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Fluorine Chemistry | Hot Paper

Formal Insertion of Alkenes Into C(sp^3)–F Bonds Mediated by Fluorine-Hydrogen Bonding

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Abstract: C–F Insertion reactions represent an attractive approach to prepare valuable fluorinated compounds. The high strength of C–F bonds and the low reactivity of the fluoride released upon C–F bond cleavage, however, mean that examples of such processes are extremely scarce in the literature. Here we report a reaction system that overcomes these challenges using hydrogen bond donors that both activate C–F bonds and allow for downstream reactions with fluoride. In the presence of hexafluoroisopropanol, benzyl and propargyl fluorides undergo efficient formal C–F bond insertion across α-fluorinated styrenes. This process, which does not require any additional fluorinating reagent, occurs under mild conditions and delivers products featuring the *gem*-difluoro motif, which is attracting increasing interest in medicinal chemistry. Moreover, readily available organic bromides can be engaged directly in a one-pot process that avoids the isolation of organic fluorides.

Introduction

Fluorinated organic compounds play important roles in many areas with circa 25% of pharmaceuticals and more than half of agrochemicals introduced since 2000 featuring a fluorine substituent.[1] With only a handful of fluorine-containing building blocks available from nature, the vast majority of these compounds must be prepared in a laboratory. This is most often achieved via selective fluorination, where individual fluorine atoms or larger fluorine-containing groups are installed at a particular site on a non-fluorinated precursor.[2] Alternatively, partially fluorinated molecules can be prepared via C–F functionalization of poly-fluorinated starting materials.[3]

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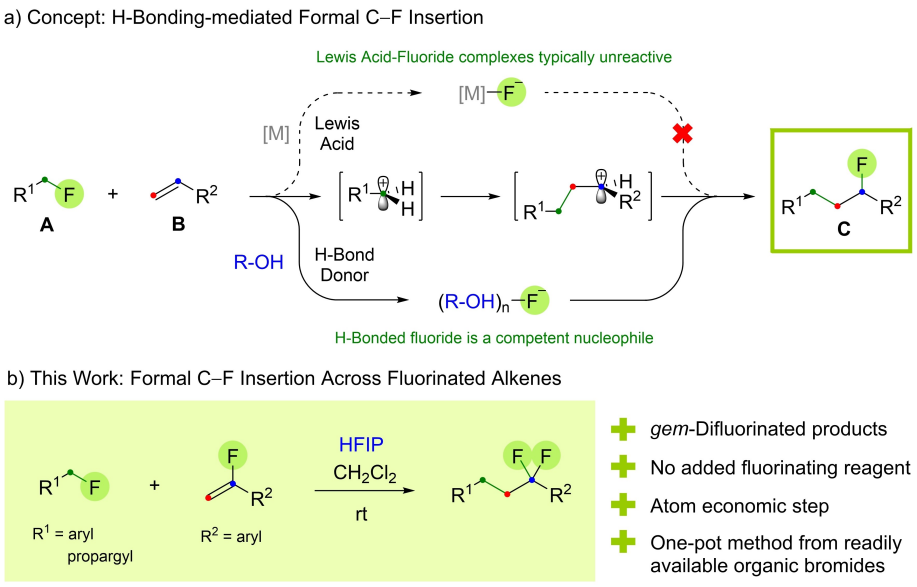
A third approach that combines aspects of both strategies is C–F insertion. A general Scheme for such a process between an alkyl fluoride **A** and an alkene **B** is shown in Scheme 1a (S_N1-type mechanism shown). The first stage of this reaction involves C–F activation of **A** with the alkyl and fluorine fragments then both adding across the alkene π-system. The overall result of this transformation is the conversion of one organofluorine compound (**A**) into another, ostensibly more complex, one (**C**) with complete atom economy and without requiring any exogenous fluorinating reagent. Insertion reactions of this type into C–X bonds of the other halogens are well-established processes in organic synthesis, yet despite the widespread utility of organofluorine compounds, reports of C–F insertion reactions are extremely scarce. In 2020, Tomisu and co-workers reported a phosphine-catalyzed insertion of electron-deficient alkynes into acid fluorides,[4] while a 2021 report by Nishimoto and Yasuda describes C–F insertion of secondary benzylic fluorides with diazoacetates.[5] Very recently, Zhang and co-workers reported a photocatalyzed formal C–F insertion across an alkene albeit with additional exogenous fluoride.[6] Despite these pioneering examples, the field remains in its infancy and there is a lack of general C–F insertion strategies.

The scarcity of C–F insertion reactions can be explained by the inherent difficulty of C–F activation. Fluorine forms the strongest single bond to carbon of any element and any cleavage process thus requires a large thermodynamic driving force. Most commonly, C–F bonds are cleaved in the presence of a metal ion or other Lewis acidic activator.[3] Although the formation of metal or semi-metal fluoride species as by-products compensates for the loss of the C–F bond in these processes, their stability generally means that the released fluoride is not available for incorporation into the product. With the aim of identifying an alternative C–F activation system that may be more suited to insertion reactions, we became interested in the reports of alkyl C–F functionalization mediated by hydrogen bond donors (HBDs).[7] Pioneered by the Paquin group, a series of reports have demonstrated that simple alcohols and water are capable of facilitating S_N2 substitution reactions of activated alkyl fluorides, while stronger HBDs such as hexafluoroisopropanol (HFIP) can even initiate S_N1-like reactivity.[8] Rather than being sequestered in a metal or semi-metal complex, the released fluoride ion in these processes is instead stabilized through strong hydrogen bonding interactions. Recent work has shown that such complexes are remarkably competent nucleophiles and could potentially react further as part of an overall C–F



Scheme 1. Formal C–F Insertion across alkenes mediated by fluorine-specific hydrogen bonding.

insertion process.[9] Here, we report the realization of this concept in a hydrogen bonding-mediated C–F insertion reaction between activated alkyl fluorides and fluorinated alkenes (Scheme 1b).

Results and Discussion

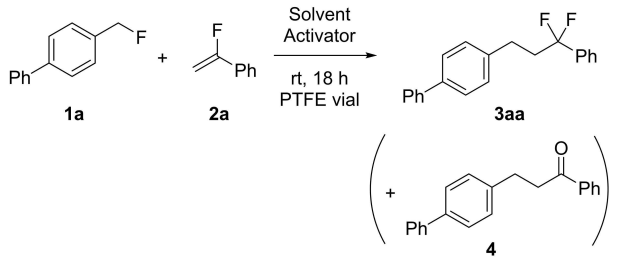
C–F Insertion into Benzyl Fluorides 1

At the beginning of the study, we sought to identify a suitable combination of substrates. The benzyl fluoride **1a** was selected as such compounds have been previously shown by Paquin to undergo S_N1-type substitution with strong HBDs.[8] As an alkene coupling partner, we selected *α*-fluorostyrene **2a**. C–F insertion of fluorinated alkenes into an alkyl fluoride would deliver products featuring a *gem*-difluoro (–CF_2–) motif. This moiety can serve as a bioisostere of ethereal oxygen atoms and is found in several pharmaceutical and agrochemical compounds.[1,10] C–F Insertion across an *α*-fluorinated alkene also provides some practical advantages. The electron withdrawing influence of the neighboring fluorine means that *gem*-difluoro groups are markedly poorer hydrogen bond acceptors than their monofluorinated counterparts, while the C–F bonds themselves are stronger.[11] This should allow for a selective reaction with C–F activation of the product being significantly more challenging than activation of the starting material. Moreover, the preference of fluorine atoms for bonding to sp^3-hybridized carbon atoms over sp^2-hybridized centers could serve as a driving force for selective nucleophilic trapping by fluoride over any potential competitive elimination.[11]

As a preliminary experiment, **1a** was reacted with 2 equiv. of **2a** in a 9:1 mixture of CH_2Cl_2 and HFIP (0.1 M) in a PTFE vial. After 18 h at rt, ^{19}F NMR analysis of the crude reaction mixture indicated the complete consumption of **1a** with the formation of a new triplet signal at −96.1 ppm (in $CDCl_3$). This peak corresponds to the *gem*-difluorinated product **3aa** with ^1H NMR indicating a yield of 17 % (Table 1, entry 1). The successful formation of **3aa** validates our proposed C–F insertion concept with a control reaction conducted in pure CH_2Cl_2 confirming the key role of HFIP as an HBD (entry 2). An optimization study was then carried out with the aim of maximizing the yield of **3aa**.[12] To our delight, a survey of different CH_2Cl_2:HFIP combinations led to a significant improvement in the reaction efficiency with a ratio of 7:3 delivering **3aa** in 77 % NMR yield (entries 3–5). Replacing CH_2Cl_2 with MeCN or toluene as the co-solvent, however, resulted in lower efficiency (entries 6,7).

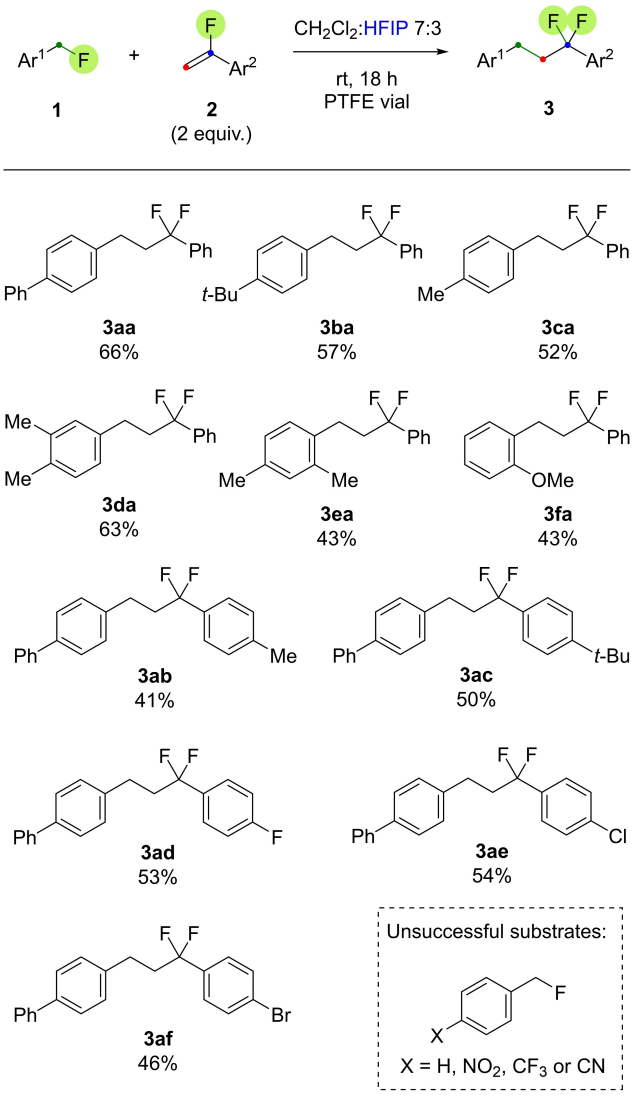
The nature of the reaction vessel had a significant impact on the process. Conducting the reaction between **1a** and **2a** in CH_2Cl_2:HFIP 7:3 in a glass Schlenk tube rather than a PTFE vial led to a notably more complex reaction mixture. While benzyl fluoride **1a** was completely consumed under these conditions, **3aa** was delivered in only 23 % NMR yield alongside ketone **4** in 27 % yield (entry 8).[13] The non-innocence of glass in hydrogen bonding-mediated substitution reactions of benzyl fluorides has been noted previously by Wang, Pedersen and co-workers.[14] In these reactions, C–F activation can be mediated by the alcohol, adventitious HF or highly Lewis acidic silicon fluoride species which result from etching of the glass surface by HF. According to our reaction design, silicon fluorides should be unsuited for C–F insertion due to the strength of the Si–F bonds and we tentatively propose that side-product **4** results from activation by such species in our system. This hypothesis is supported by the improvement in C–F insertion selectivity observed upon conducting the same reaction in a glass vessel in the presence of $NaHCO_3$ (2 equiv.), which likely sequesters any HF (entry 9). The success of the reaction in the presence of $NaHCO_3$ (45 % yield in a PTFE vial) also

Table 1: Optimization of the C–F insertion reaction between benzyl fluoride **1a** and α-fluorostyrene **2a**.



Entry	Solvent	Activator	Solvent:Activator (0.1 M)	Yield of 3 aa[a]
1	CH_2Cl_2	HFIP	9:1	17%
2	CH_2Cl_2	–	–	–
3	CH_2Cl_2	HFIP	1:9	41%
4	CH_2Cl_2	HFIP	5:5	66%
5	CH_2Cl_2	HFIP	7:3	77% (66%)
6	MeCN	HFIP	7:3	–
7	Toluene	HFIP	7:3	10%
8[b]	CH_2Cl_2	HFIP	7:3	23% **4**: 27%
9[b,c]	CH_2Cl_2	HFIP	7:3	35% **4**: 10%
10	CH_2Cl_2	H_2O	7:3	–
11	CH_2Cl_2	*i*PrOH	7:3	–
12	CH_2Cl_2	tBu_FOH	7:3	40%
13	CH_2Cl_2	$Sc(OTf)_3$ (2 equiv.)	–	– **4**: 30%
14	CH_2Cl_2	$B(C_6F_5)_3$ (2 equiv.)	–	– **4**: 40%
15	CH_2Cl_2	$BF_3{\cdot}OEt_2$ (2 equiv.)	–	45% **4**: 18%

Conditions: **1a** (0.1 mmol), **2a** (2 equiv.), Solvent: Activator (0.1 M), rt, 18 h in a PTFE vial. [a] ^{1}H NMR yield (internal standard: CH_2Br_2); isolated yields in parentheses. [b] In a glass Schlenk tube. [c] With $NaHCO_3$ (2 equiv.).



Scheme 2. Scope of the C–F insertion reaction with benzyl fluorides **1** and α-fluorostyrenes **2.** Conditions: **1** (0.3 mmol), **2** (2 equiv.), CH_2Cl_2: HFIP 7:3 (0.1 M), rt, 18 h in a PTFE vial. Isolated yields.

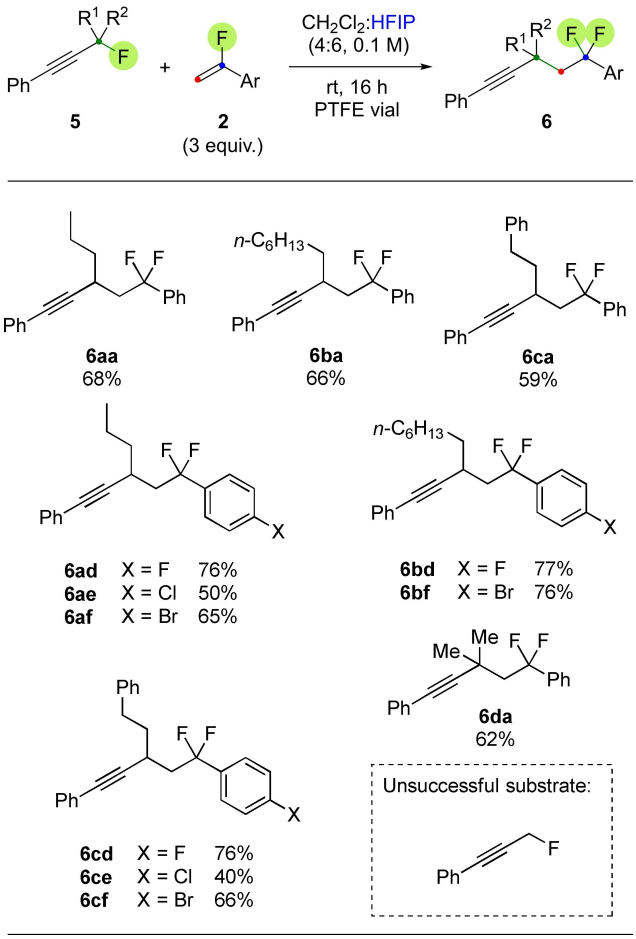
implies that adventitious HF is not the active HBD in our system and that HFIP itself is responsible for C–F bond cleavage.[15,16]

The C–F insertion process was also tested using a range of alcohols other than HFIP, however, only perfluoro-*tert*-butanol led to formation of **3aa**, albeit in a lower yield of 40% (entries 10–12). Finally, the reaction was performed using a selection of Lewis acids (2 equiv.) in place of HFIP. While C–F activation of **1a** was observed in all cases, most Lewis acids tested generated **3aa** in only low amounts with ketone **4** being a significant by-product (entries 13, 14).[13] With $BF_3{\cdot}OEt_2$, which has been previously employed for C–F insertion with diazoacetate substrates,[5] reasonable conversion to **3aa** (45%) was observed, albeit still with comparatively lower efficiency than HFIP (entry 15).[17,18]

With a set of optimized conditions in hand, the scope of the C–F insertion process was evaluated with a range of substrates **1** and **2** (Scheme 2). Alkyl groups could be incorporated at the *para*-position of the benzyl fluoride substrate with products **3ba** and **3ca** being afforded in 57% and 52% yields, respectively. Additional substitution at the *ortho*- and *meta*-positions was also tolerated while an electron-donating 2-methoxy group allowed for a successful reaction without a *para*-substituent (**3fa**, 43%). A selection of substituents was also tested on the α-fluorostyrene substrate. Alongside alkyl-substituted derivatives, halogenated styrenes could also be successfully employed in moderate yields. The chloro- and bromo-substituted products **3ad** and **3ae** are particularly noteworthy as they offer the opportunity for further functionalization via cross-coupling.[19] Unfortunately, benzyl fluoride itself or substrates with electron-withdrawing groups such as $-NO_2$, $-CF_3$ and –CN at the *para*-position led only to recovery of the starting material. The low reactivity of these substrates likely reflects the decreased stability of the intermediate benzyl cation formed in an S_N1-type process.[20]

C–F Insertion into Propargyl Fluorides 5

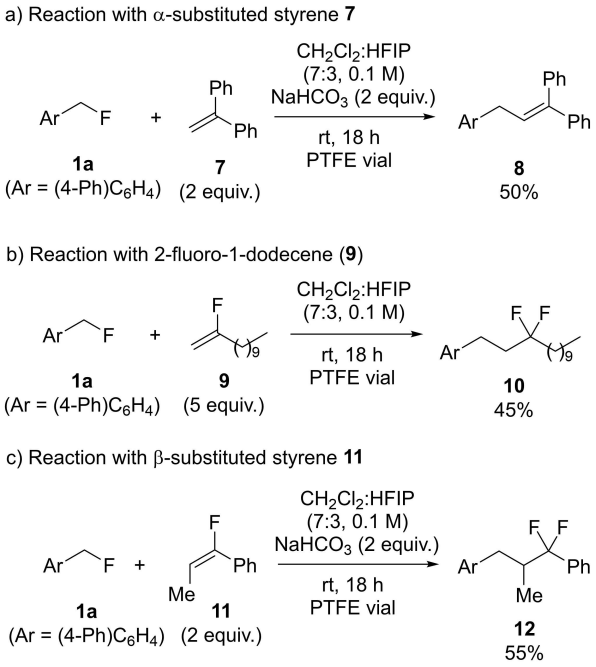
In addition to benzyl fluoride substrates, Paquin and co-workers have previously demonstrated that secondary propargyl fluorides can undergo S_N1-type nucleophilic substitution using HFIP.[8f] Subjecting compound **5a** to the standard conditions with **2a** led to the smooth formation of the desired product **6aa** in 47 % ^{1}H NMR yield. A short optimization study allowed for the improvement in NMR yield to 72 % upon increasing the equivalents of **2a** and changing the CH_2Cl_2:HFIP ratio to 5:5.[12] The results of a scope study on a range of propargyl fluorides **5** and α-fluorostyrenes **2** are shown in Scheme 3. For this study, a CH_2Cl_2:HFIP ratio of 4:6 was used as initial experiments with a 5:5 ratio often led to incomplete conversion of the propargyl fluoride. As with benzyl fluorides, halogen substituents were tolerated on the alkene coupling partner with products **6ad–af** being delivered in good yields up to 76 %. The reaction was also successful with various alkyl groups at the propargyl position, with *n*-propyl, *n*-heptyl and CH_2CH_2Ph-containing substrates each also reacting cleanly with halogenated α-fluorostyrenes **2d–f**. A tertiary propargyl fluoride was similarly suitable with product **6da**, which features *gem*-difluoro and *gem*-dimethyl groups, being isolated in 62 % yield. A primary propargylic fluoride, however, unfortunately led only to trace amounts of product.



Scheme 3. Scope of the C–F insertion reaction with propargyl fluorides **5** and α-fluorostyrenes **2**. Conditions: **5** (0.3 mmol), **2** (3 equiv.), CH_2Cl_2:HFIP 4:6 (0.1 M), rt, 16 h in a PTFE vial. Isolated yields.

Exploring Different Alkenes

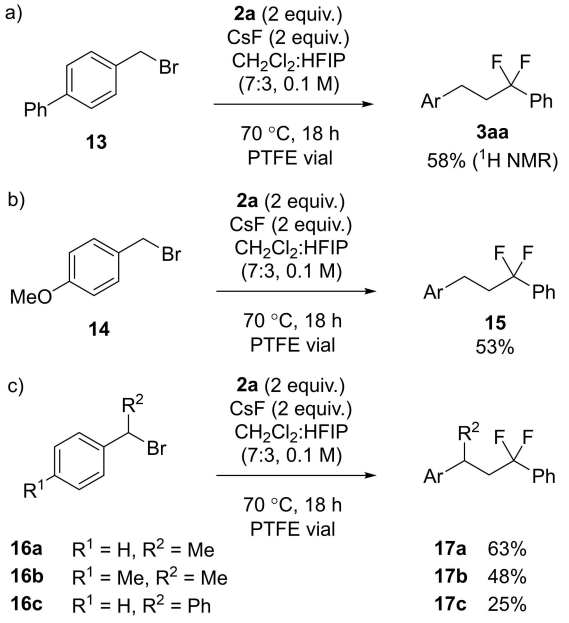
We also sought to investigate the scope of the process with different classes of alkene. Reacting **1a** with 1,1-diphenylethylene (**7**) under the standard conditions in CH_2Cl_2:HFIP 7:3 led to a complex reaction mixture; however, addition of $NaHCO_3$ (2 equiv.) resulted in clean formation of alkene **8** in 50 % yield (Scheme 4a). C–F Insertion across a non-fluorinated styrene provides a benzylic fluoride that is more activated towards C–F activation and **8** may result from onwards E1-type elimination of the C–F insertion product.[21] The importance of the fluorine substituent on the double bond led us to consider whether fluorinated aliphatic alkenes could also insert into C–F bonds under these conditions. To our delight, treating benzyl fluoride **1a** with 5 equivalents of 2-fluoro-1-dodecene (**9**) in CH_2Cl_2:HFIP 7:3 provided the corresponding *gem*-difluorinated product **10** in 45 % yield (Scheme 4b). Moreover, (*E*)-α-fluoro-**β**-methylstyrene (**11**) reacted successfully to afford product **12** in 55 %, suggesting **β**-substituted styrenes are also suitable coupling partners for C–F insertion (Scheme 4c).



Scheme 4. Reaction outcome using a) non-fluorinated styrene **7**, b) fluorinated aliphatic alkene **9** and c) (*E*)-α-fluoro-**β**-methylstyrene (**11**).

Direct One-Pot Reaction using Benzyl Bromides

Finally, in order to improve the practicality of the method and avoid the synthesis and sometimes troublesome isolation of benzyl fluorides **1**, we investigated the potential of a one-pot reaction directly from benzyl bromides. Using the standard reaction forming product **3aa** as a model process, 4-(bromomethyl)biphenyl (**13**) was reacted with CsF (2 equiv.) and α-fluorostyrene **2a** (2 equiv.) in CH_2Cl_2:HFIP 7:3 (0.1 M) at 70 °C in a sealed PTFE vial. After 18 h, we were delighted to observe the smooth formation of **3aa** in 58 % ^{1}H NMR yield (Scheme 5a). A control reaction without CsF delivered only starting material suggesting intermediate formation of the benzyl fluoride in situ is necessary and that the C–Br bond is not activated under these conditions.[22] Inspired by this result, we considered whether the stability and ready availability of benzyl bromides compared to the corresponding benzyl fluorides would allow for an increase in substrate scope. For example, in our hands, 4-methoxybenzyl fluoride proved challenging to synthesize and could not be successfully isolated and evaluated in the C–F insertion reaction. However, subjecting commercially available 4-methoxybenzyl bromide **14** to the one-pot conditions described above successfully delivered *gem*-difluoro compound **15** in 53 % isolated yield (Scheme 5b). Moreover, the benzyl bromides **16a–c** directly afforded products **17a–c** in 25–63 % isolated yields, demonstrating the suitability of synthetically challenging secondary benzyl fluorides as substrates for C–F insertion (Scheme 5c).



Scheme 5. One-pot reactions using a) 4-phenylbenzyl bromide **13**, b) 4-methoxybenzyl bromide **14** and c) secondary benzyl bromides **16a–c**.

Conclusion

In conclusion, we have developed a hydrogen bonding-mediated C–F bond insertion of fluorinated alkenes into benzyl and propargyl fluorides. This work demonstrates the ability of HFIP to activate C(sp^3)–F bonds towards heterolytic cleavage while not sequestering the released fluoride ion in an unreactive by-product. The overall result is the formation of valuable *gem*-difluorinated products from mono-fluorinated substrates under mild conditions without an additional fluorinating reagent. Furthermore, a one-pot approach has been developed that allows for readily available benzyl bromides to be engaged directly without the need to isolate benzyl fluorides. We believe this work will inspire new routes to valuable fluorinated compounds and further studies are underway in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Alcohols · Fluorine · *gem*-Difluorinated Groups · Hydrogen Bonding · Insertion Reactions

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[13] Ketone **4** was observed only in trace amounts (<3%) when using HFIP as activator in a PTFE vial.

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[15] (1,1-Difluoroethyl) benzene was observed as a side-product under the optimized conditions using a PTFE vial suggesting generated HF is sequestered by the alkene substrate. This species was observed only in traces in the presence of $NaHCO_3$ or when the reaction was conducted in a glass Schlenk tube.

[16] Other side-products observed during the optimization and scope studies include hexafluoroisopropyl ethers resulting from nucleophilic substitution of the alkyl fluoride by HFIP and polymeric diarylmethane derivatives resulting from Friedel–Crafts alkylation (see also reference 8).

[17] Interestingly, **3aa** was not observed when $BF_3{\cdot}OEt_2$ (2 equiv.) was used as activator in a glass Schlenk tube with ketone **4**

being formed in 76% ^{1}H NMR yield (see the Supporting Information).
[18] **3aa** was generated in 45% ^{1}H NMR yield along with ketone **4** in 8% yield when then reaction was conducted with 10 mol% $BF_3{\cdot}OEt_2$ (see the Supporting Information).
[19] Attempts to trap the benzylic carbocations generated upon attack of the alkene with the alternative nucleophiles, chloride (from nBu$_4$NCl, 5 equiv.), bromide (from nBu$_4$NBr, 5 equiv.) and anisole (5 equiv.) proved unsuccessful.
[20] Studies on the stereochemical outcome of the HFIP-mediated Friedel–Crafts reaction of benzyl fluorides by Paquin and O'Hagan suggest an S_N1-type mechanism predominates in that process (albeit with some remaining S_N2-character, see reference 8h). We tentatively assume the C–F insertion reaction also proceeds predominantly via S_N1 although the involvement of HF as an activator in the former case means the two systems are likely not entirely comparable.
[21] Subjecting α-methylstyrene to the same reaction conditions with **1a** and $NaHCO_3$ led to a complex reaction mixture while small peaks (<30% ^{1}H NMR yield) consistent with the elimination product were observed in the crude NMR spectrum of the analogous reaction using α-bromostyrene.
[22] The selectivity for C–F bond activation over C–Br and C–Cl bond activation was previously shown by Paquin and co-workers using HFIP as a HBD (see reference 8c).

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