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Catalytic Friedel-Crafts Reactions of Highly Electronically Deactivated Benzylic Alcohols

Vuk D. Vuković, Edward Richmond, Eléna Wolf, Joseph Moran*

Abstract: Highly electronically deactivated benzylic alcohols, including those with a CF₃ group adjacent to the OH-bearing carbon, undergo dehydrative Friedel-Crafts reactions upon exposure to catalytic Brønsted acid in HFIP solvent. Titration and kinetic experiments support the involvement of higher order solvent/acid clusters in catalysis.

The Friedel-Crafts reaction is a transformation of central importance for the synthesis of industrially relevant arenes and heteroarenes.^{1,2} The classical version requires stoichiometric quantities of Lewis acid and uses alkyl halides as starting materials, which are often generated in a separate step from alcohol precursors. Variants developed recently by Bode and Stephen have expanded the scope of the Friedel-Crafts reaction to include electronically deactivated benzylic electrophiles through the use of benzylic *N*-methylhydroxamic acids and fluorides, respectively (Figure 1, a).³ However, like the classical version, these reactions require additional steps for substrate pre-activation and use stoichiometric activating agents. The need to improve the step- and atom-economy of the Friedel-Crafts reaction prompted the *ACS Green Chemistry Pharmaceutical Roundtable* to designate the development of catalytic versions starting directly from alcohols that produce water as the only stoichiometric by-product as a top priority for green chemistry.⁴ Accordingly, the past years have witnessed numerous reports of Lewis or Brønsted acid catalyzed Friedel-Crafts reactions of electronically activated benzylic alcohols,^{5,6,7} but the inability to use electronically deactivated alcohols remains a striking limitation. For example, the ferrocenium hexafluoroantimonate boronic acid catalyst developed by Hall and McCubbin, arguably the most active catalytic system described to date, reaches its limits at primary benzylic alcohols bearing modestly deactivating substituents and restricts access to highly fluorinated molecules of potential interest to the pharmaceutical and agrochemical industries (Figure 1, b).⁶¹ Recently, we observed that hydrogen bonding interactions between Brønsted acid catalysts and co-catalysts or solvents can have profound accelerating effects and even change the kinetic concentration dependence in catalytic substitution reactions of alcohols.⁸ Herein we report that interactions between Brønsted acid catalysts and solvents of low nucleophilicity known to form H-bond clusters, such as hexafluoroisopropanol (HFIP),^{9,10,11} can be exploited to surpass current limitations of the catalytic dehydrative Friedel-Crafts reaction by enabling reactivity of highly electronically deactivated benzylic alcohols, including those bearing a geminal CF₃ group. This new method grants access to deactivated, often highly

fluorinated, diarylmethanes and diaryltrifluoroethanes from the corresponding alcohol in a single catalytic step (Figure 1, c). Mechanistic experiments support the involvement of higher order solvent/acid clusters and point to an S_N1-type mechanism.

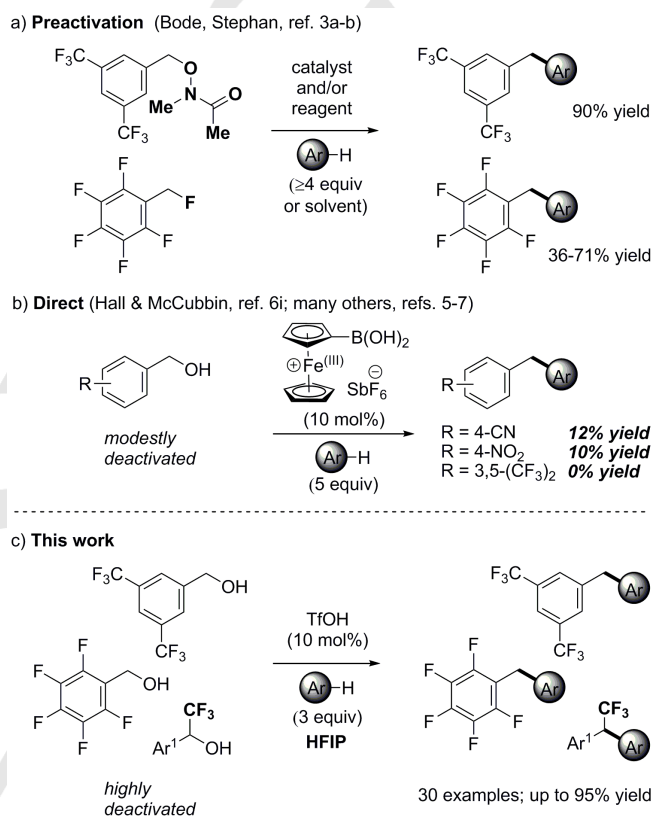
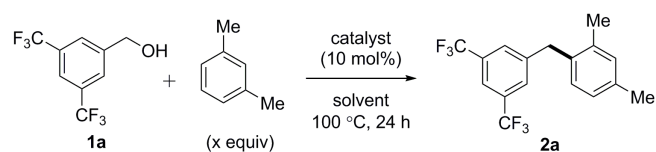


Figure 1. Friedel-Crafts reactions of highly electronically deactivated benzylic electrophiles.

Initial experiments targeted Friedel-Crafts reactivity of *m*-xylene with alcohol **1a**, which was too deactivated for catalysis by ferrocenium hexafluoroantimonate boronic acid.⁶¹ To our delight, the simple conjugate acid, HSBF₆•6H₂O, furnished modest yields of **2a** under otherwise identical conditions (Table 1, entry 1). Reactivity was improved slightly by using HFIP as the sole solvent (entry 2). TfOH furnished higher yields due to its superior thermal stability compared to HSBF₆•6H₂O (entry 3). Other strong Lewis and Brønsted acids were also effective (entries 4-5). The addition of catalytic quantities of base to the reaction mixture, or the use of sodium salts or weaker Brønsted acids completely shut down the reaction (entries 6-8). The excess of nucleophile could be reduced to 3 equiv without a large drop in yield (entry 9). Other fluorinated protic solvents were less effective (entries 10-11) and several non-fluorinated common solvents did not produce a detectable amount of **2a** (entries 12-14).

* V. D. Vuković, Dr E. Richmond, Dr E. Wolf, Dr J. Moran.
University of Strasbourg, CNRS, ISIS UMR 7006,
F-67000 Strasbourg, France.
E-mail: moran@unistra.fr

Table 1. Optimization of conditions^a

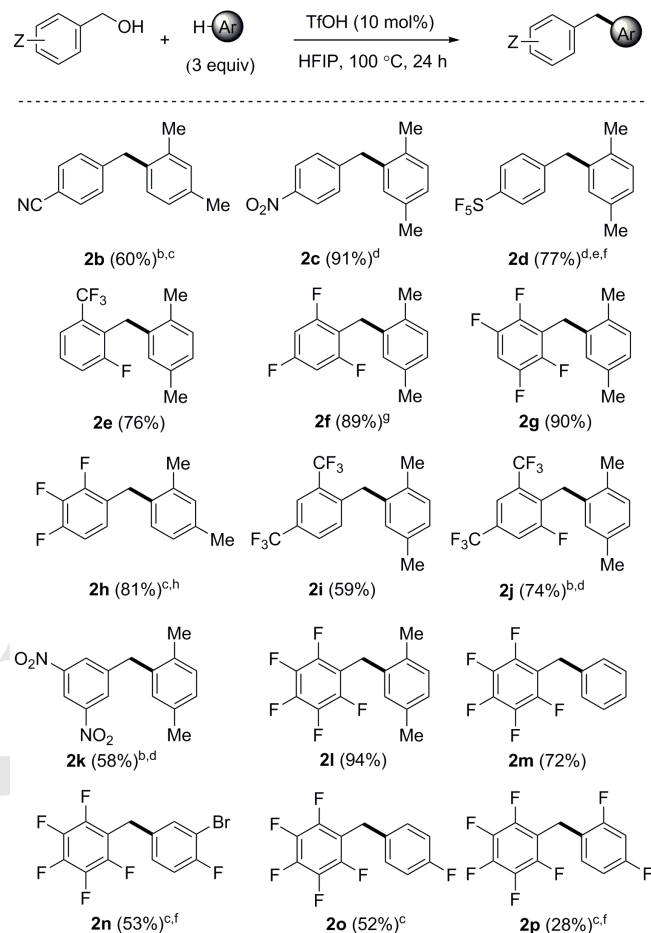
entry	catalyst	solvent	x	yield ^b (%)
1	HSbF ₆ ·6H ₂ O	HFIP/MeNO ₂ (4:1)	5	28
2	HSbF ₆ ·6H ₂ O	HFIP	5	39
3	TfOH	HFIP	5	90
4	FeCl ₃	HFIP	5	18
5	Bi(OTf) ₃	HFIP	5	90
6	HSbF ₆ ·6H ₂ O ^c	HFIP	5	<1
7	NaSbF ₆	HFIP	5	<1
8	TFA	HFIP	5	<1
9	TfOH	HFIP	3	83
10	TfOH	CF ₃ CH ₂ OH	3	19
11	TfOH	(CF ₃) ₃ COH	3	69
12	TfOH	MeNO ₂	3	<1
13	TfOH	THF	3	<1
14	TfOH	Toluene	3	<1

^aAll experiments were conducted in sealed reaction tubes. ^bIsolated yields of a mixture of regioisomers after silica gel chromatography. See SI for details.

^cConducted in the presence of 10 mol% Proton Sponge.

A variety of electronically deactivated primary benzylic alcohols and arene nucleophiles were examined to assess the scope of the transformation (Table 2). Benzylic alcohols substituted with single CN, NO₂, CF₃ and SF₅ groups reacted efficiently (**2b-2e**). Impressively, benzylic alcohols bearing up to two CF₃ groups, two NO₂ groups or up to five fluorines on the aromatic ring were well tolerated (**2i-2k**). Heteroaromatic nucleophiles were unfortunately not compatible with the reaction conditions.¹² Pleasingly, less activated nucleophiles such as benzene, fluorobenzene, 1-bromo-2-fluorobenzene and 1,3-difluorobenzene are tolerated albeit in lower yield (**2n-2p**).

The success with highly deactivated benzylic alcohols prompted us to explore the possibility that carbenium ions with adjacent electron-withdrawing groups might be generated and trapped directly from the alcohol in a catalytic manner. α -Trifluoromethyl cations are synthetically valuable intermediates but difficult to form from the alcohol with catalytic turnover due to a high activation barrier. Consequently, the desired reactivity has previously only been accessed by stepwise or *in situ* pre-activation of alcohols using stoichiometric activating agents or in concentrated H₂SO₄.^{13,14,15} Gratifyingly, our standard conditions provide the first example of catalytic access to α -trifluoromethyl cations directly from α -trifluoromethyl benzylic alcohols, as evidenced by direct dehydrative Friedel-Crafts reactions with a range of nucleophiles (Table 3). This reaction provides an efficient catalytic route to non-symmetric fluorinated analogs of the insecticide DDT, complementing existing routes to symmetric analogs.^{15,16} The parent α -trifluoromethyl benzylic

Table 2. Scope for deactivated primary benzylic alcohols^a

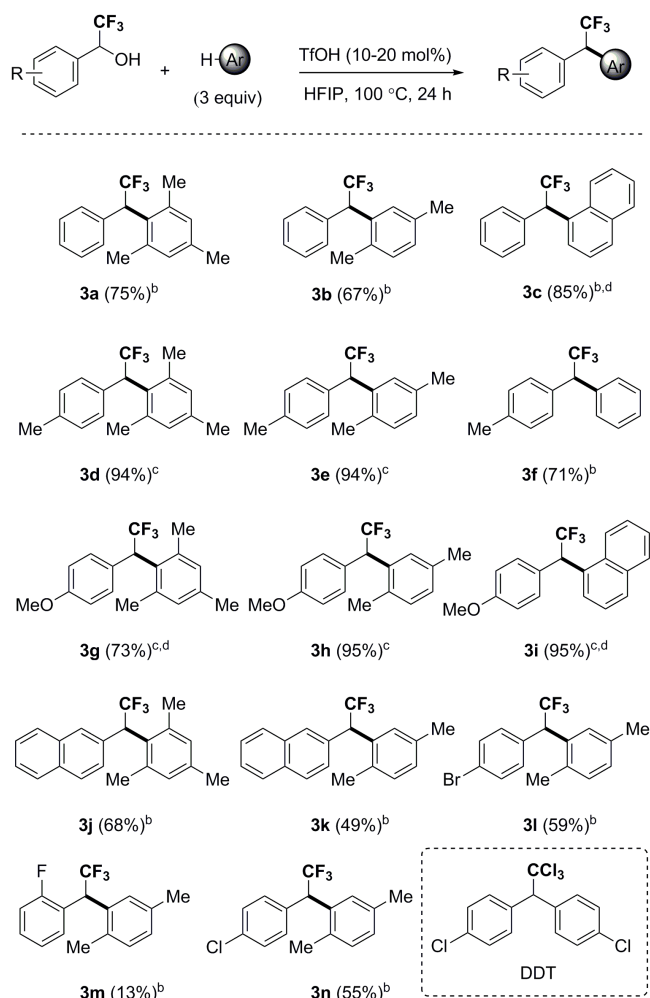
^aIsolated yields after column chromatography over silica. ^bPerformed with 20 mol% TfOH. ^cCombined yield of regioisomers. See the SI for more details.

^dReaction time was 48 h. ^ePerformed with 10 mol% HSbF₆·6H₂O as catalyst, 80 °C. ^fPerformed with 5 equiv of nucleophile. ^gPerformed at 50 °C, 30 min.

^hPerformed at 50 °C, 1 h.

alcohol and aromatic ring furnished the desired diarylmethanes in good to excellent yields (**3a-i**). Naphthyl-derived alcohols are well tolerated by the reaction system (**3j-k**). Analogs bearing halogens on the aromatic ring provide the product diarylmethanes in more modest synthetic yields (**3l-n**), but nevertheless offer a handle for further functionalization through metal-catalyzed cross-coupling reactions.

To evaluate whether factors beyond the appealing bulk properties of HFIP solvent might be crucial to expanding the limits of the dehydrative Friedel-Crafts reaction, a solution of pentafluorobenzyl alcohol (**1b**) in HFIP was titrated with TfOH and monitored by ¹H NMR (Figure 2). In addition to fast proton exchange between TfOH and the OH proton of HFIP (H_x and H_y, respectively), an increasingly downfield shift of the HFIP methine proton (H_z) was observed with increasing concentrations of TfOH. In contrast, fast proton exchange was not observed between TfOH and the OH proton of **1b** (H_n), nor was the signal corresponding to the methylene protons of **1b** (H_m) observed to shift during the titration, indicating that TfOH preferentially donates H-bonds to HFIP rather than **1b**. Mixed ethers resulting

Table 3. Scope of diaryltrifluoroethanes^a

^aIsolated yields after column chromatography over silica. ^bPerformed with 20 mol% TfOH. ^cPerformed with 10 mol% TfOH. ^dCombined yield of regioisomers. See the SI for more details. ^eReaction performed at 75 °C.

from dehydrative condensation of HFIP and **1b** were not observed, ruling out the possibility that HFIP ethers serve as a reservoir of benzylic cations.^{3a,10e} However, in the absence of arene nucleophile, ethers resulting from the dehydrative dimerization of **1b** were observed to form in small quantities when higher catalyst loadings (>40 mol% TfOH) were employed. Initial rate kinetics experiments using benzene as nucleophile revealed a first order kinetic concentration dependence on TfOH and a fifth order concentration dependence on HFIP.¹⁷ Finally, the reaction of (–)-**1d** with *p*-xylene under standard conditions led to a near complete loss of stereochemical information in the product, a result consistent

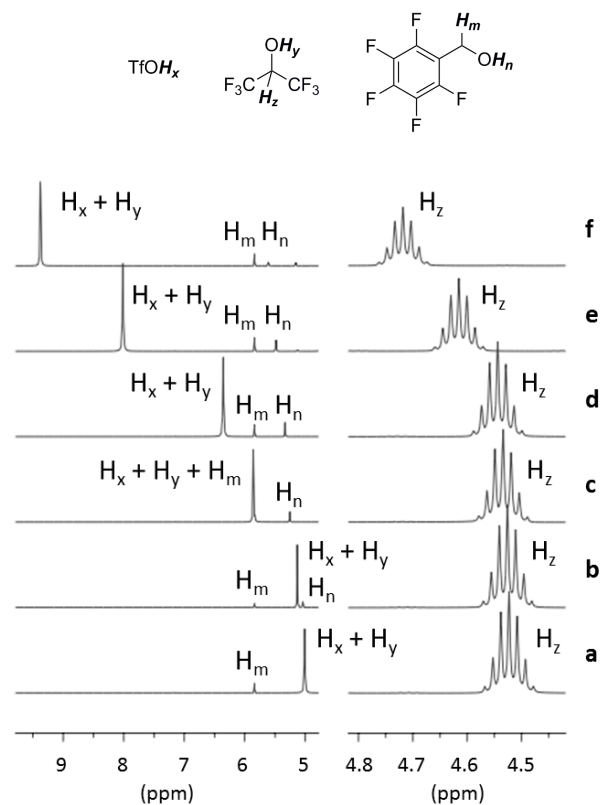
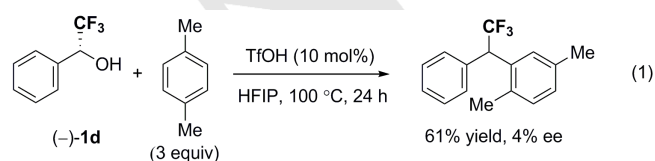


Figure 2. ¹H NMR titration of a mixture of HFIP (1 equiv) and **1b** (0.050 equiv) with TfOH (C₆D₆ as external standard). Spectra were acquired in the presence of the following quantities of TfOH: a) 0 mol%; b) 0.5 mol%; c) 5 mol%; d) 10 mol%; e) 43 mol%; f) 110 mol%.

with the intermediacy of a carbenium adjacent to the CF₃ group (eq 1). Taken together, the titration, initial rate kinetics and racemization experiments and the lack of observation of a “carbenium reservoir” support an S_N1-type mechanism where HFIP serves to interact with the Brønsted acid to generate higher order mixed aggregates that are superior, and thus the kinetically competent, catalytic species for the ionization of benzylic alcohols. The underappreciated role of HFIP as an H-bond acceptor¹⁸ with strong Brønsted acids and the importance of aggregation also lends mechanistic insight into why HFIP appears to be critical in several other Brønsted acid catalyzed reactions that have been reported recently.^{10,19}

In conclusion, we have described a simple catalytic system that significantly pushes the boundaries of the dehydrative Friedel-Crafts reaction to incorporate highly electronically deactivated benzylic alcohols, including those with a CF₃ group adjacent to the OH-bearing carbon. Interactions between the Brønsted acid and HFIP generates catalytically active aggregates in which the H-bond accepting ability of HFIP plays an important role. Further studies are underway to exploit this operationally simple approach to promote a wide variety of Brønsted acid catalyzed transformations that do not otherwise proceed in traditional solvents.

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Notes

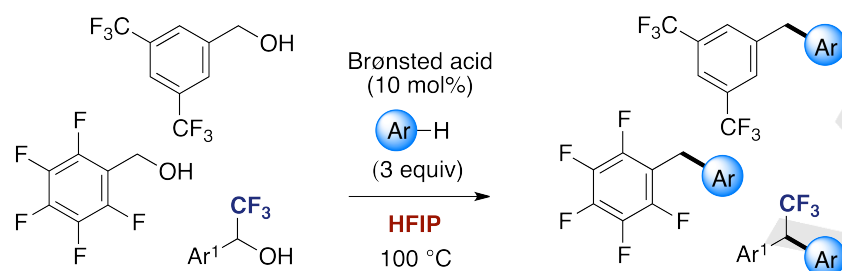
The authors declare no competing financial interest.

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Keywords: Brønsted acid catalysis; alcohols; Friedel-Crafts; carbenium ion; HFIP.

Entry for the Table of Contents: More than a solvent: The use of the fluorinated solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and a catalytic amount of a strong Brønsted acid enables dehydrative Friedel-Crafts reactions of highly deactivated benzylic alcohols. Mixed aggregates of acid and HFIP are likely to be involved in the catalysis.

COMMUNICATION



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**Catalytic Friedel-Crafts Reactions of
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■ Cooperativity between Brønsted acid and aggregates of HFIP