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COMMUNICATION

Excited-State Palladium-Catalyzed Defluorinative Arylation of Polyfluoroarenes

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Visible-light-induced excited-state palladium catalysis enables defluorinative C(sp²)–C(sp²) cross-coupling of polyfluoroarenes with aryl boronic acids under blue LED irradiation at room temperature. The $Pd(OAc)_2$/BrettPhos catalyst selectively activates C(sp²)–F bonds without external photocatalysts, affording multifluorinated biaryls in good to excellent yields through photoinduced formation of Ar–Pd(II) intermediates.

Fluorinated aromatic compounds are widely encountered in pharmaceuticals, agrochemicals, and functional materials with enhanced metabolic stability, lipophilicity, and electronic modulation.[1-3] Fluorinated biaryl motifs, in particular, are key structural elements in bioactive molecules and advanced materials, driving significant interest in efficient and selective functionalization of polyfluoroarenes.[4] Among the various strategies available, defluorinative functionalization of polyfluoroarenes has emerged as a powerful approach for constructing C–C bonds while simultaneously introducing valuable fluorinated motifs.[5] However, the activation of C(sp²)–F bonds remains challenging due to their high bond dissociation energy and the strong electronegativity of fluorine.[6] Traditional approaches often require harsh reaction conditions, specialized reagents, or prefunctionalized substrates, which limit their synthetic utility (Scheme 1a).[7-11]

In recent years, visible-light-induced strategies have enabled the generation of aryl radicals from polyfluoroarenes through selective C–F bond cleavage, thereby allowing diverse defluorinative transformations.[12, 13] The Weaver group reported the selective arylation and alkenylation of C(sp²)–F bonds in polyfluoroarenes, using electron-rich arenes and alkynes as coupling partners in the presence of an iridium photocatalyst under visible light irradiation (Scheme 1a).[14, 15] Building on this approach, our group developed a dual catalysis strategy that combines iridium photocatalyst with a nickel catalyst to enable the cross-coupling of polyfluoroarenes with aryl bromides under light (Scheme 1a).[16] Subsequently, the Chu group reported a synergistic approach combining palladium and iridium photocatalysts for the reductive cross-electrophile coupling of polyfluoroarenes with aryl triflates and bromides; however, the reaction required elevated temperatures of 70–75 °C (Scheme 1a).[17] Despite these advances, these systems typically rely on external photocatalysts and multi-catalyst reaction platforms.

More recently, visible-light-induced Pd-catalysis has emerged, enabling palladium to participate in photochemical processes beyond conventional ground-state catalytic cycles.[18-21] However, visible-light-induced defluorinative cross-coupling reactions employing Pd catalysis are unexplored.[22-29] Inspired by these studies, we envisioned that photoexcited Pd species could enable site-selective defluorinative arylation of polyfluoro- and perfluoroarenes *via* ionic or radical pathways, allowing direct C(sp²)–C(sp²) bond formation with readily available coupling partners (Scheme 1b).[30-32]

We began our investigation by examining the coupling of pentafluorobenzene (**1a**) with phenylboronic acid (**2a**) under visible-light irradiation. Initial studies revealed that $Pd(OAc)_2$ (2.5 mol%) and BrettPhos (5 mol%) in the presence of Cs_2CO_3 and 1,4-dioxane under blue LED irradiation efficiently promoted the defluorinative arylation to afford product **3a** in 76% yield. Evaluation of various phosphine ligands established BrettPhos as uniquely effective, whereas commonly employed ligands such as PPh_3, BINAP, XPhos, RuPhos, and DavePhos resulted in trace or no product formation. Screening of solvents such as MeCN, toluene, and THF resulted in significantly diminished yields, while DMA or DMSO suppressed the reactivity. Among several palladium sources tested, $Pd(TFA)_2$ and $Pd(hfacac)_2$ delivered the product in moderate yield, while $PdCl_2$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(PPh_3)_4$ were found ineffective. Evaluating different bases revealed that Cs_2CO_3 was superior, whereas other inorganic and organic bases provided moderate yields. Increasing the catalyst loading to $Pd(OAc)_2$ (5 mol%) and BrettPhos (10 mol%) improved the yield to 86%, while reducing the reaction time from 24 h to 6 h furnished the product in 88% yield. Control experiments confirmed that both visible light and the Pd/BrettPhos catalytic system are essential for the transformation, supporting a visible-light-induced palladium-catalyzed C–F bond activation process (see SI for further details).

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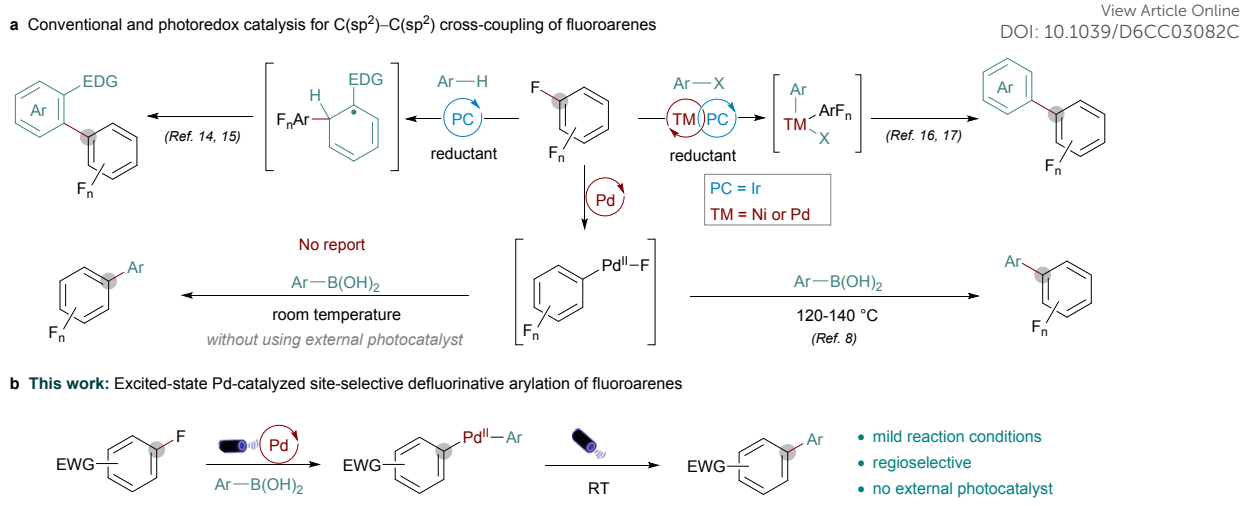
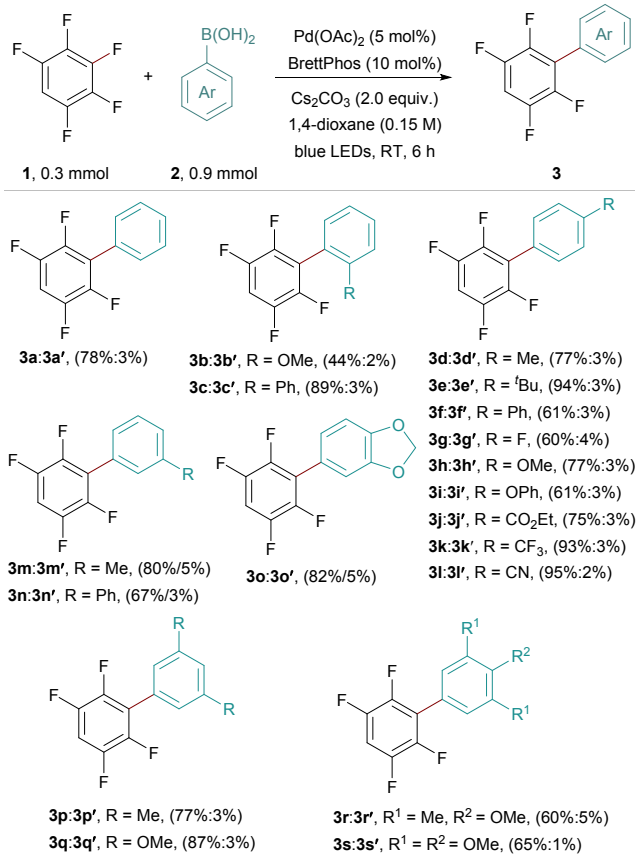


Scheme 1 Background and outline of the research.

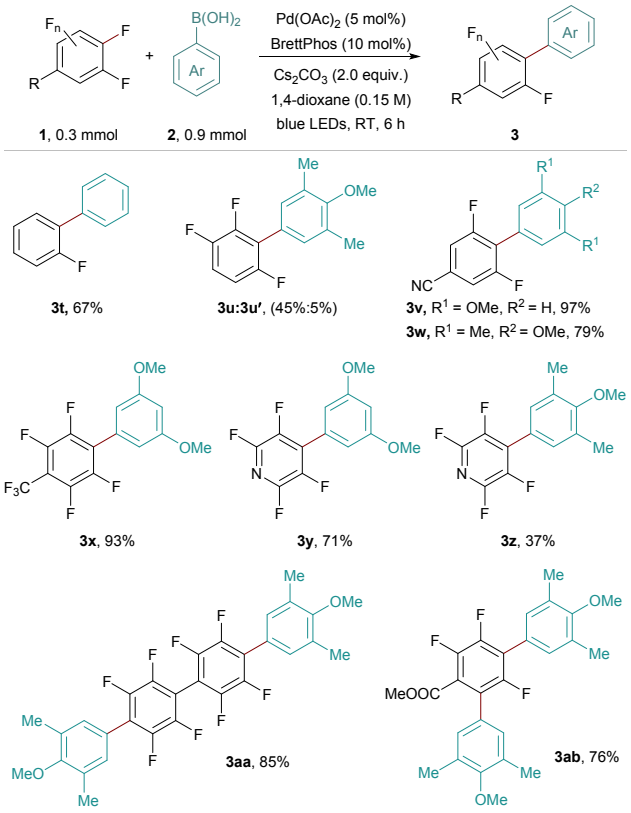
With the optimized reaction conditions in hand, we next explored the scope of excited-state Pd-catalyzed defluorinative arylation with respect to both aryl boronic acids and polyfluoroarenes (Scheme 2). A range of substituted aryl boronic acids participated smoothly to afford the corresponding fluorinated biaryl products in moderate to excellent yields. Aryl boronic acids bearing *ortho*-substituents on the aromatic ring were compatible, affording the corresponding defluorinative cross-coupled products **3b** and **3c** in 44% and 89% yields, respectively. Substrates containing *para*-substituents, including electron-donating groups (–Me, –^{t}Bu, –OMe, and –OPh) as well as electron-withdrawing substituents (–Ph, –F, –CO_2Et, –CF_3, –CN) were well tolerated to yield the products **3d**–**3l** in 60–95% yields. Boronic acids substituted at the *meta*-position were also suitable coupling partners, providing the corresponding products **3m**–**3n** in moderate to good yields (67–80%). Furthermore, di- and trisubstituted aryl boronic acids reacted smoothly under the standard conditions to furnish the C(sp^2)–C(sp^2) cross-coupled products **3o**–**3s** without substantial loss of reactivity. Interestingly, across the range of boronic acids examined, the reaction exhibited high regioselectivity (2,3,5,6-tetrafluoro-1,1'-biaryl), with the corresponding regioisomeric products (**3′**, 2,3,4,6-tetrafluoro-1,1'-biaryl) formed in less than 5% yield.

Having established the generality with respect to aryl boronic acids, we next evaluated the compatibility of different polyfluoroarenes and perfluoroarenes (Scheme 3). 1,2-difluorobenzene (**1b**) and 1,2,3,4-tetrafluorobenzene (**1c**) underwent smooth defluorinative arylation to furnish the corresponding biaryl products **3t** and **3u** in 67% and 45% yields, respectively. Importantly, substrates bearing nucleophile-sensitive functional groups, such as –CN substituent (**1d**) were well tolerated under the reaction conditions, delivering the corresponding products **3v**–**3w** in 79–97% yields. In addition, several perfluoroarenes (**1e**–**1f**) participated smoothly in the reaction, through Pd-catalyzed selective C(sp^2)–F bond activation and delivering the corresponding biaryl products **3x**–**3z** in 37–93% yields. Furthermore, a multifluorinated arene (**1g**) efficiently underwent double arylation to furnish the diarylated polyfluoroarene **3aa** in an excellent yield of 85%. When an ester-substituted polyfluoroarene (**1h**) was employed, complete site selectivity was not achieved, leading to the formation of both *ortho*- and *para*-substituted product (**3ab**) in 76% yield.

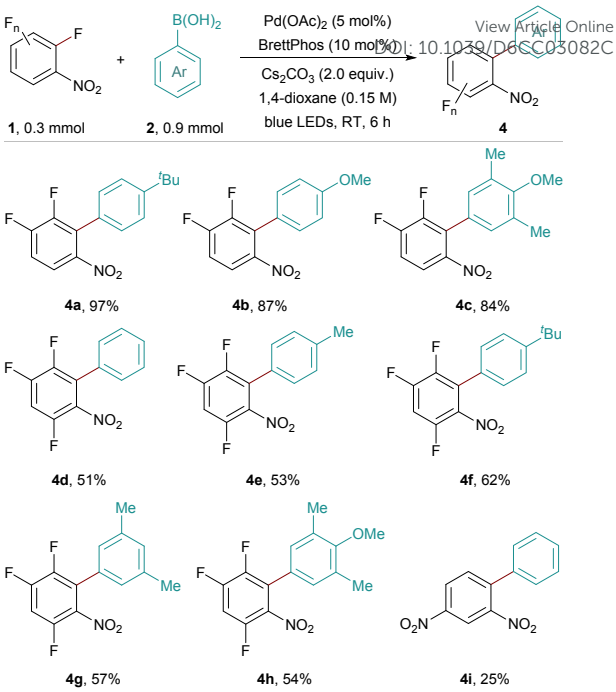
Encouraged by these results, we next investigated whether chelating substituents could influence the selectivity of the defluorination process. In particular, we hypothesized that nitro groups could act as directing groups to promote *ortho*-selective C–F bond activation. To test this hypothesis, fluorinated nitroarenes were subjected to the optimized reaction conditions (Scheme 4).



Scheme 2 Scope of the reaction with different aryl boronic acids and polyfluoroarenes. **3′** is the corresponding regioisomeric product.



Scheme 3 Scope of the reaction with different aryl boronic acids and polyfluoroarenes. **3'** is the corresponding regioisomeric product.



Scheme 4 Scope of the reaction with different aryl boronic acids and polyfluoroarenes.

Gratifyingly, these substrates underwent efficient coupling to give the corresponding *ortho*-defluorinative biaryl products **4a–4h** in good to excellent yields. For example, *para*-substituted aryl boronic acids (**2e** and **2h**) as well as a trisubstituted boronic acid (**2r**) reacted smoothly with nitroarene **1i**, providing the corresponding *ortho*-defluorinated products **4a–4c** in excellent yields (84–97%). Similarly, tetrafluoronitrobenzene (**1j**) reacted efficiently with various aryl boronic acids to afford the desired biaryl products **4d–4h** in 51–62% yields. Furthermore, the methodology could also be extended to 2,4-dinitrofluorobenzene (2,4-DNFB) (**1k**), which gave the corresponding defluorinative coupling product **4i**, albeit in a modest 25% yield. Overall, these results demonstrate the visible-light-driven functional-group tolerance, while allowing a highly selective defluorinative C(sp^2)–C(sp^2) cross-coupling of polyfluoroarenes.

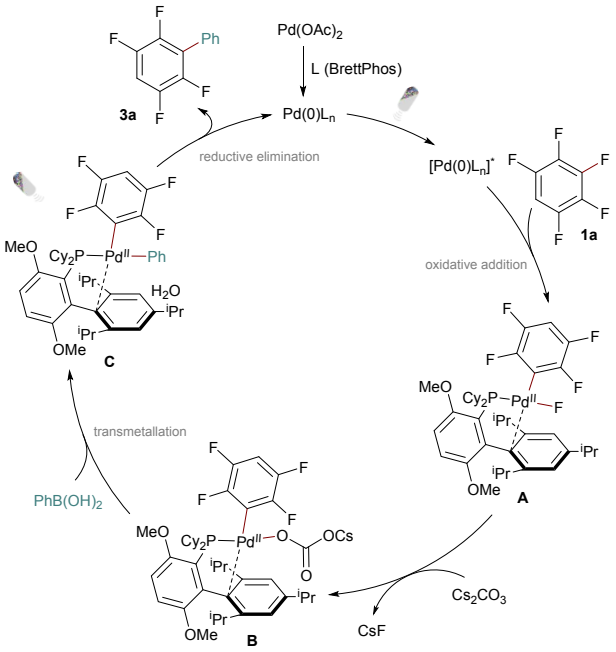
To gain insight into the reaction mechanism, radical trapping experiments were performed using TEMPO and BHT (see SI for further details). The addition of 1.0 equivalents of TEMPO significantly inhibited the product formation, however, no TEMPO–aryl adducts were detected by GC–MS or NMR analysis. This suggests that the reaction does not proceed through freely diffusing aryl radical intermediates and that TEMPO disrupts the photoexcited Pd-catalytic cycle either via Pd-coordination or excited state quenching.[33, 34] In line with this, BHT had no significant effect on the reaction which further excludes the involvement of free radical intermediates. To verify that the ligated Pd(0) complex acts as the photo absorbing species, UV–Vis absorption studies were conducted. The BrettPhos-ligated Pd(0) complex exhibited a broad absorption band in the 360–500 nm region, which overlaps well with the emission profile of the blue LEDs used in the reaction, supporting its role as a photoactive catalytic species. Notably, a red shift in the absorption was observed by increasing pentafluorobenzene concentration which suggests interaction between the Pd complex and the substrate that facilitates photoinduced C–F oxidative addition. Light on/off experiments indicate that continuous light irradiation is required for catalytic turnover, thereby excluding the possibility of a radical chain propagation process and confirming that light plays a direct role in driving the catalytic cycle.

Based on these observations and literature precedents, a plausible catalytic cycle is proposed (Scheme 5). Initially, coordination of BrettPhos to $Pd(OAc)_2$ generates the active ligated Pd(0)-species, which upon visible-light absorption is promoted to a triplet excited state. The resulting photoexcited Pd-complex is proposed to undergo oxidative addition into the C(sp^2)–F bond of the polyfluoroarene, generating a Pd(II)–aryl intermediate **A**. Subsequent ligand exchange with Cs_2CO_3 affords intermediate **B**, which then undergoes transmetalation with the aryl boronic acid to form a diaryl Pd(II) intermediate **C**. Finally, reductive elimination under light irradiation furnishes the desired defluorinative C(sp^2)–C(sp^2) cross-coupled product, thereby regenerating the active Pd(0) catalyst for the next catalytic cycle.

The observed regioselectivity can be rationalized by the preferential oxidative addition of the photoexcited Pd(0)/BrettPhos complex into the most electrophilic C(sp^2)–F bond of the polyfluoroarene. In the case of pentafluorobenzene, the C(sp^2)–F bond para to the C(sp^2)–H bond is expected to be the most activated due to the cumulative electronic influence of the neighboring ortho- and meta-fluorine substituents. Accordingly, the regioselectivity observed in this transformation is consistent with the well-established

selectivity patterns reported for nucleophilic aromatic substitution (S_NAr) reactions of polyfluoroarenes. In addition, the steric environment imparted by the BrettPhos ligand may further disfavor competing oxidative addition pathways, thereby enhancing regioselectivity. For nitro-substituted polyfluoroarenes, the strongly electron-withdrawing nitro group is proposed to activate the adjacent ortho-C(sp^2)–F bonds, resulting in a switch from para-selective to ortho-selective defluorination, as observed experimentally.

In conclusion, we have developed a visible-light-induced Pd-catalyzed defluorinative C(sp^2)–C(sp^2) cross-coupling of polyfluoroarenes with aryl boronic acids. With $Pd(OAc)_2$/BrettPhos as catalyst under blue LED irradiation, the transformation proceeds efficiently at room temperature without the need for an external photocatalyst and provides a mild and operationally simple approach for the synthesis of multifluorinated biaryl products. The protocol exhibits broad substrate scope and good functional-group tolerance, allowing



Scheme 5 Proposed mechanism.

the coupling of a wide range of aryl boronic acids with polyfluoroarenes and perfluoroarenes while maintaining high regioselectivity in C–F bond activation. Importantly, the presence of nitro substituents enables *ortho*-selective defluorination, demonstrating the potential of directing groups to control site selectivity in these transformations. The resulting multifluorinated biaryl motifs are prevalent in medicinal chemistry and materials science. We anticipate that this strategy will stimulate further development of visible-light-induced palladium-catalyzed transformations for the selective functionalization of fluorinated arenes.

Arnab Dey: methodology, investigation, validation, formal analysis, writing – original draft. Cătălin C. Anghel: investigation, validation, formal analysis. Rajesh Kancherla: methodology, writing – review and editing, supervision, project administration. Magnus Rueping: conceptualization, methodology, supervision, funding acquisition, project administration, resources, writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI:

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Data Availability Statement

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: