ORGANOMETALLICS

Dual Photoredox-/Palladium-Catalyzed Cross-Electrophile Couplings of Polyfluoroarenes with Aryl Halides and Triflates

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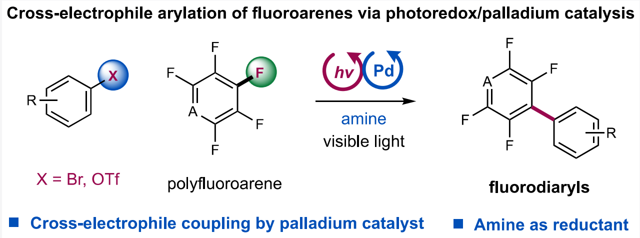
Cite This: https://dx.doi.org/10.1021/acs.organomet.0c00813 Read Online

ABSTRACT: A visible-light photoredox-/Pd-catalyzed cross-electrophile arylation of polyfluoroarenes with aryl halides and triflates in the presence of dialkylamines is reported for the first time. This synergistic protocol affords access to a series of fluorodiaryls from easily available starting materials under mild and operationally simple conditions. A series of mechanistic experiments, including the stoichiometric reactions of a ligated (aryl)Pd complex, Stern−Volmer fluorescence quenching studies, cyclic voltammetry studies, and UV−vis spectroscopy, were performed to elucidate the potential catalytic pathway in this synergistic process.



■ INTRODUCTION

Polyfluorobiaryls are prevalent motifs found in pharmaceuticals,[1] catalysts, and ligands,[2] as well as functionalized materials including organic electronics[3] and liquid crystals.[4] Thereafter, the development of efficient synthetic methods for the selective construction of polyfluorobiaryls has attracted an increasing research interest, with elegant progress having been achieved during the past 20 years. Owing to the privileged properties of palladium catalysts,[5] Pd-catalyzed polyfluoroaryl−aryl couplings represent one of the most efficient and widely employed strategies to forge fluorobiaryls,[6−8] where prefunctionalized fluoroarenes[6] (halides, benzoates, boronic acids, magnesium, etc.) are generally employed for the control of reactivity and selectivity. Alternatively, the acidic C−H bonds of fluoroarenes can serve as more economical and attractive handles for Pd-catalyzed cross-couplings with aryl nucleophiles or electrophiles.[7] Limited examples of C−F bonds of fluoroarenes, one type of more readily available fluoroarenes, have been reported, probably due to the challenges in the catalytic selective activation of C−F bonds.[8] Mechanistically, these Pd-catalyzed polyfluoroaryl couplings proceed via a two-electron Pd(0)/Pd(II) pathway. In this context, the development of a mechanistically distinct mode for the Pd-catalyzed cross-couplings of fluoroarenes under mild conditions would be of particular interest.

Catalytic cross-electrophile couplings between two electrophiles in the presence of a stoichiometric reductant (Zn, Mn, etc.), which preclude the use of organometallic agents by directly utilizing benign and abundant electrophiles, represent an attractive and practical platform for the construction of C−C bonds.[9] Recently, Weix and co-workers have successfully achieved the selective cross-electrophile couplings between two aryl electrophiles to forge valuable diaryls through nickel and palladium multimetallic catalysis.[10] In this manifold, excellent control of chemoselectivity is leveraged by a selective single-electron-transfer (SET) reduction of (aryl)Ni^{II} species rather than (aryl)Pd^{II} species mediated by Zn on the basis of the distinct properpties of nickel and palladium. Nevertheless, a similar SET event of (aryl)Pd^{II} species, a common reactive intermediate in numerous Pd-catalyzed aryl couplings, would be interesting for exploiting new Pd-catalyzed transformations yet remains elusive.

On the other hand, metallaphotoredox catalysis[11] offers a distinct mode for cross-electrophile couplings with organic reductants, through visible-light-induced single-electron transfer of a transition-metal catalyst.[12] The majority of known transformations have focused on the $C(sp^2)-C(sp^3)$ couplings via photoredox/nickel dual catalysis, utilizing the high reactivity of alkyl radicals. Herein, we report synergistic phororedox- and palladium-catalyzed[13,14] cross-electrophile couplings of polyfluoroarenes with aryl halides and triflates using an alkylamine as a stoichiometric reductant, forging polyfluorobiaryls with exclusive *para* selectivity under operationally simple and mild conditions. This photoredox/palladium protocol was inspired by the photoinduced SET C−F activation of polyfluoroarenes developed by Weaver and others[15] and complements the previously reported photoinduced S_NAr arylation of polyfluoroarenes,[15a,b] where electron-rich arenes were employed. During the preparation of this paper, Rueping and co-workers reported a photoredox-/

Special Issue: Organometallic Solutions to Challenges in Cross-Coupling

Received: December 29, 2020

nickel-catalyzed reductive arylation of polyfluoroarenes (Figure 1).[12e]

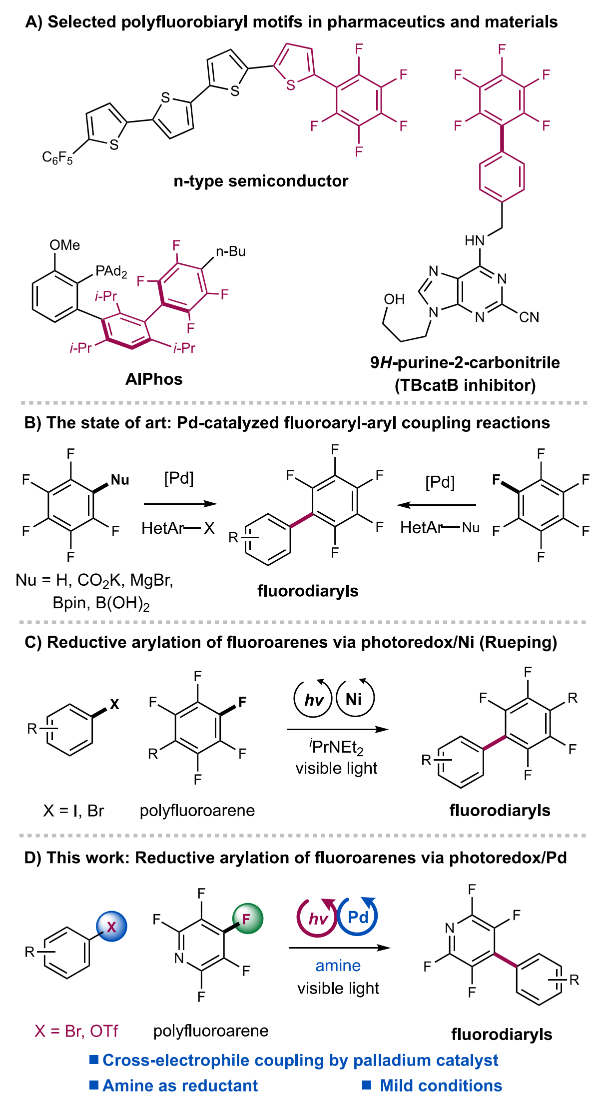
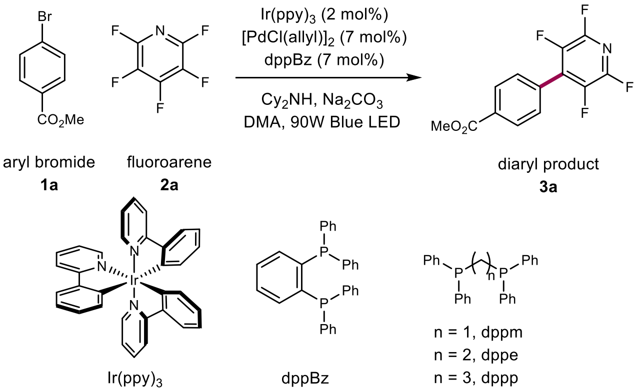


Figure 1. Catalytic fluoroaryl−aryl couplings for the construction of polyfluorodiaryls.

Table 1. Optimizations of Reaction Conditions[a]



entry	variation from the standard conditions	yield (%)
1	none	85 (78)[b]
2	$Pd(OAc)_2$, instead of $[PdCl(allyl)]_2$	trace
3	$Pd(PPh_3)_4$, instead of $[PdCl(allyl)]_2$	trace
4	$PdCl_2(PPh_3)_2$, instead of $[PdCl(allyl)]_2$	trace
5	dppe instead of dppBz	66
6	dppm instead of dppBz	34
7	dppp instead of dppBz	9
8	DIPEA, instead of Cy_2NH	15
9	Et_3N, instead of Cy_2NH	32
10	$(i\text{-}Pr)_2NH$, instead of Cy_2NH	71
11	without PC	8
12	without $[PdCl(allyl)]_2$	trace
13	without dppBz	16
14	without Cy_2NH	trace
15	without Na_2CO_3	7
16	in the dark	ND

[a] Reaction conditions: Reaction conditions: $Ir(ppy)_3$ (2 mol %), $[PdCl(allyl)]_2$ (7 mol %), dppBz (7 mol %), fluoropyridine (0.2 mmol), ArBr (2.0 equiv), Cy_2NH (0.5 equiv), Na_2CO_3 (2.0 equiv), DMA [0.05 M], 70−75 °C, 20 h. Yields were determined by GC using dodecane as the internal standard. Abbreviations: dppe = 1,2-bis(diphenylphosphino)ethane, dppm = bis(diphenylphosphino)-methane, dppp = 1,3-bis(diphenylphosphino)propane. [b] Isolated yields.

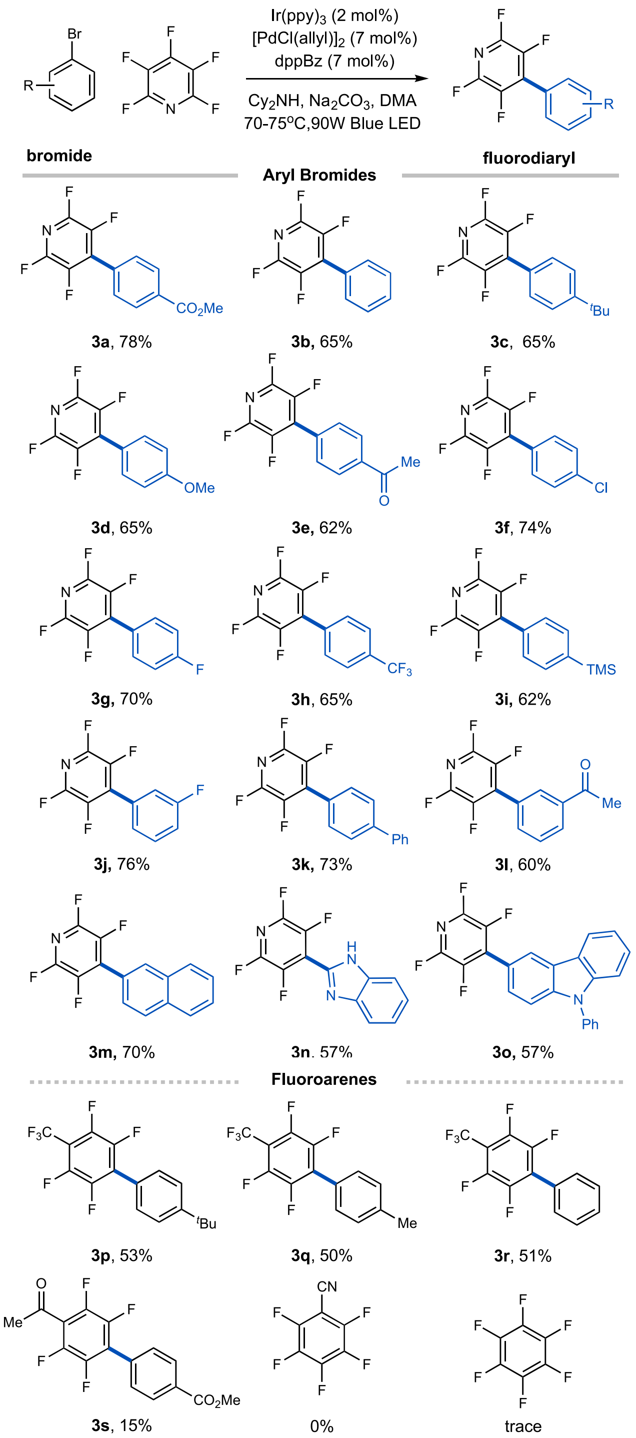
■ RESULTS AND DISCUSSION

We began our investigations by employing methyl 4-bromobenzoate (**1a**) and pentafluoropyridine (**2a**) as model substrates (Table 1). Pleasingly, we found that the combination of $Ir(ppy)_3$ as the photocatalyst, allylpalladium(II) chloride dimer $[PdCl(allyl)]_2$ as the catalyst, 1,2-bis(diphenylphosphino)benzene (dppBz) as the ligand, dicyclohexylamine (Cy_2NH) as the reductant, and Na_2CO_3 as the base could enable the selective diaryl coupling of **1a** and **2a** to afford fluorodiaryl product **3a** in 85% GC yield (entry 1). Intriguingly, the choice of palladium catalysts played a crucial effect on the coupling efficiency, as switching to other commonly employed Pd(II) catalysts or $Pd(PPh_3)_4$, which has typically been used in photoinduced Pd-catalyzed transformations,[13] led to almost no formation of product **3a** (entries 2−4).

Bidentate bis-phosphine ligands were the most effective ligand skeletons to promote the desired cross-couplings, while their bite angles affected the reaction efficiency and dppBz proved to be optimal (entries 5−7). With regard to the stoichiometric reductants, we found that, in the presence of inorganic bases such as Na_2CO_3, secondary sterically hindered amines such as Cy_2NH and $i\text{-}Pr_2NH$ performed better than common tertiary amines (e.g. $(i\text{-}Pr)_2NEt$ and Et_3N) (entries 8−10). Control experiments indicated that the palladium catalyst, reductant, and visible light were essential to this cross-electrophile coupling of fluoroarenes, as no products formed in the absence of any of them (entries 12, 14, and 16), while low yields were still obtained in the absence of a photocatalyst or a ligand (entries 11 and 13). For nonoptimal conditions, hydrodebromination and self-couplings of aryl bromides were the major side reactions observed in this photoredox/Pd system.

With the optimized conditions in hand, we turned our attention to exploring the generality of this synergistic photoredox/Pd cross-electrophile diaryl coupling. Under the optimal conditions, as depicted in Scheme 1, an array of aryl bromides incorporating electron-donating and electron-withdrawing substituents showed moderate to good efficiency in this protocol (products **3a**−**o**). The electronic property of aryl

Scheme 1. Scope of Aryl Bromides and Fluoroarenes[a]

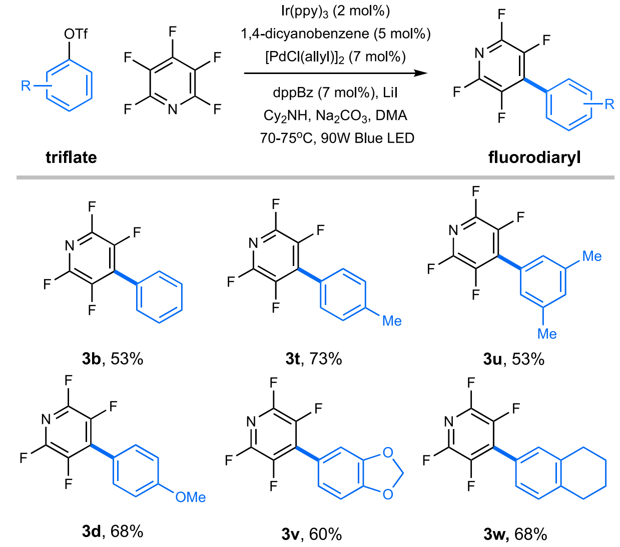


[a] Reaction conditions: Ir(ppy)$_3$ (2 mol %), [PdCl(allyl)]$_2$ (7 mol %), dppBz (7 mol %), fluoroarene (0.2 mmol), ArBr (2.0 equiv), Cy$_2$NH (0.5 equiv), Na$_2$CO$_3$ (2.0 equiv), 70–75 °C, DMA [0.05 M], 20 h. Isolated yields are given.

bromides was found to have some effect on the cross-coupling efficiency, and electron-deficient bromoarenes generally exhibited higher efficiency than electron-rich bromoarenes. The mild conditions were compatible with various functional groups including ethers, esters, halogens, ketones, and silanes (products **3a,d–l**). For multihaloarenes, exclusive chemoselectivity toward bromides was observed, as exemplified by product **3f**. Nonetheless, iodoarenes failed due to a facile self-coupling process under the photoinduced conditions. Pleasingly, the reaction of naphthyl bromide gave the desired fluorodiaryl product **3m** in moderate yield. Moreoever, bromo heteroarenes, represented by benzimidazoles and carbazoles that are privileged skeletons present in many bioactive natural products and pharmaceuticals, were competent coupling partners in this synergistic protocol, delivering the desired heteroaryl products in moderate yields (products **3n,o**). With regard to the ployfluoroarene component, a *para*-trifluoromethylated fluoroarene was a suitable substrate, undergoing selective cross-electrophile couplings with aryl bromides in synthetically useful yields (products **3p–r**). Nevertheless, other polyfluoroarenes suffered from low efficiency (**3s**).

In comparison with aryl bromides, aryl triflates can be easily prepared from more economical phenols. Under this dual photoredox/Pd protocol with 1,4-dicyanobenzene as a cophotocatalyst and LiI as an additive,[13d] we were pleased to find that aryl triflates were capable of undergoing selective cross-electrophile coupling with a fluoroarene with moderate efficiency (Scheme 2). Aryl triflates bearing electron-donating or electron-neutral substituents demonstrated good reactivity (products **3b,d,t–w**). Nonetheless, electron-deficient aryl triflates were incompetent coupling partners in the current conditions.

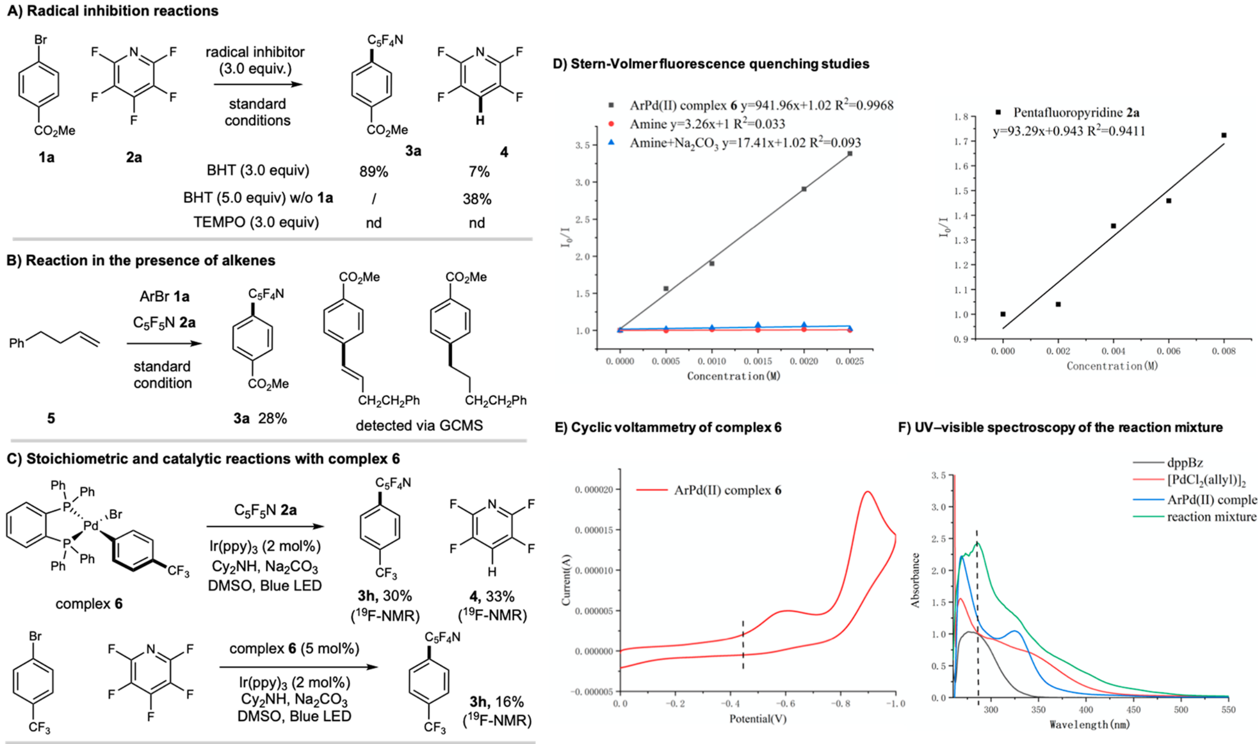
Scheme 2. Scope of Aryl Triflates[a]



[a] Reaction conditions: Ir(ppy)$_3$ (2 mol %), 1,4-dicyanobenzene (5 mol %), [PdCl(allyl)]$_2$ (7 mol %), dppBz (7 mol %), fluoropyridine (0.2 mmol), ArOTf (1.5 equiv), Cy$_2$NH (0.8 equiv), Na$_2$CO$_3$ (2.0 equiv), LiI (0.3 equiv), DMA [0.05 M], 70–75 °C, 20 h.

To elucidate the potential reaction pathway of this photoredox/Pd dual protocol, several mechanistic studies have been performed, as depicted in Scheme 3. Addition of the radical inhibitor TEMPO to the standard conditions completely shut down the desired cross-couplings, while the addition of stoichiometric amount of butylated hydroxytoluene (BHT) had no dramatic effect on the coupling efficiency (Scheme 3A). In this case, we also observed a small amount of the hydrodefluorinated pyridine **4**, the ^{19}F NMR yield of which increased to 38% with the addition of 5.0 equiv of BHT in the absence of aryl bromide (Scheme 3A). Furthermore,

Scheme 3. Mechanistic Studies: (A) Radical Inhibition Reaction; (B) Reactions in the Presence of Alkenes; (C) Stoichiometric and Catalytic Reactions with Pd(II) Complex; (D) Stern−Volmer Fluorescence Quenching Studies; (E) Cyclic Voltammetry of Pd(II) Complex; (F) UV−Vis Spectroscopy of the Reaction Mixture



subjection of alkenes, such as 4-phenyl-1-butene (**5**), into the template reaction led to a dramatic decrease in the yield of product **3a**, together with major formations of the hydroarylation product and the Heck-type product, while no fluoroarene−olefin coupling products were detected via the analysis of crude GC-MS (Scheme 3B). Next, the ligated Ar-Pd(II) complex **6** was prepared according to a previous procedure.[16] The stoichiometric reaction of Ar-Pd(II) **6** with pentafluoropyridine (**2a**) in the presence of Ir(ppy)$_3$ and Cy$_2$NH led to the formation of the desired fluorodiaryl **3h** in 30% ^{19}F NMR yield, together with a 33% yield of the hydrodefluorinated pyridine **4**; reaction of aryl bromide with **2a** with a catalytic amount of complex **6** also resulted in 16% of fluorodiaryl **3h** (Scheme 3C). These results, along with the aforementioned Heck-type products, indicated that Ar-Pd(II) could be a reactive intermediate for this reductive aryl coupling.

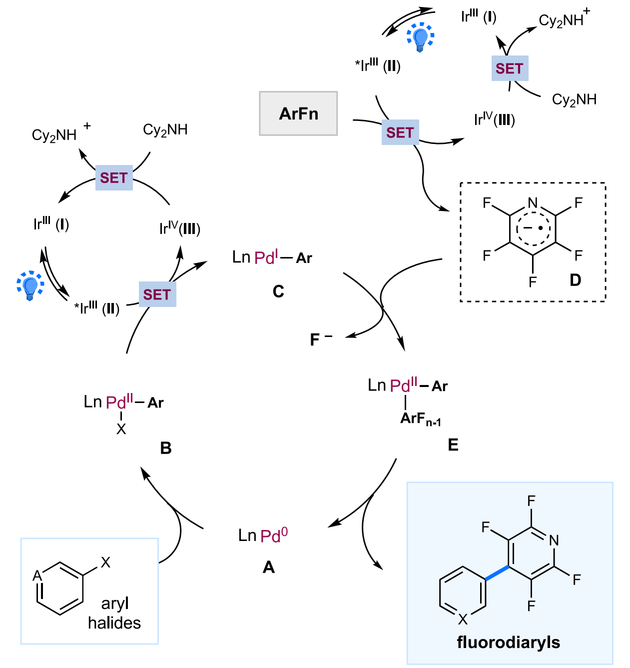
Furthermore, Stern−Volmer fluorescence quenching studies were conducted, and the results showed that the photoexicited state of *Ir(III) can be efficiently quenched by Ar-Pd(II) complex **6**, rather than by amine Cy$_2$NH with or without Na$_2$CO$_3$; on the other hand, pentafluoropyridine showed a comparatively weak quenching effect on the photocatalyst, suggesting that the oxidative quenching of *Ir^{III} by pentafluoropyridine could also occur (Scheme 3D). These quenching results were also consistent with their electrochemical behaviors. Cyclic voltammetry studies indicated that the half-redox potential of Ar-Pd(II) complex **6** ($E_{1/2}$[Pd(II)/Pd(I)] = −0.44 V vs SCE in DMA) was lower than that of pentafluoropyridine (C$_5$F$_5$N; $E_{1/2}{}^{red}$ = −2.12 V vs SCE);[17] therefore, the SET reduction of Ar−Pd(II) by *Ir^{III} should be much more thermodynamically favorable than that of pentafluoropyridine (Scheme 3E). Additionally, the UV−visible absorption spectrum of the reaction mixture exhibited a strong absorption at 275 nm that was different from those of Ar-Pd(II) complex **6** or the [PdCl(allyl)]$_2$ catalyst, indicating that a new [Pd] species could be involved in the reaction process (Scheme 3F). Nonetheless, trials for monitoring the stoichiometric reaction of Ar-Pd(II) complex **6** with Ir(ppy)$_3$ and light in the absence of fluoroarenes via ^{31}P NMR failed, probably due to the instability of [Pd] species.

On the basis of the above experimental results, a plausible mechanism was proposed (Scheme 4). Oxidative addition of Pd(0) with aryl bromide could form Ar-Pd(II) intermediate **B** ($E_{1/2}$[Pd(II)/ Pd(I)] = −0.44 V vs SCE in DMA), which could undergo a SET event with the photoexcited *Ir(III) species **II** ($E_{1/2}$[Ir^{III}*/Ir^{IV}] = −1.73 V vs SCE in MeCN)[18] to generate Ar-Pd(I) intermediate **C** and Ir(IV). At the same time, a SET event between the photoexcited *Ir(III) and fluoroarene would generate the radical anion species **D**. At this juncture, Ar-Pd(I) intermediate **C** would intercept the fluoroarene radical anion **D** to form the Ar-Pd(II)-(ArF$_{n-1}$) intermediate **E**, which subsequently could undergo reductive elimination to furnish the fluorodiaryl product, along with the regeneration of Pd(0) to close the palladium cycle. Meanwhile, the Ir(IV) species **III** would oxidize the reductant amine to regenerate the ground state of Ir(III) to complete the photocatalyst cycle. With respect to the reduction of fluoroarene, a tandem catalytic cycle enabled by the reducing Ir(II) species might be operative.[19] We also cannot exclude the reaction pathway via interception of radical anion **D** by Ar-Pd(II) **B** at this stage.

■ CONCLUSION

In summary, we have developed a mild and efficient protocol for cross-electrophile arylation of polyfluoroarenes via visible-light photoredox and palladium dual catalysis, enabling

Scheme 4. Proposed Pathway



selective access to a series of fluorobiaryls from readily available starting materials under mild conditions. These dual photoredox/Pd-catalyzed cross-electrophile diaryl couplings could proceed via a Pd(0)/Pd(I)/Pd(II) pathway, where a series of mechanistic experiments indicated that an (aryl)Pd^{II} intermediate undergoes a single-electron reduction by the photoexcited *Ir(III). We anticipate this photoredox/Pd protocol would complement the well-developed cross-electrophile coupling protocols enabled by nickel and provide some inspirations for the development of new transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.0c00813.

Experimental procedures, characterization of compounds, and mechanistic experiments (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21702029, 21901036), the Shanghai Sailing Program (19YF1400300), and the Fundamental Research Funds for the Central Universities for financial support.

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