In situ generation and synthetic applications of anhydrous hydrogen fluoride in a solid-liquid biphasic system

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The *in situ* generation of anhydrous HF by reaction of solid CaF_2 with H_2SO_4 in the presence of an organic phase containing the substrate is proposed as a simple and safe alternative to other fluorination methods. Using this method, the addition of HF to olefins to produce fluoroalkanes, the substitution of hydroxy and halide functional groups by F atoms, and the conversion of anilines to fluorobenzenes, proceed with good conversions and moderate yields. In the latter reaction, HF generation, diazotization and fluoro de-diazonization can all be carried out in one pot. Reactions can be performed at ambient temperatures and pressures. HF generation using NaF or KF as fluoride sources is less efficient due to formation of stable bifluorides. Lipophilic quaternary ammonium salts such as tetra-*n*-octylammonium bromide can be used to enhance the extraction of HF into the organic phase. The effects of solvent nature and reagent ratios are discussed.

Introduction

Anhydrous hydrogen fluoride is an important multipurpose fluorination reagent, with a worldwide yearly production capacity of 10^6 metric tons.[1] However, its extreme toxicity and corrosiveness render its transportation, storage,[2] and handling troublesome. In fact, safety factors concerning the transportation and storage of anhydrous HF are causing a continuous public debate.[3] These factors, combined with the high vapor pressure at ambient temperatures (bp 19.6 °C) which often necessitates pressurized reaction conditions, may deter researchers from its use. Circumvention of some of these difficulties using alkylammonium fluorides,[4a] boronfluorides,[4b] and amine–HF adducts has been proposed,[4c] *e.g.* by Olah and co-workers,[5] who introduced a pyridinium/poly-HF reagent in a variety of fluorination reactions.

In this paper we present a simple method for the *in situ* generation and extraction of anhydrous HF into an inert organic solvent at ambient temperatures and pressures, in which hydrofluorinations of various substrates can then be performed. Essentially based on the same raw materials employed in the large-scale industrial HF process, this technique is proposed as a simple, safe, and cheap alternative to other hydrofluorination methods. Three reactions are examined: (i) addition of HF to olefins to produce fluoroalkanes; (ii) substitution of alcohol or halide functional groups by fluorine atoms; and (iii) deaminative conversion of anilines to fluorobenzenes.

Results and discussion

Generation of anhydrous HF

In a typical reaction [eqn. (1)], 98% H_2SO_4 was added dropwise

$$CaF_{2(s)} + H_2SO_{4(l)} \xrightarrow[25\,°C,\,4\,h]{CH_2Cl_2} CaSO_{4(s)} + 2HF_{(CH_2Cl_2)} \quad (1)$$

40% conversion

to a suspension of solid CaF_2 in CH_2Cl_2 at 25 °C over a period of 3 h while monitoring the concentration of HF in the organic phase. Batch addition of the acid resulted in the formation of large solid aggregates which, because of their small surface area, arrested the reaction at low HF yields.

The HF yield was found to depend to a certain extent both on stirring and on reagent ratios. These two parameters influence the rate of H_2SO_4 diffusion through the solid $CaSO_4$ layer which forms over the CaF_2 particle. Apparently, HF is formed on the surface of the CaF_2 particle during the reaction with H_2SO_4. The solid $CaSO_4$ by-product, which is slightly soluble in H_2SO_4, overlays the CaF_2 particle, trapping some of the HF in the solid phase, and inhibits the access of H_2SO_4 reactant molecules (Fig. 1). This arrests HF production at *ca.* 40% conversion of CaF_2.

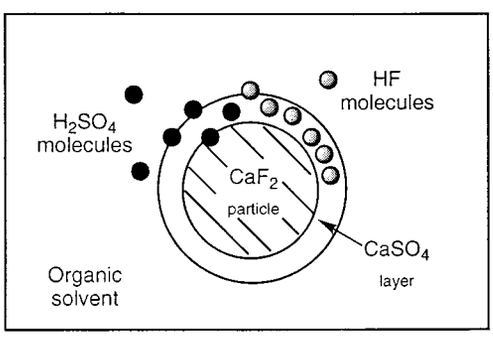


Fig. 1 Schematic representation of the solid/liquid HF generation system.

Some indication as to which organic solvent should be used may be inferred from the distribution coefficients of *aqueous HF* in organic solvents. Experiments suggested the following decreasing order: $CH_2Cl_2 \approx CHCl_3$ > toluene > mesitylene > $CCl_4 \approx$ *n*-hexane.

Using CH_2Cl_2 [eqn. (1)], the concentration of HF in the organic phase, $[HF]_{org}$, reached a plateau at 0.117 M at 25 °C. HF molecules trapped in the solid inorganic phase can be "milked" into the organic phase by replacing it with a fresh batch. In six such batches, $[HF]_{org}$ remained between 0.11 and 0.12 M. However, CaF_2 conversion remained unchanged (39–40 mol% based on the initial amount of CaF_2), meaning that no additional HF was produced.

We also found that catalytic amounts of lipophilic quaternary ammonium salts such as tetraoctylammonium bromide (TOAB) facilitated the extraction of HF into the organic liquid phase from the inorganic "solid" phase. The amount of HF extracted into the former was roughly proportional to the production of HF in the latter. Since the inorganic phase is solid,

Table 1 Extraction of HF, water, and H_2SO_4 into different organic solvents using TOAB

Entry	Solvent	$[HF]_{org}$ [a]/M	$[HF]_{org}$/M	$[H_2O]_{org}$/M	$[H_2SO_4]_{org}$/M	ΔHF [b]	$ΔH_2O$ [b]	$ΔH_2SO_4$ [b]
1	Hexane	0.025	0.065	0.001	0.001	5.0	0.1	0.7
2	Toluene	0.150	0.194	0.009	0.011	5.6	0.3	1.0
3	Mesitylene	0.135	0.179	0.008	0.010	5.5	0.2	1.0
4	CH_2Cl_2	0.165	0.213	0.005	0.002	6.0	0.1	1.2
5	$CHCl_3$	0.160	0.205	0.004	0.002	5.9	0.1	1.1
6	CCl_4	0.033	0.073	0.002	0.001	5.0	0.1	0.8

Conditions: 0.06 mol CaF_2, 0.06 mol H_2SO_4, 50 ml solvent, 0.008 M TOAB, 25 °C. [a] Control reaction (no TOAB). [b] ΔX = number of X molecules extracted into the organic phase by one TOAB molecule.

Table 2 Influence of H_2SO_4 : CaF_2 ratio on HF production and extraction into CH_2Cl_2

Entry	H_2SO_4 : CaF_2	CaF_2 conversion (%)	ΔHF [a]	$ΔH_2O$ [a]	$ΔH_2SO_4$ [a]
1	1 : 1	40	6.00	0.13	1.20
2	2 : 1	56	4.00	0.25	1.00
3	3 : 1	68	2.30	0.19	1.00
4	4 : 1	78	2.20	0.13	0.52

Conditions: 0.06 mol CaF_2, 0.06 mol H_2SO_4, 50 ml CH_2Cl_2, 0.008 M TOAB, 25 °C. [a] ΔX = number of X molecules extracted into the organic phase by one TOAB molecule.

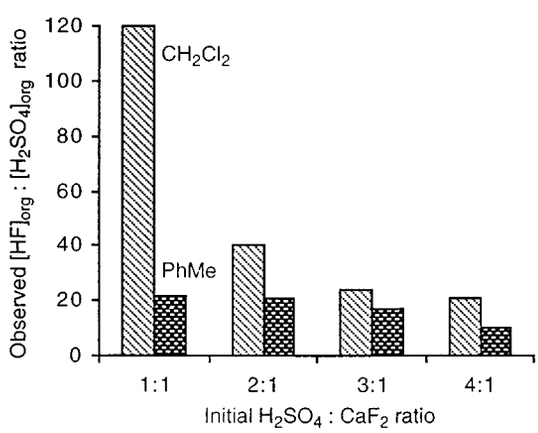


Fig. 2 Extraction of HF and H_2SO_4 at different initial reagent ratios.

all of the TOAB remained in the organic phase and the extraction took place at the solid/liquid interface. As expected[6] for this kind of system, ammonium cations with short hydrophobic chains (*e.g.* tetramethyl-, tetraethyl-, tetrapropyl-, and even tetrabutylammonium cations) were less efficient at extracting HF. However, ammonium cations with Br^- and Cl^- counterions displayed similar extraction efficacies, as did all lipophilic ammonium salts with a $C_{number} > 24$. For these reasons, TOAB was chosen as the phase-transfer catalyst for this study.

In a series of experiments, we determined the absolute concentrations of HF, water, and H_2SO_4 that were obtained in various organic solvents in the presence of catalytic amounts of TOAB (Table 1). Each molecule of TOAB extracted 5–6 molecules of HF, irrespective of solvent type. However, solvent nature did affect the $[HF]_{org}$: $[H_2SO_4]_{org}$ ratios, depending on the initial H_2SO_4 : CaF_2 ratios employed (*vide infra*).

As mentioned above, production of HF and its extraction into the organic phase was also influenced by the initial H_2SO_4 : CaF_2 ratio. However, while a higher H_2SO_4 : CaF_2 ratio led to better CaF_2 conversion, the same high amounts of H_2SO_4 had a detrimental effect on the extraction of HF into the organic phase (Table 2).

One notable distinction between polar and apolar aprotic solvents is the large difference in $[HF]_{org}$: $[H_2SO_4]_{org}$ ratios at the preferred 1 : 1 ratio of H_2SO_4 : CaF_2 (Fig. 2). This difference is significant, because it means that if *in situ* fluorination is carried out with toluene as a solvent, the excess H_2SO_4 can interfere with the reaction and/or cause side reactions (*vide infra*). CH_2Cl_2 was chosen as the solvent on account of its inertness towards both HF and H_2SO_4, combined with its high selectivity towards HF extraction.

It should be noted that some water was also produced from the reaction HF + $H_2SO_4 \rightarrow FSO_3H + H_2O$. Between 7–10% of the generated HF was consumed in this reaction at 25 °C.

We have examined NaF and KF as alternative fluoride sources. However, generation of HF using NaF or KF as fluoride ion sources was strongly influenced by the basicity of these salts, which reacted exothermically with H_2SO_4 to give stable bifluorides [eqn. (2)]. This reaction inhibited HF production

$$2MF_{(s)} + H_2SO_{4(l)} \xrightarrow{CH_2Cl_2,\ 25\ °C} MHF_{2(s)} + MHSO_{4(s)} \quad (2)$$

$$M = K, Na$$

and resulted in an $[HF]_{org}$ which was an order of magnitude lower than when CaF_2 was employed.

Based on these findings, we tested the application of the CaF_2–H_2SO_4–TOAB–CH_2Cl_2 system as a source for HF for a variety of addition and substitution reactions.

Table 3 Addition of anhydrous HF to olefins

Entry	Substrate	Time/h	Conversion (%)	Product (% yield)
1	Oct-1-ene	30	96	2-Fluorooctane (66) [a]
2	Dec-1-ene	30	95	2-Fluorodecane (86) [b]
3	Cyclohexene	2.5	86	Cyclohexyl fluoride (69) [b]
4	Oct-1-yne	15	82	2-Fluorooctene (55) [b]

Conditions: 60 mmol CaF_2, 60 mmol H_2SO_4, 20 mmol substrate, 50 ml CH_2Cl_2, 0.5 mmol TOAB, 25 °C. [a] Isolated yield. [b] Yield based on GC area, corrected by the presence of an internal standard.

Addition of generated HF to unsaturated compounds

In a typical reaction, the HF-generation system described above was employed in combination with a solution of oct-1-ene in CH_2Cl_2 as the organic liquid phase [eqn. (3)]. After 30 h of

$$CH_2{=}CH\text{-}C_6H_{13} + \tfrac{1}{2}CaF_{2(s)} + \tfrac{1}{2}H_2SO_{4(l)}$$

96% conversion

$$\xrightarrow[CH_2Cl_2,\ 25\ °C,\ 30\ h]{2.5\ mol\%\ TOAB} CH_3\text{–}CHF\text{–}C_6H_{13} + \tfrac{1}{2}CaSO_{4(s)} \quad (3)$$

66% isolated yield

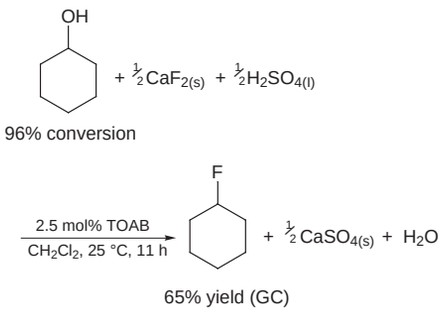
stirring at room temperature, 96% of the substrate had reacted and 2-fluorooctane was isolated in a 66% yield. Good to moderate yields were also obtained using cyclohexene, dec-1-ene, and oct-1-yne as substrates (Table 3). The main by-products were rearranged olefins, alcohols (products of the attack of water molecules formed by the reaction between HF and H_2SO_4

on the carbocation), and high molecular weight alkylation/polymerization products.

A strong dependence was found between product yield and the initial amount of water in the system (Fig. 3).

Substitution of -OH and -Cl groups

Secondary alcohols and alkyl chlorides were also converted to the corresponding fluoroalkanes in the HF-generation system described above. For example, cyclohexanol [eqn. (4)] was con-



verted to cyclohexyl fluoride (96% conversion and 65% yield after 11 h). Benzyl alcohol (85% conversion), benzoyl chloride (80% conversion), octan-2-ol (95% conversion), and decan-2-ol (95% conversion) reacted similarly to give benzyl fluoride (30% yield), benzoyl fluoride (29% yield), 2-fluorooctane (65% yield), and 2-fluorodecane (70% yield) respectively.

In both addition and substitution reactions, the presence of excess H_2SO_4 led to high-M_w, tarry, sulfur-containing products. Control experiments followed by elemental analysis showed that similar compounds were formed when alkenes/alcohols were reacted with plain H_2SO_4. Generally speaking, the rates

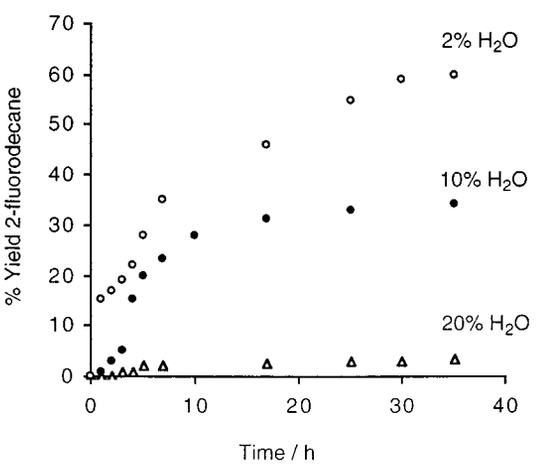


Fig. 3 Detrimental effect of water on product yield.

and the final yields of fluorinations with anhydrous HF were found to increase with solvent polarity, in the order CH_2Cl_2 > $CHCl_3$ > toluene ≈ CCl_4 ≈ cyclohexane.

One-pot synthesis of fluorobenzenes from anilines

The substitution of aromatic amine groups with fluorine atoms *via* diazotization followed by fluoro de-diazonization in the presence of fluoride donors is commonly effected using $NaNO_2$–BF_4^- (Balz–Schiemann method[7]). Use of previously prepared anhydrous HF is also known.[8] The method proposed herein enabled the entire process (including the production of the HF itself) to be performed in one pot under moderate conditions and using simple and inexpensive equipment. In an exemplary procedure (Scheme 1), aniline **1a** and $NaNO_2$ were added to a pre-mixed suspension of CaF_2–H_2SO_4 in CH_2Cl_2 and stirred at 0 °C for 15 min. The reaction vessel was then heated to 20–65 °C for the fluoro de-diazonization and then quenched with ice. Substrate conversion was 100% in all experiments. After workup, the main product isolated was fluorobenzene **2a** (30–45% isolated yield depending on specific conditions), together with phenol **3a**, benzene **4a**, and a tarry residue (typically 30–50%). Similar reactions were observed with *p*-toluidine **1b**, *p*-nitroaniline **1c**, *p*-chloroaniline **1d**, and 2-ethylaniline **1e** as substrates (Table 4).

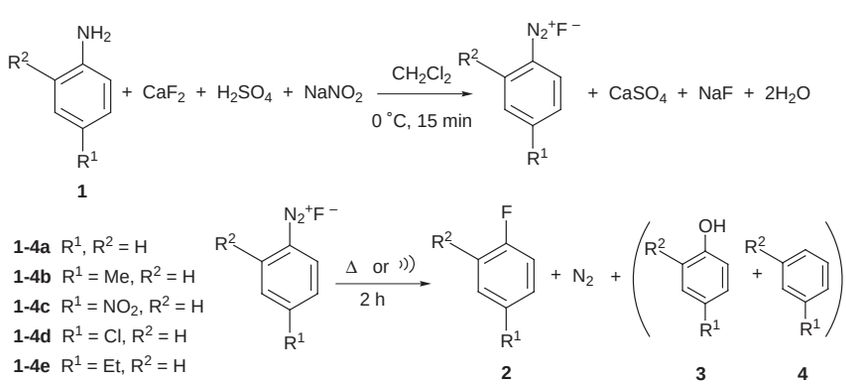
Initial, unoptimized experiments demonstrated that sonication can be used as an alternative to conventional heating/mixing in the decomposition of the diazonium salt (Table 4, entries 2–4), allowing the reaction to be performed below HF boiling temperature.

Conclusion

Using the outlined method, HF can be generated using simple equipment under moderate conditions. Following extraction into an organic solvent, it can then be employed for various *in situ* fluorinations.

Experimental

^{1}H NMR spectra were measured on a Bruker AMX 300 instrument at 300.13 MHz. ^{19}F NMR spectra were measured on a Bruker WH-300 instrument at 282.2 MHz. GC and GCMS analyses were performed using an HP-5790 gas chromatograph with a 5% diphenyl 95% dimethyl polysiloxane capillary column (25 m × 0.25 mm). Samples for GC/GCMS were diluted with 20 ml CH_2Cl_2, washed with 5 ml of 5% $NaHCO_3$ solution, dried over $MgSO_4$ and filtered through a dry NaF plug prior to injection. UV-vis spectra were recorded on a Spectronics 2000 spectrophotometer. Sonication was performed using a Heat Systems-Ultrasonics W-375 instrument operating at 50 W. Karl–Fischer titrations were performed on a Mettler DL 35 titrator with a platinum (DM 142) electrode. Fluoride ion concentrations were determined using a selective fluoride



Scheme 1 Deaminative fluorination with *in situ* generated HF.

Table 4 Deaminative fluorination of anilines

Entry	Substrate	Product (% yield)[a]	Entry	Substrate	Product (% yield)[a]
1	**1a**	**2a** (45),[b] **3a** (10), **4a** (5)	5	**1b**	**2b** (43),[b] **3b** (4)
2	**1a**[c]	**2a** (40), **3a** (10), **4a** (5)	6	**1c**	**2c** (46),[b] **3c** (8)
3	**1a**[d]	**2a** (15), **3a** (0), **4a** (0)	7	**1d**	**2d** (41), **3d** (6)
4	**1a**[e]	**2a** (45), **3a** (10), **4a** (5)	8	**1e**	**2e** (45), **3e** (5)

Conditions: 100 mmol CaF_2, 100 mmol H_2SO_4, 25 mmol substrate, 25 mmol $NaNO_2$, 50 ml CH_2Cl_2 (except where noted), 15 min at 0 °C followed by 2 h heating at 55 °C (except where noted). [a] Yield based on GC area, corrected by the presence of an internal standard. [b] Isolated yield. [c] 20 min sonication at 15 °C instead of heating. [d] 15 min sonication at 15 °C instead of heating, *n*-hexane used as solvent. [e] 20 min sonication at 15 °C instead of heating; additional 100 mmol of CaF_2 added before sonication.

electrode, with SCE as the reference electrode.†,[9] CaF_2 residues were determined by published methods.[10] Reactions were performed in capped PTFE/PE flasks sealed with PTFE tape. Keeping acetone in such vessels at 30 °C for 3 days resulted in <3% weight loss. Unless stated otherwise, chemicals were purchased from commercial firms (>98% pure) and used without further purification. Salts were vacuum dried. A standard sample of 2-fluorooctane was prepared by halogen exchange of 2-chlorooctane.[11] Products were either isolated and identified by comparison of their ^1H and ^{19}F NMR spectra to standard samples, or identified by MS data and comparison of their GC retention times with standard samples.

Typical procedure for HF generation

100 mmol (7.80 g) of dried CaF_2 was added to 50 ml of CH_2Cl_2 in a sealed 100 ml PTFE flask equipped with two PE addition/sampling tubes and a mechanical stirrer. After stirring for 1 min, 100 mmol of 98% H_2SO_4 was added dropwise over a period of 5 min (to avoid aggregation). Stainless steel balls (2 mm diameter) can be used for better crushing of the solid and obtaining a larger surface area. After stirring for 3–4 h at 25 °C, the inorganic solid phase was filtered (PTFE funnel), washed with a 1 : 1 solution of H_2O–EtOH, and neutralized with a 0.1 M solution of NaOH. The solid residue was filtered and dried under vacuum at 200 °C, weighed and analyzed for CaF_2 and $CaSO_4$. The filtrates were analyzed separately for H^+, F^-, and sulfate ions. CaF_2 conversion and HF yield (typically 37–42 mol% based on CaF_2) were determined from the overall F^- mass-balance.

Hydrofluorination of olefins/substitution of alcohols with *in situ* HF generation

Example: 2-fluorooctane. CaF_2 and H_2SO_4 were mixed in CH_2Cl_2 for 5 min as above, after which 30 mmol of oct-1-ene and 0.7 mmol of TOAB were added. The mixture was stirred for 30 h. Reaction progress was monitored by GC. At the end of the reaction, 2-fluorooctane (2.2 g, 66 mol% based on starting material) was distilled at 200 mmHg (92–94 °C). δ_H ($CDCl_3$; Me_4Si) 1.26 (3H, dd, *J* 23 and 6, CH_3CHF), 4.5 (1H, dm, *J* 48, CHF), 1.9 (2H, m, CH_2), 1.4 (10H, br m, 5 × CH_2), 0.96 (3H, t). δ_F ($CDCl_3$; $CFCl_3$) −165.0 (m). Unreacted substrate and olefinic isomerization products were brominated (Br_2) prior to separation. GC conditions: 2 min isotherm at 60 °C, heating at 15 °C min^{-1} to 250 °C, 4 min isotherm at 250 °C. Retention times (min): oct-1-ene (2.4); 2-fluorooctane (3.8); 1,2-dibromooctane (9.1); tetradecane (internal standard, 9.3).

† As this method of measurement is accurate only in aqueous solutions, the fluoride content of organic phases was determined by extracting the fluoride ions thrice with 0.2 M solutions of KNO_3 prior to measurement. Control samples containing similar strength solutions of $(n\text{-Bu})_4{}^+F^-$ in CH_2Cl_2 showed >99% extraction of fluoride ions into the aqueous phase.

Deaminative fluorination of anilines

Example: fluorobenzene. 50 mmol of CaF_2 and 50 mmol of H_2SO_4 were mixed in 50 ml CH_2Cl_2 as above for 3 h, after which the mixture was cooled to 0 °C. 25 mmol of aniline and 25 mmol of $NaNO_2$ were then added (both additions caused an exothermic reaction and the color of the mixture changed to red–brown). Formation of the diazonium salt was monitored by UV-vis spectroscopy (aqueous solution; λ_{max} = 360–380 nm; ε = 6400 M^{-1} cm^{-1}). After stirring for 15 min, the mixture was heated to 55 °C and stirred for 2 h (alternatively sonicated for 20 min at 15 °C). Fluorobenzene formation was monitored by GC. After 2 h the reaction was quenched with ice and fluorobenzene (1.08 g, 45 mol% based on starting material) was distilled over a short Vigreux column at 1 atm (84–85 °C). *m*/*z*: 96. GCMS conditions: 4 min isotherm at 40 °C, heating at 15 °C/min^{-1} to 250 °C, 2 min isotherm at 250 °C. Retention times (min): benzene (1.6); fluorobenzene (1.8); aniline (7.5); phenol (7.6); tetradecane (internal standard, 9.3).

CAUTION! Hydrogen fluoride is extremely corrosive to human tissue. Any contact may result in painful and slow-healing burns.[12] All labwork should be conducted in an efficient fume hood, with suitable facial and body protection. Glassware should not be used with HF solutions. It is important to neutralize all solutions prior to disposal. Any accident caused by HF, even if it appears minor, must *always* be treated as a serious accident requiring medical attention.

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