reaction of [Ir(ppy)$_2$(H$_2$O)$_2$]OTf **6** with **3a** efficiently afforded iridium complex **7**,[16] whereas it is difficult to prepare such a fluorinated structure through conventional methods.

To gain some mechanistic insight into the present reaction, the following experiments were conducted. In view of the fact that the rhodium boryl complex [Rh^{III}L$_n$(Bpin)$_2$] can be produced through oxidative addition of Bpin-Bpin to Rh^{I},[13,17] the reaction of a stoichiometric amount of [Rh(cod)$_2$]BF$_4$ with Bpin-Bpin was performed under standard conditions (Scheme 3a). After the reaction was run for 1 h, the reaction mixture was treated with **1a**, however, only 30 %

Scheme 2. Transformation of **3a**.



Scheme 3. Experiments for mechanistic studies. The yield was determined by ^{19}F NMR spectroscopy.

yield of **3a** was observed. This finding is in sharp contrast to the use of a catalytic amount of $[Rh(cod)_2]BF_4$ (5 mol %), for which a high yield (90 %) of **3a** was obtained (Scheme 3b). Further investigations revealed that the ratio of **2**/$[Rh(cod)_2]BF_4$ plays a critical role for the reaction efficiency (Scheme S3). When the reaction was carried out with **1a** (1.0 equiv) in the presence of a different ratio of **2**/$[Rh(cod)_2]BF_4$ (8/1 to 8/3), only low yields of **3a** were provided, along with some hydrodefluorinated product **4a**. On the basis of these results and the fact that a rhodium(V) boryl complex can be easily generated from rhodium(III) with an excess Bpin-Bpin,[17] we envision that the rhodium species $[Rh^{III}L_n(Bpin)_2]$ is not the key intermediate in the overall catalytic cycle, and a new active rhodium species is involved in the reaction, in which a high ratio of **2**/$[Rh(cod)_2]BF_4$ favors its formation. Thus, the hypothesized mechanism illustrated in Scheme 1 is less likely. In addition, the possibility that the initial step begins with the oxidative addition of the C−F bond to Rh^I has also been excluded by the control experiment (Scheme S2c).

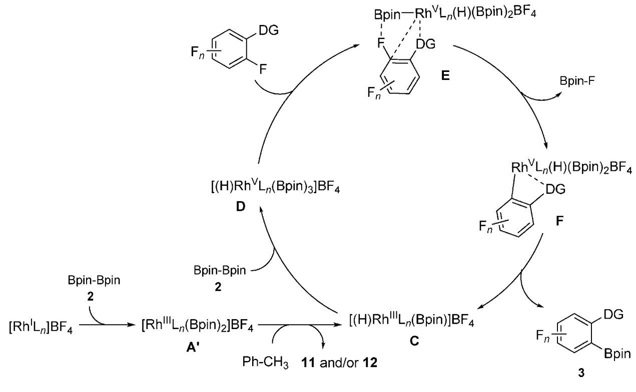
It has been demonstrated that the $[Rh^{III}L_n(Bin)_2]$ complex can react with an alkane/arene C−H bond to produce alkyl/arylboronate ester products and generate $[Rh^{III}L_n(H)(Bpin)]$.[13,17] We surmise that such a rhodium hydride complex may be involved in the overall catalytic cycle as a key intermediate, and lead to both product **3** and side product **4**. Accordingly, the reaction of Bpin-Bpin **2** (1.0 equiv) with $[Rh(cod)_2]BF_4$ (0.025 equiv) in the presence of KOAc in toluene was conducted at 80 °C (Scheme 4a). GC-MS analysis of the crude reaction showed that both borylated toluene (**11** and/or **12**) and COD derivative (**13** and **14**) were formed. These observations indicate that the solvent toluene is also involved in the reaction, and functions as a hydrogen source for the formation of $[Rh^{III}L_n(H)(Bpin)]BF_4$. This was further confirmed by the reaction of **1a** with **2** in deuterated toluene at higher reaction temperature (120 °C) (for details, see Scheme S4b). It was found that an increased yield of **4a** was produced, but **3a** remained the major product. In addition, besides the observation of the borylated toluene, a deuterated alkene species **15** was formed in the reaction process. We reason that such a deuterated product is derived from the insertion of a rhodium deuteride complex, which was generated from deuterated toluene with the rhodium boryl complex, to a COD double bond, followed by β-H elimination to finish the H/D exchange.[18] Thus, these findings demonstrated that a rhodium hydride complex is indeed generated in the reaction.

Scheme 4. Experiments for mechanistic studies. The yield was determined by ^{19}F NMR spectroscopy.

Furthermore, we also found that a moderate yield of **3a** still could be obtained when a mixture of **1a** and **2** was treated with a catalytic amount of Rh^{III} complex $(Cp^*RhCl_2)_2$ or $[Cp^*Rh^{III}(\eta^6\text{-}C_6Me_6)](PF_6)_2$ (for details, see Scheme S4c), thus indicating that a $Rh^{III/V}$ may be involved in the reaction. To further probe that the rhodium(V) boryl complex functions as a key intermediate in the C−F bond borylation, a Rh^V boryl complex $[Cp^*Rh(H)_2(Bpin)_2]$ **D-1** was synthesized according to the literature.[17b,c] It was found that in the reaction of **1a** with Bpin-Bpin catalyzed by **D-1**, **3a** was indeed generated (30 % yield, turnover number (TON) = 6, Scheme 4b). Additionally, treatment of **1a** with a stoichiometric amount of **D-1** could afford borylated fluoroarenes (**3a** and **4a**) in a higher yield (49 %, **3a** + **4a**) (Scheme 4c).

On the basis of these results, a plausible reaction mechanism through a $Rh^{III/V}$ catalytic cycle is proposed (Scheme 5). The reaction is initiated by the oxidative addition of Bpin-Bpin to Rh^I. The resulting rhodium boryl complex **A′** subsequently reacts with toluene to generate the key intermediate $[(H)Rh^{III}L_n(Bpin)]BF_4$ **C**, which was further converted to the rhodium(V) complex $[(H)Rh^VL_n(Bpin)_3]BF_4$ **D** in the presence of excess Bpin-Bpin.[17] After formation of **D**, a boryl-assisted transition state **E** is involved in the reaction, which facilitates the delivery of fluoroarylrhodium complex **F** with the formation of a strong B−F bond as driving force. Finally, reductive elimination of **F** affords product **3** and regenerates **C** simultaneously.

In conclusion, we have demonstrated the first example of a Rh-catalyzed *ortho*-selective C−F bond borylation of polyfluoroarenes with Bpin-Bpin. The reaction allows



Scheme 5. Proposed reaction mechanism.

a wide range of N-heterocycle-substituted polyfluoroarenes under mild reaction conditions, and provides an efficient and operationally simple method for the synthesis of borylated fluoroarenes that are difficult to synthesize through conventional methods. Most of these target borylated fluoroarenes are previously unknown and should become versatile and important building blocks to be used in photoelectronic materials. Preliminary mechanistic studies reveal that the solvent toluene is also involved in the reaction and functions as a hydrogen source. Although a simple and commercially available Rh^I complex $[Rh(cod)_2]BF_4$ is employed as a catalyst for the current reaction, a $Rh^{III/V}$ catalytic cycle may be involved in the reaction, in which rhodium hydride complex $[(H)Rh^{III}L_n(Bpin)]$ is a key intermediate. Further studies to uncover the detailed reaction mechanism and applications of the method for photomaterials are underway in our laboratory.

Keywords: borylation · C–F activation · fluoroarenes · homogeneous catalysis · rhodium

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9075–9078
Angew. Chem. **2015**, *127*, 9203–9206

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Received: January 6, 2015
Revised: May 14, 2015