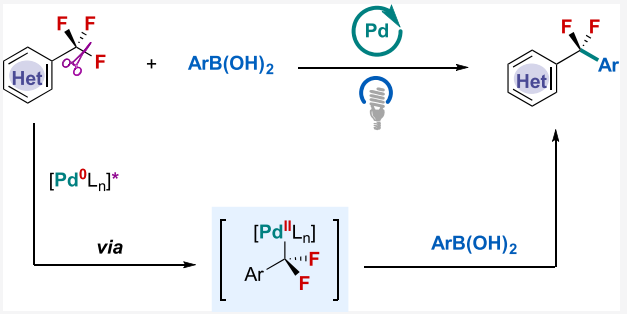
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Visible-Light-Induced Palladium-Catalyzed Selective Defluoroarylation of Trifluoromethylarenes with Arylboronic Acids

Yun-Cheng Luo, Fei-Fei Tong, Yanxia Zhang, Chun-Yang He, and Xingang Zhang*

Cite This: J. Am. Chem. Soc. 2021, 143, 13971−13979
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Selective functionalization of inactive C(sp^3)−F bonds to prepare medicinally interesting aryldifluoromethylated compounds remains challenging. One promising route is the transition-metal-catalyzed cross-coupling through oxidative addition of the C(sp^3)−F bond in trifluoromethylarenes ($ArCF_3$), which are ideal precursors for this process due to their ready availability and low cost. Here, we report an unprecedented excited-state palladium catalysis strategy for selective defluoroarylation of trifluoromethylarenes with arylboronic acids. This visible-light-induced palladium-catalyzed cross-coupling proceeds under mild reaction conditions and allows transformation of a variety of arylboronic acids and $ArCF_3$. Preliminary mechanistic studies reveal that the oxidative addition of the C(sp^3)−F bond in $ArCF_3$ to excited-state palladium(0) via a single electron transfer pathway is responsible for the C(sp^3)−F bond activation.



INTRODUCTION

The prominent applications of organofluorinated compounds in life and materials sciences have triggered substantial endeavors in tailoring organic molecules with fluorine atom(s).[1] Over the past decade, impressive achievements have been made in the field, most of which focus on the site-selective fluorination and fluoroalkylation reactions.[2] Recently, the selective C−F bond functionalization to prepare fluorinated compounds has received increasing attention, because of its significance in both fundamental research and applications in chemical synthesis and degradation of environmentally persistent fluorinated molecules.[3] As a consequence, important progress in the selective functionalization of the C(sp^2)−F bond has been achieved (Figure 1A).[3a,c] However, the reaction of the C(sp^3)−F bond on an inactive skeleton, such as trifluoromethylarenes ($ArCF_3$), remains challenging (Figure 1A).[3d,e] Especially, powerful transition-metal catalysis has not yet been utilized in activating the inactive C−F bond in CF_3, because of difficulties in oxidative addition of robust C(sp^3)−F bonds in perfluoroalkyl groups (e.g., CF_3).[4,5] As such, a new method to overcome this formidable challenge is highly desirable.

$ArCF_3$ are a series of ideal precursors to prepare medicinally interesting difluoroalkylated arenes ($ArCF_2$−FG),[1] due to their ready availability, low cost, and avoiding of multistep synthesis of difluoroalkylating reagents. Generally, three different α,α-difluororobenzylic intermediates can be generated *in situ* from $ArCF_3$ (Figure 1B): (1) nucleophilic α,α-difluororobenzylic anions generated by two-electron reduction (e.g., using low-valent metal or electrochemical reductions);[6] (2) electrophilic α,α-difluororobenzylic cations through strong Lewis acid-promoted processes;[7] (3) α,α-difluororobenzylic radicals generated by single-electron reduction (e.g., using excited photocatalysts).[8] Besides the three well-established pathways, we envisioned that the transition-metal-catalyzed cross-coupling through oxidative addition of a C−F bond in $ArCF_3$ would open a new pathway in the selective functionalization of the inactive C(sp^3)−F bond. Such a strategy would provide new mechanistic insight into the C−F bond activation, and it would enable the direct synthesis of medicinally interesting $ArCF_2$−Ar structures (Figure 1D),[9] which are difficult to achieve by the aforementioned methods due to the over-defluorinations and lack of an efficient catalytic system.

To realize this transition-metal-catalyzed strategy, two crucial issues should be addressed: (1) the oxidative addition of a transition metal to the C(sp^3)−F bond in CF_3, one of the strongest single bonds to carbon (Figure 1C);[4] (2) the suppression of over-defluorination side reactions, which probably follow the dissociation of the first C−F bond in CF_3 with a relatively faster reaction rate, because of the decreasing bond dissociation energy (BDE) of the C−F bonds

Received: July 18, 2021
Published: August 19, 2021

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

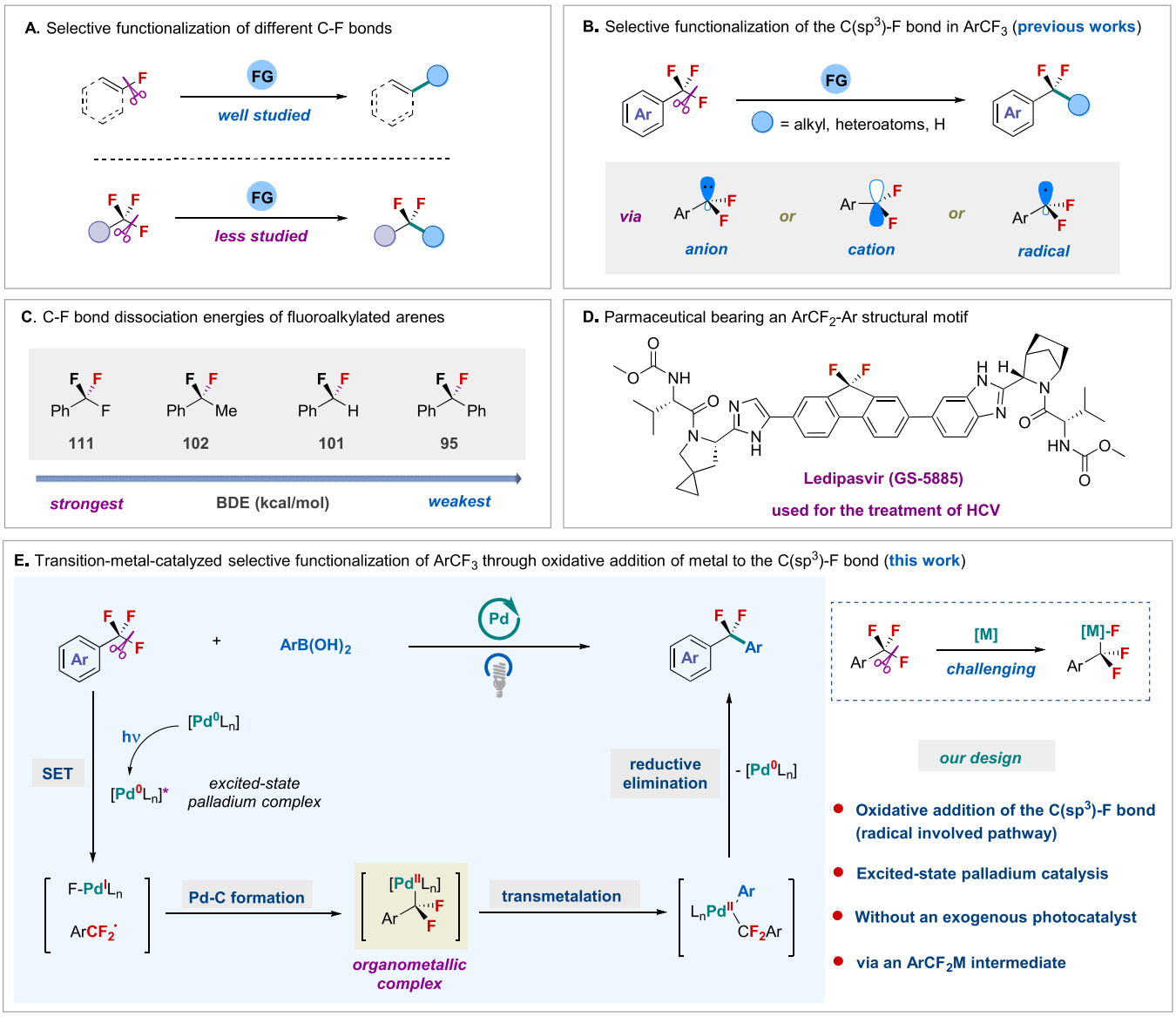


Figure 1. Selective functionalization of different C−F bonds and a selected example of a pharmaceutical bearing a $ArCF_2$−Ar structural motif. (A) Selective functionalization of different C−F bonds. (B) Selective functionalization of the $C(sp^3)$−F bond in $ArCF_3$. (C) Bond dissociation energies (BDEs, calculated by DFT; see the Supporting Information) of C−F bonds. (D) Selected pharmaceutical bearing an $ArCF_2$−Ar structural motif. (E) Current excited-state palladium-catalyzed defluoroarylation of $ArCF_3$.

in the resulting difluoroalkylated arenes (Figure 1C).[8f] To date, only rare examples of transition-metal-mediated cleavage of the $C(sp^3)$−F bond in CF_3 have been reported, through a concerted oxidative addition process using nickel(0) complexes.[10] But the catalytic reaction involving such a process leads to over-defluorination of all three $C(sp^3)$−F bonds in CF_3. To overcome these daunting challenges, we hypothesized a novel radical-involved oxidative addition strategy (Figure 1E). In this hypothesis, an excited-state palladium complex[11] is generated by irradiation of a ground-state palladium complex with visible light, which then undergoes oxidative addition to the $C(sp^3)$−F bond in $ArCF_3$, via a single-electron-transfer (SET) pathway, to form an α,α-difluororobenzylic palladium(II) complex $[ArCF_2Pd(L_n)X]$ (**A**). Subsequently, the transmetalation of **A** with an arylmetal, followed by reductive elimination, delivers the final product $ArCF_2$−Ar. Herein, we report this visible-light-induced palladium-catalyzed selective defluoroarylation of $ArCF_3$ with arylboronic acids, representing the first example of selective carbofunctionalization of the $C(sp^3)$−F bond in CF_3 through transition-metal-catalyzed cross-coupling (Figure 1E). This novel catalytic system of an excited-state palladium complex, without an exogenous photocatalyst, shows unprecedented reactivity toward $C(sp^3)$−F bond activation of (Het)$ArCF_3$, while the previous photoinduced palladium catalysts can only realize the transformations of $C(sp^3)$−Br or $C(sp^3)$−I bonds.[11a,d]

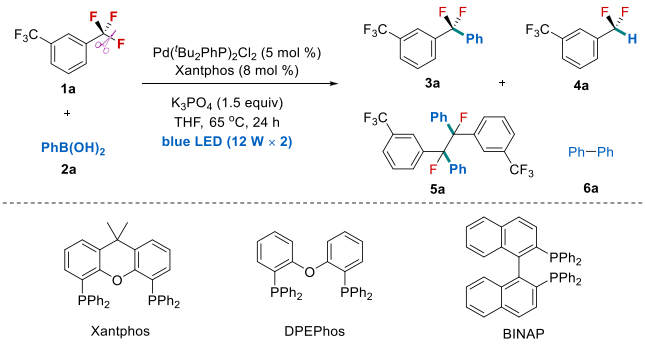
RESULTS AND DISCUSSION

Accordingly, arylboronic acids were chosen as one of the coupling partners for this reaction, because they are readily available, are moisture insensitive, and are able to facilitate transmetalation of $ArCF_2Pd(L_n)$−F species by forming a stronger B−F bond.[4a,12] In a model coupling process, we found that the catalytic mono-defluoroarylation can be achieved through a combination of palladium catalyst $Pd(^tBu_2PhP)_2Cl_2$ and the bidentate phosphine ligand Xantphos under the

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

irradiation of blue light (Table 1; for details, see the Supporting Information, SI). The desired product, diaryldifluoromethane **3a**, was obtained in 60% yield (determined by ^{19}F NMR) from the reaction of 1,3-ditrifluoromethylbenzene **1a** (6.0 equiv) with phenylboronic acid **2a** (1.0 equiv) in the presence of Pd(^{t}Bu$_2$PhP)$_2$Cl$_2$ (5 mol %), Xantphos (7.5 mol %), and a Bronsted base (K_3PO_4) under irradiation of blue LED (12 W × 2) in tetrahydrofuran (THF) at 65 °C (entry 1).

Table 1. Representative Results for the Optimization of the Reaction Conditions[a]



entry	reaction conditions	3a (%)[b]	4a (%)[c]	5a (%)[b]
1	"standard condition"	60	1	6
2	**1a** (2.0 equiv)	51	3	8
3	**1a** (1.0 equiv)	37	5	7
4[d]	**1a** (1 equiv)	51	4	4
5	Ir(ppy)$_3$ (1 mol %) was used	58	1	5
6	DPEPhos instead of Xantphos	15	1	3
7	BINAP instead of Xanphos	1	<1	1
8	Pd(PPh$_3$)$_4$ instead of Pd(P^{t}Bu$_2$Ph)$_2$Cl$_2$	47	4	2
9	Pd(PPh$_3$)$_4$ instead of Pd(P^{t}Bu$_2$Ph)$_2$Cl$_2$ and Xantphos	22	4	nd
10	Pd(P^{t}Bu$_2$Ph)$_2$ instead of Pd(P^{t}Bu$_2$Ph)$_2$Cl$_2$ and Xantphos	nd		nd
11	no [Pd]	nd		nd
12	no Xantphos	nd		nd
13	no light	nd		nd

[a]Reaction conditions (unless otherwise specified): **1a** (6 equiv), **2** (0.3 mmol, 1.0 equiv), THF (2 mL). The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard. [b]The yield was calculated based on **2a**. [c]The yield was calculated based on **1a**. nd, not detected. [d]**2** (2.0 equiv) was used, and KOH (2 equiv) instead of K_3PO_4 (1.5 equiv).

No defluoroarylation of the second CF_3 group was observed during the reaction process. Decreasing the loading amount of **1a** from 6.0 equiv to 2.0 equiv led to a slightly lower yield of **3a** (51%) with increasing formation of over-defluorinated side product **5a** (entry 2). The use of equimolar equivalencies of **1a** and **2a** significantly decreased the yield of **3a** to 37% (entry 3). Further optimization of the reaction conditions using one more equivalent of **2a** with KOH as the base could also provide **3a** in 51% yield (entry 4; for details, see Table S7). The addition of an iridium photocatalyst to the reaction did not improve the reaction efficiency (entry 5). Switching Xantphos with DPEPhos or BINAP dramatically diminished the yield (entries 6 and 7). Pd(PPh$_3$)$_4$ could also act as a catalyst, but a lower yield (47%) was obtained (entry 8). The sole use of Pd(PPh$_3$)$_4$ without Xantphos could lead to **3a** in 22% yield (entry 9), and no **3a** was observed with Pd(P^{t}Bu$_2$Ph)$_2$ as the catalyst (entry 10). The absence of palladium, Xantphos, or blue light totally shut down the reaction (entries 11−13), demonstrating the essential role of palladium, triarylphosphine, and blue light in promoting the reaction. The moderate yield of **3a** was obtained because of the homocoupling of phenylboronic acid **2a** and the formation of over-defluorinated side product **5a** from **3a**. However, attempts to increase the reaction efficiency by using different phenylboronic acid esters failed. The formation of **5a** is probably ascribed to the identical reduction potential of starting material **1a** and product **3a** ($E_{p/2}$ for **1a**/**1a**$^{\bullet-}$ and **3a**/**3a**$^{\bullet-}$ are both −2.68 V vs Fc$^+$/Fc in MeCN) (see Figure 2), leading to the SET reduction of **1a** and **3a** indiscriminately. As a result, the over-defluorinated side product **5a** was generated by a sequential defluorodimerization from **3a**. This is in sharp contrast to previous reports for the hydrodefluorination and defluoroalkylation of $ArCF_3$ via a SET pathway,[8] in which the suppression of over-defluorinations took advantage of the lower reduction potentials of the resulting aryldifluoromethylated products than $ArCF_3$, enabling the selective formation of desired C−F bond functionalized products. We also examined the dual nickel/photoredox catalytic system,[13] but no desired product was observed. Although a moderate yield of **3a** was obtained, this reaction trades off the overall yield loss from the multistep synthesis of difluoroalkylating reagents.[14] Most importantly, this transformation fundamentally demonstrates the feasibility of photoinduced palladium catalysis in the selective activation of an inactive C(sp^3)−F bond, thereby paving a new way to access fluorinated compounds.

With the viable reaction conditions in hand, we examined the substrate scope of this visible-light-induced palladium-

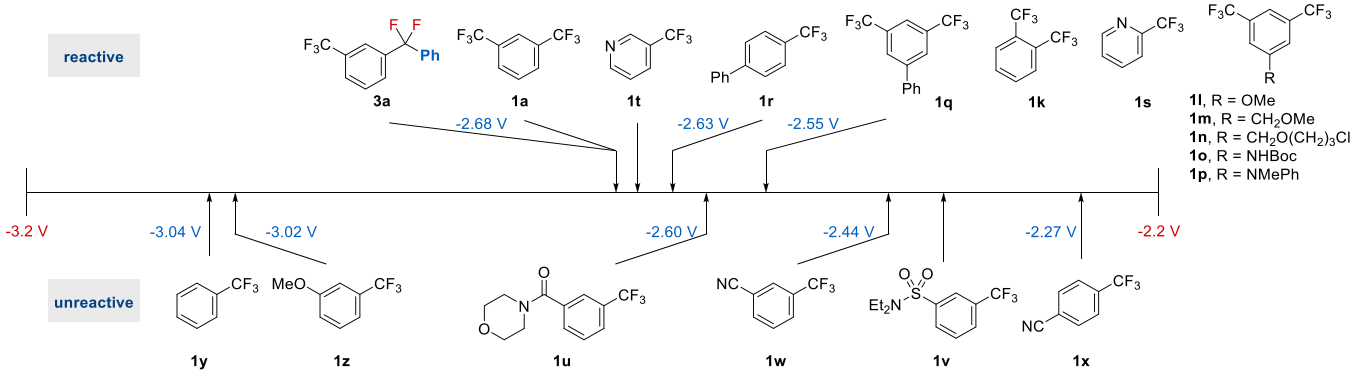
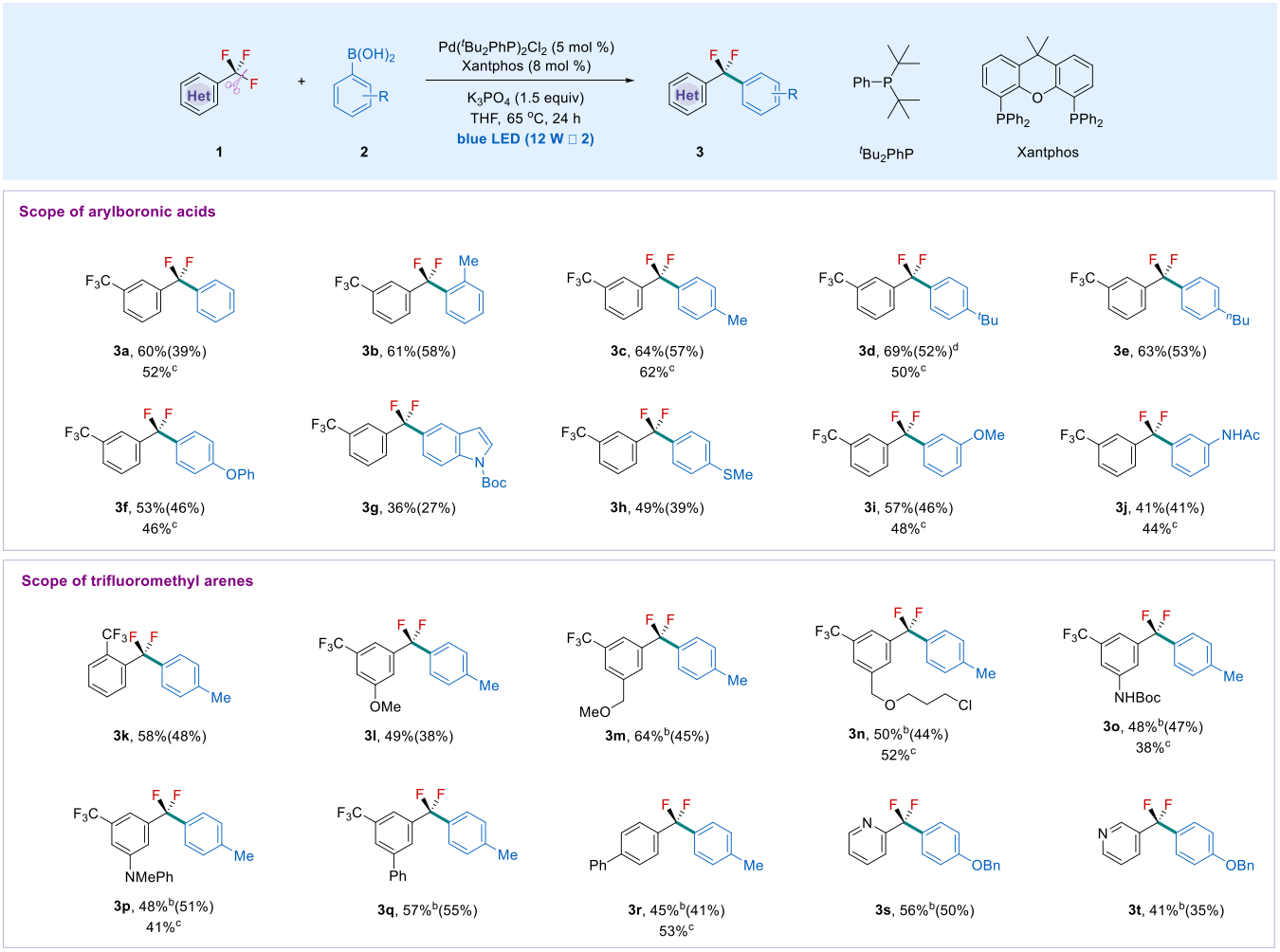


Figure 2. Half-peak reduction potentials ($E_{p/2}$ vs Fc$^+$/Fc in MeCN) of trifluoromethylarenes and diaryldifluoromethanes **3a**.

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

Scheme 1. Selective Defluoroarylation of Trifluoromethylarenes with Aryboronic Acids[a]



[a]Reaction conditions: **1** (6 equiv), **2** (0.3 mmol, 1.0 equiv), THF (2 mL). The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard; the number given in parentheses is the isolated yield. [b]Three equiv of **1** was used. [c]**1** (1.0 equiv), **2** (2.0 equiv), and KOH (2 equiv) were used. [d]The reaction was conducted on a 1 mmol scale: **1a** (6.0 equiv), **2d** (1.0 equiv), THF (6.7 mL).

catalyzed process (Scheme 1). Overall, the reaction of **1a** with a variety of arylboronic acids afforded the corresponding defluoroarylated products **3a**–**3j** in synthetically useful to moderate yields. In the case of **3a**, the low isolated yield is because of its volatility. Trifluoromethylbenzenes bearing different functional groups, such as methoxyl, alkyl chloride, BocNH, PhMeN, and phenyl groups, were also applicable to the reaction (**3l**–**3r**). Furthermore, heteroaryl-containing substrates did not inhibit the reaction, with synthetically useful yields obtained (**3g**, **3s**, and **3t**). However, aryl bromide containing substrates were not a competent coupling partner, due to their easy formation of cross-coupling products with aryl boronic acids. The reaction can also be scaled up, as demonstrated by the 1 mmol scale synthesis of **3d** without deterioration of the reaction efficiency. Additionally, the use of 1 equiv of trifluoromethylarene could also lead to comparable yields (**3a**, **3c**, **3d**, **3f**, **3i**, **3j**, **3n**–**3p**, and **3r**).

We also found that both the redox activity and substituents on the aromatic ring of trifluoro(hetero)arenes are critical to the reaction efficiency. Trifluoro(hetero)arenes **1a** and **1k**–**1t**, which have reduction potentials $E_{p/2}(\mathbf{1}/\mathbf{1}^{\bullet-})$ ranging from −2.68 to −2.27 V (vs Fc^+/Fc in MeCN), are suitable substrates. However, amide-, cyano-, and sulfonyl-containing substrates **1u**–**1x**, which possess similar reduction potentials ($E_{p/2}(\mathbf{1}/\mathbf{1}^{\bullet-})$ = −2.60 to −2.27 V vs Fc^+/Fc in MeCN) to **1a** and **1k**–**1t** ($E_{p/2}(\mathbf{1}/\mathbf{1}^{\bullet-})$ = −2.68 to −2.55 V vs Fc^+/Fc in MeCN), were not applicable to the reaction (Figure 2), suggesting that the suitable substrates should bear no electron-withdrawing group that conjugates to the aromatic ring. These findings are different from the previous photoredox-catalyzed C–F bond functionalization of trifluoromethylarenes,[8d,e] in which **1u**–**1x** were suitable substrates, thus indicating that a novel C–F bond activation mode of $ArCF_3$ is involved in this visible-light-induced palladium-catalyzed process. Trifluoromethylbenzene **1y** and 1-methoxy-3-(trifluoromethyl)benzene **1z** were also examined, failing to provide the desired products. In contrast, the corresponding substrates (**1a** and **1l**) bearing the second CF_3 group on the aromatic ring could successfully promote the reaction, due to the strong electron-withdrawing effect of the additional CF_3 group, which can increase the reduction potential of the substrates, thus rendering them more reactive to accept an electron for the C–F bond activation via a SET pathway (Figure 2).

To gain mechanistic insight into this visible-light-induced palladium-catalyzed process, we conducted several experiments (Figure 3). ^{31}P NMR monitoring of the reaction of **1a** with **2a**

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

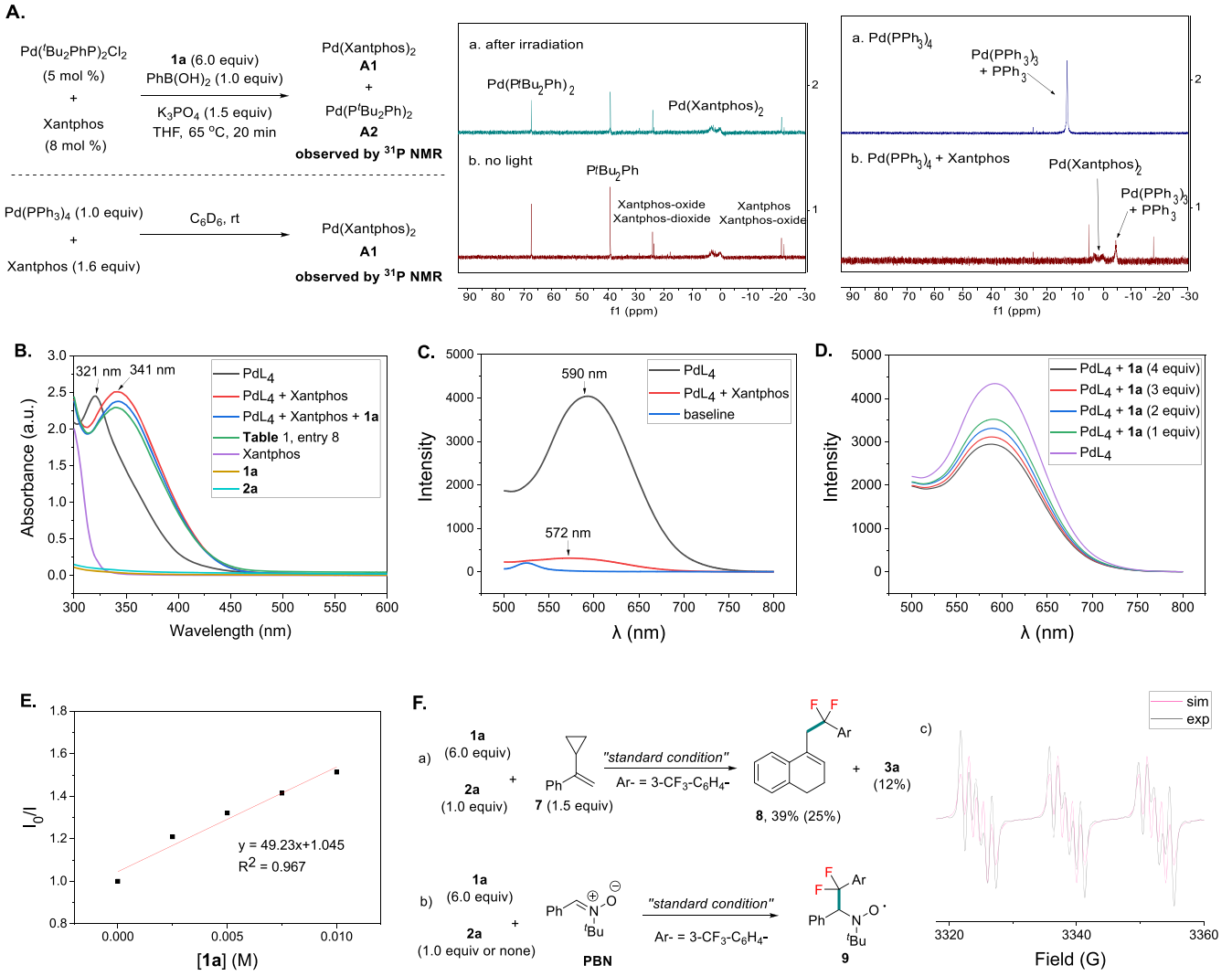
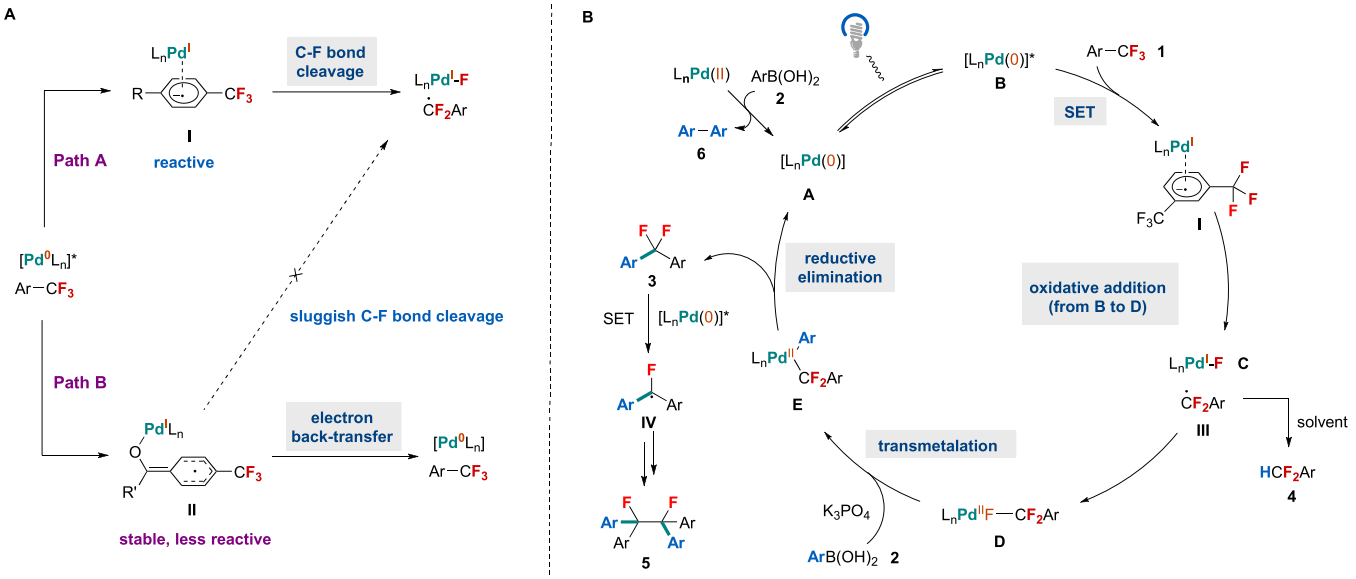


Figure 3. Mechanistic studies. (A) ^{31}P NMR monitoring experiments of the palladium catalysts. (B) UV−vis absorption experiments in THF. (C) Emission spectra of $Pd(PPh_3)_4$ and the mixture of $Pd(PPh_3)_4$ and Xantphos (irradiation at 450 nm). (D and E) Stern−Volmer luminescence quenching of $Pd(PPh_3)_4$ by **1a**. (F) Radical trapping experiments: (a) radical clock experiment, with the number given in parentheses being the isolated yield; (b) EPR study of the reaction with PBN; (c) EPR spectra of **9**. PdL_4 = $Pd(PPh_3)_4$.

under standard reaction conditions in the absence of blue light showed that two new palladium species, $Pd(Xantphos)_2$ (**A1**)[11g,15] and $Pd(^tBu_2PhP)_2$ (**A2**),[16] were formed during the reaction process (Figure 3A). **A1** and **A2** still coexisted in the reaction after irradiation. Complex **A1** could also be formed from the mixture of $Pd(PPh_3)_4$ with Xantphos (Figure 3A).[17] Since **A2** is not an active palladium catalyst for the reaction (Table 1, entry 10), and the combination of $Pd(PPh_3)_4$ with Xantphos could also provide the final product **3a** (Table 1, entry 8), we supposed that **A1** may be the active species in promoting the reaction by forming an excited-state palladium complex.[11g] To support this deduction, UV−vis absorption experiments were conducted (Figure 3B), in which $Pd(PPh_3)_4$ was used for the mechanistic studies because both $Pd(PPh_3)_4$ and the combination of $Pd(PPh_3)_4$ with Xantphos are active for the reaction (Table 1, entries 8 and 9). We found that the combination of $Pd(PPh_3)_4$ with Xantphos caused a bathochromic shift (Figure 3B), demonstrating that a new palladium species was formed during the reaction process, which is likely corresponding to **A1**. The addition of **1a** and **2a** to the solution did not change the absorption band, and no visible light absorption was observed for **1a**, **2a**, and Xantphos (Figure 3B), thus excluding the possibility of forming a donor−acceptor complex in the reaction. Additionally, orange-red luminescence ($\lambda_{max\text{-}Em}$) at the wavelength of 572 nm in THF was observed by combination of $Pd(PPh_3)_4$ with Xantphos (Figure 3C). These results suggest that only the Pd(0) complex was responsible for the absorption of blue light ($\lambda \approx 450$ nm), and palladium species **A1** may serve as the active catalyst for the formation of an excited-state palladium complex. As for the role of **A2**, we proposed that it probably acts as a Pd(0) catalyst reservoir to control the concentration of the active catalyst, thus facilitating the overall catalytic cycle. We also conducted Stern−Volmer luminescence quenching experiments (Figure 3D and E) and found that the excited-state [Pd(0)]* complex was efficiently quenched by trifluoromethylarene **1a**. Finally, a radical clock experiment by using α-cyclopropylstyrene **7** as a probe and electron paramagnetic resonance (EPR) studies of the reaction of **1a** and **2a** with spin-trapping agent phenyl *tert*-butyl nitrone (PBN) demonstrated that an α,α-difluororobenzylic radical is involved in the reaction (Figure 3F and Figures S29−S33). Additionally, the

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

Scheme 2. Proposed Reaction Mechanism: (A) Proposed Mechanisms of [Pd(0)]*-Catalyzed C−F Bond Activation; (B) Proposed Mechanism of Visible-Light-Induced Pd-Catalyzed Defluoroarylation of $ArCF_3$ with Arylboronic Acids



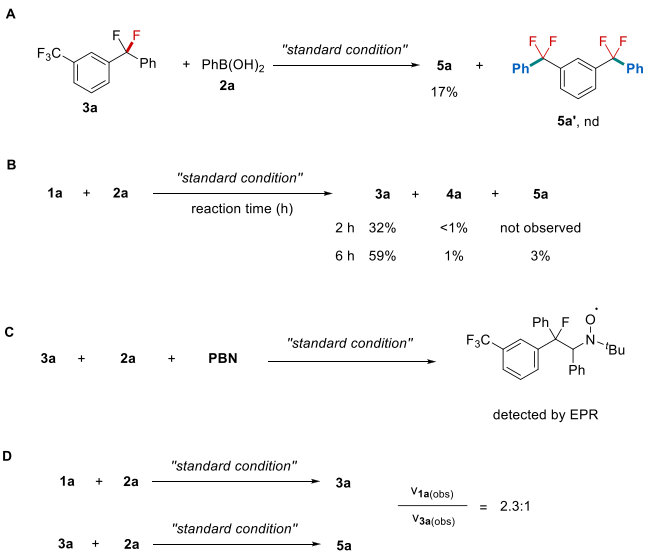
EPR experiment showed that the absence of arylboronic acid could also lead to spin adduct **9**, suggesting that palladium instead of arylboronic acid participates in the C−F bond activation.

Based on the above results, a radical-involved C−F bond oxidative addition mechanism is proposed. An *α*,*α*-difluorobenzylic radical is generated by an excited-state $[Pd(0)L_n]^*$ species though SET reduction of trifluoromethylarenes (Scheme 2A, path A). According to the luminescence emission of **A1** and its cyclic voltammogram data, the oxidation potential of excited-state **A1*** was calculated to be $E_{1/2}([Pd^I]/[Pd^0]^*) = -2.76$ V vs Fc^+/Fc in THF (SI, Table S8), which is able to reduce trifluoromethylarenes **1a** and **1k**−**1t** ($E_{p/2}(\mathbf{1}/\mathbf{1}^{\bullet-}) = -2.68$ V to -2.55 V vs Fc^+/Fc in MeCN). For the inactivity of trifluoromethylarenes **1u**−**1x** bearing an electron-withdrawing group with a *π*-system conjugated to the aromatic ring, we proposed that the coordination of palladium(I) with the heteroatom (O or N) of the electron-withdrawing group may result in an enolate-formed radical anion,[18] such as intermediate **II**, after SET reduction (Scheme 2A, path B). Compared to the sluggish C−F bond cleavage process,[19] this Pd(I)-stabilized trifluoromethylarene radical anion **II** favors electron back-transfer and returns to the ground-state $Pd(0)L_n$ and trifluoromethylarene.[8b]

Overall, a plausible mechanism is depicted in Scheme 2B. Trifluoromethylarene **1** undergoes single-electron reduction by photoexcited $[Pd(0)L_n]^*$ (**B**) to generate *α*,*α*-difluororobenzylic radical **III** and $[F\text{-}Pd(I)L_n]$ species **C** through C−F bond cleavage. Subsequently, recombination of the resulting radical with **C** leads to *α*,*α*-difluororobenzylic palladium complex $[ArCF_2\text{-}Pd(II)FL_n]$ (**D**). Meanwhile, radical **III** is able to abstract hydride from solvent THF to produce $ArCF_2H$ **4**, which is not an intermediate en route to **3**, because treatment of $ArCF_2H$ **4** with arylboronic acids **2** under standard reaction conditions failed to provide **3** (for details, see SI). Transmetalation of palladium complex **D** with arylboronic acid **2** produces key intermediate $[ArCF_2\text{-}Pd(II)L_n\text{-}Ar]$ (**E**), in which the [Pd-F] species may facilitate the transmetalation step by forming a [B-F] species.[20] Finally, reductive elimination of **E** delivers product **3** and regenerates palladium(0) catalyst **A** simultaneously. **A** is subsequently irradiated by visible light to form excited-state palladium complex **B**.

On the other hand, the competitive photoinduced over-defluorination/dimerization reaction can also occur after the formation of **3**, thus decreasing the yield of final product **3**. This deduction was supported by reaction of **3a** with **2a** under standard reaction conditions, in which over-defluorinated **5a** was indeed generated (Scheme 3A). Furthermore, the real-time monitoring of reaction of **1a** with **2a** under standard reaction conditions showed that compound **5a** could not be observed when a ∼30% yield of **3a** was formed (Scheme 3B). We also conducted an EPR experiment and found that a diaryl monofluoromethyl radical **IV** was involved in the reaction (Scheme 3C). These results suggest that an excited-state palladium-catalyzed radical-involved defluorodimerization of **3** would be a possible pathway for the formation of **5** (Scheme

Scheme 3. Mechanistic Studies of Generation of Over-defluorinated Product 5



https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

2B), and the previously reported carbene-involved mechanism via intermediate **E** seems unlikely.[21] To identify the selectivity of C−F bond activation between **1a** and **3a**, we conducted kinetic studies and found that the initial rate of defluoroarylation of **1a** is 2.3 times faster than that of defluorodimerization of **3a** when the initial concentration of **1a** is equal to the initial concentration of **3a** (Scheme 3D and Figure 4). This

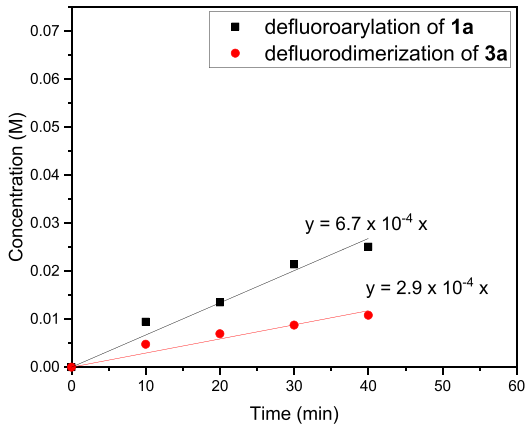


Figure 4. Kinetic studies of defluoroarylation of **1a** (black line, **1a** (0.5 equiv), **2a** (1.0 equiv)) and defluorodimerization of **3a** (red line: **3a** (0.5 equiv), **2a** (1.0 equiv)).

finding indicates that, although **1a** and **3a** possess identical reduction potentials, these bond activations can be different between **1a** and **3a**, depending on the deliberate control of elementary steps in the catalytic cycle. To be specific, we can increase the concentration of **1** to facilitate its SET reduction by an excited-state palladium complex and/or fine-tuning the reaction parameters (such as the base, the concentration of arylboronic acid, and the ligand) that enables the faster rate of formation of **3** from intermediate **III** than that of generation of **5** through dimerization of **IV** (Scheme 2B), thus increasing the selectivity of C−F bond activation in $ArCF_3$ over $ArCF_2$-Ar. In addition, the steric effect of **3a** may also differentiate C−F bond activation steps from the photoexcited Pd.

CONCLUSIONS

In conclusion, we have developed an unprecedented visible-light-induced palladium-catalyzed process for selective C-(sp^3)−F bond arylation of trifluoromethylarenes with arylboronic acids. The reaction proceeds under mild reaction conditions and allows transformation of a variety of arylboronic acids and trifluoromethylarenes. Mechanistic studies reveal that the excited-state palladium complex induces the C(sp^3)−F bond oxidative addition via a SET pathway to generate the α,α-difluororobenzylic palladium complex. This novel visible-light-induced oxidative addition of a C−F bond to a transition metal, without an exogenous photocatalyst, opens a new chapter to access fluorinated compounds by selective C(sp^3)−F bond functionalization of readily available and inexpensive fluorine sources through transition-metal-catalyzed cross-couplings. The intriguing ability of the excited-state palladium complex to activate inactive a C(sp^3)−F bond may also prompt the research area in palladium catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07459.

Experimental procedures, characterization of new compounds, and computational details (PDF)

AUTHOR INFORMATION

Corresponding Author

Xingang Zhang − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China;* orcid.org/0000-0002-4406-6533; Email: xgzhang@mail.sioc.ac.cn

Authors

Yun-Cheng Luo − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Fei-Fei Tong − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Yanxia Zhang − *Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China*

Chun-Yang He − *Key Laboratory of Biocatalysis & Chiral Drug Synthesis of Guizhou Province, Generic Drug Research Center of Guizhou Province, Zunyi Medical University, Zunyi, Guizhou 563003, China;* orcid.org/0000-0002-0599-7335

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.1c07459

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support for this work was provided by the National Natural Science Foundation of China (21931013, 21790362) and the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB20000000).

REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (b) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822−5880. (c) Leitz, D.; Seifert, M. Fluorine: A Paradoxical Element. By Alain Tressaud. *Angew. Chem., Int. Ed.* **2019**, *58*, 16356. (d) Moschner, J.; Stulberg, V.; Fernandes, R.; Huhmann, S.; Leppkes, J.; Koksch, B. Approaches to Obtaining Fluorinated α-Amino Acids. *Chem. Rev.* **2019**, *119*, 10718−10801.

(2) For selected recent reviews, see: (a) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Mono-

fluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174. (b) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. *Chem. Rev.* **2015**, *115*, 826−870. (c) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon-Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887−3964. (d) Feng, Z.; Xiao, Y.-L.; Zhang, X. Transition-Metal (Cu, Pd, Ni)-Catalyzed Difluoroalkylation via Cross-Coupling with Difluoroalkyl Halides. *Acc. Chem. Res.* **2018**, *51*, 2264−2278. (e) Szpera, R.; Moseley, D. F. J.; Smith, L. B.; Sterling, A. J.; Gouverneur, V. The Fluorination of C-H Bonds: Developments and Perspectives. *Angew. Chem., Int. Ed.* **2019**, *58*, 14824−14848.

(3) For selected reviews, see: (a) Amii, H.; Uneyama, K. C-F Bond Activation in Organic Synthesis. *Chem. Rev.* **2009**, *109*, 2119−2183. (b) Stahl, T.; Klare, H. F. T.; Oestreich, M. Main-Group Lewis Acids for C−F Bond Activation. *ACS Catal.* **2013**, *3*, 1578−1587. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C-F Bond Activation to Access Fluorinated Building Blocks. *Chem. Rev.* **2015**, *115*, 931−972. (d) Fujita, T.; Fuchibe, K.; Ichikawa, J. Transition-Metal-Mediated and -Catalyzed C-F Bond Activation by Fluorine Elimination. *Angew. Chem., Int. Ed.* **2019**, *58*, 390−402. (e) Gupta, R.; Jaiswal, A. K.; Mandal, D.; Young, R. D. A Frustrated Lewis Pair Solution to a Frustrating Problem: Mono-Selective Functionalization of C-F Bonds in Di- and Trifluoromethyl Groups. *Synlett* **2020**, *31*, 933−937.

(4) (a) Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007; pp 211−217. (b) O'Hagan, D. Understanding Organofluorine Chemistry. An Introduction to the C-F Bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.

(5) For transition-metal-catalyzed functionalization of activated C(sp^3)−F bonds, see: (a) Hintermann, L.; Läng, F.; Maire, P.; Togni, A. Interactions of Cationic Palladium(II)- and Platinum(II)-η^3-Allyl Complexes with Fluoride: Is Asymmetric Allylic Fluorination a Viable Reaction? *Eur. J. Inorg. Chem.* **2006**, *2006*, 1397−1412. (b) Hazari, A.; Gouverneur, V.; Brown, J. M. Palladium-Catalyzed Substitution of Allylic Fluorides. *Angew. Chem., Int. Ed.* **2009**, *48*, 1296−1299. (c) Pigeon, X.; Bergeron, M.; Barabe, F.; Dube, P.; Frost, H. N.; Paquin, J.-F. Activation of Allylic C-F bonds: Palladium-Catalyzed Allylic Amination of 3,3-Difluoropropenes. *Angew. Chem., Int. Ed.* **2010**, *49*, 1123−1127. (d) Butcher, T. W.; Yang, J. L.; Amberg, W. M.; Watkins, N. B.; Wilkinson, N. D.; Hartwig, J. F. Desymmetrization of Difluoromethylene Groups by C-F Bond Activation. *Nature* **2020**, *583*, 548−553.

(6) (a) Saboureau, C.; Troupel, M.; Sibille, S.; Périchon, J. Electroreductive Coupling of Trifluoromethylarenes with Electrophiles: Synthetic Applications. *J. Chem. Soc., Chem. Commun.* **1989**, 1138−1139. (b) Clavel, P.; Léger-Lambert, M. P.; Biran, C.; Serein-Spirau, F.; Bordeau, M.; Roques, N.; Marzouk, H. Selective Electrosynthesis of (Trimethylsilyldifluoro)methylbenzene, a $PhCF_2^-$ Precursor; Conditions for a Molar Scale Preparation without HMPA. *Synthesis* **1999**, *1999*, 829−834. (c) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. A New C-F Bond-Cleavage Route for the Synthesis of Octafluoro[2.2]paracyclophane. *J. Org. Chem.* **2001**, *66*, 7216−7218. (d) Clavel, P.; Lessene, G.; Biran, C.; Bordeau, M.; Roques, N.; Trévin, S.; Montauzon, D. D. Selective Electrochemical Synthesis and Reactivity of Functional Benzylic Fluorosilylsynthons. *J. Fluorine Chem.* **2001**, *107*, 301−310. (e) Yamauchi, Y.; Fukuhara, T.; Hara, S.; Senboku, H. Electrochemical Carboxylation of α,α-Difluorotoluene Derivatives and Its Application to the Synthesis of α-Fluorinated Nonsteroidal Anti-Inflammatory Drugs. *Synlett* **2008**, *2008*, 438−442. (f) Utsumi, S.; Katagiri, T.; Uneyama, K. Cu-Deposits on Mg Metal Surfaces Promote Electron Transfer Reactions. *Tetrahedron* **2012**, *68*, 1085−1091. (g) Munoz, S. B.; Ni, C.; Zhang, Z.; Wang, F.; Shao, N.; Mathew, T.; Olah, G. A.; Prakash, G. K. S. Selective Late-Stage Hydrodefluorination of Trifluoromethylarenes: A Facile Access to Difluoromethylarenes. *Eur. J. Org. Chem.* **2017**, *2017*, 2322−2326.

(7) (a) Pozdnyakovich, Y. V.; Shteingarts, V. D. Fluorine-Containing Carbocations. III. Alkylation of Polyfluorobenzenes with Polyfluorinated α,α-Difluorobenzyl Cations and Generation of Polyfluorinated α-Fluorodiphenylmethyl Cations. *J. Fluorine Chem.* **1974**, *4*, 297−316. (b) Yoshida, S.; Shimomori, K.; Kim, Y.; Hosoya, T. Single C-F Bond Cleavage of Trifluoromethylarenes with an *ortho*-Silyl Group. *Angew. Chem., Int. Ed.* **2016**, *55*, 10406−10409. (c) Mezhenkova, T. V.; Karpov, V. M.; Zonov, Y. V. Formation of Polyfluorofluorenes in the Reactions of Perfluoro-1,1-diphenylalkanes with Antimony Pentafluoride. *J. Fluorine Chem.* **2018**, *207*, 59−66. (d) Mandal, D.; Gupta, R.; Jaiswal, A. K.; Young, R. D. Frustrated Lewis-Pair-Meditated Selective Single Fluoride Substitution in Trifluoromethyl Groups. *J. Am. Chem. Soc.* **2020**, *142*, 2572−2578.

(8) (a) Mattay, J.; Runsink, J.; Rumbach, T.; Ly, C.; Gersdorf, J. Selectivity and Charge Transfer in Photoreactions of α,α,α-Trifluorotoluene with Olefins. *J. Am. Chem. Soc.* **1985**, *107*, 2557−2558. (b) Kako, M.; Morita, T.; Torihara, T.; Nakadaira, Y. Photoinduced Novel Silylation of CF_3-substituted Benzenes with Disilane and Trisilane. *J. Chem. Soc., Chem. Commun.* **1993**, 678−680. (c) Nakadaira, Y.; Kawasaki, M.; Zhou, D.-Y.; Kako, M. Photochemical Reactions of CF_3-Substituted Benzenes with Tetraalkylated Group 14 Organometals. *Main Group Met. Chem.* **1994**, *17*, 553−557. (d) Chen, K.; Berg, N.; Gschwind, R.; König, B. Selective Single C(sp^3)-F Bond Cleavage in Trifluoromethylarenes: Merging Visible-Light Catalysis with Lewis Acid Activation. *J. Am. Chem. Soc.* **2017**, *139*, 18444−18447. (e) Wang, H.; Jui, N. T. Catalytic Defluoroalkylation of Trifluoromethylaromatics with Unactivated Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 163−166. (f) Luo, C.; Bandar, J. S. Selective Defluoroallylation of Trifluoromethylarenes. *J. Am. Chem. Soc.* **2019**, *141*, 14120−14125. (g) Vogt, D. B.; Seath, C. P.; Wang, H.; Jui, N. T. Selective C-F Functionalization of Unactivated Trifluoromethylarenes. *J. Am. Chem. Soc.* **2019**, *141*, 13203−13211. (h) Sap, J. B. I.; Straathof, N. J. W.; Knauber, T.; Meyer, C. F.; Médebielle, M.; Buglioni, L.; Genicot, C.; Trabanco, A. A.; Noël, T.; Am Ende, C. W.; Gouverneur, V. Organophotoredox Hydrodefluorination of Trifluoromethylarenes with Translational Applicability to Drug Discovery. *J. Am. Chem. Soc.* **2020**, *142*, 9181−9187.

(9) Link, J. O.; Taylor, J. G.; Xu, L.; Mitchell, M.; Guo, H.; Liu, H.; Kato, D.; Kirschberg, T.; Sun, J.; Squires, N.; Parrish, J.; Keller, T.; Yang, Z.-Y.; Yang, C.; Matles, M.; Wang, Y.; Wang, K.; Cheng, G.; Tian, Y.; Mogalian, E.; Mondou, E.; Cornpropst, M.; Perry, J.; Desai, M. C. Discovery of Ledipasvir (GS-5885): A Potent, Once-Daily Oral NS5A Inhibitor for the Treatment of Hepatitis C Virus Infection. *J. Med. Chem.* **2014**, *57*, 2033−2046.

(10) (a) Iwamoto, H.; Imiya, H.; Ohashi, M.; Ogoshi, S. Cleavage of C(sp^3)−F Bonds in Trifluoromethylarenes Using a Bis(NHC)-nickel(0) Complex. *J. Am. Chem. Soc.* **2020**, *142*, 19360−19367. (b) Doi, R.; Kikushima, K.; Ohashi, M.; Ogoshi, S. Synthesis, Characterization, and Unique Catalytic Activities of a Fluorinated Nickel Enolate. *J. Am. Chem. Soc.* **2015**, *137*, 3276−3282. (c) The palladium-catalyzed hydrodefluorination of $ArCF_3$ has also been reported; however, the reaction mechanism is unclear, see: Dang, H.; Whittaker, A. M.; Lalic, G. Catalytic Activation of a Single C-F Bond in Trifluoromethyl Arenes. *Chem. Sci.* **2016**, *7*, 505−509.

(11) For excited-state palladium-catalyzed reactions, see: (a) Chuentragool, P.; Kurandina, D.; Gevorgyan, V. Catalysis with Palladium Complexes Photoexcited by Visible Light. *Angew. Chem., Int. Ed.* **2019**, *58*, 11586−11598. (b) Kancherla, R.; Muralirajan, K.; Maity, B.; Zhu, C.; Krach, P. E.; Cavallo, L.; Rueping, M. Oxidative Addition to Palladium(0) Made Easy through Photoexcited-State Metal Catalysis: Experiment and Computation. *Angew. Chem., Int. Ed.* **2019**, *58*, 3412−3416. (c) Zhao, B.; Shang, R.; Wang, G.-Z.; Wang, S.; Chen, H.; Fu, Y. Palladium-Catalyzed Dual Ligand-Enabled Alkylation of Silyl Enol Ether and Enamide under Irradiation: Scope, Mechanism, and Theoretical Elucidation of Hybrid Alkyl Pd(I)-Radical Species. *ACS Catal.* **2020**, *10*, 1334−1343. (d) Zhou, W.-J.; Cao, G.-M.; Zhang, Z.-P.; Yu, D.-G. Visible Light-induced Palladium-

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979

catalysis in Organic Synthesis. *Chem. Lett.* **2019**, *48*, 181−191. (e) Huang, H.-M.; Koy, M.; Serrano, E.; Pflüger, P. M.; Schwarz, J. L.; Glorius, F. Catalytic radical generation of π-allylpalladium complexes. *Nat. Catal.* **2020**, *3*, 393−400. (f) Torres, G. M.; Liu, Y.; Arndtsen, B. A. A Dual Light-Driven Palladium Catalyst: Breaking the Barriers in Carbonylation Reactions. *Science* **2020**, *368*, 318−323. (g) Zhang, Z.; Rogers, C. R.; Weiss, E. A. Energy Transfer from CdS QDs to a Photogenerated Pd Complex Enhances the Rate and Selectivity of a Pd-Photocatalyzed Heck Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 495−501.

(12) Haartz, J. C.; Mcdaniel, D. H. Fluoride-Ion Affinity of Some Lewis-Acids. *J. Am. Chem. Soc.* **1973**, *95*, 8562−8565.

(13) (a) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp^3-sp^2 Cross-Coupling. *Acc. Chem. Res.* **2016**, *49*, 1429−1439. (b) Milligan, J. A.; Phelan, J. P.; Badir, S. O.; Molander, G. A. Alkyl Carbon-Carbon Bond Formation by Nickel/Photoredox Cross-Coupling. *Angew. Chem., Int. Ed.* **2019**, *58*, 6152−6163. (c) Wenger, O. S. Photoactive Nickel Complexes in Cross-Coupling Catalysis. Wenger, O. S. *Chem. - Eur. J.* **2021**, *27*, 2270−2278.

(14) (a) Gu, J.-W.; Guo, W.-H.; Zhang, X. Synthesis of Diaryldifluoromethanes by Pd-Catalyzed Difluoroalkylation of Arylboronic Acids. *Org. Chem. Front.* **2015**, *2*, 38−41. (b) Xiao, Y.-L.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. Nickel-Catalyzed Difluoroalkylation of (Hetero)Arylborons with Unactivated 1-Bromo-1,1-difluoroalkanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 5837−5841. (c) Gao, X.; Cheng, R.; Xiao, Y.-L.; Wan, X.-L.; Zhang, X. Copper-Catalyzed Highly Enantioselective Difluoroalkylation of Secondary Propargyl Sulfonates with Difluoroenoxysilanes. *Chem.* **2019**, *5*, 2987−2999.

(15) Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. New Insights into Xantphos/Pd-Catalyzed C−N Bond Forming Reactions: A Structural and Kinetic Study. *Organometallics* **2006**, *25*, 82−91.

(16) (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. Bis(tertiary phosphine)Palladium(0) and -Platinum(0) Complexes: Preparations and Crystal and Molecular Structures. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858. (b) Yoshida, T.; Otsuka, S. Reactions of Two-Coordinate Phosphine Platinum(0) and Palladium(0) Compounds. Ligand Exchange and Reactivities toward Small Molecules. *J. Am. Chem. Soc.* **1977**, *99*, 2134−2140.

(17) (a) Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. Triarylphosphine and Ethylene Complexes of Zerovalent Nickel, Palladium, and Platinum. *J. Am. Chem. Soc.* **1972**, *94*, 2669−2676. (b) Caspar, J. V. Long-Lived Reactive Excited States of Zero-Valent Phosphine, Phosphite, and Arsine Complexes of Nickel, Palladium and Platinum. *J. Am. Chem. Soc.* **1985**, *107*, 6718−6719.

(18) (a) Kessel, S. L.; Emberson, R. M.; Debrunner, P. G.; Hendrickson, D. N. Iron(III), Manganese(III), and Cobalt(III) Complexes with Single Chelating *o*-Semiquinone Ligands. *Inorg. Chem.* **1980**, *19*, 1170−1178. (b) Hou, Z. M.; Fujita, A.; Yamazaki, H.; Wakatsuki, Y. First Isolation of a Tris(ketyl) Metal Complex. *J. Am. Chem. Soc.* **1996**, *118*, 7843−7844. (c) Hou, Z. M.; Fujita, A.; Zhang, Y. G.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y. One-Electron Reduction of Aromatic Ketones by Low-Valent Lanthanides. Isolation, Structural Characterization, and Reactivity of Lanthanide Ketyl Complexes. *J. Am. Chem. Soc.* **1998**, *120*, 754−766.

(19) Andrieux, C. P.; Combellas, C.; Kanoufi, F.; Savéant, J.-M.; Thiébault, A. Dynamics of Bond Breaking in Ion Radicals. Mechanisms and Reactivity in the Reductive Cleavage of Carbon−Fluorine Bonds of Fluoromethylarenes. *J. Am. Chem. Soc.* **1997**, *119*, 9527−9540.

(20) $[PhB(OH)_2F]K$ was observed by ^{19}F NMR during the reaction process (for details, see the Supporting Information), indicating that [Pd-F] species **D** may facilitate the catalytic cycle.

(21) Wolfe, M. M. W.; Shanahan, J. P.; Kampf, J. W.; Szymczak, N. K. Defluorinative Functionalization of Pd(II) Fluoroalkyl Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 18698−18705.

https://doi.org/10.1021/jacs.1c07459
J. Am. Chem. Soc. 2021, 143, 13971−13979