C-F Activation

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C–C Coupling of Benzyl Fluorides Catalyzed by an Electrophilic Phosphonium Cation

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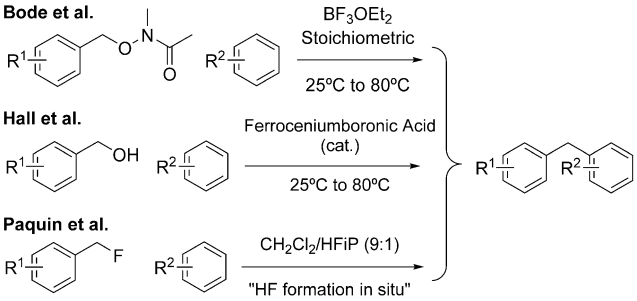
Dedicated to Professor Gerhard Erker on the occasion of his 70th birthday

Abstract: *The activation and cleavage of benzyl fluorides by the electrophilic organofluorophosphonium catalyst, $[(C_6F_5)_3PF][B(C_6F_5)_4]$, is reported and used for the preparation of 1,1-diarylalkanes (37 examples) and substituted aryl homoallylic alkenes (14 examples). This procedure involves mild conditions, avoids harmful waste, and is compatible with a range of substituted arenes and allylic silanes.*

C–F bonds are the strongest single bonds with carbon.[1] This feature is exploited to great advantage in the design of new drugs, as C–F fragments offer metabolic stability. However, this stability also means that such compounds are environmentally persistent, thus generating a potential hazard in the form of environmental pollutants. While many methods have been developed for the formation of C–F bonds,[2] recently attention has turned toward strategies for the activation and cleavage of C–F bonds.[3] The cleavage of $C(sp^2)$–F bonds using transition metal complexes is well established, while the activation of $C(sp^3)$–F is less studied. Nonetheless, main group reagents and more specifically, strong Lewis acids, have garnered success in such C–F cleavage reactions.[4] In our laboratories, a procedure for defluorination was developed that employs highly electrophilic phosphonium cations (EPCs).[5] As these species are typically fluorophosphonium cations, the Lewis acidity of these electron deficient cations is derived from the positive charge on the phosphorus atom and the σ* orbital on phosphorus, which is oriented *trans* with respect to fluoride. Using catalytic EPCs, we have previously shown that such systems are capable of mediating hydrodefluorination of alkyl- and aryl-fluorides, hydrosilylation of saturated moieties,[6] ketone deoxygenation,[7] dehydrocoupling of silanes with proton donors,[8] activation of hydrogen, and olefin hydrogenation.[9]

Friedel–Crafts reactions have long been known and exploited.[10] Indeed, Friedel–Crafts reactions afford a rare metal-free option for C–C coupling reactions. However, such reactions normally require harsh conditions and generate harmful by-products. One important class of compounds that can be prepared by Friedel–Crafts reactions are diarylmethanes. Such species are important intermediates in medicinal and agricultural chemistry.[11] While transition-metal-based methods have been developed to achieve such targets,[12] several metal-free methods have been described,[13] the majority involving Lewis acid-mediated Friedel–Crafts chemistry (see Scheme 1). A remarkable procedure is described by Bode and Schäfer, in which benzyl hydroxamates and a stoichiometric amount of BF_3OEt_2 are employed to generate diarylmethanes.[14] Hall et al.[15] described direct Friedel–Crafts coupling with deactivated benzylic alcohol using ferroceniumboronic acids. Although halogens are well known as good leaving groups, benzyl fluorides are very stable and generally unreactive. In 2014, Paquin et al. described a clever method for acid activation of fluorides and subsequent functionalization.[16] While this approach is interesting, it does exploit HFIP to initiate the reaction, generating HF as the catalyst, which limits scale-up because of the toxicity of this chemical.



Scheme 1. Recent methods for the preparation of diarylmethanes.

Very recently our group reported the activation of CF_3 in arylation reactions. This process and subsequent rapid hydrodefluorination are catalyzed by EPCs.[17] While this example represents a conceptual advancement on existing techniques, the complex and challenging reaction displays some limitations in scope. Herein, we describe the activation of benzyl fluorides and subsequent C–C bond coupling with arenes. This procedure, which uses benzyl fluorides, is a convenient compliment to the corresponding CF_3 chemistry. It broadens both the synthetic access and scope of arylations to include a large number of electron-poor and -rich arenes, as well as heterocycles. Moreover, competition experiments demonstrate the selectivity of EPC catalysts for benzyl fluoride in the presence of other benzyl halides. This method was also shown to be useful for the coupling of benzyl fluorides with allylic silanes.

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The reaction of benzyl fluorides with C_6D_6, toluene, and *p*-xylene in the presence of $[FP(C_6F_5)_3][B(C_6F_5)_4]$ (1 mol%) and Et_3SiH (1.2 equiv) proceeded at 25°C for 1 h with the evolution of H_2. These reactions afforded the diarylmethanes $PhCH_2C_6D_5$ **1**, $PhCH_2C_6H_4Me$ **2**, and $PhCH_2C_6H_3Me_2$ **3** in isolated yields of 82, 65, and 74%, respectively (see Table 1). The generated cationic intermediate reacts with toluene to give substitution at *ortho*- and *para*-positions in a 1:1 mixture (see proceeding text and Scheme 2). Similarly, the corresponding *p*-*tert*-butylbenzyl fluoride reacts with C_6D_6, *p*-xylene, 1,2-dimethylbenzene, mesitylene, and methoxybenzene to give the respective diarylmethanes **4**–**8** in high yields of isolated products (75–92%). Similarly, incorporation of various substituents on the benzyl fluoride moiety (3,5-di-*tert*-butyl-, 3-methoxy-, 4-halo- (Br, Cl, F), 2-chloro-, 3-fluoro-, 2-CF_3-, 4-CF_3-, or 3,4-difluoro-) did not prevent catalytic aryl-coupling to benzene, *p*-xylene, 2,4-di-*tert*-butylbenzene, or 1,2,4,5-tetramethylbenzene, affording the diarylalkane materials **9**–**22** in yields ranging from 36–94%. Notably, the formation of **16** and **18** demonstrate preferential reaction of the benzyl fluoride moiety in the presence of CF_3 fragments. Additionally, the formation of **22** by reaction of $1,3,5\text{-}(t\text{Bu})_3C_6H_3$ with benzyl fluoride prompts the loss of a *t*Bu-group.

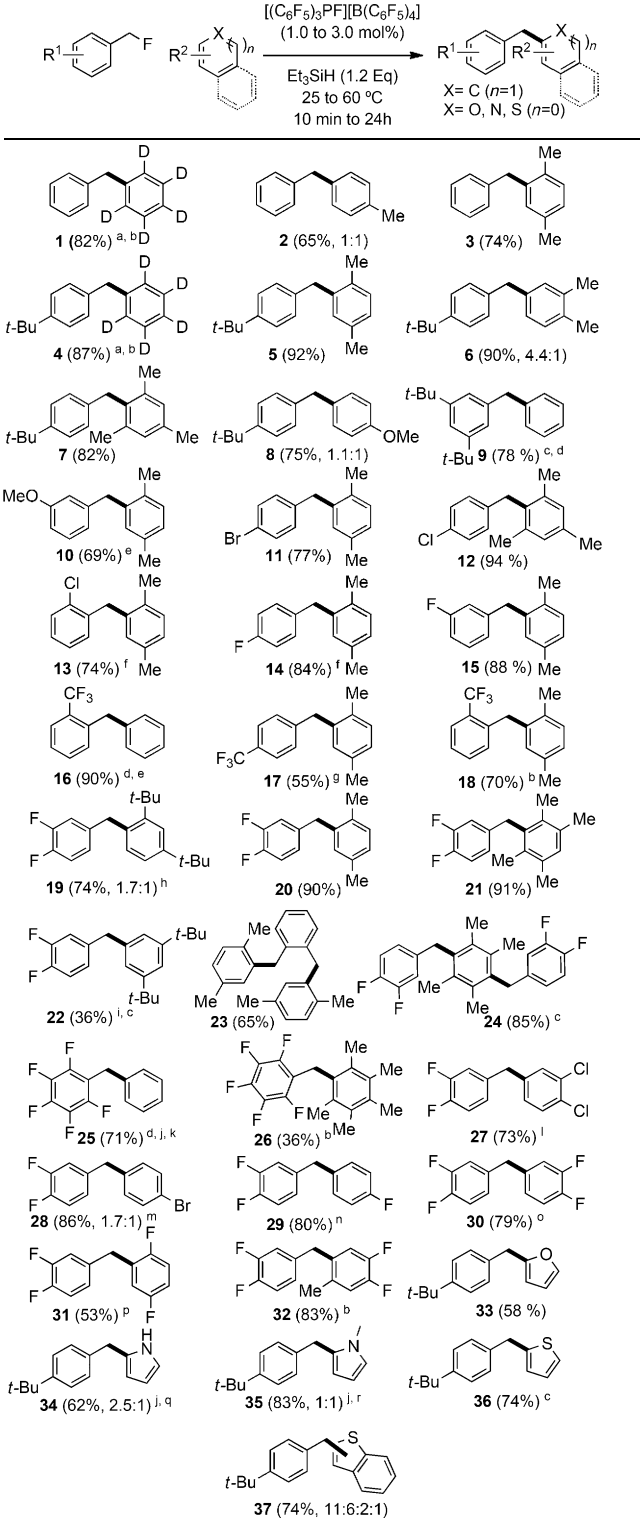
These reactions can be exploited to achieve double arylation. For example, using $1,2\text{-}(FCH_2)_2C_6H_4$ and *p*-xylene, the doubly coupled product $1,2\text{-}((1,4Me_2C_6H_3)2\text{-}CH_2)_2C_6H_4$ **23** was obtained in 65% yield, while two equivalents of 3,4-difluorobenzyl fluoride reacted with 1,2,4,5-tetramethylbenzene to give $C_6Me_4(CH_2C_6F_2H_3)_2$ **24** in 85% yield.

Analogous coupling of pentafluorophenyl benzyl fluoride with benzene or pentamethylbenzene afforded **25** and **26** in yields of 71 and 36%, respectively. The latter species is particularly interesting as it provides linked electron-rich and -deficient arene rings. Compound **26** was also characterized by X-ray crystallography (Supporting Information; CCDC 1471968 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre).

The above reactions generally demonstrate benzyl–aryl coupling using electron-rich benzene derivatives. Probing this C–C bond-forming reaction further, catalytic reactions using 3,4-difluorobenzyl fluoride were shown to couple with electron-deficient arenes, including 1,2-dichlorobenzene, bromobenzene, fluorobenzene, 1,2- and 1,4-difluorobenzene, and 1,2-difluoro-4-methylbenzene, affording the corresponding diarylmethanes **27**–**32** in yields ranging from 53–86% (in these cases it was necessary to increase the catalyst loading to 3 mol%).

Benzylation of heterocycles was also possible. For example, treatment of furan at 25°C with benzyl fluoride, silane, and the EPC catalyst, afforded $(2\text{-}PhCH_2)C_4H_3O$ **33**, albeit only in 58% yield of isolated product. The corresponding reactions with pyrrole and *N*-methylpyrrole required warming to 60°C to furnish $(2\text{-}PhCH_2)C_4H_3NR$ (R = H **34**, Me **35**) in 62 and 83% yield, respectively. In a similar fashion, the corresponding benzylation of thiophene and benzothiophene gave **36** and **37**, both in 74% yield.

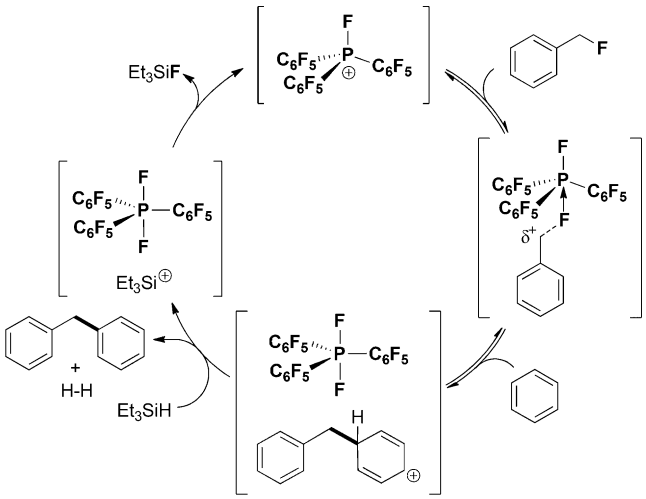
Table 1: Arylation of benzyl fluorides.



Yields of isolated products. Conditions: cat. ($[(C_6F_5)_3PF][B(C_6F_5)_4]$, 1.0 mol%), arene (5.0 equiv), Et_3SiH (1.2 equiv), 10 min at 25°C, unless otherwise stated. [a] C_6D_6 solvent; [b] 1 h; [c] 30 min; [d] C_6H_6 solvent; [e] 12 h; [f] 3 h; [g] 2 d; [h] 16 h; [i] arene = 1,3,5-tri-*tert*-butylbenzene; [j] 60°C; [k] 2 h; [l] cat. (3.0 mol%), *o*-$C_6H_4Cl_2$ solvent, 16 h at 25°C; [m] C_6H_5Br solvent; [n] cat. (3.0 mol%), C_6H_5F solvent, 30 min at 25°C; [o] cat. (3.0 mol%), *o*-$C_6H_4F_2$ solvent, 30 min at 25°C; [p] cat. (3.0 mol%), *p*-$C_6H_4F_2$ solvent, 16 h at 25°C; [q] 4 d; [r] 20 h.

The formation of **16**–**18** illustrates that benzyl fluoride fragments react selectively in the presence of CF_3 substituents, in contrast with our previous report of CF_3 arylation using phosphonium cation catalysts. Indeed, treatment of $(2\text{-}CF_3)C_6H_4CH_2F$ with an excess of silane and catalyst resulted in the benzylation and subsequent activation of the CF_3 group,[17] affording 9,10-dihydroanthracene **38**. This reaction was performed on a near gram scale.

The possibility of acid catalysis mediated by in situ generated HF was considered and ruled out, as silane reacts immediately with HF to give Et_3SiF and H_2. Moreover, combining of reagents under catalytic conditions without fluorophosphonium salts showed no reaction, thus suggesting a coupling mechanism involving activation of the benzyl fluoride moiety by $[FP(C_6F_5)_3][B(C_6F_5)_4]$ (Scheme 2).



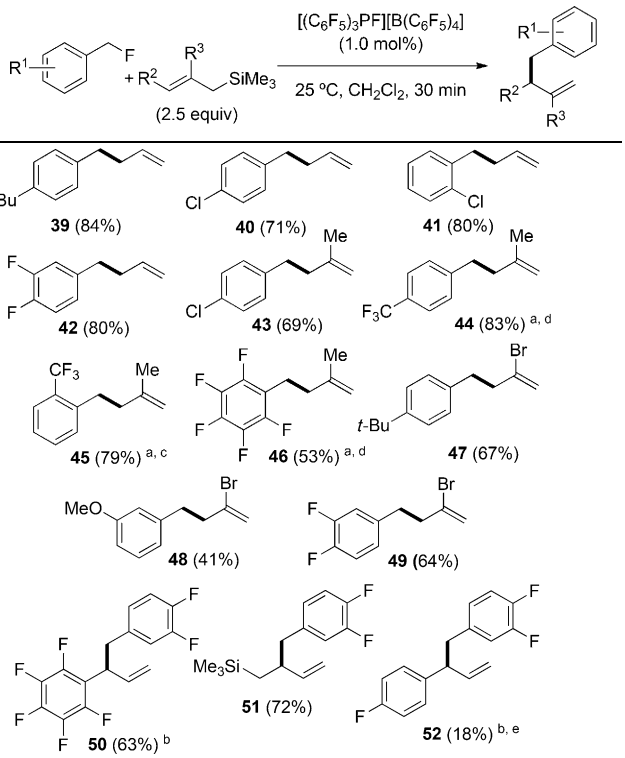
Scheme 2. Proposed mechanistic pathway.

Generation of the fluorophosphorane and a benzyl carbocation prompts electrophilic aromatic substitution. The resulting cation reacts with silane to afford hydrogen, while the generated silylium ion abstracts fluoride from difluorophosphorane, liberating fluorosilane, and regenerating the electrophilic phosphonium cation for re-entry into the catalytic cycle. This mechanism is consistent with previously reported calculations describing related CF_3 activations.[5a] In support of this mechanism, the evolution of hydrogen during the reaction was experimentally detected by ^{1}H-NMR spectroscopy, while the independent treatment of $[FP(C_6F_5)_3][B(C_6F_5)_4]$ with benzyl fluoride alone was shown to result in the instantaneous generation of $F_2P(C_6F_5)_3$. It is noteworthy that previous studies have ruled out silylium catalysis for closely related phosphonium cation mediated hydrodefluorination chemistry.[5a]

The specific selectivity of the EPC catalysts for C–F was probed. The corresponding reactions using benzyl chlorides or bromides with benzene also gave complete conversion into the benzylated arene products. Competing reactions in which one equivalent of benzyl bromide and benzyl chloride were reacted in the presence of one equivalent of silane, gave rise to a 50:50 mixture of the products and residual benzyl bromide or benzyl chloride, indicating no selectivity. However, analogous competing reactions involving either benzyl bromide or benzyl chloride and benzyl fluoride resulted in exclusive consumption of benzyl fluoride, leaving the benzyl chloride or benzyl bromide untouched (see Supporting Information).[18]

This reactivity was further extended to reaction of benzyl fluorides with allylic silanes, affording catalytic metal-free sp^3–sp^3 C–C coupling reactions. To this end, 1-*tert*-butyl-4-(fluoromethyl)benzene (1.0 equiv) was combined with allyl trimethylsilane (2.5 equiv) in the presence of $[FP(C_6F_5)_3][B(C_6F_5)_4]$ (1.5 mol%), furnishing the homoallylic benzyl product $PhCH_2CH_2CH{=}CH_2$ **39** in 30 min, with an isolated yield of 84%. Analogous reactions involving substituted benzyl fluorides, afforded the corresponding homoallylic benzyl coupling products **40**–**42** in yields of 71–80% (Table 2). It was even possible to combine trimethyl(2-methylallyl)silane with various benzyl fluorides, generating the coupling products **43**–**46** in yields ranging from 53–83% in 30 min at 25 °C. Similarly, trimethyl(2-bromoallyl)silane generated products **47**–**49** in yields of 41–64% (Table 2) with complete selectivity for the 2-bromo products. The reaction of 3,4-difluorobenzyl fluoride with (*E*)-trimethyl(3-(perfluorophenyl)allyl) silane, or 1,4-bis(trimethylsilyl) but-2-ene, gave the branched coupling products **50** and **51** in yields of 63 and 72%, whereas the corresponding reaction of (*E*)-(3-(4-fluorophenyl)allyl) trimethylsilane gave

Table 2: Reaction of benzyl fluorides and allylic silanes.



Conditions: cat. ($[(C_6F_5)_3PF][B(C_6F_5)_4]$, 1.0 mol%), allylic silanes (2.5 equiv), 30 min at 25 °C, unless otherwise stated; [a] 60 °C; [b] 1 h; [c] 4 h; [d] 16 h; [e] C_6F_6 solvent.

the branched product in low yield as a result of the competitive Friedel–Crafts reaction.

Significantly, the Hosomi–Sakurai allylation[19] or sp^3–sp^3 C–C reactions are widely used in organic chemistry. However, they normally involve substrates such as alcohols, acetates, ethers, ketones, or imines, and stoichiometric or catalytic amount of Lewis acids. To our knowledge, the present reactions are the first reported in which benzyl fluorides are used as substrates. Notably, this reactivity could not be extended to triflurometh ylphenyl derivatives, irrespective of the use of higher catalyst loadings, higher temperatures, or extended reaction times.

In summary, we have reported the coupling of benzyl fluorides with arenes and allylic silanes, catalyzed by EPCs under mild conditions and with short reaction times. These reactions are compatible with several functional groups and both electron-rich and electron-poor arenes, as well as heterocycles. Additionally, these reactions were shown to be selective for C–F bonds in the presence of benzyl chlorides and benzyl bromides. The mechanistic pathway proposed is based on both experimental observations and previously reported calculations. These reactions broaden the scope of EPC catalysts, illuminating a method for C–F bond functionalization of benzylic fluorides. Finally, we have shown that the present transformations can also be used in tandem with our previously reported CF_3 functionalization procedure.

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Keywords: arylation reactions · benzyl fluorides · $C(sp^3)$–$C(sp^3)$ coupling · homogeneous catalysis · phosphonium cations

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