(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
19 December 2024 (19.12.2024)

WIPO | PCT

(10) **International Publication Number**
WO 2024/256871 A2

(51) **International Patent Classification:**
C07C 201/12 (2006.01) ***C07D 251/28*** (2006.01)
C07C 253/30 (2006.01) ***C01B 9/08*** (2006.01)
C07D 213/61 (2006.01)

(21) **International Application Number:**
PCT/IB2024/000319

(22) **International Filing Date:**
13 June 2024 (13.06.2024)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
63/521,147 15 June 2023 (15.06.2023) US

(71) **Applicant: FLUOROK LIMITED** [GB/GB]; 7400 The Quorum, Alec Issigonis Way, Oxford OX4 2JZ (GB).

(72) **Inventors: PUPO, Gabriele**; c/o Fluorok Limited, 7400 The Quorum, Alec Issigonis Way, Oxford OX4 2JZ (GB). **IBBA, Francesco**; c/o Fluorok Limited, 7400 The Quorum, Alec Issigonis Way, Oxford OX4 2JZ (GB). **FERGUSON-LEITCH, Jamie**; c/o Fluorok Limited, 7400 The Quorum, Alec Issigonis Way, Oxford OX4 2JZ (GB). **BABRA, Jasraj, Singh**; c/o Fluorok Limited, 7400 The Quorum, Alec Issigonis Way, Oxford OX4 2JZ (GB).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

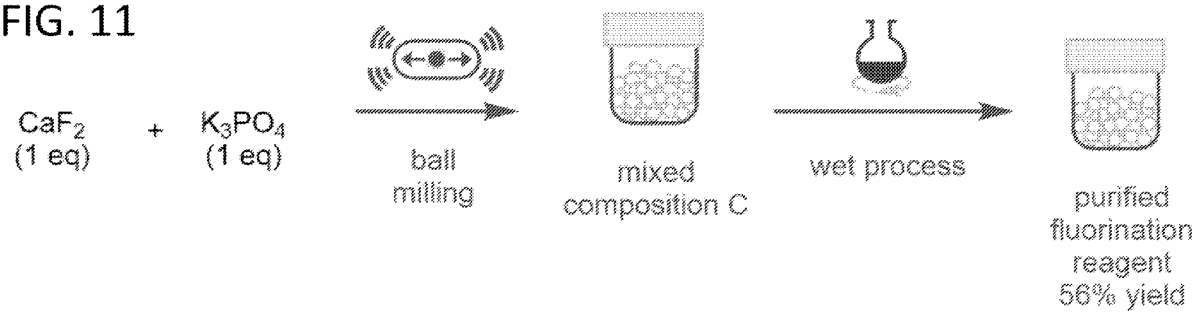
(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title:** FLUORINATION METHODS, REAGENTS, FLUORINATED COMPOSITIONS, AND METHODS OF MANUFACTURE

FIG. 11



(57) **Abstract:** Provided herein are compositions and methods of manufacturing compositions useful in producing fluorinated products.

FLUORINATION METHODS, REAGENTS, FLUORINATED COMPOSITIONS, AND METHODS OF MANUFACTURE

CROSS-REFERENCE

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/521,147, filed June 15, 2023, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Use of hazardous and toxic reagents, such as HF, to manufacture and produce fluorination reagents is dangerous and harmful to the environment. Provided herein are processes for manufacturing fluorination reagents or reagent compositions reducing and/or eliminating use of dangerous reagents.

SUMMARY OF THE INVENTION

[0003] In one aspect provided herein are methods for manufacturing fluorination reagents. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, methods provided herein comprise combining a first salt with a second salt to form a mixed composition. In some embodiments, the first salt can comprise calcium and fluorine. In some embodiments, methods provided herein comprise applying mechanical force to a combination of a first salt and a second salt to form a mixed composition. In some embodiments, methods provided herein comprise subjecting the mixed composition to a fluid composition and collecting a resultant fluid thereof. In some embodiments, subjecting the mixed composition to a fluid composition produces a solid component and a resultant fluid.

[0004] In some embodiments, methods provided herein comprise concentrating the resultant fluid. In some embodiments, concentrating the resultant fluid forms a crude fluorination reagent that can be further purified to provide a purified fluorination reagent. In some embodiments, concentrating the resultant fluid produces a reagent concentrate or precipitate. In some embodiments, methods provided herein comprise washing the fluorination reagent with a solvent to produce a reagent wash. In some embodiments, washing the fluorination reagent provides a second solid component and fluid reagent wash. In some embodiments, the reagent wash comprises a fluorination reagent. In some embodiments, the reagent wash comprises a purified fluorination reagent.

[0005] In some embodiments, methods provided herein comprise concentrating the reagent wash to form a fluorination reagent. In some embodiments, concentrating the reagent wash provides a purified fluorination reagent. In some embodiments, the purified fluorination reagent has a higher concentration of fluorine compared to the crude fluorination reagent. In some embodiments, methods provided herein comprise contacting fluorination reagents with starting reagents to provide fluorinated products. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, contacting fluorination reagents with starting reagents fluorinates the starting reagents.

[0006] In one aspect, provided herein are methods for fluorinating starting reagents using fluorination reagents. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, fluorinating starting reagents using fluorination reagents provides fluorinated products. In some embodiments, methods provided herein comprise providing a fluorination reagent and a starting reagent. In some embodiments, the fluorination reagent comprises an alkali metal, fluoride, and at least one additional ion. In some embodiments, the alkali metal can comprise lithium, potassium, or sodium. In some embodiments, fluorination reagents can comprise an amount of phosphorous.

[0007] In some embodiments, an amount of phosphorous in the fluorination reagent is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm). In some embodiments, an amount of phosphorous in the fluorination reagent is 0.015 % to about 12.5 % by weight (wt %). In some embodiments, fluorination reagents can be characterized by at least 1 (e.g., at least 2, at least 3, at least 5, at least 10, at least 20, at least 50, and/or at least 70) of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28. In some embodiments, methods provided herein comprise contacting starting reagents with fluorination reagents fluorinates starting reagents to yield fluorinated products. In some embodiments, contacting starting reagents with fluorination reagents provides fluorinated products.

[0008] In some embodiments, methods for manufacturing fluorination reagents provided herein can comprise adjusting the pH of the resultant fluid prior to concentrating the resultant fluid. In some embodiments, the resultant fluid can be adjusted to a pH of about 6 to about 8. In some embodiments, an amount of phosphorous in a fluorination reagent is about 0.015 % to about 12.5 % by weight (wt %). In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, methods for manufacturing fluorination reagents, and methods for fluorinating starting reagents provided herein can comprise an amount of calcium in the fluorination reagent.

[0009] In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, crude fluorination reagents are purified at least in part using a filtration process. In some embodiments, a filtrate is concentrated and/or dried during any step or process of any method described herein. In some embodiments, the filtration process comprises passing any solution described herein through the same or a plurality of filtration modules a plurality of times (e.g., by making three or more consecutive passes through the same module and/or by passing once each through three consecutively coupled modules). In some embodiments, a fluorine recovery of a filtration process employed herein is greater than 90% (e.g., greater than 95% or greater than 99%). In some embodiments, a rejection of one or more contaminants by a filtration process employed in any method described herein is greater than 90% (e.g., greater than 95% or greater than 99%). In some embodiments, an amount of calcium in the fluorination reagents is about 0.01 % to about 15 % by weight (wt %). In some embodiments, methods for manufacturing fluorination reagents provided herein can further comprise providing the mixed composition subjected to the fluid composition as the first salt. In some embodiments, the first salt is a recovered waste material. In some embodiments, the first salt comprises low purity calcium and fluoride. In some embodiments, the first salt can comprise calcium and fluorine in less than 80 weight percent in total.

[0010] In some embodiments, pH of the resultant fluid is adjusted with an acid. In some embodiments, the acid can comprise a strong acid, a weak acid, a polyprotic acid, and/or combinations thereof. In some embodiments, the acid can comprise phosphoric acid, hydrochloric acid, boric acid, silicic acid, formic acid, acetic acid, benzoic acid, oxalic acid, sulfuric acid, sulfurous acid, carbonic acid, and/or combinations thereof. In some embodiments, the acid can comprise hydrochloric acid, phosphoric acid, sulfuric acid, and/or combinations thereof.

[0011] In some embodiments, the resultant fluid can be adjusted to a pH of about 5 to about 10 (e.g., about 6 to about 9). In some embodiments, the fluid composition has a pH of about 7 or more (e.g., about 10 or more). In some embodiments, the fluid composition has a pH of about 12 to about 13. In some embodiments, a combination of the fluid composition and the mixed composition is at any suitable temperature. In some embodiments, a combination of the fluid composition and the mixed composition is at a temperature of about 0 to about 120 °C. In some embodiments, a combination of the fluid composition and the mixed composition is at a temperature of 80 °C or more.

[0012] In some embodiments, a combination of the fluid composition and the mixed composition is at a temperature of 110 °C or less. In some embodiments, the mixed composition is subjected to the fluid composition for any suitable time. In some embodiments, the mixed composition is subjected to the fluid composition for about 0 hours to about 8 hours. In some embodiments, the mixed composition is subjected to the fluid composition for about 1 hour or more. In some embodiments, the mixed composition is subjected to the fluid composition for about 6 hours or less. In some embodiments, the mixed composition is subjected to the fluid composition for about 2 hours.

[0013] In some embodiments, the fluid composition has a boiling point of about 30 °C or more (e.g., about 70 °C or more, about 120 °C or more). In some embodiments, the fluid composition has a boiling point of about 240 °C or less. In some embodiments, a combination of the solvent and fluorination reagent is at any suitable temperature. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, a combination of the solvent and fluorination reagent is at a temperature of about -20 to about 240 °C. In some embodiments, a combination of the solvent and fluorination reagent is at a temperature of about 80 °C or more. In some embodiments, a combination of the solvent and the fluorination reagent is at a temperature of about 60 °C. In some embodiments, a combination of the solvent and fluorination reagent is at a temperature of about 235 °C or less.

[0014] In some embodiments, fluorination reagents are washed with a solvent for about 4 hours to about 48 hours (e.g., about 8 hours to about 36 hours, about 10 hours to about 28 hours). In some embodiments, fluorination reagents are washed with a solvent for about 8 hours or more. In some embodiments, fluorination reagents are washed with a solvent for about 36 hours or less. In some embodiments, fluorination reagents are washed with a solvent for about 18 hours. In some embodiments, a solvent has a boiling point of about 30 °C or more (e.g., about 70 °C or more, about 120 °C or more). In some embodiments, a solvent has a boiling point of about 240 °C or less. In some embodiments, a solvent is an organic solvent, water, an alcohol, a polar aprotic solvent, a halocarbon, and/or combinations thereof. In some embodiments, a fluid composition is an organic solvent, water, an alcohol, a polar aprotic solvent, a halocarbon, and/or combinations thereof.

[0015] In some embodiments, a solvent is acetonitrile, propionitrile, butyronitrile, toluene, 1,2-dichlorobenzene, chlorobenzene, fluorobenzene, 1,2-difluorobenzene, dichloroethane, trifluorotoluene, chloroform, sulfolane, DMF, DMSO, an alcohol (e.g., tert-butanol, tert-amyl alcohol), water, and/or combinations thereof. In some embodiments, a fluid composition is acetonitrile, propionitrile, butyronitrile, toluene, 1,2-dichlorobenzene, chlorobenzene, fluorobenzene, 1,2-difluorobenzene, dichloroethane, trifluorotoluene, chloroform, sulfolane, DMF, DMSO, an alcohol (e.g., tert-butanol, tert-amyl alcohol), water, and/or combinations thereof. In some embodiments, a solvent is acetonitrile, propionitrile, butyronitrile, and/or combinations thereof.

[0016] In some embodiments, a fluid composition is acetonitrile, propionitrile, butyronitrile, and/or combinations thereof. In some embodiments, the second salt is a metal hydroxide, a metal sulphite, a metal sulphate, a carbonate, or an inorganic phosphate (e.g., a pyrophosphate). In some embodiments, the second salt comprises NaOH, KOH, Na_2SO_3, K_2SO_3, $KHSO_4$, $CaCO_3$, H_2CO_3, K_2CO_3, Na_2CO_3., $K_4P_2O_7$, $Na_4P_2O_7$, Na_3PO_4, Li_3PO_4, $KHCO_3$, K_2CO_3, $NaHCO_3$, Cs_2CO_3,

K_2HPO_4, KH_2PO_4, K_3PO_4, KPO_3, $K_5P_3O_{10}$, K_2SO_4, titanium phosphate, aluminum phosphate, uranium phosphate, and/or combinations thereof.

[0017] In some embodiments, methods for manufacturing fluorination reagents, and methods for fluorinating starting reagents provided herein can comprise fluorination reagents with an amount phosphorous. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, an amount of phosphorous in the fluorination reagent is about 1 ppm to 25 ppm (e.g., about 1 ppm to about 10 ppm, about 5 ppm to about 15 ppm, about 10 ppm to about 20 ppm, or about 15 ppm to about 25 ppm). In some embodiments, an amount of phosphorous in the fluorination reagent is about 0.02 % to about 10 % by weight (wt %) (e.g., about 0.05 wt % to about 8 wt %, about 0.1 wt % to about 6 wt %, about 0.5 wt% to about 5 wt %, about 1 wt% to about 4 wt %). In some embodiments, an amount of phosphorous in the fluorination reagent is about 0.015 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt % or more, about 0.5 wt % or more).

[0018] In some embodiments, an amount of phosphorous in the fluorination reagent is about 5 % by weight (wt %) or less (e.g., about 3 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less, about 0.05 wt % or less). In some embodiments, a powder x-ray diffraction spectrum of the fluorination reagent comprises characteristic 2θ reflections at about 5.2°,31.5°, 36.8° and/or combinations thereof. In some embodiments, methods for manufacturing fluorination reagents provided herein can comprise fluorination reagents, wherein about 10 to about 80% (e.g., about 30 to about 60%) of fluoride in the first salt is converted into a fluoride of the fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments fluorination reagents are crude fluorination reagents that can be further purified to provide purified fluorination reagents.

[0019] In some embodiments, methods for manufacturing fluorination reagents, and methods for fluorinating starting reagents provided herein can comprise activated fluorination reagents. In some embodiments activated fluorination reagents can be used as a fluorinating agent in that form. In some embodiments, methods for fluorinating starting reagents provided herein can comprise starting reagents (e.g., organic compounds).

[0020] In some embodiments, starting reagents can comprise organic compounds (e.g., aromatic organic compounds). In some embodiments, the organic compound comprises 1-chloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1-chloro-2,4-dinitrobenzene, 1,4-dichloro-2-nitrobenzene, 2-chloro-5-nitropyridine, 2-chloronicotinonitrile, 2,3,5,6-tetrachloroterephthalonitrile, 2,6-dichlorobenzonitrile, pentachloropyridine, 2,3,5,6-tetrachloroterephthalonitrile, 2,6-dichlorobenzonitrile, 2,3,5,6-tetrachloro-4-fluoropyridine, 2,4,6-

trichloro-1,3,5-triazine, 1,3-dinitrobenzene, or 2,4-dichloro-1-nitrobenzene. In some embodiments, the at least one additional ion of the purified fluorination reagent comprises (i) at least one cation and at least one anion; or (ii) at least one zwitterion (e.g., psilocybin). In some embodiments, the at least one cation comprises K^+, Na^+, Ca^{2+}, Li^+, or Cs^+.

[0021] In some embodiments, the at least one anion comprises a hydroxide, a sulphate, a carbonate, a phosphate, or a pyrophosphate. In some embodiments, fluorination reagents are contacted with starting reagents under mechanochemical conditions (e.g., ball mill). In some embodiments fluorination reagents are contacted with starting reagents in a reaction mixture. In some embodiments, the reaction mixture comprises a reaction solvent (e.g., an organic solvent, water, an alcohol, a polar aprotic solvent, a halocarbon, and/or combinations thereof). In some embodiments, the reaction solvent is acetonitrile, DMF, DMSO, sulfolane, and/or combinations thereof.

[0022] In some embodiments, the reaction mixture further comprises an ammonium salt (e.g., TMAC). In some embodiments, the reaction mixture is at a temperature of about 50 to about 200 °C. In some embodiments, the reaction mixture is at a temperature of about 50 °C or more (e.g., about 70 °C or more, about 110 °C or more, about 140 °C or more). In some embodiments, the reaction mixture is refluxed at a reaction temperature. In some embodiments, the reaction temperature and/or a reflux temperature is about 100 to about 175 °C. In some embodiments, the reaction mixture is stirred in a pressure vessel. In some embodiments, the reaction is performed in a heated twin-screw extruder. In some embodiments, fluorination reagents are contacted with starting reagents for about 1 hour to about 36 hours (e.g., about 2 hours to about 6 hours, about 12 hours to about 24 hours). In some embodiments, fluorination reagents are contacted with starting reagents for about 24 hours or less (e.g., about 12 hours or less, about 6 hours or less). In some embodiments, fluorination reagents are contacted with starting reagents for about 1 hour or more (e.g., about 2 hours or more, about 16 hours or more).

[0023] In one aspect, provided herein are compositions comprising fluorination reagents. In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide a purified fluorination reagent. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, fluorination reagents comprise an alkali metal, fluoride, and at least one additional ion. In some embodiments, the alkali metal can comprise lithium, potassium, or sodium. In some embodiments, fluorination reagents can comprise an amount of phosphorous. In some embodiments, an amount of phosphorous in the fluorination reagent is 0.015 % to about 12.5 % by weight (wt %). In some embodiments, fluorination reagents can be characterized by at least 1 (e.g., at least 2, at least 3, at least 5, at least 10, at least 20, at least 50, and/or at least 70) of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28. In some embodiments, fluorination reagents can be used to fluorinate starting reagents to provide fluorinated products.

[0024] In some embodiments, compositions comprising fluorination reagents provided herein can comprise an amount of calcium from about 0.01 % to about 15 % by weight (wt %). In some embodiments, fluorination reagents are crude fluorination reagents that can be further purified to provide purified fluorination reagents. In some embodiments, fluorination reagents are purified fluorination reagents. In some embodiments, an amount of phosphorous in the fluorination reagent is about 1 ppm to 25 ppm (e.g., about 1 ppm to about 10 ppm, about 5 ppm to about 15 ppm, about 10 ppm to about 20 ppm, or about 15 ppm to about 25 ppm). In some embodiments, an amount of phosphorous in the fluorination reagent is about 0.02 % to about 10 % by weight (wt %) (e.g., about 0.05 wt % to about 8 wt %, about 0.1 wt % to about 6 wt %, about 0.5 wt% to about 5 wt %, about 1 wt% to about 4 wt %). In some embodiments, an amount of phosphorous in the fluorination reagent is about 0.015 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt % or more, about 0.5 wt % or more). In some embodiments, an amount of phosphorous in the fluorination reagent is about 5 % by weight (wt %) or less (e.g., about 3 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less, about 0.05 wt % or less). In some embodiments, the at least one additional ion comprises (i) at least one cation and at least one anion; or (ii) at least one zwitterion (e.g., psilocybin). In some embodiments, the at least one cation comprises K^+, Na^+, Ca^{2+}, Li^+, or Cs^+. In some embodiments, the at least one anion comprises a hydroxide, a sulphate, a carbonate, a phosphate, a pyrophosphate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings (also “Figure” and “FIG.” herein), of which:

[0026] **FIG. 1** illustrates an exemplary schematic of a mechanochemical method for combining one or more salts provided herein to form a mixed composition.

[0027] **FIG. 2** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein.

[0028] **FIG. 3** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein.

[0029] **FIG. 4** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein.

[0030] **FIG. 5** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein.

[0031] **FIG. 6** illustrates an exemplary schematic of a process for screening different mixed compositions provided herein, having either K^+ or Cs^+ as counter-ion.

[0032] **FIG. 7** illustrates an exemplary schematic of a process for screening different mixed compositions provided herein with Na^+ as counter-ion. Na_3PO_4 or $NaHCO_3$ were subjected to modified conditions accounting for the lower solubility in water (volume of water increased, volume of methanol decreased) of the resulting fluorination reagent.

[0033] **FIG. 8** illustrates an exemplary schematic of a process for screening a mixed composition provided herein with Li^+ as counter-ion derived from Li_3PO_4. Mixed composition was subjected to modified conditions according to the lower solubility in water of the resulting fluorination reagent.

[0034] **FIG. 9** illustrates an exemplary schematic of a screening process for manufacturing a fluorination reagent provided herein at different pH values

[0035] **FIG. 10** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein from a first salt provided herein.

[0036] **FIG. 11** illustrates a simplified exemplary schematic process for manufacturing a fluorination reagent provided herein.

[0037] **FIG. 12** illustrates an exemplary schematic of a method of using a fluorination reagent provided herein to fluorinate aromatic compounds.

[0038] **FIG. 13** illustrates a schematic of a method of using a fluorination reagent provided herein to fluorinate an aromatic compound.

[0039] **FIG. 14** illustrates an exemplary schematic of a process for manufacturing a fluorination reagent provided herein.

DETAILED DESCRIPTION

Certain Definitions

[0040] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

Detailed Description

[0041] Provided herein are fluorination reagents and compositions, as well as methods of making and using such fluorination reagents and compositions. In some instances, such reagents and compositions are useful in producing fluorinated products in high yield and/or without the need for use of toxic reagents, such as HF.

[0042] In some embodiments, provided herein is a method of manufacturing a fluorination reagent. In specific embodiments, the method comprises (1) combining (e.g., in the solid state) a first salt with a second salt, the first salt comprising fluoride (e.g., and calcium); and (2) subjecting a combination of the first salt and the second salt to a (e.g., aqueous) fluid composition. In some embodiments, the resultant fluid composition is subsequently concentrated (e.g., by evaporation or other suitable method) to produce a fluorination reagent composition.

[0043] In certain embodiments, the fluorination reagent composition is further washed with a (e.g., organic) solvent (e.g., an alcohol, such as methanol) to produce a reagent wash. In specific embodiments a (e.g., purified) fluorination reagent composition is recovered from the reagent wash (e.g., after filtering residual solids from the reagent wash). In some embodiments, separating a purified fluorination reagent from residual solids and/or separating contaminants from a resultant solution can independently comprise: centrifugation (e.g., using a decanter centrifuge and/or a disk stack centrifuge), press filtration, microfiltration, nanofiltration, ultrafiltration, cross-flow membrane filtration and/or combinations thereof.

[0044] In some embodiments, crude fluorination reagents are purified at least in part using a filtration process. In some embodiments, a filtrate is concentrated and/or dried during any step or process of any method described herein. In some embodiments, the filtration process comprises passing any solution described herein through the same or a plurality of filtration modules a plurality of times (e.g., by making three or more consecutive passes through the same module and/or by passing once each through three consecutively coupled modules). In some embodiments, a fluorine recovery of a filtration process employed herein is greater than 90% (e.g., greater than 95% or greater than 99%). In some embodiments, a rejection of one or more contaminants by a filtration process employed in any method described herein is greater than 90% (e.g., greater than 95% or greater than 99%). In some embodiments, provided herein is a method of manufacturing a purified fluorination reagent, the method comprising:

a. combining a first salt with a second salt to form a mixed composition, the first salt comprising calcium and fluoride;
b. subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
c. concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
d. washing the crude fluorination reagent with a solvent (e.g., an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
e. concentrating the reagent wash to form a purified fluorination reagent (e.g., the purified fluorination reagent having a higher concentration of fluorine compared to the crude fluorination reagent).

[0045] In specific embodiments, provided herein is a method of manufacturing a purified fluorination reagent, the method comprising:

a. combining a first salt with a second salt to form a mixed composition, the first salt comprising calcium and fluoride;
b. applying mechanical force to the mixed composition;
c. subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
d. concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
e. washing the crude fluorination reagent with a solvent (e.g., an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
f. concentrating the reagent wash to form a purified fluorination reagent (e.g., the purified fluorination reagent having a higher concentration of fluorine compared to the crude fluorination reagent).

[0046] In certain embodiments, provided herein are compositions or methods of providing (e.g., making, manufacturing, or the like) compositions comprising reagents or reagent compositions. In some embodiments, reagents or reagent compositions provided herein are high purity and/or low-phosphorous reagents or reagent compositions. In some embodiments, presence of high purity and/or low phosphorous (e.g., a purified fluorination reagent provided herein) allows for the use of a reagent or reagent composition that produces high yield fluorination (e.g., relative to otherwise similar reagents/compositions having lower purity and/or higher phosphorous content). In certain embodiments, reagent or reagent compositions provided herein provide an improved rate of fluorination (e.g., at least about 10% improved). In certain embodiments (e.g., purified) reagents or reagent compositions provided herein have a higher fluorine content compared to (e.g., crude) reagents or reagent compositions provided herein. In some embodiments (e.g., purified) reagents or reagent compositions provide a rate of fluorination of a starting reagent (e.g., aromatic compound) that is higher when compared to a rate of fluorination provided by a (e.g., crude) reagent or reagent composition provided herein.

[0047] In some embodiments, any reagent or reagent composition provided herein comprises a metal (e.g., alkali metal, alkaline earth metal). In certain embodiments, a reagent or reagent composition comprises an alkali metal. In specific embodiments, a reagent or reagent composition provided herein comprises an alkali metal (such as lithium, potassium, or sodium), fluoride, and (e.g., at least one additional) ion.

[0048] In certain embodiments, any composition provided herein comprises an ion (e.g., at least one additional ion herein). In some embodiments, a reagent (e.g., fluorination reagent, such as a purified fluorination reagent, or crude fluorination reagent) or (e.g., reagent) composition (e.g., any reagent or mixed composition, such as used in making of a reagent) provided herein comprises (e.g., at least one additional) ion. In specific embodiments, a reagent or reagent composition provided herein comprises at least one additional ion. In certain embodiments, a (e.g., salt or salt comprising a) composition provided herein comprises (e.g., at least one additional) ion. In specific embodiments, a (e.g., salt or salt comprising a) composition provided herein comprises at least one additional ion.

[0049] In some embodiments, an (e.g., at least one additional) ion provided herein comprises a cation, anion, and/or zwitterion. In some embodiments, an (e.g., at least one) cation provided herein comprises an alkali metal, alkaline earth metal, transition metal, other metal, cationic complex or ligand, or the like. In specific embodiments, an (e.g., at least one) cation provided herein is K^+, Na^+, Rb^+, Ca^{2+}, Mg^{2+}, Fe^{2+}, Fe^{3+}, Cu^+, Cu^{2+}, Ag^+, Li^+, NH_4^+, Sr^+, Ba^{2+}, Zn^{2+}, Cd^{2+}, Al^{3+}, $[Co(NH_3)_6]^{3+}$, Co^{3+}, Co^{2+}, U^{2+}, U^{4+}, U^{6+}, Ni^{2+}, and/or Cs^+. In still more specific embodiments, (e.g., at least one) cation is K^+, Na^+, Ca^{2+}, Li^+, and/or Cs.$^+$

[0050] In certain embodiments, an (e.g., at least one) anion provided herein comprises a hydroxide, a sulphate, a carbonate, a phosphate, a pyrophosphate, a halide, a chlorate, a nitrate, a carbonate, a hydride, a sulfite, or the like. In specific embodiments, an (e.g., at least one) anion provided herein is a hydroxide, a sulphate, a carbonate, a phosphate, and/or a pyrophosphate.

[0051] In certain embodiments, an (e.g., at least one) zwitterion provided herein comprises an amino acid, a betaine, sulfamic acid, an acid, an aromatic compound, and/or a phospholipid. In specific embodiments, an (e.g., at least one) zwitterion provided herein is an amino acid, trimethylglycine, cocamidopropyl betaine, sulfamic acid, anthranilic acid, psilocybin, and/or phosphatidylcholine. In still more specific embodiments, an (e.g., at least one) zwitterion provided herein is psilocybin.

[0052] In certain embodiments, provided herein are reagents and reagent compositions with high purity and/or low levels of impurities (e.g., phosphorous, calcium, or the like). In some embodiments, high purity and low-content phosphorous allows for the use of a reagent or reagent composition that produces high-yield fluorination relative to other reagent or reagent compositions having low purity and/or higher phosphorous content. In certain embodiments, high purity and low-content calcium allows for the use of a reagent or reagent composition that produces high-yield fluorination relative to other reagent or reagent compositions having low purity and/or higher calcium content. In some instances, low-content calcium and/or phosphorous and high purity reagent or reagent compositions allow substantially improved fluorination capabilities.

[0053] In some embodiments, any reagent or reagent composition provided herein (and/or produced or used herein) comprises low-content phosphorus. In certain embodiments, any reagent or reagent composition provided herein (and/or produced or used herein) comprises phosphorous in an amount of about 0.015 % to about 12.5 % by weight (wt %) (w/w). In some embodiments, a reagent or reagent composition provided herein comprises phosphorous in an amount of about 0.015 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt % or more, about 0.5 wt % or more). In certain embodiments, a reagent or reagent composition provided herein comprises phosphorous in an amount of about 1 % by weight or less (e.g., about 1 wt % or less, about 0.5 wt% or less, about 0.1 wt% or less, about 0.05 wt % or less).

[0054] In some embodiments, a reagent or reagent composition provided herein comprises phosphorous in an amount of about 0.05 % to about 10 wt % (e.g., about 0.1 wt % to about 6 wt %, about 0.5 wt% to about 5 wt %, about 1 wt% to about 4 wt %). In certain embodiments, a reagent or reagent composition provided herein comprises phosphorous in an amount of about 5 wt % or less (e.g., about 3 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less).

[0055] In specific embodiments, a reagent or reagent composition provided herein comprises phosphorous in an amount of about 0.05 wt % to about 0.2 wt %.

[0056] In some embodiments, any reagent or reagent composition provided herein (and/or produced or used herein) comprises low-content calcium. In certain embodiments, any reagent or reagent composition provided herein (and/or produced or used herein) comprises calcium in an amount of about 0.01 % to about 15 % by weight (wt %) (w/w). In some embodiments, a reagent or reagent composition provided herein comprises calcium in an amount of about 0.01 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt% or more, about 0.5 wt % or more, about 1 wt % or more). In certain embodiments, a reagent or reagent composition provided herein comprises calcium in an amount of about 2 % by weight or less (e.g., about 1 wt% or less, about 0.5 wt% or less, about 0.1 wt % or less, about 0.05 wt% or less).

[0057] In some embodiments, a reagent or reagent composition provided herein comprises calcium in an amount of about 0.05 wt % to about 12 wt % (e.g., about 0.1 wt % to about 8 wt %, about 0.5 wt % to about 4 wt %). In certain embodiments, a reagent or reagent composition provided herein comprises calcium in an amount of about 6 wt % or less (e.g., about 4 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less, about 0.05 wt % or less).

[0058] In specific embodiments, a reagent or reagent composition provided herein comprises calcium in an amount of about 0.01 % to about 0.05 wt %.

[0059] In certain embodiments, a powder x-ray diffraction spectrum of a reagent or reagent composition provided herein comprises characteristic 2θ reflections at about 5.2°. In some embodiments, a powder x-ray diffraction spectrum of a reagent or reagent composition provided herein comprises characteristic 2θ reflections at 5.2°, 31.5°, and/or 36.8°. In certain embodiments, a powder x-ray diffraction spectrum of a reagent or reagent composition provided herein may further comprise peaks corresponding ±0.2°2θ to one or more 2-theta values from Tables 5, 6A, 8, 9, 12, 14-18, 20, 21, 23, and/or 25-28. In specific embodiments, a powder x-ray diffraction spectrum of a reagent or reagent composition provided herein comprises characteristic 2θ reflections at 5.2°, 31.5°, and 36.8°.

[0060] In certain embodiments, any reagent or reagent composition provided herein comprises high-content fluorine. In some embodiments, fluorine conversion (or F conversion) refers to a relative proportion or percentage (%) of fluorine from a (e.g., first) salt or salt composition provided herein that is converted to a reagent or reagent composition provided herein. In some embodiments, about 10 % to about 80 % of fluorine from a (e.g., first) salt or salt composition provided herein is converted into a (e.g., fluorination) reagent or reagent composition provided herein. In specific embodiments, about 30% to about 60% of fluorine from a (e.g., first) salt or salt composition provided herein is converted into a (e.g., fluorination) reagent or reagent composition provided herein.

[0061] In certain embodiments, Fluorine wt% or F wt% refers to fluorine content by weight in a reagent or reagent composition provided herein. In certain embodiments, Fluorine wt% or F wt% is measured by any suitable method (e.g., quantitative ^{19}F NMR). In some embodiments, a weight % of fluorine (F wt%) in a (e.g., fluorination) reagent or reagent composition provided herein is about 8% to about 75% (e.g., about 10% to about 70%, about 20% to about 60%, about 30% to about 50%, about 45% to about 55%). In specific embodiments, a weight % of fluorine (F wt%) in a (e.g., fluorination) reagent or reagent composition provided herein is about 20% or more (e.g., about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more). In still more specific embodiments, a weight % of fluorine (F wt%) in a (e.g., fluorination) reagent or reagent composition provided herein is about 75% or less.

[0062] In certain embodiments, a (e.g., fluorination) reagent or reagent composition provided herein can be characterized by X-ray powder diffraction (XRPD) using Cu Kα1 (λ = 1.5406 Å) and/or Cu Kα2 (λ = 1.5444 Å). Due to differences in instruments, samples, and sample preparation, peak values are often reported with the modifier "±0.2°2θ". This is common practice in the solid-state chemical arts because of the variation inherent in peak values.

[0063] In certain embodiments, a (e.g., fluorination) reagent or reagent composition provided herein can have an XRPD pattern comprising peaks corresponding ±0.2°2θ to at least 1, at least 2, at least 3, at least 5, at least 10, at least 20, at least 50, and/or at least 70 of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28 provided herein. In some embodiments, a (e.g., fluorination) reagent or reagent composition provided herein can have an XRPD pattern comprising peaks corresponding ±0.2°2θ to at least 10%, at least 30%, at least 50%, at least 70%, at least 90%, and/or 100% of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28 provided herein. In specific embodiments, a (e.g., fluorination) reagent or reagent composition provided herein can have an XRPD pattern comprising peaks corresponding ±0.2°2θ to at least 30% of the 50 2-theta values reported in Table 5 provided herein (the (e.g., fluorination) reagent or reagent composition may have an XRPD pattern comprising peaks corresponding to at least 15 of the 2-theta values, modified ±0.2°2θ, in Table 5).

[0064] Table 5 illustrates X-ray powder diffraction using Cu Kα1 (λ = 1.5406 Å) and/or Cu Kα2 (λ = 1.5444 Å) for a (e.g., fluorination) reagent or reagent composition provided herein (e.g., mixed composition C as provided herein in Example 3B).

[0065] In certain embodiments a method provided herein comprises combining a first salt and a second salt.

[0066] In some embodiments, a first salt provided herein comprises fluoride. In specific embodiments, the first salt comprises calcium and fluoride. In some embodiments, the first salt further comprises additional ions, such as cations and/or anions provided herein. In specific embodiments, the first salt comprises CaF_2, $Ca_5(PO_4)_3F$, and/or combinations thereof.

[0067] In some embodiments, the first salt or composition comprising the first salt comprises fluoride. In specific embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride. In some embodiments, the first salt or composition comprising the first salt further comprises additional ions, such as cations and/or anions provided herein. In specific embodiments, the first salt or composition comprising the first salt comprises CaF_2, $Ca_5(PO_4)_3F$, and/or combinations thereof.

[0068] In some embodiments, a first salt (e.g., a first salt provided herein) or a composition comprising a first salt provided herein is sourced from a material with low-value, low-purity, such as a waste material. In specific embodiments, the first salt provided herein is sourced from a waste material (e.g., calcium fluoride). In yet more specific embodiments, a composition comprising the first salt provided herein is sourced from a waste material. In certain embodiments, provided herein are methods for manufacturing reagents or reagent composition with waste materials. In some embodiments, a waste material (e.g., a waste material provided herein) comprises a raw, processed, and/or treated waste material. In certain embodiments, a waste material provided herein is a (e.g., recovered) waste product (e.g., sourced from an industrial process). In some embodiments, a waste material herein is a (e.g., recovered) waste product from an industrial process such as semiconductor manufacturing, fluorochemical manufacturing, pharmaceutical manufacturing, or the like. In certain embodiments, a waste material provided herein comprises fluorine (or a fluorinated salt), fluorapatite, calcium fluoride (e.g., in low purity), CFC-12, per- and polyfluoroalkyl substances (PFAs), or the like. In specific embodiments, a waste material provided herein comprises fluorine, or a fluorinated salt (e.g., in low purity). In yet more specific embodiments, a waste material provided herein comprises fluorine and calcium (e.g., in low purity). In certain instances, a waste material provided herein may be used as a raw, processed, or treated waste material to provide reagent or reagent compositions provided herein.

[0069] In certain embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 20% or less. In some embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 30% or less. In certain embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 40% or less. In certain embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 50% or less. In some embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 60% or less. In some embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 70% or less. In some embodiments, the first salt or composition comprising the first salt comprises calcium and fluoride in a collective amount of about 80% or less.

[0070] In certain embodiments, the first salt comprises calcium and fluoride in a collective amount of about 20% or less. In some embodiments, the first salt comprises calcium and fluoride in a collective amount of about 30% or less. In certain embodiments, the first salt comprises calcium and fluoride in a collective amount of about 40% or less. In certain embodiments, the first salt comprises calcium and fluoride in a collective amount of about 50% or less. In some embodiments, the first salt comprises calcium and fluoride in a collective amount of about 60% or less. In some embodiments, the first salt comprises calcium and fluoride in a collective amount of about 70% or less. In some embodiments, the first salt comprises calcium and fluoride in a collective amount of about 80% or less.

[0071] In some embodiments, a second salt (e.g., a second salt provided) herein comprises a metal, such as an alkali metal or an alkaline earth metal. In certain embodiments, the second salt comprises a metal (e.g., an alkali metal or an alkaline earth metal) and an anion (e.g., such as a phosphate, hydroxide, sulphate, carbonate, and/or sulphite). In some embodiments, the second salt comprises sodium, lithium, cesium, potassium, and/or combinations thereof. In certain embodiments, the second salt further comprises phosphate (e.g., such as an inorganic phosphate or a pyrophosphate), hydroxide, carbonate, sulphite, and/or a sulphate. In specific embodiments, the second salt is NaOH, Na_2SO_3, K_2SO_3, KOH, $KHSO_4$, K_2HPO_4, KH_2PO_4, K_3PO_4, Na_3PO_4, Li_3PO_4, K_2CO_3, Na_2CO_3, $NaHCO_3$, Cs_2CO_3, K_2SO_4, KPO_3, $K_5P_3O_{10}$, $K_4P_2O_7$, $Na_4P_2O_7$, titanium phosphate, aluminum phosphate, uranium phosphate, and/or combinations of one or more thereof. In some embodiments, the second salt further comprises additional ions, such as cations and/or anions provided herein.

[0072] In some embodiments, the second salt or composition comprising the second salt comprises a metal, such as an alkali metal or an alkaline earth metal. In certain embodiments, the second salt or composition comprising the second salt comprises a metal (e.g., an alkali metal or an alkaline earth metal) and an anion (e.g., such as a phosphate, hydroxide, sulphate, carbonate, and/or sulphite). In some embodiments, the second salt or composition comprising the second salt comprises sodium, lithium, cesium, potassium, and/or combinations thereof. In certain embodiments, the second salt further comprises phosphate (e.g., such as an inorganic phosphate or a pyrophosphate), hydroxide, carbonate, sulphite, and/or a sulphate. In specific embodiments, the second salt or composition comprising the second salt is NaOH, Na_2SO_3, K_2SO_3, KOH, $KHSO_4$, K_2HPO_4, KH_2PO_4, K_3PO_4, Na_3PO_4, Li_3PO_4, K_2CO_3, Na_2CO_3, $NaHCO_3$, Cs_2CO_3 , K_2SO_4, KPO_3, $K_5P_3O_{10}$, $K_4P_2O_7$, $Na_4P_2O_7$, titanium phosphate, aluminum phosphate, uranium phosphate, and/or combinations of one or more thereof. In some embodiments, the second salt or composition comprising the second salt further comprises additional ions, such as cations and/or anions provided herein.

[0073] In some embodiments, provided herein is a composition or a method comprising combining a first salt (or a composition comprising the first salt) and a second salt (or a composition comprising the second salt) (e.g., a first salt or a second salt provided herein). In certain embodiments, a ratio of a first ion in a first salt (or a composition comprising the first salt) provided herein to a second ion in a second salt (or a composition comprising the second salt) provided herein is about 0.1:5 to about 5:0.1. In specific embodiments, a ratio of the first ion in the first salt (or a composition comprising the first salt) to the second ion in the second salt (or a composition comprising the second salt) is about 1:1. In yet more specific embodiments, a ratio of the first ion in the first salt (or a composition comprising the first salt) to the second ion in the second salt (or a composition comprising the second salt) is about 1:2.

[0074] In certain embodiments, the first salt (or a composition comprising the first salt) and the second salt (or a composition comprising the second salt) of any method provided herein are combined in any suitable manner (e.g., thereby providing a mixed composition described herein). In some embodiments, both the first salt (or a composition comprising the first salt) and the second salt (or a composition comprising the second salt) are combined as solids. In specific embodiments, the first salt (or a composition comprising the first salt) and the second salt (or a composition comprising the second salt) are combined to form a solid salt combination. In some embodiments, a method provided herein comprises applying a mechanical force to a mixed composition provided herein (e.g., comprising the first salt or a composition comprising the first salt and the second salt or a composition comprising the second salt). In specific embodiments, any suitable mechanical force provide herein is used.

[0075] In certain embodiments, a (e.g., mixed) composition provided herein comprises a first salt. In specific embodiments, the first salt comprises fluoride. In specific embodiments, the first salt comprises calcium and fluoride. In certain embodiments, a (e.g., mixed) composition provided herein comprises a second salt.

[0076] In certain embodiments, a mechanical force (e.g., a mechanical force provided herein) comprises any suitable mechanical force, such as by using a ball mill, a planetary mill, a mortar and pestle, a twin-screw-extruder, an attritor, a drum mill, an ultrasonic bath, a mechanical press, and/or combinations of one or more thereof. In certain embodiments, a mechanical force is applied using a high-shear mixer, an in-line homogenizer, one or more bead mills, and/or combinations thereof. In certain embodiments, mechanical force provided herein is provided with a ball mill. In some embodiments, mechanical force is applied by increasing a pressure within a sealed vessel (e.g., to greater than 100, 200, or 2000 kPa). In some embodiments, a ball mill provided herein comprises a jar and balls (e.g., with a weight of about 1 g to about 20 g). In certain embodiments, a first (e.g., salt) composition provided herein and a second (e.g., salt) composition provided herein are combined in a jar and balls are added. In some embodiments, mechanical force provided herein is provided with a twin screw-extruder, such as by extruding a combination of (e.g., salt) compositions provided herein at varying screw speeds, screw temperatures, residence times, or the like. A twin screw-extruder provided herein is fixed with a gravimetric single screw feeder (e.g., hopper) for programmed addition of (e.g., salt) compositions provided herein.

[0077] In specific embodiments, mechanical force is applied under any suitable condition, such as at a selected or varying frequency, time, temperature, cycles, or the like. In some embodiments, a mechanical force provided herein is applied at a frequency of about 0.5 Hz to about 60 kHz (e.g., about 10 Hz to about 20 kHz). In certain embodiments, a mechanical force provided herein is applied at a frequency of about 5 Hz or more (e.g., about 10 Hz or more, about 20 Hz or more, about 30 Hz or more). In specific embodiments, a mechanical force provided herein is applied at about 35 Hz. In certain embodiments, a mechanical force provided herein is applied for about 1 cycle to about 50 cycles (e.g., about 5 to about 40 cycles, about 10 to about 30 cycles). In some embodiments, a mechanical force provided herein is applied for 1 cycle or more. In specific embodiments, a mechanical force provided herein is applied for 10 cycles. In some embodiments, mechanical force is applied to one or more compositions in solution-phase. In some embodiments, mechanical force is applied to one or more compositions in solid-phase.

[0078] In certain embodiments, mechanical force provided herein is applied at a temperature of about 20 to about 300 ° C (e.g., about 50 to about 250 ° C, about 100 to about 200 ° C). In some embodiments, mechanical force provided herein is applied at a temperature of about 20 ° C or more (e.g., about 50 ° C or more, about 100 ° C or more, about 150 ° C or more). In some embodiments, the reaction mixture is refluxed at a reaction temperature. In some embodiments, the reaction temperature and/or a reflux temperature is about 100 to about 175 °C. In some embodiments, the reaction mixture is stirred in a pressure vessel. In some embodiments, the reaction is performed in a heated twin-screw extruder. In specific embodiments, mechanical force provided herein is applied at a temperature of about 25 ° C (e.g., at room temperature).

[0079] In certain embodiments, a mechanical force provided herein is applied for about 5 minutes to about 3 hours (e.g., about 10 minutes to about 2.5 hours, about 20 minutes to about 2 hours, about 30 minutes to about 1.5 hours). In some embodiments, a mechanical force provided herein is applied for about 5 minutes or more (e.g., about 15 minutes or more, about 30 minutes or more, about 45 minutes or more, about 1 hour or more, about 2 hours or more). In specific embodiments, mechanical force provided herein is applied for about 45 minutes.

[0080] In some instances, varying time, frequency, temperature, and/or the like of a mechanical force (e.g., a mechanical force provided herein) provides high yields of a reagent (e.g., fluorination reagent, such as a purified fluorination reagent, or crude fluorination reagent) or (e.g., reagent) composition (e.g., any reagent or mixed composition, such as used in making of a reagent) provided herein.

[0081] In certain embodiments, a method provided herein comprises combining a first composition and a second composition, the first composition comprising a first salt and the second composition comprising a second salt. In more specific embodiments, the first and/or the second composition is a waste material provided herein (e.g., raw, processed, or treated waste material).

[0082] In some embodiments, provided herein is a composition or a method comprising subjecting a (e.g., mixed) composition to a (e.g., fluid) composition. In certain embodiments, the (e.g., mixed) composition of any method provided herein is subjected to a (e.g., fluid) composition (e.g., thereby forming a reagent or reagent composition, such as described herein). In some embodiments, the (e.g., mixed) composition is subjected to a (e.g., fluid) composition under any suitable conditions, such as at any selected temperature, with any selected volume of fluid composition, with stirring or other agitation, at any selected pH (e.g., using a buffer), for any selected period of time, or the like.

[0083] In certain embodiments, an (e.g., fluid) composition provided herein comprises any suitable solvent. In specific embodiments, a fluid composition (e.g., a fluid composition provided herein) comprises a solvent. In certain embodiments, a fluid composition provided herein comprises any suitable solvent (e.g., water or an organic solvent). In specific embodiments, a fluid composition provided herein comprises a solvent (e.g., water).

[0084] In some embodiments, a solvent (e.g., a solvent provided herein) is any suitable solvent, such as a polar aprotic solvent, water, an alcohol, a halocarbon and/or a combination thereof. In certain embodiments, a solvent provided herein is acetonitrile, propionitrile, butyronitrile, toluene, 1,2-dichlorobenzene, chlorobenzene, fluorobenzene, 1,2-difluorobenzene, dichloroethane, trifluorotoluene, chloroform, sulfolane, DMF, DMSO, tert-butanol, tert-amyl alcohol, water, and/or combinations thereof.

[0085] In some embodiments, a solvent provided herein is selected according to its characteristics, such as boiling point, ability to solubilize a composition provided herein, polarity, pH, or the like.

[0086] In certain embodiments, a solvent provided herein has a boiling point of about 30 °C or more. In some embodiments, a solvent provided herein has a boiling point of about 70 °C or more. In certain embodiments, a solvent or (e.g., fluid) composition provided herein has a boiling point of about 120 °C or more. In some embodiments, a solvent or (e.g., fluid) composition provided herein has a boiling point of about 240 °C or less.

[0087] In some embodiments, a (e.g., mixed) composition provided herein is subjected to a (e.g., fluid) composition provided herein for about 0 to about 8 hours. In certain embodiments, a (e.g., mixed) composition is subjected to a (e.g., fluid) composition for about 1 hour or more. In some embodiments, a (e.g., mixed) composition is subjected to a (e.g., fluid) composition for about 6 hours or less. In specific embodiments, a (e.g., mixed) composition is subjected to a (e.g., fluid) composition for about 2 hours.

[0088] In certain embodiments, a combination of a (e.g., mixed) composition provided herein and a (e.g., fluid) composition provided herein is at a temperature of about 0 to about 120 °C. In some embodiments, a combination of a (e.g., mixed) composition and a (e.g., fluid) composition is at a temperature of about 80 °C or more. In certain embodiments, a combination of a (e.g., mixed) composition and a (e.g., fluid) composition is at a temperature of about 110 °C or less. In certain instances, the selected temperature of a combination of a (e.g., mixed) composition and (e.g., fluid) composition provided herein increases a yield of a reagent or reagent composition provided herein.

[0089] In certain embodiments, a (e.g., mixed) composition provided herein is subjected to a (e.g., fluid) composition at a selected pH of about 3 to about 12. In some embodiments, pH of a (e.g., fluid) composition provided herein can be modified in any suitable manner (e.g., by using a buffer). In certain embodiments, the selected pH is about 4 or more. In some embodiments, the selected pH is about 7 or more. In certain embodiments, the selected pH is about 10 or more.

[0090] In certain embodiments, a (e.g., mixed) composition of any method provided herein is subjected to a (e.g., fluid) composition provided herein, thereby forming a resultant fluid (e.g., comprising a (e.g., crude) reagent or reagent composition that can be further purified to provide a (e.g., purified reagent or reagent composition) and a washed (e.g., mixed) composition. In some embodiments, the washed (e.g., mixed) composition is a solid. In certain embodiments, the resultant fluid comprises a reagent or reagent composition, such as described herein. In specific embodiments, the resultant fluid comprises a crude reagent or reagent composition provided herein.

[0091] In certain embodiments, a method provided herein comprises adjusting pH (e.g., by any suitable means) of a (e.g., resultant) fluid described herein. In some embodiments, the pH of a resultant fluid of any method provided herein is adjusted (e.g., using an acid, base, and/or buffer).

[0092] In certain embodiments, pH of a resultant fluid provided herein is adjusted to a pH of about 5 to about 10. In some embodiments, pH of a resultant fluid is adjusted to a pH of about 6 to about 9. In certain embodiments, pH of a resultant fluid is adjusted to a pH of about 6 to about 8 (e.g., thereby neutralizing the resultant fluid). In certain embodiments, a pH of a resultant fluid is adjusted based on a presence of an alkaline impurity in the first salt (e.g., to a pH of about 6). In certain embodiments, a pH of the resultant fluid is adjusted to a pH compatible with one or more downstream processes of a method described herein (e.g., a pH may be adjusted to about 7, about 8, or about 9 for a process requiring neutral or mildly basic solutions, such as when using a pH sensitive filtration media). In some cases, the pH of the resultant fluid is adjusted for compatibility with and/or separation on one or more ion exchange columns.

[0093] In some embodiments, pH of a resultant fluid provided herein is adjusted to a pH of about 8 to about 14. In certain embodiments, pH of a resultant fluid is adjusted to a pH of about 12 to about 13.

[0094] In certain embodiments, pH of a (e.g., resultant) fluid provided herein is adjusted with any suitable acid or base. In some embodiments, pH of a resultant fluid is adjusted (e.g., neutralized) with a (e.g., polyprotic) acid. In specific embodiments, a resultant fluid described herein is neutralized.

[0095] In certain embodiments, an acid (e.g., an acid provided herein) is any suitable acid, such as a strong acid, a weak acid, a polyprotic acid, and/or a combination thereof. In some embodiments, an acid provided herein is phosphoric acid, hydrochloric acid, formic acid, acetic acid, sulfuric acid, sulfurous acid, carbonic acid, benzoic acid, boric acid, silicic acid, oxalic acid, and/or a combination thereof. In certain embodiments, use of polyprotic acids (e.g., phosphoric acid) provided herein avoids releasing additional anions.

[0096] In certain embodiments, a base (e.g., a base provided herein) is any suitable base, such as a strong base, a weak base, an organic base, or the like. In some embodiments, a base provided herein comprises a hydroxide, an amine, ammonia, a pyridine, and/or a combination thereof. In certain embodiments, a base provided herein is NaOH, KOH, or LiOH. In specific embodiments, a base provided herein is KOH.

[0097] In certain embodiments, the washed (e.g., mixed) composition comprises a salt (e.g., a first salt as described herein). In some embodiments, a method provided herein comprises combining the washed (e.g., mixed) composition and a second salt as provided herein (e.g., thereby forming a mixed composition described herein). In specific embodiments, a mixed composition provided herein comprises the washed (e.g., mixed) composition. In certain embodiments, a washed (e.g, mixed) composition described herein is provided as a first salt provided herein (e.g., thereby providing for sustainable manufacturing of a reagent or reagent composition described herein). In some instances, providing a washed (e.g., mixed) composition described herein as the first salt in methods and compositions described herein provides for sustainable manufacturing of reagents or reagent compositions. In certain instances, providing a washed (e.g., mixed) composition described herein as the first salt in methods and compositions described herein reduces the cost of waste disposal and/or the cost manufacturing a reagent or reagent composition provided herein.

[0098] In certain embodiments, provided herein is a composition or a method comprising concentrating a resultant fluid described herein (e.g., thereby forming a reagent or reagent composition, such as described herein). In some embodiments, a resultant fluid provided herein is concentrated by any suitable method and/or to any suitable endpoint provided herein. In certain embodiments, concentrating a resultant fluid described herein provides a (e.g., crude) reagent or reagent composition (e.g., a reagent concentrate or precipitate). In specific embodiments, concentrating a resultant fluid described herein provides a crude reagent or reagent composition (e.g., a reagent concentrate or precipitate). In yet more specific embodiments, the (e.g., crude) reagent or reagent composition is useful for fluorinating an organic compound provided herein (e.g., a starting reagent).

[0099] In certain embodiments, any suitable concentration method is used, such as by drying, lyophilizing, evaporating (e.g., using a rotary evaporator), distilling, or the like. In some embodiments, any fluid or wash provided herein is concentrated to any suitable endpoint (e.g., by about 10% or more). In specific embodiments, a resultant fluid described herein is concentrated by drying, evaporation, and/or a combination thereof. In still more specific embodiments, a resultant fluid described herein is concentrated under reduced pressure. In yet more specific embodiments, a resultant fluid described herein is concentrated under reduced pressure thereby providing a (e.g., crude) reagent or reagent composition provided herein.

[0100] In some embodiments, alternate concentration methods may be performed prior to, during, after, or in place of drying, lyophilizing, evaporating, distilling or the like. In some embodiments, alternate concentration methods comprise reverse osmosis, ultra-high pressure reverse osmosis, falling film evaporation, agitated thin film evaporation, spray-drying, and/or any combination of two or more thereof (e.g., up to, and including, a combination of all methods thereof).

[0101] In some embodiments, provided herein is a composition or a method comprising washing a (e.g., crude) reagent or reagent composition with a (e.g., solvent) composition. In certain embodiments, a (e.g., solvent) composition is any suitable solvent. In some embodiments, a (e.g., solvent) composition is any (e.g., organic) solvent provided herein. In certain embodiments, the (e.g., crude) reagent or reagent composition of any method provided herein is washed with a (e.g., organic) solvent (e.g., thereby forming a reagent or reagent composition, such as described herein). In some embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent under any suitable conditions, such as at a targeted temperature, with any selected volume of fluid composition, with stirring or other agitation, at any selected pH (e.g., using a buffer), at any selected temperature, for any selected period of time, or the like. In specific embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with an organic solvent (e.g., an alcohol).

[0102] In some embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for about 4 hours to about 48 hours. In certain embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for about 8 hours to about 36 hours. In some embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for about 10 hours to about

28 hours. In certain embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for 8 hours or more. In some embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for 36 hours or less. In specific embodiments, a (e.g., crude) reagent or reagent composition provided herein is washed with a (e.g., organic) solvent for about 18 hours.

[0103] In certain embodiments, a combination of a (e.g., crude) reagent or reagent composition provided herein and a (e.g., organic) solvent is at a temperature of about -20 to about 240 °C. In some embodiments, a combination of the (e.g., crude) reagent or reagent composition and the (e.g., organic) solvent is at a temperature of about 80 °C or more. In certain embodiments, a combination of the (e.g., crude) reagent or reagent composition and the (e.g., organic) solvent is at a temperature of about 235 °C or less.

[0104] In some embodiments, a (e.g., crude) reagent or reagent composition of any method provided herein is washed with a (e.g., organic) solvent described herein, thereby providing a reagent wash (e.g., a fluid reagent wash) and a washed (e.g., reagent) composition. In certain embodiments, a (e.g., crude) reagent or reagent composition of any method provided herein is washed with a (e.g., organic) solvent, thereby providing a reagent wash (e.g., comprising a (e.g., purified) reagent or reagent composition). In some embodiments, the (e.g., fluid) reagent wash comprises a reagent or reagent composition, such as described herein. In specific embodiments, the (e.g., fluid) reagent wash comprises a purified reagent or reagent composition provided herein.

[0105] In certain embodiments, provided herein is a composition or a method comprising concentrating a (e.g., fluid) reagent wash described herein (e.g., thereby forming a reagent or reagent composition, such as described herein). In some embodiments, a (e.g., fluid) reagent wash provided herein is concentrated by any suitable method and/or to any suitable endpoint provided herein. In certain embodiments, concentrating (e.g., fluid) reagent wash provided herein provides and/or produces a (e.g., purified) reagent or reagent composition (e.g., a reagent wash concentrate or reagent precipitate). In specific embodiments, the (e.g., purified) reagent or reagent composition is useful for fluorinating an organic compound provided herein (e.g., a starting reagent).

[0106] In certain embodiments, a reagent or reagent composition provided herein is activated, whereby the reagent or reagent composition comprises an (e.g., fluorination) reagent or reagent composition that can be used to fluorinate a starting reagent (e.g., organic compound) in that form. In some embodiments, any reagent or reagent composition provided herein comprises a fluorination reagent or reagent composition. In specific embodiments, an (e.g., crude) reagent or reagent composition provided herein comprises a fluorination reagent or reagent composition provided herein. In yet more specific embodiments, a (e.g., purified) reagent or reagent composition provided herein comprises a fluorination reagent or reagent composition provided herein.

[0107] In certain embodiments, provided herein is a method for fluorinating a starting reagent (e.g., organic compound). In some embodiments, a starting reagent (e.g., a starting reagent provided herein) is an organic compound. In specific embodiments, a starting reagent provided herein is an aromatic organic compound. In certain embodiments, starting reagents provided herein comprise a leaving group (e.g., chlorine, iodine, bromine, nitro). In specific embodiments, a leaving group of a starting reagent provided herein is chlorine. In still more specific embodiments, a leaving group of a starting reagent is nitro. In some embodiments, a starting reagent (e.g., a starting reagent provided herein) comprises an aliphatic and/or or an aromatic organic compound substituted with one or more halogens selected from the group of Cl, Br, and I, or the like. In certain embodiments the starting reagent comprises a haloaromatic (e.g., chloroaromatic), haloalkyl compound (e.g., monohaloalkyl compound, dihaloalkyl compound, trihaloalkyl compound), chlorobenzene, haloheteroaromatics, wherein each compound may be optionally substituted with an electron withdrawing group (e.g., CN, nitro, or the like). In some embodiments, a starting reagent provided herein is 1-chloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1-chloro-2,4-dinitrobenzene, 1,4-dichloro-2-nitrobenzene, 2-chloro-5-nitropyridine, 2-chloronicotinonitrile, 2,3,5,6-tetrachloroterephthalonitrile, 2,6-dichlorobenzonitrile, pentachloropyridine, 2,3,5,6-tetrachloro-4-fluoropyridine, 2,4,6-trichloro-1,3,5-triazine, 1,3-dinitrobenzene, and/or 2,4-dichloro-1-nitrobenzene.

[0108] In some instances, a reagent or reagent composition provided herein is used to fluorinate starting reagents provided herein to provide high value, high yield fluorinated reagents without the use of toxic chemicals such as HF.

[0109] In certain embodiments, provided herein is a composition or a method comprising contacting a starting reagent provided herein with a reagent or reagent composition described herein (e.g., thereby fluorinating the starting reagent and providing a fluorinated product). In some embodiments, a starting reagent provided herein contacted with a reagent or reagent composition provided herein provides a fluorinated (e.g., organic) compound (e.g., a fluorinated product provided herein). In some embodiments, the starting reagent is contacted with the reagent or reagent composition under any suitable conditions, such as at any selected temperature, with stirring or other agitation, at any selected pH, for any selected period of time, or the like.

[0110] In certain embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 50 to about 200 °C. In some embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 50 °C or more. In certain embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 70 °C or more. In some embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 110 °C or more. In certain embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 140 °C or more. In specific embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 80 °C. In still more specific embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 150 °C. In yet more specific embodiments, a combination of the (e.g., fluorination) reagent or reagent composition and the starting reagent is at a temperature of about 120 °C.

[0111] In certain embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition for about 1 hour to about 36 hours (e.g., about 2 hours to about 6 hours, about 12 hours to about 24 hours). In some embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition for about 24 hours or less (e.g., about 12 hours or less, about 6 hours or less). In certain embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition for about 1 hour or more (e.g., about 2 hours or more, about 16 hours or more). In specific embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition for about 3 hours. In yet more specific embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition for about 18 hours.

[0112] In certain embodiments, an amount of a reagent or reagent composition contacted with a starting reagent is calculated based at least in part on a number of fluorine atoms to be added to a starting reagent to yield a resulting fluorinated compound (e.g., a fluorinated product provided herein). In some embodiments, the amount of the (e.g., fluorination) reagent or reagent composition provided herein is about 0.5 equivalents to about 10 equivalents of the starting reagent multiplied by a number of fluorine atoms to be added. In specific embodiments, the amount of reagent or reagent composition comprises about 1 eq or more per fluorine atoms to be added. In yet more specific embodiments, the amount of reagent or reagent composition comprises about 1.5 eq or more per fluorine atoms to be added. In still more specific embodiments, the amount of reagent or reagent composition comprises about 2 eq per fluorine atoms to be added.

[0113] In some embodiments, a starting reagent (e.g., aromatic organic compound) provided herein is contacted with a (e.g., fluorination) reagent or reagent composition provided herein under mechanochemical conditions to provide a fluorinated (e.g., organic) compound. In specific embodiments, any suitable mechanical force is used as provided herein and under any suitable conditions as provided herein. In still more specific embodiments, a starting reagent (e.g., a starting reagent provided herein) is combined with a (e.g., fluorination) reagent or reagent composition provided herein in a laboratory mixer mill (e.g., and milled for 2 hours at 35 Hz) thereby providing a fluorinated compound.

[0114] In certain embodiments, a starting reagent (e.g., aromatic organic compound) is contacted with a (e.g., fluorination) reagent or reagent composition provided herein in a reaction mixture. In some embodiments a reaction mixture provided herein comprises a starting reagent (e.g., aromatic organic compound), a (e.g., fluorination) reagent or reagent composition, and a reaction (e.g., organic) solvent. In certain embodiments, a reaction solvent is any suitable solvent (e.g., organic solvent) provided herein. In specific embodiments, the reaction solvent is DMSO, acetonitrile, DMF, and/or sulfolane.

[0115] In some embodiments, the starting reagent is contacted with the (e.g., fluorination) reagent or reagent composition with any selected volume of reaction solvent. In certain embodiments, a reaction mixture provided herein further comprises an ammonium salt. In specific embodiments, a reaction mixture provided herein comprises a starting reagent (e.g., aromatic organic compound), a (e.g., fluorination) reagent or reagent composition, a reaction (e.g., organic) solvent, and an ammonium salt. In certain embodiments, an ammonium salt provided herein comprises ammonium sulfate, ammonium bicarbonate, ammonium chloride (e.g., tetramethyl ammonium chloride (TMAC)), ammonium iodide, ammonium benzoate, benzyltrimethyl, ammonium hydroxide, ammonium carbonate, ammonium dichromate, ammonium acetate, ammonium bromide, sodium tetradecyl sulfate, and/or combinations thereof ammonium iodate. In specific embodiments, an ammonium salt provided herein is TMAC. In certain instances, addition of an ammonium salt to a reaction mixture (e.g., a reaction mixture provided herein) results in high yields of a fluorinated product (e.g., a fluorinated provided herein).

[0116] In certain embodiments, an amount an ammonium salt (e.g., an ammonium salt provided herein) is about 0 equivalents to about 5 equivalents of a starting reagent provided herein (e.g., about 0.5 to about 4 equivalents, about 1 to about 3 equivalents). In some embodiments, the amount of the ammonium salt is about 0.5 or more (e.g., about 0.75 or more, about 1 or more, about 2 or more, about 3 or more) equivalents of the starting reagent. In certain embodiments, the amount of ammonium salt is about 4 or less (e.g., about 3 or less, about 2 or less, about 1 or less, about 0.5 or less,) equivalents of the starting reagent. In specific embodiments, the amount of the ammonium salt is about 1 equivalent of the starting reagent.

[0117] In certain embodiments, a reaction mixture provided herein further comprises a trapping agent (e.g., a trapping agent provided herein). In specific embodiments, a reaction mixture provided herein comprises a starting reagent (e.g., aromatic organic compound), a (e.g., fluorination) reagent or reagent composition, a reaction (e.g., organic) solvent, and a trapping agent. In specific embodiments, a trapping agent comprises phthaloyl chloride.

[0118] In certain embodiments, an amount a trapping agent (e.g., a trapping agent provided herein) is about 0 equivalents to about 5 equivalents of a starting reagent provided herein (e.g., about 0.5 to about 4 equivalents, about 1 to about 3 equivalents). In some embodiments, the amount of trapping agent is about 0.5 or more (e.g., about 0.75 or more, about 1 or more, about 2 or more, about 3 or more) equivalents of the starting reagent. In certain embodiments, the amount of trapping agent is about 4 or less (e.g., about 3 or less, about 2 or less, about 1 or less, about 0.5 or less,) equivalents of the starting reagent. In specific embodiments, the amount of trapping agent is about 1 equivalent of the starting reagent.

[0119] In certain embodiments, a starting reagent provided herein contacted with a (e.g., fluorination) reagent or reagent composition provided herein fluorinates the starting reagent and provides a fluorinated product (e.g., fluorinated aromatic compound). In some embodiments, a leaving group (e.g., chlorine) of a starting reagent provided herein is replaced with fluorine. In certain embodiments, contacting a starting reagent with a (e.g., fluorination) reagent or reagent composition provided herein provides a fluorinated product in a yield of about 10% or more (e.g., about 20% or more, about 30% or more, about 40% or more, about 50% or more, about 60% or more, about 70% or more, about 80% or more, about 90% or more). In certain embodiments, a yield of a fluorinated product provided herein is about 10% to about 95% (e.g., about 20% to about 80%, about 30% to about 70%, about 40% to about 60%).

[0120] In some embodiments, a fluorinated product provided herein comprises a haloaromatic (e.g., fluoroaromatic), haloalkyl compound (e.g., monohaloalkyl compound, dihaloalkyl compound, trihaloalkyl compound), fluorobenzene, haloheteroaromatic, wherein each compound may be optionally substituted with an electron withdrawing group (e.g., CN, nitro, or the like). In some embodiments, a fluorinated product provided herein is 2-chloro-1-fluoro-4-nitrobenzene, 1-fluoro-4-nitrobenzene, 1-fluoro-2-nitrobenzene, 1-fluoro-2,4-dinitrobenzene, 4-chloro-1-fluoro-2-nitrobenzene, 2-fluoro-5-nitropyridine, 2-fluoronicotinonitrile, 2,3,5,6-tetrafluoroterephthalonitrile, 2,6-difluorobenzonitrile, 2-chloro-6-fluorobenzonitrile, 3,5-dichloro-2,4,6-trifluoropyridine, 2,3,5-trichloro-4,6-difluoropyridine, 2,3,5,6-tetrachloro-4-fluoropyridine, 2,4,6-trifluoro-1,3,5-triazine, 1-fluoro-3-nitrobenzene, and/or 2,4,6-trifluoro-1,3,5-triazine.

[0121] In certain embodiments, any of the steps provided herein can comprise any of the methods provided herein.

[0122] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

EXAMPLES

[0123] Example 1: Applying mechanical force to a combination of a first and second salt to form a mixed composition

[0124] To a 50 mL stainless steel milling jar was charged calcium fluoride, CaF_2, (1 equiv.), and an activator provided in Table 1 (1). The jar was sealed finger tight and fastened to the MM500 Vario before milling for 10 cycles (1 hour at 35 Hz followed by 45 min at 5 Hz). For mixed composition B only, additional K_2HPO_4 (1 eq) was added to the mixture in the stainless steel milling jar. The jar was sealed finger tight and fastened to the MM500 Vario a second milling for 10 cycles (1 hour at 35 Hz followed by 45 min at 5 Hz). The jar was removed from the mill and taken to a fume cupboard before opening. The solid residue was removed and collected. An exemplary scheme is provided in FIG. 1.

Table 1

Mixed Composition ID	Fluorine source - equivalents	Activator - equivalents
A	CaF_2 - 1 equiv.	K_2HPO_4 - 1 equiv.
B	CaF_2 - 1 equiv.	K_2HPO_4 - 2 equiv.
C	CaF_2 - 1 equiv.	K_3PO_4 – 1 equiv.
D	CaF_2 from waste stream (ca. 70% pure) - 1 equiv.	K_3PO_4 – 1 equiv.
E	CaF_2 1 - equiv.	Na_3PO_4 – 1 equiv.
F	CaF_2 1 - equiv.	Li_3PO_4 – 1 equiv.
G	CaF_2 1 - equiv.	$KHCO_3$ – 1 equiv.
H	CaF_2 1 - equiv.	K_2CO_3 – 1 equiv.
I	CaF_2 1 - equiv.	Na_2CO_3 – 1 equiv.
J	CaF_2 1 - equiv.	$NaHCO_3$ – 1 equiv.
K	CaF_2 1 - equiv.	Cs_2CO_3 – 1 equiv.
L	CaF_2 1 - equiv.	K_2SO_4 – 1 equiv.
M	CaF_2 1 - equiv.	$K_4P_2O_7$ – 1 equiv.

[0125] Example 2: formation of a reagent or reagent composition

[0126] A mixed composition provided in Table 1 was suspended in water (1-5 mL/g of mixed composition), the pH measured and adjusted if necessary. The suspension was stirred and heated at 100 C for 2 h. The mixture was allowed to cool to room temperature before adjusting to pH = 7. methanol (2-20 volumes) was added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The off-white solid was collected and dried.

[0127] When necessary, the resultant off-white solid was subjected to an additional purification step by stirring in methanol (30-40 mL/g) at 50 °C for 1 h, then cooled down to rt and filtered. The filtrate was collected evaporated under reduced pressure and dried to yield a purified fluorination reagent.

[0128] Example 3A: formation of a reagent or reagent composition

[0129] Mixed composition C provided in Table 1 (10.0 g, 34.4 mmol) was stirred in water (20.0 mL, pH = 12-13) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to pH of 7 by addition of aqueous H_3PO_4. 200 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The off-white fluorination reagent solid was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content (2.80 g, 54% fluorine conversion, 25 F wt%), the results of which are provided in Table 2 below.

Table 2

scale	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
10 g	2.80	54	25

[0130] The off-white solid was stirred in methanol (115 mL) at 50 C for 1 h, then cooled down to rt and filtered. The filtrate was collected evaporated under reduced pressure and dried to yield an off-white purified fluorination reagent solid. The purified fluorination reagent solid was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 3 below. An exemplary reaction scheme is provided in FIG. 2.

Table 3

scale	**Purified Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
10 g	2.10	52	32

[0131] Example 3B: formation or a reagent or reagent composition

[0132] Mixed composition C provided in Table 1 (49.0 g, 168 mmol) was stirred in water (150 mL, pH = 12-13) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to pH of 7 by addition of ~ 20 ml of H_3PO_4 20% (aqueous). 300 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was concentrated under reduced pressure to a small volume. Methanol (100 mL) was added to the flask and the suspension stirred at 50 °C for 1 h, then cooled down to rt and filtered. The filtrate was collected evaporated under reduced pressure and dried to yield an off-white purified fluorination reagent solid. The purified fluorination reagent solid was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 4 below. An exemplary reaction scheme is provided in FIG. 2. Powder X-ray diffraction data for the prepared fluorination reagents is found in Table 5 below.

Table 4

scale	Purified Fluorination reagent [g]	F conversion [%]	F content [wt %]
49g	11.5	56	32

Table 5: XRPD of fluorination reagent prepared from mixed composition C

Angle (°2Θ)	Intensity [a.u.]
17.1065	48.03
18.1243	56.65
19.8556	180.49
20.1077	443.85
21.7697	127.08
24.6649	55.53
26.0729	59.75
26.5044	765.05
27.8025	593.63
28.8975	1146.01
29.6196	1502.66
30.7473	181.75
33.5278	3742.12
34.1891	299.51
34.5311	619.91
34.5606	259.81
35.0389	711.86
36.0813	137.03
36.6838	132.76
40.8449	35.02
41.6134	472.23
42.5274	1030.97
44.3484	550.71
44.5738	159.05

46.2653	170.23
46.7412	525.11
48.0764	2597.43
49.0280	84.97
49.1401	118.82
50.1292	60.09
50.5421	71.06
52.0373	83.41
52.4004	213.73
54.0201	207.41
57.1244	590.72
57.7184	226.83
58.4393	49.82
59.8714	1179.03
61.9070	71.87
63.7016	161.22
64.6762	99.11
66.3163	159.72
66.7518	92.20
67.6036	93.35
70.4056	467.93
72.3758	149.53
72.5514	50.60
75.0914	61.76
75.2740	47.83
77.8145	372.80

[0133] Example 3C: formation of a reagent or reagent composition

[0134] Mixed composition D provided in Table 1 (10.0 g, 34.4 mmol) was stirred in water (20.0 mL, pH = 12-13) and heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to pH of 7 by addition of aqueous H_3PO_4. 200 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The off-white fluorination reagent solid was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content (3 g, 55% fluorine conversion, 25

F wt%), the results of which are provided in Table 6A below. Powder X-ray diffraction data for the prepared fluorination reagent is provided in Table 6B below.

Table 6A

scale	Fluorination reagent [g]	F conversion [%]	F content [wt %]
10 g	3.00	55	25

Table 6B

Angle (◦2Θ)	Intensity [a.u.]
12.8689	51.99
17.4819	271.74
17.8960	472.31
18.1887	416.67
20.9623	93.84
21.9116	728.18
23.4371	230.99
24.7485	1286.15
25.3210	922.82
26.1421	459.83
26.5258	96.62
27.7058	205.00
28.9791	2536.77
29.4011	1213.05
29.6356	364.01
30.1091	335.66
30.8271	1365.52
31.1301	235.95
31.3794	790.08
32.3708	555.36
32.8706	1985.52
33.5827	6213.00
34.2771	1862.59
35.2179	823.40
35.2928	1295.04
35.4354	657.06
35.9477	347.55

36.5433	615.99
36.7457	1492.84
38.3784	476.01
38.8432	416.73
39.5464	136.09
39.7938	1249.15
41.7371	359.16
42.5554	343.10
42.8300	53.89
43.9465	598.17
44.5691	186.48
44.8782	796.16
45.3749	417.47
45.8780	64.49
46.3119	200.45
47.0548	71.15
47.8125	446.69
48.1839	3137.85
49.5439	582.86
50.6176	617.33
51.8703	313.40
52.2140	345.70
53.2401	316.97
53.6387	245.41
54.6143	717.36
55.5791	165.82
57.1380	1395.91
58.1668	238.33
59.9018	897.15
59.9586	829.53
61.2654	197.41
61.7787	99.04
62.1436	136.31
63.7160	120.52

64.2548	432.01
67.2843	173.44
69.2047	130.37
70.2165	285.16
70.4314	919.98
72.1080	100.14
74.4980	240.52
74.8330	165.13
75.9673	186.75
77.6316	160.17
77.8384	508.94

[0135] Example 4A: formation of a reagent or reagent composition

[0136] Mixed composition A exemplified in Table 1 (10.00 g, 39.64 mmol) was mixed with (50.0 mL) and the pH adjusted to > 12 by addition of aqueous KOH. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to neutral by addition of aqueous H_3PO_4. 500 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure, the filter residue was collected and dried separately. The dry filtrate was collected as an off-white fluorination reagent solid (2.20 g, 28% fluorine conversion, 18 F wt%).

[0137] The off-white solid was stirred in methanol (150 mL) at 50 °C for 1 h, then cooled down to rt and filtered. The filtrate was collected, evaporated under reduced pressure, and dried to yield an off-white purified fluorination reagent solid. (1.20 g, 23% F conversion, 28 fluorine wt%).

[0138] The process was run again with Mixed composition A exemplified in Table 1 (4.00 g). The results for both are shown below in Table 7. An exemplary reaction scheme is provided in FIG. 3. Powder X-ray diffraction data for the fluorination reagents prepared from Mixed composition A are found in Table 8 (10 g scale, 28 fluorine wt %) and Table 9 (4 g scale, 31 fluorine wt %) below.

Table 7

scale	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
10 g	1.2	23	28
4 g	0.5	26	31

Table 8: XRPD of fluorination reagent prepared from (10 g) mixed composition A

Angle (◦2Θ)	**Intensity [a.u.]**
17.1147	158.82
19.8741	565.37
20.1050	687.66
20.1342	610.72
21.7811	368.86
25.6546	347.33
26.5311	1518.79
27.8092	983.53
28.4015	440.37
28.9150	4111.80
29.6464	2052.47
33.5038	25921.00
34.5678	2637.62
35.0559	2070.16
36.1116	346.84
36.6764	421.99
38.8696	283.48
40.3412	179.39
40.5919	170.88
40.8721	82.62
41.6380	1028.10
42.5567	2401.08
44.3712	1417.75
44.6017	466.23
46.1873	277.43
46.2926	605.21
46.6807	979.27
46.7684	1580.09
48.0821	7000.61
49.0481	275.31
49.1625	344.89
50.1505	253.11
52.0608	237.44

52.4271	556.46
54.0471	625.41
57.1344	626.11
57.2283	178.09
57.7436	620.87
58.4729	186.91
59.8421	1334.05
61.9480	220.46
63.7277	528.85
64.7087	267.23
65.9425	98.25
66.3410	421.75
66.7862	282.93
67.6265	309.82
70.3510	1336.10
72.4041	425.63
72.5810	140.32
75.1310	135.71
75.2931	140.95
76.5641	113.81

Table 9: XRPD of fluorination reagent prepared from (4 g) mixed composition A

Angle (◦2Θ)	**Intensity [a.u.]**
28.879963	2162.271033
29.294767	483.229326
33.506059	4400.807977
44.431065	98.839284
48.061582	4462
49.465252	224.428037
57.058226	1405.278705
59.776309	1699.869244
59.864398	2232.893381
70.309257	1518.410093
70.387665	620.314622
77.739699	567.352216

[0139] Example 4B: formation of a reagent or reagent composition from recycled first salt

[0140] The dry filter residue of Example 4A (9 g) was mixed with K_2HPO_4 (1 equiv., 3.5 g) in a stainless steel milling jar. The stainless steel milling jar was sealed finger tight and fastened to a MM500 Vario before milling for 10 cycles of 1 hour at 35 Hz followed by 45 min at 5 Hz. The jar was removed from the mill and taken to a fume cupboard before opening. The solid residue was removed and collected. The resulting solid (5.4 g) was collected and mixed with water (10.0 mL) and the pH adjusted to > 12 by addition of aqueous KOH. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to a pH of 7 by addition of aqueous H_3PO_4. 100 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated, dried and collected as an off-white solid (0.315 g, 15 F wt %).

[0141] Example 4C: formation of a purified reagent or reagent composition from recycled first salt

[0142] The off-white solid of Example 4B can be further stirred in methanol (30-40 volumes) at 50 °C for 1 h, then cooled down to rt and filtered. The filtrate can be collected evaporated under reduced pressure and dried to yield a purified fluorination reagent.

[0143] Example 5A: formation of a reagent or reagent composition

[0144] Mixed composition A (4.00 g, 15.9 mmol) was mixed with water (10.0 mL) and the pH adjusted to > 12 by addition of aqueous KOH. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The dry filtrate was collected as an off-white solid.

[0145] The off-white solid was stirred in methanol (200 mL) at 70 °C for 2 h, then cooled down to rt and filtered. The filtrate was collected, evaporated under reduced pressure, and dried to yield an off-white solid. ^{19}F NMR was taken to determine fluoride content, the results of which are provided in Table 10 below.

Table 10

Mixed composition - scale	**pH**	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
A – 4 g	14	0.4	15	21

[0146] Example 5B: formation of a reagent or reagent composition

[0147] Mixed composition B (4.00 g, 15.9 mmol) was mixed with water (10.0 mL) and the pH adjusted to > 12 by addition of aqueous KOH. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature. The mixture was filtered washing with methanol.

The filtrate was evaporated under reduced pressure. The dry filtrate was collected as an off-white solid.

[0148] The off-white solid was stirred in methanol (200 mL) at 70 °C for 2 h, then cooled down to rt and filtered. The filtrate was collected, evaporated under reduced pressure, and dried to yield an off-white solid. ^{19}F NMR was taken to determine fluoride content, the results of which are provided in Table 11 below. Powder X-ray diffraction data for the prepared fluorination reagent is provided in Table 12 below.

Table 11

Mixed composition - scale	**pH**	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
B – 4 g	14	0.5	35	25

Table 12: XRPD data of fluorination reagent prepared from mixed composition B (without neutralization)

Angle (◦2Θ)	**Intensity [a.u.]**
12.8146	100.05
28.9058	2234.16
29.4276	717.19
29.6799	215.05
31.4783	416.54
32.1320	218.91
32.3404	283.44
32.6210	448.67
33.5010	17695.00
35.3175	212.09
36.6993	543.24
38.5603	177.35
39.0849	99.40
39.7143	394.08
41.2993	149.85
48.0958	6957.93
57.0879	1106.40
59.8717	1715.94
70.3749	736.12
77.7822	358.67

[0149] Example 5C: formation of a reagent or reagent composition

[0150] Mixed composition A (4.00 g, 15.9 mmol) was mixed with water (10.0 mL). The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The dry filtrate was collected as an off-white solid.

[0151] The off-white solid was stirred in methanol (200 mL) at 70 °C for 2 h, then cooled down to rt and filtered. The filtrate was collected, evaporated under reduced pressure, and dried to yield an off-white solid. The pH was maintained at 9 throughout. ^{19}F NMR was taken to determine fluoride content, the results of which are provided in Table 13 below.

Table 13

Mixed composition - scale	**pH**	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
A – 4 g	9	0.16	5	18

[0152] Example 6: formation of a reagent or reagent composition

[0153] Mixed composition A (10.00 g, 39.64 mmol) was mixed with methanol (500.0 mL). The mixture was heated at 70 °C for 18 h. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The dry filtrate was collected as an off-white solid (0.61 g, 10% F conversion, 24 F wt%). An exemplary reaction scheme is provided in FIG. 4.

[0154] Example 7: formation of a reagent or reagent composition

[0155] Mixed composition A (30.00 g, 1 Eq, 120 mmol) was mixed with water (75.0 mL) and the pH adjusted to > 12 by addition of aqueous KOH. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to neutral by addition of HCl 1M. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was then stirred in methanol (500 mL) at 70 °C for 18 h then filtered. The filtrate was collected evaporated under reduced pressure and dried to yield an off-white solid. (4.0 g, 17 % yield, 19 F wt%). An exemplary reaction scheme is provided in FIG. 5.

[0156] Example 8: formation of a reagent or reagent composition varying second salt

[0157] 10.00 g of a mixed composition provided in Table 1 (here, mixed composition M, H, G, and K), was mixed with water (20.0 mL), the pH was measured and adjusted to >12 by addition of aqueous KOH, where necessary. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to neutral pH by addition of aqueous H_3PO_4. 200 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The fluorination reagent, an off-white solid, was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 14 below. An exemplary reaction scheme is provided in FIG. 6. Powder X-ray diffraction data for the prepared fluorination reagents are found in Tables 15-18 below.

Table 14

Mixed Composition ID	**Fluorination reagent [g]**	**F conversion [%]**	**F content [wt %]**
M	0.4	18	18
H	1.3	1	6
G	1.4	1	4
K	2.1	3	1

Table 15: XRPD of fluorination reagent prepared from mixed composition M

Angle (°2Θ)	**Intensity [a.u.]**
17.4506	228.41
17.8311	650.58
18.1319	123.32
20.9499	382.50
21.1013	183.79
21.8676	446.46
23.5686	163.57
24.6918	190.95
25.2573	371.98
25.9337	147.55
26.0856	114.73
28.0206	269.37
28.9125	727.57
29.3922	3112.00
30.0864	2921.29
30.3734	2369.73
30.7862	624.93
31.0713	272.88
31.4364	456.61
32.1882	540.24
32.8190	1563.86
33.5283	2399.98
34.2240	706.83

35.2057	1051.35
35.6026	565.55
36.8177	387.97
37.0231	218.98
37.3653	202.19
38.3233	447.83
39.7459	1056.74
40.4239	290.19
41.6487	198.52
42.6188	963.20
42.9152	401.39
43.8824	502.49
44.5220	239.76
44.8261	176.80
47.2605	307.81
48.0984	1934.89
49.4803	696.62
50.5814	240.32
51.8112	157.99
52.1363	171.97
53.5725	440.08
54.7155	183.14
56.1696	158.17
57.0849	268.44
58.0625	298.14
59.8655	280.89
60.9355	360.83
61.2181	157.52
62.4228	196.46
63.1638	330.76
64.3204	560.78
68.7156	161.31
70.4687	151.80
74.8345	380.55

Table 16: XRPD of fluorination reagent prepared from mixed composition H

Angle (◦2Θ)	Intensity [a.u.]
11.5476	129.21
12.0755	453.98
12.7945	124.63
12.8470	293.63
15.5270	19.86
16.8828	67.73
17.4088	139.49
18.1293	270.70
20.9125	55.83
23.1656	308.90
23.3855	140.82
24.1126	309.26
24.2549	388.40
24.6921	482.43
24.8751	93.33
25.7931	276.64
26.0825	277.57
26.5048	119.29
26.9170	54.64
27.6484	120.22
28.6688	190.42
28.8454	442.46
29.0173	177.35
29.3472	1258.99
29.6254	730.55
29.8582	820.50
30.0873	844.34
30.3783	189.51
30.7520	1714.50
31.2822	1694.98
31.6642	1110.50
31.7933	357.03

32.1569	432.44
32.3589	430.78
32.6413	550.98
33.6862	421.01
34.1055	1390.28
34.2493	1188.34
34.4644	209.17
35.1792	644.32
35.3855	827.56
35.8901	128.68
36.1652	544.90
36.4809	571.82
36.6978	1327.93
38.0465	808.32
38.8323	782.70
39.7438	637.80
40.3945	183.87
40.6164	143.32
41.3288	262.75
41.6851	371.06
42.5490	248.40
43.3659	159.97
43.9206	79.07
44.5118	323.81
44.8279	635.98
45.3404	194.81
46.2022	399.29
47.2445	698.83
47.7686	557.42
48.1356	308.08
48.6691	310.64
48.9179	200.93
49.3057	571.10
49.6079	350.57

49.7337	224.09
50.1169	250.69
50.5718	422.93
51.4615	202.31
52.1672	199.16
53.1825	718.81
53.6325	182.97
54.4276	1226.98
55.4016	512.87
57.2671	594.44
58.1097	220.28
60.8110	231.02
62.1094	77.36
64.0144	168.28
65.2949	58.18
66.3867	163.63
67.6263	141.24
69.1765	62.89
70.1992	94.25
70.7696	134.59
71.9451	231.78
74.7848	73.07
77.5274	149.72
79.6765	64.94

Table 17: XRPD of fluorination reagent prepared from mixed composition G

Angle (◦2Θ)	**Intensity [a.u.]**
11.5829	85.67
12.1014	148.09
12.8322	707.34
16.9071	35.52
17.5073	44.65
23.1934	264.89
24.2756	674.32
24.8439	213.54

25.7631	526.33
26.5338	91.54
26.9031	137.00
28.8516	695.94
29.3567	674.62
29.6637	1376.83
30.1082	414.13
30.4032	297.30
30.7711	946.18
31.2902	1305.12
31.8092	421.20
32.1257	1267.21
32.3275	1455.00
32.6283	1312.53
34.1348	1143.01
35.3906	509.82
36.1724	253.32
36.5012	424.37
36.7227	584.60
38.0341	354.97
38.5642	602.80
39.1423	271.68
39.2781	288.28
39.7476	727.40
40.3948	325.22
40.6391	146.35
41.3146	461.51
41.6451	500.01
43.4043	83.84
44.5055	183.19
44.9667	116.16
46.2331	282.67
46.7851	188.59
47.3525	373.61

47.7606	398.27
48.1556	374.24
48.6084	303.24
48.9070	373.56
49.3353	460.85
49.6724	453.13
50.1571	173.76
50.6723	712.56
51.4397	781.36
52.2968	1006.63
53.1909	579.62
53.6531	204.99
54.3623	502.55
55.3887	775.81
60.7460	217.03
63.8645	66.77
66.3916	106.60
67.0278	109.55
67.6573	107.85
69.9609	244.08
71.7240	69.16
74.8739	73.67
79.9131	100.71

Table 18: XRPD of fluorination reagent prepared from mixed composition K

Angle (◦2Θ)	**Intensity [a.u.]**
16.4885	148.49
18.3868	275.63
18.7087	1626.00
19.6088	138.85
21.1936	387.53
22.7945	181.75
22.9570	483.86
23.2081	95.52
23.4725	219.91

24.5379	1533.78
26.4959	169.60
26.9955	733.55
27.4932	366.41
27.7371	785.86
27.8630	277.96
28.0694	453.24
28.2066	462.93
28.3765	932.99
29.1334	1330.05
29.8420	185.56
31.5218	151.14
32.4871	295.58
33.1917	151.36
33.3628	230.36
34.0021	579.17
34.2980	72.05
34.5871	170.11
35.4054	86.68
36.8453	676.26
37.5055	322.75
37.7247	365.54
37.8981	1193.39
42.2169	269.35
42.4730	174.33
44.5460	175.68
46.0331	243.32
46.4503	174.55
46.9098	864.24
47.9529	210.13
50.1859	108.83
50.9924	244.38
54.9055	278.98
58.0021	156.03

58.5049	286.43
61.3167	115.10
61.8176	149.08
64.1583	95.39
64.6226	110.87
65.6169	267.56
67.5741	86.28
68.9028	113.64

[0158] Example 9: formation of a reagent or reagent composition varying second salt

[0159] 5.00 g of a mixed composition provided in Table 1 (here, mixed composition E and mixed composition J), was mixed with water (100.0 mL), the pH was measured and adjusted to >12 by addition of aqueous NaOH, where necessary. The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to neutral pH by addition of aqueous H_3PO_4. 25 ml of methanol were added, and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The fluorination reagent, an off-white solid, was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 19. An exemplary reaction scheme is provided in FIG. 7. Powder X-ray diffraction data for the prepared fluorination reagents are found in Tables 20-21 below.

Table 19

Mixed Composition ID	Fluorination reagent [g]	F conversion [%]	F content [wt %]
E	1.2	32	21
J	6.5	6	2

Table 20: XRPD of fluorination reagent prepared from mixed composition E

Angle (°2Θ)	Intensity [a.u.]
10.4959	458.76
16.7789	850.97
17.1457	121.67
17.3570	136.72
18.2080	362.34
19.1147	984.16
20.0991	316.39

20.3322	258.31
21.0528	182.68
22.0575	306.21
22.4962	427.89
22.7954	177.83
23.2203	729.74
23.5489	343.89
23.7876	237.80
24.2664	192.10
25.3053	92.52
25.7810	190.05
25.9692	264.14
26.5388	919.60
26.7504	70.73
27.0039	47.41
27.3033	649.34
27.5279	203.53
28.0372	316.22
28.3005	139.83
29.0119	381.12
29.6895	232.76
30.0172	280.99
30.3265	245.70
30.5306	458.48
31.1208	792.34
31.3789	525.40
31.8722	1449.86
32.1143	449.49
32.6178	691.06
33.0691	574.82
33.3615	618.12
33.9129	241.20
34.5446	296.47
34.6628	170.16

35.1065	253.83
35.5345	191.07
36.0087	426.12
36.3575	339.64
38.8663	9269.00
39.8085	401.02
40.7505	139.74
43.2445	303.22
43.7568	275.54
46.0709	90.07
46.5925	217.85
47.4424	963.47
48.1114	234.34
48.6984	164.14
49.3971	42.38
50.2728	128.28
50.7211	90.84
51.0257	194.28
51.8824	44.34
52.3405	599.18
53.0147	266.36
53.5880	469.12
54.2602	53.36
55.0988	64.27
56.0900	7195.71
57.8471	863.26
63.0507	193.92
64.0070	185.17
64.7708	154.07
65.6062	216.40
66.9502	396.25
68.2918	132.24
69.3483	40.21
70.3180	1931.76

Table 21: XRPD of fluorination reagent prepared from mixed composition J

Angle (◦2Θ)	**Intensity [a.u.]**
10.5097	345.84
14.9568	129.96
16.7613	400.27
17.1184	92.27
18.1196	443.91
18.2834	213.18
19.0881	839.36
20.1193	92.95
22.3429	1818.67
23.1365	2415.26
24.2422	135.48
25.5432	424.02
25.9946	1131.30
26.5088	709.59
27.2736	680.06
28.9330	496.83
29.1713	401.01
29.6637	200.66
30.1670	1547.37
30.3996	2332.73
31.0668	2101.75
31.8924	5045.00
32.9118	1733.15
33.3633	939.07
33.7821	888.16
34.4480	2378.60
35.2990	1369.79
35.9677	263.08
36.3292	361.34
36.6693	535.94
36.8556	741.50
37.7831	1140.84

38.8109	1805.57
39.7762	409.52
40.7097	941.50
41.0145	1110.77
42.3873	252.78
43.7189	472.83
44.4925	911.25
45.5123	736.37
45.7948	701.99
46.0445	332.86
46.6023	334.79
47.3135	1226.70
47.6604	563.19
48.4919	563.49
50.3274	425.14
52.2396	822.29
53.4718	1110.42
54.2802	634.30
55.2299	414.52
56.0487	2016.68
56.9641	280.39
57.7560	624.47
58.1406	1736.36
60.7622	332.00
63.1373	496.02
64.2242	626.31
66.2219	847.78
70.1050	2060.06
75.0040	47.99
79.2255	362.26

[0160] Example 10: formation of a reagent or reagent composition varying second salt

[0161] Mixed composition F provided in Table 1 (2.5 g), was mixed with water (200.0 mL). The mixture was heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature and the suspension filtered. The filtrate was evaporated under reduced pressure. The fluorination reagent, an off-white solid, was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 22. An exemplary reaction scheme is provided in FIG. 8. Powder X-ray diffraction data for the prepared fluorination reagent is found in Table 23 below.

Table 22

Mixed composition	Fluorination reagent [g]	F conversion [%]	F content [wt %]
F	1.0	55	10

Table 23: XRPD of fluorination reagent prepared from mixed composition F

Angle (°2Θ)	Intensity [a.u.]
16.8808	3513.13
17.3666	2289.09
18.3445	1330.58
22.3064	14156.31
22.4936	12085.85
23.2768	12065.91
24.8657	5847.07
25.9091	1096.17
27.3519	2111.57
28.8859	1860.24
29.1681	1941.91
30.3360	699.21
30.9213	1304.70
31.4363	1922.90
31.9241	2404.72
33.0341	963.20
33.6357	1833.76
33.8910	9779.70
34.1156	4701.81
35.1194	2793.63

36.7679	5952.46
38.1273	1978.69
38.6718	7626.09
38.9588	1864.99
39.4716	1699.94
39.9749	2101.27
40.3958	804.74
40.7636	1159.80
41.1062	861.03
41.7030	2111.84
43.3854	501.08
43.6919	1396.02
44.9463	16043.00
45.8703	309.41
46.6823	772.26
47.0926	844.80
47.9154	1640.90
48.5232	528.67
49.3644	1105.38
49.8530	752.92
50.9726	1160.12
51.7225	1124.73
52.2474	264.13
52.7536	513.07
53.2648	624.94
53.7700	411.21
54.4684	502.63
55.1921	956.70
55.9065	953.42
57.0410	2746.46
58.1358	279.96
58.8165	1554.11
60.4760	1823.70
60.9412	1515.42

62.0197	1508.50
65.4542	2299.09
73.2782	1625.72
78.6511	2029.44
79.9348	181.64

[0162] Example 11: formation of a reagent or reagent composition

[0163] Mixed composition C, provided in Table 1, (5.0 g, 17.2 mmol) was mixed with water (10.0 mL) and the pH adjusted to the desired value, as provided in Table 6, with either aqueous KOH or aqueous H_3PO_4. The mixture was then heated at 100 °C for 2 h. The mixture was allowed to cool to room temperature before adjusting to neutral. 100 ml of methanol were added and the suspension stirred for 30 minutes. The mixture was filtered washing with methanol. The filtrate was evaporated under reduced pressure. The fluorination reagent, an off-white solid, was collected and analyzed by quantitative ^{19}F NMR to determine fluoride content, the results of which are provided in Table 24. An exemplary reaction scheme is provided in FIG. 9. Powder X-ray diffraction data for the prepared fluorination reagents are found in Tables 25-28 below.

Table 24

pH	**F conversion [%]**	**F content [wt %]**
14	38	26
12.5	48	31
10	13	22
7	8	18

Table 25: XRPD of fluorination reagent with pH adjusted to 14

Angle (°2Θ)	**Intensity [a.u.]**
15.5786	79.60
17.4082	263.88
18.1281	460.66
20.8996	116.14
23.3993	339.83
24.6884	662.97
25.5587	69.11
26.0863	375.90
26.5174	156.37
27.6604	88.77

28.9339	2364.48
29.4290	2144.68
30.0374	279.51
30.7663	1668.53
31.4474	3316.58
33.5356	5386.00
34.2341	1093.02
35.1811	1201.37
35.4073	1569.84
36.7097	2301.04
38.8131	697.52
39.7915	379.31
41.6852	397.98
42.5004	232.89
42.8009	157.34
43.9201	165.24
44.4750	241.55
44.8268	707.03
45.3333	278.02
46.3008	722.86
48.1180	4761.55
48.8971	272.59
50.5594	515.91
51.2907	427.50
51.6563	252.12
52.1479	218.53
53.3722	197.20
54.7184	1252.16
57.0967	737.11
58.2269	695.04
59.9095	480.03
60.9726	416.90
64.2126	459.29
65.4745	380.39

70.2865	587.69
76.9868	344.63
77.7306	300.36

Table 26: XRPD of fluorination reagent with pH adjusted to 12.5

Angle (◦2Θ)	**Intensity [a.u.]**
17.5055	48.26
25.5754	178.50
25.7837	206.89
28.9412	4150.59
29.4049	861.95
33.5235	27079.00
36.6752	583.07
38.7621	285.92
39.0685	103.42
39.7278	234.65
41.4731	301.52
48.1384	5837.30
53.2519	85.83
57.1315	948.02
59.9038	2696.86
70.4103	1872.08
77.8195	544.74

Table 27: XRPD of fluorination reagent with pH adjusted to 10

Angle (◦2Θ)	**Intensity [a.u.]**
12.8213	81.12
17.3984	244.34
17.5192	109.87
18.1304	729.24
20.9096	183.99
23.4085	447.48
24.6909	1078.95
26.0922	636.17
26.4939	173.47

27.6461	258.02
28.9330	2783.51
29.3942	2049.90
29.6237	514.56
30.0280	327.97
30.7670	2323.37
31.3667	1933.55
31.4929	1682.42
33.5350	5559.94
34.2396	1293.09
35.1680	1548.97
35.4137	1993.19
36.6897	3218.28
38.8048	425.16
39.7484	616.74
41.6858	720.17
42.5306	298.55
43.9261	258.80
44.8264	944.53
45.3244	385.88
46.3450	267.36
48.1338	2130.95
50.5672	769.47
53.2894	339.27
54.7055	1112.17
57.0903	1009.68
58.2057	537.08
59.9032	1048.38
62.1809	278.28
64.0724	820.59
65.5149	231.86
70.1879	203.41
70.3908	599.00
77.7309	363.10

Table 28: XRPD of fluorination reagent with pH adjusted to 7

Angle (◦2Θ)	Intensity [a.u.]
17.4790	279.90
17.8407	244.85
18.1469	328.74
20.9400	77.91
21.8619	487.47
23.4125	302.41
24.7054	586.86
24.8664	130.07
25.2672	632.90
26.1044	345.31
26.5197	115.84
27.6584	90.43
28.9527	2340.78
29.3906	2705.41
30.7913	1121.09
31.0889	117.93
31.3805	1435.64
32.8248	1929.30
33.5592	10418.00
34.2462	1613.17
35.1968	1035.86
35.4026	1629.10
36.7206	2388.91
38.3450	487.80
38.7746	278.83
39.7594	1350.71
41.7114	326.74
42.5160	231.66
42.8220	110.18
43.8788	150.82
43.9399	185.45
44.5413	233.52

44.8499	536.16
45.3538	271.89
46.2989	314.29
47.7987	624.15
48.1449	5417.42
49.5072	864.03
50.5837	379.29
51.7971	367.92
53.2378	582.85
54.7186	511.18
57.1267	1293.06
58.1604	371.01
59.9307	873.03
61.0858	402.74
61.7330	163.16
62.1479	159.80
63.8272	467.81
64.2757	361.57
65.4506	165.07
67.2619	267.76
68.7360	148.53
70.1799	319.00
70.4270	841.98
74.4506	324.00
75.9206	147.61
77.8291	380.36

[0164] Example 12: formation of a reagent or reagent composition

[0165] CaF_2 (4.00 g, 1 Eq, 51.2 mmol) and KOH (5.75 g, 2 Eq, 102 mmol) were stirred in water (100 ml) for 18 hours at 100 °C. The mixture was filtered, and the filtrate neutralized with aqueous H_3PO_4 before evaporation under reduced pressure. The crude was redissolved in methanol (200 mL) and stirred at 70 °C overnight. The suspension was filtered and the filtrate evaporated to yield 100 mg of material containing fluoride. F conversion was 3%. An exemplary reaction scheme is provided in FIG. 10.

[0166] Additional purified reagents were prepared using a scheme similar to that provided in **FIG. 14**. A reactor described herein was charged with tripotassium phosphate, and mechanical force was applied according to methods described herein. The reactor was charged with calcium fluoride, heated to reflux, and aged before cooling to room temperature whilst continuing to apply mechanical force.

[0167] A resultant suspension was charged into a benchtop centrifuge. The solids were then separated and were combined with water to form a slurry which was cycled through the centrifuge. The liquids were charged into a container equipped with an overhead stirrer and stirring commenced. The solution was charged with phosphoric acid until a pH of 6 was obtained and stirring was performed for 1 hour.

[0168] The liquids were charged to and concentrated using a rotary evaporator to yield a white crystalline powder. A reactor as described herein was charged with methanol, mechanical force was applied, and the reactor was charged the white crystalline powder. The stirred suspension was heated, aged, cooled to room temperature, and discharged from the reactor. The resulting suspension was siphoned onto a Buchner funnel and filtered. The filter cake was re-slurried in methanol and then re-filtered.

[0169] The subsequent combined filtrates were then charged to a rotary evaporator and concentrated *in vacuo* to afford a crystalline solid comprising a purified fluorination reagent.

[0170] Production of a purified fluorination reagent was also achieved using reactions at elevated temperatures (including 150 °C) in a pressure flask, as well as using high shear mixing and/or a homogenizer as a reactor, as described herein.

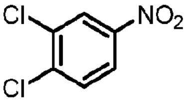
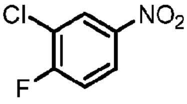
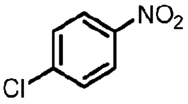
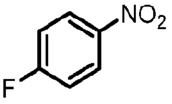
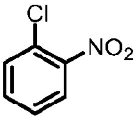
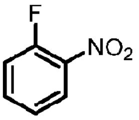
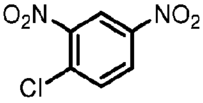
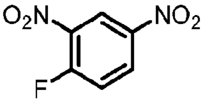
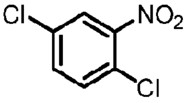
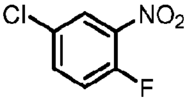
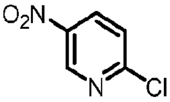
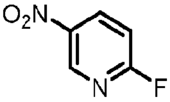
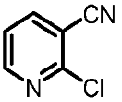
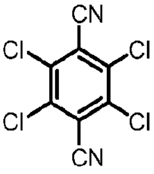
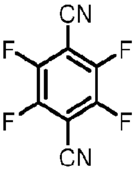
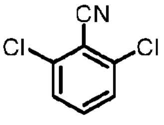
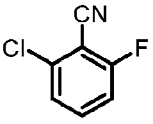
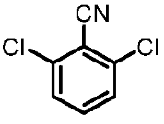
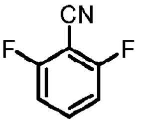
[0171] For example, production of a purified fluorination reagent using a reactor equipped with an in-line homogeniser comprised charging the reactor, sealing the reactor, and applying mechanical force. The reaction mixture was and then cooled to room temperature. The resulting suspension was purified using similar methods to those described throughout this example. Further, spray-drying was tested for purification and produced similar results.

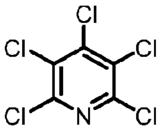
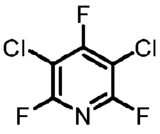
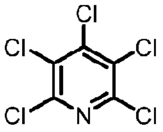
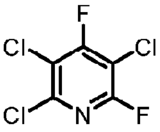
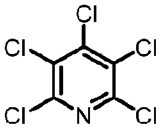
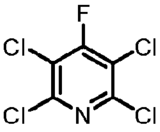
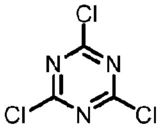
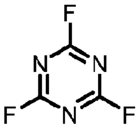
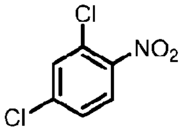
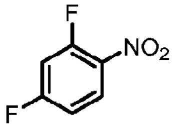
[0172] Example 13: formation of fluorinated compounds using purified fluorination reagent

[0173] Purified fluorination reagent prepared from mixed composition C in Table 1 (1.5 to 6 eq) and TMAC (1 eq) was stirred in a reaction solvent with an aromatic compound (1 eq), and under the conditions provided in Table 7. An exemplary scheme for the preparation of the purified fluorination reagent from mixed composition C is provided in FIG. 11.

[0174] Reaction procedure: To an oven dried screw-cap vial, the solids were added followed by the solvent before sealing under a nitrogen atmosphere. The mixture was heated to the desired temperature for the required amount of time. After this time, the mixture was allowed to cool and an internal standard (*p*-fluoroanisole or α,α,α-trifluorotoluene) was added and analyzed by quantitative ^{19}F NMR. An exemplary reaction scheme is provided in FIG. 12. Exemplary results are provided in Table 29.

Table 29

Compound	**Reaction solvent (temperature, reaction time)**	**Fluorinated compound**	**Yield (%)**	**Fluorination reagent equivalent**
	DMSO, 150 °C, 3 h		91	1.5
	DMSO, 150 °C, 3 h		75	1.5
	DMSO, 150 °C, 3 h		45	1.5
	MeCN, 80 °C, 3 h		20	1.5
	DMSO, 150 °C, 3 h		30	1.5
	DMSO, 80 °C, 18 h		54	1.5
	DMSO, 80 °C, 18 h		11	1.5
	DMF, 120 °C, 18 h		52	6
	Sulfolane, 150 °C, 18 h		40	6
	Sulfolane, 150 °C, 18 h		45	6

	DMSO, 80 C, 18h		20	6
	DMSO, 80 C, 18h		50	6
	DMSO, 80 C, 18h		25	6
	Sulfolane, 100 C, 3h		5	6
	DMSO, 150, 3h		80	6

[0175] Example 14: formation of fluorinated compounds using purified fluorination reagent

[0176] Purified fluorination reagent prepared from mixed composition C in Table 1 (6 eq per fluorine in aromatic compound) and phthaloyl dichloride (1 eq) was stirred with an aromatic compound (1 eq) in sulfolane at 150 °C for 3 h. The concentration of aromatic compound in the reaction mixture was 0.25 M. A fluorinated compound was recovered with a yield of 10%. The reaction scheme is provided in FIG. 13.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of manufacturing a purified fluorination reagent, the method comprising:
   (a) combining a first salt with a second salt to form a mixed composition, the first salt comprising calcium and fluoride;
   (b) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
   (c) concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
   (d) washing the crude fluorination reagent with a solvent (e.g., water or an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
   (e) concentrating the reagent wash to form a purified fluorination reagent (e.g., the purified fluorination reagent having a higher concentration of fluorine compared to the crude fluorination reagent).
2. A method of manufacturing a purified fluorination reagent, the method comprising:
   (a) combining a first salt with a second salt, the first salt comprising calcium and fluoride;
   (b) applying mechanical force to the combination of the first salt and the second salt to form a mixed composition;
   (c) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
   (d) concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
   (e) washing the crude fluorination reagent with a solvent (e.g., water or an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
   (f) concentrating the reagent wash to form a purified fluorination reagent (e.g., the purified fluorination reagent having a higher concentration of fluorine compared to the crude fluorination reagent).
3. A method of manufacturing a purified fluorination reagent, the method comprising:
   (a) combining a first salt with a second salt to form a mixed composition, the first salt comprising calcium and fluoride;
   (b) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof; and
   (c) concentrating the resultant fluid to produce a purified fluorination reagent (e.g., a reagent concentrate or precipitate).
4. A method of manufacturing a purified fluorination reagent, the method comprising:

(a) combining a first salt with a second salt, the first salt comprising calcium and fluoride;
(b) applying mechanical force to the combination of the first salt and the second salt to form a mixed composition;
(c) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof; and
(d) concentrating the resultant fluid to produce a purified fluorination reagent (e.g., a reagent concentrate or precipitate).

5. The method of any one of the preceding claims, wherein (a), (b), and (c) are performed substantially simultaneously, wherein (a), (b), and (c) are performed sequentially, or wherein (c) is performed prior to (b), and/or further comprising adjusting the pH of the resultant fluid (e.g., to a pH of about 6 to about 8) prior to concentrating the resultant fluid.
6. The method of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 0.015 % to about 12.5 % by weight (wt %) or is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm).
7. The method of any one of the preceding claims, wherein an amount of calcium in the purified fluorination reagent is about 0.01 % to about 15 % by weight (wt %) or is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm).
8. A method of fluorinating a starting reagent using a purified fluorination reagent to yield a fluorinated product, comprising:
(a) providing a purified fluorination reagent comprising an alkali metal comprising lithium, potassium, or sodium, fluoride, and at least one additional ion, wherein an amount of phosphorous in the purified fluorination reagent is about 0.015 % to about 12.5 % by weight (wt %), or is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm);
(b) providing a starting reagent;
(c) contacting the starting reagent with the purified fluorination reagent, whereby the starting reagent is fluorinated, thereby yielding the fluorinated product.
9. A method of fluorinating a starting reagent using a purified fluorination reagent to yield a fluorinated product, comprising:
(a) providing a purified fluorination reagent comprising an alkali metal comprising lithium, potassium, or sodium, fluoride, and at least one additional ion, the purified fluorination reagent being characterized by at least 1 (e.g., at least 2, at least 3, at least 5, at least 10, at least 20, at least 50, and/or at least 70) of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28;
(b) providing a starting reagent;

(c) contacting the starting reagent with the purified fluorination reagent, whereby the starting reagent is fluorinated, thereby yielding the fluorinated product.

10. A method of manufacturing a purified fluorination reagent to provide a fluorinated product, the method comprising:
    (a) combining a first salt with a second salt to form a mixed composition, the first salt comprising calcium and fluoride;
    (b) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
    (c) concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
    (d) washing the crude fluorination reagent with a solvent (e.g., water or an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
    (e) concentrating the reagent wash to form a purified fluorination reagent (e.g., the purified fluorination reagent having a higher concentration of fluorine compared to the crude fluorination reagent).
    (f) contacting the purified fluorination reagent with a starting reagent, whereby the starting reagent is fluorinated, thereby providing a fluorinated product.
11. A method of manufacturing a purified fluorination reagent to provide a fluorinated product, the method comprising:
    (a) combining a first salt with a second salt, the first salt comprising calcium and fluoride;
    (b) applying mechanical force to the combination of the first salt and the second salt to form a mixed composition;
    (c) subjecting the mixed composition to a fluid composition (to produce a solid component and a resultant fluid) and collecting a resultant fluid thereof;
    (d) concentrating the resultant fluid to produce a crude fluorination reagent (e.g., a reagent concentrate or precipitate);
    (e) washing the crude fluorination reagent with a solvent (e.g., water or an alcohol) to produce a reagent wash (a second solid component and fluid reagent wash); and
    (f) concentrating the reagent wash to form a purified fluorination reagent (e.g., a purified reagent concentrate or precipitate).
    (g) contacting the purified fluorination reagent with a starting reagent, whereby the starting reagent is fluorinated, thereby providing a fluorinated product.
12. The method of any one of the preceding claims, further comprising providing the mixed composition subjected to the fluid composition as the first salt.

13. The method of any one of the preceding claims, wherein the first salt is a recovered waste material.
14. The method of any one of the preceding claims wherein the first salt comprises low purity calcium and fluoride (e.g., less than 80 weight percent in total is calcium and fluorine).
15. The method of any one of the preceding claims, wherein the pH of the resultant fluid is adjusted with an acid (e.g., strong acid, weak acid, polyprotic acid, and/or combinations thereof).
16. The method of any one of the preceding claims wherein the acid comprises phosphoric acid, hydrochloric acid, boric acid, silicic acid, formic acid, acetic acid, benzoic acid, oxalic acid, sulfuric acid, sulfurous acid, carbonic acid, and/or combinations thereof.
17. The method of any one of the preceding claims, wherein the acid comprises hydrochloric acid, phosphoric acid, sulfuric acid, and/or combinations thereof.
18. The method of any one of the preceding claims, wherein the pH of the resultant fluid is adjusted to a pH of about 5 to about 10 (e.g., about 6 to about 9).
19. The method of any one of the preceding claims, wherein the fluid composition has a pH of about 7 or more (e.g., about 10 or more).
20. The method of any one of the preceding claims, wherein the fluid composition has a pH of about 12 to about 13.
21. The method of any one of the preceding claims, wherein a combination of the fluid composition and the mixed composition is at a temperature of about 0 to about 200 °C.
22. The method of any one of the preceding claims, wherein a combination of the fluid composition and the mixed composition is at a temperature of 80 °C or more.
23. The method of any one of the preceding claims, wherein a combination of the fluid composition and the mixed composition is at a temperature of 110 °C or less.
24. The method of any one of the preceding claims, wherein the mixed composition is subjected to the fluid composition for about 0 hours to about 8 hours.
25. The method of any one of the preceding claims, wherein the mixed composition is subjected to the fluid composition for about 1 hour or more.
26. The method of any one of the preceding claims, wherein the mixed composition is subjected to the fluid composition for about 6 hours or less.
27. The method of any one of the preceding claims, wherein the mixed composition is subjected to the fluid composition for about 2 hours.
28. The method of any one of the preceding claims, wherein the fluid composition has a boiling point of about 30 °C or more (e.g., about 70 °C or more, about 120 °C or more).

29. The method of any one of the preceding claims, wherein the fluid composition has a boiling point of about 240 °C or less.
30. The method of any one of the preceding claims, wherein a combination of the solvent and the crude fluorination reagent is at a temperature of about -20 to about 240 °C.
31. The method of any one of the preceding claims, wherein a combination of the solvent and the crude fluorination reagent is at a temperature of about 80 °C or more.
32. The method of any one of the preceding claims, wherein a combination of the solvent and the crude fluorination reagent is at a temperature of about 60 °C.
33. The method of any one of the preceding claims, wherein a combination of the solvent and the crude fluorination reagent is at a temperature of about 235 °C or less.
34. The method of any one of the preceding claims, wherein the crude fluorination reagent is washed with the solvent for about 4 hours to about 48 hours (e.g., about 8 hours to about 36 hours, about 10 hours to about 28 hours).
35. The method of any one of the preceding claims, wherein the crude fluorination reagent is washed with the solvent for about 8 hours or more.
36. The method of any one of the preceding claims, wherein the crude fluorination reagent is washed with the solvent for about 36 hours or less.
37. The method of any one of the preceding claims, wherein the crude fluorination reagent is washed with the solvent for about 18 hours.
38. The method of any one of the preceding claims, wherein the solvent has a boiling point of about 30 °C or more (e.g., about 70 °C or more, about 120 °C or more).
39. The method of any one of the preceding claims, wherein the solvent has a boiling point of about 240 °C or less.
40. The method of any one of the preceding claims, wherein the solvent and/or the fluid composition is an organic solvent, water, an alcohol, a polar aprotic solvent, a halocarbon, and/or combinations thereof.
41. The method of any one of the preceding claims, wherein the solvent and/or the fluid composition is acetonitrile, propionitrile, butyronitrile, toluene, 1,2-dichlorobenzene, chlorobenzene, fluorobenzene, 1,2-difluorobenzene, dichloroethane, trifluorotoluene, chloroform, sulfolane, DMF, DMSO, an alcohol (e.g., tert-butanol, tert-amyl alcohol), water, and/or combinations thereof.
42. The method of any one of the preceding claims, wherein the solvent and/or the fluid composition is acetonitrile, propionitrile, butyronitrile, and/or combinations thereof.

43. The method of any one of the preceding claims, wherein the second salt is a metal hydroxide, a metal sulphite, a metal sulphate, a carbonate, or an inorganic phosphate (e.g., a pyrophosphate).
44. The method of any one of the preceding claims, wherein the second salt comprises NaOH, KOH, Na_2SO_3, K_2SO_3, $KHSO_4$, $CaCO_3$, H_2CO_3, K_2CO_3, Na_2CO_3., $K_4P_2O_7$, $Na_4P_2O_7$, Na_3PO_4, Li_3PO_4, $KHCO_3$, K_2CO_3, $NaHCO_3$, Cs_2CO_3, K_2HPO_4, KH_2PO_4, K_3PO_4, KPO_3, $K_5P_3O_{10}$, K_2SO_4, titanium phosphate, aluminum phosphate, uranium phosphate, and/or combinations thereof.
45. The method of any one of the preceding claims, wherein an amount phosphorous in the purified fluorination reagent is about 0.02 % to about 10 % by weight (wt %) (e.g., about 0.05 wt % to about 8 wt %, about 0.1 wt % to about 6 wt %, about 0.5 wt% to about 5 wt %, about 1 wt% to about 4 wt %), or wherein an amount phosphorous in the purified fluorination reagent is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm).
46. The method of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 0.015 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt % or more, about 0.5 wt % or more) or is about 1 ppm to about 25 ppm (e.g., about 1 ppm, about 10 ppm, about 20 ppm, or about 25 ppm).
47. The method of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 5 % by weight (wt %) or less (e.g., about 3 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less, about 0.05 wt % or less).
48. The method of any one of the preceding claims, wherein a powder x-ray diffraction spectrum of the crude fluorination reagent comprises characteristic 2θ reflections at about 5.2°,31.5°, 36.8° and/or combinations thereof.
49. The method of any one of the preceding claims, wherein about 10 to about 80% (e.g., about 30 to about 60%) of fluoride in the first salt is converted into a fluoride of the purified fluorination reagent.
50. The method of any one of the preceding claims, wherein the purified fluorination reagent is activated (e.g., can be used as a fluorinating agent in that form).
51. The method of any one of the preceding claims, wherein the starting reagent is an organic compound (e.g., aromatic organic compound).
52. The method of any one of the preceding claims, wherein the organic compound comprises 1-chloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1,2-dichloro-4-nitrobenzene, 1-chloro-2,4-dinitrobenzene, 1,4-dichloro-2-nitrobenzene, 2-chloro-5-nitropyridine, 2-

chloronicotinonitrile, 2,3,5,6-tetrachloroterephthalonitrile, 2,6-dichlorobenzonitrile, pentachloropyridine, 2,3,5,6-tetrachloroterephthalonitrile, 2,6-dichlorobenzonitrile, 2,3,5,6-tetrachloro-4-fluoropyridine, 2,4,6-trichloro-1,3,5-triazine, 1,3-dinitrobenzene, or 2,4-dichloro-1-nitrobenzene.

53. The method of any one of the preceding claims, wherein the at least one additional ion of the purified fluorination reagent comprises (i) at least one cation and at least one anion; or (ii) at least one zwitterion (e.g., psilocybin).
54. The method of any one of the preceding claims, wherein the at least one cation comprises K^+, Na^+, Ca^{2+}, Li^+, or Cs^+.
55. The method of any one of the preceding claims, wherein the at least one anion comprises a hydroxide, a sulphate, a carbonate, a phosphate, a chloride, an iodide, or a pyrophosphate.
56. The method of any one of the preceding claims, wherein the purified fluorination reagent is contacted with the starting reagent under mechanochemical conditions (e.g., ball mill).
57. The method of any of the preceding claims, wherein the purified fluorination reagent is contacted with the starting reagent in a reaction mixture.
58. The method of any one of the preceding claims wherein the reaction mixture comprises a reaction solvent (e.g., an organic solvent, water, an alcohol, a polar aprotic solvent, a halocarbon, and/or combinations thereof).
59. The method of any one of the preceding claims, wherein the reaction solvent is acetonitrile, DMF, DMSO, sulfolane, and/or combinations thereof.
60. The method of any one of the preceding claims, wherein the reaction mixture further comprises an ammonium salt (e.g., TMAC) and/or a phase transfer agent (e.g., a crown ether).
61. The method of any one of the preceding claims, wherein the reaction mixture is at a temperature of about 50 to about 200 °C.
62. The method of any one of the preceding claims, wherein the reaction mixture is at a temperature of about 50 °C or more (e.g., about 70 °C or more, about 110 °C or more, about 140 °C or more).
63. The method of any one of the preceding claims, wherein the purified fluorination reagent is contacted with the starting reagent for about 1 hour to about 36 hours (e.g., about 2 hours to about 6 hours, about 12 hours to about 24 hours).
64. The method of any one of the preceding claims, wherein the purified fluorination reagent is contacted with the starting reagent for about 24 hours or less (e.g., about 12 hours or less, about 6 hours or less).

65. The method of any one of the preceding claims, wherein the purified fluorination reagent is contacted with the starting reagent for about 1 hour or more (e.g., about 2 hours or more, about 16 hours or more).
66. A purified fluorination reagent comprising an alkali metal comprising lithium, potassium, or sodium, fluoride, and at least one additional ion, wherein an amount of phosphorous in the purified fluorination is about 0.015 % to about 12.5 % by weight (wt %).
67. A purified fluorination reagent comprising potassium, fluoride, and at least one additional ion, the purified fluorination reagent being characterized by at least 1 (e.g., at least 2, at least 3, at least 5, at least 10, at least 20, at least 50, and/or at least 70) of the 2-theta values reported in any one of Tables 5, 6A, 8, 9, 12, 15-18, 20, 21, 23, 25-28.
68. The purified fluorination reagent of any one of the preceding claims, wherein an amount of calcium in the purified fluorination reagent is about 0.01 % to about 15 % by weight (wt %).
69. The purified fluorination reagent of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 0.02 % to about 10 % by weight (wt %) (e.g., about 0.05 wt % to about 8 wt %, about 0.1 wt % to about 6 wt %, about 0.5 wt% to about 5 wt %, about 1 wt% to about 4 wt %).
70. The purified fluorination reagent of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 0.015 % by weight (wt %) or more (e.g., about 0.05 wt % or more, about 0.1 wt % or more, about 0.5 wt % or more)
71. The purified fluorination reagent of any one of the preceding claims, wherein an amount of phosphorous in the purified fluorination reagent is about 5 % by weight (wt %) or less (e.g., about 3 wt % or less, about 2 wt % or less, about 1 wt % or less, about 0.5 wt % or less, about 0.1 wt % or less, about 0.05 wt % or less).
72. The purified fluorination reagent of any one of the preceding claims, wherein the at least one additional ion comprises (i) at least one cation and at least one anion; or (ii) at least one zwitterion (e.g., psilocybin).
73. The purified fluorination reagent of any one of the preceding claims, wherein the at least one cation comprises K^+, Na^+, Ca^{2+}, Li^+, or Cs^+.
74. The purified fluorination reagent of any one of the preceding claims, wherein the at least one anion comprises a hydroxide, a sulphate, a carbonate, a phosphate, a pyrophosphate.

FIG. 1

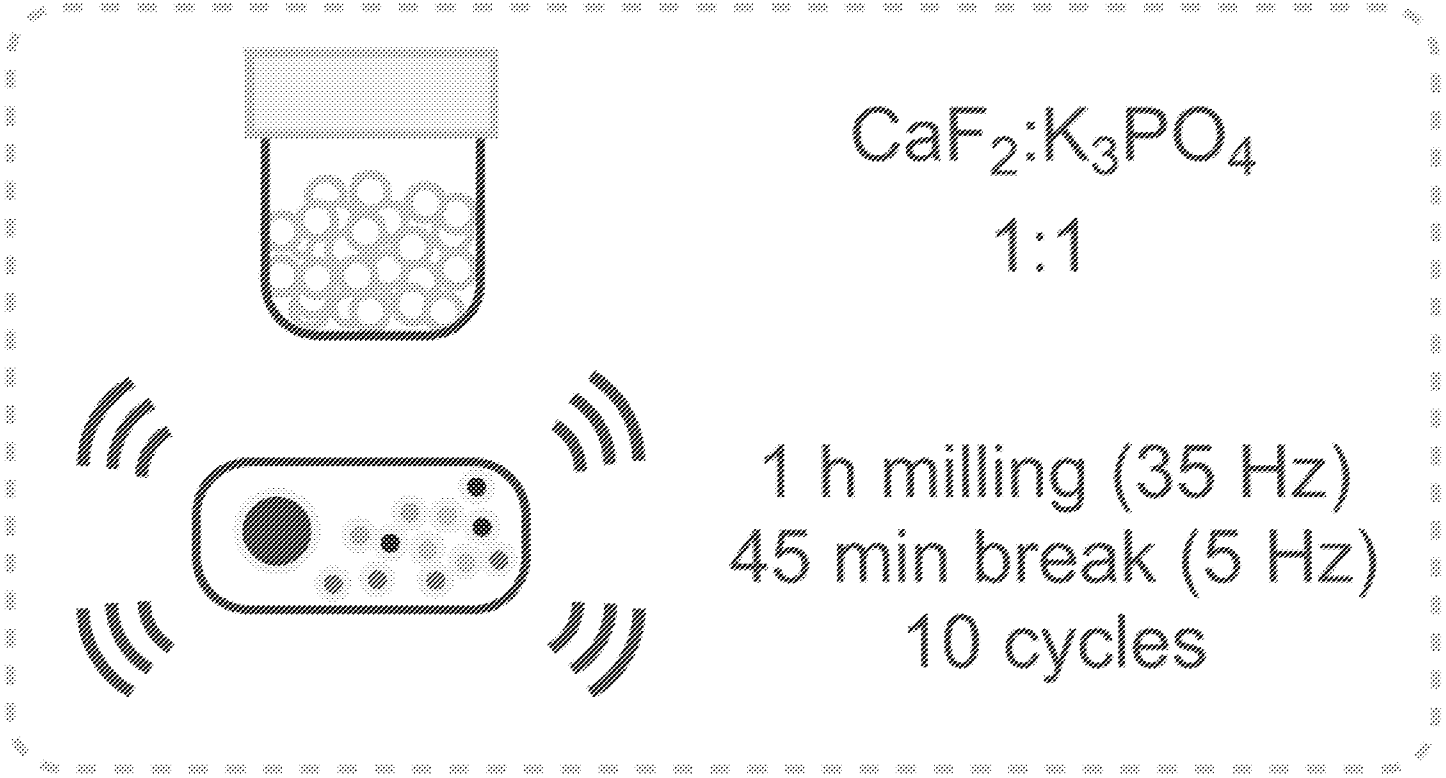


FIG. 2

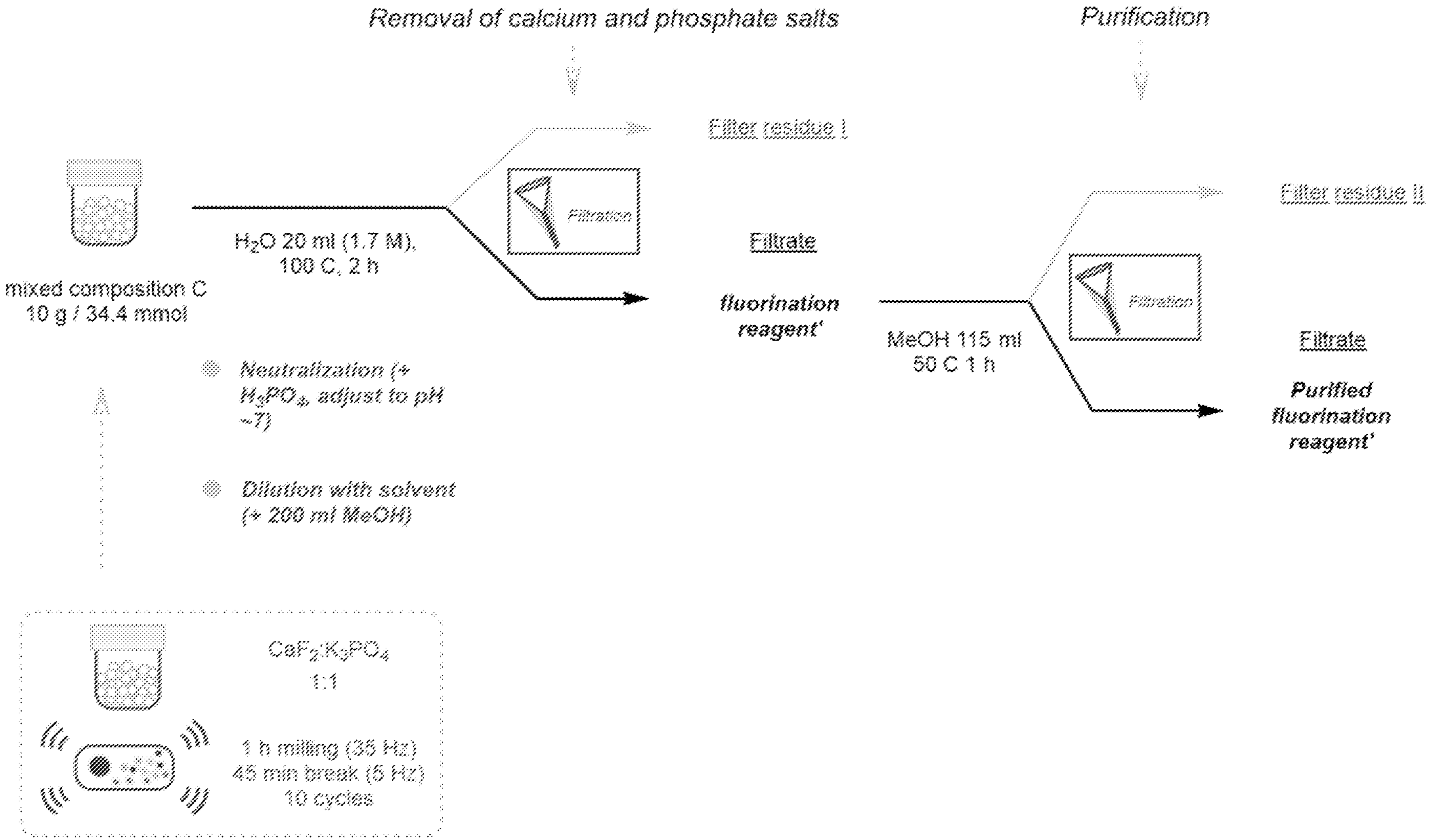

Removal of calcium and phosphate salts
Purification
mixed composition C
10 g / 34.4 mmol
H_2O 20 ml (1.7 M),
100 C, 2 h
Filtration
Filter residue I
Filtrate
fluorination reagent'
MeOH 115 ml
50 C 1 h
Filtration
Filter residue II
Filtrate
Purified fluorination reagent'
Neutralization (+ H_3PO_4, adjust to pH ~7)
Dilution with solvent (+ 200 ml MeOH)
CaF_2:K_3PO_4
1:1
1 h milling (35 Hz)
45 min break (5 Hz)
10 cycles

FIG. 3

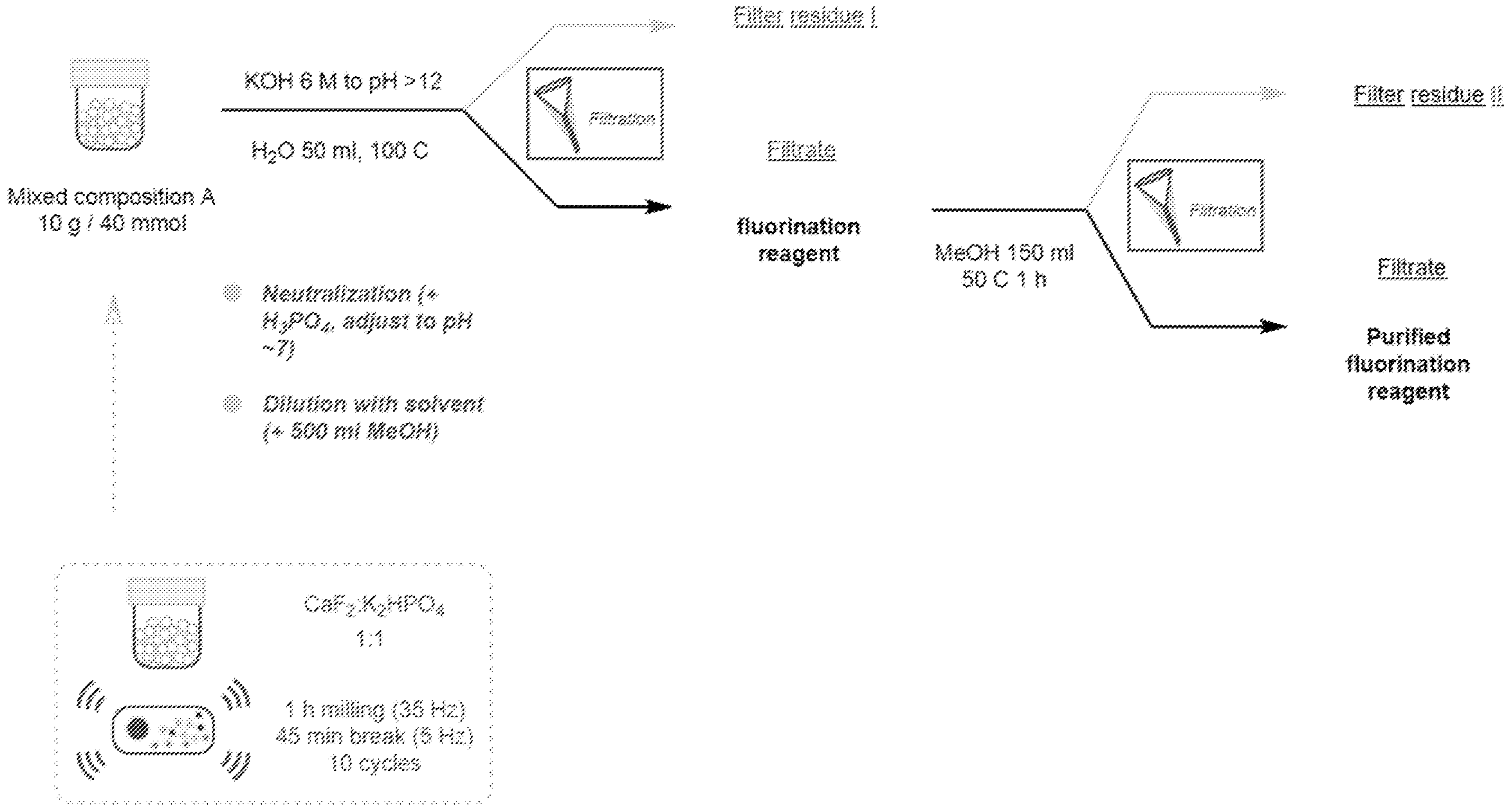

Mixed composition A
10 g / 40 mmol
KOH 6 M to pH >12
H_2O 50 ml, 100 C
Filtration
Filter residue I
Filtrate
fluorination reagent
Neutralization (+ H_3PO_4, adjust to pH ~7)
Dilution with solvent (+ 500 ml MeOH)
MeOH 150 ml
50 C 1 h
Filtration
Filter residue II
Filtrate
Purified fluorination reagent
CaF_2:K_2HPO_4
1:1
1 h milling (35 Hz)
45 min break (5 Hz)
10 cycles

FIG. 4

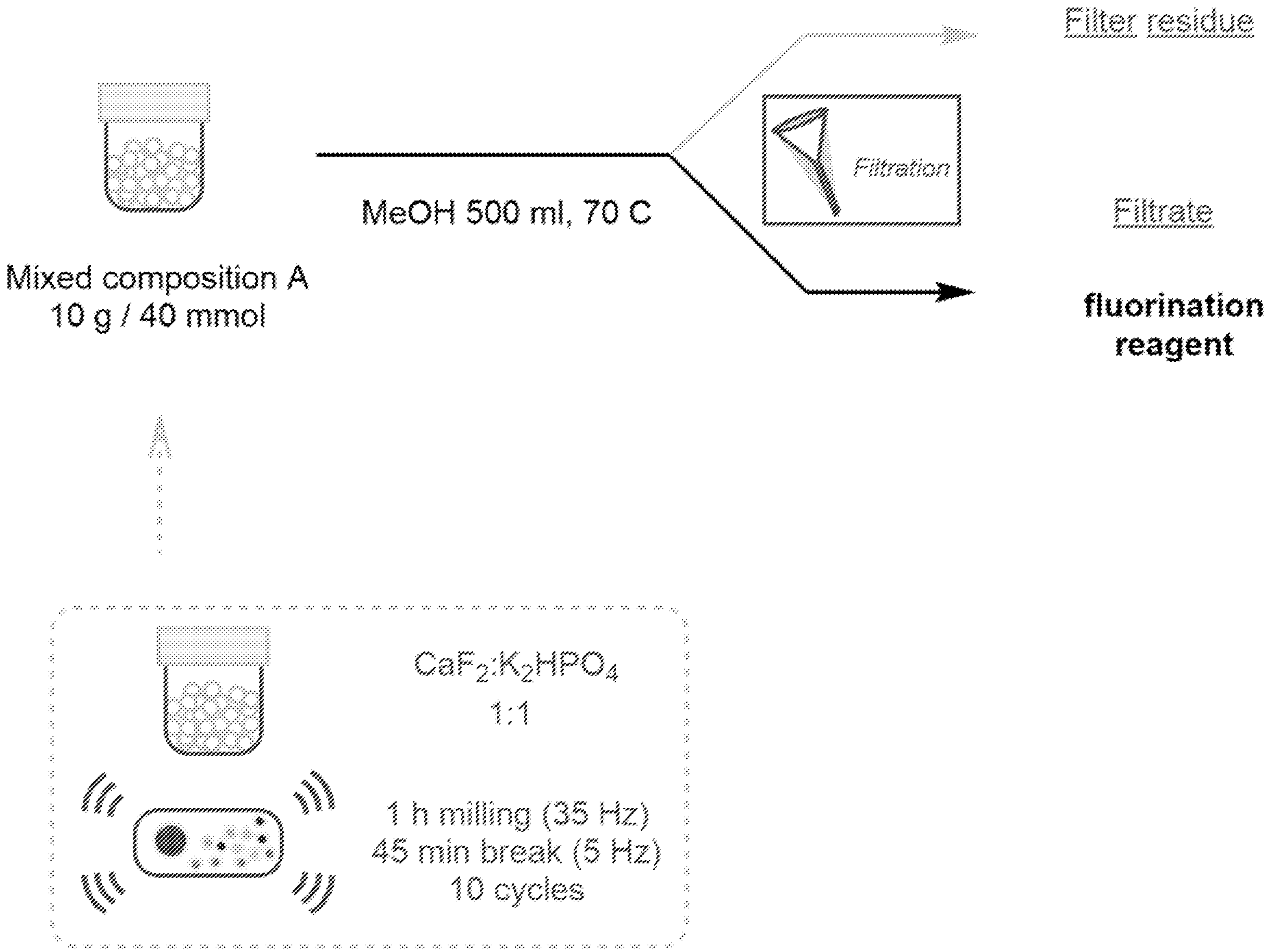

Mixed composition A
10 g / 40 mmol
MeOH 500 ml, 70 C
Filtration
Filter residue
Filtrate
fluorination reagent
CaF_2:K_2HPO_4
1:1
1 h milling (35 Hz)
45 min break (5 Hz)
10 cycles

FIG. 5

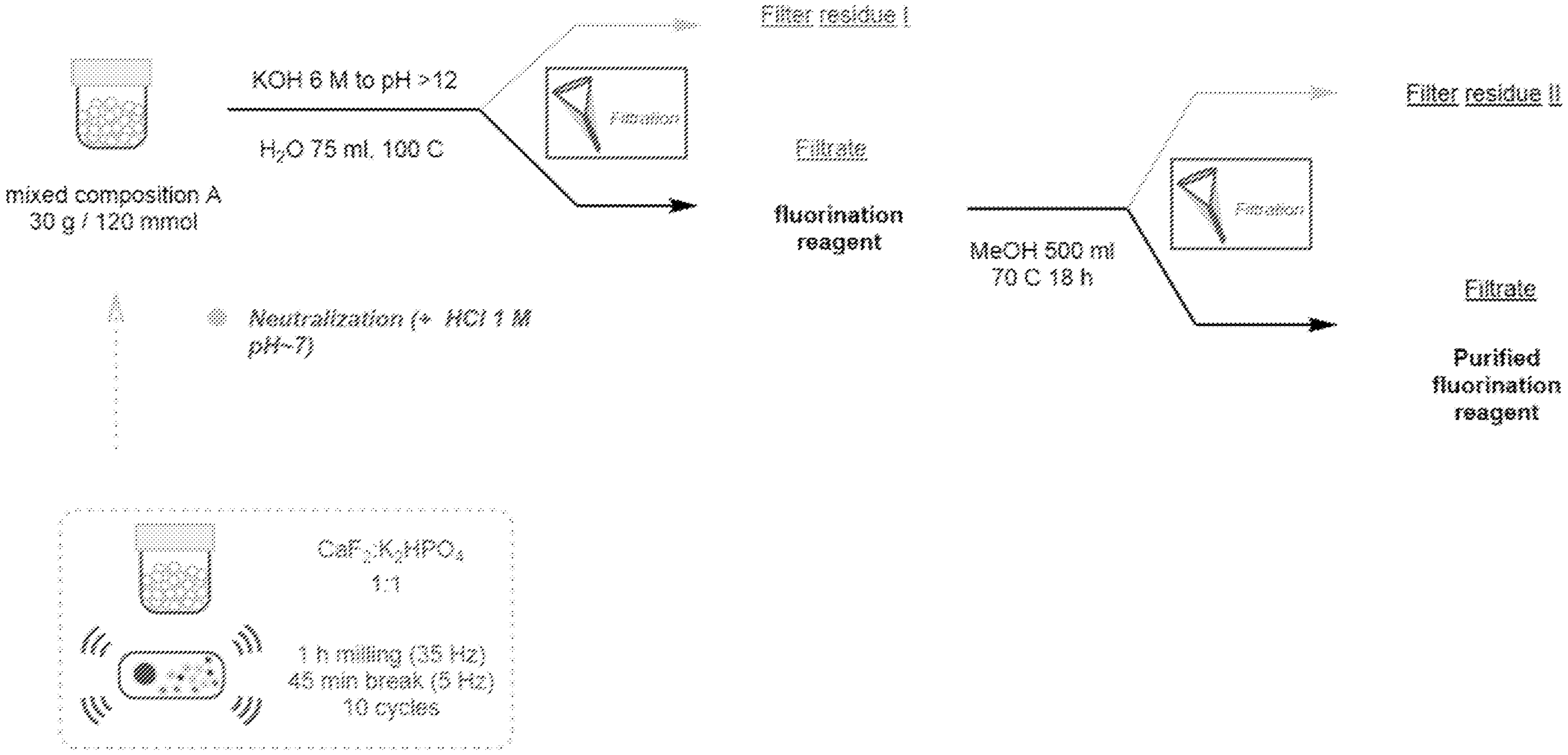

mixed composition A
30 g / 120 mmol
KOH 6 M to pH >12
H$_2$O 75 ml, 100 C
Filtration
Filter residue I
Filtrate
fluorination reagent
MeOH 500 ml
70 C 18 h
Filtration
Filter residue II
Filtrate
Purified fluorination reagent
Neutralization (+ HCl 1 M pH~7)
CaF$_2$:K$_2$HPO$_4$
1:1
1 h milling (35 Hz)
45 min break (5 Hz)
10 cycles

FIG. 6

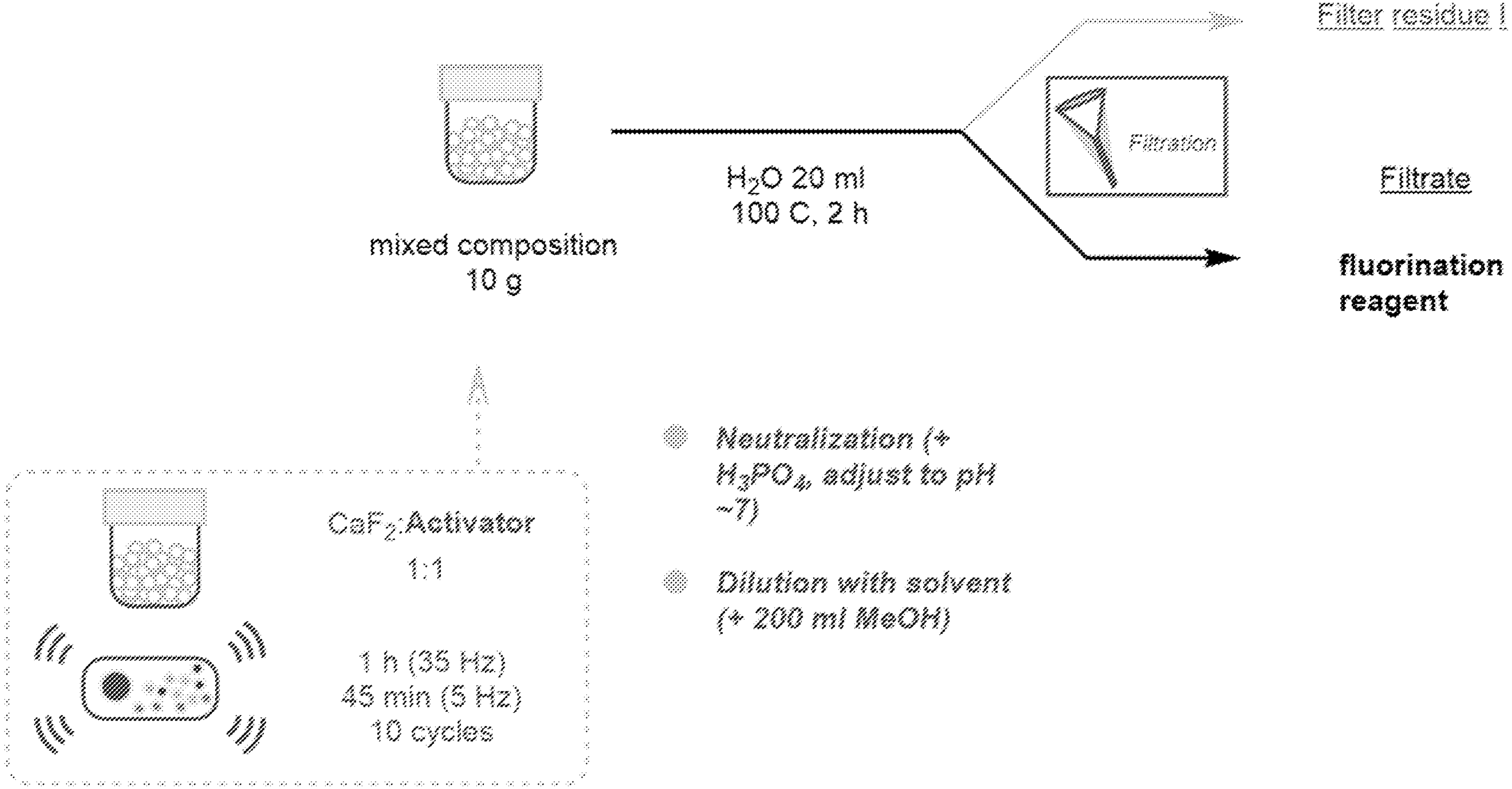

mixed composition
10 g
H_2O 20 ml
100 C, 2 h
Filtration
Filter residue I
Filtrate
fluorination reagent
CaF$_2$:Activator
1:1
1 h (35 Hz)
45 min (5 Hz)
10 cycles
Neutralization (+ H_3PO_4, adjust to pH ~7)
Dilution with solvent (+ 200 ml MeOH)

FIG. 7

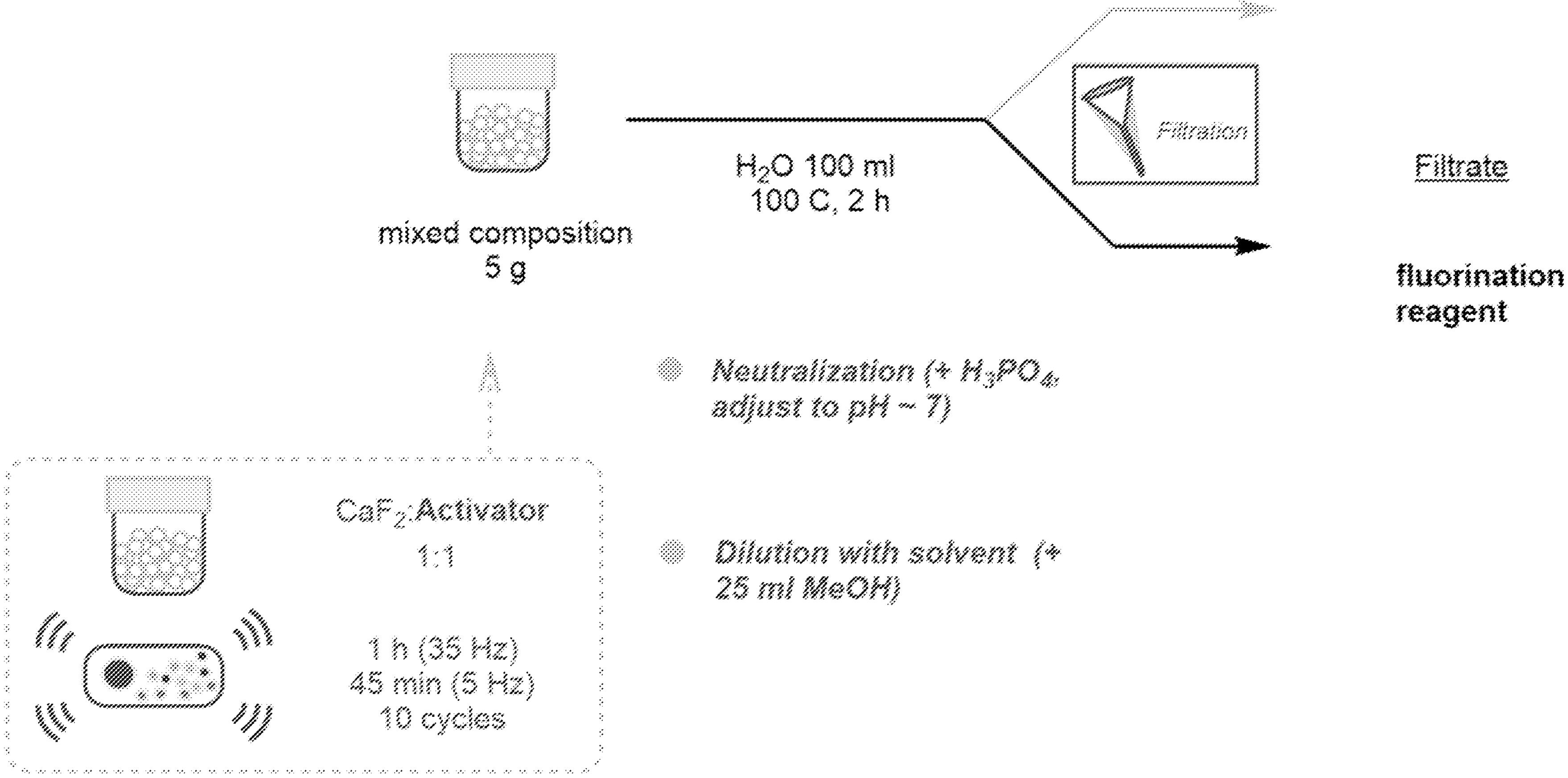

mixed composition
5 g
H_2O 100 ml
100 C, 2 h
Filtration
Filtrate
fluorination
reagent
Neutralization (+ H_3PO_4, adjust to pH ~ 7)
Dilution with solvent (+ 25 ml MeOH)
CaF_2:Activator
1:1
1 h (35 Hz)
45 min (5 Hz)
10 cycles

FIG. 8

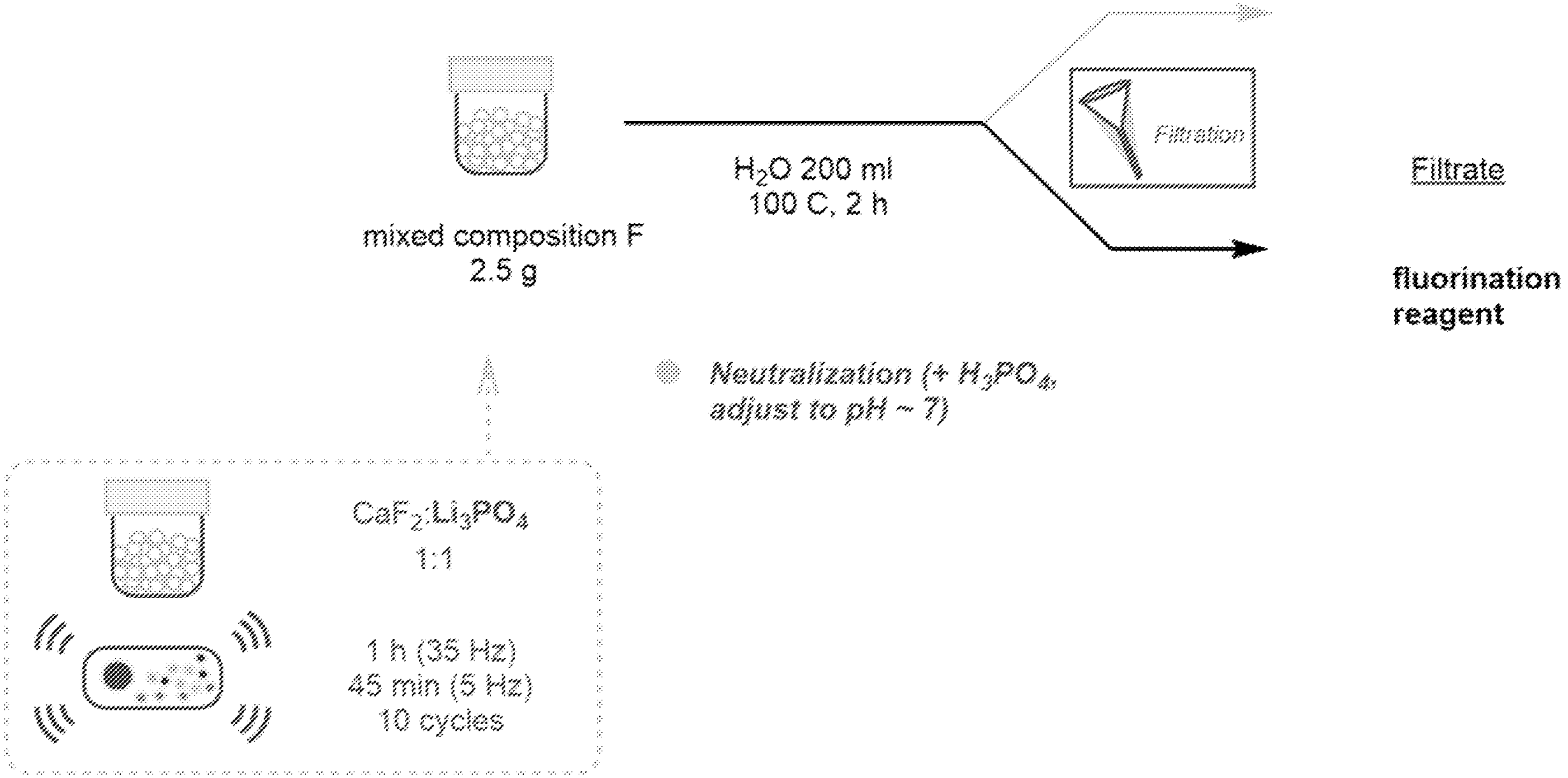

mixed composition F
2.5 g
H_2O 200 ml
100 C, 2 h
Filtration
Filtrate
fluorination reagent
Neutralization (+ H_3PO_4, adjust to pH ~ 7)
CaF_2:Li_3PO_4
1:1
1 h (35 Hz)
45 min (5 Hz)
10 cycles

FIG. 9

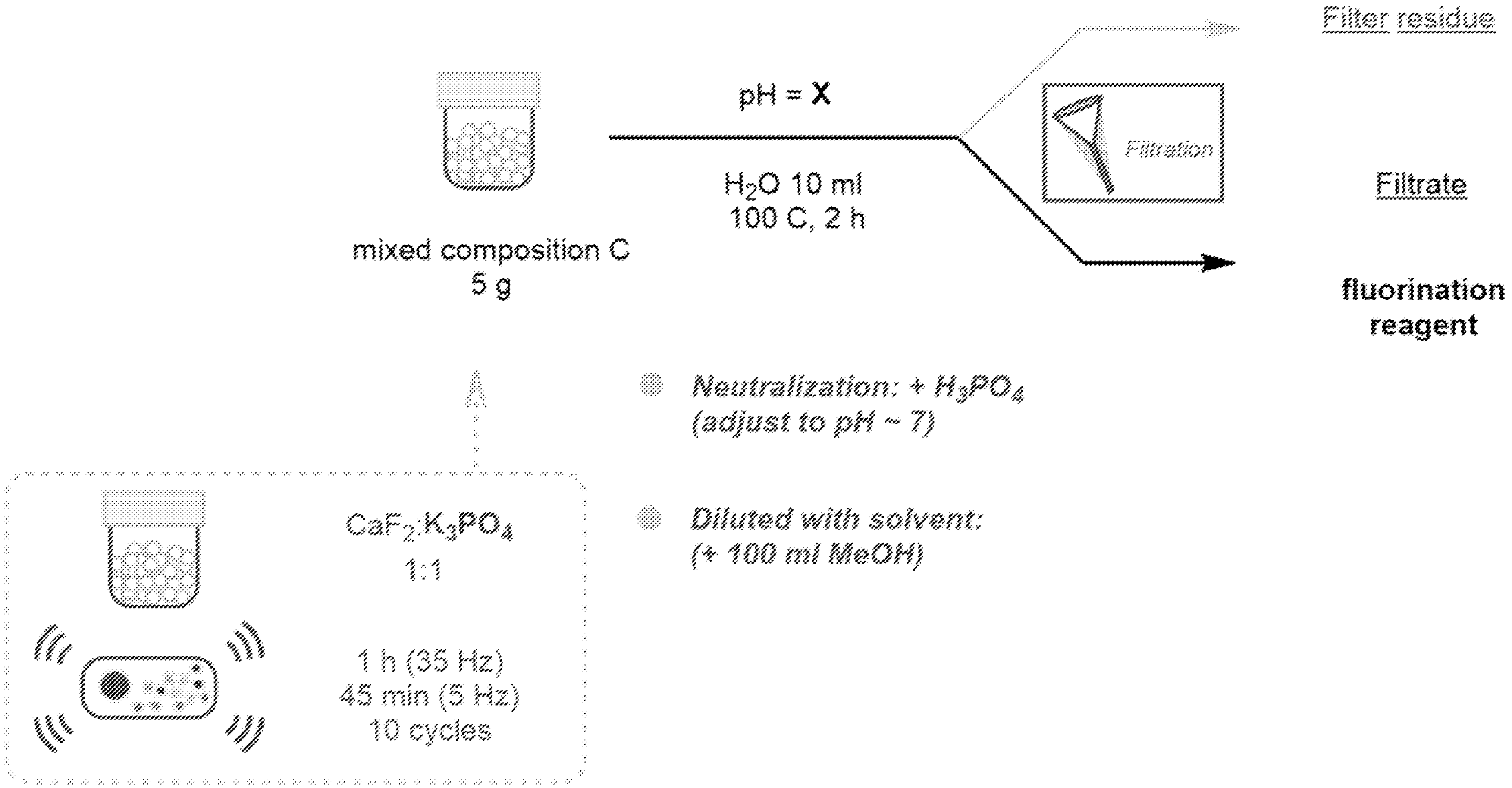

mixed composition C
5 g
pH = X
H_2O 10 ml
100 C, 2 h
Filtration
Filter residue
Filtrate
fluorination reagent
Neutralization: + H_3PO_4
(adjust to pH ~ 7)
Diluted with solvent:
(+ 100 ml MeOH)
CaF_2:K_3PO_4
1:1
1 h (35 Hz)
45 min (5 Hz)
10 cycles

FIG. 10

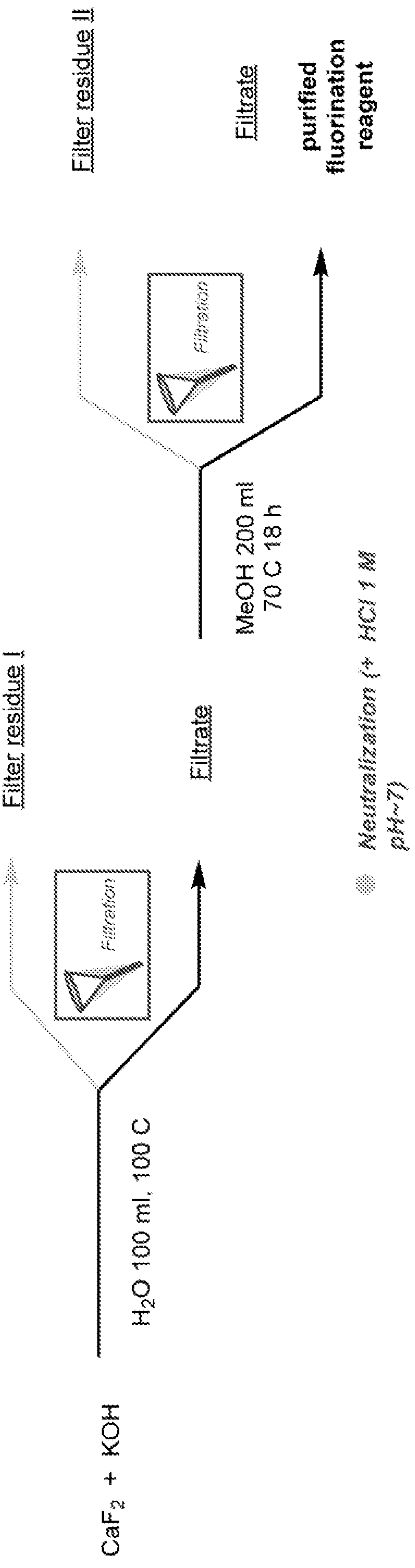

CaF2 + KOH
H2O 100 ml, 100 C
Filtration
Filter residue I
Filtrate
MeOH 200 ml
70 C 18 h
Filtration
Filter residue II
Filtrate
purified fluorination reagent
Neutralization (+ HCl 1 M pH~7)

FIG. 11

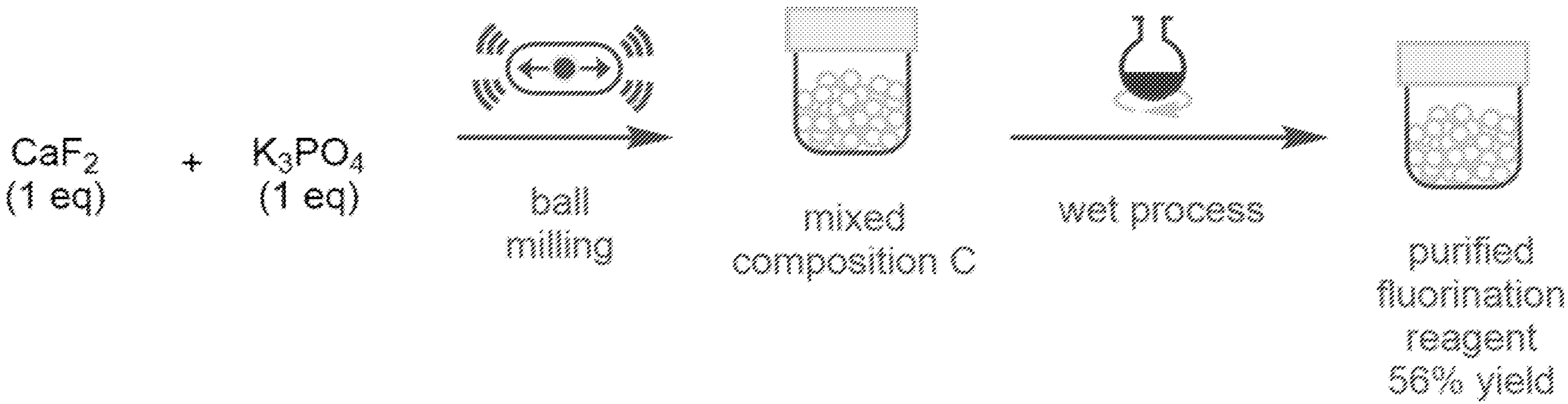

CaF$_2$
(1 eq)
+
K$_3$PO$_4$
(1 eq)
ball
milling
mixed
composition C
wet process
purified
fluorination
reagent
56% yield

FIG. 12

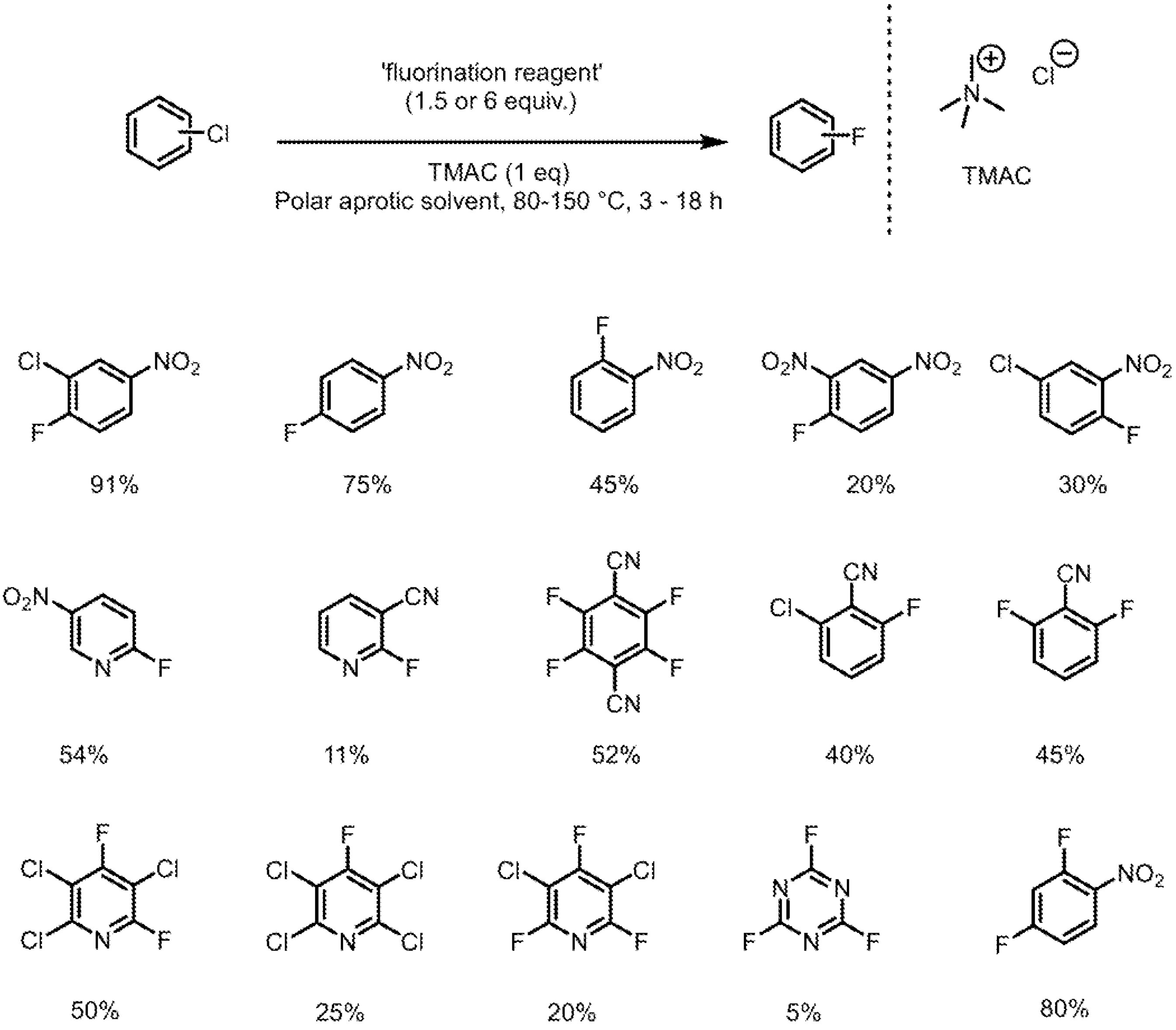

Cl
'fluorination reagent'
(1.5 or 6 equiv.)
TMAC (1 eq)
Polar aprotic solvent, 80-150 °C, 3 - 18 h
F
N
Cl
TMAC
Cl
NO2
F
91%
NO2
F
75%
F
NO2
45%
O2N
NO2
F
20%
Cl
NO2
F
30%
O2N
N
F
54%
CN
N
F
11%
CN
F
F
F
F
CN
52%
CN
Cl
F
40%
CN
F
F
45%
F
Cl
Cl
Cl
N
F
50%
F
Cl
Cl
Cl
N
Cl
25%
F
Cl
Cl
F
N
F
20%
F
N
N
F
N
F
5%
F
NO2
F
80%

FIG. 13

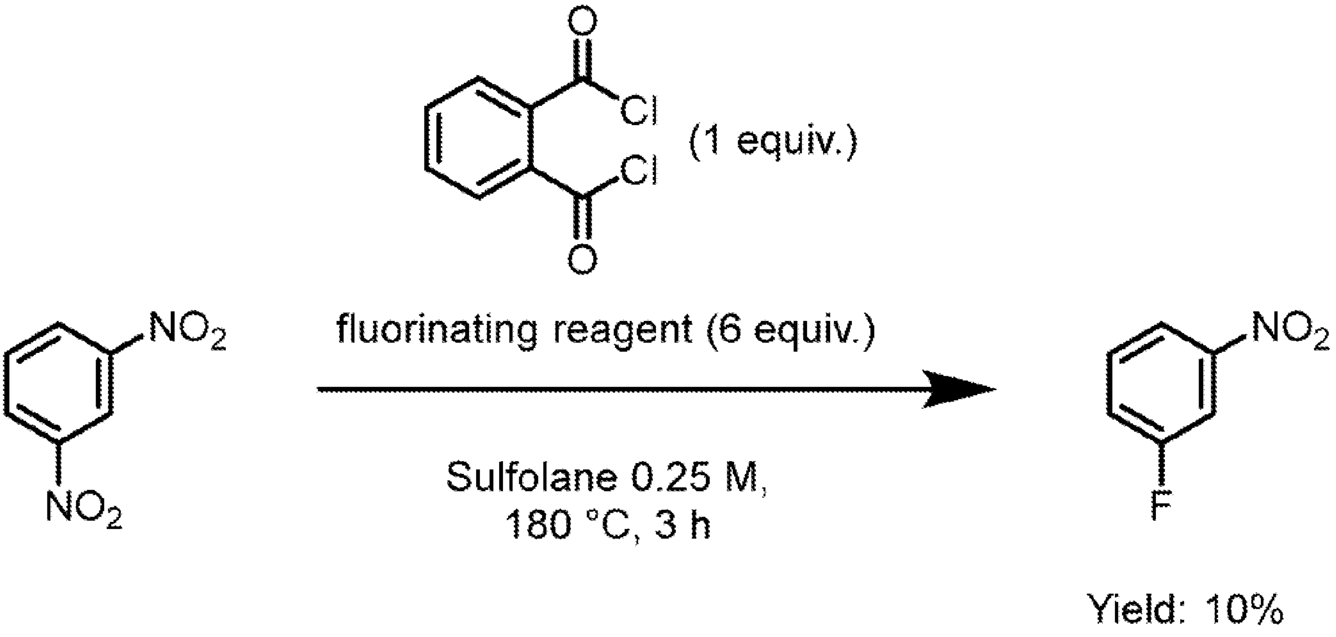
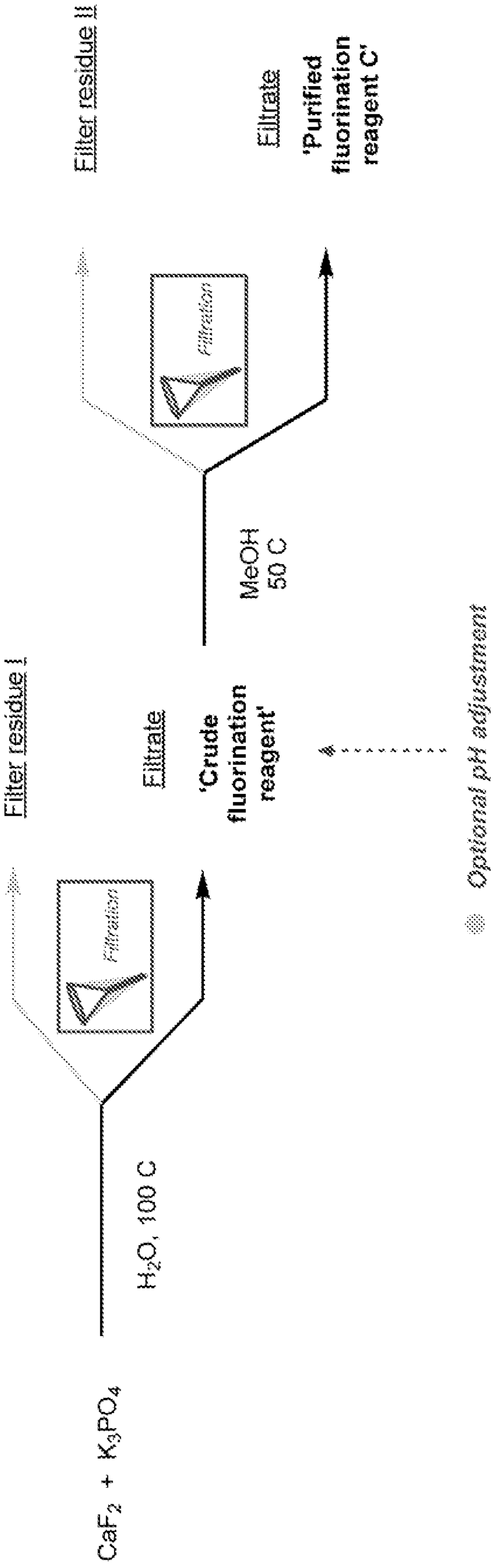

(1 equiv.)
fluorinating reagent (6 equiv.)
Sulfolane 0.25 M,
180 °C, 3 h
Yield: 10%

FIG. 14


CaF_2 + K_3PO_4
H_2O, 100 C
Filtration
Filter residue I
Filtrate
'Crude fluorination reagent'
MeOH 50 C
Filtration
Filter residue II
Filtrate
'Purified fluorination reagent C'
Optional pH adjustment