



## Short Communication

## Faster initiation in the Friedel-Crafts reaction of benzyl fluorides using trifluoroacetic acid as activator



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## ABSTRACT

We report that the addition of a catalytic amount of trifluoroacetic acid (TFA) shortens the induction period associated with the 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)-promoted Friedel-Crafts reaction of benzylic fluorides. This faster initiation is due to TFA's strong hydrogen-bond donation capability, not its Brønsted acidity. The improved reaction conditions were applied to a set of substrates, demonstrating how they could improve yields and reliability of this transformation.

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## 1. Introduction

The activation and nucleophilic substitution of C–F bonds has been an increasingly popular field of research over the last decades [1]. This interest is at least partially fuelled by the fundamental challenge of breaking the strongest single bond that carbon can make with any atom [2]. Furthermore, selective cleavage of C–F bonds has potentially important applications in the synthesis of functionalized compounds or in environmental sciences. To enhance the breadth of available methods, we recently reported an unusual strategy towards C–F activation, using the ability of fluorine to act as hydrogen-bond acceptor [3]. For instance, we have demonstrated that activated alkyl fluorides could undergo a bimolecular nucleophilic substitution reaction with various nucleophiles in the presence of water as a hydrogen-bond donor [4]. In addition, we have reported on alcohol-promoted amination of benzylic fluorides [5]. Finally, we have described the Friedel-Crafts reaction of benzyl fluorides (Fig. 1A) [6]. While benzylic fluorides were known to be somewhat reactive, especially in strong acidic conditions [7], their activation using hydrogen bond donors (HBD) was unprecedented. In this reaction, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) [8] is used both as an activator and as a polar, ionizing solvent. However, this reaction was plagued by an induction period of about 170 min for typical substrates, which could vary according to the exact nature of the benzylic fluoride employed. In order to provide a more reliable system, we decided

to explore conditions that would systematically allow for a faster initiation period. Herein, we report that the addition of a catalytic amount of trifluoroacetic acid (TFA) can efficiently serve this purpose. In addition, this mode of activation allows the reaction to be performed, with some substrates, in milder conditions (Fig. 1B).

## 2. Results and discussion

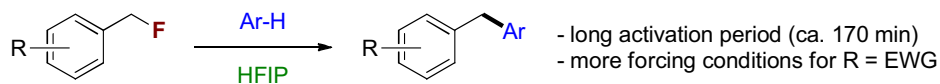
This idea originally stemmed from our mechanistic rationale for the Friedel-Crafts reaction of benzyl fluorides using HFIP as the activator, shown in Fig. 2 [6,9]. To initiate the whole process, HFIP forms a hydrogen-bond with benzylic fluoride **1**, forming complex **2** [10]. C–F bond ionization then occurs to form strongly stabilized fluoride **3** and carbocation **4**, which upon electrophilic aromatic substitution with Ar<sup>2</sup>-H generates the desired diarylmethane **5** and a proton. This proton eventually leads to the formation of HF, which we realize is a stronger HBD than HFIP thus acts as the active catalyst for the next catalytic cycles [11]. Evidence in support of this mechanistic proposal was obtained through various experiments that demonstrated the importance and involvement of HF, as well as by the measurement of substrate conversion as a function of reaction time, for a typical compound under standard conditions. Indeed, this experiment revealed an unexpected induction period of about 170 min and a sigmoid increase of product concentration (c.f. Fig. 3), both effects hinting at an autocatalytic reaction promoted by the generated HF.

Therefore, considering HFIP serves to initiate the first round of C–F cleavage through its hydrogen-bond donating capacity ( $\alpha = 1.96$ ) [12], we hypothesized that using instead a catalytic amount of an even stronger HBD could trigger the reaction and

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### A. Previous work



### B. This work: TFA-initiated Friedel-Crafts reaction of benzylic fluorides

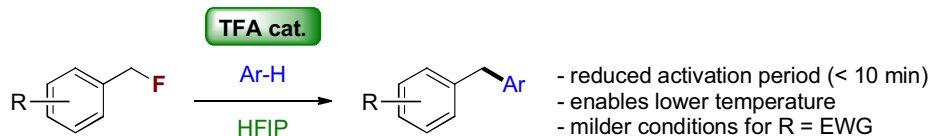


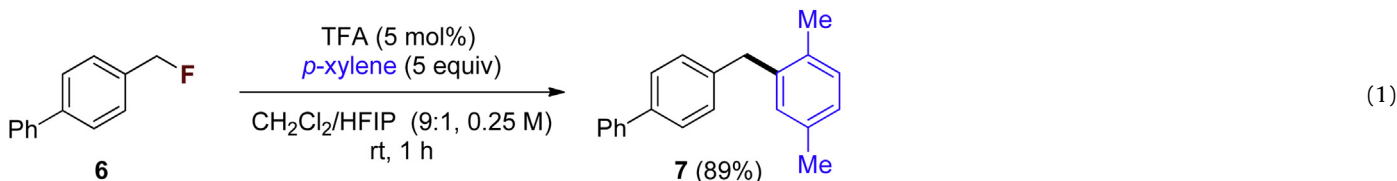
Fig. 1. Previous work and current work.

release HF, which in any case should be the strongest catalyst [13]. To this end, the Friedel-Crafts reaction of benzyl fluoride **6** with *p*-xylene in  $\text{CH}_2\text{Cl}_2$  was investigated, without HFIP, as a co-solvent, but in the presence of 5 mol% of various dry acids (Table 1). No reaction took place when using a catalytic amount of HFIP. In this case, we hypothesize that its concentration is too low to provide an efficient activation. Unsurprisingly, no reaction occurred when acetic acid (AcOH) was tried. Indeed, AcOH has a  $\alpha$  value of 1.12 [11], so is a weaker HBD than HFIP. Chloroacetic acid provided the same result. While its  $\alpha$  value is unknown, we expect that it should not be much higher than AcOH. Interestingly, those results also indicate that the Brønsted acidity of the activator is not an important factor in the initiation step (i.e., the initiation doesn't involve the formal protonation of the C–F bond) as AcOH and chloroacetic acid are much more acidic than HFIP [14]. Indeed, the  $\text{p}K_a$  values in  $\text{H}_2\text{O}$  for AcOH, chloroacetic acid, and HFIP are respectively 4.76, 2.86 and 9.3 [7]. However, when trifluoroacetic acid ( $\text{p}K_a = -0.25$ ) was used, full conversion and a 50% isolated yield of the desired product (**7**) was obtained after 18 h. The  $\alpha$  value for TFA has not been measured, but has been calculated to be 2.38 [15]. Hence, this result confirms our idea that stronger hydrogen-bond donors than HFIP can initiate the Friedel-Crafts reaction of benzylic fluorides.

At that point, although it was clear that HFIP could be replaced with TFA as the activator, we realized that HFIP does play other beneficial roles, since much better yields were obtained using our previous conditions (i.e. with HFIP, but no TFA) [6]. This is likely because of HFIP's polar nature, high-ionizing power and hydrogen-bonding stabilization of charged species, a phenomenon also observed in our XtalFluor-E mediated Friedel-Crafts reaction of benzylic alcohols [16]. To quantify this effect, a reaction initiated by TFA, but in the presence of HFIP was run. Fewer by-products were observed resulting in very good 89% yield in only 1 h. These optimized conditions, depicted in Eq. (1), were used for the rest of the study.

With optimized and reliable conditions in hand, we then sought to evaluate the scope of the reaction (Table 2). Using the reaction of fluoride **6** with toluene, we obtained a 89% yield in only 1.5 h, along with a 2.5:1 *para:ortho* selectivity (entry 1). Interestingly, we could also run the reaction at  $0^\circ\text{C}$ , leading to a better regioselectivity, albeit a longer reaction time was required and a significantly reduced yield was observed (entry 2). This is nonetheless interesting since without TFA, no reaction would occur at  $0^\circ\text{C}$ . Other nucleophiles, such as naphthalene (entry 3) or benzene (entry 4) could be employed. Electron-rich benzylic fluorides, such as **9**, spontaneously decomposed under the reaction conditions, as was observed without TFA (entry 5) [17]. Electron-poor substrates, which required harsh conditions to react in our previous system [6], benefited from the greatest improvements. Indeed, halogenated fluorides **10–12** promptly reacted at  $45^\circ\text{C}$ , in the presence of catalytic TFA (entries 6–8). Those milder conditions concomitantly furnished better isolated yields of the diarylmethanes. Overall, while limitations of this Friedel-Crafts procedure are similar with or without TFA, the use of this additive makes all reactions occur faster, under more gentle conditions, more reliably, and with better yields and selectivities. This is especially true for electron-poor substrates, which are less prone to the initial C–F cleavage to liberate the strongest catalyst HF.

In conclusion, we have reported that the addition of catalytic TFA shortens the induction period associated with the HFIP-promoted Friedel-Crafts reaction of benzylic fluorides. While TFA helps initiate the catalytic cycle, HF still likely is the active catalyst, and HFIP is still required for its polar and HBD capacities. Our improved reaction conditions were applied to a set of representative substrates, demonstrating how they could improve yields, reliability and initiation of this transformation. Study on the exploitation of the fastest initiation using TFA in other C–F bond activation system are underway and will be reported in due course.



We next examined the  $^1\text{H}$  NMR conversion vs time of the reaction between benzyl fluoride **6** with *p*-xylene with and without TFA to assess the effect on the initiation period (Fig. 3). This experiment revealed a dramatic reduction in the induction period from ca. 170 min (without TFA) to ca. 10 min (with 5 mol% of TFA).

## 3. Experimental

### 3.1. General

Solvents were purified using a Vacuum Atmospheres Inc. Solvent Purification System. All commercially available

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