Palladium-Catalyzed Direct Arylation of Electron-Deficient Polyfluoroarenes with Arylboronic Acids

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ABSTRACT



The palladium-catalyzed direct arylation of electron-deficient arenes that contain two or more fluorine groups with arylboronic acids was realized. The key to achieving a broad substrate scope with respect to both polyfluorobenzenes and arylboronic acids is the choice of bases depending on acidities of polyfluorobenzenes.

The prevalence of the biaryl substructure in biologically active molecules and functional materials has prompted synthetic chemists to seek efficient methods for the construction of this class of molecules.¹ Consequently, the transition metal-catalyzed cross-coupling reactions between aryl halides and organometallics have evolved into the most powerful synthetic tools for generation of biaryl compounds.² The recent advances in metal-catalyzed C—H bond functionalization suggest that it is possible to achieve similar transformations without the need for the preactivation of coupling partners (e.g., preparations of aryl halides and organometallic reagents).^{3,4} Strategies for functionalization of C—H bonds

not only offer the most efficient synthetic route to the target compounds,⁵ but also in some cases provide a solution to the problem arising from the use of unstable or hard to prepare organometallic reagents in traditional cross-coupling

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reactions.^{6–8} In this regard, Fagnou⁶ and Daugulis⁷ have successfully developed the direct arylation of electrondeficient polyfluoroarenes or heterocycles for synthesis of fluorobiaryl or heterocycle-containing biaryl compounds.

Recently, efforts made by Yu,9 Shi,10 and others11 have led to the development of palladium-catalyzed C-H bond arylation with organoboron reagents, and Murai and Kakiuchi disclosed a ruthenium-catalyzed ortho C-H arylation of acetophenones with boronic esters.¹² Copper-¹³ and ironbased catalysts¹⁴ have successfully been exploited as a costefficient replacement for palladium-based catalysts for the direct arylation of arenes with arylboronic acids. These reported reactions are limited to directing group-containing or electron-rich arenes. However, to date, no example has been reported that involves the direct arylation of electrondeficient arenes with organoboron reagents, except for a few substrates bearing directing groups.^{9b} In view of the importance of electron-deficient fluorobiaryls in medicinal¹⁵ and materials chemistry,¹⁶ the discovery of new reactions for the synthesis of these valuable compounds remains highly desirable. Herein, we report a palladium-catalyzed method for the direct arylation of electron-deficient polyfluoroarenes with organoboron reagents and also present the result of the preliminary mechanistic study on this reaction.

To achieve the direct arylation of fluoroarenes with arylboronic acids, we need to address the following issue: the cleavage of the C-H bond of electron-deficient fluoroarene generally requires basic conditions that also accelerate

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the transmetalation between the arylboronic acid and the Pd(II) species, whereas the fast transmetalation would readily lead to the undesired homocoupling of arylboronic acid if the C–H bond cleavage is relatively slow,¹⁷ thus hampering the generation of the desired cross-coupling product. Our strategy to solve this problem is to simultaneously add a weak base, which we believe promotes the C–H bond cleavage, and a weak acid, which we believe reduces the transmetalation rate of arylboronic acid, and therefore suppresses the undesired homocoupling.^{10b}

A variety of reaction parameters were screened with the reaction of pentafluorobenzene (1) with 1.5 equiv of phenylboronic acid (2) as a model reaction system. Selected results that illustrate the effect of acid and base on this reaction are listed in Table 1. In the presence of 5 mol % of

Table 1. Selected Screening Results for Pd-Catalyzed Direct

 Arylation of Pentafluorobenzene with Phenylboronic $Acid^a$

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|-------|---|---|----------------|
| entry | base (equiv) | acid (0.3 equiv) | yield $(\%)^b$ |
| 1 | | | trace |
| 2 | $K_2CO_3(2)$ | | 75 |
| 3 | $Na_{2}CO_{3}(2)$ | | 70 |
| 4 | $Cs_2CO_3(2)$ | | 7 |
| 5 | $K_{3}PO_{4}(2)$ | | 80 |
| 6 | KOAc (2) | | 69 |
| 7 | $K_2HPO_4(2)$ | | 71 |
| 8 | p-Me-C ₆ H ₄ -CO ₂ K (2) | | 55 |
| 9 | $K_2CO_3(2)$ | ^t BuCO ₂ H | 72 |
| 10 | $K_2CO_3(2)$ | p-Me-C ₆ H ₄ -CO ₂ H | 84 |
| 11 | $K_{2}CO_{3}(2)$ | o-MeO-C ₆ H ₄ -CO ₂ H | 80 |
| 12 | $K_2 CO_3 (2)$ | o-O ₂ N-C ₆ H ₄ -CO ₂ H | 79 |

14K₃PO₄ (2) p-Me-C₆H₄-CO₂H 88 15K₂CO₃ (0.5) p-Me-C₆H₄-CO₂H 89 16 K₃PO₄ (0.5) p-Me-C₆H₄-CO₂H 85 17 $K_2CO_3(0.5)$ p-Me-C₆H₄-CO₂H 90^c ^a 0.2 mmol scale, 2 mL of DMA (0.1 M). ^b Isolated yields. ^c Pd(OAc)₂ (2 mol %) and phenylboronic acid (1.2 equiv).

 $p-\text{Me-C}_6\text{H}_4-\text{CO}_2\text{H}$

13

KF (2.5)

Pd(OAc)₂ as a catalyst and 2 equiv of Ag_2CO_3 as an oxidant, the reaction carried out in dimethylacetamide (DMA) at 110 °C in the absence of any additive did not afford the desired product in appreciable quantities. Instead, it produced the undesired biphenyl from homocoupling of phenylboronic acid (entry 1, Table 1). The addition of 2 equiv of K₂CO₃ led to the formation of the desired arylation product in 75% yield (entry 2, Table 1). Both Na₂CO₃ and KOAc gave a slightly lower yield (entries 3 and 6, Table 1), but Cs₂CO₃ was almost ineffective for this reaction (entry 4, Table 1). K₃PO₄ was found to be superior to K₂CO₃ (entry 5, Table 1). As expected, the addition of carboxylic acids efficiently

77

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inhibited the homocoupling of phenylboronic acid in the presence of 2.0 equiv of bases. Screening several carboxylic acids and their loadings revealed that 0.3 equiv of p-toluic acid in combination with 2.0 equiv of K₃PO₄ or K₂CO₃ provided excellent yields (entries 9-14). We can rule out the possibility that the beneficial effect of *p*-toluic acid arises from potassium p-toluate or K₂HPO₄ formed in situ from the reaction of p-toluic acid with K₃PO₄ since neither K_2 HPO₄ nor potassium *p*-toluate gave a comparable yield in the absence of acid (entries 7 and 8, Table 1). Reducing the amount of K₂CO₃ to 0.5 equiv further improved the reaction in the presence of 0.3 equiv of p-toluic acid (entry 15, Table 1). Gratifyingly, 2 mol % of Pd(OAc)₂ in conjunction with 0.5 equiv of K₂CO₃ and 0.3 equiv of p-toluic acid effected the reaction of pentafluorobenzene with 1.2 equiv of phenylboronic acid with 90% yield (entry 17, Table 1). This reaction also occurred in other polar solvents such as DMSO to give somewhat lower yields than that in DMA, but did not occur in nonpolar or less polar solvents such as toluene and dioxane. The other common oxidants for the Pd(0)/Pd(II) system such as a variety of Cu(II) salts and oxygen were ineffective for this reaction, and other silver sources such as Ag₂O and AgOAc were less efficient than Ag₂CO₃.

The scope of this reaction with respect to organoboron reagents was further explored by employing the conditions of entry 17 in Table 1. As shown in Scheme 1, a range of

Scheme 1. Pd-Catalyzed Direct Arylation of Pentafluorobenzene with Various Arylboronic Acids^{*a*}



^{*a*} Reaction conditions: pentafluorobenzene **1** (0.2 mmol), arylboronic acid (1.2 equiv), $Pd(OAc)_2$ (2 mol %), K_2CO_3 (0.5 equiv), Ag_2CO_3 (2 equiv), *p*-Me-C₆H₄-CO₂H (0.3 equiv), DMA (2 mL, 0.1 M), 110 °C, 10 h. ^{*b*} Pd(OAc)_2 (5 mol %) and 4-methylbenzeneboronic acid neopentyl ester (1.5 equiv). ^{*c*} Pd(OAc)_2 (5 mol %), arylboronic acid (1.5 equiv), and K_2CO_3 (2 equiv). ^{*d*} KF (2.5 equiv) as base instead of K_2CO_3 . ^{*e*} 5 mmol scale.

organoboron reagents can serve as arylating reagents for the direct arylation of pentafluorobenzene, affording the desired products in moderate to excellent yields. The reactivity of organoboron reagents was observed to rely on the electronic nature of substituents on the aromatic rings. Electrondonating substituents were generally beneficial for this

3348

transformation (3b-d,f) except for the case involving the dimethylamino group, in which 5 mol % of Pd(OAc)₂, 1.5 equiv of arylboronic acid, and 2 equiv of K₂CO₃ were required to obtain a good yield (3g). Although electrondeficient arylboronic acids suffered from their relatively poor reactivities, using 2.5 equiv of KF in place of 0.5 equiv of K₂CO₃ gave rise to synthetically useful yields (3h and 3i). This transformation can be scaled up, as illustrated by the reaction on 5 mmol scale that offered a yield comparable to that on 0.2 mmol scale (3a, Scheme 1). When the arylboronic acid bearing the ortho-substituent on the aromatic ring was used as a coupling partner, neither the cross-coupling product nor the homocoupling product was formed, indicative of the sensitivity of this transformation to steric hindrance (3j).

The substrate scope with respect to polyfluorobenzenes was also investigated and is presented in Scheme 2. Under

Scheme 2. Pd-Catalyzed Direct Arylation of Various Polyfluoroarenes with Arylboronic Acids^{*a*}



^{*a*} Reaction conditions: **3k**–**q**: polyfluoroarene (0.2 mmol), arylboronic acid (1.2 equiv), Pd(OAc)₂ (2 mol %), K₂CO₃ (0.5 equiv), Ag₂CO₃ (2 equiv), *p*-Me-C₆H₄-CO₂H (0.3 equiv), DMA (2 mL, 0.1 M), 110 °C, 10 h. **3r**–**z**: polyfluoroarene (3 equiv), arylboronic acid (0.2 mmol), Pd(OAc)₂ (5 mol %), K₃PO₄ (0.5 equiv), Ag₂CO₃ (2 equiv), 'BuCO₂H (0.6 equiv), DMA (2 mL, 0.1 M), 120 °C, 10 h. ^{*b*} Pd(OAc)₂ (5 mol %), arylboronic acid (1.5 equiv) and K₂CO₃ (2 equiv). ^{*c*} *p*-Me-C₆H₄-CO₂K (0.5 equiv) as base instead of K₃PO₄.

the standard conditions, both 2,3,5,6-tetrafluoroanisole and 2,3,5,6-tetrafluorotoluene smoothly underwent direct arylation with moderate to good yields obtained (3k-q). However, these reaction conditions are not suitable for other polyfluorobenzenes such as 1,3,5-trifluorobenzene. It has been established that the reactivity of the C-H bond in electron-deficient arenes depends directly on its acidity. In light of this, we speculated that the identification of the proper base for a specific polyfluorobenzene might be crucial for obtaining efficient transformation. Moreover, the acid required by this reaction system to suppress the homocou-

pling must match the base used for deprotonation of the polyfluorobenzene. We were pleased to achieve the direct arylation of more C-H acidic polyfluorobenzenes such as 2,3,5,6-tetrafluoropyridine and 2,3,5,6-tetrafluorobenzonitrile by using 0.5 equiv of potassium p-toluate as a base in conjunction with 0.6 equiv of pivalic acid and increasing the amount of polyfluorobenzene (3:1 ratio of polyfluorobenzene to arylboronic acid) (3r and 3s), and to realize the direct arylation of less C-H acidic polyfluorobenzenes by using 0.5 equiv of K₃PO₄ combined with 0.6 equiv of pivalic acid (3t-z). As a result, a wide range of polyfluorobenzenes, some of which contain bromo, cyano, keto, and methoxy groups, can be arylated with arylboronic acids. Although more than one potential site for reaction is available in some of the polyfluorobenzenes, the reactions of these polyfluorobenzenes mainly generated monoarylated product, as exemplified by the reaction of 1,3,5-trifluorobenzene (3x). The direct arylation of 1,3-difluorobenzene occurred preferentially at the most acidic C-H bond, which is flanked by two C-F bonds (3y). In contrast, the reaction of 2,4difluorobenzophenone occurred exclusively at the position that is meta to the benzoyl group and para to a fluoride group (3z). The palladium-catalyzed meta-selective C-H bond olefination directed by the benzoyl group has been observed by Yu recently.¹⁸

Two different mechanisms are possible for the direct arylation of polyfluorobenzenes with arylboronic acids (Scheme 3). Path A involves the initial formation of



arylpalladium species via the transmetalation from boron to palladium, followed by the palladation of fluorobenzene via concerted metalation—deprotonation^{6c,19,20} and reductive elimination. Path B begins with the formation of fluoroarylpalladium species via the cleavage of the C–H bond of fluorobenzene, followed by the transmetalation from boron to the fluoroarylpalladium intermediate and reductive elimination.

To distinguish between path A and path B, we carried out preliminary mechanistic studies. Stoichiometric reaction of

2,4,5-trimethoxyphenylpalladium trifluoroacetate complex 4^{21} with pentafluorobenzene in DMSO gave the arylated product in 28% yield as well as a lot of the homocoupling product from the palladium complex 4 [eq 1], indicating that an arylpalladium complex is able to arylate electron-deficient polyfluorobenzene via C-H bond cleavage. Further experimentation showed that 5 mol % of palladium complex 4 as a catalyst efficiently catalyzed the direct arylation of pentafluorobenzene with phenylboronic acid in 84% yield, suggesting that the direct arylation of polyfluorobenzene most likely involves the formation of an arylpalldium intermediate and subsequent reaction of the palladium species with fluorobenzene. As shown in Scheme 1, when sterically demanding o-tolylboronic acid was used, neither crosscoupling nor homocoupling took place. No homocoupling product from o-tolylboronic acid reveals that the transmetalation that generates arylpalladium species was inhibited owing to steric factors.¹⁷ If the transmetalation precedes the palladation of fluorobenzene in a catalytic cycle, the inhibition of transmetalation could be the reason why o-tolylboronic acid did not react with 1. Although path B cannot be ruled out, these observations favor path A. The intermolecular kinetic isotope effect ($k_{H/D} = 1.7$) in the direct arylation of 2,3,5,6-tetrafluoroanisole with 2 indicated that the C-H bond cleavage was involved in the rate-limiting step.



In conclusion, we have demonstrated a palladiumcatalyzed method for the direct arylation of electron-deficient polyfluorobenzenes with arylboronic acids. This method exhibits a broad substrate scope with respect to both polyfluorobenzenes and arylboronic acids, which is attributed to the choice of bases depending on the acidities of the polyfluorobenzenes. The preliminary mechanistic studies suggested that this reaction may involve initial transmetalation from boron to palladium, followed by palladation of fluorobenzene and reductive elimination. Further efforts are underway to expand the substrate scope of this method to other electron-deficient arenes.

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Supporting Information Available: Detailed experimental procedures and characterization for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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