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Benzylation

Friedel–Crafts Reaction of Benzyl Fluorides: Selective Activation of C–F Bonds as Enabled by Hydrogen Bonding**

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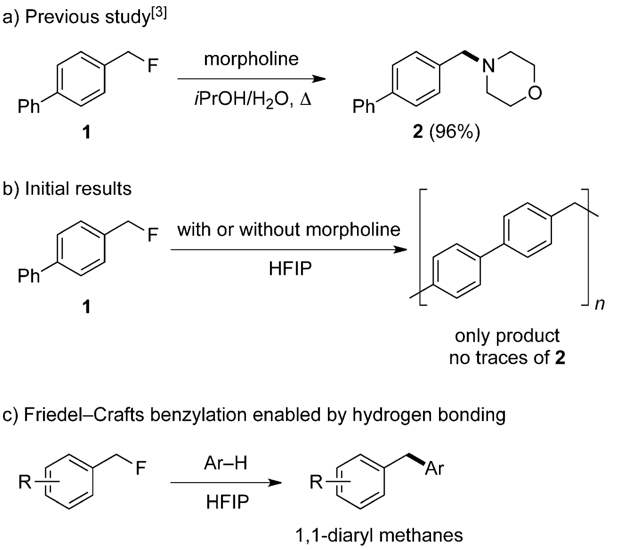
Abstract: *A Friedel–Crafts benzylation of arenes with benzyl fluorides has been developed. The reaction produces 1,1-diaryl alkanes in good yield under mild conditions without the need for a transition metal or a strong Lewis acid. A mechanism involving activation of the C–F bond through hydrogen bonding is proposed. This mode of activation enables the selective reaction of benzylic C–F bonds in the presence of other benzylic leaving groups.*

The substitution of C–F bonds has been a subject of intensive research for a number of years.[1] Part of the interest in this process is the fundamental prospect of being able to activate the strongest single bond with carbon.[2] Potential applications in synthetic organic chemistry and in environmental sciences have also stimulated research in this area. In line with our efforts in designing new synthetic methodology involving the activation of C–F bonds, we recently reported a new strategy toward this goal on the basis of hydrogen bonding.[3] Specifically, we showed that activated alkyl fluorides could undergo a bimolecular nucleophilic substitution reaction with various nucleophiles in the presence of water as a hydrogen-bond donor (HBD; Scheme 1 a). Calculations demonstrated that in this system, stabilization of the transition state occurred through hydrogen bonding between the fluorine atom and water molecules. The possibility that the fluorine atom of a C–F bond could act as a hydrogen-bond acceptor has been a subject of debate for some time,[4] as the analysis of crystal-structure databases generated only a few examples of structures consistent with a C–F···H bond.[5] However, spectroscopic and computational evidence now convincingly support the existence of this interaction in solution.[6] Thus, although water is a good hydrogen-bond donor ($\alpha = 1.17$),[7] we wondered what would happen with stronger HBDs, such as fluorinated alcohols.[8] Our hypothesis was that the use of a stronger HBD would result in stronger hydrogen bonds, which themselves would correlate with a stronger activation, and hence an acceleration of the reaction. To test this hypothesis, we selected 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),[9] one of the strongest HBD solvents ($\alpha = 1.96$), as a potential replacement for water. When benzylic fluoride **1** was treated with morpholine in HFIP, none of the benzylic amine **2** was observed; rather, an insoluble polymer with a 1,1-diaryl methane backbone was isolated (Scheme 1 b).[10–12] We hypothesized that the stronger HBD capability of HFIP could favor direct ionization of the benzyl fluoride to generate a benzyl carbocation,[13,14] which polymerized through a Friedel–Crafts reaction.



Scheme 1. A previous study, an unexpected result, and the goal of this study.

On the basis of this result, we envisioned that the treatment of benzylic fluorides with nucleophilic arenes in the presence of HFIP could provide facile access to 1,1-diaryl methanes (Scheme 1 c). Herein, we document Friedel–Crafts benzylation[15,16] with benzylic fluorides as enabled by hydrogen bonding. This method is notable on a number of grounds: It provides access to 1,1-diaryl alkanes, which are valuable synthetic building blocks in medicinal and agrochemistry; it does not require a transition metal or a strong Lewis acid; and it expands the use of benzylic fluorides[17] as building blocks in organic synthesis, exploiting a new type of reactivity.

Under optimized conditions [Ar–H (5 equiv), HFIP/CH_2Cl_2 (1:9), room temperature, 18 h],[10] we evaluated the reactivity of arene nucleophiles with benzyl fluoride **3** (Scheme 2). Various electron-rich or electron-neutral aromatic compounds[18] could be used, and the corresponding 1,1-

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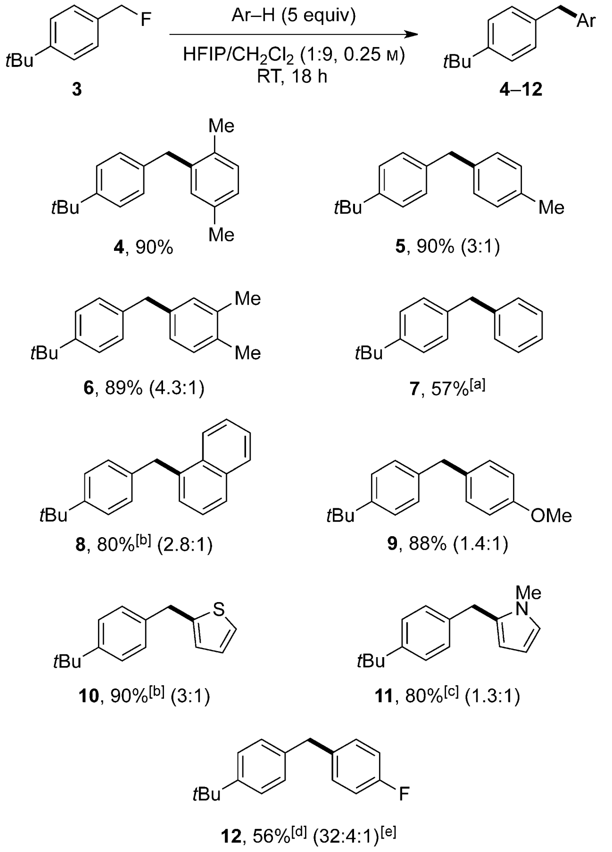
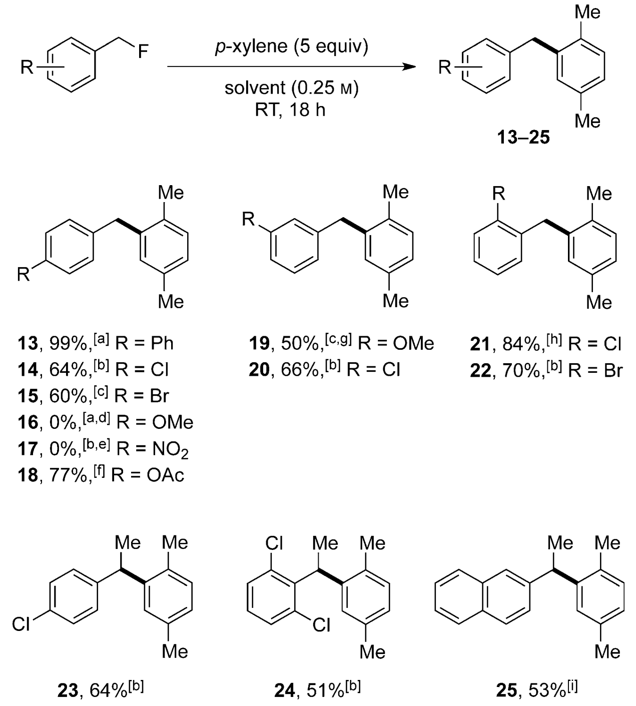


Scheme 2. Benzylation of **3** with various arenes. The yields given are for the isolated product. The ratio of regioisomers was determined by ^{1}H NMR spectroscopic analysis and is given in parentheses with the major isomer shown. [a] The solvent used was HFIP/benzene (1:9). [b] The reaction was carried out with 10 equivalents of the arene. [c] Reaction conditions: HFIP/DCE (1:9), *N*-methylpyrrole (10 equiv), 60 °C. [d] The solvent used was HFIP/fluorobenzene (1:9). [e] Ratio of the *para*:*ortho*:*meta* isomers. DCE = 1,2-dichloroethane.

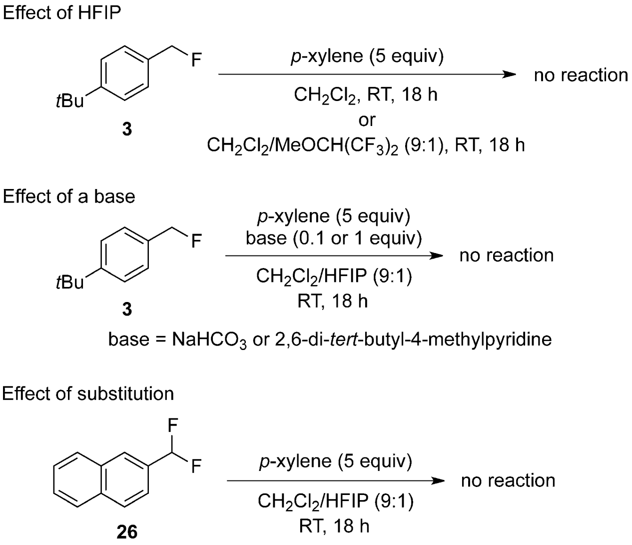


Scheme 3. Benzylation of various benzyl fluorides with *p*-xylene. The yields given are for the isolated product. [a] The solvent used was HFIP/CH$_2$Cl$_2$ (1:9). [b] Reaction conditions: HFIP/DCE (1:1), 60 °C. [c] The solvent used was HFIP/CH$_2$Cl$_2$ (1:1). [d] Decomposition was observed. [e] No reaction was observed. [f] The solvent used was HFIP/CH$_2$Cl$_2$ (9:1). [g] The reaction was carried out with 10 equivalents of *p*-xylene. [h] The solvent used was HFIP (100%). [i] Reaction conditions: *p*-xylene (20 equiv), HFIP/CH$_2$Cl$_2$ (1:9, 0.1 M).

diaryl methanes could be isolated in moderate to excellent yield. Interestingly, no reaction was observed when electron-rich arenes bearing good hydrogen-bond-accepting groups, such as an ester (e.g. phenyl acetate) or an amide (e.g. acetanilide), were used. In those cases, we suspect that HFIP forms hydrogen bonds to those functional groups rather than interacting with the C−F bond (see below). Deactivated arenes, such as chlorobenzene, 1,4-dichlorobenzene, and α,α,α-trifluorotoluene, provided the expected product in only very low yields (< 5%), and a polymer corresponding to the self-polymerization of **3** was observed instead. Overall, these results indicate that as long as the nucleophilicity of the arene is superior to that of the benzylic fluoride or the nucleophile is present in large excess, the desired Friedel–Crafts reaction can be observed instead of polymerization.

Next, the reactivity of the benzylic fluoride partner was investigated with *p*-xylene as the arene nucleophile (Scheme 3). A phenyl group and halogens were found to be well-tolerated as substituents, although in most cases a higher concentration of HFIP and/or slight heating (60 °C) was required for full conversion. The use of a benzyl fluoride bearing a strongly activating group, such as a 4-methoxybenzyl fluoride,[19] was not possible, since it decomposed readily under the reaction conditions. In the case of 4-nitrobenzyl fluoride, a strongly deactivated benzylic fluoride, no reaction was observed. Positioning of the methoxy group in the *meta* position or its replacement with a less-electron-donating substituent, such as an acetoxy group, enabled the reactions to proceed as expected. Finally, the use of secondary benzylic fluorides was possible as long as the aromatic ring was electron-poor.

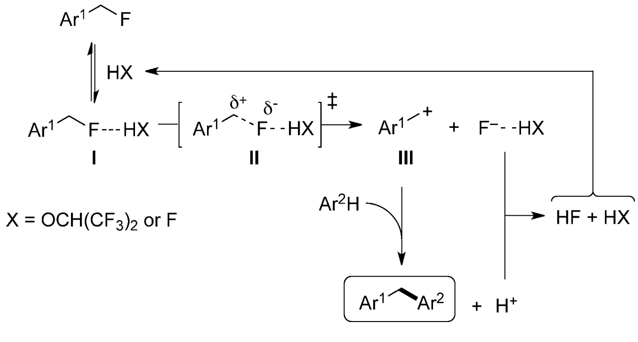
The unique reactivity profile of the benzylic fluorides under these conditions prompted us to probe the reaction mechanism (Scheme 4). First, no conversion was observed without HFIP or if HFIP was replaced with its methyl ether, and **3** was recovered. This result clearly demonstrates that the presence of HFIP is crucial to trigger the reaction of the benzylic fluorides, and that its hydrogen-bond-donating capability is important. Furthermore, the polar nature and high ionizing power of HFIP[9] may also play an important role in facilitating the reaction. Second, as it has been suggested that HF could initiate such transformations,[20] we carried out reactions in the presence of a base (NaHCO$_3$ or 2,6-di-*tert*-butyl-4-methylpyridine). In all cases, no reaction was observed, and **3** was recovered. These results point toward the potential role of HF as the active catalyst, which is supported by the finding that HF generated in situ promoted the reaction.[10] Finally, benzylic difluoride **26** or a benzylic trifluoride (not shown) did not react under various condi-



Scheme 4. Probing the reaction mechanism.

tions.[10] These results suggest that the fluorine atom is involved in the initiation step as a hydrogen-bond acceptor,[21] since it was demonstrated recently[6c,f] that the fluorine atom on a CHF moiety is a better hydrogen-bond acceptor that the fluorine atoms on a CF_2 motif. Practically, this last result suggests that selective activation of benzylic CH_2F in the presence of benzylic CHF_2 or CF_3 is possible under these conditions.

With these results in mind, we propose the following mechanistic explanation for the transformation (Scheme 5): To initiate the process, attractive hydrogen bonding between the benzylic fluoride and HFIP, one of the strongest HBD solvents ($\alpha = 1.96$),[7] would generate complex **I**.[4,22,23] Dalvit et al. showed recently that hydrogen bonds between benzyl fluoride and 4-fluorophenol exist in solution.[6f] They also calculated that the interaction of fluoroethane with methanol has a binding energy of -4.33 kcal mol^{-1} and meets all theoretical requirements to be called a hydrogen bond.[6f,24] This value corroborates those calculated for the fluoromethane–water dimer (-4.20 kcal mol^{-1})[6c] and for benzyl fluoride with water (-4.6 kcal mol^{-1}).[3] Since HFIP and HF are both stronger HBDs than water or methanol, we expect the interaction in **I** to be energetically significant. The importance of this interaction would explain the absence of reactivity observed with aromatic nucleophiles containing a carbonyl group, which would compete[25] with the benzyl fluoride for HFIP, or when the methyl ether of HFIP was used (see Scheme 4).



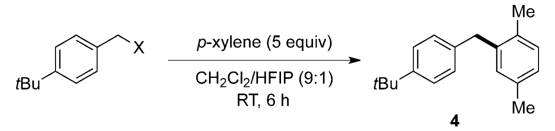
Scheme 5. Mechanistic hypothesis.

After the formation of **I**, ionization of the C–F bond would proceed to generate transition-state-like **II**. As the fluorine atom is more negatively charged in **II**, we expect stronger hydrogen bonds and thus better stabilization. Indeed, Paquin, Legault, and co-workers calculated that at the transition state for the S_N2 substitution of benzyl fluoride by morpholine in the presence of water, a stabilization energy of -11.1 kcal mol^{-1} was attributable to the F···H–O hydrogen bond.[3] Complete ionization would then generate the carbocation **III**, along with hydrogen-bonded F^-. For X = F, this species is known as bifluoride, a strongly hydrogen bonded anion (dissociation energy: 39 ± 1 kcal mol^{-1}).[26] Intermediate **III** would then react by electrophilic aromatic substitution with Ar^2–H to yield the desired diaryl methane, along with a proton, which would eventually combine with fluoride to generate HF. As HF is also a very strong HBD[27] it will then enter the reaction as the active catalyst, thus turning over more benzylic fluoride and generating even more HF in an autocatalytic system. Indeed, preliminary kinetic experiments show an induction period as well as a sigmoid variation of product concentration over time,[10] both typical observations in autocatalytic systems.[28] Overall, the driving force for this transformation would be the formation of stronger hydrogen bonds along the reaction pathway. Either HFIP or HF could act as the HBD catalyst. However, given that the significance of the hydrogen bond increases along the reaction coordinate and with HF, being a better donor, we believe that HFIP serves as the initiator, whereas HF is likely to be the active catalyst. Overall, this mode of activation contrasts drastically with the use of strong Lewis acids (e.g. $AlCl_3$, $BF_3{\cdot}Et_2O$) in previously described Friedel–Crafts reactions of benzyl fluorides.[20,29]

With the evidence for the importance of the hydrogen-bonding interaction along the reaction path, we wondered, as C–X bonds (X = Cl, Br, or I) are very weak hydrogen-bond acceptors,[30] if selective activation of a C–F bond would be possible. Initially, we compared the reactivity of various benzylic halides (Table 1). Remarkably, under the standard reaction conditions, only the benzylic fluoride reacted completely (Table 1, entry 1). No conversion was observed with the other halides (Table 1, entries 2 and 3). Other potential hydrogen-bond-accepting leaving groups were also evaluated (Table 1, entries 4–6). A benzylic alcohol,[31] ether, and acetate were unreactive under these reaction conditions.

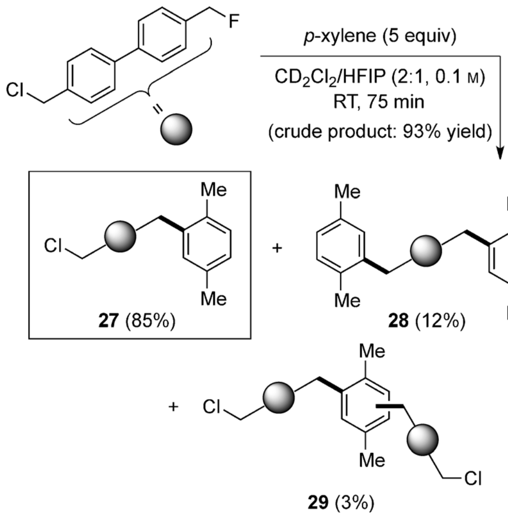
Finally, the unique reactivity of the benzylic C–F bond under these conditions was demonstrated on a bifunctional molecule bearing both a benzylic chloride and a benzylic fluoride (Scheme 6). Under slightly modified conditions, the reaction reached completion in 75 min. The crude product[32] was isolated in excellent yield (93 %) and was composed of the desired product (**27**; 85 % of the crude product) along with a double benzylation product **28** (formed by reaction at both benzylic positions; ca. 12 %) and a small amount of a product **29** formed by a second alkylation on the xylene ring but with

Table 1: Comparison of different leaving groups.



Entry	X	Conversion [%][a]
1	F	87
2	Cl	0
3	Br	0
4[b]	OH	0
5[b]	OMe	0
6[b]	OAc	0

[a] Conversion was determined by $^{1}H/^{19}F$ NMR spectroscopy. [b] The reaction time was 18 h.



Scheme 6. Selective activation of a C–F bond in the presence of a similar C–Cl bond.

the benzylic chloride intact (ca. 3%). Interestingly, careful monitoring of the reaction by NMR spectroscopy showed that reaction of the C–Cl bond only starts once all the C–F bonds have reacted.

In conclusion, we have reported the Friedel–Crafts benzylation of various arenes with benzylic fluorides as enabled by hydrogen bonding. The reaction provides access to 1,1-diaryl alkanes under mild conditions without the need for a transition metal or a strong Lewis acid. This mode of activation enables the selective reaction of benzylic C–F bonds in the presence of other benzylic leaving groups.

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