Defluorinative Functionalization of Pd (II) Fluoroalkyl Complexes

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Supporting Information Placeholder

ABSTRACT: When subjected to arylboranes, anionic trifluoromethyl and difluorobenzyl palladium(II) complexes undergo fluoride abstraction followed by 1,1-migratory insertion. The resulting intermediate fluoroalkyl species can be induced to undergo a subsequent transmetalation and reductive elimination from either an *in situ* formed fluoroboronate ($FB(Ar_3)^-$) or an exogenous boronic acid/ester ($ArB(OR)_2$) and nucleophilic activator, representing a net defluorinative arylation reaction. The latter method enabled a structurally diverse substrate scope to be prepared in one pot from a representative aryl palladium-CF_3 complex either discretely isolated or generated in situ from $Pd(PPh_3)_4$ and other commercially available reagents.

INTRODUCTION

Fluoroalkylated compounds are rapidly gaining prominence in materials science,[1] agrochemistry,[2] and medicinal chemistry.[3] For instance, nearly 30-40% of new FDA approved drugs in 2018[4] and 2019[5-6] contain an organofluorine unit, compared to 17% during the 2000's.[7] When compared to non-fluorinated analogues, bioactive organic compounds that contain a –C-F instead of a –C-H bond often have distinct chemical and biological properties, including higher metabolic stability and lipophilicity *in vivo*.[3] Consequently, the development of strategies to both install and further diversify organofluorinated compounds[8-9] is at the forefront of efforts within the synthetic community.[10-17] Routes to install the $-CF_3$ group are most numerous, likely due to the availability of Me_3SiCF_3 as a reagent.[18] In contrast, significantly fewer routes are known to install other fluoroalkyl groups, such as $R–CF_2–R$ and R–CFH–R.[19-26] Transition metal-based cross-coupling has become a widely used strategy for assembling and reductively eliminating fluorinated alkyl groups and a coupling partner in order to broadly access organofluorinated compounds.[26-28]

Heterolytic C–F defluorination and subsequent attack by nucleophiles[29-30] is an attractive approach for building new carbon-carbon[31-33] and carbon-heteroatom bonds.[34-37] However, defluorination methods require specialized substrates that stabilize the resulting carbocation and/or a potent Lewis acid that can *poly*defluorinate $-CF_n$ groups.[38] Metal fluorocarbenes, accessible from defluorination of metal fluoroalkyl complexes,[39-40] offer an attractive alternative to carbocation intermediates because they are similarly susceptible to nucleophilic attack, can have increased stability, and allow preassembly of nucleophilic partners on a metal precursor. These features can be used to promote selective functionalization of $-CF_2R$ groups.

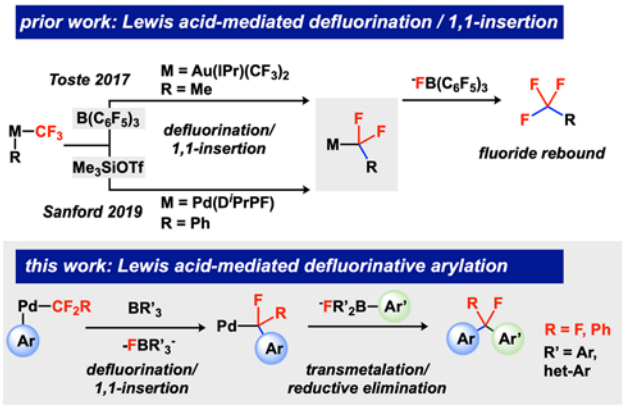


Figure 1. Prior work demonstrating defluorination induced 1,1-insertion (top), and Lewis acid-mediated defluorinative arylation (bottom). In the Sanford example, CsF was added 30 min. after Me_3SiOTf.[41]

Defluorination of metal fluoroalkyl complexes can be promoted by introducing a Lewis acid. Acid-induced defluorination typically requires fluorophilic reagents such as boranes (BR_3) and silylium cations (SiR_3^+), which abstract a fluoride (F^-) from a metal fluoroalkyl.[39-44] The intermediate metal fluorocarbenes that form can be susceptible to either nucleophilic attack, or alternatively, can undergo 1,1 insertions. Recent examples by Baker[42] as well as Fürstner[45] showed that a $M=CF_2$ can react with pyridine or even weak nucleophiles to form $M\text{-}CF_2X$ adducts (X = pyridine, OTf, NTf_2).

Complementary to exogenous nucleophilic addition to M=CF_2 adducts, Sanford[41] and Toste[46] reported separate examples where an intermediate (R)M=CF_2, formed by defluorination of a (R)M-CF_3, underwent 1,1 insertion into a metal aryl or alkyl (Figure 1). In the latter case, the product reacted with exogenous F^-, which was used as a strategy to install ^{18}F for radiolabeling.[46] Alternatively, three coordinate Pd-CF_3 complexes have been shown to undergo thermal defluorination via unimolecular α-fluoride elimination en route to Ar/CF_3 reductive elimination. However, under stoichiometric reaction conditions, the proposed Pd(CF_2)(F)(Ph)(PR_3) intermediate was found to transmetalate with another equivalent of a Pd(Ph) complex to afford diphenyldifluoromethane in a competitive, but low yielding (< 22%) pathway.[47] Importantly, formation the difluorodiphenyl methane side product provides precedent for defluorination/transmetalation strategies at palladium to prepare difluorobenyl linkages.

We hypothesized that, rather than reintroducing F^- as a nucleophile, Pd fluoroalkyl complexes are uniquely situated to react with a variety of nucleophilic aryl reagents. We targeted a series of boron based reagents capable of promoting a defluorination reaction coupled with transmetalation of a nucleophile to enable a distinct set of functionalization reactions accessible from simple metal fluoroalkyl precursors. Our group recently disclosed a Lewis acid/base pair strategy to access anionic –CF_2Ar synthons, enabling facile diversification from simple H–CF_2Ar precursors.[24] Stoichiometric Pd-cross-coupling of the –CF_2Ar reagents provided difluorodiarylmethane products, likely through transmetalation to Pd(II), followed by reductive elimination. These reactions provide an entry point into species that may be functionalized through a net defluorinative arylation reaction.

RESULTS AND DISCUSSION

To prepare fluoroalkylated complexes amenable to rapid diversification, we targeted the isolation of (PPh_3)$_n$(Ar)Pd-CF_2Ph; a likely intermediate during the cross-coupling reaction sequence. Introduction of the –CF_2Ph synthon, [K(18-crown-6)][PhCF_2-$B_3N_3Me_6$], to (PPh_3)$_2$(3,5-(CF_3)$_2$Ph)PdBr in tetrahydrofuran (THF), at 23 °C for 22 h, suppressed reductive elimination, enabling access to the transmetalated adduct, (PPh_3)(3,5-(CF_3)$_2$Ph)Pd(CF_2Ph)Br^- (**1a**), as an isolable product in 85% yield (Figure 2A).

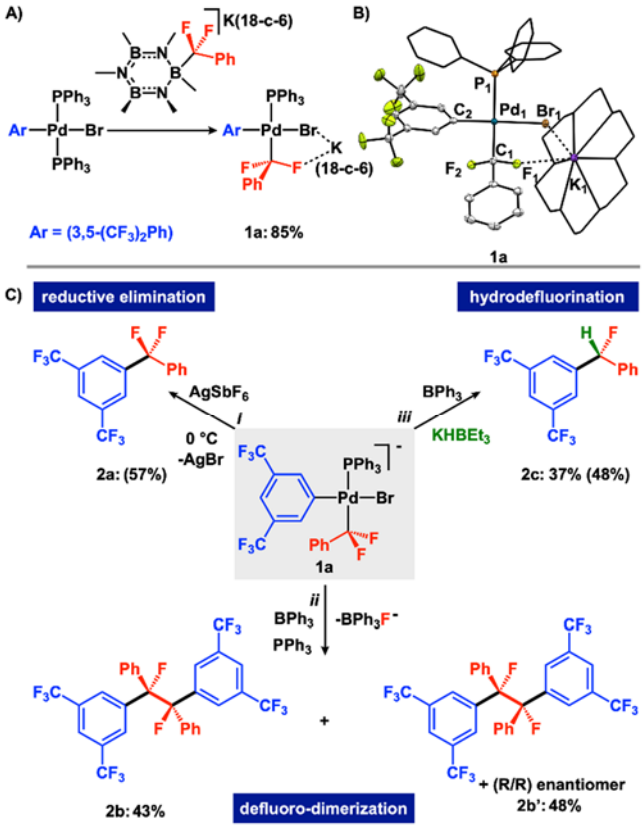


Figure 2. A) Preparation of **1a**. B) X-ray structure of **1a**, Pd_1–C_1 distance 2.0735(19) Å, ellipsoids shown at 50%, H-atoms removed and non-essential aryl rings wireframed for clarity. C) Diversification of **1a**: i) 1 eq. $AgSbF_6$ at 0 °C (1 h) affords **2a**, ii) 1 eq. BPh_3 (5 min), followed by of 1 eq. PPh_3 (17 h) at RT affords **2b/2b'** and iii) 1 eq. BPh_3 (15 min), followed by 1 eq. $KHBEt_3$ at RT for 17 h affords **2c**.

Crystals suitable for an X-ray diffraction experiment were obtained from diethyl ether, and the structure revealed an anionic [LX_3Pd]$^-$ complex (Figure 2B). This formulation contrasts with the common L_2X_2Pd products of similar reactions with non-fluorinated alkyl nucleophiles.[48] Unlike transmetalation of an aryl group to palladium(II)aryl-bromide complexes, PPh_3 is displaced as opposed to bromide, forming an anionic complex with potassium 18-crown-6 as the counter cation.[48] **1a** exhibits a Pd_1-C_1 distance of 2.0735(19) Å, which is similar to the Pd-C distance of the anionic Pd complex, Pd(CF_3)$_3PPh_3^-$ (2.062(5) Å).[49-50] The structure indicates an *associated* potassium counter ion interacting with both a fluorine atom of CF_2Ph (K1-F1 = 2.8310(12) Å), as well as Br (K1-Br1 = 3.2286(4) Å).

Analysis of the ^{19}F NMR spectrum in C_6D_6 of **1a** revealed two resonances: a singlet at -62.16 ppm (6F) (from 3,5-(C*F*$_3$)$_2$Ph) and a doublet at -69.08 ppm (2F) with a coupling constant of 39.3 Hz, consistent with the formation of a Pd-*CF*$_2$Ph.[41] The ^{31}P NMR spectrum contained a triplet at 18.75 ppm, also exhibiting a coupling constant of 39.3 Hz, which we assign as $^3J_{P\text{-}F}$.[41] Finally, the ^1H NMR spectrum revealed aromatic resonances for the –CF_2Ph moiety (5H) that integrate 1:1 with respect to one PPh_3 molecule (15H). Importantly, the ^{19}F NMR splitting pattern corresponds to a single equivalent of PPh_3 for each CF_2Ph unit, consistent with the uncommon anionic formulation from the solid-state structural analysis.

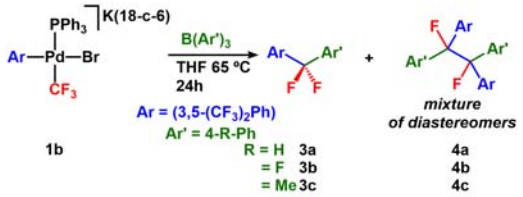
We investigated subsequent reactivity of **1a** with a series of Lewis acidic reagents in order to assess possible fluoroalkyl diversification routes through this single precursor. Subjecting **1a** to 50 °C for 45 h induced C(sp^2)-C(sp^3) reductive elimination to form [$PhCF_2$(3,5-$(CF_3)_2$Ph)] (**2a**) in 71% yield, as assessed by ^{19}F NMR spectroscopy. Addition of 1 equiv. $AgSbF_6$ had a dramatic effect: **2a** was afforded in 57% yield after just 1 hour at 0 °C (Figure 2C, left). Another strategy to diversify **1a** is *via* the α-fluorine-carbon bond, a motif that has been shown to be reactive toward strong fluorophiles in late transition metals.[41,46]

In contrast to the ionic Lewis acid (Ag^+), we observed distinct product profiles when using a borane Lewis acid. Subjecting **1a** to 1 equiv. BPh_3 at 25 °C in THF for 5 minutes followed by 1 equiv PPh_3 for 17 h resulted in a color change from yellow to red. Analyses by GCMS (m/2 = 321) and ^{19}F NMR spectroscopy (-148.87 ppm and -148.57) were consistent with formation of isomers of (3,5-$(CF_3)_2$Ph(CFPh))$_2$, formulated as **2b** and **2b'** (Figure 2C bottom).[51] The loss of fluorine in the products, relative the starting material, implies a defluorinated intermediate during the reaction. A plausible pathway to these products involves borane-mediated defluorination from **1a**, followed by 1,1-migratory insertion of the aryl group into the resulting fluorocarbene to form a Pd-fluorodibenzyl species that undergoes C(sp^3)-C(sp^3) coupling (see S24). These products are fluorinated versions of (CHArAr')$_2$, which have been reported as sources of carbon radicals following *C-C* bond homolysis and capable of forming new C-O bonds (e.g. Ph_2CHOMe from $(HCPh_2)_2$ and MeOH).[52] By extension, the formation of **2b/2b'** from **1a** provides an entry point to (CFArAr')$_2$ products, enabling access to compounds that can potentially be further diversified into medicinally relevant fluorinated ethers.[53]

We hypothesized that, in addition to undergoing homocoupling to afford **2b/2b'**, the defluorinated intermediate might be intercepted with another nucleophile, such as H^-, and undergo a subsequent reductive elimination. In support, we found that after allowing a mixture of **1a**/1 equiv. BPh_3 to react for 15 minutes at 25 °C, addition of 1 equiv. $KHBEt_3$ resulted in a net hydrodefluorination reaction to form ((3,5-$(CF_3)_2$Ph)(Ph)CHF), **2c**, in 48% (37% isolated) yield (Figure 2C, right). This reaction represents a simple strategy to access monofluoromethylene arenes, which are pharmaceutical targets[54] and are typically accessed through alternative reagents and/or precursors.[19,20,23,55]

To evaluate if the borane-induced defluorinative functionalization reaction is general, we prepared the Pd-CF_3 complex, (PPh_3)(3,5-$(CF_3)_2$Ph)Pd(CF_3)Br^-, **1b**, through an analogous route to **1a**. **1b** exhibits a similar solution structure to **1a**, as assessed by heteronuclear NMR spectroscopy (see SI). The X-ray crystal structure of **1b** confirmed the structural similarities, with a Pd_1-C_1 bond distance of 2.068(9) Å in addition to a K_1-F_1 distance of 2.735(5) Å for the associated K^+ counterion. Given these structural similarities, we hypothesized that **1b** might exhibit analogous reactivity to **1a**.

Upon addition of **1b** to 1 equiv. BPh_3 in THF for 24 h at 65 °C we observed difluorodiarylmethane (**3a**) and difluorotetraarylethane (**4a**) products (Figure 3). These products are either singly- (**3**) or doubly- (**4**) defluorinated and both contain an additional –Ph group. To assess the origin of the –Ph group, we repeated the experiment above with a 4-substituted triphenyl borane (B(*4*-R-Ph)$_3$) where the Ph groups on B were replaced with *4*-F-Ph. Similar to the product observed using BPh_3, we found *4*-F-Ph transfer to form **3b** and **4b**, and we propose that both B(*4*-R-Ph)$_3$ reagents (R= H and F) are competent for defluorination and arylation. These results illustrate a tandem sequence for select B(*4*-R-Ph)$_3$ reagents that is distinct from reported reactions using $B(C_6F_5)_3$:[46] instead of F^- rebound, we propose that the FB(*4*-R-Ph)$_3^-$ species generated after F^- abstraction is competent for transmetalation to palladium.



Entry	Conditions	Yield 3	Yield 4	Ratio 4/3
1	R=H	17 ± 4	28 ± 7	1.6
2	R=F	3 ± 2	41 ± 16	12
3	R=Me	12 ± 2	17 ± 2	1.4
4	2 eq. BAr'$_3$, R=F	0.5 ± 0.5	47 ± 6	98
5	0.75 eq. BAr'$_3$, R=F, 2 eq. PPh_3,	35 ± 9	10 ± 3	0.3

Figure 3. Influence of (B(*4*-R-Ph)$_3$) identity on the formation of **3** and **4** from **1b**. BR_3 and **1b** were allowed to react at 65 °C for 24 h. *Yields determined by ^{19}F NMR integration with respect to C_6H_5F or $C_6H_5OCF_3$ internal standard. Entries 1-3 = 0.008 M, entries 4 and 5 = 0.01 M.

In support of this hypothesis, when the electronic environment surrounding the borane was varied, the ratio of **3** to **4** was affected. After 24 hours at 65 °C, we observed differing selectivities of **4** to **3** (B(*4*-F-Ph)$_3$ = 12; BPh_3 = 1.6; B(*4*-Me-Ph)$_3$ = 1.4). Our rationale for this difference in selectivity is an electronic interplay between fluorophilicity of B(*4*-R-Ph)$_3$ and nucleophilicity of the *–Ar* group within FB(*4*-R-Ph)$_3^-$. We hypothesized that the double fluoride abstraction reaction could be favored by increasing the stoichiometry of B(*4*-R-Ph)$_3$. In support, the reaction of **1b** with 2 equiv. of BPh_3 exhibited 98:1 selectivity for **4b** (entry 4; 48 % yield). Conversely, substoichiometric borane (0.75 equiv.) and 2 equiv. PPh_3 *switched* the selectivity for the formation of **3b** 0.3 (entry 5), consistent with favored reductive elimination from the singly defluorinated product. In contrast to these results, when $B(C_6F_5)_3$ was used in place of B(*4*-R-Ph)$_3$, we observed no transfer of $–C_6F_5$ after 16 h at 65 °C. Although fluorinated triaryl boron Lewis acids ($B(C_6F_5)_3$) have been shown to defluorinate M-CF_3 units,[42,45-46] in the current system, the BAr'$_3$ unit promotes a tandem reactivity sequence not previously reported.

We hypothesized that, although $B(C_6F_5)_3$ would be capable of abstracting a fluoride from **1b** and undergoing subsequent 1,1-migratory insertion, the resulting transmetalation from the fluoroborate ($FB(C_6F_5)_3^-$) would be difficult compared to B(*4*-R-Ph)$_3$.[56-59] The combined fluoride affinity and difficult transmetalation of the $–C_6F_5$ group made $B(C_6F_5)_3$ an ideal reagent to investigate the proposed defluorination/1,1-migratory insertion intermediates (Figure 4). We targeted the product of 1,1-migratory insertion by stirring **1b** with $B(C_6F_5)_3$ for 15 min.; however, the resulting complex decomposed during workup, preventing isolation. To arrest decomposition

of the proposed coordinatively-unsaturated intermediate, we introduced 1 equivalent of PPh_3 after 5 min. of stirring **1b** with $B(C_6F_5)_3$. ^{31}P and ^{19}F NMR spectra exhibited triplet resonances at 30.22 ppm ($J_{P\text{-}F}$ = 42.0 Hz) and -45.36 ppm ($J_{P\text{-}F}$ = 42.2 Hz) respectively, which are consistent with *trans*- phosphines that are *cis*- to a difluoromethyl aryl (–CF_2Ar) ligand, and the structure *trans*-[$Pd(PPh_3)_2(CF_2Ar)Br$] (**1c**). The –CF_2Ar fluorine resonance is downfield of the corresponding resonance in **1a** (-69.08 ppm), and consistent with a *cis*, rather than *trans* orientation of the –CF_2Ar with respect to the phosphine ligand.[49] Similar species $(PEt_3)Pd(II)CF_3Br$ and $(PEt_3)Pd(II)(C_6F_5)Br$ are known to be stable at 25 °C.[60]

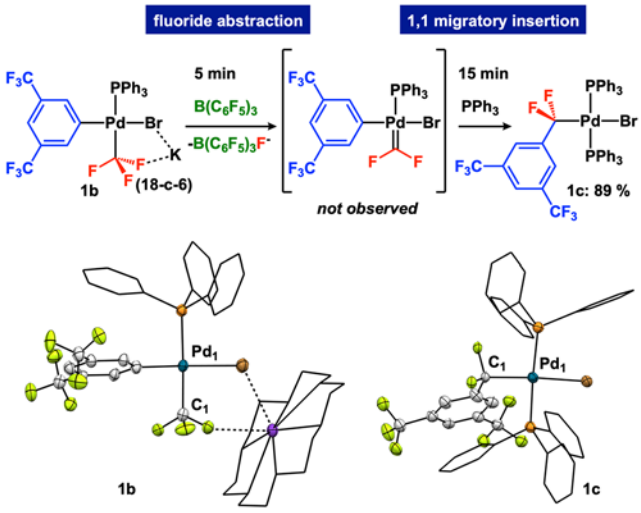


Figure 4. Preparation and X-ray structure of **1c**. Elongation of Pd_1–C_1 observed **1b**: 2.068(9) Å vs. **1c**: 2.176(8) Å, ellipsoids shown at 30%), H-atoms removed and non-essential aryl rings wireframed for clarity.

Isolation of **1c** proceeded in 89 % yield and the structure was confirmed by X-ray crystallography. Bond distances in the X-ray crystal structure featured an elongation of the Pd_1-C_1 bond when comparing **1c** to **1a** and **1b** (2.176(8) Å, 2.0735(19) Å and 2.068(9) Å respectively**)**. This distinction is reflective of the difference between the charges of the complexes [neutral vs. (-1)]; similar charge-dependent Pd-C bond lengths have been reported for Pd–CF_3 complexes.[49] Importantly, isolation of fluoride abstraction product **1c** supports formation of a palladium difluorocarbene intermediate and 1,1-migratory insertion upon addition of Lewis acids.

To understand relative trends that govern the formation of fluorocarbene intermediates by fluoride abstraction, we employed a computational assessment of borane Lewis acidity *via* Fluoride Ion Affinity (FIA).[61] The FIA analysis, performed at the B3LYP/6-31G(d,p)//6-311++G(d,2p) M(SDD) level of theory, was used to establish the relative fluorophilicity of Lewis acids required to initiate the reaction (Figure 5). Within a representative set of borane Lewis acids (BF_3, BAr_3, $ArB(OH)_2$), the FIA spans ~40 kcal/mol, illustrating a substantial change in driving force that is possible by changing the identity of the groups surrounding boron.

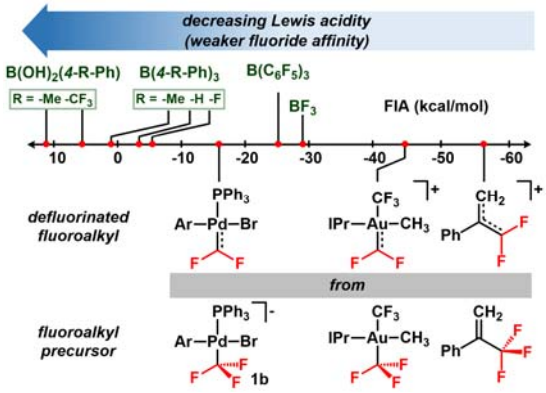


Figure 5. Fluoride ion affinity (FIA) scale for Lewis acids and defluorinated fluoroalkyl products. FIA reported as the ΔG of fluoride abstraction from CF_3O^- to form CF_2O (i.e. CF_2O FIA = 0 kcal/mol).

To provide insight into the relative abilities of Lewis acids to abstract fluoride from either M-CF_2R moieties, or organofluorine compounds, we calculated FIA for the defluorinated products (i.e. fluorocarbene intermediates) as competitive Lewis acids. Relative to fluoride abstraction from $(IPr)(Me)Au(CF_3)_2$ (shown to undergo F^- abstraction by $B(C_6F_5)_3$ with F^- rebound),[46] we found that abstraction from Pd-CF_3 (**1b**) was 31 kcal/mol easier. The large FIA energy difference between Au and Pd difluorocarbenes may be a consequence of the relative charges of the formed species (cationic vs neutral, respectively). Importantly, the acidity requirement of organometallic fluoroalkyl groups is *lower* than organic -CF_3 groups, which typically require potent Lewis acids for fluoride abstraction.[38,62-63] For example, fluoride abstraction from phenyl-trifluoropropene[31] was found to be 41 kcal/mol more difficult than from **1b**, illustrating the intrinsic stabilization provided by using fluoroalkyl metal precursors, rather than metal-free fluoroalkyls. Overall, the mild defluorination requirements from anionic palladium fluoralkyl complexes are due to a combination of charge effects and metal-stabilization.

While BAr_3 compounds are attractive single use reagents that can both abstract F^- and deliver an –Ar group, their use for these purposes in synthetic methodology is limited.[64-65] In contrast, aryl boronic acids and esters are commercially available and widely used but are only weakly Lewis acidic (*vide supra*).[66] As shown above, the FIAs between select BAr_3 reagents that perform F^- abstraction are within 5 kcal/mol of the corresponding $ArB(OH)_2$ reagents. Thus, we hypothesized that $ArB(OH)_2$ compounds may be sufficiently fluorophilic to promote fluoride abstraction from **1b**. To assess these reactions, **1b** was allowed to react with 1 equiv of a given Lewis acid at room temperature for 1 hour, while monitoring by ^{19}F NMR spectroscopy. Consumption of the Pd-CF_3 resonance was dependent on the Lewis acidity of the additive: $B(C_6F_5)_3$ and $B(4\text{-F-Ph})_3$ (100%), $B(4\text{-Me-Ph})_3$ (28%), $(HO)_2B(4\text{-}CF_3\text{-Ph})$ (29%), and $(HO)_2B(4\text{-Me-Ph})$ (6%).[67] Although fluoride abstraction is achievable using $(HO)_2B(4\text{-Me-Ph})$, attempts to promote a defluorinative arylation of **1b** with 2 equivalents of $(HO)_2B(4\text{-Me-Ph})$ afforded $(3,5\text{-}(CF_3)_2Ph)CF_2(4\text{-Me-Ph})$ in low yields (21 %).

We hypothesized that the two elementary steps (defluorination and –Ar transmetalation) might be separated using a pair of commercially available reagents: (1) a borane that abstracts F^- but does *not* transmetalate –Ar, and (2) a

boronic acid/ester with a nucleophilic activator. $B(C_6F_5)_3$ met the criteria for (1) because complete F^- abstraction occurs within 5 min, with no incorporation of a $-C_6F_5$ group, even after 16 h at 65 °C. We identified reagent-compatibility as the crucial factor needed to develop a defluorinative arylation method using two different boron reagents. To mitigate the deleterious reactions (i.e. formation of $[X\text{–}B(C_6F_5)_3^-]$ or $[Ph_3P\text{–}B(C_6F_5)_3]$[68]; X=nucleophilic activator of Ar–$B(OR)_2$), $B(C_6F_5)_3$ and **1b** were allowed to react in THF for 5 minutes (> 95 % consumption of **1b**) prior to adding other reactants. Subsequent introduction of 1 eq. of $(HO)_2B$(*4*-CF_3-Ph) followed by the nucleophilic activator and heating to 80 °C for 16h afforded (3,5-(CF_3)-Ph)CF_2(*4*-CF_3-Ph) as the major product. Using 1 eq. of either $[NMe_4][F]$ or KO^{t}Bu as nucleophilic activators afforded (3,5-(CF_3)-Ph)CF_2(*4*-CF_3-Ph) in 12% and 41% yield respectively. However, using 2 equiv of $[NMe_4][F]$ improved yields to 44% while excess KO^{t}Bu reduced yields. Further optimization included addition of exogeneous PPh_3 and the use of dioxane as a solvent. The optimized protocol was to allow **1b** and $B(C_6F_5)_3$ to react for 5 min, followed by subsequent addition of 1 eq. PPh_3, then $(HO)_2B$(*4*-CF_3-Ph) and 2 eq. $[NMe_4][F]$ using dioxane as a solvent with stirring at 80 °C for 16 hours, which improved the yield to 84 %. This method was generalizable to a variety of pinacol boronic esters as well as boronic acids (Figure 6).[69]

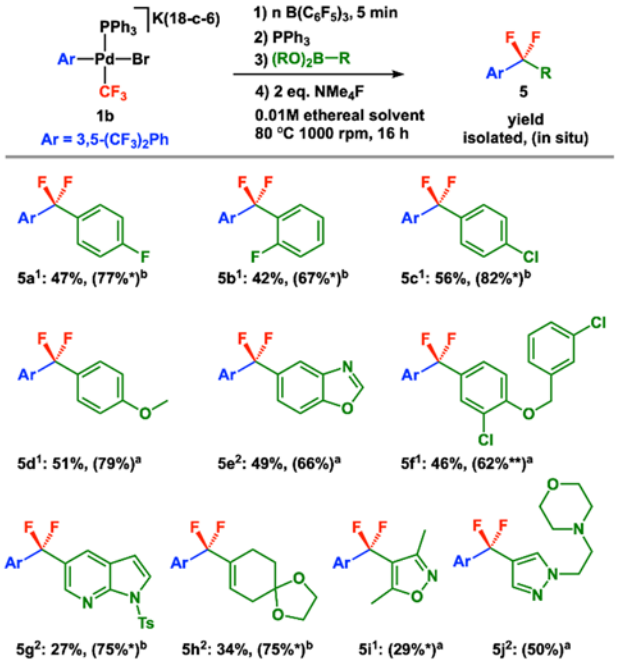


Figure 6. Scope in boronic acid[1]/pinacol ester[2]. **1b** mixed with $B(C_6F_5)_3$ for 5 min, then 1 eq. PPh_3 added, followed by 1 eq. $(RO)_2BR$ and 2 eq. NMe_4F at 23 °C. Reactions were stirred at 1000 rpm at 80 °C for 16 h. Isolated reported, and (*in situ*) yields determined by ^{19}F NMR integration against $PhOCF_3$ internal standard. All reactions refer to 0.1 mmol scale unless otherwise noted. [a]: 1 eq. $B(C_6F_5)_3$, dioxane solvent. [b]: 1.1 eq. $B(C_6F_5)_3$, THF solvent. *0.005 mmol scale. **94 °C.

The defluorinative arylation method tolerates simple electronic and steric variations of the aryl boronic acid. We obtained similar chemical yields for electron withdrawing (*4*-Cl-Ph; **5c** = 82%) and electron donating (*4*-OMe-Ph; **5d** = 79%) boronic acids, indicating minimal electronic influence. In contrast, o*rtho*-substitution afforded a slightly decreased yield; (*2*-F-Ph; **5b** = 67%), compared to *para* substitution (*4*-F-Ph; **5a** = 77%).

To examine the broad-scope compatibility of the defluorinative arylation method, we assessed select boronic acids and pinacol boronic esters containing medicinally relevant heterocycles and commonly used protecting groups. Halogenated benzyl phenyl ethers are known to be active inhibitors of bacterial phenylalanyl-tRNA synthetase.[70] Use of a related chloro-substituted benzyl phenyl ether substrate afforded **5f** in good yield 46%, (62% *in situ*). Benzoxazole is a pro-nucleophilic coupling partner in the recent synthesis of a PDE4 inhibitor,[71] where the 2-C–H bond is a prime target for further functionalization to form drug candidates.[71] Thus, methods that allow the incorporation of benzoxazole motifs with retention of the 2-position C-H bond provide an additional entry point for subsequent diversification. Importantly, we found that the defluorinative arylation method is indeed mild enough to tolerate the key C–H bond at the 2-position, forming **5e** in 49% yield (66% *in situ*). Fluorination of this class of molecules represents an attractive route to generating a library of polyfluorinated benzoxazoles.[72] Other 5-membered heterocycles including isoxazole and pyrazole were also tolerated, forming **5i** and **5j** in 29% and 50% chemical yield, respectively.[73] Although several heterocycles were tolerated, those containing N-H bonds required protection. Pyrrolo[2,3-b]-pyridines are attractive drug candidates since certain examples have been identified as Focal Adhesion Kinase (FAK) inhibitors, and have great potential in oncology.[74] After tosylation of 1-H pyrrolo pyridine, **5g** formed in high chemical yield (75%).

In addition to aryl boronic acids/esters, we found that vinyl boronic esters were also effective coupling partners. Substrate **5h** was formed in 75% chemical yield (34% isolated). This substrate contains an olefin as well as acetal-protected ketone, both of which are functional handles for further diversification. Overall, the defluorinative arylation of aryl, heteroaryl and vinyl boronic acids and pinacol esters represents an attractive strategy to easily prepare difluoromethyl aryl compounds containing pharmaceutically-relevant moieties.

To demonstrate the synthetic utility of the defluorinative arylation methodology, we developed a sequential 4 step, 1-pot procedure to convert aryl and heteroaryl halides directly into diaryl difluoromethane compounds. We evaluated this approach by preparing **5c** in 1-pot. Following oxidative addition of 3,5-bis(trifluoromethyl)-bromobenzene with $Pd(PPh_3)_4$ at 80 °C in THF, **1b** was formed after addition of 2 eq. $TMSCF_3$, KO^{t}Bu and 18-crown-6 in 46% chemical yield.[75] Although $[K(18\text{-crown-6})][CF_3\text{-}B_3N_3Me_6]$ was used in the reaction development (affording **1b** in 53% yield and 90% selectivity), we found that $TMSCF_3$ can also serve as a source of CF_3^-. $TMSCF_3$ afforded lower purity **1b** with additional side products (73% selectivity; see S68-69), although these were not deleterious to later steps. Subsequent defluorinative arylation in the same reaction vessel afforded **5c** in 38% chemical yield over all 4 steps (Figure 7). This result compares well to the yield of the defluorinative arylation reaction from isolated **1b** (Figure 6) and indicates minimal reduction in yield between using either a 1-pot method (82 % steps 3,4) or a discretely isolated Pd-CF_3 complex (82 %).[76]

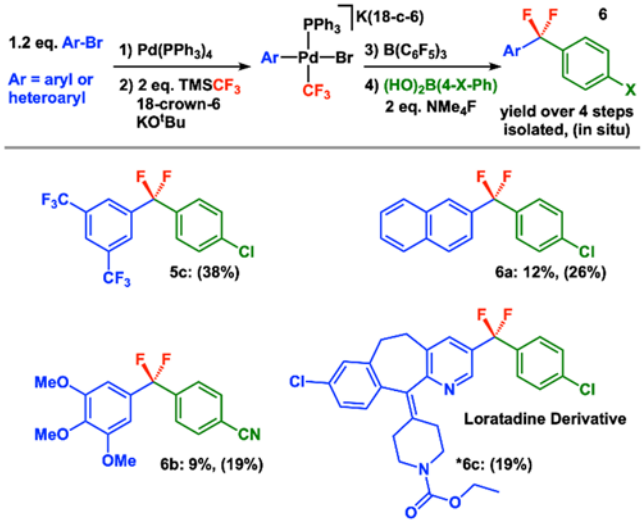


Figure 7. Scope in aryl bromide. 1) $Pd(PPh_3)_4$ was stirred with 1.2 eq. aryl bromide at 80 °C for 4 h in THF. 2) 2 eq. $TMSCF_3$ added with 18-crown-6 and KO^tBu and stirred at 23 °C for 2-3 h. 3) $B(C_6F_5)_3$ added at 23 °C for 5 min. 4) 1 eq. $(HO)_2B(4\text{-X-Ph})$ and 2 eq. NMe_4F added and stirred at 1000 rpm at 80 °C for 18 h. Isolated reported, and (*in situ*) yields determined by ^{19}F NMR integration against $PhOCF_3$ internal standard. All reactions refer to 0.15 mmol scale unless otherwise noted. *0.004 mmol scale with 2 eq. of $B(C_6F_5)_3$ used in step 3.

The 1-pot method for defluorinative arylation was applied directly to a series of (hetero)aryl bromides. 2-bromonaphthalene and the electron-rich 1,2,3-trimethoxy-5-bromobenzene were both competent for the reaction sequence, generating **6a** and **6b** in 26% and 19% chemical yield, respectively, across all 4-steps.[77] Finally, we showcased the compatibility of the defluorinative arylation strategy with pharmaceutically-relevant precursors by preparing **6c**, a difluoromethylarylated derivative of Loratadine in 19% chemical yield over 4-steps.

In contrast to the preparation of $ArCF_2Ar'$ compounds by Pd cross-coupling, which requires either bromodifluoromethyl- or difluoromethyl arenes, entry into these species via a $-CF_3$ unit is an attractive alternate route that obviates the requirement for $ArCF_2X$ reagents (X=H, Br).[3,24] While useful methods exist for coupling other RCF_2Br electrophiles that include vinyl groups[78] and heterocycles[79] we propose that the defluorinative arylation method may be of particular interest for high-throughput screening and drug discovery. Stoichiometric coupling reactions at Pd have been recently shown as a strategy to rapidly generate a library of targets for SAR studies.[80]

CONCLUSION

In conclusion, we have harnessed the unique reactivity of the C–F bond within anionic Pd fluoroalkyl complexes to construct molecules with new $-CF_2-$ linkages. Through analysis of Lewis acidity requirements for the defluorination reaction, we discovered a reaction sequence using mild boron-based Lewis acids that provides access to reactive Pd difluorocarbenes: species that undergo 1,1-migratory insertion into a Pd-aryl bond. The resulting Pd-CF_2Ar species can be induced to form Ar'-CF_2-Ar compounds by reacting with either $FBAr'_3^-$ (formed from defluorination with BAr'_3) or using widely available Ar'-$B(OR)_2$ reagents via transmetalation/reductive elimination. This tandem reaction sequence provides access to Ar'–CF_2Ar, heteroaryl–CF_2Ar, vinyl–CF_2Ar products that may exhibit improved pharmacokinetic properties.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic information for **1a**, **1b** and **1c** (CIF)

Synthetic details and characterization (PDF)

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Notes

The authors declare no competing financial interests.

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