

**SOLID ALCOHOL SOLVATES OF
TETRAALKYLAMMONIUM FLUORIDES
AND METHODS OF PRODUCTION**

FIELD

[0001] The present technology relates generally to solid alcohol solvates of tetraalkylammonium fluorides as well as methods useful for synthesizing such solid alcohol solvates, including crystalline solid alcohol solvates that are stable at room temperature (*i.e.*, about 23 °C).

SUMMARY

[0002] In an aspect, the present technology provides a solid alcohol solvate of a tetra(C₁-C₆ alkyl)ammonium fluoride and a C_x alcohol, wherein *x* is 3, 5, 6, 7, 8, 9, or 10. In any embodiment herein, the tetra(C₁-C₆ alkyl)ammonium fluoride may be a tetrabutylammonium fluoride. In any embodiment herein, the solid alcohol solvate may be tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride. In any embodiment herein, the solid alcohol solvate may be in a crystalline form. The present technology also provides, in an aspect, a hydrate of a solid alcohol solvate of a tetra(C₁-C₆ alkyl)ammonium fluoride and a C_x alcohol, wherein *x* is 3, 5, 6, 7, 8, 9, or 10.

[0003] In an aspect, the present technology provides a method that includes combining an ammonium fluoride or a hydrate thereof with a solvent comprising an alcohol to form a mixture; and isolating a solid alcohol solvate from the mixture.

[0004] In a further aspect, the present technology provides a process that includes combining a hydrate of an ammonium fluoride with a solvent comprising an alcohol to form a mixture; and distilling the mixture to yield a second mixture substantially free of water.

[0005] It should be appreciated that all combinations of the foregoing concepts and additional concepts discussed in greater detail below (provided such concepts are not mutually inconsistent) are contemplated as being part of the subject matter disclosed herein.

In particular, all combinations of claimed subject matter appearing at the end of this disclosure are contemplated as being part of the subject matter disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 provides an image of solid tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride at about 23 °C via a Leica DVM6A microscope (Objective: FOV 12.55; Working Distance: 33 mm; Max Magnification: 675:1; Exposure Time: 30 ms; Resolution: 2MP (1600x1200); Zoom: 6.87x; Numerical Aperture: 0.125; TL Light Intensity: 90; RL Intensity: 30; SLI Intensity: -10; CXI Light Intensity: 80; BLI Light Intensity: 90; Color Saturation: 24.31373; Movement: Z then Lambda; Filters: None).

[0007] FIG. 2 provides an image taken of solid tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride in mineral oil at about 23 °C via a Leica DVM6A microscope (Objective: FOV 12.55; Working Distance: 33 mm; Max Magnification: 675:1; Exposure Time: 30 ms; Resolution: 2MP (1600x1200); Zoom: 1.8x; Numerical Aperture: 0.032; TL Light Intensity: 60; RL Intensity: 30; SLI Intensity: -10; CXI Light Intensity: 40; BLI Light Intensity: 60; Color Saturation: 24.31373; Movement: Z then Lambda; Filters: None).

DETAILED DESCRIPTION

[0008] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced with any other embodiment(s).

[0009] As used herein and in the appended claims, singular articles such as “a” and “an” and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited

herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, “such as”) provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0010] As used herein, “about” will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term – for example, “about 10 wt. %” would be understood to mean “9 wt. % to 11 wt. %.” It is to be understood that when “about” precedes a term, the term is to be construed as disclosing “about” the term as well as the term without modification by “about” – for example, “about 10 wt. %” discloses “9 wt. % to 11 wt. %” as well as disclosing “10 wt. %.”

[0011] The phrase “and/or” as used in the present disclosure will be understood to mean any one of the recited members individually or a combination of any two or more thereof – for example, “A, B, and/or C” would mean “A or B or C; A and B; A and C; B and C; or the combination of A, B, and C.”

[0012] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C¹⁴, P³² and S³⁵ are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0013] In general, “substituted” refers to an organic group as defined below (*e.g.*, an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group is

substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include: halogens (*i.e.*, F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclyl, heterocyclalkyl, heterocyclloxy, and heterocyclalkoxy groups; carbonyls (oxo); carboxylates; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; pentafluorosulfanyl (*i.e.*, SF₅), sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; and nitriles (*i.e.*, CN).

[0014] Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups may also be substituted with substituted or unsubstituted alkyl, alkenyl, and alkynyl groups as defined below.

[0015] Alkyl groups include straight chain and branched chain alkyl groups having from 1 to 12 carbon atoms, and typically from 1 to 10 carbons or, in some embodiments, from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Alkyl groups may be substituted or unsubstituted. Examples of straight chain alkyl groups include groups such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above, and include without limitation haloalkyl (e.g., trifluoromethyl), hydroxyalkyl, thioalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, carboxyalkyl, and the like.

[0016] Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Aryl groups herein include monocyclic, bicyclic and tricyclic ring systems. Aryl groups may be substituted or unsubstituted. Thus, aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, fluorenyl, phenanthrenyl, anthracenyl, indenyl, indanyl, pentalenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6-10 carbon atoms in the ring portions of the groups. In

some embodiments, the aryl groups are phenyl or naphthyl. The phrase “aryl groups” includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like). Representative substituted aryl groups may be mono-substituted (e.g., tolyl) or substituted more than once. For example, monosubstituted aryl groups include, but are not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which may be substituted with substituents such as those listed above.

[0017] Heterocyclyl groups include aromatic (also referred to as heteroaryl) and non-aromatic ring compounds containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, and S. Heterocyclyl groups may be substituted or unsubstituted. In some embodiments, the heterocyclyl group contains 1, 2, 3 or 4 heteroatoms. In some embodiments, heterocyclyl groups include mono-, bi- and tricyclic rings having 3 to 16 ring members, whereas other such groups have 3 to 6, 3 to 10, 3 to 12, or 3 to 14 ring members. Heterocyclyl groups encompass aromatic, partially unsaturated and saturated ring systems, such as, for example, imidazolyl, imidazoliny and imidazolidinyl groups. The phrase “heterocyclyl group” includes fused ring species including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxinyl, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. The phrase includes heterocyclyl groups that have other groups, such as alkyl, oxo or halo groups, bonded to one of the ring members, referred to as “substituted heterocyclyl groups”. Heterocyclyl groups include, but are not limited to, aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrothiophenyl, tetrahydrofuranly, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranly, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, dihydropyridyl, dihydrodithiiny, dihydrodithionyl, homopiperazinyl, quinuclidyl, indolyl, indolinyl, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indoliziny, benzotriazolyl, benzimidazolyl, benzofuranly, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxazinyl, benzodithiiny, benzoxathiiny, benzothiazinyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl,

benzo[1,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl), triazolopyridyl, isoxazolopyridyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, quinolizinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups.

Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed above.

[0018] Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups may be substituted or unsubstituted. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl, azaindolyl (pyrrolopyridinyl), indazolyl, benzimidazolyl, imidazopyridinyl (azabenzimidazolyl), pyrazolopyridinyl, triazolopyridinyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups include fused ring compounds in which all rings are aromatic such as indolyl groups and include fused ring compounds in which only one of the rings is aromatic, such as 2,3-dihydro indolyl groups. Representative substituted heteroaryl groups may be substituted one or more times with various substituents such as those listed above.

[0019] The term “halogen” or “halo” as used herein refers to bromine, chlorine, fluorine, or iodine. In some embodiments, the halogen is fluorine. In other embodiments, the halogen is chlorine or bromine.

[0020] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed

range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 atoms refers to groups having 1, 2, or 3 atoms. Similarly, a group having 1-5 atoms refers to groups having 1, 2, 3, 4, or 5 atoms, and so forth.

[0021] As understood by one of ordinary skill in the art, “molecular weight” (also known as “relative molar mass”) is a dimensionless quantity but is converted to molar mass by multiplying by 1 gram/mole or by multiplying by 1 Da – for example, a compound with a weight-average molecular weight of 5,000 has a weight-average molar mass of 5,000 g/mol and a weight-average molar mass of 5,000 Da.

[0022] As used herein, “substantially free of water” and “substantially water-free” refer to a product or composition that includes less than 1 wt.% water.

The Present Technology

[0023] Tetramethylammonium fluoride ((CH₃)₄NF; “TMAF”) and tetra-*n*-butylammonium fluoride ((CH₃CH₂CH₂CH₂)₄NF; “TBAF”; “*n*-Bu₄NF”) are commonly used as sources of fluoride ions in organic solvents for organic compound synthesis. For example, TBAF and TMAF may be used to remove silyl protecting groups and/or as a mild base.

[0024] Different methods for synthesizing TBAF and TMAF have been described. For example, TBAF may be prepared by contacting hydrofluoric acid with an ion-exchange resin and then tetra-*n*-butylammonium bromide. Similarly, TMAF can be prepared by neutralizing tetramethylammonium hydroxide with hydrofluoric acid. However, many of these synthesis methods result in trace amounts of water that is difficult to remove, as well as impurities such as HF₂⁻.

[0025] Anhydrous TBAF and TMAF are of interest because the fluoride ion is a stronger hydrogen bond acceptor (*i.e.*, a stronger Brønsted-Lowry base) when not associated with water molecules. While some methods of synthesizing anhydrous TBAF and anhydrous TMAF have been set forth, anhydrous TBAF and anhydrous TMAF are not only prone to degradation but must be stored under anhydrous conditions.

[0026] The present technology addresses the above-discussed deficiencies as well as provides additional advantages. Thus, in an aspect, the present technology provides a solid alcohol solvate of a tetra(C₁-C₆ alkyl)ammonium fluoride and a C_x alcohol, wherein *x* is 3, 5, 6, 7, 8, 9, or 10. A person of ordinary skill in the art would readily understand an alcohol solvate may also be referred to as an “alcoholate.” The C_x alcohol of the solid alcohol solvate may be *n*-propanol, *iso*-propanol, *n*-pentanol, *iso*-pentanol, *tert*-amyl alcohol ((CH₃)₂C(OH)CH₂CH₃; 2-methylbutan-2-ol), neopentanol, *n*-hexanol, a branched hexanol, *n*-heptanol, a branched heptanol, *n*-octanol, a branched octanol, *n*-nonanol, a branched nonanol, *n*-decanol, a branched decanol, or a combination of any two or more thereof. The C₁-C₆ alkyl of the tetra(C₁-C₆ alkyl)ammonium fluoride may, in any embodiment herein, be, *e.g.*, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *tert*-amyl, or neopentyl.

[0027] In any embodiment herein, the tetra(C₁-C₆ alkyl)ammonium fluoride may include tetramethylammonium fluoride, tetraethylammonium fluoride, a tetrapropylammonium fluoride, a tetrabutylammonium fluoride, a tetrapentylammonium fluoride, or a combination of any two or more thereof. The ammonium fluoride or hydrate thereof may, in any embodiment herein, include tetramethylammonium fluoride, tetraethylammonium fluoride, tetra-*n*-propylammonium fluoride, tetra-*iso*-propylammonium fluoride, tetra-*n*-butylammonium fluoride, tetra-*iso*-butylammonium fluoride, tetra-*tert*-butylammonium fluoride, tetra-*n*-pentylammonium fluoride, tetra-*iso*-pentylammonium fluoride, tetra-*tert*-amylammonium fluoride, tetraneopentylammonium fluoride, or a combination of any two or more thereof.

[0028] Thus, in any embodiment herein, it may be that the tetra(C₁-C₆ alkyl)ammonium fluoride is tetra-*n*-butylammonium fluoride. For example, it may be that the solid alcohol solvate is tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride, also

referred to as “tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate).” In any embodiment herein, the solid alcohol solvate may be substantially free of water, and may include less than 0.5 wt.% water, less than 0.2 wt.% water, less than 0.18 wt.% water, less than 0.16 wt.% water, less than 0.14 wt.% water, less than 0.12 wt.% water, less than 0.10 wt.% water, less than 0.08 wt.% water, less than 0.06 wt.% water, less than 0.04 wt.% water, less than 0.02 wt.% water, less than 0.01 wt.% water, or less than 0.001 wt.% water. In any embodiment herein, the solid alcohol solvate may be anhydrous. Further, the solid alcohol solvate may, in any embodiment herein, be in a crystalline form (*e.g.*, crystalline tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride).

[0029] In another aspect, the present technology provides a method that includes combining an ammonium fluoride or a hydrate thereof with a solvent—the solvent including an alcohol—to form a mixture; and isolating a solid alcohol solvate from the mixture. The ammonium fluoride or hydrate thereof may include tetra(C₁-C₆ alkyl)ammonium fluoride and/or a hydrate of tetra(C₁-C₆ alkyl)ammonium fluoride.

[0030] The ammonium fluoride or hydrate thereof may, in any embodiment herein of the method, include tetramethylammonium fluoride, a hydrate of tetramethylammonium fluoride, tetraethylammonium fluoride, a hydrate of tetraethylammonium fluoride, a tetrapropylammonium fluoride, a hydrate of a tetrapropylammonium, a tetrabutylammonium fluoride, a hydrate of a tetrabutylammonium fluoride, a tetrapentylammonium fluoride, a hydrate of a tetrapentylammonium fluoride, or a combination of any two or more thereof. The ammonium fluoride or hydrate thereof may, in any embodiment herein, include tetramethylammonium fluoride, a hydrate of tetramethylammonium fluoride, tetraethylammonium fluoride, a hydrate of tetraethylammonium fluoride, tetra-*n*-propylammonium fluoride, a hydrate of tetra-*n*-propylammonium, tetra-*iso*-propylammonium fluoride, a hydrate of tetra-*iso*-propylammonium fluoride, tetra-*n*-butylammonium fluoride, a hydrate of tetra-*n*-butylammonium fluoride, tetra-*iso*-butylammonium fluoride, a hydrate of tetra-*iso*-butylammonium fluoride, tetra-*tert*-butylammonium fluoride, a hydrate of tetra-*tert*-butylammonium fluoride, tetra-*n*-pentylammonium fluoride, a hydrate of tetra-*n*-pentylammonium fluoride, tetra-*iso*-pentylammonium fluoride, a hydrate of tetra-*iso*-pentylammonium fluoride, tetra-*tert*-amylammonium fluoride, a hydrate of tetra-*tert*-

amylammonium fluoride, tetraneopentyammonium fluoride, a hydrate of tetraneopentyammonium fluoride, or a combination of any two or more thereof.

[0031] The alcohol, in any embodiment herein of the method, may include methanol, ethanol, *n*-propanol, *iso*-propanol, *n*-butanol, *iso*-butanol, *tert*-butanol, *n*-pentanol, *iso*-pentanol, *tert*-amyl alcohol ((CH₃)₂C(OH)CH₂CH₃; 2-methylbutan-2-ol), neopentanol, *n*-hexanol, a branched hexanol, *n*-heptanol, a branched heptanol, *n*-octanol, a branched octanol, *n*-nonanol, a branched nonanol, *n*-decanol, a branched decanol, or a combination of any two or more thereof. In any embodiment herein of the method, the solid alcohol solvate may be tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride, tetra-*n*-butylammonium tetra(*tert*-butyl alcohol) fluoride, or tetramethylammonium *tert*-amyl alcohol fluoride.

[0032] In any embodiment herein, the method may include heating the mixture to provide a heated mixture and isolating the solid alcohol solvate from the heated mixture. Heating the mixture, according to any embodiment herein, may include heating for about 1 hour to about 10 hours. Thus, in any embodiment herein, heating the mixture may include heating for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, or any range including and/or in between any two of these values (*e.g.*, heating for about 3 hours to about 9 hours; heating from about 5 hours to about 7 hours). In any embodiment herein, heating the mixture may include heating to maintain the temperature of the solvent prior to combining the ammonium fluoride or hydrate thereof and/or heating to temperatures above about 23 °C, such as from about 50 °C to about 100 °C—thus, in any embodiment herein, heating the mixture may include heating to a temperature of about 50 °C, about 55 °C, about 60 °C, about 65 °C, about 70 °C, about 75 °C, about 80 °C, about 85 °C, about 90 °C, about 95 °C, about 100 °C, or any range including and/or in between any two of these values. For example, the mixture may be heated to a temperature of about 70 °C to about 90 °C or about 80 °C to about 85 °C.

[0033] The mixture may, in any embodiment disclosed herein, include 1 molar equivalent of the ammonium fluoride or hydrate thereof (for a hydrate of an ammonium fluoride, the molar equivalent is based on molar equivalents of ammonium fluoride in the hydrate, not on molar equivalents of the hydrate) and about 5 to about 50 molar equivalents

of the alcohol; thus, the molar equivalents of the alcohol may be about 5 molar equivalents, about 10 molar equivalents, about 15 molar equivalents, about 20 molar equivalents, about 25 molar equivalents, about 30 molar equivalents, about 35 molar equivalents, about 40 molar equivalents, about 45 molar equivalents, about 50 molar equivalents, or any range including and/or in between any two of these values. For example, in any embodiment herein, the mixture may include 1 molar equivalent of the ammonium fluoride or hydrate thereof and about 10 to about 15 molar equivalents of the alcohol.

[0034] The mixture may, in any embodiment herein, further include a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof. For example, the mixture may further include a heptane and/or may further include benzene, toluene, or a combination thereof. In any embodiment herein, such a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof may be included in the solvent prior to combining with the ammonium fluoride or hydrate thereof, combined with the ammonium fluoride or hydrate thereof prior to combining with the solvent, concurrently when combining the ammonium fluoride or hydrate thereof with the solvent, and/or subsequent to combining the ammonium fluoride or hydrate thereof with the solvent but prior to isolating the solid alcohol solvate from the mixture. In any embodiment where the mixture includes a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof, the mixture may include 1 molar equivalent of the ammonium fluoride or hydrate thereof (as noted earlier in this disclosure, for a hydrate of an ammonium fluoride, the molar equivalent is based on molar equivalents of ammonium fluoride in the hydrate, not on molar equivalents of the hydrate) and about 1 to about 10 molar equivalents of the C₃-C₁₀ alkane, the C₆-C₁₀ aromatic hydrocarbon, or the combination thereof; thus, the mixture may include the C₃-C₁₀ alkane, the C₆-C₁₀ aromatic hydrocarbon, or the combination thereof in an amount of about 1 molar equivalent, about 2 molar equivalents, about 3 molar equivalents, about 4 molar equivalents, about 5 molar equivalents, about 6 molar equivalents, about 7 molar equivalents, about 8 molar equivalents, about 9 molar equivalents, about 10 molar equivalents, or any range including and/or in between any two of these values.

[0035] As disclosed previously, the method includes isolating the solid alcohol solvate from the mixture. Isolating the solid alcohol solvate may include, in any embodiment herein, distilling the mixture to yield the solid alcohol solvate—for example, distilling the

mixture to collect a distillate in a Dean-Stark apparatus. Isolating the solid alcohol solvate may include, in any embodiment herein, an absolute pressure of about 50 mmHg to about 500 mmHg; thus, in any embodiments herein, the absolute pressure may be about 50 mmHg, about 100 mmHg, about 150 mmHg, about 200 mmHg, about 250 mmHg, about 300 mmHg, about 350 mmHg, about 400 mmHg, about 450 mmHg, about 500 mmHg, or any range including and/or in between any two of these values.

[0036] Isolating the solid alcohol solvate may, in any embodiment herein, include isolating a solid alcohol solvate of the ammonium fluoride and the alcohol that is substantially free of water and/or isolating an anhydrous solid alcohol solvate of the ammonium fluoride and the alcohol.

[0037] In a further aspect, the present technology also provides a hydrate of a solid alcohol solvate of any aspect and/or any embodiment disclosed herein. Such hydrates may form during manufacture of the solid alcohol solvate, or hydrates may form over time due to the hygroscopic nature of the solid alcohol solvate. The identification and preparation of any particular hydrate is within the skill of the ordinary artisan of synthetic organic chemistry.

[0038] In an aspect, the present technology provides a process where the process includes combining a hydrate of an ammonium fluoride with a solvent (the solvent including an alcohol) to form a mixture; and distilling the mixture to yield a second mixture substantially free of water. The alcohol, in any embodiment herein of the process, may include methanol, ethanol, *n*-propanol, *iso*-propanol, *n*-butanol, *iso*-butanol, *tert*-butanol, *n*-pentanol, *iso*-pentanol, *tert*-amyl alcohol ((CH₃)₂C(OH)CH₂CH₃; 2-methylbutan-2-ol), neopentanol, *n*-hexanol, a branched hexanol, *n*-heptanol, a branched heptanol, *n*-octanol, a branched octanol, *n*-nonanol, a branched nonanol, *n*-decanol, a branched decanol, or a combination of any two or more thereof. In any embodiment herein, the second mixture may include less than 0.5 wt.% water, less than 0.2 wt.% water, less than 0.18 wt.% water, less than 0.16 wt.% water, less than 0.14 wt.% water, less than 0.12 wt.% water, less than 0.10 wt.% water, less than 0.08 wt.% water, less than 0.06 wt.% water, less than 0.04 wt.% water, less than 0.02 wt.% water, less than 0.01 wt.% water, or less than 0.001 wt.% water. In any embodiment herein, the second mixture may be anhydrous.

[0039] Distilling the mixture may, in any embodiment of the process, include collecting a distillate in a Dean-Stark apparatus. In any embodiment of the process, distilling the mixture may include an absolute pressure of about 50 mmHg to about 500 mmHg; thus, in any embodiment herein of the process, the absolute pressure may be about 50 mmHg, about 100 mmHg, about 150 mmHg, about 200 mmHg, about 250 mmHg, about 300 mmHg, about 350 mmHg, about 400 mmHg, about 450 mmHg, about 500 mmHg, or any range including and/or in between any two of these values.

[0040] The hydrate of the ammonium fluoride ("the hydrate") may be a hydrate of a tetra(C₁-C₆ alkyl)ammonium fluoride. The hydrate of the ammonium fluoride may, in any embodiment disclosed herein of the process, include a hydrate of tetramethylammonium fluoride, a hydrate of tetraethylammonium fluoride, a hydrate of a tetrapropylammonium, a hydrate of a tetrabutylammonium fluoride, a hydrate of a tetrapentylammonium fluoride, or a combination of any two or more thereof. The hydrate of the ammonium fluoride may, in any embodiment disclosed herein of the process, include a hydrate of tetramethylammonium fluoride, a hydrate of tetraethylammonium fluoride, a hydrate of tetra-*n*-propylammonium, a hydrate of tetra-*iso*-propylammonium fluoride, a hydrate of tetra-*n*-butylammonium fluoride, a hydrate of tetra-*iso*-butylammonium fluoride, a hydrate of tetra-*tert*-butylammonium fluoride, a hydrate of tetra-*n*-pentylammonium fluoride, a hydrate of tetra-*iso*-pentylammonium fluoride, a hydrate of tetra-*tert*-amylammonium fluoride, a hydrate of tetraneopentylammonium fluoride, or a combination of any two or more thereof.

[0041] Distilling the mixture, in any embodiment herein of the process, may include heating the mixture to a temperature of about 50 °C to about 100 °C. Thus, in any embodiment herein of the process, heating the mixture may include heating to a temperature of about 50 °C, about 55 °C, about 60 °C, about 65 °C, about 70 °C, about 75 °C, about 80 °C, about 85 °C, about 90 °C, about 95 °C, about 100 °C, or any range including and/or in between any two of these values. For example, in the process the mixture may be heated to a temperature of about 70 °C to about 90 °C or about 80 °C to about 85 °C. Heating the mixture, according to any embodiment herein of the process, may include heating for about 1 hour to about 10 hours. Thus, in any embodiment herein of the process, heating the mixture may include heating for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6

hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, or any range including and/or in between any two of these values (*e.g.*, heating for about 3 hours to about 9 hours; heating from about 5 hours to about 7 hours).

[0042] The mixture may, in any embodiment disclosed herein of the process, include 1 molar equivalent of ammonium fluoride—based on molar equivalents of ammonium fluoride in the hydrate, not on molar equivalents of the hydrate—and about 5 to about 50 molar equivalents of the alcohol; thus, the molar equivalents of the alcohol may be about 5 molar equivalents, about 10 molar equivalents, about 15 molar equivalents, about 20 molar equivalents, about 25 molar equivalents, about 30 molar equivalents, about 35 molar equivalents, about 40 molar equivalents, about 45 molar equivalents, about 50 molar equivalents, or any range including and/or in between any two of these values. For example, in any embodiment herein of the process, the mixture may include about 10 to about 15 molar equivalents of the alcohol.

[0043] The mixture may, in any embodiment herein of the process, further include a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof. For example, the mixture may further include a heptane and/or may further include benzene, toluene, or a combination thereof. In any embodiment herein of the process, such a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof may be included in the solvent prior to combining with the hydrate, combined with the hydrate prior to combining with the solvent, concurrently when combining the hydrate with the solvent, and/or subsequent to combining the hydrate with the solvent but prior to distilling the mixture. In any embodiment of the process where the mixture includes a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof, the mixture may include 1 molar equivalent of ammonium fluoride (as noted earlier in this disclosure, based on molar equivalents of ammonium fluoride in the hydrate, not on molar equivalents of the hydrate) and about 1 to about 10 molar equivalents of the C₃-C₁₀ alkane, the C₆-C₁₀ aromatic hydrocarbon, or the combination thereof; thus, the mixture may include the C₃-C₁₀ alkane, the C₆-C₁₀ aromatic hydrocarbon, or the combination thereof in an amount of about 1 molar equivalent, about 2 molar equivalents, about 3 molar equivalents, about 4 molar equivalents, about 5 molar equivalents, about 6 molar equivalents,

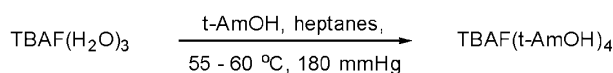
about 7 molar equivalents, about 8 molar equivalents, about 9 molar equivalents, about 10 molar equivalents, or any range including and/or in between any two of these values.

[0044] The present technology, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present technology.

EXAMPLES

Example 1 – Preparation of TBAF(*t*-AmOH)₄

Scheme I – Generation of tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate).



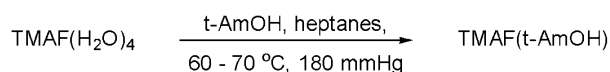
[0045] To a 250 mL jacketed 4-neck round-bottom flask equipped with an overhead stirrer, a nitrogen inlet, a thermocouple and a reflux condenser with a Dean-Stark trap was charged tetra-*n*-butylammonium fluoride trihydrate (15.0 g, 1.0 equivalent), *tert*-amyl alcohol (62.9 g, 15.0 equivalents) and heptanes (mixed isomers, 19.1 g, 4.0 equivalents). The resulting stirred mixture was heated to reflux under reduced pressure (180 mmHg, 55 to 60 °C) for 4 h and/or until water content of the reaction mixture decreased to less than 0.2% by Karl-Fischer titration. All volatiles were then removed under reduced pressure (15 mmHg, 40 °C) to give tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate) (29.1 g, >99% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 3.46-3.41 (m, 8H), 1.72-1.63 (m, 8H), 1.54-1.40 (m, 16H), 1.20 (s, 12H), 1.19 (s, 12H), 1.02-0.98 (m, 12H), 0.94-0.89 (m, 12H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -123.9 ppm.

[0046] The tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate) was found to be solid and crystalline at 23 °C. Purely by way of illustration, FIG. 1 provides an image of the tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate) at 23 °C in ambient air via a Leica DVM6A microscope (Objective: FOV 12.55; Working Distance: 33 mm; Max Magnification: 675:1; Exposure Time: 30 ms; Resolution: 2MP (1600x1200); Zoom: 6.87x;

Numerical Aperture: 0.125; TL Light Intensity: 90; RL Intensity: 30; SLI Intensity: -10; CXI Light Intensity: 80; BLI Light Intensity: 90; Color Saturation: 24.31373; Movement: Z then Lambda; Filters: None). Likewise, purely by way of illustration, FIG. 2 provides an image taken of the tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate) in mineral oil at 23 °C via a Leica DVM6A microscope (Objective: FOV 12.55; Working Distance: 33 mm; Max Magnification: 675:1; Exposure Time: 30 ms; Resolution: 2MP (1600x1200); Zoom: 1.8x; Numerical Aperture: 0.032; TL Light Intensity: 60; RL Intensity: 30; SLI Intensity: -10; CXI Light Intensity: 40; BLI Light Intensity: 60; Color Saturation: 24.31373; Movement: Z then Lambda; Filters: None). The solid, crystalline tetra-*n*-butylammonium fluoride tetrakis(*tert*-amyl alcoholate) was further found to remain stable in ambient air at 23 °C in a desiccator for over 6 months.

Example 2 – Preparation of a Substantially Water-Free TMAF Solution

Scheme II – Exemplary Generation of a Substantially Water-Free TMAF solution.



[0047] A 100 mL 3-neck round bottom flask was fitted with a nitrogen inlet, a thermocouple, and a Dean-Stark apparatus with a reflux condenser. To the flask at room temperature was added tetramethylammonium fluoride tetrahydrate (3.78 g, 22.9 mmol, 1.0 equivalents), *tert*-amyl alcohol (69.9 g, 34 equivalents) and heptanes (14.5 g, 6 equivalents). Stirring was started, a vacuum was applied to lower the pressure to 180 mmHg, and the temperature of the solution was increased to 60-70 °C for reflux. These conditions were maintained for 4 h to give a solution that was 0.08% water by Karl-Fischer titration. The vacuum was broken with nitrogen and the reaction cooled to room temperature under nitrogen to afford tetramethylammonium fluoride (2.13 g, 22.9 mmol, 100%, 5.32 wt.%) as a substantially water-free solution in *t*-AmOH/heptanes. *Characterization Data for Substantially Water-Free TMAF in t-AmOH/heptanes solution.* ¹H NMR (400 MHz, MeOH-d₄) δ 3.10 (s, 12H), 1.40 (q, *J* = 7.56 Hz, 38.4H), 1.07 (s, 113.6H), 0.82 (t, *J* = 7.52 Hz, 55.0H) ppm. ¹⁹F NMR (376 MHz, MeOH-d₄) δ -149.4 ppm.

Example 3 – Preparation of solid TMAF(*t*-AmOH)_{*n*}

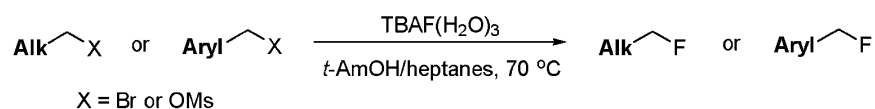
[0048] Portions of the solution of Example 2 were each further subjected to reduced pressure (15 mmHg, 40 °C) to provide TMAF(*t*-AmOH)_{*n*} as a crystalline solid, where *n* varied from 0.9 to 1.7 depending on the amount of residual solvent.

[0049] *Characterization Data for TMAF(t-AmOH)_{1.6} after isolation as a solid.* ¹H NMR (400 MHz, MeOH-d₄) δ 3.11 (s, 12H), 1.40 (q, *J* = 8.02 Hz, 3.3H), 1.07 (s, 9.9H), 0.82 (t, *J* = 7.72 Hz, 4.8H) ppm. ¹⁹F NMR (376 MHz, MeOH-d₄) δ -151.9 ppm.

Exemplary General Methods A-E

[0050] Fluorination reactions were performed according to the below-described General Methods A-E. Examples 4-9 thereafter disclose a subset of particular fluorination reactions performed and the results thereof.

[0051] *General Method A: Fluorination using in situ prepared TBAF solution substantially free of water.*

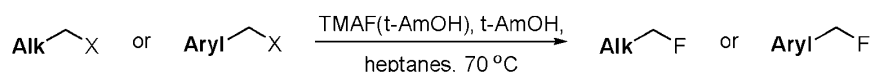
Scheme III

[0052] To a 100 mL 3-neck round-bottom flask equipped with a magnetic stirrer, a nitrogen inlet, a thermocouple and a reflux condenser with a Dean-Stark trap was charged tetra-*n*-butylammonium fluoride trihydrate (15.0 g, 1.2 equivalents), *tert*-amyl alcohol (8.5 V) and heptanes (mixed isomers, 3 V). The resulting stirred mixture was heated to reflux under reduced pressure (180 mmHg, 55 to 60 °C) for 4 h and/or until water content of the reaction mixture decreased to less than 0.2% by Karl-Fischer titration. The vacuum was released, and temperature adjusted to 65 to 75 °C. The bromide or mesylate (1.0 equivalents) was charged and the mixture stirred at 65 to 75 °C for 1 h. The mixture was then cooled to ambient temperature, quenched with water (10 V) and diluted with heptanes (mixed isomers, 3 V). The phases were split, and the aqueous layer was extracted with heptanes (mixed

isomers, 3 V). The combined organics were washed with water (2 x 5 V), dried over MgSO_4 , filtered, and concentrated under reduced pressure to give the alkyl fluoride product.

[0053] *General Method B: Fluorination using in situ prepared TMAF solution substantially free of water*

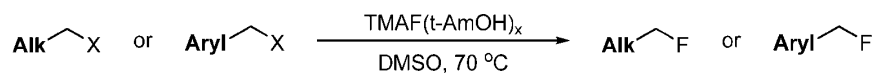
Scheme IV



[0054] To a nitrogen flushed 100 mL round-bottom flask containing the substantially water-free solution of TMAF (1.2 to 1.5 equivalents) in *t*-AmOH/heptanes (0.2 – 0.3 M) produced according to Example 2 was added the substrate (1.0 equivalent) in one portion at room temperature. The reaction was heated to 70 °C and monitored by ^1H NMR for conversion.

[0055] *General Method C: Fluorination using solid TMAF(*t*-AmOH)*

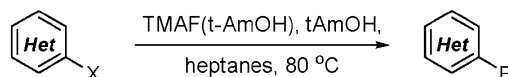
Scheme V – Reaction of TMAF(*t*-AmOH) in DMSO to provide fluorinated products.



[0056] To a nitrogen flushed 50 mL round-bottom flask equipped with a stir bar was added the substrate (1.0 equivalents), followed by solid TMAF(*t*-AmOH)_{*n*} (1.2 to 1.5 equivalents of fluoride; prepared according to Example 2), and then anhydrous DMSO (0.2-0.3 M). The reaction was heated to 70 °C and monitored by ^1H NMR for conversion.

[0057] *General Method D: Fluorination of aryl halides in alcohol/heptanes solution*

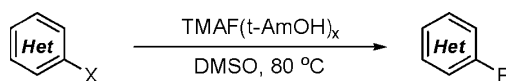
Scheme VI – Reaction of aryl halides and heteroaryl halides in *t*-AmOH/heptanes



[0058] To a nitrogen flushed 100 mL round-bottom flask containing a substantially water-free solution of TMAF (1.2 to 1.5 equivalents) in *t*-AmOH/heptanes (0.2-0.3 M) prepared according to Example 2 was added the substrate (1.0 equivalent) in one portion at room temperature. The reaction was heated to 80 °C and monitored by ¹H NMR for conversion.

[0059] **General Method E: Fluorination of aryl halides in DMSO**

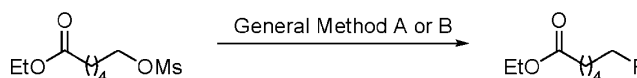
Scheme VII – Reaction of aryl halides and heteroaryl halides with TMAF(*t*-AmOH) in DMSO



[0060] To a nitrogen flushed 50 mL round-bottom flask equipped with a stir bar was added the aryl halide (1.0 equivalent), followed by solid TMAF(*t*-AmOH)_{*n*} (1.2 to 1.5 equivalents of fluoride; prepared according to Example 2), and then anhydrous DMSO (0.2-0.3 M). The reaction was heated to 80 °C and monitored by ¹H NMR for conversion.

Example 4 – Synthesis of ethyl 6-fluorohexanoate

Scheme VIII – Reaction of ethyl 6-(methanesulfonyloxy)hexanoate using **General Method A** or **General Method B** to provide ethyl 6-fluorohexanoate.



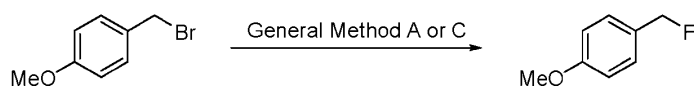
[0061] According to **General Method A**, ethyl 6-(methanesulfonyloxy)hexanoate (2.00 g) was converted to ethyl 6-fluorohexanoate (1.14 g, 84% yield, colorless oil). ¹H NMR (400 MHz, CDCl₃) δ 4.43 (dt, *J* = 47.3, 6.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.78-1.64 (m, 4H), 1.48-1.41 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -218.4 ppm.

[0062] According to **General Method B**, to the substantially water-free solution of TMAF (0.47 g, 5.1 mmol, 1.3 equivalents) in *t*-AmOH/heptanes (15.66 g, 0.3 M) was added

the alkyl mesylate (0.90 g, 3.8 mmol, 1.0 equivalent) in one portion at room temperature. The solution was heated to 70 °C for 1 h. The reaction was then cooled and analyzed without further purification to afford the fluorinated product (0.55 g, 3.4 mmol, 90.3%, 3.1 wt.%) as a solution in *t*-AmOH/heptanes.

Example 5 – Synthesis of 4-methoxybenzyl fluoride

Scheme IX – Reaction of 4-methoxybenzyl bromide using **General Method A** or **General Method C** to provide 4-methoxybenzyl fluoride.

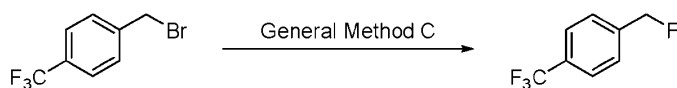


[0063] According to **General Method A**, 4-methoxybenzyl bromide (2.00 g) was converted to 4-methoxybenzyl fluoride (1.09 g, 78% yield, colorless oil). . ¹H NMR (400 MHz, DMSO) δ 7.04-7.01 (m, 2H), 6.62-6.60 (d, *J* = 7.95 Hz, 2H) 4.99 (d, *J* = 48.78 Hz, 2H), 3.52 (s, 3H) ppm. ¹⁹F NMR (376 MHz, DMSO) δ -59.7 ppm.

[0064] According to **General Method C**, to a round-bottom flask under nitrogen was added 4-(bromomethyl)anisole (1.11 g, 5.5 mmol, 1.0 equivalent), followed by solid TMAF(*t*-AmOH)_{1.1} (1.28 g, 6.7 mmol, 1.2 equivalents) and DMSO (27.41 g, 0.2 M) at room temperature. The solution was heated to 70 °C for 1 h. The reaction was then cooled and analyzed without further purification to afford the fluorinated product (0.63 g, 4.5 mmol, 80.7%, 1.8 wt.%) as a solution in DMSO.

Example 6 – Synthesis of 1-(fluoromethyl)-4-(trifluoromethyl)benzene

Scheme X – Reaction of 1-(bromomethyl)-4-(trifluoromethyl)benzene using **General Method C** to provide 1-(fluoromethyl)-4-(trifluoromethyl)benzene.

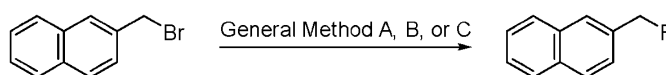


[0065] According to **General Method C**, to a round-bottom flask under nitrogen was added 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.92 g, 3.8 mmol, 1.0 equivalent) along

with solid TMAF(*t*-AmOH)_{1.1} (0.92 g, 4.8 mmol, 1.3 equivalents) and DMSO (23.05 g, 0.20 M) at room temperature. The solution was heated to 70 °C for 1 h. The reaction was then cooled and analyzed without further purification to afford the fluorinated product (0.62 g, 3.5 mmol, 90.3%, 2.5 wt.%) as a solution in DMSO. ¹H NMR (400 MHz, DMSO) δ 7.38 (d, *J* = 8.04 Hz, 2H), 7.24 (d, *J* = 7.96 Hz, 2H), 5.19 (d, *J* = 47.18 Hz, 2H) ppm.

Example 7 – Synthesis of 2-(fluoromethyl)naphthalene

Scheme XI – Reaction of 2-(bromomethyl)naphthalene using **General Method A, General Method B, or General Method C** to provide 2-(fluoromethyl)naphthalene.



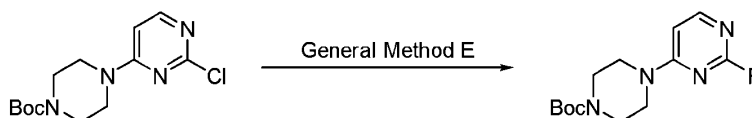
[0066] According to **General Method A**, 2-(bromomethyl)naphthalene (2.00 g) was converted to 2-(fluoromethyl)naphthalene (1.29 g, 89% yield, white solid). ¹H NMR (400 MHz, DMSO) δ 7.92-7.87 (m, 4H), 7.56-7.51 (m, 3H), 5.58 (d, *J* = 47.74 Hz, 2H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ -206.7 ppm.

[0067] According to **General Method B**, to the substantially water-free solution of TMAF (0.52 g, 5.6 mmol, 1.3 equivalents) in *t*-AmOH/heptanes (15.36 g, 0.2 M) in the round-bottom flask under nitrogen was added 2-(bromomethyl)naphthalene (0.93 g, 4.2 mmol, 1.0 equivalent) in one portion at room temperature. The solution was heated to 70 °C for 1 h. After the reaction was concentrated under reduced pressure, diluted with heptanes, and then filtered to remove the salts. The reaction afforded 2-(fluoromethyl)naphthalene (0.56 g, 3.5 mmol, 84.2%, 54.2 wt.% in heptanes) as a solution in heptanes.

[0068] According to **General Method C**, to a round-bottom flask under nitrogen was added 2-(bromomethyl)naphthalene (0.99 g, 4.5 mmol, 1.0 equivalent) along with solid TMAF(*t*-AmOH)_{1.1} (1.06 g, 5.5 mmol, 1.2 equivalents) and anhydrous DMSO (22.44 g, 0.2 M) at room temperature. The solution was heated to 70 °C for 1 h. The reaction was then cooled and analyzed without further purification to afford the fluorinated product (0.62 g, 3.9 mmol, 86.0%, 2.6 wt.%) as a solution in *t*-AmOH/heptanes.

Example 8 – Synthesis of *tert*-butyl 4-(2-fluoropyrimidin-4-yl)piperazine-1-carboxylate

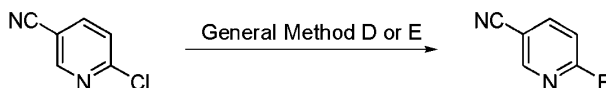
Scheme XII – Reaction of *tert*-butyl 4-(2-chloropyrimidin-4-yl)piperazine-1-carboxylate using **General Method E** to provide *tert*-butyl 4-(2-fluoropyrimidin-4-yl)piperazine-1-carboxylate.



[0069] According to **General Method E**, to the round-bottom flask was added *tert*-butyl 4-(2-chloropyrimidin-4-yl)piperazine-1-carboxylate (0.20 g, 0.7 mmol, 1.0 equivalent) followed by TMAF(*t*-AmOH)_{1.6} (0.21 g, 0.9 mmol, 1.3 equivalents) and anhydrous DMSO (3.70 g, 0.2 M). The temperature was increased to 80 °C. After 0.5 h, the reaction was cooled to afford *tert*-butyl 4-(2-fluoropyrimidin-4-yl)piperazine-1-carboxylate (0.18 g, 0.6 mmol, 97.3%, 4.4 wt.%) as a solution in DMSO. ¹H NMR (400 MHz, DMSO) δ 8.23 (dd, 1H, *J* = 6.12, 2.60 Hz), 6.92 (dd, 1H, *J* = 6.04, 4.72 Hz), 3.75 (br s, 4H), 3.54-3.52 (m, 4H), 1.53 (s, 9H) ppm. ¹⁹F NMR (376 MHz, DMSO) δ -45.6 ppm.

Example 9 – Synthesis of 6-fluoronicotinonitrile

Scheme XIII – Reaction of 6-chloronicotinonitrile using **General Method D or General Method E** to provide 6-fluoronicotinonitrile.



[0070] According to **General Method D**, to a nitrogen flushed 50 mL round-bottom flask containing the substantially water-free solution of TMAF (0.24 g, 2.6 mmol, 1.8 equivalents) in *t*-AmOH/heptanes (0.3 M) was added 6-chloronicotinonitrile (0.20 g, 1.4 mmol, 1.0 equivalents) in one portion at room temperature. The reaction was heated to 80 °C. After 2 h, the reaction was cooled to afford the product (0.10 g, 0.8 mmol, 57.1%, 2.04 wt.%) as a solution in *t*-AmOH/heptanes.

[0071] According to **General Method E**, to the round-bottom flask was added 6-chloronicotinonitrile (0.20 g, 1.4 mmol, 1.0 equivalents) followed by TMAF(*t*-AmOH)_{1.6} (0.45 g, 1.9 mmol, 1.3 equivalents) and anhydrous DMSO (5.30 g, 0.3 M). The temperature was increased to 80 °C. After 10 min, the reaction was cooled to afford 6-fluoronicotinonitrile (0.13 g, 1.1 mmol, 75.2%, 2.18 wt.%) as a solution in DMSO. ¹H NMR (400 MHz, DMSO) δ 8.90 (d, 1H, *J* = 2.32 Hz), 8.65-8.61 (m, 1H), 7.56 (dd, 1H, *J* = 8.60, 2.48 Hz) ppm. ¹⁹F NMR (376 MHz, DMSO) δ -59.8 ppm.

[0072] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

[0073] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially of” will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase “consisting of” excludes any element not specified. Finally, it will be understood that disclosure of one of the foregoing terms also discloses embodiments using any of the other two terms or their equivalents.

[0074] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and compositions within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the

scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds, compositions, or biological systems, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[0075] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0076] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member.

[0077] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[0078] Other embodiments are set forth in the following claims.

WHAT IS CLAIMED IS:

1. A solid alcohol solvate of a tetra(C₁-C₆ alkyl)ammonium fluoride and a C_x alcohol, wherein *x* is 3, 5, 6, 7, 8, 9, or 10.
2. The solid alcohol solvate of claim 1, wherein the tetra(C₁-C₆ alkyl)ammonium fluoride is a tetrabutylammonium fluoride.
3. The solid alcohol solvate of claim 1 or claim 2, wherein the solid alcohol solvate is tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride.
4. The solid alcohol solvate of any one of claims 1-3, wherein the solid alcohol solvate is in a crystalline form.
5. A hydrate of an alcohol solvate of any one of claims 1-4.
6. A method comprising
combining an ammonium fluoride or a hydrate thereof with a solvent
comprising an alcohol to form a mixture; and
isolating a solid alcohol solvate from the mixture.
7. The method of claim 6, wherein isolating the solid alcohol solvate comprises distilling the mixture to yield the solid alcohol solvate.
8. The method of claim 6 or claim 7, wherein the ammonium fluoride or hydrate thereof is tetra(C₁-C₆ alkyl)ammonium fluoride or a hydrate of tetra(C₁-C₆ alkyl)ammonium fluoride.
9. The method of any one of claims 6-8, wherein the ammonium fluoride or hydrate thereof is a tetrabutylammonium fluoride, a hydrate of a tetrabutylammonium fluoride, tetramethylammonium fluoride, or a hydrate of tetramethylammonium fluoride.
10. The method of any one of claims 6-9, wherein the mixture further comprises a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof.
11. The method of claim 10, wherein the C₅-C₁₀ alkane comprises a heptane.

12. The method of claim 10 or claim 11, wherein the C₆-C₁₀ aromatic hydrocarbon comprises benzene, toluene, or a combination thereof.
13. The method of any one of claims 6-12, wherein the method comprises
combining the ammonium fluoride or hydrate thereof with the solvent
comprising the alcohol to form the mixture;
heating the mixture to a temperature of about 50 °C to about 100 °C to provide
a heated mixture; and
isolating the solid alcohol solvate from the heated mixture.
14. The method of claim 13, wherein heating the mixture comprises heating for about 1 hour
to about 10 hours.
15. The method of any one of claims 6-14, wherein the mixture comprises 1 molar
equivalent of the ammonium fluoride or hydrate thereof and about 5 to about 50 molar
equivalents of the alcohol.
16. The method of any one of claims 6-15, wherein the mixture comprises 1 molar
equivalent of the ammonium fluoride or hydrate thereof and about 10 to about 20
molar equivalents of the alcohol.
17. The method of any one of claims 6-16, wherein the mixture comprises 1 molar
equivalent of the ammonium fluoride or hydrate thereof and about 10 to about 15
molar equivalents of the alcohol.
18. The method of any one of claims 10-17, wherein the mixture comprises 1 molar
equivalent of the ammonium fluoride or hydrate thereof and about 1 to about 10 molar
equivalents of the C₃-C₁₀ alkane, the C₆-C₁₀ aromatic hydrocarbon, or the
combination thereof.
19. The method of any one of claims 6-18, wherein isolating the solid alcohol solvate from
the mixture comprises distilling the mixture to collect a distillate in a Dean-Stark
apparatus.

20. The method of any one of claims 6-19, wherein isolating the solid alcohol solvate comprises an absolute pressure of about 50 mmHg to about 500 mmHg.
21. The method of any one of claims 6-20, wherein the alcohol comprises *tert*-butanol or *tert*-amyl alcohol.
22. The method of any one of claims 6-21, wherein the solid alcohol solvate is tetra-*n*-butylammonium tetra(*tert*-amyl alcohol) fluoride, tetra-*n*-butylammonium tetra(*tert*-butyl alcohol) fluoride, or tetramethylammonium *tert*-amyl alcohol fluoride.
23. The method of any one of claims 6-22, wherein isolating the solid alcohol solvate comprises isolating the solid alcohol solvate substantially free of water.
24. The method of any one of claims 6-23, wherein isolating the solid alcohol solvate comprises isolating an anhydrous solid alcohol solvate of the ammonium fluoride and the alcohol.
25. A process comprising
 - combining a hydrate of an ammonium fluoride with a solvent comprising an alcohol to form a mixture; and
 - distilling the mixture to yield a second mixture substantially free of water.
26. The process of claim 25, wherein the hydrate comprises a hydrate of tetra(C₁-C₆ alkyl)ammonium fluoride.
27. The process of claim 25 or claim 26, wherein the hydrate is a hydrate of a tetrabutylammonium fluoride or a hydrate of tetramethylammonium fluoride.
28. The process of any one of claims 25-27, wherein the mixture further comprises a C₅-C₁₀ alkane, a C₆-C₁₀ aromatic hydrocarbon, or a combination thereof.
29. The process of any one of claims 25-28, wherein distilling the mixture comprises heating the mixture to a temperature of about 50 °C to about 100 °C.
30. The process of any one of claims 25-29, wherein distilling the mixture comprises collecting a distillate in a Dean-Stark apparatus.

31. The process of any one of claims 25-30, wherein distilling the mixture comprises an absolute pressure of about 50 mmHg to about 500 mmHg.
32. The process of any one of claims 25-31, wherein the alcohol comprises *tert*-butanol and/or *tert*-amyl alcohol.
33. The process of any one of claims 25-32, wherein the second mixture comprises less than 0.2 wt.% water.
34. The process of any one of claims 25-33, wherein the second mixture is anhydrous.