Fluorochemicals from fluorspar via a phosphate-enabled mechanochemical process that bypasses HF

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Abstract: All fluorochemicals including elemental fluorine, nucleophilic, electrophilic, and radical fluorinating reagents are prepared from hydrogen fluoride (HF). This highly toxic and corrosive gas is produced by reaction of acid grade fluorspar (> 97% CaF_2) with sulfuric acid under harsh conditions. The use of fluorspar to produce fluorochemicals *via* a process that bypasses HF is highly desirable but remains an unsolved problem due to the prohibitive insolubility of CaF_2. Inspired by calcium phosphate biomineralization, we herein disclose a protocol of treating acid grade fluorspar with K_2HPO_4 under mechanochemical conditions. The process affords a solid composed of crystalline $K_3(HPO_4)F$ and $K_{2-x}Ca_y(PO_3F)_a(PO_4)_b$, found suitable for forging S–F and C–F bonds.

One-Sentence Summary: A versatile inorganic fluorinating reagent is prepared by mechanochemical activation of fluorspar with a phosphate salt.

Fluorochemicals have a wide range of applications in the metallurgical industry, Li-ion batteries, electronics, fluoropolymers, refrigerants, agrochemicals and pharmaceuticals (*1*, *2*). All fluorine atoms incorporated into fluorochemicals including nucleophilic, electrophilic, and radical fluorinating reagents, originate from naturally occurring fluorspar (calcium fluoride, CaF_2). For the production of fluorochemicals, this mineral must be converted into hydrogen fluoride (HF) (*3*, *4*), a process first reported by C. W. Scheele in 1771 (*5*) (Fig. 1A). Today, current practice in industry still relies on this energy-intensive process, entailing reaction of acid grade fluorspar (acidspar, > 97% CaF_2) with sulfuric acid at elevated temperatures to generate HF, which is stored as liquefied gas, or used as an aqueous solution (*6*). Safety is a primary concern because HF is highly toxic and must therefore be handled with extreme caution. Despite stringent safety guidelines, HF spills have occurred, some with fatal accidents and detrimental impact on the environment (*7*). Our research ambition is to rejuvenate fluorine chemistry with current global challenges in mind, through the invention of safe and sustainable fluorination methods of non-persistent fluorochemicals. A paradigm shift for academia and industry would be to access essential fluorochemicals directly from fluorspar avoiding the production of HF, thus decreasing energy requirements, and streamlining the current high-maintenance supply chains. The challenge is considerable because CaF_2 chemistry is viewed as inaccessible due to its high lattice energy (ΔU_L 2640 kJ mol^{-1}), and prohibitive insolubility in organic solvents (*8*). Herein, we disclose a solution to this long-standing challenge, and report that the activation of acid grade fluorspar with a potassium phosphate salt under mechanochemical conditions affords a fluorinating reagent for direct S–F and C(sp^3/sp^2)–F bond construction (Fig. 1B).

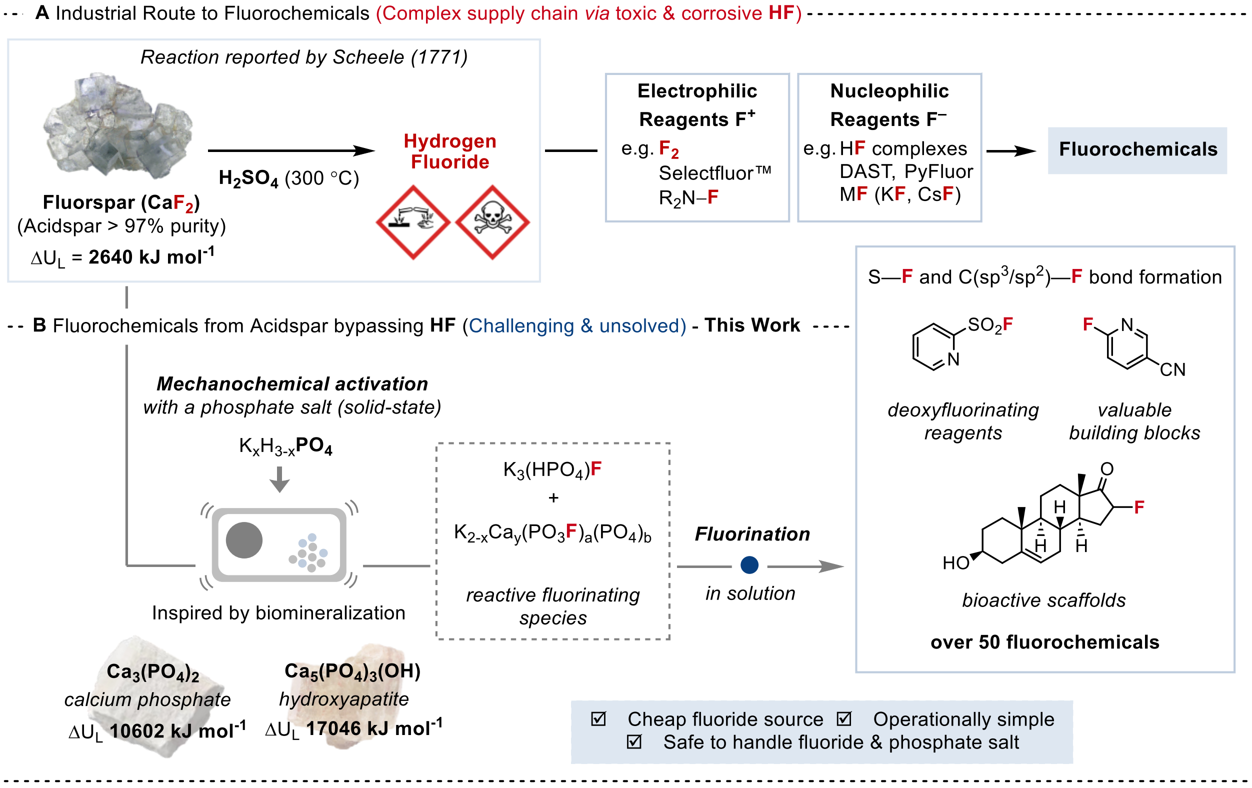

Fig. 1. Synthesis of fluorochemicals from fluorspar (CaF_2). (**A**) Current industrial route to fluorochemicals *via* hydrogen fluoride. (**B**) Synthesis of a inorganic fluorinating reagent upon treatment of acid grade fluorspar with a phosphate salt under mechanochemical conditions, and applications to monofluorinated chemicals (this work). DAST, diethylaminosulfur trifluoride.

CaF_2 (m.p. ~ 1420 °C) is a white solid which is poorly soluble in water (0.016 g L^{-1} at 20 ^{o}C) and insoluble in organic solvents (*9*). Limited chemistry is known to date for the production of fluorochemicals using CaF_2. Rare examples report its use in the synthesis of $LiPF_6$, PF_5, POF_3 or $Ca(SO_3F)_2$ under extremely harsh conditions (*10*–*12*). Synthetic porous CaF_2 obtained from soda lime and HF was reported for the conversion of α-chloro ethers to α-fluoro ethers at 200 °C (*13*). Soluble calcium fluoride complexes have also been prepared and characterized, but there is no report on their use for organic fluorination reactions (*14*, *15*). As part of our studies on alkali metal fluorides for asymmetric fluorinations (*16*, *17*), we expanded our interest to CaF_2 with the ultimate aim to use acid grade fluorspar (> 97% CaF_2) as a fluoride source for the preparation of fluorochemicals. For direct fluorination with CaF_2, we considered the formation of a calcium by-product of lattice energy higher than 2640 kJ mol^{-1}, as a thermodynamic driving force (*8*, *18*). Calcium phosphate (bio)mineralization is essential to the formation of bones and teeth, and other pathological calcifications (*19*), and served as inspiration for initial investigation. Specifically, we conceived a study probing the reactivity of CaF_2 in the presence of inorganic phosphate salts. In this scenario, one possible calcium by-product formed upon displacing fluoride from CaF_2 with phosphate ions is $Ca_3(PO_4)_2$ (ΔU_L 3534 kJ mol^{-1} per Ca). Exploratory experiments combining CaF_2

with phosphate salts and various substrates under a range of conditions gave trace amounts of product (table S1). Attempted optimization revealed that solution-phase chemistry had poor prognosis for improvement, prompting a changeover to solid-state chemistry. Mechanochemical ball milling was attractive as a promising technology enabling transformations independent of reactant solubility and aiding solid-state diffusion kinetics (*20–24*). The knowledge that doping fluorite-type compounds with monovalent cations can improve (even if marginally) fluoride mobility in solid electrolytes for fluoride ion batteries encouraged us to explore K^+ phosphate salts to activate CaF_2 in the solid-state (*25*). Ion metathesis would then release KF (or a derivative thereof), a commonly used nucleophilic fluorinating reagent.

Initial experimentation focused on S–F bond formation. Sulfur(VI) fluoride exchange (SuFEx) is a powerful click reaction with applications in chemical biology and materials science (*26*). Moreover, sulfonyl fluorides are commonly employed as fluorinating reagents (*27*), and are more stable than common precursor sulfonyl chlorides, thereby offering a modest contribution to compensate for the energetic penalty incurred upon CaF_2 dissociation. For reference, the homolytic bond dissociation energy of the S–F bond in SO_2F_2 (379 ± 18 kJ mol^{-1}) is larger than S–Cl in SO_2Cl_2 (192 ± 17 kJ mol^{-1}) (*26*). Exploratory experiments were conducted in a stainless-steel milling jar (15 mL) at 30 Hz using one stainless-steel ball (1 x 4 g). The reaction of 4-toluenesulfonyl chloride (TsCl) with CaF_2 (5 equiv) for 1 h did not afford 4-toluenesulfonyl fluoride (TsF, **1**); a control experiment replacing CaF_2 with KF (1.1 equiv) gave full conversion (> 95%) (table S2). Gratifyingly, the use of CaF_2 (5 equiv) in the presence of K_3PO_4 (2 equiv) or K_2HPO_4 (2 equiv) led to the formation of TsF (**1**) in 7% and 17% yield (as measured by ^{19}F NMR spectroscopy), respectively. However, KH_2PO_4 was ineffective (table S3). Milling CaF_2 (4 equiv) and K_2HPO_4 (2 equiv) for 3 h prior to addition of TsCl, and further milling of this mixture for 3 hours, gave 66% of **1** with no recovery of starting material (table S6). The finding that partial degradation of both TsCl and TsF took place under these conditions led to a refined protocol involving milling CaF_2 (4 equiv) with K_2HPO_4 (4 equiv), and using the resulting powder for the fluorination of TsCl in solution (*t*BuOH, 0.25 M) at 100 ^{o}C (tables S7 to S12).

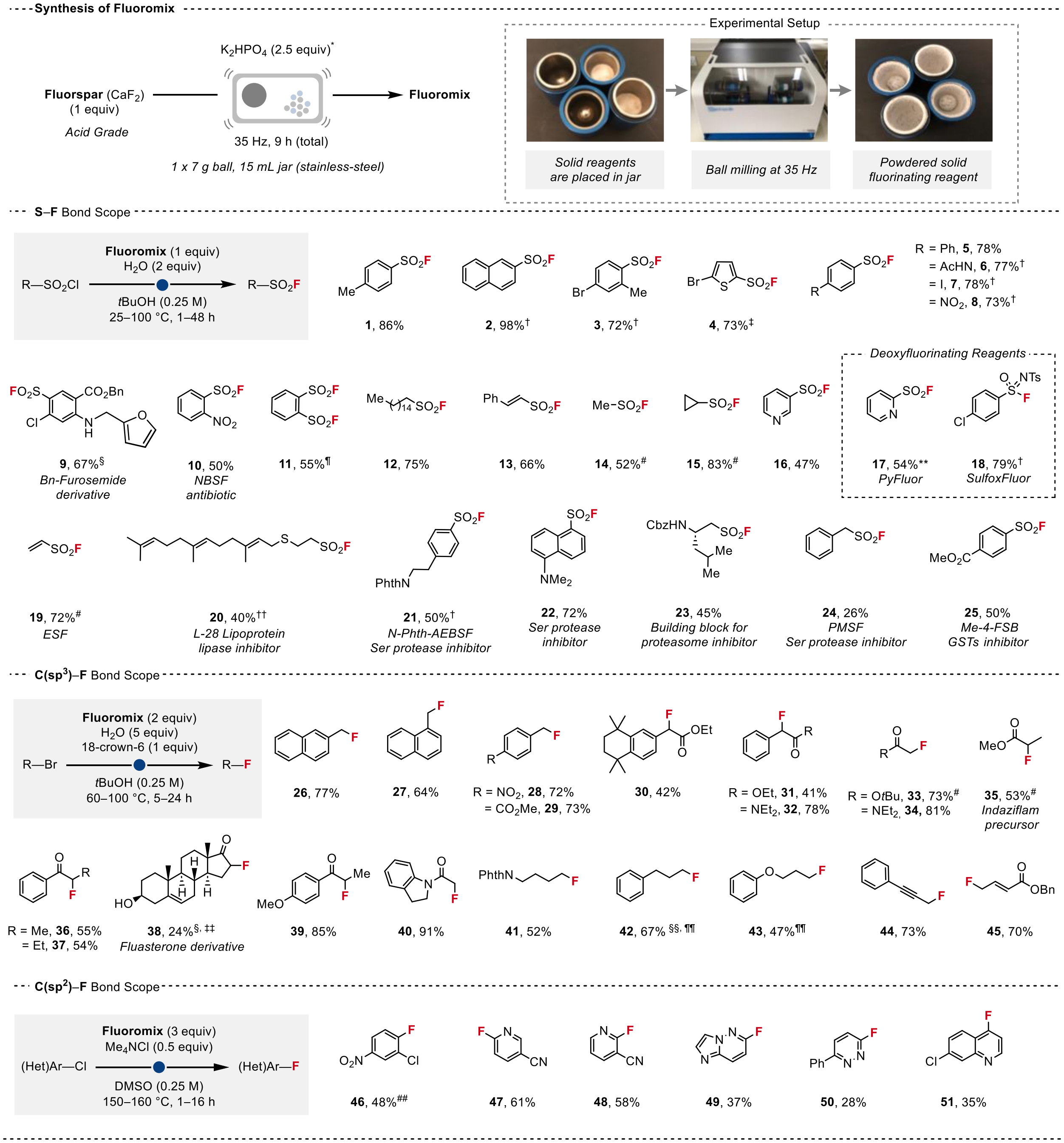

Fig. 2. Scope of S−F bond and C−F bond formation. Scope of S−F bond formation (top) and C−F bond formation (bottom). All yields are for isolated products (0.5 mmol scale unless otherwise stated). [*]anhydrous K_2HPO_4 added to acid grade fluorspar in three stages during ball milling (see fig. S6); [†]EtCN as solvent; [‡]using 1.2 equiv of Fluoromix; [§]0.25 mmol scale; [¶]using 2.2 equiv of Fluoromix; [#] ^{19}F NMR yields using 4-fluoroanisole as internal standard; [**]1,2-DCB as solvent; [††]yield over 2 steps, prepared *via* addition of *trans*, *trans*-farnesyl mercaptan (**S7**) to ESF (**19**); [‡‡]isolated as a diastereomeric mixture (1:2 α:β); [§§]from R–I; [¶¶]using 2.5 equiv of Fluoromix; [##]using 4.0 equiv of Fluoromix. DCB, dichlorobenzene.

This method afforded **1** in 81% (^{19}F NMR yield). Gratifyingly, replacement of synthetic reagent grade CaF_2 with acid grade fluorspar was equally effective (table S13). The sequential milling of acid grade fluorspar (1 equiv) with three portions of K_2HPO_4 (overall 2.5 equiv) at 35 Hz gave a fluorinating reagent (Fluoromix) of improved reactivity in the presence of H_2O (2 equiv), affording **1** isolated in 86% yield using one instead of four equivalents of CaF_2 (figs. S1 to S4). This optimized protocol afforded various sulfonyl fluorides of importance in medicinal chemistry, chemical biology, and materials science with yields up to 98% (Fig. 2). The scope includes the multi-purpose fluorochemical ethenesulfonyl fluoride (ESF, **19**), antibiotic pharmacophore NBSF (**10**), enzyme inhibitors (**20–25**) (*28*), and deoxyfluorination reagents PyFluor (**17**) and SulfoxFluor (**18**) (*29*, *30*). We also examined the possibility of C(sp^3)–F bond formation using Fluoromix. These reactions were best performed in the presence of 18-crown-6. A range of benzylic and alkyl fluorides, α-fluoroketones, -esters and -amides were prepared in yields up to 91% (**26–45**). As a case study for C(sp^2)–F bond formation, we selected (hetero)aryl chlorides which underwent fluorination in DMSO in modest yields (**46–51**), affording (hetero)aryl fluorides which are valuable building blocks for pharmaceuticals and agrochemicals (*1*).

Mechanistic studies gave insight on the composition of Fluoromix, and how it serves as a fluorinating reagent. For the identification of the water-soluble species, a sample of Fluoromix was stirred in D_2O. Centrifugation followed by ^{19}F NMR analysis of the supernatant showed a signal at -121.9 ppm assigned to fluoride (fig. S9). A second ^{19}F peak was observed and assigned as FPO_3^{2-} (δ = -73.8 ppm, and $^1J_{P\text{-}F}$ = 864 Hz). A signal at δ = 2.7 ppm identified as HPO_4^{2-}, and the doublet diagnostic of FPO_3^{2-} at δ = 1.1 ppm ($^1J_{P\text{-}F}$ = 864 Hz) were observed by ^{31}P NMR. The matter derived from ball milling CaF_2 with K_2HPO_4 (Fluoromix) is stable (fig. S12), and amenable to *ex-situ* analysis by x-ray powder diffraction (PXRD) to determine the composition of the bulk crystalline phase (Fig. 3). Analysis revealed new crystalline phases identified as $K_3(HPO_4)F$ and $K_{2-x}Ca_y(PO_3F)_a(PO_4)_b$ along with residual crystalline CaF_2. No crystalline fluorapatite ($Ca_5(PO_4)_3F$) was detected. In considering the structures of these new inorganic salts, we hypothesized that ion metathesis between CaF_2 and K_2HPO_4 might occur to afford calcium hydrogen phosphate ($CaHPO_4$) and potassium fluoride (KF), or derivatives thereof. With this in mind, mechanistic experiments were carried out, which demonstrated that a new crystalline phase $\mathbf{X_{(K)}}$ is formed upon ball milling of KF with K_2HPO_4 (Fig. 3A). $\mathbf{X_{(K)}}$ is present in Fluoromix, and is shown to be $K_3(HPO_4)F$ (Figs. 3B and 3C), which is isostructural to $K_3(PO_3F)F$ and $K_3(SO_4)F$ (*31*, *32*). The reactivity of independently prepared $\mathbf{X_{(K)}}$ was investigated using TsCl under optimized solution-phase conditions. $\mathbf{X_{(K)}}$ proved to be a highly effective fluorinating reagent comparable to Fluoromix itself (Fig. 3D). Further ball milling of $\mathbf{X_{(K)}}$ ($K_3(HPO_4)F$) with $CaHPO_4$ afforded a new material $\mathbf{Y_{(KCa)}}$, which is also present in Fluoromix (Figs. 3A and 3B). $\mathbf{Y_{(KCa)}}$ contains both crystalline and amorphous phases. The crystalline phase of $\mathbf{Y_{(KCa)}}$ has the proposed composition $K_{2-x}Ca_y(PO_3F)_a(PO_4)_b$ featuring both K^+ and Ca^{2+} (Fig. 3C), and is topologically closely related to the reported structure of $K_3CaH(PO_4)_2$ (*33*). $K_{2-x}Ca_y(PO_3F)_a(PO_4)_b$ was independently generated by ball milling $CaHPO_4$ sequentially with KF and then K_2HPO_4. We noted that the solid matter generated by milling $CaHPO_4$ with KF is amorphous, and afforded the crystalline phase of $\mathbf{Y_{(KCa)}}$ upon milling with K_2HPO_4 (figs. S19 and S21). The ^{19}F NMR spectrum of **$Y_{(KCa)}$** in D_2O displays a resonance of FPO_3^{2-} (δ = -73.9 ppm, and $^1J_{P\text{-}F}$ = 865 Hz), along with a signal attributed to fluoride (δ = -122.2 ppm) (fig. S18). As a fluorinating reagent, **$Y_{(KCa)}$** shows a level of performance markedly lower than Fluoromix (Fig. 3D). Collectively, these data shed light on the composition and reactivity of Fluoromix, and indicate that component **$X_{(K)}$** is a superior fluorinating reagent to **$Y_{(KCa)}$**.

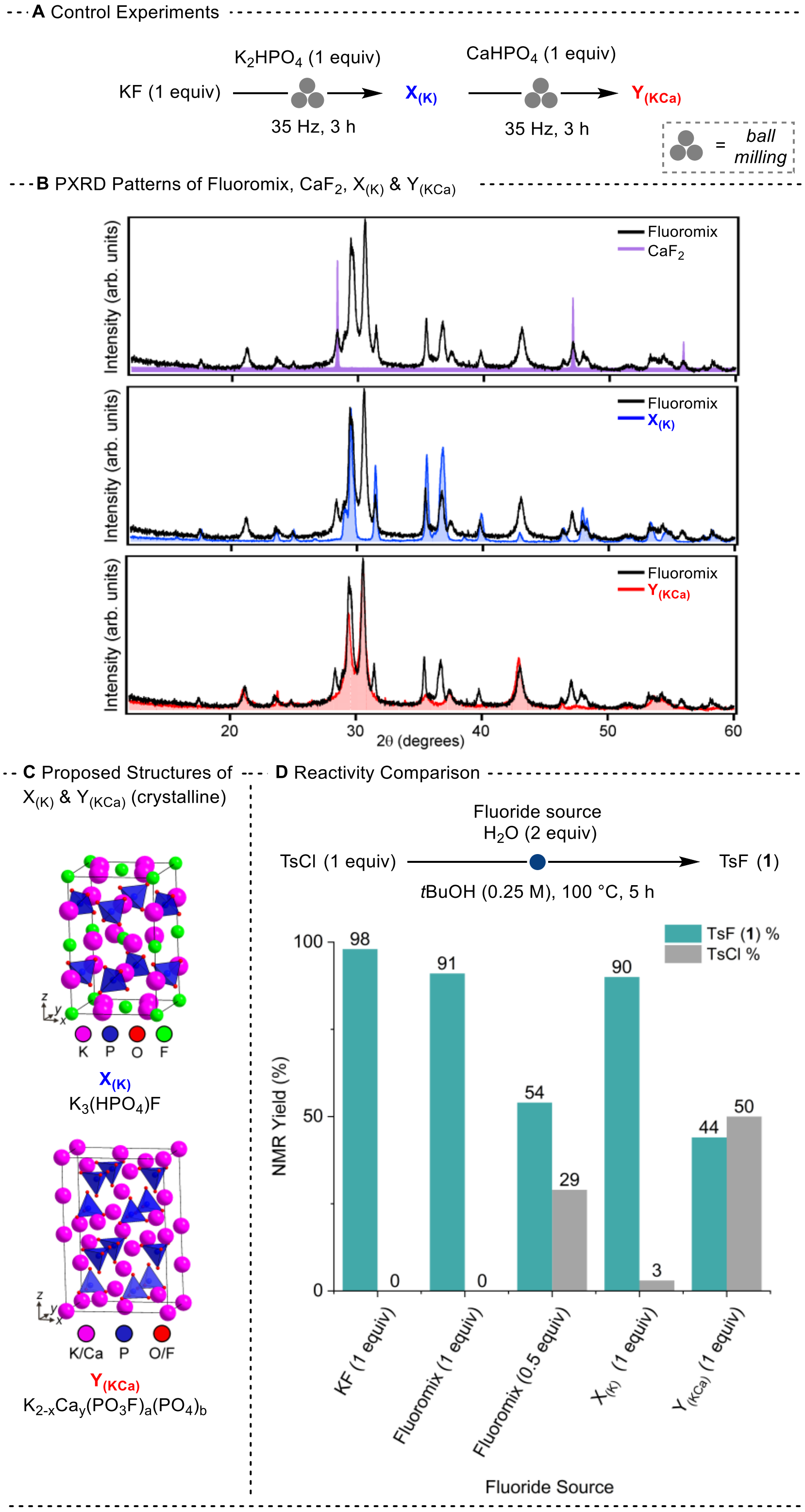

Fig. 3. Mechanistic investigation. (**A**) Preparation of **X$_{(K)}$** and **Y$_{(KCa)}$**. (**B**) X-ray powder diffraction patterns of the species observed in Fluoromix. (**C**) Proposed structures of **X$_{(K)}$** as K$_3$(HPO$_4$)F and **Y$_{(KCa)}$** as K$_{2-x}$Ca$_y$(PO$_3$F)$_a$(PO$_4$)$_b$ (crystalline phases). (**D**) Fluorination of TsCl using KF, Fluoromix, **X$_{(K)}$** and **Y$_{(KCa)}$** (0.125 mmol scale, yield measured by ^{19}F NMR and ^{1}H NMR spectroscopy, further details in fig. S23).

This study presents a direct pathway to fluorochemicals from acid grade fluorspar applying an operationally simple process consisting of activating CaF_2 with K_2HPO_4 under mechanochemical conditions. Mechanistic studies enabled the identification of $K_3(HPO_4)F$ and $K_{2-x}Ca_y(PO_3F)_a(PO_4)_b$ as crystalline constituents serving as fluorinating reagents for the synthesis of sulfonyl fluorides, alpha-fluoroketones, -esters and -amides, benzylic fluorides, alkyl fluorides, and (hetero)aryl fluorides. In the future, the development of methods to convert Fluoromix into a broader range of fluorochemicals including routinely used fluorinating reagents can be envisaged. CaF_2 may therefore become a direct source of fluoride for the production of fluorochemicals with a process bypassing the production of HF.

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Supplementary Materials

Materials and Methods

Figs. S1 to S26

Tables S1 to S23

NMR Spectra

References (*34*–*99*)

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