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C–F Activation of hydrofluorocarbons (HFCs) mediated by aluminum reagents

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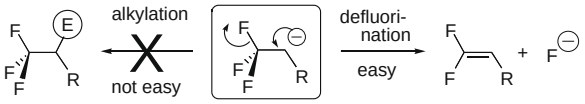
ABSTRACT

In the presence of various aluminum reagents, the difluoromethylene group (CF_2) in selected hydrofluorocarbons (HFCs) undergoes a Friedel–Crafts type reaction with aromatic compounds in satisfactory yields.

The selective substitution of hydrogen by fluorine is a valuable strategy for the preparation of organic compounds with distinctive physicochemical and therapeutic properties.[1–7] Compared to other heteroatoms, fluorine is not an easy atom to introduce in an organic compound. Fluorine incorporation is normally done using electrophilic or nucleophilic fluorinating agents, or using fluorinated building blocks.[2–4] The former approach does have drawbacks, as some reagents are expensive or require stringent reaction conditions. On the other hand, a significant number of fluorine-containing building blocks originate from ozone-depleting substances (ODS), and have been banned by the Montreal Protocol. In our search to find new non-ODS fluorinated building blocks, we turned our attention to three- or four-carbon hydrofluorocarbons (HFCs) as promising building blocks. Many of these materials have been used mainly in specific applications (e.g., refrigeration), most are cheap industrial feedstock, eco-friendly, and liquids near 0 °C. HFCs possess multiple fluorine atoms per molecule, so that even after exchanging one or two fluorines there remain enough fluorine atoms to produce a valuable building block.[3] But lack of a synthetic handle (functional group) makes most HFCs difficult to be used in synthesis. Herein we report an aluminum Lewis acid-promoted C–F bond activation that allows Friedel–Crafts-type arylations of HFC245fa (CF_3–CH_2–CHF_2), and that condition can also be used with other non-functionalized fluoroaliphatic substrates.

Our first aim was the conversion of HFC245fa into the synthetic equivalent of the trifluoroethyl group. Despite its potential application in chemistry and biology, the CF_3–CH_2– group is a challenging target. Its synthesis has eluded traditional approaches because of its inherent tendency to defluorinate upon deprotonation (Eq. 1).



(1)

A number of indirect approaches have been sought with the aim of stabilizing the trifluoroethyl group using electron-withdrawing groups (R = sulfone, ketone, ester, and phosphine oxide) or halides,[8–12] but these substituents had to be first installed and then removed. Hartwig and coworkers tackled this challenge by using trifluoroethyl iodide to form a palladium complex and used it as a coupling partner with a lithiated tolyl anion in moderate yield.[13] But this protocol required stoichiometric amounts of an expensive transition metal. A method that would deliver directly the trifluoroethyl group would extend significantly the range of synthetic applications.

Chemists have taken a great interest in carbon–fluorine bond activation to synthesize fluorinated active pharmaceutical ingredients.[14–25] In general, activation of mono-substituted C–F bond is relative easy, examples include Ni- or Cu-catalyzed cross-coupling reaction of alkyl fluorides with Grignard reagents,[26–28] and a low-valent niobium-mediated C–F bond activation.[29,30] However, unlike other halogens, each additional fluorine atom strengthens the C–F bond, so actually the carbon–fluorine bond in CF_2 containing compounds is stronger than the carbon–fluorine bond in mono-fluorine substituted compounds.[4] Thus, the activation of a C–F bond in non-activated CF_2-containing compounds is a greater challenge. Cleavage of the very strong C–F bonds in HFC245fa may require coordination with an strong activating reagent such as aluminum and boron, both of which bind strongly with fluorine (159 and 181 kcal/mol, respectively)[2] and both aluminum and boron reagents have been used successfully to activate mono-substituted alkyl fluorides.[31–35]

We decided to screen commercially available boron and aluminum reagents that could activate HFC245fa, and allow its

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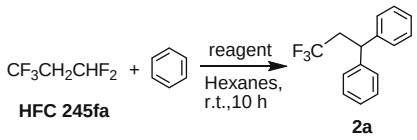
Table 1
Optimization of reaction conditions[a]



Entry	Reagent	Yield (%)/[**2a**][b]
1	$BF_3{\cdot}OEt_2$	No reaction
2	BCl_3	No reaction
3	BCl_3[c]	No reaction
4	Et_3B	No reaction
5	Cy_2BCl	No reaction
6	$NbCl_4$	No reaction
7	$AlCl_3$[d]	Trace
8	$AlCl_3$	52
9	$EtAlCl_2$	83
10	Me_2AlCl	35
11	Et_2AlCl	46
12	Et_2AlCl[d]	Trace
13	Me_3Al	No reaction

[a] General conditions: HFC 245fa 2.0 mmol, benzene 1.0 mL, Lewis acid 1.0 mmol, Hexanes 1.0 mL.
[b] Isolated yield based on the Lewis acid loading.
[c] At 80 °C.
[d] At 0 °C.

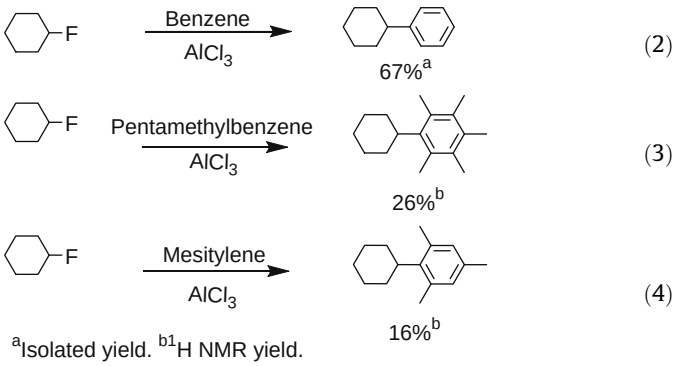
subsequent electrophilic trapping with a nucleophile (benzene, see Table 1). No reaction took place using boron halides or alkyl boron at room temperature, or even at 80 °C (Table 1, entries 1–5). Low-valent niobium catalyst is also ineffective (Table 1, entry 6). To our delight, using $AlCl_3$ at 0 °C, we observed traces of diarylated product **2a** (Table 1, entry 7); by increasing the temperature of the reaction we increased the yield to 52% (Table 1, entry 8). However, fine tuning the Lewis acidity of $AlCl_3$ by replacing one chlorine atom with an ethyl group improved the yield (83%) substantially (Table 1, entry 9). Replacing two chlorines with alkyl groups lowered the yield of **2a** (Table 1, entries 10–12) and diminishing the Lewis acidity of the aluminum reagent by replacing all chlorines with alkyl groups led to no reaction at all (Table 1, entry 13).

From these results we can see that CFH_2, CF_2H, and CF_3 groups have different reactivities (CFH_2 > CF_2H > CF_3). This fact allowed us to substitute both fluorines in CF_2H without affecting the CF_3 group, but we were not able to selectively replace one of the two C–F bonds. This result can be explained by the fact that additional fluorine atoms will strengthen the neighboring C–F bonds.

Having found conditions to activate HFC245fa, we decided to examine the scope of this reaction using other simple aromatic substrates (Table 2). Using benzene, toluene, or *p*-xylene, we obtained the corresponding bisarylated trifluoroethyl derivatives in good yields (Table 2, entries 1–3).[36] Other CF_2-containing compounds also work under similar conditions (Table 2, entry 4).

We also screened some other CF_2-containing compounds (**1c–h**, Scheme 1), but selective activation of those CF_2 groups proved to be difficult. Under similar condition to those used in Table 2, there was no reaction between **1c** and benzene. This may be due to the strong deactivation effect of neighboring fluorine atoms. Reaction of **1d** with benzene gave a complex mixture due to possible polymerization of **1d** in the presence of the strong Lewis acid. Also, there were no reactions between **1e–g** and benzene; this may be due to the deactivation of aluminum Lewis acid by oxygen and nitrogen functionalities present in **1e–g**. The reaction of **1h** with benzene gave only a hydrolyzed product after work-up.

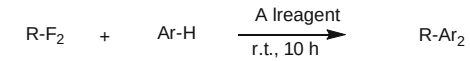
Mono-substituted alkyl fluorides can also undergo a Friedel–Crafts-type reaction under similar conditions, but due to the prone rearrangements of carbocation intermediates, the yields were only moderate (Eqs. 2–4).

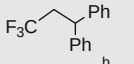
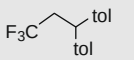
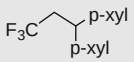
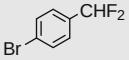
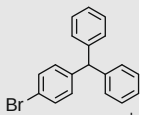


[a]Isolated yield. [b1]H NMR yield.

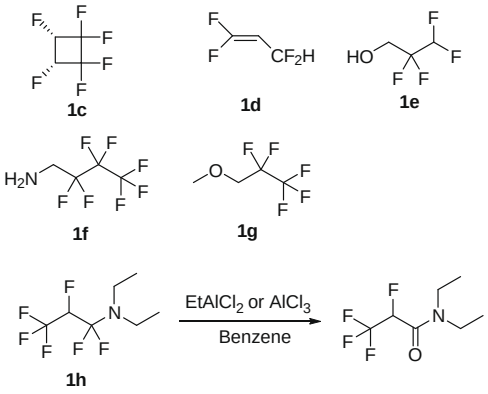
In summary, we have discovered an aluminum Lewis acid-mediated reaction of the difluoromethylene group (CF_2) in HFC245fa with simple aromatic nucleophiles, in satisfactory yields. Potentially, the scope of this reaction could be expanded to other HFCs containing CF_2 or CF groups.

Table 2
Reactions of difluoro compounds (R-F_2) with aromatic substrates (Ar-H)



Entry	R-F_2	Ar-H	Al reagent	R-Ar_2 (%)
1	HFC245fa **1a**	Benzene[a]	$EtAlCl_2$	 **2a**, 83[b]
2	**1a**	Toluene[a]	$EtAlCl_2$	 **2b**, 71[b]
3	**1a**	*p*-Xylene[a]	$EtAlCl_2$	 **2c**, 76[b]
4	 **1b**	Benzene[c]	$AlCl_3$	 **2d**, 39[d]

[a] HFC245fa (2.0 mmol), Hexanes (1.0 mL), ArH (1.0 mL), $EtAlCl_2$ (1.0 mmol).
[b] Isolated yield based on $EtAlCl_2$.
[c] R-F_2 (0.5 mmol), ArH (1.0 mL), $AlCl_3$ (0.5 mmol), Hexanes (1.0 mL).
[d] Isolated yield.



Scheme 1. Other CF_2 containing substrates screened.

Acknowledgments

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36. *Typical procedure for preparation of* **2a**: To a solution of HFC245fa (268 mg, 2.0 mmol) in benzene (1.0 mL) and hexanes (1.0 mL) was added a 1.0 M solution of $EtAlCl_2$ in hexanes (1.0 mL, 1 mmol) at room temperature. The mixture was stirred for 10 h at room temperature; afterwards the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (eluent: ethyl acetate/petroleum ether = 1/100) to give product **2a** (208 mg, 83%) as a colorless oil. IR (neat) ν 3030, 1600, 1495, 1381, 1256, 1132, 700, 610 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.89–2.97 (2H, m), 4.35 (1H, t, J = 7.5 Hz), 7.17–7.34 (10H, m); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 39.8 (q, J_{C-F} = 27.5 Hz), 45.3, 126.7 (q, J_{C-F} = 277.2 Hz), 127.1, 127.7, 129.0, 143.0; ^{19}F NMR ($CDCl_3$, 470 MHz) δ 64.1 (t, J_{H-F} = 19.7 Hz); MS (EI) m/z 250 (M^+), 164 (100); Anal. Calcd for $C_{15}H_{13}F_3$: C, 71.99; H, 5.24. Found: C, 71.73; H, 5.32.