

Pd-Catalyzed Oxidative C–H Arylation of (Poly)fluoroarenes with Aryl Pinacol Boronates and Experimental and Theoretical Studies of its Reaction Mechanism

Yudha P. Budiman,^{*,[a]} Miftahussurur Hamidi Putra,^[b] Muhammad R. Ramadhan,^[a] Raiza Hannifah,^[a] Christian Luz,^[d] Ilham Z. Ghafara,^[a] Rustaman Rustaman,^[a] Engela E. Ernawati,^[a] Tri Mayanti,^[a] Axel Groß,^[b, c] Udo Radius,^[d] and Todd B. Marder^[d]

We report the synergistic combination of Pd(OAc)₂ and Ag₂O for the oxidative C–H arylation of (poly)fluoroarenes with aryl pinacol boronates (Ar-Bpin) in DMF as the solvent. This procedure can be conducted easily in air, and without using additional ligands, to afford the fluorinated unsymmetrical biaryl products in up to 98% yield. Experimental studies suggest that the formation of [PdL₂(C₆F₅)₂] in DMF as coordinating solvent does not take place under the reaction conditions as it is stable to reductive elimination and thus would

deactivate the catalyst. Thus, the intermediate [Pd-(DMF)₂(Ar_F)(Ar)] must be formed selectively to give desired arylation products. DFT calculations predict a low barrier (5.87 kcal/mol) for the concerted metalation deprotonation (CMD) process between C₆F₅H and the Pd(II) species formed after transmetalation between the Pd(II)X₂ complex and aryl-Bpin which forms a Pd-Ar_{rich} species. Thus a Pd(Ar_{rich})(Ar_{poor}) complex is generated selectively which undergoes reductive elimination to generate the unsymmetrical biaryl product.

Introduction

An increasing number of applications of fluoroaryl-containing compounds in materials,^[1] agrochemicals,^[2] and pharmaceuticals^[3] encourages the development of new strategies to synthesize such classes of compounds. Procedures to functionalize fluorinated arenes and the conversion of fluoroarenes into more complex organic molecules has been reported using fluoroaryl boronates,^[4,5] magnesium,^[6] lithium,^[7,8] zinc,^[9,10] or silicon reagents,^[11] as well as halides,^[12] and carboxylic acids.^[13] However, the development of synthetic procedures to modify fluoroarenes via direct C–F^[14] or C–H^[15] functionalization is highly desirable as it decreases the number of synthetic steps, waste, cost, and energy usage.

The acidities of C–H bonds in polyfluoroarenes and their reactions with transition metals were reviewed by Eisenstein and Perutz *et al.*^[16a,b] and Gorelsky *et al.*^[16c] It was concluded that the fluorination of arenes decreases the pK_a, with the

greatest effect being for a C–H *ortho*-to-fluorine. The reductions of the pK_a by *ortho*, *meta*, and *para* fluorines are 5.2, 3, and 1.4, respectively.^[16] In addition, the M–C bond strength is increased by the number of *ortho*-fluorine substituents, thus generating stronger M–C bonds as intermediates in transition metal-catalyzed processes.^[16a,b] In a recent example, Chirik *et al.* studied, in detail the cobalt-catalyzed borylation of 1-fluoro-3-trifluoromethylbenzene. Their DFT calculations and experiments showed the preference for C–H oxidative addition *ortho*-to-fluorine rather than *meta*-to-fluorine to form the strongest Co–C bond in the intermediate, leading to *ortho*-to-fluorine borylation as the major product.^[17]

The involvement of silver(I) reagents in Pd-catalyzed C–H functionalizations of (poly)fluoroarenes with aryl halides typically requires phosphine ligands (Scheme 1A and B). In addition, DFT calculations and experimental studies by Larrosa *et al.* and Hartwig *et al.* showed that phosphine ligated silver(I) functions to cleave the C–H bond *ortho*-to-fluorine instead of, or in competition with, palladium.^[15c,18a] Notably, they reported that silver-mediated C–H activations failed in the absence of phosphine ligands. Perutz *et al.* reported that even though a silver salt such as Ag₂CO₃ is highly insoluble in all common solvents, interestingly, the solubility can be increased in the presence of bulky phosphine ligand such as XPhos, cleaving the C–H bond of C₆F₅H to form the isolable complex [Ag-(Xphos)(C₆F₅)].^[18b] Nitrogen-based coordinating solvents such as pyridine can also increase the solubility of Ag₂O. Recently, cluster complexes [{Ag₂L₂(Ar_F)₂]_n (Ar_F = C₆F₅, 3-Br-C₆F₄, and 4-H-C₆F₄; L = pyridine) have been synthesized *via* C–H activation of polyfluoroarenes with Ag₂O in pyridine as the solvent.^[19]

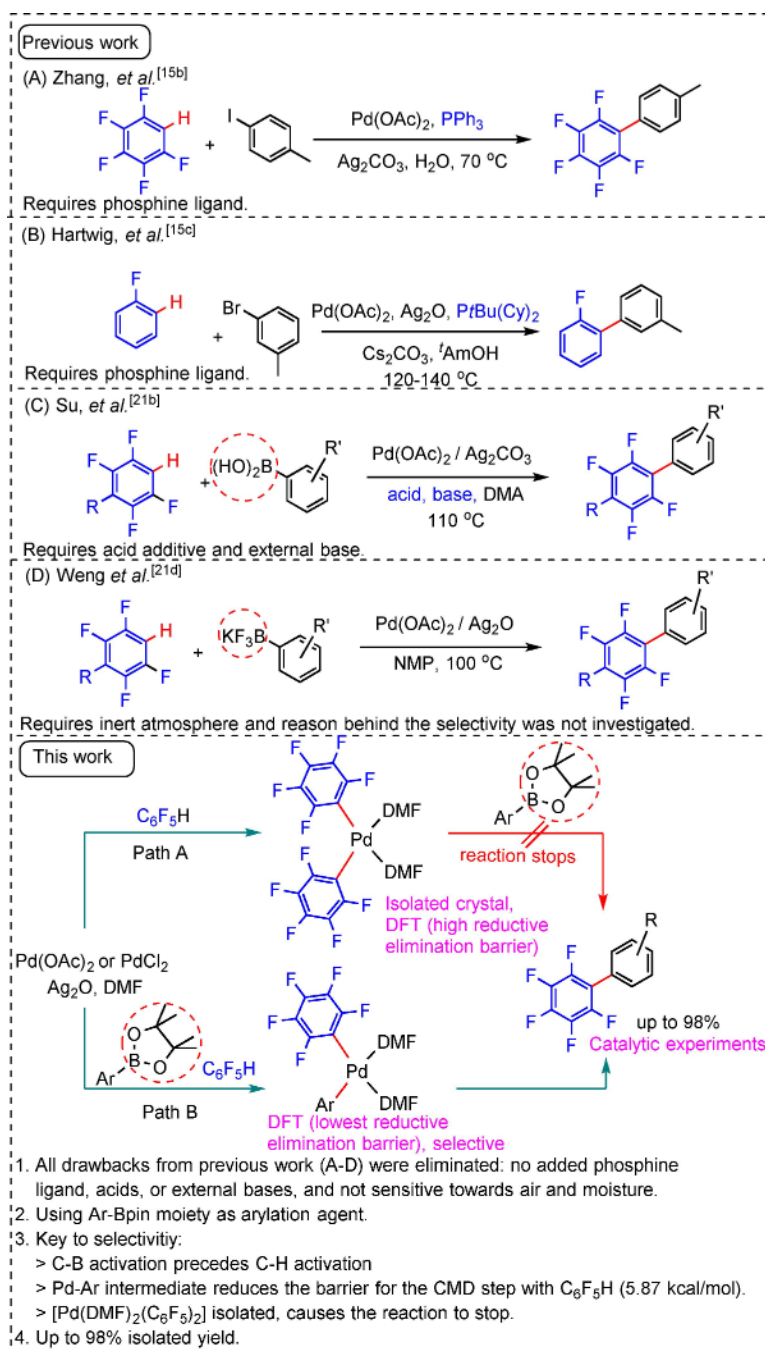
Reports on C–H arylation of (poly)fluoroarenes have been reviewed by Doucet,^[15a] and by Budiman, Perutz, Steel, Radius, and Marder.^[15d] C–H bonds of polyfluoroarenes have been

[a] Y. P. Budiman, M. R. Ramadhan, R. Hannifah, I. Z. Ghafara, R. Rustaman, E. E. Ernawati, T. Mayanti
Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, 45363 Sumedang, Indonesia
E-mail: y.p.budiman@unpad.ac.id

[b] M. H. Putra, A. Groß
Institute of Theoretical Chemistry, Ulm University, 89081 Ulm, Germany

[c] A. Groß
Helmholtz Institute Ulm (HIU), Electrochemical Energy Storage, 89069 Ulm, Germany

[d] C. Luz, U. Radius, T. B. Marder
Institute of Inorganic Chemistry and Institute for Sustainable Chemistry & Catalysis with Boron, Julius-Maximilians-Universität Würzburg, Am Hubland, 97074 Würzburg, Germany



Scheme 1. Pd/Ag systems involved in C–H arylation of (poly)fluoroarenes.

reported to undergo arylation with electrophiles such as aryl halides,^[15,20a–k] or pseudohalides such as, aryl sulfonates,^[20l] mesylates,^[20l,m] and tosylates,^[20m,n] or sulfides.^[20o] On the other hand, oxidative C–H arylation of (poly)fluoroarenes with nucleophilic organometallic reagents is more challenging due to the possible generation of homocoupling byproducts. Organometallic reagents that are able to be polyfluoroarylated include aryl boronates,^[21a–d] germanes,^[21e] silanes,^[21f] and sulfinic acid sodium salts.^[21g] C–H arylation of arenes with aryl-B(OH)₂ was initially reported by Itami *et al.*^[21a] in 2008. The reaction is mediated by a stoichiometric amount of Cu(OCOCF₃)₂ and

CF₃CO₂H, at 80 °C, in air. However, this method is limited to electron rich arene substrates and 5-membered *N*-heteroarenes and, notably, simple substrates such as benzene, and toluene cannot be employed. In 2009, Su *et al.*^[21b] reported the Pd/Ag-catalyzed C–H arylation of polyfluoroarenes with electron-rich aryl-B(OH)₂ (Scheme 1C). Although fluoroarene bearing 2–5 fluorines could be employed, efficiency was low when difluoroarenes were used or when the C–H bond was not flanked by two *ortho*-fluorines. However, in addition to the use of 2 equiv. of silver salts, both bases and acids were also added. Interestingly, similar conditions to those of Su *et al.* were

utilized by Shi *et al.* in 2011, to fluoroarylate aryl C–H bonds; that process requires the addition of acid (HOAc) and *i*Pr₂S, but showed good scope of both (poly)fluoroarenes and arenes. However, mono-substituted arenes gave multiple products. They proposed a mechanism involving initial activation/transmetalation of the fluoroarene C–H bond. In 2013, Weng *et al.*^[21d] reported the Pd/Ag-catalyzed C–H arylation of polyfluoroarenes with nucleophilic aryl-BF₃K reagents using N-methylpyrrolidone (NMP) as the solvent (Scheme 1D). However, the reason underlying its selectivity was not investigated and the reaction required an inert atmosphere. To the best of our knowledge, DFT calculations to examine the reasons behind the selectivity of Pd/Ag catalyzed polyfluoroarylations of aryl boronates or boronic acids as well as the employment of Ar-Bpin compounds for the C–H arylation of (poly)fluoroarenes have not previously been reported.

Recently, we reported the generation of the stable complex [Pd(MeCN)₂(C₆F₅)₂] *via* direct C–H activation of C₆F₅H with a synergistic combination of Pd(OAc)₂ and Ag₂O.^[5d] However, we also described the palladium-catalyzed homocoupling of (poly)fluorinated aryl boronates Ar_F-Bpin, which proceeds smoothly in a “weakly-coordinating” arene solvent as long as no ancillary ligands or strongly coordinating solvents are present. Otherwise, the reaction typically stops at the [PdL₂(Ar_F)₂] stage after two transmetalation steps when more strongly coordinating solvents or ligands are present. The silver oxide Ag₂O likely assists the transmetalation process generating palladium hydroxides and also re-oxidizes Pd(0) to Pd(II) after reductive elimination of the biaryl product to restart the catalytic cycle. As the reductive elimination from [Pd-(MeCN)₂(Ar_F)₂] is difficult due to the high barrier when both aryl rings have two *ortho*-fluorines, we hypothesized that reductive elimination might be more facile from a mixed bis(aryl) Pd complex [PdL₂(Ar_F)(Ar_{rich})] containing one electron-poor Ar_F and one electron-rich aryl moiety. This would allow the development of processes leading to selective formation of heterobiaryls containing one fluoroaryl moiety. The advantage of this strategy is that the possible competitive homocoupling of arenes containing two *ortho*-fluorines can be eliminated as long as the ligands are sufficiently good donors.^[5d,22]

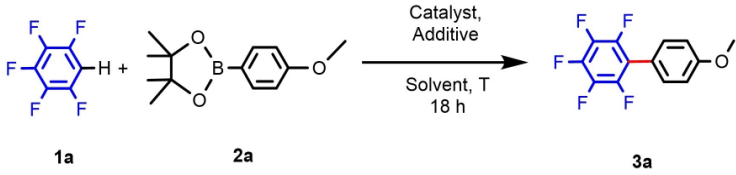
We report herein the synergistic Pd(OAc)₂/Ag₂O mediated oxidative C–H arylation of polyfluoroarenes with aryl-Bpin and experimental and, importantly, theoretical studies of the reaction mechanism. This reaction is not sensitive towards air or moisture. We compared the selectivity using aryl-B(OR)₂ (B-(OR)₂=B(OH)₂ and Bpin), noting that the C–H arylation occurs selectively with the more electron-rich Bpin moiety. The key issue regarding selectivity was studied *via* DFT calculations to gain additional insight into why [Pd(DMF)₂(Ar)(C₆F₅)] is formed selectively, thus leading to the desired cross-coupling product. Importantly, we note that the presence of an electron-rich aryl ligand on the Pd(II) intermediate reduces the energy barrier for the CMD process with C₆F₅H.

Results and Discussion

We previously reported that reductive elimination from [Pd-(L)₂(C₆F₅)₂] to give C₆F₅-C₆F₅ is difficult as the energy barrier is too high.^[5d] This energy barrier can be reduced by employing very weakly donating/coordinating solvents such as arenes in the absence of any added ligands. Computations indicated that coupling reactions carried out in aromatic solvents, which are, in general, weak σ donors and π -acceptors, are feasible, as the reductive elimination process is exergonic and the overall barrier for reductive elimination is reduced. The lower barrier for the reductive elimination process from [(η^5 -Ar)Pd(C₆F₅)₂] intermediates is the result of favorable π back-bonding from Pd(Ar_F)₂ to the arene ligand in the transition state and of arene ligand ring slippage, i.e., the adjustment of the arene ring to the developing charge in the reductive elimination transition state.

Thus, to develop a cross-coupling procedure for electron-poor partially fluorinated arenes with electron rich aryl boronates Ar-Bpin, the formation of *cis*-[PdL₂(Ar_F)₂] has to be avoided and *cis*-[PdL₂(Ar_F)(Ar)] has to be formed selectively to result in the reductive elimination of Ar-Ar_F. Widely commercially available aryl pinacol boronates (aryl-Bpin) and boronic acids (aryl-B(OH)₂) were chosen as nucleophilic aryl sources.

In the hope that the homocoupling side-product Ar_F-Ar_F would not be generated, we started our investigations using the same conditions as employed for our fluoroaryl homocoupling,^[5d] but now in the presence of aryl boronates (Ar-Bpin). The reaction of 0.6 mmol of C₆F₅H with 0.4 mmol of 4-MeO-C₆H₄-Bpin was chosen as a model (Table 1). In the first screening, 10 mol% of Pd(OAc)₂ was used as the catalyst and 0.6 mmol of Ag₂O as an additive in MeCN as the solvent at 80 °C. These standard conditions afforded the arylated product **3a** in 64% isolated yield (Table 1, entry 1) and homocoupling product **2a** was detected in yields lower than 30%. Interestingly, the selectivity toward the formation of **3a** increased significantly when DMF was used as the solvent at 100 °C, and **3a** was isolated in an excellent yield of 93% (entry 2). Homocoupling was not detected under these conditions by GCMS. This better performance might be due to the better ability of DMF to coordinate with silver, thus increasing the solubility of the silver salt.^[20] It must be noted that previous work on Pd/Ag catalyzed C–H arylation of (poly)fluoroarenes with aryl halides required phosphine ligands to enhance the reactivity,^[15,18] however, employing [Pd(PPh₃)₄] in this reaction led to very poor yields of the desired product (entry 3). The best performance was obtained when decreasing the catalyst loading to 5 mol% (entry 4). It must be noted that this reaction is quite tolerant to oxygen and moisture as open-air reaction led to 92% yield (entry 5), whereas Weng's method for the arylation of (poly)fluoroarenes with aryl-BF₃K employs an inert atmosphere.^[21] Bases such as CsF were found to generate (poly)fluorobiphenyls in copper-catalyzed Suzuki-Miyaura cross-coupling reactions; however, adding CsF to our process led to poor performance (entry 6). Using another coordinating solvent such as DMSO decreased the yield to 48% (entry 7). An excellent yield was also obtained using PdCl₂ as the catalyst

Table 1. Screening of the reaction conditions for the Pd-catalyzed C–H Arylation of C₆F₅H with MeO-C₆H₄-Bpin.^[a]


Entry	Catalyst	Additive	Solvent	T (°C)	Yield (%) ^[b]
1	Pd(OAc) ₂	Ag ₂ O	MeCN	80	64
2	Pd(OAc) ₂	Ag ₂ O	DMF	100	93
3	Pd(PPh ₃) ₄	Ag ₂ O	DMF	100	13
4	Pd(OAc) ₂ ^[c]	Ag ₂ O	DMF	100	98
5	Pd(OAc) ₂ ^[c]	Ag ₂ O	DMF	100	92 ^[d]
6	Pd(OAc) ₂	Ag ₂ O + CsF ^[e]	DMF	100	35
7	Pd(OAc) ₂	Ag ₂ O	DMSO	100	48
8	PdCl ₂	Ag ₂ O	DMF	100	92
9	Cu(OAc) ₂	Ag ₂ O	DMF	100	0
10	Pd(OAc) ₂	AgOAc ^[f]	DMF	100	50
11	Pd(OAc) ₂	AgNO ₃ ^[f]	DMF	100	40
12	Pd(OAc) ₂ ^[c]	O ₂	DMF	100	30

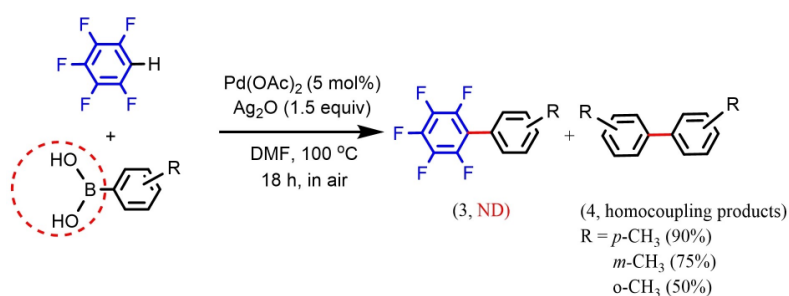
^[a]General conditions: **1a** (0.6 mmol), **2a** (0.4 mmol), catalyst (10 mol%), additive (1.5 equiv). ^[b]Isolated yield after column chromatography. ^[c]5 mol% of catalyst. ^[d]in air. ^[e]2 equiv. of CsF. ^[f]3 equiv. of additive.

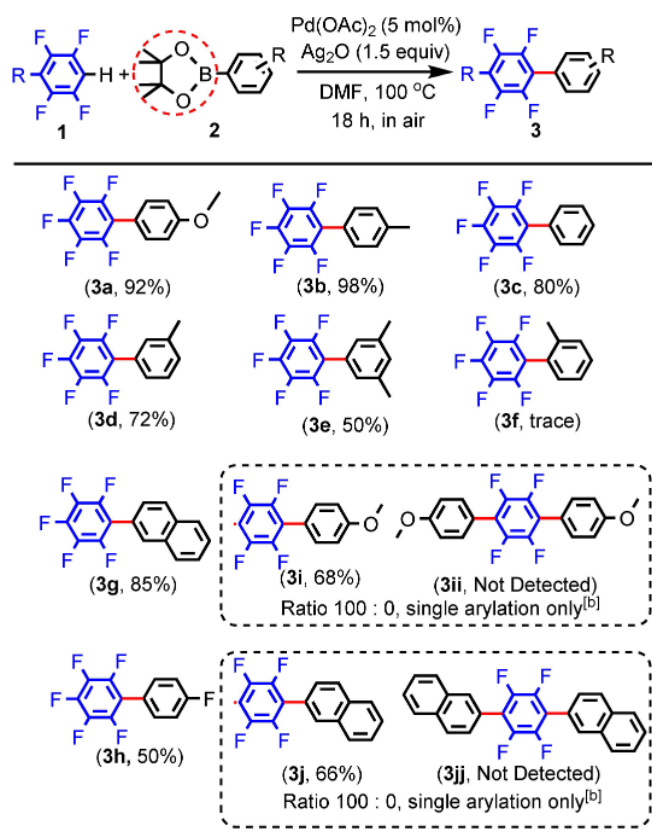
(entry 8). It must be noted that, under Weng's conditions, employing PdCl₂ with as Ar–BF₃K led to a poor yield.^[21] Arylated product was not observed when using Cu(OAc)₂ as the catalyst (entry 9). Other types of oxidants such as AgOAc and AgNO₃ gave fair yields (entry 10,11), and O₂ as the oxidant in the absence of Ag salts led to poor performance (entry 12). We chose the conditions in air as stated in entry 5 for further investigations.

Furthermore, we tried to employ aryl boronic acids (Ar–B(OH)₂) as substrates for the C–H arylation of C₆F₅H. In general, the cross-coupling failed when using aryl boronic acids 2/3/4-H₃C–C₆H₄–B(OH)₂ and no arylation product was detected (Scheme 2). In this case, homocoupling prevailed and the homocoupling product of the electron-rich aryl Ar_F–Ar_F (not of the fluorinated aryl Ar_F–Ar_F) was the only product detected. Thus, the reactivity of organoboron compounds is substantially influenced by the substituents attached to the boron

atom,^[4,23,24] making Ar–B(OH)₂ more reactive than Ar–Bpin and, as a result, double transmetalation of aryl-B(OH)₂ at palladium was faster than the introduction of the C₆F₅ ring to the Pd center. Thus, the correct choice of boronate ester is crucial for this chemistry.

Having determined the optimal conditions for the C–H arylation, we next investigated the scope of the reactions of C₆F₅H with different aryl-Bpin substrates (Scheme 3). Those bearing electron-donating groups (EDG), such as methoxy and methyl, at the *para*-position (**3a**, **3b**) gave excellent yields, better than phenyl-Bpin (**3c**) and the one bearing electron-withdrawing substituent (**3h**). The presence of EDG methyl or dimethyl groups at the *meta*-positions gave fair to moderate yields (**3d**, **e**), whereas employing a sterically more hindered substrate such as 2-methyl-phenyl-Bpin was not viable (**3f**). Naphthalene derivatives are of great interest in blue organic light-emitting diodes (OLED),^[25] thus we employed

**Scheme 2.** Attempted C–H arylation of C₆F₅H with Ar–B(OH)₂ instead of Ar–Bpin analogues.



^[a]General conditions: **1** (0.6 mmol), **2** (0.4 mmol), Pd(OAc)₂ (5 mol%), Ag₂O (1.5 equiv). ^[b]Ag₂O (1 equiv). Isolated yields are reported.

Scheme 3. Scope of the Pd-catalyzed C–H arylation of ArF_n with Ar-Bpin.^[a]

naphthalene-2-Bpin in our reaction, and 85% of the arylated product was isolated (**3g**).

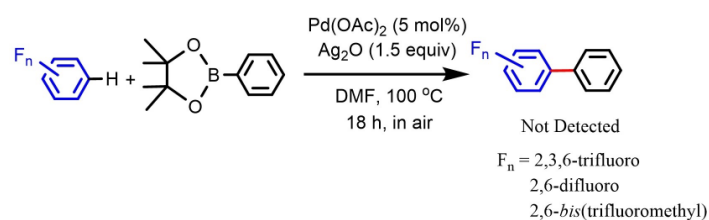
Furthermore, we varied the number of fluorine atoms on the fluorinated arene in coupling reactions with aryl-Bpin. While 1,2,4,5-tetrafluorobenzene has two equivalent C–H bonds, interestingly, C–H arylation of 1,2,4,5-tetrafluorobenzene with 4-methoxy-phenyl-Bpin and naphthalene-2-Bpin, using 1 equiv.

of Ag₂O, led to moderate to good yields of the monocoupling products (**3i**, **3j**) and no dual arylation products were detected by GCMS (**3ii**, **3jj**). Notably, C–H arylation of 1,2,4,5-tetrafluorobenzene was only observed in trace amounts if the amount of silver oxide was in excess (1.5 equiv). These conditions cannot be applied to arenes containing less than 4 fluorine substituents (Scheme 4).

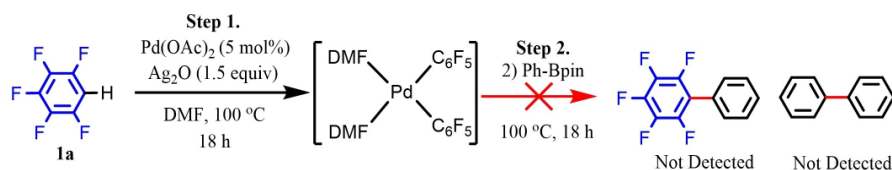
To explore the mechanism, two step reactions were conducted in a one-pot process (Scheme 5). First, reacting C₆F₅H with Pd(OAc)₂ and Ag₂O in DMF for 18 h at 100 °C resulted in the formation of the complex *cis*-[Pd(DMF)₂(C₆F₅)₂] according to ¹⁹F NMR spectroscopy; however, we did not observe formation of an Ag–C₆F₅ complex (see Figure S1 in the Supporting Information). Afterwards, phenyl-Bpin was added and stirring was continued for 18 h. Interestingly, neither cross-coupling products nor homocoupling of C₆F₅H or phenyl-Bpin were observed (Scheme 5). We repeated the reaction with 0.6 mmol of C₆F₅H (**1a**), with 0.2 mmol of Pd(OAc)₂ and 1.2 mmol of Ag₂O in 4 mL of DMF for 15 h at 100 °C, and again obtained *cis*-[Pd(DMF)₂(C₆F₅)₂], indicating that the reaction stopped after the double CMD steps (Scheme 5 and Figure 1). Thus, *cis*-[Pd(DMF)₂(C₆F₅)₂] is not a viable intermediate in the cross-coupling reaction. As a consequence, transfer of aryl groups from both aryl-Bpin and C₆F₅H must occur to form [Pd(DMF)₂(Ar)(C₆F₅)] as an intermediate.

Next, we investigated the role of 1.5 equiv. of Ag₂O, with regard to whether it activates both aryl-Bpin and C₆F₅H or only one of them. When Ag₂O was introduced to *p*-MeO–C₆H₄-Bpin in a wet and air atmosphere or in anhydrous DMF under an inert atmosphere, at 100 °C, for 18 h, without addition of the Pd catalyst, we observed that under both conditions, the *p*-MeO–C₆H₅ remained nearly quantitatively with only traces of *p*-MeO–C₆H₅ being formed by protodeborylation (Scheme 6, and see Figures S2 and S3 in the Supporting Information). This implies that Ag₂O does not cleave the C–B bond of the aryl-Bpin.

Hartwig reported H/D exchange experiments suggesting that Ag₂O needs an ancillary phosphine ligand to be able to cleave a C–H bond *ortho* to two fluorines whereas, in the



Scheme 4. Attempted C–H arylation of other fluorinated arenes.



Scheme 5. Attempts at sequential Pd-catalyzed C–H arylation divided into two steps.

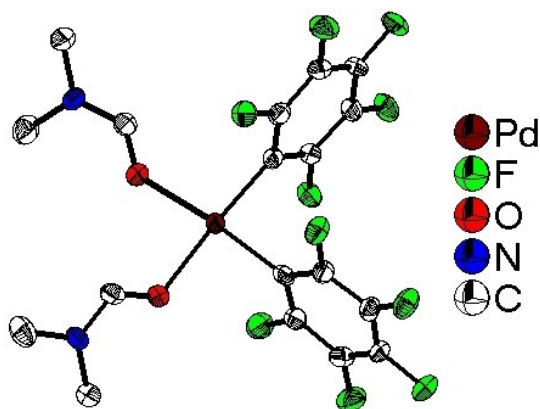
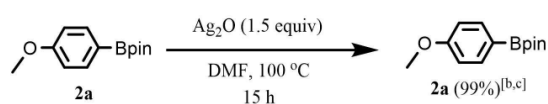


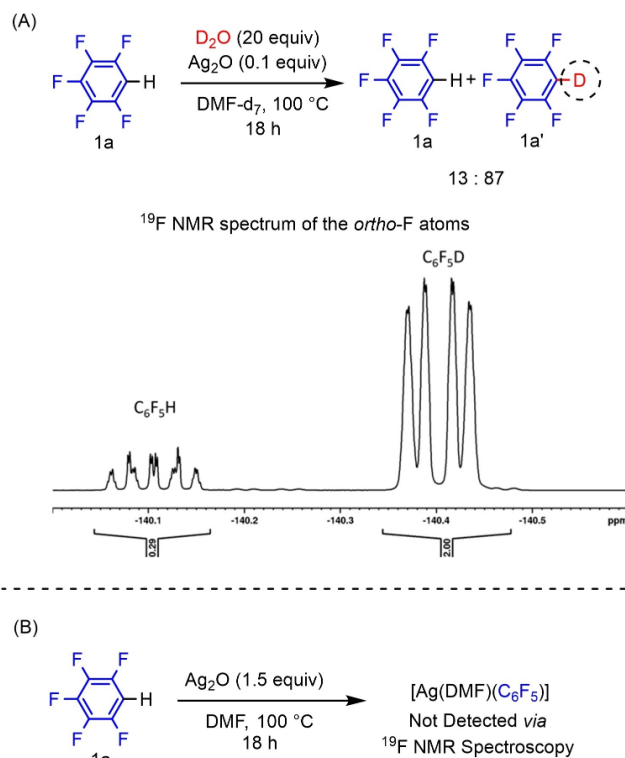
Figure 1. Molecular structure of **5a** [Pd(DMF)₂(C₆F₅)₂] determined by single-crystal X-ray diffraction at 100 K. Ellipsoids are drawn at the 50% probability level, and H atoms are omitted for clarity. Colors: purple (palladium), green (fluorine), red (oxygen), blue (nitrogen), white (carbon). Pd–C_{ipso}(C₆F₅) = 1.972(4), 1.987(4) Å; Pd–O_{ipso} = 2.107(3), 2.118(3) Å; C_{ipso}(C₆F₅)...C_{ipso}(C₆F₅) = 2.706(5) Å; C_{ipso}–Pd–C_{ipso} = 86.21(17)°; O_{ipso}–Pd–O_{ipso} = 84.34(11)°; C_{ipso}–Pd–O_{ipso} = 90.60(14)°, 98.78(13)°; ∠ Ar–Ar = 102.95(14)°.



^[a]Conditions: **2a** (0.2 mmol), Ag₂O (1.5 equiv), in DMF (2 mL), 100 °C, 15 h. GC yield is reported with mesitylene as an internal standard. ^[b]The reaction was conducted in anhydrous DMF under an inert atmosphere (see also Figure S2, in the Supporting Information). ^[c]The reaction was conducted in wet DMF in air (see also Figure S3, in Supporting Information).

Scheme 6. Possibility of C–B activation of aryl-Bpin with Ag₂O.^[a]

absence of a ligand, Ag₂O failed to cleave the C–H bond.^[15b] With that in mind, and in the absence of a phosphine ligand, we reacted C₆F₅H with D₂O (20 equiv) and Ag₂O (0.1 equiv) in DMF or DMF-d₇ at 100 °C for 18 h and, interestingly, we observed C₆F₅D in 87% conversion based on ¹⁹F NMR spectroscopy (Scheme 7A, and Figures S5–12 in the Supporting Information). Importantly, no hydroxyaryl species were detected by NMR or GCMS, and no reaction or H/D exchange was observed in the absence of D₂O. Recently, Junk *et al.* reported that reaction of Ag₂O with C₆F₅H in pyridine led to the formation of [Ag₂(py)₂(C₆F₅)₂]_n.^[19] Following Junk's procedure, but using DMF as the solvent instead of pyridine (Scheme 7B), we did not observe any ¹⁹F NMR chemical shifts arising from an Ag–C₆F₅ complex (Figure S4 in the Supporting Information). Similarly, Perutz and Fairlamb reported that a reaction of [Ag(PPh₃)(OAc)] with C₆F₅H and D₂O in DMF gave 37% deuteration.^[18c] However, they showed that when AgOAc and PPh₃ were reacted with C₆F₅H and, notably, without D₂O, interestingly, no Ag–C₆F₅ was detected. While we have not observed any Ag–C₆F₅ complex directly (Schemes 7A and 7B), we cannot completely rule out its presence in extremely low concentrations or with a very short lifetime, and do not know exactly what form Ag₂O takes in wet DMF. Clearly, though, it does catalyze H/D exchange in C₆F₅H.



Scheme 7. Possibility of C–H activation of C₆F₅H with Ag₂O.

We were interested in investigating the selectivity of our cross-coupling process using density functional theory (DFT) at the B3LYP/def2-TZVP/vdW-D3BJ/SMD-level of theory (Figure 2). Previously, several groups have reported the ability of Ag₂O to accelerate the rate of Suzuki–Miyaura coupling.^[26] DFT computations and experiments by Korenaga *et al.*^[26a] and Osakada *et al.*^[26b] assumed that the acceleration by Ag₂O in the presence of moisture results from the replacement of halide ligands on the Pd(II) complex to generate hydroxy-palladium species with higher ability for transmetalation with aryl boronates. Therefore, we assumed that the good catalytic performance using combinations of either PdCl₂ or Pd(OAc)₂ with Ag₂O in wet DMF solvents is due to the replacement of X ligands to form the highly reactive Pd complex [Pd(DMF)₂(OH)₂]. Thus, our calculations started with Rxn I from [Pd(DMF)₂(OH)₂]. Farina, Hartwig, and Amatore reported kinetic studies indicating that transmetalation occurs at a three-coordinate Pd(II) complex.^[27–29] Espinet reported the dissociation of moderately coordinating solvents such as MeCN,^[30] or THF^[31] from [PdL₂R₂] to form three-coordinate [PdLR₂] during catalytic coupling processes. Thus, in Rxn I, the formation of a three-coordinate Pd-complex occurs from [Pd(DMF)₂(OH)₂] by dissociating a single molecule of a moderately coordinating solvent DMF and, subsequently, [Pd(DMF)(OH)₂] interacts with aryl-Bpin to form Intermediate 2 with a total reaction free energy (ΔG) of 4.17 kcal/mol.

Afterwards, as the catalytic reaction involves two different nucleophilic aryls, the question is which aryl moiety transmetalates to the Pd(II) first? DFT computations imply that transmetalation of [Pd(DMF)(OH)₂] with aryl-Bpin to form [Pd-

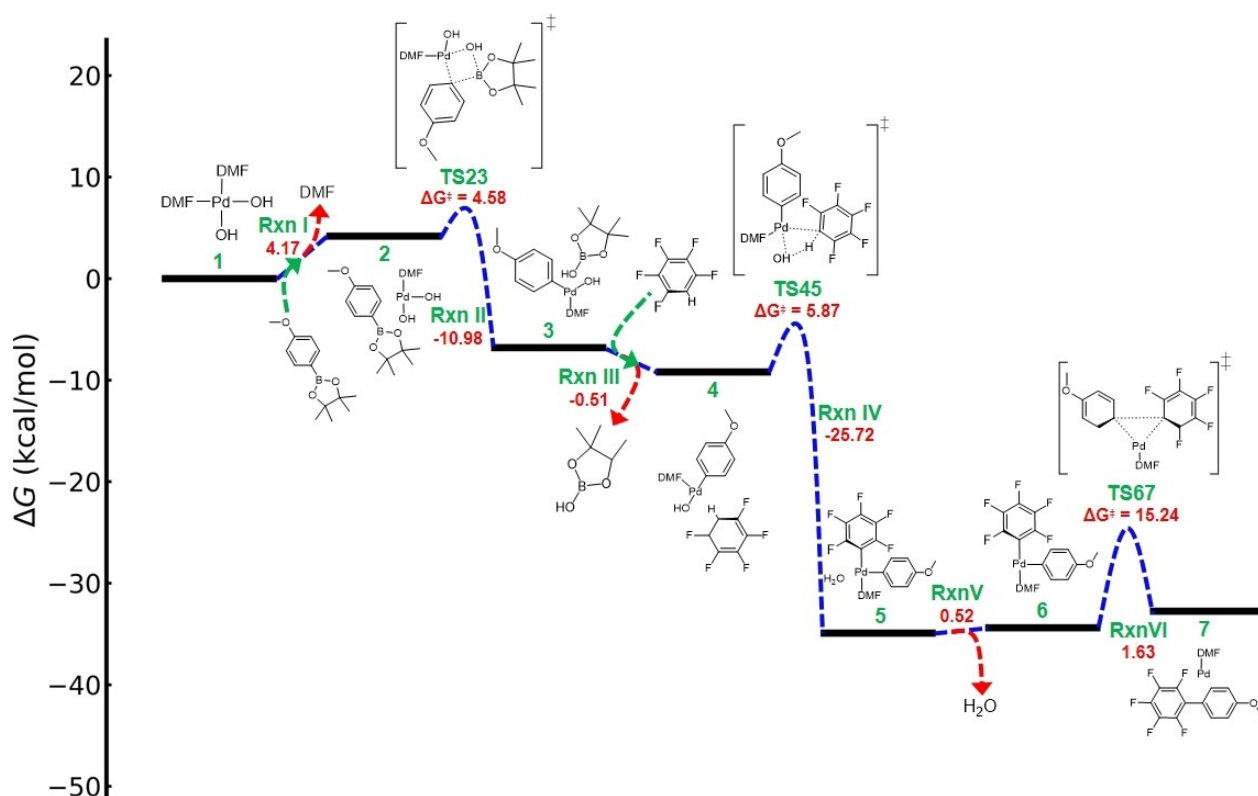


Figure 2. DFT calculations at the B3LYP/def2-TZVP/vdW–D3BJ/SMD-level of theory for the mechanism of the Pd-catalyzed direct C–H arylation of polyfluoroarenes with aryl-Bpin in Scheme 8 (for details see the Supporting Information).

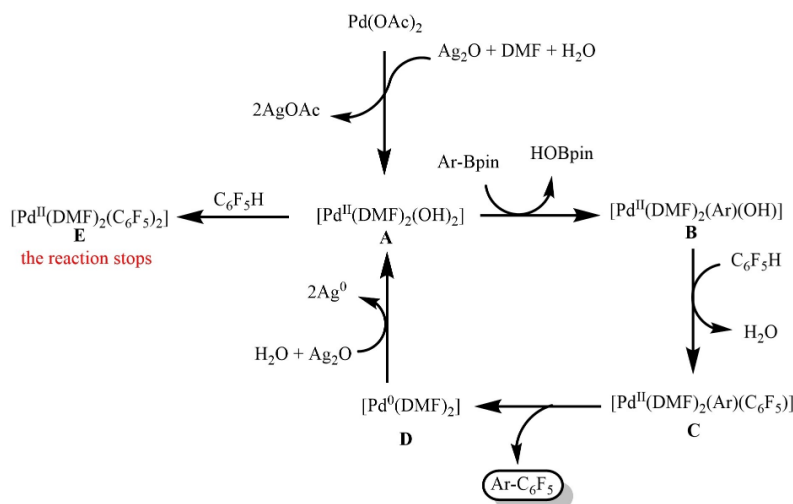
(DMF)(Ar)(OH)] and Bpin(OH) (Intermediate 3) in Rxn II occurs first. From our simulation, the computed reaction free energy (ΔG) and energy barrier (ΔG^\ddagger) are -10.98 kcal/mol and 4.58 kcal/mol, respectively. This transmetalation reaction has a slightly higher reaction free energy than a CMD reaction with C_6F_5H ($\Delta G = -11.21$ kcal/mol), but the energy barrier for the CMD reaction with C_6F_5H is much higher than that for the transmetalation reaction with aryl-Bpin which is 27.38 kcal/mol (see the Supporting Information). Thus, transmetalation with aryl-Bpin is favored in the first arylation process over the CMD reaction with C_6F_5H .

After [Pd(DMF)(Ar)(OH)] and Bpin(OH) are formed, the reaction path continues by Rxn III, *i.e.*, dissociation of Bpin(OH) and interaction between C_6F_5H and [Pd(DMF)(Ar)(OH)] to form Intermediate 4. The total reaction free energy of Rxn III is -0.51 kcal/mol. The reaction is followed by the CMD reaction between [Pd(DMF)(Ar)(OH)] and C_6F_5H to form [Pd(DMF)(Ar)(C_6F_5)] and H_2O (Intermediate 5, see Rxn IV in Figure 2). According to our DFT calculations, Rxn IV occurs with a ΔG of -25.72 kcal/mol and an ΔG^\ddagger of 5.87 kcal/mol. Interestingly, this CMD reaction has a very low barrier and is more exergonic compared to the CMD reaction of C_6F_5H with [Pd(DMF)(OH) $_2$] (27.38 kcal/mol) (*vide supra*). On the other hand, the transmetalation reaction between [Pd(DMF)(Ar)(OH)] and ArBpin has a higher energy barrier of 18.55 kcal/mol, with a reaction energy relatively similar to the CMD reaction, which is -26.73 kcal/mol (see the Supporting Information). Therefore, the first transmetalation reaction between [(DMF)Pd(OH) $_2$] and aryl-Bpin

contributes to decreasing both the reaction free energy and, especially, the energy barrier, as an electron-rich Ar moiety on Pd helps to activate the electron-poor, C_6F_5H .^[32]

Once [Pd(DMF)(Ar)(C_6F_5)] has been formed, reductive elimination gives Ar- C_6F_5 and Pd(0)-DMF, as shown in Rxn VI (Figure 2), with a reaction free energy and energy barrier of 1.63 kcal/mol and 15.24 kcal/mol, respectively. Notably, it has been reported that the highest rate of reductive elimination of Ar–Ar' from [PdL $_2$ (Ar)(Ar')] occurs when an electron-rich and an electron-poor aryl group are involved.^[5,32] Those factors may also influence the selectivity of this Pd-catalyzed C–H arylation of polyfluoroarenes.

Based on DFT calculations, experimental, and literature studies, we propose the mechanism for the arylation of C_6F_5H with aryl-Bpin depicted in Scheme 8. First, in the presence of a trace amount of moisture in DMF as the coordinating solvent, Ag_2O assists the generation of hydroxy palladium (A),^[26] which is more reactive for transmetalation with aryl-Bpin to give [Pd^{II}(DMF) $_2$ (Ar)(OH)] (B). This is followed by a CMD process with C_6F_5H to transfer of C_6F_5 to Pd to give intermediate [Pd^{II}(DMF) $_2$ (Ar)(C_6F_5)] (C). Following reductive elimination of the biaryl product from C, Ag_2O oxidizes [(DMF) $_2$ Pd⁰] (D) to regenerate the catalytically active Pd(II) complex (A). Importantly, the barrier for the reaction of [Pd⁰(DMF) $_2$ (OH) $_2$] with C_6F_5H is high, as reaction of two molecules of C_6F_5H to give [Pd^{II}(DMF) $_2$ (C_6F_5) $_2$] (E) would stop the catalytic cycle.



Scheme 8. Proposed mechanism for the Pd-catalyzed direct C–H arylation of polyfluoroarenes with aryl-Bpin.

Conclusions

In summary, we report the synergistic combination of $\text{Pd}(\text{OAc})_2$ with Ag_2O to mediate the C–H arylation of (poly)fluoroarenes with aryl-Bpin. This reaction can be conducted in air, in contrast to that reported by Weng *et al.* for the C–H arylation of polyfluoroarenes with aryl- BF_3K , in which the reaction was carried out under an inert atmosphere. Ar–Ar homocoupling dominates over Ar–Ar_F cross-coupling using Ar–B(OH)₂ in place of Ar-Bpin, possibly due to the higher Lewis acidity of the boron moiety in the former, leading to faster transmetalation of Ar–B(OH)₂ with $[\text{Pd}(\text{DMF})(\text{Ar})(\text{OH})]$. Our experiments reveal that C–B bond activation of aryl-Bpin by silver(I) did not occur. On the other hand, even though H/D exchange of $\text{C}_6\text{F}_5\text{H}$ in the presence of Ag_2O occurred to give $\text{C}_6\text{F}_5\text{D}$, we did not observe the formation of any Ag– C_6F_5 complex *via* NMR spectroscopy. Thus, C–H activation of $\text{C}_6\text{F}_5\text{H}$ directly by a Pd(II) complex was calculated using DFT. These DFT calculations predict that transmetalation of the Pd(II) complex with aryl-Bpin occurs first and, interestingly, reduces the energy barrier for the CMD process between the $[\text{Pd}(\text{Ar}_{\text{rich}})(\text{OH})]$ complex and $\text{C}_6\text{F}_5\text{H}$. It must be noted that in the presence and/or with the assistance of Ag_2O , transfer of 2 equiv. of C_6F_5 to Pd(II) leading to the formation of $[\text{PdL}_2(\text{C}_6\text{F}_5)_2]$, must not occur under our catalytic conditions as it would cause the reaction to stop. Thus, the reaction must selectively generate the $[\text{Pd}(\text{Ar}_F)(\text{Ar})]$ intermediate. Therefore, the reductive elimination product, Ar– C_6F_5 , is generated selectively. Additional applications of Pd/Ag systems for C–H functionalizations are being explored in our laboratory.

Crystallographic Details

Crystal data collection and processing parameters are given in the Supporting Information. CCDC-2327275 (**5a**) contains the supplementary crystallographic data for this paper. These data

are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

Y.P.B. thanks the Universitas Padjadjaran for a Lecturer Competency Research Grant (RKDU) (Project No. 1549/UN6.3.1/PT.00/2023). Y.P.B. and T.M. thank the Universitas Padjadjaran for an Academic Leadership Grant (ALG) (Project No. 1549/UN6.3.1/PT.00/2023). We thank AllyChem for generous gifts of B_2pin_2 . M.H.P. and A.G. thank the DFG for financial support through Project C5 of the Transregional Collaborative Research Centre TRR234 Catalight (Project No.364549901). Computer time for DFT calculation on the JUSTUS cluster at Ulm University provided by the bwHPC initiative and the bwHPC–C5 project funded by the Baden-Württemberg government (MWK) and the German Research Foundation (DFG) is gratefully acknowledged. T.B.M. and U.R. thank the Julius-Maximilians-Universität Würzburg for support.

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 supplementary material of this article.

Keywords: homogeneous catalysis · fluorine · palladium · silver · organoboron

- [1] a) V. A. Montes, G. Li, R. Pohl, J. Shinar, *Adv. Mater.* **2004**, *16*, 2001–2003; b) T. Tsuzuki, N. Shirasawa, T. Suzuki, S. Tokito, *Adv. Mater.* **2003**, *15*, 1455–1458; c) M. S. Jang, S. Y. Song, H. K. Shim, *Polymer* **2000**, *41*, 5675–5679; d) R. Ragni, A. Punzi, F. Babudri, G. M. Farinola, *Eur. J. Org. Chem.* **2018**, 3500–3519; e) F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.* **2007**, 1003–102.
- [2] a) P. Jeschke, *Pest Manage. Sci.* **2010**, *66*, 10–27; b) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16–29; c) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *iScience* **2020**, *23*, 101467; d) P. Jeschke, *ChemBioChem* **2004**, *5*, 570–589.
- [3] a) J. Wang, M. S. Rosello, J. L. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; b) H.-J. Böhm, D. Banner, B. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; c) C. D. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; d) J.-P. Begue, D. Bonnet-Delpon, *J. Fluorine Chem.* **2006**, *127*, 992–1012; e) K. L. Kirk, *J. Fluorine Chem.* **2006**, *127*, 1013–1029; f) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; g) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359–4369; h) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071–1081; i) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640.
- [4] For a review on the synthesis and applications of fluorinated aryl boronates, see: Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder, *Adv. Synth. Catal.* **2021**, *363*, 2224–2255.
- [5] a) J. Zhou, M. W. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc.* **2016**, *138*, 5250–5253; b) Y.-M. Tian, X.-N. Guo, M. W. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen, T. B. Marder, *J. Am. Chem. Soc.* **2018**, *140*, 17612–17623; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder, *ChemCatChem* **2019**, *11*, 5387–5396; d) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius, T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 6036–6050; e) Z. Liu, Y. P. Budiman, Y.-M. Tian, A. Friedrich, M. Huang, S. A. Westcott, U. Radius, T. B. Marder, *Chem. Eur. J.* **2020**, *26*, 17267–17274; f) Y. P. Budiman, S. Lorenzen, Z. Liu, U. Radius, T. B. Marder, *Chem. Eur. J.* **2021**, *27*, 3869–3874; g) Z. Liu, G. K. Kole, Y. P. Budiman, Y.-M. Tian, A. Friedrich, X. Luo, S. A. Westcott, U. Radius, T. B. Marder, *Angew. Chem. Int. Ed.* **2021**, *60*, 16529–16538.
- [6] J. Wang, G. Meng, K. Xie, L. Li, H. Sun, Z. Huang, *ACS Catal.* **2017**, *7*, 7421–7430.
- [7] K. Maruoka, I. Shimada, M. Akakura, H. Yamamoto, *Synlett* **1994**, *10*, 847–848.
- [8] T. D. Moseev, M. V. Varaksin, D. A. Gorlov, E. A. Nikiforov, D. S. Kopchuk, E. S. Starnovskaya, A. F. Khasanov, G. V. Zyryanov, V. N. Charushin, O. N. Chupakhin, *J. Fluorine Chem.* **2019**, *224*, 89–99.
- [9] N. Sugita, S. Hayashi, S. Ishii, T. Takanami, *Catalysts* **2013**, *3*, 839–852.
- [10] X. Yi, R. Mao, L. Lavrencic, X. Hu, *Angew. Chem. Int. Ed.* **2021**, *60*, 23557–23563.
- [11] H. Fang, Q. He, G. Liu, Z. Huang, *Org. Lett.* **2020**, *22*, 9298–9302.
- [12] A. Sapegin, M. Krasavin, *Tetrahedron Lett.* **2018**, *59*, 1948–1951.
- [13] R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu, L. Liu, *Angew. Chem. Int. Ed.* **2009**, *48*, 9350–9354.
- [14] a) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015**, *115*, 931–941; b) L. Keyes, J. A. Love, *Aromatic C–F Activation: Converting Fluoroarenes to Useful Building Blocks*, in *C–H and C–X Bond Functionalization*, (Ed.: X. Ribas), Royal Society of Chemistry, Cambridge, U.K., **2013**.
- [15] a) M. He, J.-F. Soule, H. Doucet, *ChemCatChem* **2014**, *6*, 1824–1859; b) F. Chem, Q.-Q. Min, X. Zhang, *J. Org. Chem.* **2012**, *77*, 2992–2998; c) A. Tlahuext-Aca, S. Y. Lee, S. Sakamoto, J. F. Hartwig, *ACS Catal.* **2021**, *11*, 1430–1434; d) Y. P. Budiman, R. N. Perutz, P. Steel, U. Radius, T. B. Marder, *Chem. Rev.* **2024**, *124*, DOI: 10.1021/acs.chemrev.3c00793.
- [16] a) O. Eisenstein, J. Milani, R. N. Perutz, *Chem. Rev.* **2017**, *117*, 8710–8753; b) R. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res.* **2011**, *44*, 333–348; c) S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153–164.
- [17] T. Pabst, J. V. Obligacion, E. Rochette, I. Pappas, P. J. Chirik, *J. Am. Chem. Soc.* **2019**, *141*, 15378–15389.
- [18] a) D. Whitaker, J. Burés, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 8384–8387; b) G. Atvahan, T. F. N. Tanner, A. C. Whitwood, I. J. S. Fairlamb, R. N. Perutz, *Organometallics* **2022**, *41*, 3175–3184; c) G. M. H. Platt, P. M. Aguiar, G. Athavan, J. T. W. Bray, N. W. J. Scott, I. J. S. Fairlamb, R. N. Perutz, *Organometallics* **2023**, *42*, 2378–2394.
- [19] Z. Guo, J. Luu, V. Blair, G. B. Deacon, P. C. Junk, *Eur. J. Inorg. Chem.* **2019**, 1018–1029.
- [20] a) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; b) M. Lafrance, D. Shore, K. Fagnou, *Org. Lett.* **2006**, *8*, 5097–5100; c) Y. Shen, X.-X. Wu, S. Chen, Y. Xia, Y.-M. Liang, *Chem. Commun.* **2018**, *54*, 2256–2259; d) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129; e) J. Ponce-de-Leon, G. Marcos-Ayuso, J. A. Casares, P. Espinet, *Chem. Commun.* **2022**, *58*, 3146–3149; f) M. Simonetti, G. J. P. Perry, X. C. Camberio, F. Julia-Hernandez, J. N. Arokianathar, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 3596–3606; g) Z. Fu, Q. Xiong, W. Zhang, Z. Li, H. Cai, *Tetrahedron Lett.* **2015**, *56*, 123–126; h) T. D. Moseev, M. V. Varaksin, D. A. Gorlov, V. N. Charushin, O. N. Chupakhin, *Org. Biomol. Chem.* **2021**, *19*, 4429–4459; i) O. Y. Yuen, M. P. Leung, C. M. So, R. W.-Y. Sun, F. Y. Kwong, *J. Org. Chem.* **2018**, *83*, 9008–9017; j) F. Abdellaoui, H. B. Ammar, J.-F. Soulé, H. Doucet, *Catal. Commun.* **2015**, *71*, 13–16; k) O. Y. Yuen, M. Charoensak, C. M. So, C. Kuhakarn, F. Y. Kwong, *Chem. Asian J.* **2015**, *10*, 857–861; l) J. W. W. Chang, E. Y. Chia, C. L. L. Chai, J. Seayad, *Org. Biomol. Chem.* **2012**, *10*, 2289–2299; m) D. S. Lee, P. Y. Choy, C. M. So, J. Wang, C. P. Lau, F. Y. Kwong, *RSC Adv.* **2012**, *2*, 9179–9182; n) S. Fan, J. Han, X. Zhang, *Org. Lett.* **2011**, *13*, 4374–4377; o) S. Otsuka, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2015**, *21*, 14703–14707.
- [21] a) I. Ban, T. Sudo, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 3607–3609; b) Y. Wei, J. Kan, M. Wang, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 3346–3349; c) H. Li, J. Liu, C.-L. Sun, B.-J. Li, Z.-J. Shi, *Org. Lett.* **2011**, *13*, 276–27; d) X. Fang, Y. Huang, X. Chen, X. Lin, Z. Bai, K.-W. Huang, Y. Yuang, Z. Weng, *J. Fluorine Chem.* **2013**, *151*, 50–57; e) A. Dahiya, C. Fricke, F. Schoenebeck, *J. Am. Chem. Soc.* **2020**, *142*, 7754–7759; f) H. Fan, Y. Shang, W. Su, *Eur. J. Org. Chem.* **2014**, 3323–3327; g) T. Miao, L. Wang, *Adv. Synth. Catal.* **2014**, *356*, 429–436.
- [22] R. Diaz-Torres, S. Alvarez, *Dalton Trans.* **2011**, *40*, 10742–10750.
- [23] T. D. Quach, R. A. Batey, *Org. Lett.* **2003**, *5*, 4397–4400.
- [24] C. C. Tzschucke, J. M. Murphy, J. F. Hartwig, *Org. Lett.* **2007**, *9*, 761–764.
- [25] M. S. Gong, H. S. Lee, Y. M. Jeon, *J. Mater. Chem.* **2010**, *20*, 10735–10746.
- [26] a) T. Korenaga, T. Kosaki, R. Fukumura, T. Ema, T. Sakai, *Org. Lett.* **2005**, *7*, 4915–4917; b) Y. Nishihara, H. Onodera, K. Osakada, *Chem. Commun.* **2004**, 192–193; c) J. Uenishi, J. M. Beau, R. W. Armstrong, Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.
- [27] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
- [28] J. Louie, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599.
- [29] C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe, L. Ricard, *J. Am. Chem. Soc.* **2003**, *125*, 4212–4222.
- [30] M. Perez-Rodriguez, A. A. C. Braga, M. Garcia-Melchor, M. H. Perez-Temprano, J. A. Casares, G. Ujaque, A. R. de Lera, R. Alvarez, F. Maseras, P. Espinet, *J. Am. Chem. Soc.* **2009**, *131*, 3650–3657.
- [31] E. Gioria, J. del Pozo, J. M. Martínez-Ilarduya, P. Espinet, *Angew. Chem. Int. Ed.* **2016**, *55*, 13276–13280.
- [32] This is in line studies by Su *et al.* (see: ref 21b) who reported Pd(OAc)₂/Ag₂CO₃ mediated C–H arylation of polyfluoroarenes, with aryl-B(OH)₂ in the presence of external acids and bases. Their preliminary mechanistic studies suggested that Ar–B(OH)₂ transmetalation precedes Ar_F–H activation, but the alternative order could not be ruled out.
- [33] J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936–1947.