

Production of ^{18}F -Labeled Radiopharmaceuticals

Part 1
(PET radiochemistry lecture #4)

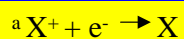
Contents of Lecture

- Properties of fluorine
- Production of fluorine-18
- Classical radiofluoridation methods
- ‘Electrophilic’ radiofluorination chemistry
 - labeling agents
 - labeling chemistry

Some Properties of Fluorine

- Electronic

	H	F	Cl	Comment on F
Electronic configuration	1s ¹	...2s ² 2p ⁵	..3s ² 3p ⁵	More electrons than H! F is isoelectronic with OH
Electronegativity (Pauling)	2.1	4.0	3.0	Major effects on neighboring groups (<i>p</i> K _a and reactivity)
Electron affinity (kJ/atom) ^a	73	328	349	e-pair repulsions important with F!
Ionisation energy (kJ/g atom) ^b	1260	1612	1200	F ⁺ less likely than X ⁺



Some Properties of Fluorine

- Steric

	H	F	Cl	Comment on F
Atomic radius (Å)	0.53	0.42	0.79	F similar to H
Van der Waal's radius (Å)	1.20	1.47	1.75	F intermediate

Some Properties of Fluorine

- Bonding

	H	F	Cl	Comment on F
Bond energies of C-X (kJ/mole) ^a	400	464	~ 320	Greater thermal stability
Bond lengths of C-X (Å) ^b	1.091	1.317	1.766	Steric effect less important with F than Cl
H-bonding	√	√	X	F may mimic OH
Preference as a leaving group	H ⁺	F ⁻	Cl ⁻	Contrasting chemistry

^a For CX₄

^d Covalent radii in CX₄

Properties of Fluorine

- Lipophilicity

	H	F	Cl	Comment on F
Alkyl-C-X (ΔlogP)	0.23	-0.38	0.06	F not lipophilic
Aryl-C-X (ΔlogP)	0.23	0.37	0.94	F not very lipophilic

LogP = log of partition coefficient (P) between octanol and water

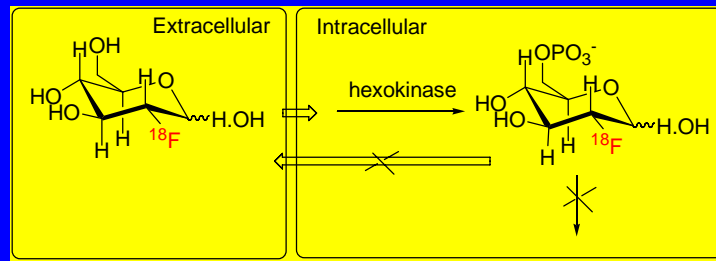
Decay Characteristics of ^{18}F

^{18}F decay:	96.9% by β^+ -emission 3.1% by EC
Decay product:	^{18}O
Half-life:	109.8 min
Maximal positron energy:	0.635 MeV
Maximal positron range:	2.4 mm in water

Why is Fluorine-18 Useful for Imaging?

- Half-life of ^{18}F allows the study of longer processes than ^{11}C
- The positron range is shorter than for ^{11}C
- Aryl C–F bonds are generally stable *in vivo*
- Many drug molecules contain F, and are possible candidates for isotopic labeling, and for radioligand or radiotracer development
- Compounds may be labeled by adding groups containing ^{18}F (non-isotopic labeling)
- A mono-fluoro derivative of an endogenous compound may pass as a steric equivalent *in vivo*, to the extent that it is accepted as a substrate by the first enzyme encountered on its metabolic pathway

[¹⁸F]2-Fluoro-2-deoxy-D-glucose (FDG)

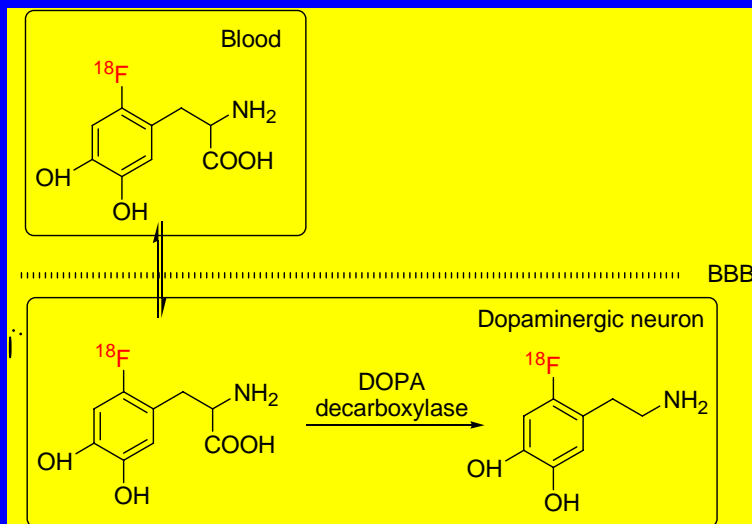


- FDG mimics endogenous glucose in that it is susceptible to phosphorylation by hexokinase
- However, unlike glucose-6-phosphate, the generated 2-fluoro-glucose-6-phosphate resists further enzymatic transformation and so becomes entrapped intracellularly
- FDG is therefore widely used to measure regional glucose metabolism with PET

[¹⁸F]L-6-Fluoro-DOPA (FDOPA)

- FDOPA mimics the anti-Parkinsonian drug, L-DOPA
- FDOPA is taken up into brain dopaminergic neurons, and is decarboxylated
- Placement of the ¹⁸F in the remote 6 position has least affect on the pK_a of the OH groups, and hence the radiotracer is handled by the decarboxylase enzyme in a very similar manner to the parent drug, L-DOPA
- FDOPA is widely used in PET neurological studies to mark dopaminergic neurons

$[^{18}\text{F}]L\text{-}6\text{-Fluoro-DOPA (FDOPA)}$ - Neuronal uptake



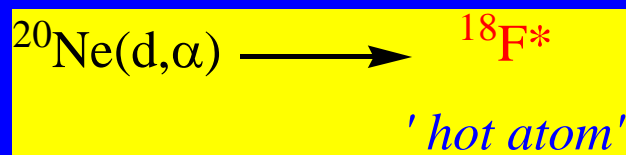
Data for Some Important Reactions Producing ^{18}F

Reaction	Target isotope (%)	Threshold energy (MeV)	Maximal cross section (mb)	Energy at maximal cross section (MeV)	Calculated thick target yield at saturation (GBq/ μA)
$^{16}\text{O}(^3\text{He},p)^{18}\text{F}$ plus $^{16}\text{O}(^3\text{He},n)^{18}\text{Ne}^{\alpha}$	99.76	0	~ 400	~ 8	1.35 ($E_{^3\text{He}} = 35 \text{ MeV}$)
$^{16}\text{O}(\alpha,pn)^{18}\text{F}$	99.76	23.2	~ 136	36	1.00 ($E_{\alpha} = 40 \text{ MeV}$)
$^{18}\text{O}(p,n)^{18}\text{F}$	0.205	2.5	~ 700	5	4.07 ($E_p = 8 \text{ MeV}$) 8.88 ($E_p = 16 \text{ MeV}$)
$^{20}\text{Ne}(d,\alpha)^{18}\text{F}$	90.5	0	~ 230	6	1.89 ($E_d = 8 \text{ MeV}$) 2.81 ($E_d = 10 \text{ MeV}$)

α ^{18}Ne Decays to ^{18}F with a half-life of 1.67 s

Production of CA [^{18}F]Fluorine (1)

- By deuteron irradiation of neon-0.1% fluorine

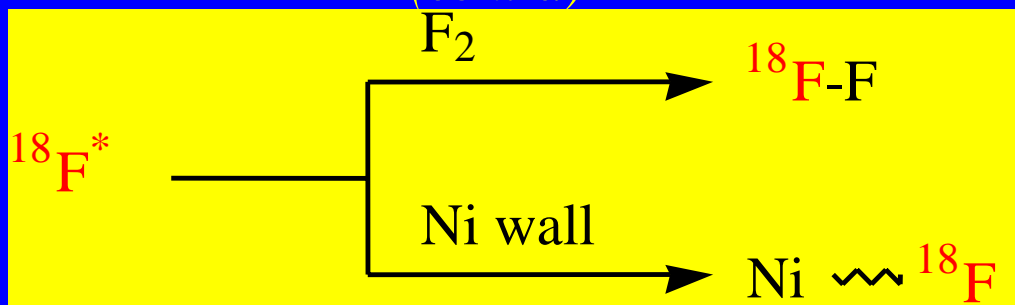


- Deuteron irradiation of neon with added fluorine ($\sim 0.1\%$ v/v) at a pressure up to 25 bar in a nickel target gives CA [^{18}F]fluorine
- High beam currents (*e.g.* 50 μA) of 10 MeV deuterons
or
- low beam currents (*e.g.* 20 μA) of 17 MeV deuterons give useful activities

Production of CA [^{18}F]Fluorine (1)

- By deuteron irradiation of neon-0.1% fluorine

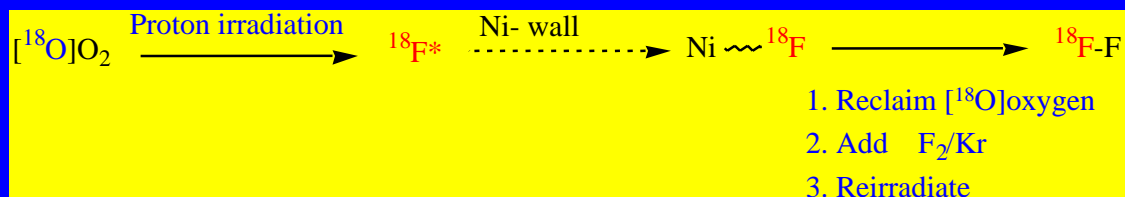
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- Nucleogenic ^{18}F ($^{18}\text{F}^*$) may exchange with added fluorine or diffuse to the target wall to be adsorbed as nickel fluoride
- $> 0.1\%$ fluorine (60–250 μmol) is needed for efficient exchange
- Monel or nickel targets, passivated with fluorine (1%) during irradiation, give good recovery ($\sim 70\%$) of radioactivity as [^{18}F]fluorine

Production of CA [^{18}F]Fluorine (2)

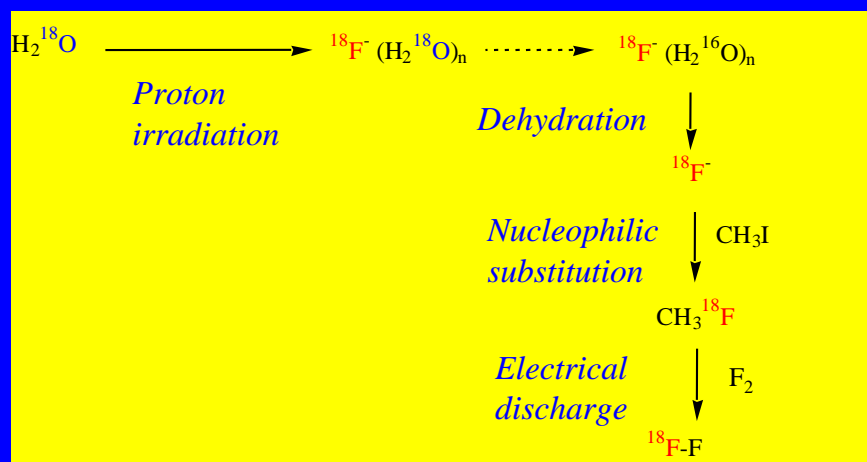
- Via proton irradiation of ^{18}O -enriched oxygen



- Proton irradiation of [^{18}O]oxygen in a nickel target, followed by cryogenic recovery of the precious target material, leaves ^{18}F attached to the target walls
- Re-irradiation of the target filled with a noble gas plus fluorine gives CA [^{18}F]fluorine
- This process gives greater activity and specific radioactivity than the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ reaction; ~ 60% of the radioactivity is recovered with only 30 μmol of added fluorine.

Production of CA [^{18}F]Fluorine (3)

- Via proton irradiation of ^{18}O -enriched water

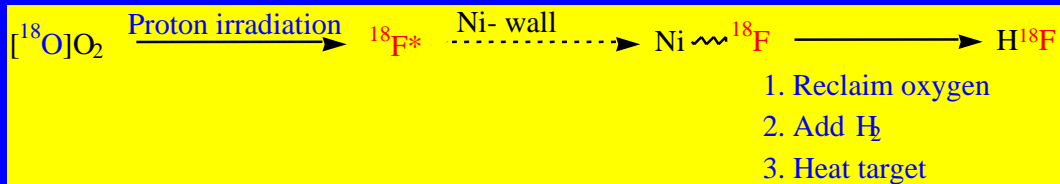


- [^{18}F]Fluorine can be produced at a high CA specific radioactivity (~ 20 GBq/ μmol ; 500 mCi/ μmol) from NCA [^{18}F]fluoride
- The final stage involves an electrical discharge for exchange of fluorine-18 between [^{18}F]fluoromethane and a trace of added fluorine

Production of CA *'^[18F]Hydrogen Fluoride'*

- ¹⁸F can be produced by the ²⁰Ne(d,α)¹⁸F reaction on Ne containing 15% H₂ in Inconel targets
- To retrieve the radioactivity in anhydrous form the target must be heated and flushed with a noble gas
- However, reproducible and efficient recovery is notoriously difficult to achieve unless carrier is generated within the target by some means, for example by adding CF₄ to the target gas
- The recovered radioactivity is putatively anhydrous [¹⁸F]HF, but may, on the basis of its thermal properties, be some other chemical form, such as [¹⁸F]NH₄F

Production of NCA *'^[18F]Hydrogen Fluoride'*



- NCA "anhydrous [¹⁸F]hydrogen fluoride" may be produced by the ¹⁸O(p,n)¹⁸F reaction on ¹⁸O-enriched oxygen, followed by cryogenic recovery of the target material and recovery of the radioactivity from the target by heating during a hydrogen sweep

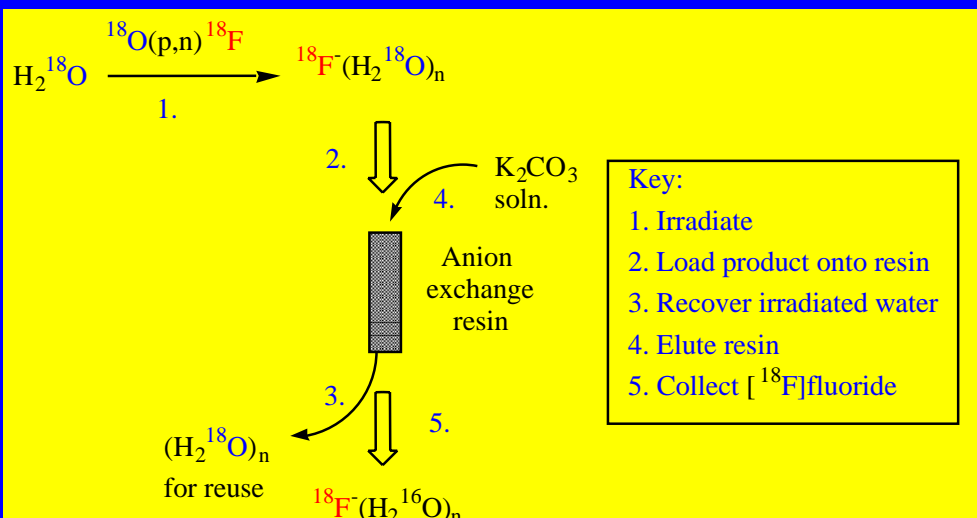
NCA [^{18}F]Fluoride (1)

- By proton irradiation of ^{18}O -enriched water

- Targets may use < 1 mL of ^{18}O -enriched water
- Target materials containing Cr, Fe or Co are undesirable, as they possibly produce unreactive [^{18}F]metal fluorides, but Ni, Ti and Ag are acceptable
- Though ^{18}O -enriched water is expensive, it can be re-used after distillation or after recovery of the [^{18}F]fluoride by, for example, adsorption on an anion exchange column
- The process is intrinsically high yielding
- Very high specific radioactivities can be achieved from fluoride-free water

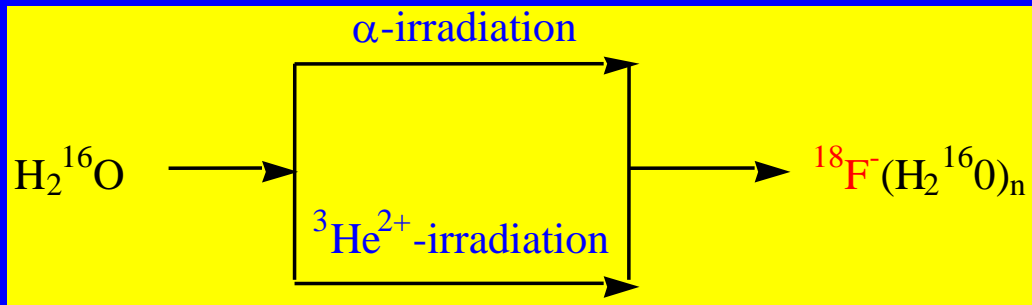
NCA [^{18}F]Fluoride (1)

- By proton irradiation of ^{18}O -enriched water
(cont'd)



NCA [^{18}F]Fluoride (2)

- By irradiation of natural water



- NCA [^{18}F]fluoride can be produced by irradiating water with high energy (> 24 MeV) α -particles, or, for higher yield, lower energy $^3\text{He}^{2+}$ ions.
- These processes are low yielding relative to the proton irradiation of oxygen-18 and are seldom used.

Some Typical Production Parameters for ^{18}F

Production reaction	Irradiation conditions (MeV, μA , min)	Main product(s)	Typical yield (GBq)	Typical specific radioactivity (GBq/ μmol)	
d on ^{20}Ne (0.1% F_2)	14, 15, 120	^{18}F -F	13.6	~ 0.2	(CA)
d on ^{20}Ne (15% H_2) ^a	11.25, 25, 60	H^{18}F	9.25		(NCA)
d on ^{20}Ne (6.7% H_2) ^b	11.25, 25, 60	^{18}F _{aq.}	9.25	>370	(NCA)
^3He on H_2^{16}O	36, 40, 60	^{18}F _{aq.}	14.8	138	(NCA)
α on H_2^{16}O	30, 35, 60	^{18}F _{aq.}	1.48		(NCA)
p on H_2^{18}O	15, 20, 60	^{18}F _{aq.}	44	370	(NCA)
p on ^{18}O -O	19, 20, 20	^{18}F -F	44		(CA)

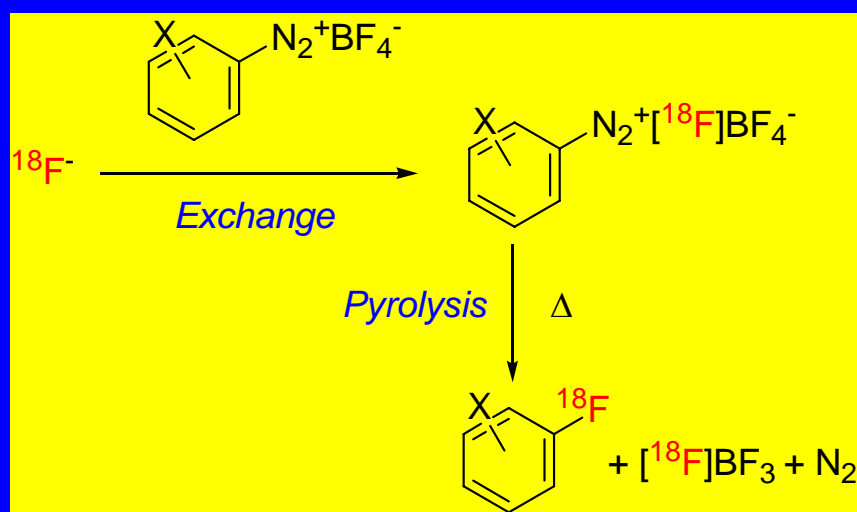
^a Activity recovered by heating target while flushed with helium.

^b Activity recovered by washing evacuated target with water.

Classical Methods for Radiofluorination

- Balz-Schiemann Reaction
- Modified Balz-Schiemann Reaction
- Wallach-type Reaction

Balz-Schiemann Reaction

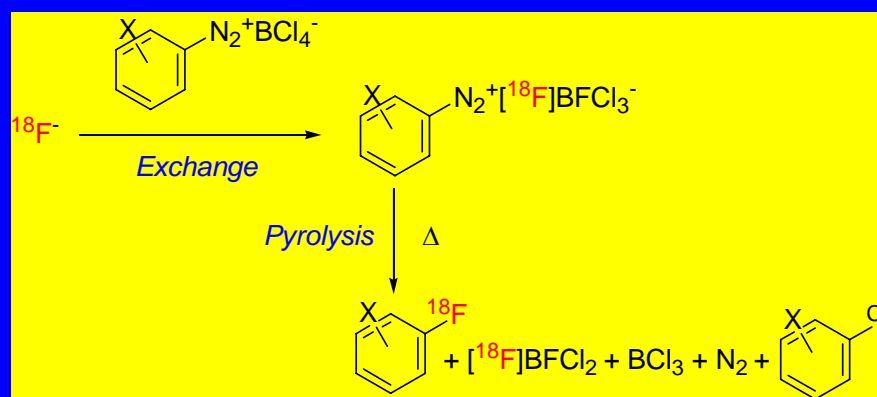


- An ^{18}F aryldiazonium tetrafluoroborate is prepared by exchange of tetrafluoroborate with ^{18}F fluoride
- This salt is then decomposed pyrolytically

Balz-Schiemann Reaction (cont'd)

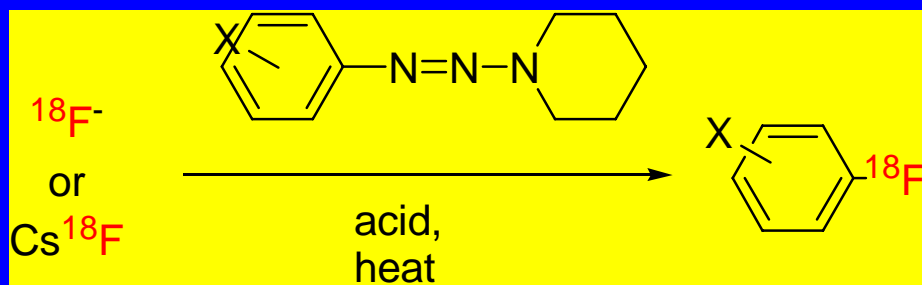
- The radioactivity is partitioned equally between the F atoms of the desired [^{18}F]fluoroarene and the byproduct, [^{18}F]boron trifluoride
- The process is therefore CA with a maximal theoretical yield of 25%
- Many compounds have been labeled in this manner, particularly amino acids such as L-phenylalanine, L-tryptophan, L-tyrosine and L-DOPA
- Yields are often much lower than theoretical
- The method is regiospecific; all isomers of the amino acids can be prepared
- The method is quite tolerant of functionality

Modified Balz-Schiemann Reaction



- An [^{18}F]aryldiazonium fluorotrichloroborate is prepared by exchange of tetrachloroborate salt with [^{18}F]fluoride
- This salt is then decomposed pyrolytically
- The process is NCA

Wallach-type Reaction



- The decomposition of an aryltriazene by [^{18}F]hydrogen fluoride or anhydrous [^{18}F]caesium fluoride in acidic media, is used to prepare [^{18}F]fluoroarenes
- Piperidinylaryltriazenes are often used
- The method is regiospecific and NCA
- An intermediate in the reaction scavenges all available anions giving various products including hydrogen-substituted product, leading to difficult separation
- Yields tend to be very low except for simple substrates

'Electrophilic' Radiofluorination

- 'Electrophilic' – its meaning with respect to fluorine

- On thermodynamic grounds, the free electrophilic species F^+ is not recognised to exist in solution, even transiently
- However, F bound to an electron-withdrawing group is often regarded as a source of F^+ , since such compounds often lead to the products expected from electrophilic addition or substitution in olefins and arenes, respectively
- These reactions are frequently classed as 'electrophilic' even though this is not always justified by their possibly complex mechanisms
- For convenience the term 'electrophilic' is used here to denote fluorinations giving the products expected from formally 'electrophilic-type' additions or substitutions

Some 'Electrophilic' Radiofluorination Agents

[¹⁸ F]Fluorine	(¹⁸ F-F)	CA
[¹⁸ F]Halogen fluorides	(' ¹⁸ F-I'; ' ¹⁸ F-Br')	NCA
[¹⁸ F]Xenon difluoride	(¹⁸ FXeF)	CA
[¹⁸ F]N-F compounds	(R ₂ N- ¹⁸ F)	CA
[¹⁸ F]Perchloryl fluoride	(ClO ₃ ¹⁸ F)	CA
[¹⁸ F]Acetyl hypofluorite	(MeCOO ¹⁸ F)	CA

Fluorine (F₂) - Properties

- Fluorine participates in 'electrophilic' additions and substitutions but is also extremely and violently reactive in oxidations and non-selective free radical reactions
- The low solubility of fluorine in many solvents can result in reactions at the liquid-gas interface
- This phenomenon and the exothermic nature of these reactions can lead to local hot spots and unwanted side reactions
- Any degree of regioselectivity in the direct fluorination of organic compounds is therefore difficult to achieve

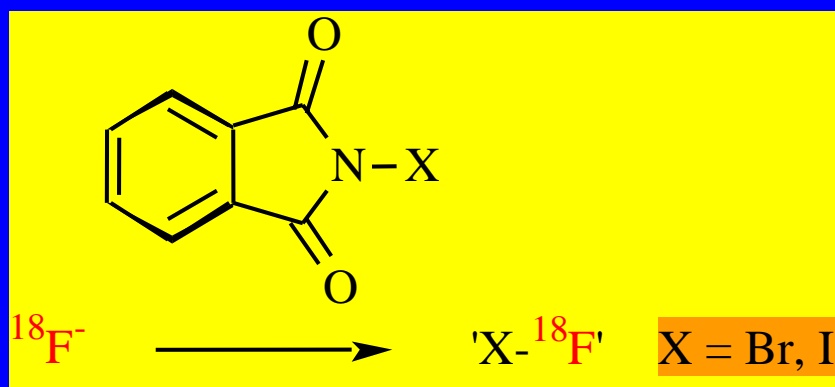
[¹⁸F]Fluorine (¹⁸F-F)

- Properties

- [¹⁸F]Fluorine from the ²⁰Ne(d,α)¹⁸F reaction is already diluted about 500-fold with neon, which renders it sufficiently controllable for some low temperature applications
- Nonetheless, radiofluorinated mixtures are generally obtained and radiochemical yields tend to be low
- Furthermore, only a limited range of adequately resistant solvents, having generally poor capacity for fluorine, may be employed.
- Examples are freon, dichloromethane, anhydrous hydrogen fluoride, trifluoroacetic acid, glacial acetic acid and water

'[¹⁸F]Halogen Fluorides'

- Preparation



- '[¹⁸F]Halogen fluorides' (Br¹⁸F, I¹⁸F) have been prepared *in situ* from NCA [¹⁸F]fluoride and halogenating agents, such as *N*-bromosuccinimide and *N*-iodosuccinimide.

[¹⁸F]Xenon Difluoride

- Preparation

By direct reaction of xenon with fluorine



- Radiochemical yield is 43-70%

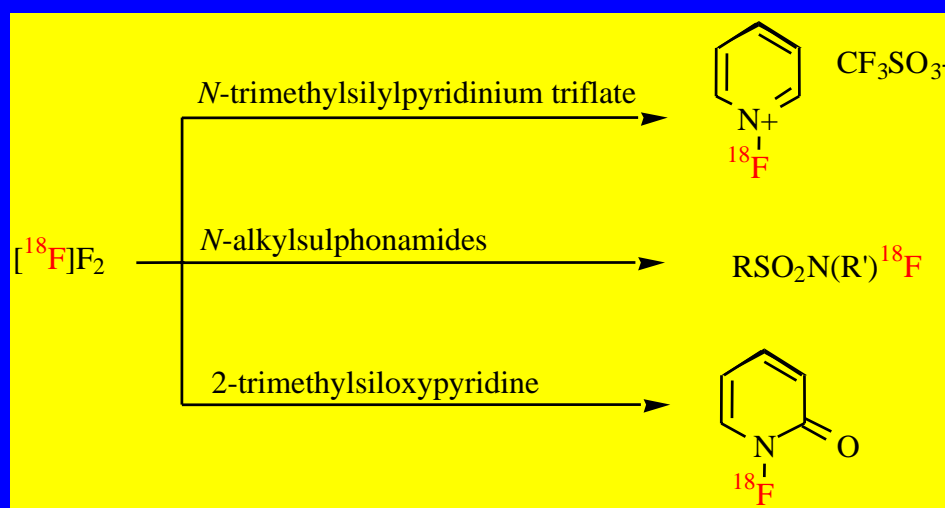
By 'exchange'



- High radiochemical yield (90%) can be obtained
- Specific radioactivity is low

[¹⁸F]N-F Compounds

- Preparation



- N -fluoro-2-pyridone, N -fluoro-pyridinium triflate and N -fluoro-trifluoromethane-sulphonamide have been labeled in good yield (~50%)
- Little radiochemistry has so far been described with these agents

[¹⁸F]Perchloryl Fluoride

- Preparation



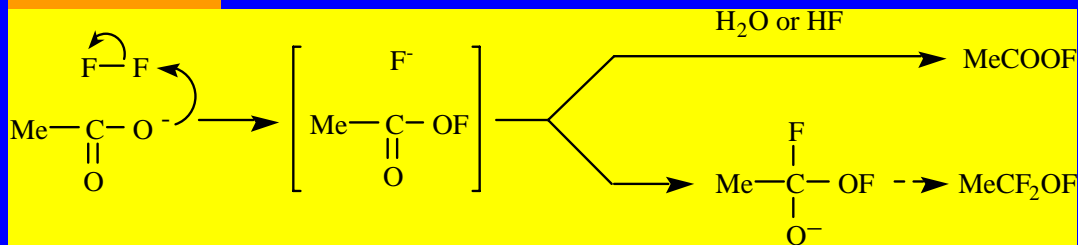
- Radiochemical yield is 23%
- Virtually no usage

[¹⁸F]Acetyl Hypofluorite

- Preparation



Mechanism

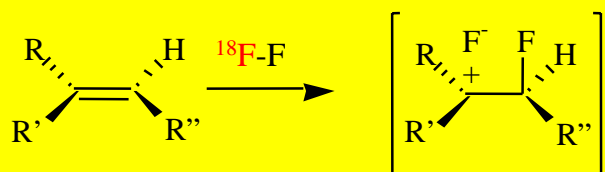


- Reactions of [¹⁸F]F₂ with a potassium acetate-acetic acid complex or sodium acetate trihydrate give near theoretical radiochemical yields (50%)
- [¹⁸F]Acetyl hypofluorite is soluble in a wide range of inert solvents (*e.g.* CF₃CO₂H, AcOH, MeOH, MeNO₂, DMF, dioxane, CH₂Cl₂, CHCl₃, CFC₃, CCl₄, hexane)
- Acetyl hypofluorite may be regarded as a 'taming carrier' for fluorine

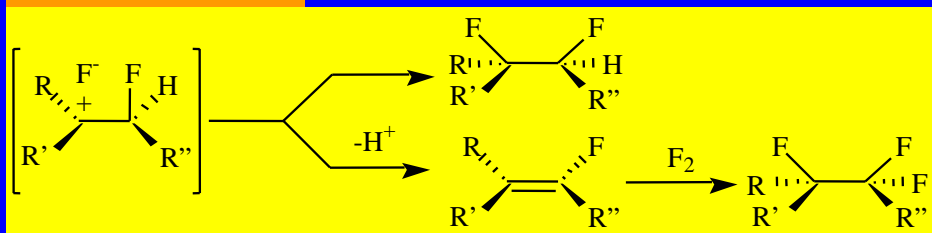
'Electrophilic' Addition

- [^{18}F]Fluorine to alkenes

Syn addition



Further reactions

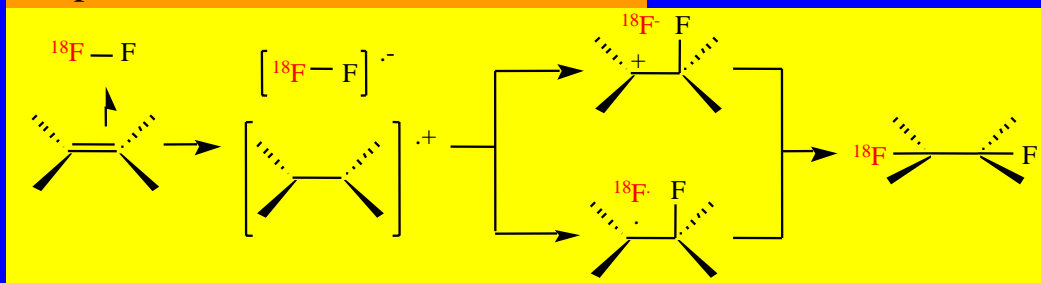


Reaction works best if R or R' is electron-donating and can stabilise a positive charge

'Electrophilic' Addition

- [^{18}F]Fluorine to alkenes (cont'd)

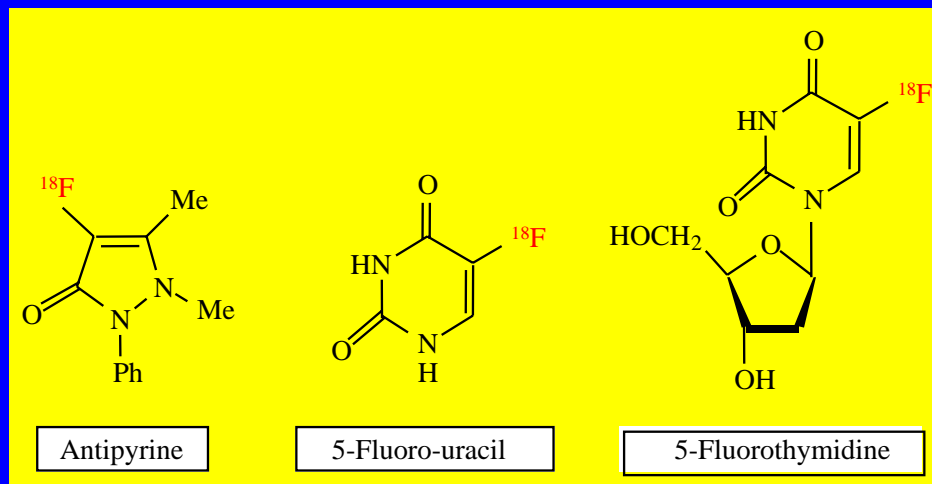
Proposed electron transfer mechanism



- This mechanism perhaps accounts better for product distribution in many reactions, without invoking an improbable heterolytic scission of the F-F bond

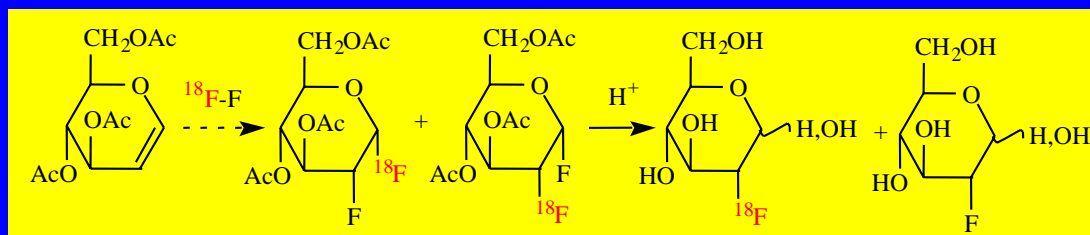
'Electrophilic' Addition

- Some radiopharmaceuticals prepared by addition of [^{18}F]fluorine to alkenes



'Electrophilic' Addition

- Preparation of FDG by [^{18}F]fluorine addition

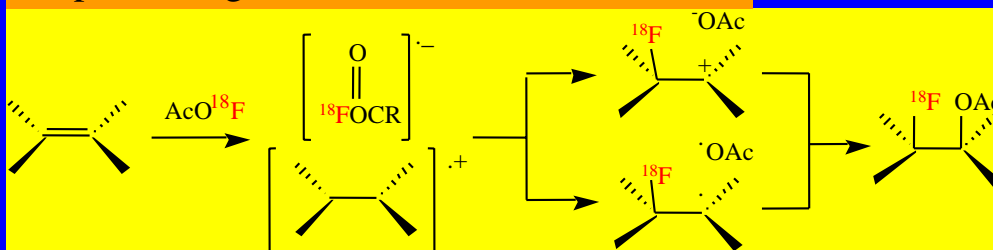


- *Syn* addition to the least hindered face of the substrate occurs preferentially
- Hence, FDG is produced in ninefold greater yield than its 2-epimer, [^{18}F]2-fluoro-2-deoxy-D-mannose
- Radiochemical yield is 10%

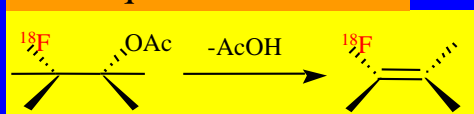
'Electrophilic' Addition

- [^{18}F]Acetyl hypofluorite to alkenes

Proposed single electron transfer mechanism

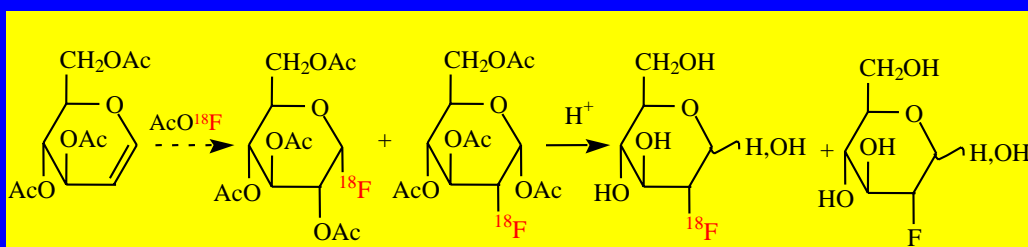


Subsequent elimination



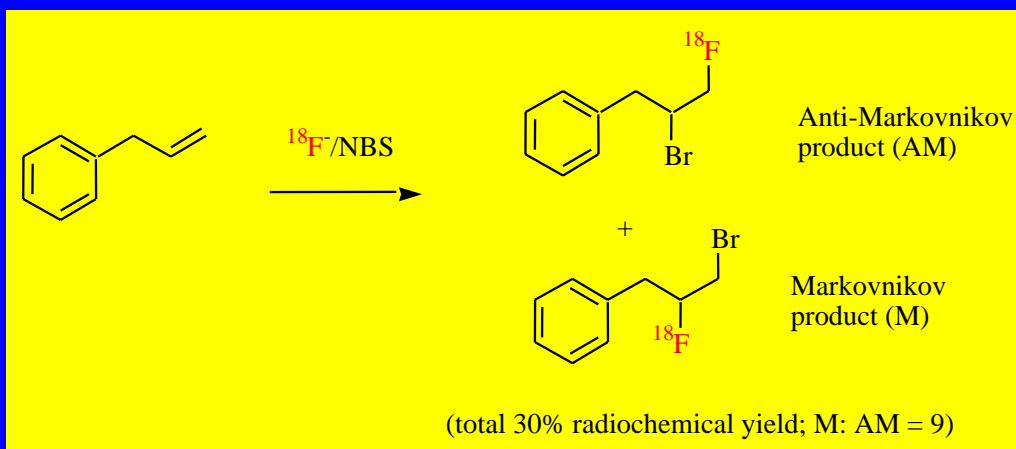
'Electrophilic' Addition

- Preparation of FDG by [^{18}F]acetyl hypofluorite addition



- The fluorination of 3,4,6-*tri-O*-acetyl-D-glucal in freon with [^{18}F]acetyl hypofluorite, rather than [^{18}F]fluorine, followed by hydrolysis, doubles the radiochemical yield of FDG to 20% and reduces the yield of the epimer byproduct to 1%

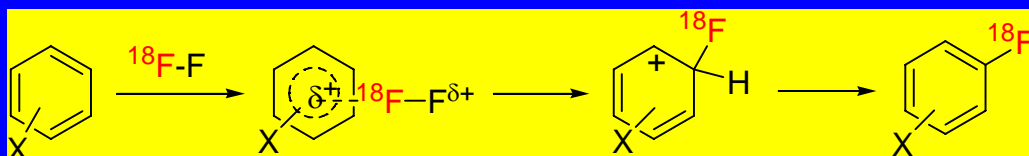
[¹⁸F]XF Addition to Alkenes



- The Markovnikov addition product dominates over the anti-Markovnikov product
- The reaction can be performed CA or NCA

Aromatic Radiofluorination (1)

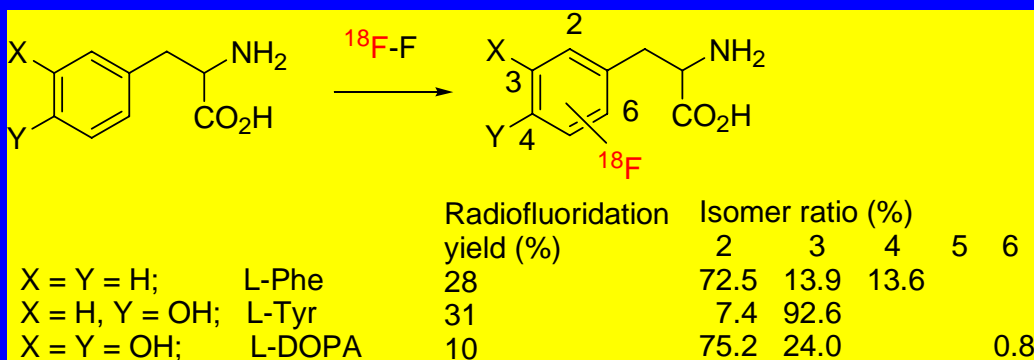
- By [¹⁸F]fluorine - mechanism



- Some arenes can be directly fluorinated in low but useful yields
- For low temperature ($-78\text{ }^{\circ}\text{C}$) additions of dilute fluorine (0.76% in N_2) to a large excess of substituted benzene, the substitution pattern is as expected for electrophilic substitution and supports the proposal of a polar substitution mechanism (above)

Aromatic Radiofluorination (2)

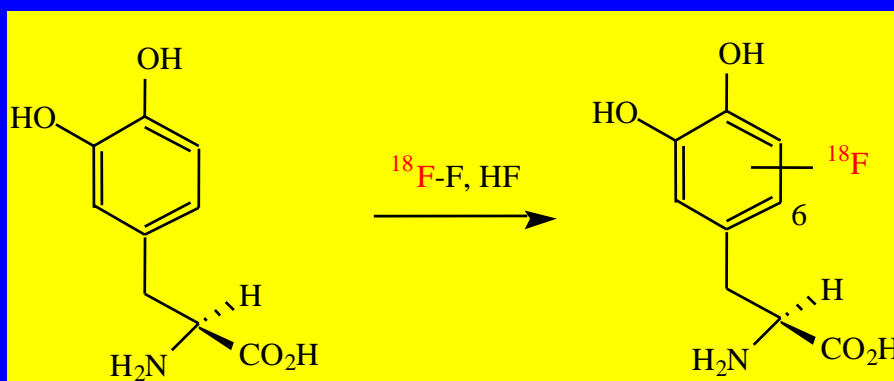
- By [^{18}F]fluorine in trifluoroacetic acid



- Direct treatment of the amino acids in trifluoroacetic acid with [^{18}F]fluorine at 0°C leads to substitution predominantly *ortho* to the strongest electron-donating group

Aromatic Radiofluorination (3)

- By [^{18}F]fluorine in anhydrous hydrogen fluoride

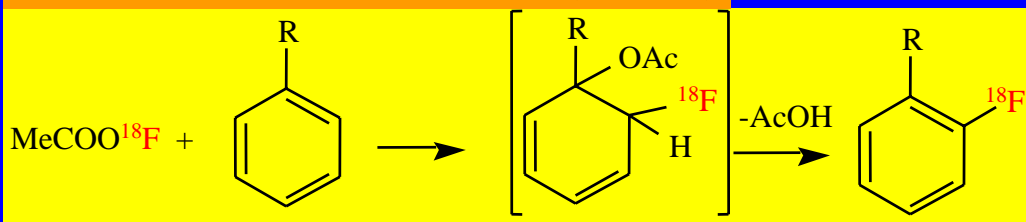


- Direct radiofluorination of L-DOPA in anhydrous HF gives ~ 25% of fluoroarenes with the 2-, 5- and 6-fluoro isomers of L-DOPA in the ratio of 7: 1: 12
- Recycle HPLC gives pure FDOPA in 3% radiochemical yield
- Radiochemical yield is enhanced 3-fold in the presence of BF_3

Aromatic Radiofluorination (4)

- By [^{18}F]acetyl hypofluorite

Addition-elimination mechanism (in freon)

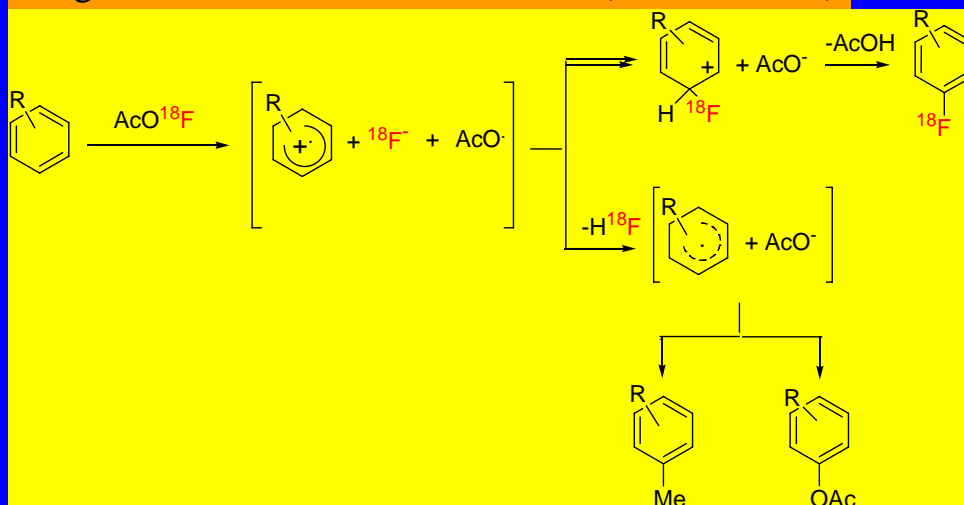


- Acetyl hypofluorite reacts directly with arenes, but only well with those that are activated by an electron-donating substituent, especially alkoxy, acetylamino and hydroxy
- *Ortho* fluorination generally occurs in strong preference to *para* fluorination.
- An addition-elimination mechanism has been proposed to account for the dominance of *ortho* substitution in freon

Aromatic Radiofluorination (4)

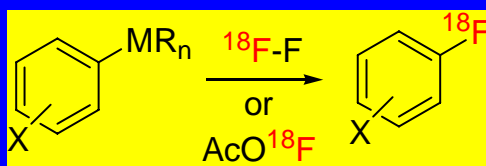
- By [^{18}F]acetyl hypofluorite (cont'd)

Single electron transfer mechanism (in acetic acid)



[¹⁸F]Fluorodemallation

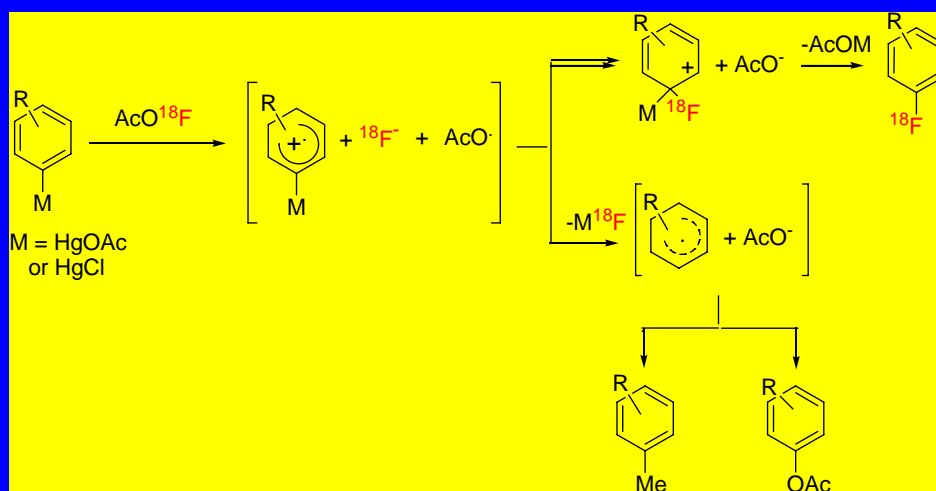
- *At aryl carbon-metal bonds*



- *Ips*o displacement of a metal (M) from a metalloarene by [¹⁸F]fluorine or [¹⁸F]acetyl hypofluorite is a regioselective route to many [¹⁸F]fluoroarenes
- M may be Sn, Si, Ge or Pb from Group IV or Hg
- Generally, fluorodemallation is fast, high yielding, regioselective and facile, even on rings containing deactivating substituents
- The success of this reaction is derived from the weakness and greater polarity of the aryl C–M bond relative to the aryl C–H bond

[¹⁸F]Fluorodemallation

- *Mechanism proposed for fluorodemercuration*



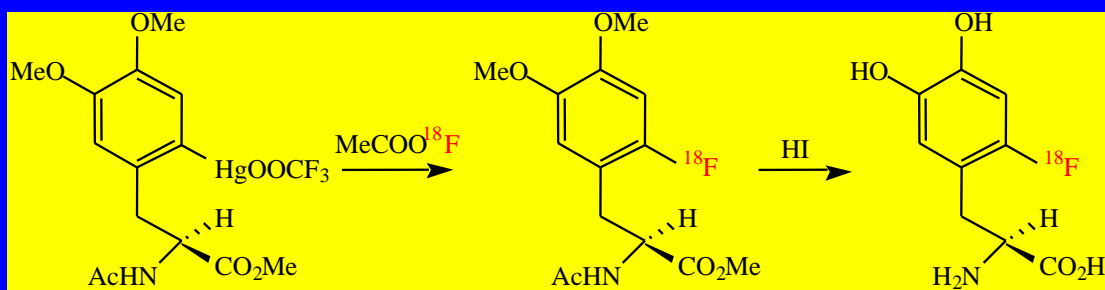
[¹⁸F]Fluorodemallation

- General features

- Reactivity is aryl-Hg ~ aryl-Sn > aryl-Ge ~ aryl-Si
i.e. in inverse order of aryl C–M bond strength.
- Fluorodemercuration with acetyl hypofluorite is *regiospecific*
- Aryl-tri-*n*-butyltins treated with [¹⁸F]fluorine or [¹⁸F]acetyl hypofluorite give *ipso*-substituted [¹⁸F]fluoroarenes in similarly high radiochemical yield (measured from [¹⁸F]fluorine).
- Electron-withdrawing substituents (*e.g.* 4-CF₃, 4-CN) reduce the yield of ring radiofluorination in aryltrimethyl-tin, -germanium and -silicon compounds

[¹⁸F]Fluorodemallation

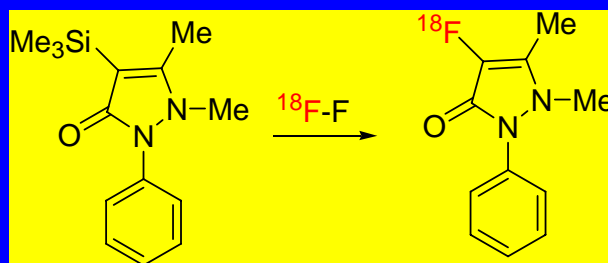
- Synthesis of FDOPA



- FDOPA can be isolated in 12% radiochemical yield (decay corrected)
- Similar radiosyntheses have been devised with alkyl-tin and alkyl-silicon leaving groups

[¹⁸F]Fluorodemetalation

- At alkenyl-metal bonds



- Radiofluorodestannylation, though not possible at an alkyl C-Sn bond, because of the high bond strength, is possible at an alkenyl C-Sn or alkenyl C-Si bond
- The radiochemical yield in the above example is 18%

Conclusions

- The use of CA [¹⁸F]fluorine and its electrophilic derivatives, particularly [¹⁸F]acetyl hypofluorite, are the only well-established methods for introducing ¹⁸F into electron-rich arenes
- These labeling agents retain their importance mainly on this basis, despite their disadvantages of low specific radioactivity, possibility of only moderately high production and at least 50% waste of initial radioactivity