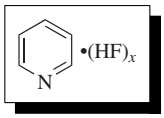
Pyridinium Poly(hydrogenfluoride)[1]



($C_5H_5N{\cdot}9HF$; 30% pyridine,70% HF by wt)
[32001-55-1] $C_5H_{14}F_9N$ (MW 259.20)
InChI = 1/C5H5N.9FH/c1-2-4-6-5-3-1;;;;;;;;;/h1-5H;9*1H
InChIKey = SABNUQZTPOUCIR-UHFFFAOYAR

(convenient, less volatile form of anhydrous HF with enhanced nucleophilicity; substitutes F for secondary or tertiary hydroxy groups,[2] other halides,[3] or primary amine[4] groups; adds HF to alkenes and alkynes;[1d] with halonium ion sources, halofluorinates alkenes and alkynes;[1a,5] opens and adds HF to oxiranes (epoxides), aziridines, azirines, and cyclopropanes;[1] oxidatively fluorinates when combined with electrolytic processes or Pb^{IV} compounds[1c,e])

Alternate Names: Olah's reagent; hydrogen fluoride–pyridine.

Physical Data: dissoc 55 °C; at 80–110 °C, liq phase is primarily py·5HF; at reflux (160–170 °C) the stoichiometry is py·3HF; low-temperature phase behavior and X-ray crystal structures for some phases are known.[6]

Solubility: sol CH_2Cl_2, MeCN, Et_2O, THF, toluene, sulfolane.

Form Supplied in: light brown liquid in plastic bottles; H_2O most likely impurity (from HF used); commercially available.

Preparative Methods: condensation of anhydrous ***Hydrogen Fluoride*** into ***Pyridine*** at −78 °C, followed by gradual warming to rt; *caution*: highly exothermic.[1d,e]

Purification: best approach is to purify components (pyridine, HF) before mixing.[7] HF can also be dried using ***Antimony(V) Fluoride***,[8] BiF_5,[8,9] high-pressure ***Fluorine***,[10] or electrolysis.

Handling, Storage, and Precautions: toxic, hygroscopic, corrosive. Moisture drastically inhibits fluorination activity. Compatible materials: polyethylene, fluoro polymers (FEP, PFA, PTFE). Hydrogen pressure may accumulate in metal HF storage containers. Avoid contact with glass. ***Sodium Fluoride***, aq base, and $CaCl_2$ are useful for neutralization and workup. Reagent contains a small equilibrium concentration of HF. Although the reduced HF vapor pressure in py·$(HF)_x$ reduces the potential for exposure, extreme care should be used in handling this material; handle only in a fume hood, wear safety goggles or a face shield, and wear appropriate impermeable clothing. Effects of exposure to HF are often delayed for several hours, but the burns are extremely painful and can be slow to heal. Exposure to py·$(HF)_x$ should be treated in the same way as for HF. Thus users and coworkers should be familiar with and be prepared to administer the proper first aid treatment.[11]

Original Commentary

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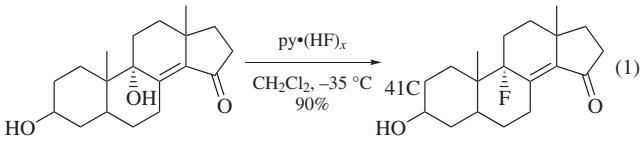
Substitution Reactions.

Fluorodehydroxylation. Secondary and tertiary alcohols react with py·$(HF)_x$ to give alkyl fluorides. The tertiary compounds react quickly at temperatures as low as −70 °C, while rt is usually sufficient for secondary alcohols. This can provide significant regioselectivity as shown for reactions at the competitive sites in a steroid (eq 1).[12] Primary alcohols require the addition of NaF for the substitution to occur. The probable S_N2 mechanism of the reaction is illustrated by the lack of rearrangement upon fluorination of neopentyl alcohol (eq 2)[2] (for alternative reagents, see fluoroalkylamine reagents (FAR), ***N,N-Diethylaminosulfur Trifluoride*** (DAST).

Halogen Exchange. No fluorination of tertiary alkyl halides occurs unless the halide is abstracted by an agent such as a nitronium salt (eq 3).[3] Related $R_3N{\cdot}3HF$ complexes are more effective for nucleophilic halide replacement.[1c]



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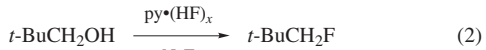

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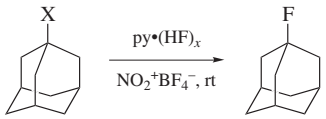
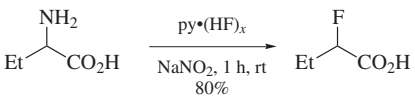


(3)

X = Cl, Br, I

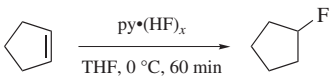
Fluorodeamination. Substitution of F for NH_2 is achieved by an in situ diazotization–fluorinative dediazotization sequence. For example, α-fluorocarboxylic acids are obtained from α-amino acids, as shown for 2-aminobutanoic acid (eq 4).[4] Retention of configuration is usually observed.



(4)

Addition Reactions.

Hydrofluorination of Alkenes and Alkynes. Addition of HF takes place in Markovnikov fashion. Among alkenes, branched derivatives and cycloalkenes give higher yields (eq 5).[1d,e] As expected, *gem*-difluoro derivatives are obtained from alkynes (eq 6).[1d] THF is often used as a cosolvent since the starting materials are generally insoluble in py·$(HF)_x$. The related melamine·$(HF)_x$ reagent is especially effective for hydrofluorination of unsaturated substrates and can be used repeatedly in pentane or CCl_4 two-phase systems.[1c]



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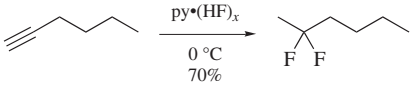
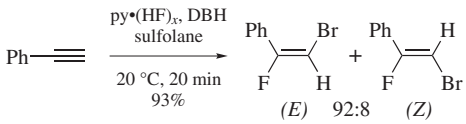


(6)

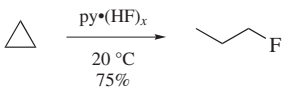
Halofluorination of Alkenes and Alkynes. When these unsaturated compounds are combined with py·$(HF)_x$ and a source of halonium ion (e.g. *N*-halosuccinimides, *N*-haloacetamides, or ***1,3-Dibromo-5,5-dimethylhydantoin*** (DBH)), addition of XF (X = Cl, Br, I) to the multiple bond is the result. Alkenes provide several potentially useful extensions from the initial 1,2-halofluoroalkane products.[1a] For example, addition of ***Silver(I) Fluoride*** to the initial product results in halogen exchange yielding vicinal difluorides without isolation of the intermediates. Similarly, reduction of the intermediates with a tin hydride reagent gives products corresponding to Markovnikov addition of HF to the starting alkene. Elimination reactions of the intermediates with base lead to vinyl fluorides. Alkene halofluorination was found to exhibit Markovnikov and anti-Markovnikov orientation in the case of 1-phenyl-4-*t*-butylcyclohexene.[13]

Bromofluorination of phenylacetylene using py·$(HF)_x$ and DBH in sulfolane (eq 7)[5] gave a mixture of (*Z*) and (*E*) isomers but with good regio- and stereoselectivity.



(7)

Ring-opening Fluorination. The fluoride ion donor ability of py·$(HF)_x$ is shown by the cleavage of cyclopropane (eq 8),[14] in which fluoride traps the primary cation before it can rearrange. Regioselective conversion of oxiranes to fluorohydrins has become an important process in the steroid field (eq 9).[15] An iterative cyclization/ring opening approach has served in the conversion of a tetrachlorocyclohexanol to its tetrafluoro analog with complete regio- and stereoselectivity.[16] In the case of aziridines the ring opening is regioselective in that fluoride becomes bound to the carbon best able to stabilize a positive charge, but the stereochemistry depends strongly on the starting material and the fluorinating agent.[1c,e] Substituted 1-azirines give difluorinated amines or α-fluoro ketones, depending on the substituents.[1c,e]



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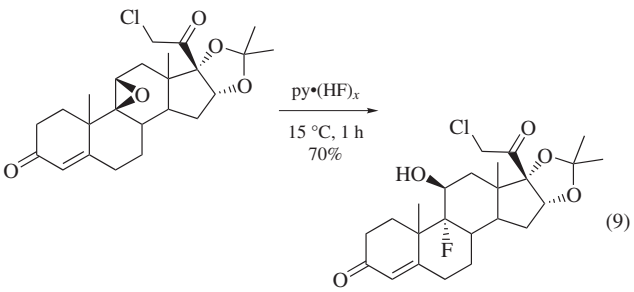
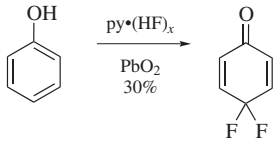


(9)

Oxidative Fluorination. With py·$(HF)_x$ and stoichiometric amounts of Pb^{IV}, phenols are converted to difluorodienones (eq 10). Benzene reacts very slowly to give the same product.[1b,c] Similar reactions can be conducted using anodic oxidation in place of the lead compounds. In both situations, cations or radical cations are proposed as the initially generated species, which then react with fluoride. For these reactions, ***Triethylamine***·3HF is used most often.



(10)

First Update

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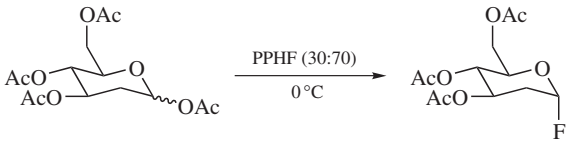
Substitution Reactions.

Fluorodehydroxylation. Pyridinium poly(hydrogen fluoride) (PPHF, Olah's reagent) is frequently used for the preparation of fluorine-containing carbohydrates and steroids via fluorodehydroxylation. It was found that in the reaction of fully acetylated sugars with 50–70% PPHF, only the anomeric OAc group was substituted by fluorine to give predominantly the thermodynamically more stable α-isomer (eq 11).[18] 2-α-Hydroxy-androst-4-ene-3,17-dione when reacted with PPHF gives 6-β-fluoroandrost-4-ene-3,17-dione through a S_N2'-type mechanism (eq 12).[19] PPHF has also been utilized for the formation of amino acid fluorides from amino acids for subsequent peptide coupling reactions.[20]



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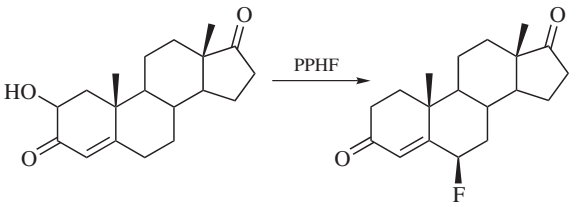

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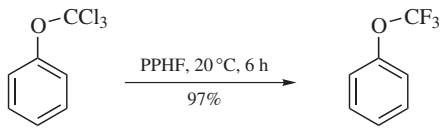
Halogen Exchange. PPHF is a convenient fluorinating agent for the preparation of organofluorine compounds from organochlorine compounds (particularly, those with activated C–Cl bonds) via halogen-exchange reactions. For instance, trichloromethoxybenzene can be readily converted to trifluoromethoxybenzene with PPHF at ambient temperature in almost quantitative yield (eq 13).[21] The reaction of 2,2-dichloro-2-(4′-nitrophenyl) acetonitrile with mercury(II) oxide and PPHF gave 2,2-difluoro-2-(4′-nitrophenyl)acetonitrile in 81% yield (eq 14).[22] Muddukrishna and Padma have converted alkylchlorosilanes to the corresponding fluorosilanes using PPHF (eqs 15 and 16).[23] The reaction has

been extended to tetrachloro, trichloro, and tris(amino)silanes.[24] Oxide of vanadium (V) and chlorides of chromium (III), iron (III), and Co(II) at room temperature react with excess PPHF to provide the respective pyridinium salts of hexafluorovanadate (V), hexafluorochromate (III), hexafluoroferrate (III) in high yields.[25] Several ternary metal oxides have also been converted to their respective ternary metal fluorides with PPHF.[26]



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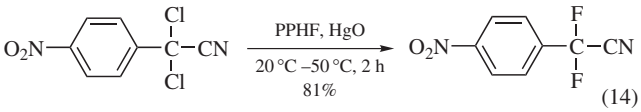
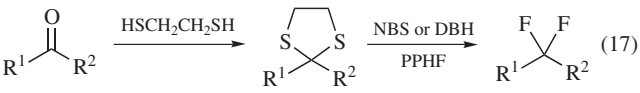


(14)

$(CH_3)_3SiCl \xrightarrow{PPHF} (CH_3)_3SiF$ (15)

$(CH_3)_2SiCl_2 \xrightarrow{PPHF} (CH_3)_2SiF_2$ (16)

Desulfurative Fluorination. Desulfurative fluorination of dithiolanes is a widely used method to prepare *gem*-difluorinated compounds from ketones (eq 17).[27] This method is an inexpensive alternative for the SF_4 fluorination (or its derivatives such as DAST and Deoxofluor). The combination of PPHF and *N*-bromosuccinimide (NBS)[28] or 1,3-dibromo-5,5-dimethylhydantoin (DBH) is a reagent equivalent of BrF, which is the real desulfurative fluorination agent. The use of *N*-iodosuccinimide (instead of NBS or DBH) and PPHF can sometimes increase the product yield by diminishing the possibility of halogenated ring side-products (eq 18).[29] A combination of sulfuryl chloride or sulfuryl fluoride with PPHF has been utilized for the desulfurative fluorination of dithiolanes.[30] *gem*-Difluorination of a number of 2,2-diaryl-1,3-dithiolanes were also achieved using Selectfluor and PPHF.[31] Similar protocols can also be extended to *gem*-trifluorination of orthothio esters to give trifluoromethyl compounds (eq 19).[32] In addition, desulfurative fluorination of dithiolanes can also be achieved using nitrosonium tetrafluoroborate (NO^+ BF_4^-)/PPHF reagent system (eq 20).[33] The reagent system also converts aryl alkyl sulfides to alkyl fluorides (eq 21).[33]



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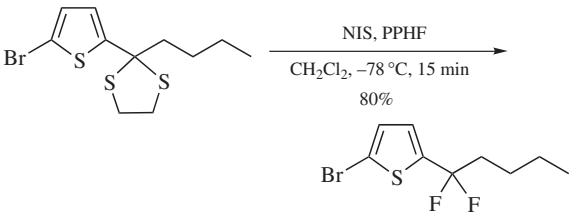

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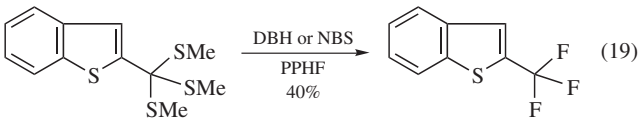

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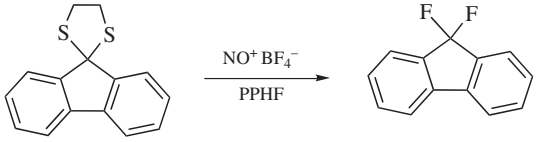

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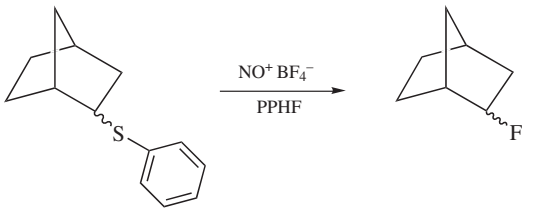
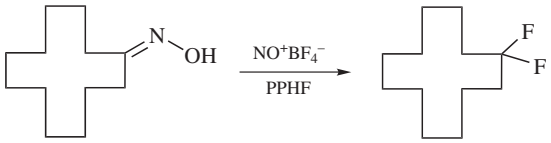


(21)

Denitrosative Fluorination. Selective *gem*-difluorination of ketoximes were achieved with nitrosonium tetrafluoroborate (NO^+ BF_4^-)/PPHF reagent system (eq 22).[34] Under similar reaction conditions, diarylacetylenes are fully fluorinated (eq 23) to the corresponding tetrafluoroethane[35] (formal two moles of fluorine addition product) involving initial NOF addition on the triple bond followed by HF addition and subsequent deoximinative *gem*-difluorination.



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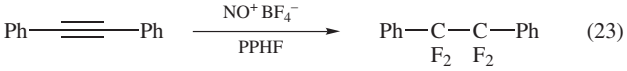
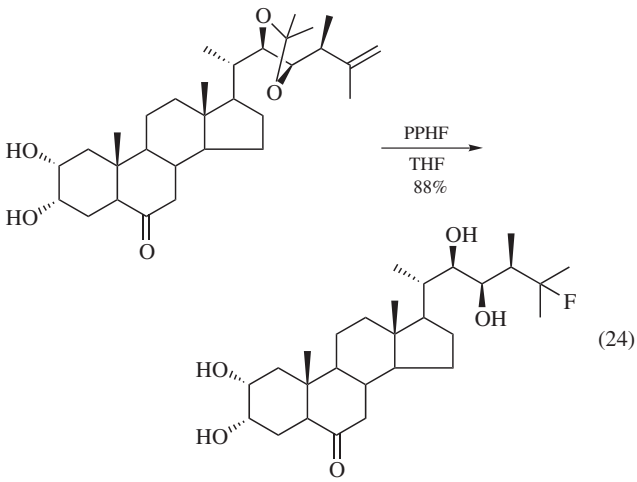


(23)

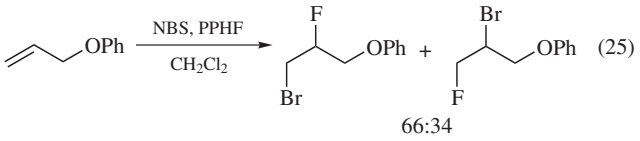
Hydrofluorination of Alkenes and Alkynes. Hydrofluorination of alkenes and alkynes with PPHF is a convenient and inexpensive way to introduce fluorine atom(s) into organic molecules in Markovnikov fashion. For example, 25-fluorocastasterone can be easily obtained by the treatment of an alkene precursor with PPHF (eq 24).[36]



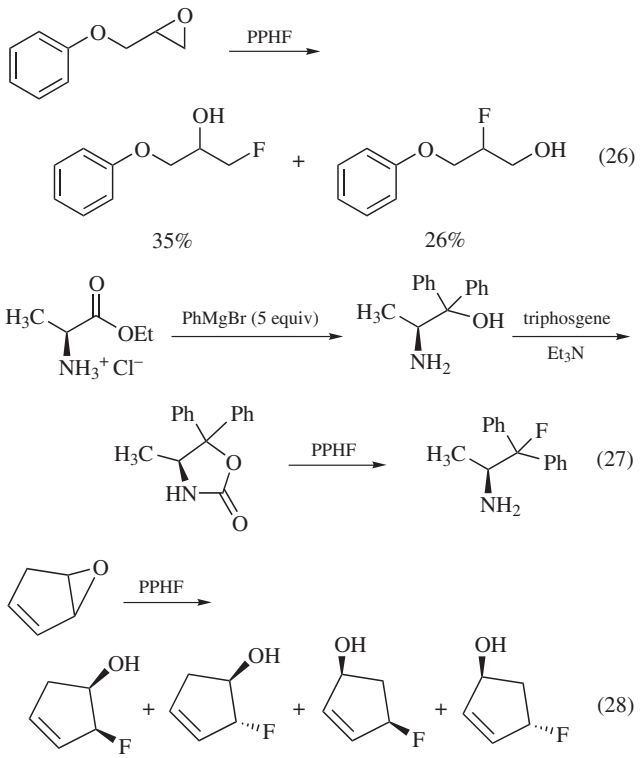
(24)

Halofluorination of Alkenes and Alkynes. The regiochemistry of halofluorination of alkenes and alkynes with PPHF/halogen source usually exhibits Markovnikov orientation.

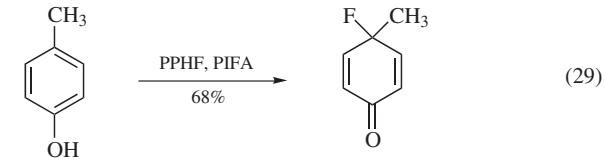
However, Haufe and co-workers reported that the regioselectivity of bromofluorination of functionalized 1-alkenes with NBS and amine-PPHF depends mainly on the character of functional groups in the neighborhood of the double bond and only weakly from the nature of the fluorinating agent.[37] Electron-withdrawing groups in allylic or homoallylic position to the double bond destabilize the carbenium center in 2-position and as a result anti-Markovnikov-oriented products were produced (eq 25).[37]

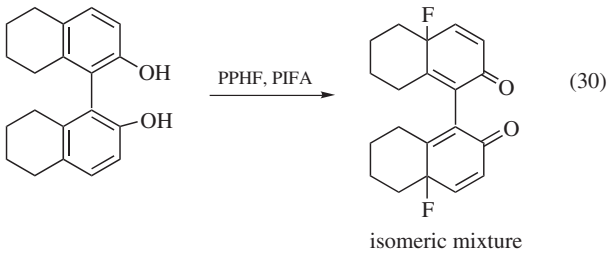


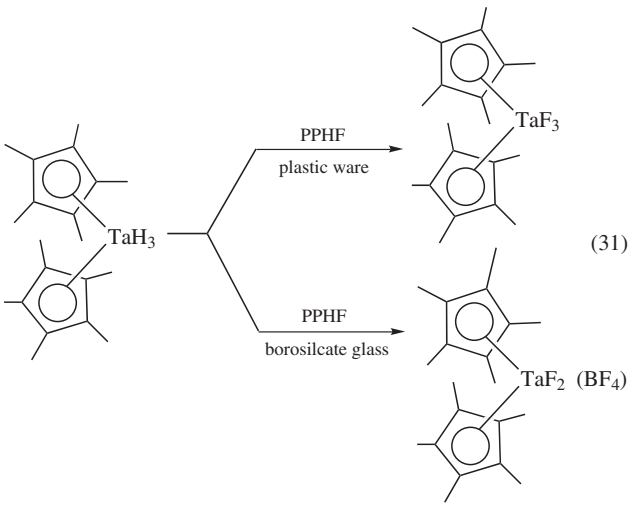
Ring-opening Fluorination. In the ring opening reactions of epoxides with PPHF, the regioisomer derived from more stable carbocation is formed (S_N1-like reaction) though there is no evidence for the formation of a free carbocation.[38] However, the electron-withdrawing character of the α-substituents on the epoxides also plays an important role in the regiochemistry of the reactions (eq 26).[38] O'Hagan et al. reported that treatment of enantiomerically pure (*S*)-4-alkyl-5,5-diphenyloxazolidinones (derived from the appropriate amino acids) with PPHF generated (*S*)-α-(fluorodiphenylmethyl)-alkylamines (eq 27).[39] Ring opening of 3,4-epoxycyclopentene led to four isomeric fluorohydrins (eq 28) that were subsequently converted to four isomeric vicinal difluorides upon subsequent DAST treatment.[40] Butadiene monoepoxide has also been converted to 2-fluoro-3-buten-1-ol with PPHF containing 42 wt % HF.[41]



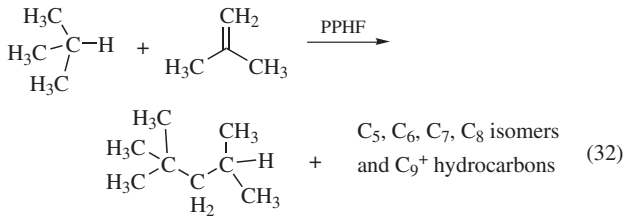
Oxidative Fluorination. PPHF combined with diacetoxyiodobenzene (PIDA) or bis(trifluoroacetoxy)iodobenzene is effective for the fluorination of *para*-substituted phenols to give a variety of 4-fluorocyclohexa-2,5-dienones in good yields (eq 29).[42] The method has been adopted for the preparation of atropoisomeric fluorocyclohexadienones as isomeric mixtures (eq 30).[42] In a novel oxidative fluorination, permethyltantolocene trihydride complex has been oxidatively fluorinated in PPHF medium in a plastic vessel (eq 31).[43] On the contrary, in a borosilcate glass vessel, the tetrafluoroborate complex is obtained (eq 31).[43]

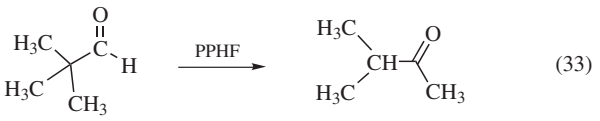




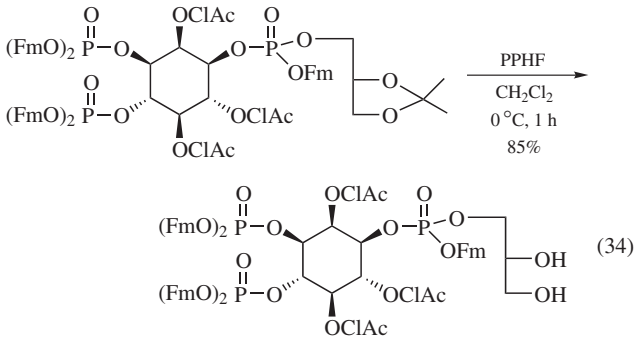


Acid-catalyzed Reactions. As a typical ionic liquid, PPHF is a convenient medium and serves as HF equivalent (Bronsted acid catalyst) with decreased volatility. Olah, Prakash, and co-workers reported that PPHF showed excellent catalytic performance in the isobutane–isobutylene alkyaltion reactions giving excellent yields of high octane alkylates (eq 32).[44] PPHF is also able to provide ample acidity for complete isomerization of pivalaldehyde to methyl isopropyl ketone (eq 33).[45] Ionic hydrogenation of benzylic ketones to their respective hydrocarbons were also achieved using triethylsilane and PPHF.[46]





Deprotection Reactions. Acetals, ketals, and silyl ethers can be smoothly cleaved by the action of PPHF.[47–50] For instance, the isopropylidene acetal in the inositol derivative was efficiently cleaved with 40 equivalent of PPHF to afford quite unstable diol product in 85% yield (eq 34), suppressing the migration and decomposition of the phosphate functionality.[47]



Related Reagents. Several applications of $Et_3N{\cdot}3HF$ and melamine·$(HF)_x$ have been mentioned above. In addition, 2,4,6-trimethylpyridine·$(HF)_x$ [*45725-47-1*] is useful since it is a commercially available solid melting at 90 °C. A polymer-supported agent containing about 35–40% HF, poly[4-vinylpyridinium poly (hydrogen fluoride)], is also available.[17]

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