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Boryl Radicals

Amine-Ligated Boryl Radicals Enables Direct C—F Borylation and Cross-Couplings of Polyfluoroarenes

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Abstract: Polyfluoroarenes are privileged scaffolds in pharmaceutical and materials science, yet their synthesis remains challenging. Aromatic borylation offers a modular entry point for derivatization via Suzuki–Miyaura cross-coupling, but progress is hindered by two persistent issues: the difficulty of direct borylation on electron-deficient polyfluoroarenes, and the pronounced susceptibility of the resulting boron species to rapid protodeboronation under standard cross-coupling conditions. Here, we present an orthogonal strategy that addresses both limitations. Amine-ligated boryl radicals enable direct radical C—F borylation of polyfluoroarenes under visible-light photoredox catalysis. The resulting amine–borane adducts are crystalline, bench-stable, and resistant to protodeboronation, allowing their direct use in Pd-catalyzed Suzuki–Miyaura cross-couplings. This platform provides scalable and broadly applicable access to functionalized polyfluoroarenes and overcomes some of the synthetic constraints associated with these valuable motifs.

Introduction

Polyfluoroarenes are privileged motifs in the design of functional materials due to their unique physicochemical properties. These units typically exhibit low oxidation potential, strong ability to undergo intermolecular interactions, and high metabolic stability.[1–17] Their societal and medicinal relevance is underscored by the approval of over 10 polyfluoroaryl-containing drugs by the FDA in 2018 alone (Scheme 1a).[15–17] Despite their significance, the synthetic accessibility of highly functionalized polyfluoroarenes remains challenging, posing a major bottleneck for their application in medicinal and material chemistry.

Organoboron compounds are among the most versatile and widely used building blocks in organic synthesis.[18–25] They enable numerous transformations that are now indispensable tools for molecular construction and diversification. In particular, the Nobel Prize-winning Suzuki–Miyaura cross-coupling accounts for >20% of all synthetic processes in medicinal chemistry.[26] Accordingly, a key goal in advancing polyfluoroarene synthesis would be the preparation of organoboron derivatives that are amenable to cross-coupling (Scheme 1b). Achieving this requires addressing two interconnected limitations: 1) the lack of efficient methods for the direct borylation of these cores,[27–31] and 2) the intrinsic instability of polyfluoroarylboron species under Suzuki–Miyaura conditions, where they are prone to extremely rapid protodeboronation.[32,33]

Conventional approaches to aromatic borylation typically rely on Miyaura borylation of aryl halides or direct C—H activation.[34–37] While polyfluoroarenes bearing C—H or halide substituents can, in principle, be engaged, their commercial availability is often limited. A more attractive route would involve direct C—F borylation. However, the strength ($BDE_{C–F}$ > 120 kcal mol^{-1}) and low polarizability of C—F bond make this strategy inherently difficult.[38–42] Progress has been made using Rh- or Ni-catalysis,[27–31] but these approaches remain limited in scope and practicality.

An alternative approach to C—F functionalization involves single-electron pathways via radical intermediates.[40–50] In this context, *N*-heterocyclic carbene (NHC)-ligated boryl radicals **A** have been applied to C—F borylation of polyfluoroarenes **2** (Scheme 1c).[51–55] However, the resulting NHC—BH_2—polyfluoroarenes **B** products do not directly participate in Suzuki–Miyaura cross-couplings, thus limiting their utility as synthetic building blocks.[56]

We recently introduced carboxylic acid-functionalized amine–borane complex **1** as effective boryl radical precursor.[57] This species undergoes oxidative

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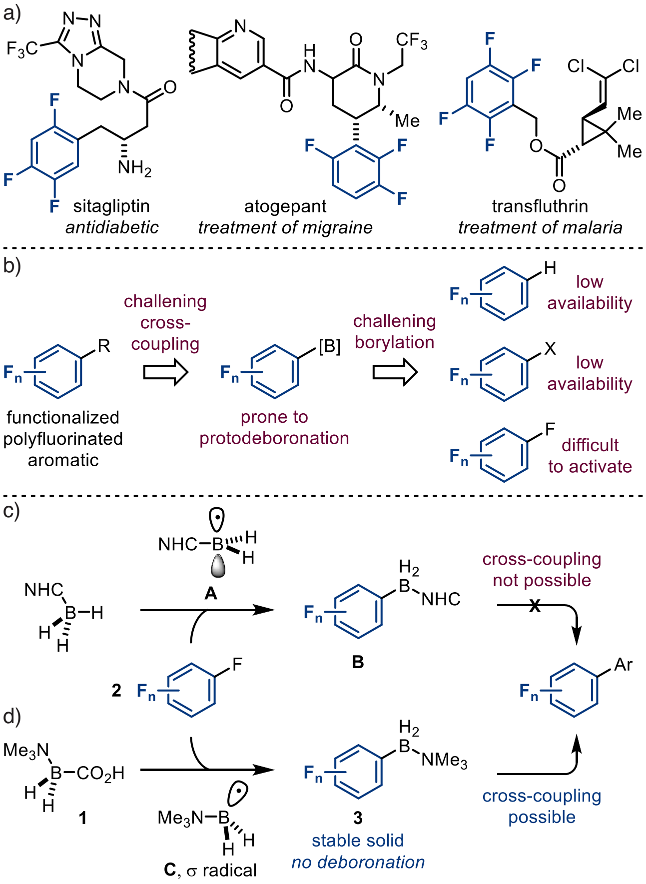


Scheme 1. a) Example of bioactive molecules containing polyfluoroarene motifs. b) Preparation and challenges of polyfluoroarenes via Suzuki–Miyaura cross-coupling. c) NHC-ligated boryl radicals enable C—F borylation but the resulting products cannot be cross-coupled. d) This work successfully explores the synthesis and cross-coupling reactivity of polyfluoroarene amine–boranes.

decarboxylation under reductive quenching photoredox conditions to generate amine-ligated boryl radical **C**. Owing to its σ-conjugated structure, this radical exhibits high nucleophilicity,[58–61] enabling efficient reactions with styrenes, imines, and Giese-type acceptors.[57,62–70] Here, we demonstrate that this photoredox platform can be successfully applied to the direct radical C(sp^2)—F borylation of polyfluoroarenes **2** (Scheme 1d). Crucially, the resulting polyfluoroaryl amine–borane adducts **3** are bench-stable, crystalline solids that do not undergo protodeboronation under basic aqueous conditions. These features allow their direct use in Suzuki–Miyaura cross-couplings with a wide array of aryl halides, enabling streamlined access to structurally diverse polyfluoroarenes.

Results and Discussion

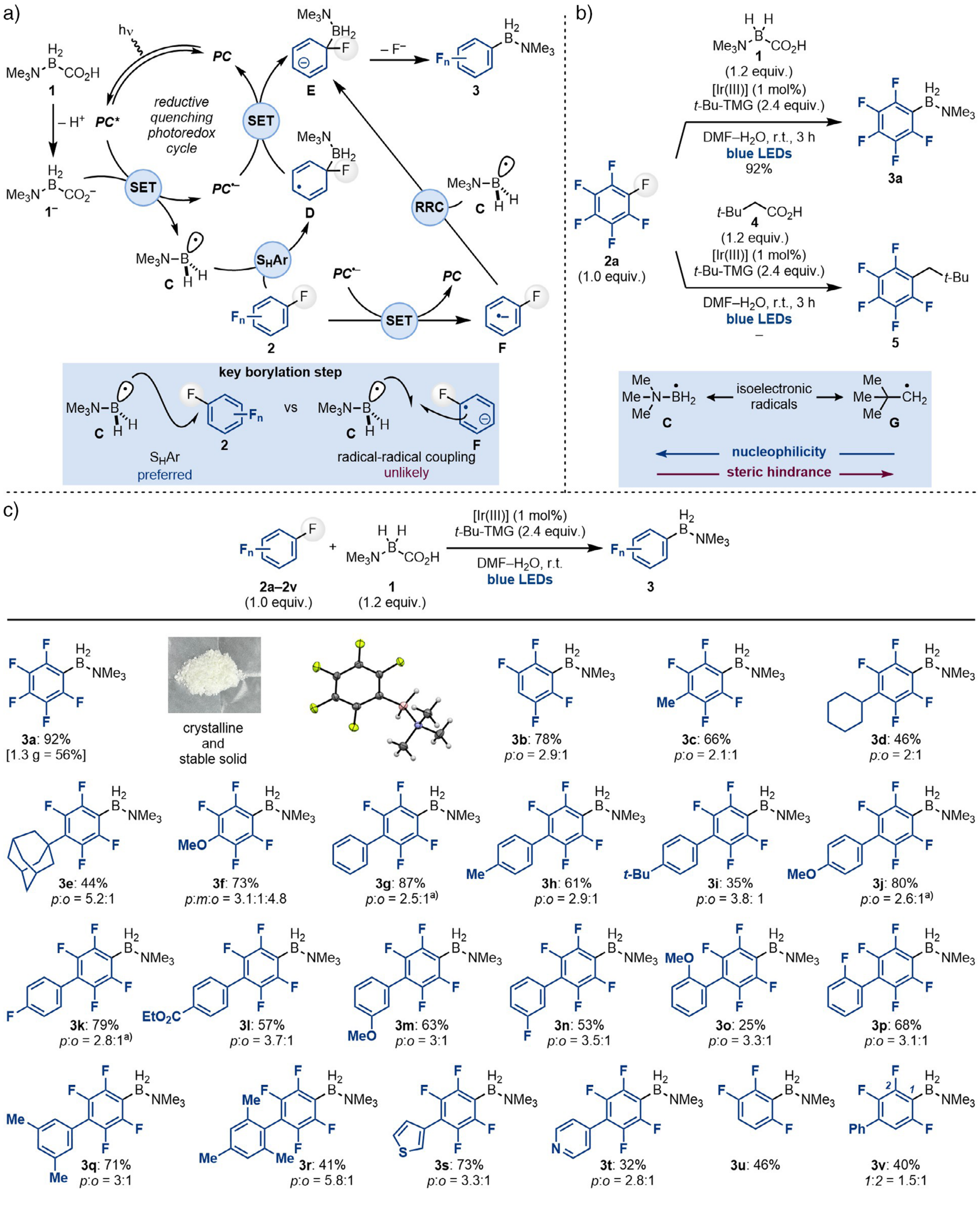
Radical Borylation of Polyfluoroarenes. Reaction Development and Scope

At the outset of our work, we proposed that the direct C—F borylation of polyfluoroarenes with amine-ligated boryl radicals could be centred on a reductive quenching photoredox cycle (Scheme 2a). Specifically, single-electron oxidation of the deprotonated borane precursor ($\mathbf{1}^-$) by a visible-light excited photocatalyst (***PC**) would trigger decarboxylation, furnishing the nucleophilic boryl radical **C**. From this point, two mechanistic pathways could operate in parallel to afford the borylated product **3**. In the first scenario, homolytic aromatic substitution ($\mathrm{S_H}$Ar) by addition of **C** to the polyfluoroarene **2** would generate a cyclohexadienyl radical intermediate **D**, which could undergo SET with the reduced photocatalyst ($\boldsymbol{PC}^{\bullet-}$) to form the Meisenheimer-type anion **E**. Subsequent elimination of fluoride would restore aromaticity and deliver the desired perfluoroaromatic amine-borane product **3**. Alternatively, SET reduction of **2** by $\boldsymbol{PC}^{\bullet-}$ could form the stabilized aryl radical anion **F**, which could then engage in a radical–radical coupling with **C**. This latter process may be facilitated by the persistent radical effect.[71]

With this mechanistic framework in hand, we proceeded to evaluate the reaction experimentally (Scheme 2b). Gratifyingly, the C—F borylation of **2a** with **1** was achieved using Ir(dtbppy)(ppy)$_2$ as the photocatalyst, *t*-Bu-TMG as the base, in DMF/H$_2$O solvent system under blue LED irradiation (Scheme 2b). Under these conditions, the desired adduct **3a** was obtained in 92% yield as a bench-stable and crystalline solid (see Scheme 2c for its X-ray crystal structure). When the reaction was performed on a 50-fold scale (10.0 mmol), **3a** was obtained in slightly lower yield demonstrating the operational simplicity and scalability of the method.

To support our mechanistic proposal, we conducted a series of experimental studies. Luminescence quenching experiments were performed using Ir(dtbppy)(ppy)$_2$ as the photocatalyst. Stern–Volmer analysis revealed efficient quenching of the excited-state photocatalyst by [**1**–*t*Bu-TMG], consistent with initiation via single-electron oxidation of its deprotonated form. Regarding the potential mechanistic bifurcation, we consider the formation of a polyfluoroaryl radical anion **F** to be unlikely. The reduction potential of **2a**, $E_{\mathrm{red}} = -2.38$ V (versus SCE in CH$_3$CN), is far beyond the reducing power of the [Ir(II)] species, $E_{\mathrm{Ir(II/III)}} = -1.51$ V (versus SCE in CH$_3$CN),[72,73] rendering a direct SET thermodynamically challenging. Conversely, DFT calculations at the SMD(DMF)/UM06-2X/6–31 + G(3d,2p) level support the feasibility of the $\mathrm{S_H}$Ar pathway. The computed activation barrier for the addition of **C** to **2a** ($\Delta G^{\ddagger} = +8.0$ kcal mol^{-1}) is consistent with a fast process, while the reaction is highly exergonic ($\Delta G^{\circ} = -18.3$ kcal mol^{-1}). These data are consistent with a mechanism based on $\mathrm{S_H}$Ar–reduction–elimination sequence.

An additional mechanistic feature worth highlighting lies in the electronic character and steric features of the amine-ligated boryl radical **C**. Although this species is formally isoelectronic with the alkyl radical **G**, it exhibits significantly greater nucleophilic character and lower steric hindrance due to the longer B—N bond (Scheme 2b).[62] These two properties likely enhance its reactivity in the key $\mathrm{S_H}$Ar step. Indeed, when *tert*-butylacetic acid **4** was tested under identical conditions, no formation of the isoelectronic C-centered product **5** was observed. This result underscores the importance of the unique nucleophilic and steric properties



Scheme 2. a) Mechanistic proposal for the direct C–F borylation of polyfluoroarenes via amine-ligated boryl radical reactivity. b) Optimized conditions and key radical properties c) Substrate scope. [a)] DMSO was used as the solvent instead of DMF.

of the amine–borane precursor in enabling the observed C—F borylation reactivity.

With the optimized conditions in hand, we next examined the scope of the C(sp^2)—F borylation reaction (Scheme 2c). Pentafluorobenzene underwent efficient borylation to afford product **3b** in 78% yield as a 2.9:1 mixture of regioisomers, favoring *para*- over *ortho*-substitution, with no detectable *meta*-functionalization. Substituted pentafluorobenzene derivatives were subsequently evaluated and similarly yielded predominantly the *para*-regioisomers in good yields. The reaction tolerated alkyl substituents such as methyl (**3c**), cyclohexyl (**3d**), and adamantyl (**3e**). Notably, these groups contain benzylic or tertiary positions that are typically prone to HAT,[74] yet no side reactions were observed. In the case of the sterically demanding adamantyl group, the *para*:*ortho* selectivity increased to 5.2:1, likely due to steric bias favoring distal radical addition.

We further demonstrated compatibility with electron-donating methoxy substituents directly attached to the perfluoroaryl core (**3f**). Despite the potential of this group to disrupt polar effects that may stabilize the Meisenheimer intermediate during the substitution step, the corresponding product was obtained in high yield.

We then turned to biaryl systems featuring a perfluoroaryl ring. A series of substituted biaryls underwent selective borylation on the perfluoroaryl ring, with a strong preference for 1,4-disubstitution. Electron-neutral and electron-rich aryl groups, including phenyl (**3g**), *para*-methyl (**3h**), *tert*-butyl (**3i**), methoxy (**3j**), fluoro (**3k**), and ester (**3l**), were all compatible. Additionally, *meta*- and *ortho*-substituted biaryl derivatives (**3m**–**3p**), as well as di-*meta* (**3q**) and di-*ortho*,*para* (**3r**) substitution patterns on the non-fluorinated ring, also participated effectively. In these cases, increased steric demand on the aryl partner further reinforced *para*-selectivity in the borylation step.

Heteroaryl-substituted polyfluoroarenes were also suitable substrates, affording products **3s** and **3t** in good and moderate yields, respectively. The successful formation of **3t** is particularly notable, as amine-ligated boryl radicals are known to engage in Minisci-type reactivity, which could otherwise result in undesired C2-functionalization of pyridine. Under our conditions, no such side reaction was observed. However, pentafluoropyridine proved incompatible in our system (see the Supporting Information). Finally, tetrafluorobenzene derivatives were found to be viable radical acceptors, delivering borylated products **3u** and **3v** in good yields. A further decrease in the number of fluorine atoms on the arene nucleus resulted in limitations under the present reaction system, as exemplified by tri- and difluoroarenes.

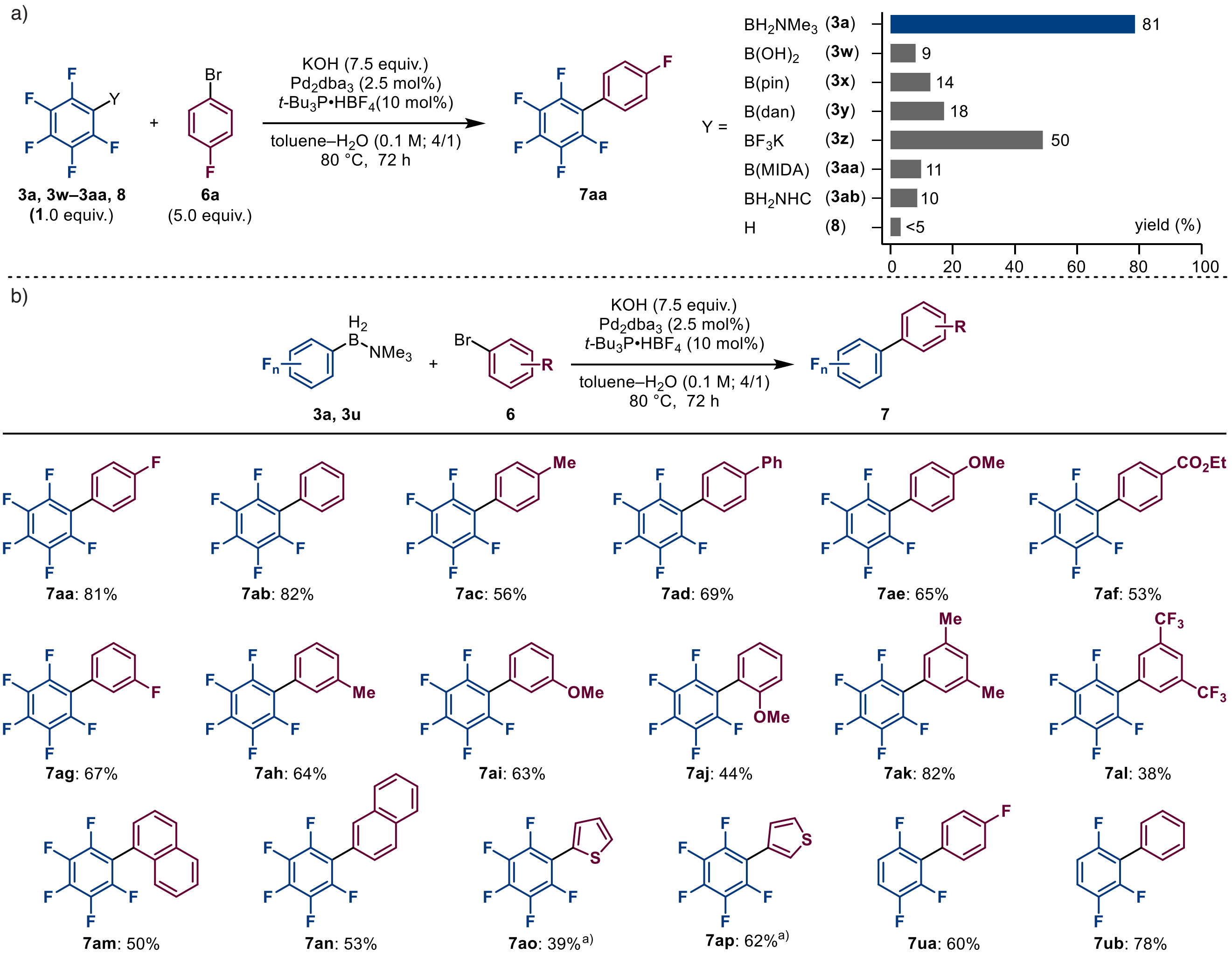
Suzuki–Miyaura Cross-Couplings of Perfluroaromatic Amine–Boranes

To fully realize the synthetic potential of these novel polyfluoroaryl amine-boranes, we sought to explore their ability to act as transmetallating partners in Pd-catalyzed Suzuki–Miyaura cross-coupling. Specifically, the reaction between **3a** and *para*-fluorobromobenzene (**6a**) was examined using $Pd_2(dba)_3$ and *t*-$Bu_3P \bullet HBF_4$ as the catalyst system, with KOH in toluene–H_2O at 80 °C. Under these conditions, the cross-coupled product **7aa** was obtained in 81% yield (Scheme 3a).

Cross-coupling reactions of polyfluorinated arylboron reagents are typically challenging due to their low nucleophilicity and high susceptibility to protodeboronation under aqueous basic conditions. This issue is particularly pronounced in highly fluorinated systems, where the half-life of pentafluoroboronic acid is estimated at only ∼2.6 ms at elevated temperatures.[32,33] While strategies involving tailored reaction conditions[75,76] and specialized catalyst systems[77,78] have been developed to mitigate these limitations, few approaches leverage the intrinsic properties of the boron species themselves. Notably, Yoshida reported the use of naphthalene-1,8-diaminato (dan)-protected boronates to enhance stability,[79] although their protocol requires copper co-catalysis to enable transmetallation. To benchmark the reactivity of **3a**, we compared its performance with that of various pentafluoroarylboron analogues under identical coupling conditions (Scheme 3a). As anticipated, commonly employed boron reagents, including boronic acid (**3w**), pinacol ester (**3x**), dan-protected boronate (**3y**), potassium trifluoroborate (**3z**), and MIDA boronate (**3aa**), gave significantly lower yields of **7aa** with considerable protodeboronation. Furthermore, NHC—BH_2—pentafluorobenzene (**3ab**), which was synthesized via a radical C—F borylation,[51–54] afforded **7aa** in only 10% yield, suggesting that NHC—BH_2 adducts are incompatible with direct Suzuki–Miyaura cross-couplings. This, in turn, highlights the utility of our strategy based on radical borylation using amine-ligated boryl radicals followed by Suzuki–Miyaura cross-coupling. These reduced performances are attributed to their limited hydrolytic stability and poor transmetallation efficiency under the reaction conditions. Furthermore, a control reaction using pentafluorobenzene (**8**) in place of **3a** led to only trace formation of **7aa**. This result rules out a mechanistic pathway involving protodeboronation followed by direct C—H arylation and supports that the coupling proceeds through an organoboron intermediate.

With the optimized conditions in hand, we next explored the scope of aryl bromides (Scheme 3b). A variety of substrates—including simple bromobenzene (**6b**), *para*-substituted derivatives (**6c**–**6f**), *meta*- (**6g**–**6i**), *ortho*- (**6j**), and 3,5-disubstituted systems (**6k**, **6l**) were well tolerated, delivering the corresponding products (**7aa**–**7al**) in good yields with little dependence on electronic effects. The method was further extended to 1- and 2-bromonaphthalene (**6m**, **6n**) and heteroaryl bromides (**6o**, **6p**), demonstrating broad substrate compatibility.

Finally, we confirmed the generality of this transformation using the tetrafluorophenyl amine–borane complex (**3u**), which also underwent smooth cross-coupling under the standard conditions. These results highlight the unique stability and reactivity of the amine–borane platform in enabling otherwise challenging Suzuki–Miyaura transformations.



Scheme 3. a) Optimized conditions for the Suzuki—Miyaura cross-coupling between boronate complex **3a** and aryl bromides **6a** as well as reactivity comparison with other perfluoroaromatic organoborons. b) Substrate scope. [a)] Pd_2dba_3 (0.005 mmol, 5 mol%) and t-Bu_3P•HBF_4 (0.02 mmol, 20 mol%) were used.

Conclusions

We have developed a photoredox strategy for the direct C–F borylation of polyfluoroarenes using amine-ligated boryl radicals. This method grants access to bench-stable polyfluoroaryl amine–borane adducts that can be directly engaged in Suzuki–Miyaura cross-coupling reactions. The success of this approach stems from the high nucleophilicity of the amine-ligated boryl radical, which enables efficient homolytic aromatic substitution of electron-deficient fluoroarenes. Crucially, the resulting boron adducts exhibit pronounced resistance to protodeboronation, a major limitation of conventional polyfluoroarylboron species. This stability permits cross-coupling under standard conditions without the need for specialized ligands, additives, or co-catalysts. Overall, this work establishes a platform for the modular functionalization of polyfluoroarenes and may prove valuable for the late-stage diversification of functional molecules in pharmaceuticals, agrochemicals, and optoelectronic materials.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Amine–borane • Amine-ligated boryl radicals • Polyfluoroarene • Protodeboronation • Suzuki–Miyaura cross-coupling

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