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In situ activation of benzyl alcohols with XtalFluor-E: formation of 1,1-diarylmethanes and 1,1,1-triarylmethanes through Friedel–Crafts benzylation†

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The Friedel–Crafts benzylation of arenes using benzyl alcohols activated *in situ* with XtalFluor-E is described. A wide range of 1,1-diarylmethanes and 1,1,1-triarylmethanes were prepared under experimentally simple and mild conditions, without the need for a transition metal or a strong Lewis acid. Notably, the reactivity observed demonstrates the potential of XtalFluor-E to induce C–OH bond ionization and S_N1 reactivity of benzylic alcohols.

1,1-Diarylmethanes and 1,1,1-triarylmethanes as well as related structures represent important cores in medicinal chemistry and materials sciences.[1] While a number of approaches exist for their synthesis, the Friedel–Crafts benzylation (FCB) reaction remains the simplest and the most widely used one.[2] We have recently reported the synthesis of 1,1-diarylmethanes (**3**) using benzylic fluorides (**2**) as enabled by hydrogen-bonding (**2** → **3**, Fig. 1).[3] The benzyl fluorides (**2**) were generally prepared from the benzyl alcohol (**1**) through deoxofluorination (1 step) or a halogenation/substitution sequence (2 steps). Given the fact that HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), required for the FCB using benzyl fluorides, has a very low nucleophilicity,[4] we wondered if it would be possible to accomplish both steps in the same reaction vessel, *i.e.* performing the deoxofluorination in the presence of the reagent needed for the FCB step (**1** → **3**, Fig. 1).

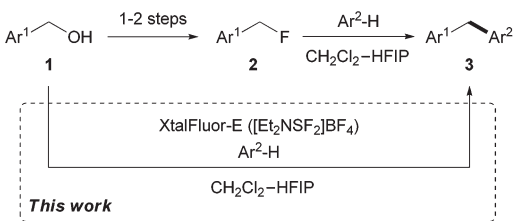
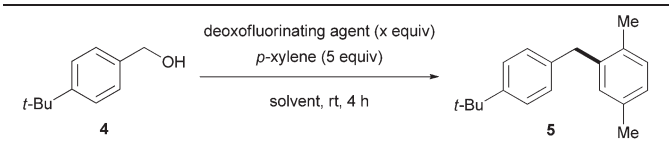


Fig. 1 Previous and current work.

We first probed this idea by performing test reactions using 4-*tert*-butylbenzyl alcohol (**4**) and *p*-xylene (Table 1). Using DAST (diethylaminosulfur trifluoride)[5] as the deoxofluorination agent in a CH_2Cl_2–HFIP (9 : 1) mixture, the 1,1-diarylmethane **5** was isolated in a promising 68% yield (entry 1). When the reaction was performed without HFIP, a slightly lower yield (entry 2) was obtained. The crude NMR spectra for both reactions showed traces of the benzyl fluoride (**2**; R = 4-*t*-Bu) supporting our initial hypothesis that the reaction would proceed through the *in situ* formation of the benzyl fluoride. However, this hypothesis conflicted with the results obtained with XtalFluor-E ($[Et_2NSF_2]BF_4$), a more thermally stable deoxofluorinating agent.[6] Indeed, using a slight excess of XtalFluor-E (1.1 equiv.) in a CH_2Cl_2–HFIP (9 : 1) mixture, product **5** was also obtained, in a quantitative yield (entry 3). As expected when using XtalFluor-E, a reagent that requires an external source of fluoride to induce the deoxofluorination reaction,[6] no benzylic fluoride could be detected in the crude NMR spectra of the reaction, thus raising questions concerning the

Table 1 Selected optimization results



Entry	Solvent	Deoxofluorinating agent (equiv)	Yield[a] (%)
1	CH_2Cl_2–HFIP (9 : 1)	DAST (1.1)	68
2	CH_2Cl_2	DAST (1.1)	62
3	CH_2Cl_2–HFIP (9 : 1)	XtalFluor-E (1.1)	100
4	CH_2Cl_2–HFIP (9 : 1)	XtalFluor-E (1.0)	89
5	CH_2Cl_2–HFIP (19 : 1)	XtalFluor-E (1.1)	87
6	CH_2Cl_2	XtalFluor-E (1.1)	82

[a] Isolated yield of **5**.

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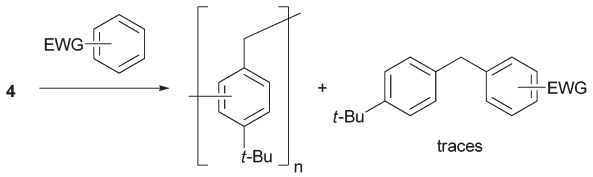
possible mechanism for the FCB using this activating agent. Reducing the amount of XtalFluor-E (entry 4), of HFIP (entry 5) or performing the reaction in CH_2Cl_2 only (entry 6) all resulted in reduced yield. XtalFluor-E is a known activating agent for the S_N2 substitution of alcohols,[7] yet had never been described as an effective stand-alone promoter for the S_N1 reaction of benzyl alcohols.

Herein, we report our results concerning this Friedel–Crafts benzylation of arenes using *in situ* activation of benzylic alcohols[8] or 1,1-diarylmethanols with XtalFluor-E to generate 1,1-diarylmethanes or 1,1,1-triarylmethanes respectively. In addition, we present evidence that the reaction proceeds through the *in situ* formation of an activated alkoxy-*N*,*N*-diethylaminodifluorosulfane intermediate. Finally, the reactivity observed herein demonstrates the potential of XtalFluor-E to act as an equivalent of triflic anhydride in other transformations where the ionization of a benzylic C–OH bond is necessary.

Using the optimized conditions (Table 1, entry 3), we investigated the use of various arene nucleophiles using 4-*tert*-butylbenzyl alcohol (**4**) and the results are shown in Table 2. Various electron-rich or electron-neutral aromatic compounds[9] could be used and the corresponding 1,1-diarylmethanes could be isolated in good to excellent yield.[10,11] Benzene or slightly deactivated fluorobenzene generated better yields when used as the co-solvent. More deactivated arenes, such as chlorobenzene or α,α,α-trifluorotoluene provided only very low yields (<5%) of the expected product and a polymer corresponding to the self-polymerization of **4** was observed instead (Scheme 1). Informatively, both acetanilide and phenylacetate provided moderate to good yield of the corresponding product.[12] This result contrasts drastically with our previous findings on the Friedel–Crafts of benzyl fluorides where no conversion was observed with those arenes,[3] suggesting that a different mechanism may be operating.



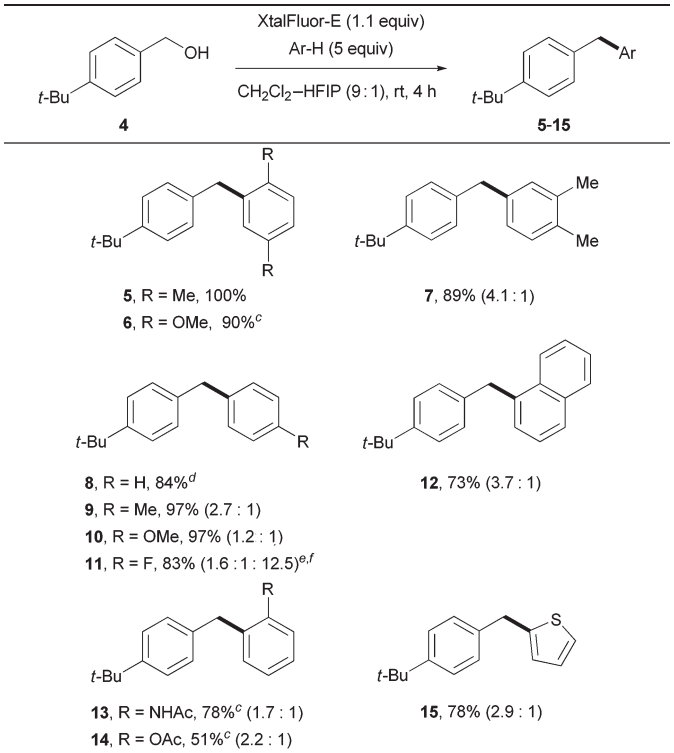
Scheme 1 Self-polymerization of **4** observed for electron-poor arenes.

We next evaluated the reactivity of various benzyl alcohols under the optimized conditions using *p*-xylene as the nucleophile (Table 3). Numerous substituents are fully tolerated, including a phenyl group and halogens. In a few cases, increasing the amount of XtalFluor-E and/or a longer reaction time was necessary to obtain full conversion. The presence of a methoxy group in *para* position was not tolerated as self-polymerization was observed. Moving the methoxy in *meta* position or replacing it by a less electro-donating substituent, such as an acetoxy group, allowed the reactions to proceed as expected. Surprisingly, the presence of a nitro group did not prevent the reaction as it was the case with benzyl fluorides,[3] again pointing toward a different mechanism. The use of 3-pyridinemethanol provided the desired product **27** in low NMR yield demonstrating that heterocyclic-based alcohols could be tolerated although further optimization will be necessary. Finally, using 4-(chloromethyl)benzyl alcohol, a bifunctional substrate bearing both a benzylic chloride and a benzylic alcohol, a chemoselective reaction occurred on the hydroxyl group and **28** was isolated in good yield.

We then investigated the reactivity of secondary alcohols. When 1-phenylethanol derivatives were used under the standard conditions, the desired products were observed, albeit in low yields, along with numerous side-products (including elimination products). In order to avoid any elimination, we sought to produce 1,1,1-triarylmethanes from 1,1-diarylmethanols, and the results are shown in Table 4. In all cases, the desired product was obtained in good to excellent yield.

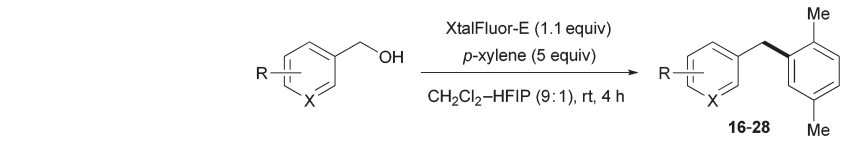
While investigating the FCB using benzylic alcohols, we noticed a few results that contrasted with those obtained using benzyl fluorides (*vide supra*). All of which suggested that the initial steps in this system may be mechanistically distinct from our previous work and this was confirmed by examining the effect of added base. In the Friedel–Crafts reaction of benzylic fluorides, the presence of base was shown to inhibit

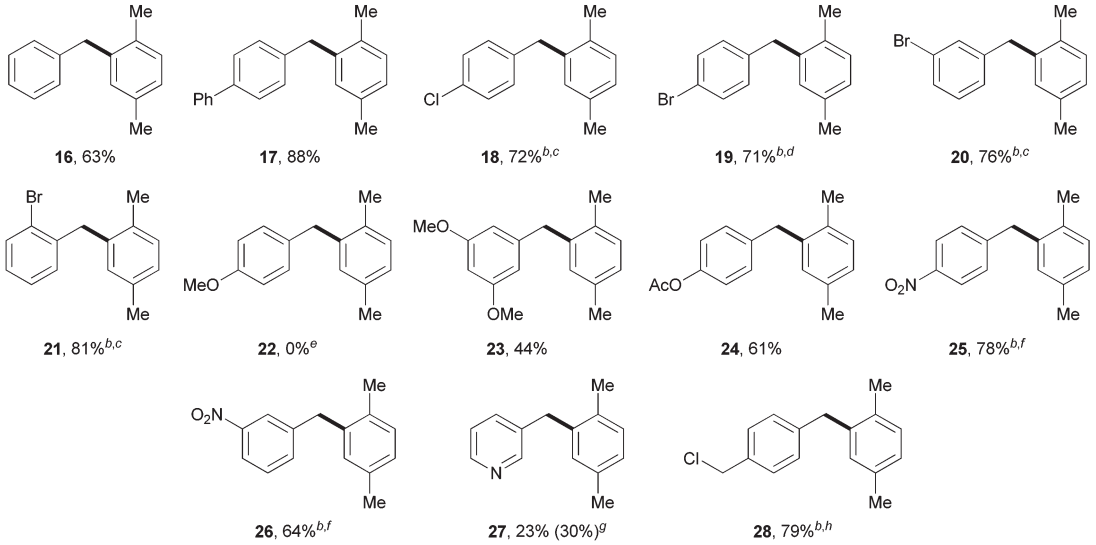
Table 2 Benzylation of **4** with various arenes[a,b]



[a] Isolated yield. [b] Ratio of regioisomers determined by ^{1}H NMR analysis with the major regioisomer shown. [c] Yield estimated by NMR. [d] Reaction was run in a benzene–HFIP (9 : 1) mixture at 60 °C for 18 h. [e] Reaction was run in a fluorobenzene–HFIP (9 : 1) mixture at 60 °C for 18 h. [f] Ratio of regioisomers (*ortho* : *meta* : *para*) determined by ^{1}H NMR analysis with the major regioisomer shown.

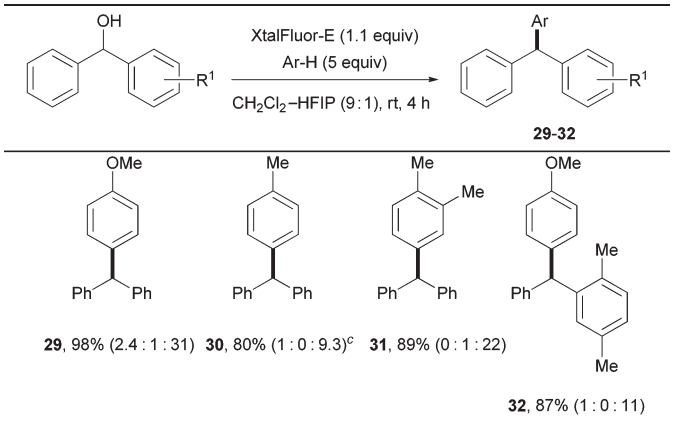
Table 3 Benzylation of various benzyl alcohols with *p*-xylene[a]



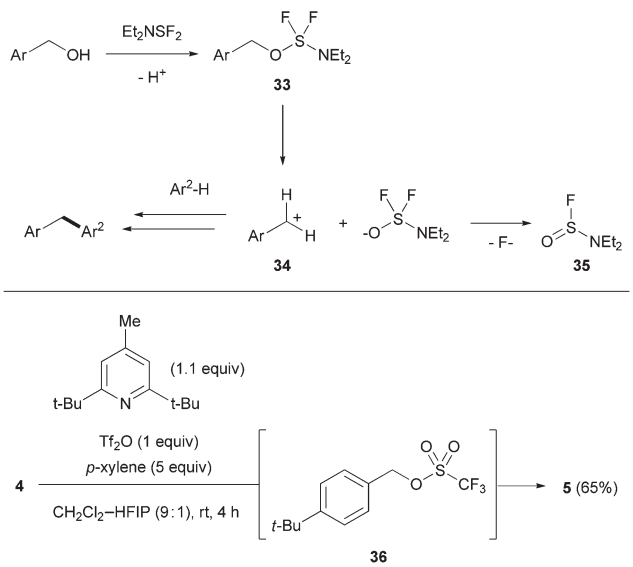


[a] Isolated yield. [b] 2.0 equiv of XtalFluor-E were used. [c] Reaction time was 48 h. [d] Reaction time was 24 h. [e] Decomposition. [f] Reaction time was 72 h. [g] Yield estimated by NMR. [h] Reaction time was 18 h.

Table 4 Synthesis of 1,1,1-triarylmethanes[a,b]



[a] Isolated yield. [b] Ratio of regioisomers (*ortho* : *meta* : *para*) determined by ^{1}H NMR analysis. [c] Reaction was run in a toluene–HFIP (9 : 1) mixture.



Scheme 2 Mechanistic hypothesis and reactivity of a benzyl triflate generated *in situ*. The BF_4^- counter-ion has been omitted for clarity.

the reaction through the neutralization of HF, the active catalyst.[3] In the present system, addition of 0.1 or 1 equivalent of a base ($NaHCO_3$ or 2,6-di(*tert*-butyl)-4-methylpyridine) had limited effect on the reaction and the product was isolated in similar yields.[13] Based on those experiments and observations, our current mechanistic hypothesis is shown in Scheme 2. The benzylic alcohol would react with XtalFluor-E to generate an alkoxy-*N*,*N*-diethylaminodifluorosulfane (**33**).[6,14] Ionization would provide a stabilized benzylic carbocation (**34**)[15] along with diethylaminosulfinyl fluoride (**35**) after fluoride loss.[16] The fact that using deactivated arenes as nucleophiles provided essentially a product corresponding to the self-polymerization of **4** (c.f. Scheme 1) suggests that this ionization step is

irreversible as opposed to what has been observed by Bode for the FCB of benzyl hydroxamates in the presence of $BF_3{\cdot}Et_2O$.[17] The benzylic carbocation **34** would react with the arene nucleophile (Ar^2–H) to produce the 1,1-diarylmethane product.

This proposal is further supported by the fact that, as shown in Scheme 2, *in situ* generated benzyl triflate **36**, which bears some structural resemblance with the proposed alkoxy-*N*,*N*-diethylaminodifluorosulfane intermediate **33**, reacted in a similar fashion providing the 1,1-diarylmethane **5** in an unoptimized 65% isolated yield (89% NMR yield). Finally, while in this system HFIP is not directly involved in the transformation, the slight improvements observed in its presence (c.f. Table 1) suggest that it may nevertheless facilitate the reaction, likely because of its polar nature and high ionizing power.[4]

In summary, we have reported the Friedel–Crafts benzylation of arenes using benzyl alcohols, which are activated *in situ* with XtalFluor-E. A wide range of 1,1-diarylmethanes and 1,1,1-triarylmethanes can be prepared in moderate to excellent yields. The reaction proceeds under experimentally simple and mild conditions, without the need for a transition metal or a strong Lewis acid. Notably, the reactivity observed herein demonstrates the potential of XtalFluor-E to induce C–OH bond ionization and S_N1 reactivity of benzyl alcohols.

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