Fluorine-18 Radiochemistry

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Scholars Trained in Advanced Radiochemistry Technology

Outline

1. PET radioisotopes
2. Properties of fluorine
3. Basic principles in radiochemistry of short-lived isotopes
    i. Quantities
    ii. Specific activity
    iii. Radiolysis

4. Fluorine chemistry
    i. Source of Fluorine-18
    ii. Electrophilic and nucleophilic fluorine reagents

5. Electrophilic fluorination ("F^+")
6. Nucleophilic fluorination ("F^-")
    i. General workflow
    ii. Aromatic nucleophilic substitution (S_{NAr})
    iii. Aliphatic nucleophilic substitution (S_{N2})
        i. Mechanism
        ii. Solvents
        iii. Leaving groups, activating groups

PET Radioisotopes

1. Moderate half-lives
2. High specific activity

Table 1. Comparative physical properties of the most common used radionuclides

Radionuclide	Half-life	Decay [a]	Maximum specific activity [b] (GBq mol^{-1})	mg GBq^{-1}	mg Ci^{-1}
^{11}C	20.4 min	β^+ (99 %)	3.4×10^{11}	3.5 10^{-8}	1.2×10^{-6}
^{13}N	9.96 min	β^+ (99 %)	6.9×10^{11}	2.0 10^{-8}	6.9×0^{-7}
^{15}O	2.07 min	β^+ (99.9 %)	3.4×10^{12}	4.7 10^{-9}	1.6×10^{-7}
^{18}F	109.7 min	β^+ (97 %)	6.3×10^{10}	3.0 10^{-7}	1.0×10^{-5}
^{3}H	12.3 years	β^- (100 %)	1.1×10^{6}	2.7 10^{-3}	0.1
^{14}C	5730 years	β^- (100 %)	2.3×10^{3}	6.0	224
^{125}I	60 days	γ (EC)	8×10^{7}	1.5 10^{-3}	5.8×10^{-2}
^{99m}Tc	6 h	γ (IT)	1.9×10^{10}	5.2 10^{-6}	1.9×10^{-4}

[a] EC: electron capture; IT: Isomeric Transition.
[b] Defined as the number of decay N per second and per mole.

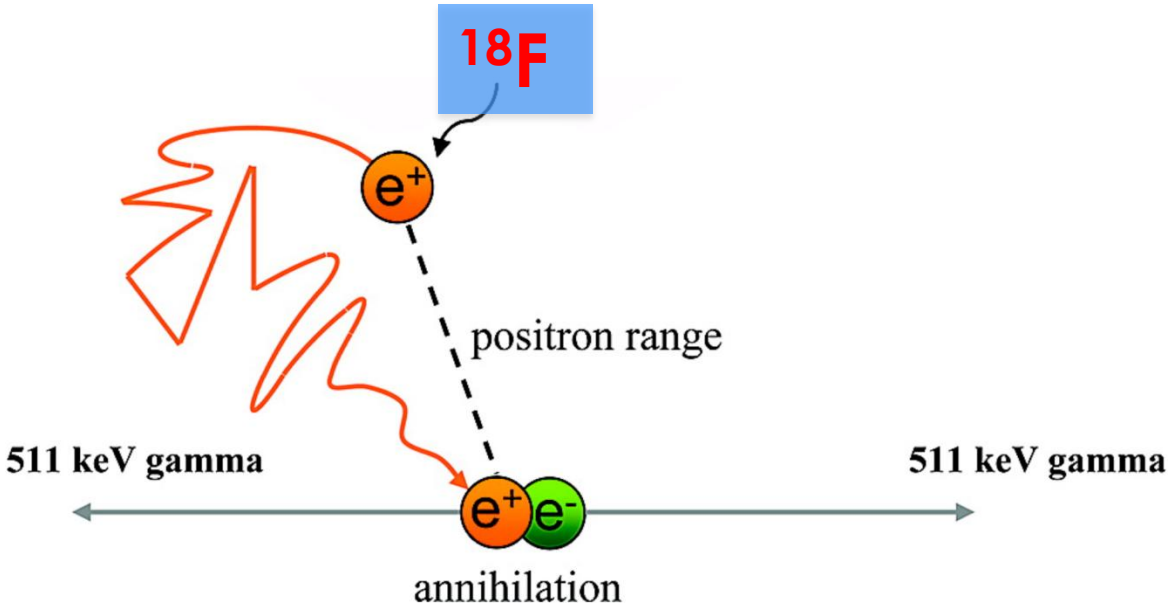
3. Low positron energy- shortest diffusion ranges < 2.4 mm

Table 5. Comparison of maximum energy and linear range of the commonly used positron emitters

Radionuclide	Maximum energy (MeV)	Maximum linear range in H_2O (mm)
^{11}C	0.96	4.12
^{13}N	1.19	5.39
^{15}O	1.72	8.20
^{18}F	0.635	2.39

M.-C. Lasne et al. Topics in Current Chemistry. 2002. 22

F18: Ideal Positron-Emitting Radionuclide



- Low positron energy and short range in tissue (high resolution)
- 97% β^+ decay
- high specific activity
- can be produced in large amount in a cyclotron (>10 Ci)
- can be labeled in high radiochemical yields for PET tracers
- acceptable radiation dosimetry for multiple studies in a patient
- allow transportation from production site to PET imaging centers ($T_{1/2}$= 109.7 min)

Slide from Clifton Shen, M248 2009

Properties of Fluorine

1. F bioisostere with O (size and electronegativity)
2. F most electronegative (highest number of protons in nucleus)

Element (X)	van der Waals radius [Å]	Electronegativity (Pauling scale)	Bond length of C–X [Å]
H	1.20	2.20	1.09
O	1.52	3.44	1.43
F	1.47	3.98	1.35

M.-C. Lasne et al. Topics in Current Chemistry. 2002. 22

3. C-F bond is the strongest and is highly polarized

Table 2 The van der Waals radii (Bondi)[6] and average C–X bond lengths of some common elements

Van der Waals radii/Å	H (1.2) Si (2.1)	C (1.70) P (1.8)	N (1.55) S (1.8)	O (1.52) Cl (1.74)	**F (1.47)**
Bond lengths/Å	C–H (1.09) C–Si (1.85)	C–C (1.54) C–P (1.84)	C–N (1.47) C–S (1.82)	C–O (1.43) C–Cl (1.77)	**C–F (1.35)**

O'Hagan et al. Chem. Soc. Rev. 2008, 37, 308-319

Hydration energy 507 kJ/moles

$F^- (H_2O)_n$

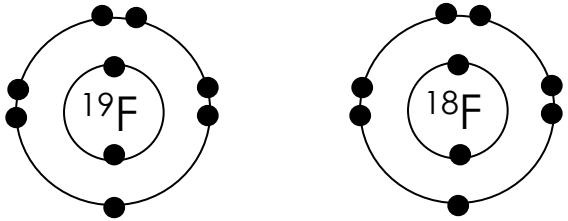
$F^- + H^{\delta+}$ → HF (bonding): 565 kJ/moles

Properties of Fluorine

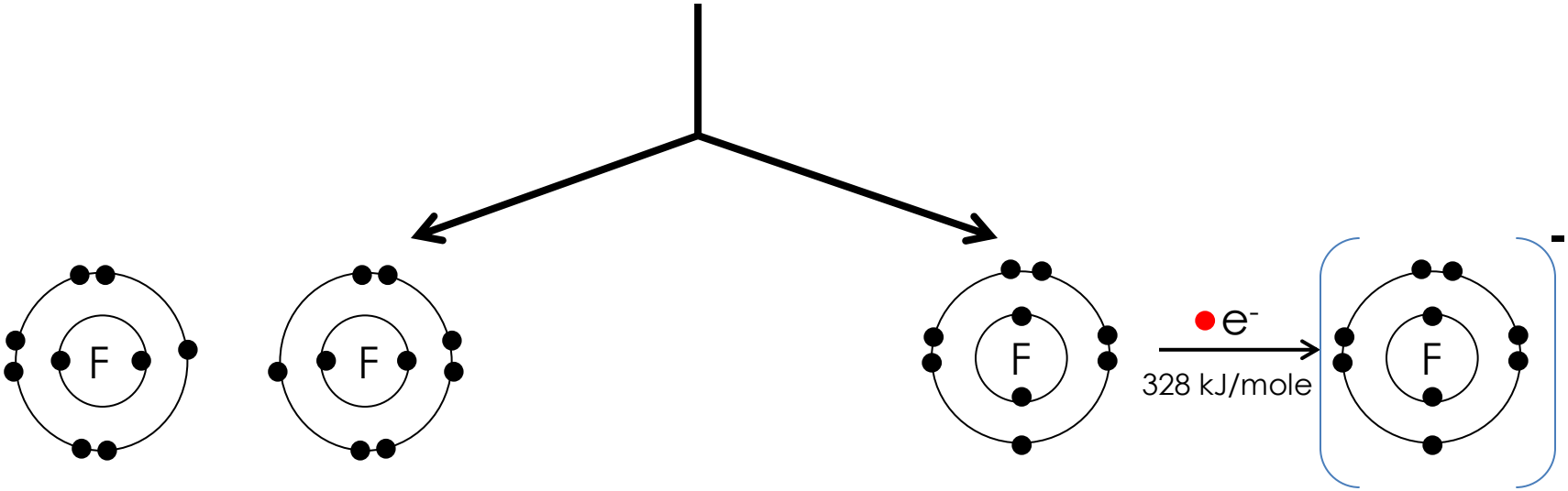
Atomic number → ($^{19}_{9}F$ *and* $^{18}_{9}F$) ← # Neutrons + Protons

Atomic mass → ($^{19}_{9}F$ *and* $^{18}_{9}F$) ← # Protons

1s2 2s2 2p5



Electron configuration→ chemical reactivity (electrons!!)



1s2 2s2 2p6 → OCTET!

("F+") F-F bond weakest (159 kJ/mole)

EXTREMELY REACTIVE

1s2 2s2 2p6 → OCTET!

("F-) Donate a pair of electron (nucleophilic) or H acceptor (base)

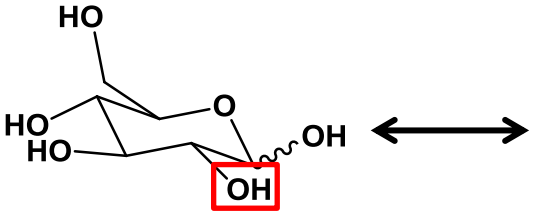
Where to Label?
i.e.: PET probe design

Fluorine ~ **H**: size and valence e$^-$ (isosteres)
~ **O**: electronegativity

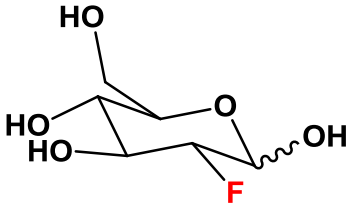
Synthetic method consideration

(1) Chemoselectivitiy and (2) regioselectivity: which carbon?

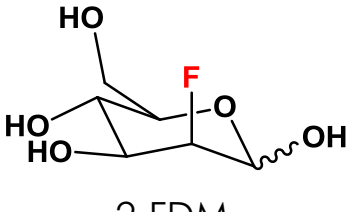
(3) Stereoselectivity: spatial orientation of F relative to other functional groups?



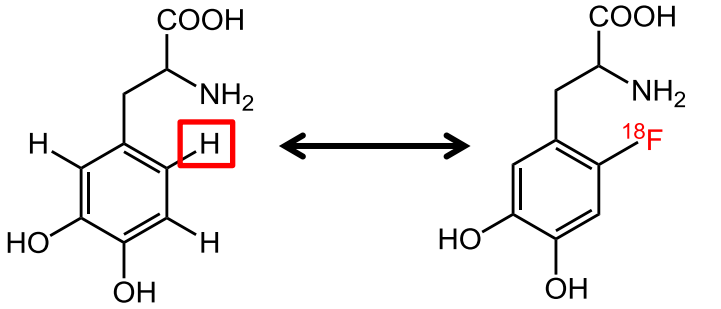
Glucose



2-FDG

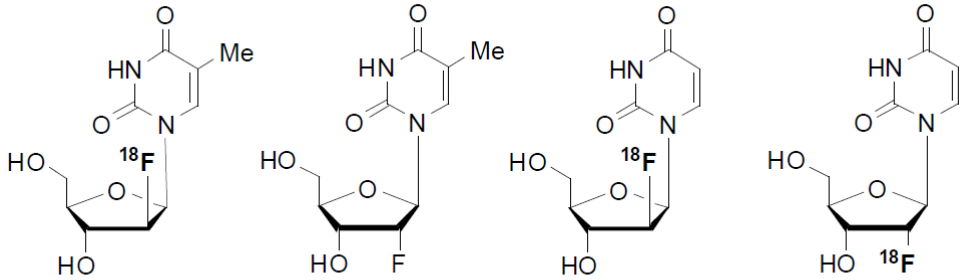


2-FDM



L-DOPA

6-fluoro-L-DOPA



38, [^{18}F]FMAU

39, FTdR

40, [^{18}F]FAU

10, [^{18}F]FUdR

Thymidine derivatives

ONLY IN RADIOCHEMISTRY

Specific Activity

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield

$$\frac{Radioactivity\ (Ci)}{Mass\ (\mu moles)}$$

Molecules of F-18

Molecules of ~~F-18~~ + F-19

Maximum theoretical SA of F-18 ion ~ 1710 Ci/µmole

F19 x20-40

In reality, SA F-18 ions ([18F]F^- /[^{18}O]H_2O] obtained from the cyclotron ~ 50-100 Ci/µmole

F19 x10-50

SA of [^{18}F]FDG = 2-5 Ci/µmole

How to measure specific activity of fluorine-18?: [^{18}F]F_2? [^{18}F]F^-?

Casella VR et al. ***1980***. J Nucl Med 21:750

Coenen et al. ***1986***, Appl Radiat Isot 37:1135

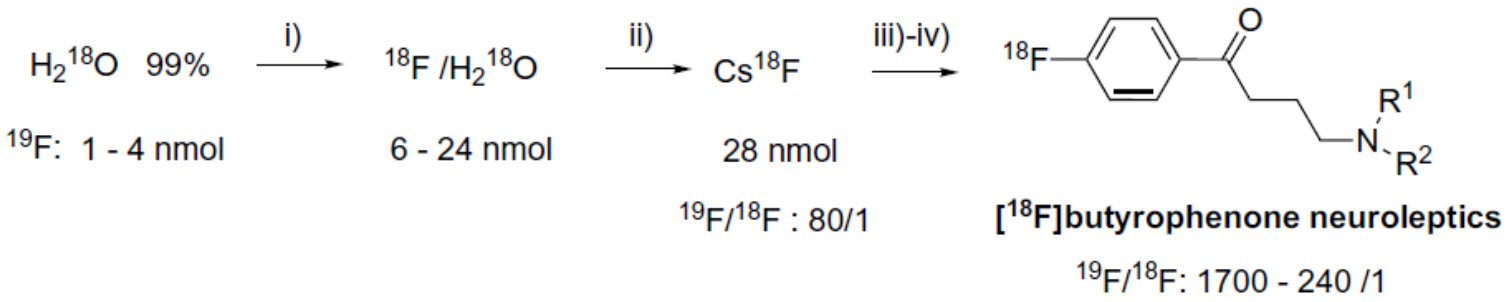
Small M. et al., Anal Chem. ***1975***. Anal Chem 47, 1801

Syntheses and Specific Activity Determinations of No-Carrier-Added Fluorine-18-Labeled Neuroleptic Drugs

Chyng-Yann Shiue, Joanna S. Fowler, Alfred P. Wolf, Masazumi Watanabe, and Carroll D. Arnett

Chemistry Department, Brookhaven National Laboratory, Upton, New York

J Nucl Med 26:181–186, 1985



Scheme 1. i) irradiation; ii) Cs_2CO_3; iii) *p*-nitrobenzonitrile, DMSO, 140 °C, 10 min; iv) cyclopropyllithium, Et_2O; v) HCl, MeOH, 110 °C, 7 min; vi) R^1R^2NH, KI, 100 °C, DMF-THF

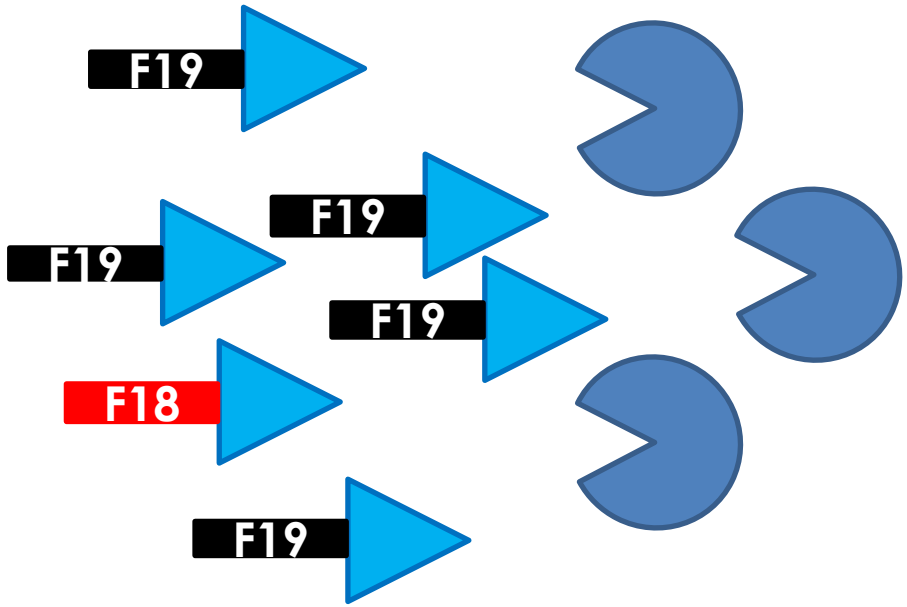
M.-C. Lasne et al. Topics in Current Chemistry. 2002. 22

Why is SA important?

For imaging receptors (cell surface receptors, brains…etc)

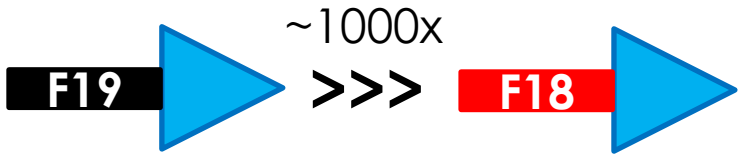
- limited number
- Irreversible binding

Fluorine-18/19 molecules



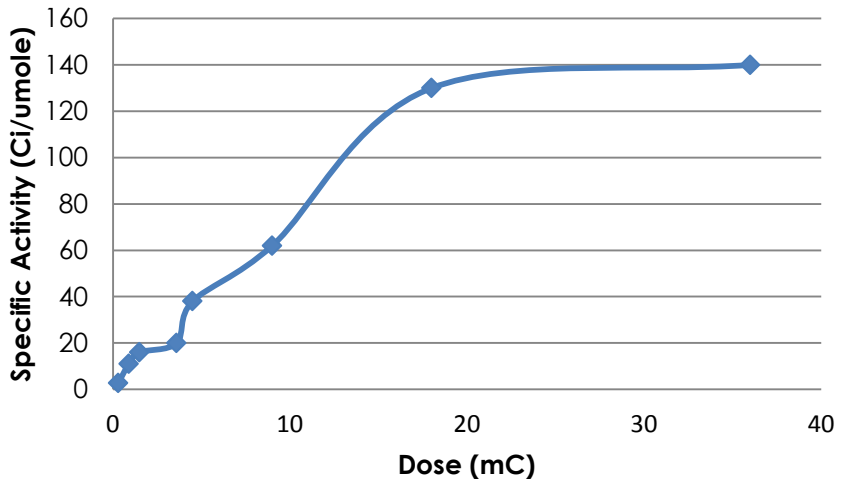
Receptors

General rule of thumb:



What affects SA of F18 ion?

1. Radioactivity, bombardment time and dose

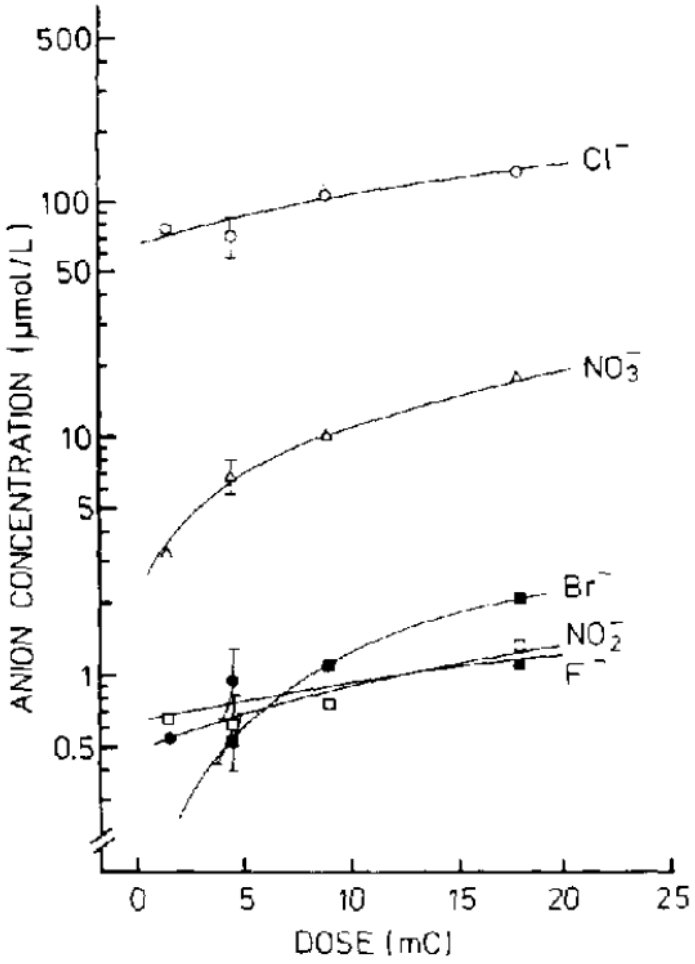


- Higher radioactivity, higher SA?

Table 1. Specific radioactivity of ^{18}F, saturation activity and activity at EOB as functions of dose and dose rate for the nuclear reaction $^{18}O(p, n)^{18}F$ (target system B, see also text)

Dose (mC)	$t_{(irr.)}$ (min)	Dose rate (μA)	$A_{(EOB)}$ (mCi)	$A_{(EOSB)}$ (mCi/μA)	Sp. act. (Ci/μmol)
0.3	5	1	3.5	114	2.7
0.9	15	1	11.6	128	11
1.5	5	5	16.1	103	16
3.0	5	10	31.5	101	—
3.6	60	1	33.9	107	20
4.5	15	5	47.3	105	38
9.0	15	10	78.0	86	62
18.0	60	5	159.1	101	130
36.0	60	10	269.3	85	140

2. Ions contamination from target



Solin O., Appl Radiat Isot. ***1988***, 39, 1065-1071

3. Contamination from materials

(a) Radiolysis in Teflon tubing and components

- Radioactivity levels
- Incubation time

Table 1. Carrier mass from 11.1 GBq (300 mCi) exposure to system components

Teflon item	Surface (cm^2)	Time (min)	Mass (nmol)
1.5 mm Teflon tubing (790 cm)	252	1.25	72
Teflon resin holder	3.8	3	47
Teflon tube in reaction vessel	1.7	20	170
Rheodyne slider valve	2.3	1.25	6.3
Control-reagents only	0	0	25
Control-mock target water	0	0	23
All components	267	N/A	357

Controlled experiments ***without*** Teflon tubing: 25-51 Ci/umole
In the presence of Teflon tubing average SA ~ 0.6 Ci/umole

(b) Contamination from reagents

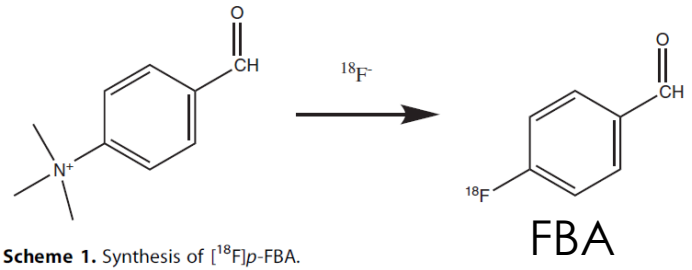
K_2CO_3 ~ 10 nmole of F19
K222 = ~ 30 nmole of F19
Precursor ~ negligible

(c) Contamination from QMA resins

SAX resin
Resin vs no resin: 5000 vs 700 mCi/umole

Berridge M.S. et al., JLRC. ***2009***, 52, 543-548
Pike V. et al., Curr Radiopharm. ***2009***, 2, 1.

How to measure specific activity of labeled molecules?



Scheme 1. Synthesis of [^{18}F]*p*-FBA.

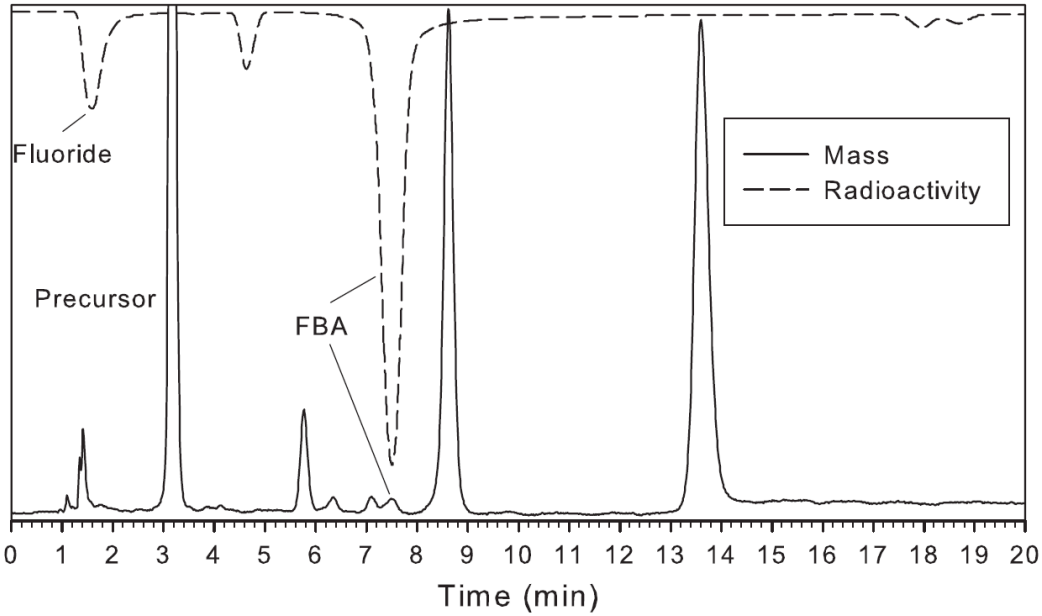


Figure 1. Chromatogram representative of analytical results, from a synthesis in a non-Teflon apparatus: target irradiation 40 µA, 10 min, 13.6 GBq (367 mCi) [^{18}F]fluoride EOB, 0.03 nmole injected on HPLC, 7.8 nmole total carrier in sample, specific activity 1.185 TBq (32,027 mCi)/µmole at 60 min EOB.

Measure cold mass after probes decay.

1. Develop calibration curve
2. Commonly used detection techniques:
   - HPLC (UV detection for UV-active molecules)
   - Pulsed amperometric (carbohydrates, non-UV active molecules)

Berridge M.S. et al., JLRC. ***2009***, 52, 543-548

Only in radiochemistry

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield

Theoretical specific activity 1710 Ci/μmole

1 Ci radioactivity ~ 60 nmoles fluoride ion

Typical reaction conditions

Precursors and reagent : 10-100 mmoles

Reaction rate of stoichiometry S_N2 = [Substrate] x [nucleophiles]

Reaction rate of S_N2 in radiochemistry = [Substrate]

Increased in [Substrate], increasing reaction rates

Detection? Rates? Concentrations?

Basic Radiochemistry

Transient Toxicity of 2-Deoxy-2-[^{18}F]Fluoro-D-Glucose in Mammalian Cells: Concise Communication

A. I. Kassis, S. J. Adelstein, A. P. Wolf, J. G. Fowler, and C.-Y. Shiue

Harvard Medical School, Boston, Massachusetts, and Brookhaven National Laboratory, Upton, New York

The kinetics of uptake and toxicity of the positron emitter F-18 have been examined in a cultured cell line. 2-Deoxy-2[^{18}F]fluoro-D-glucose (^{18}FDG) concentrated rapidly within Chinese hamster V79 cells, and the uptake was linear with the extracellular radioactive concentrations. Whereas ^{18}FDG synthesized 2 hr before the incubation did not appear to be toxic, that synthesized 5 hr previously was highly toxic. Toxicity was transient and independent of both the extracellular/intracellular radioactive concentration and the energy released from the decay of fluorine-18. Similarly synthesized nonradioactive FDG and Na^{18}F were not toxic under comparable experimental conditions. We conclude that this transient toxicity is due to an unidentified chemical species that is cytocidal following intracellular localization. These toxic levels are not likely to be achieved in the clinical use of ^{18}FDG due to dilution factors that are orders of magnitude greater than those used in these in vitro studies.

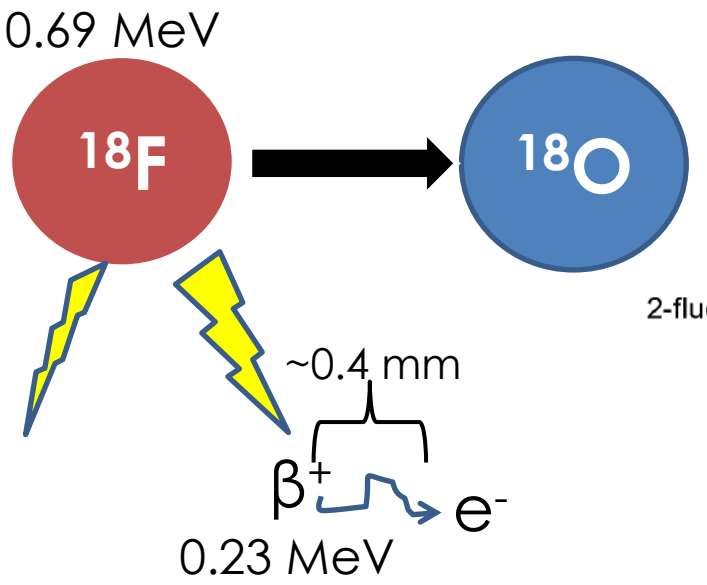
J Nucl Med 24: 1055–1059, 1983

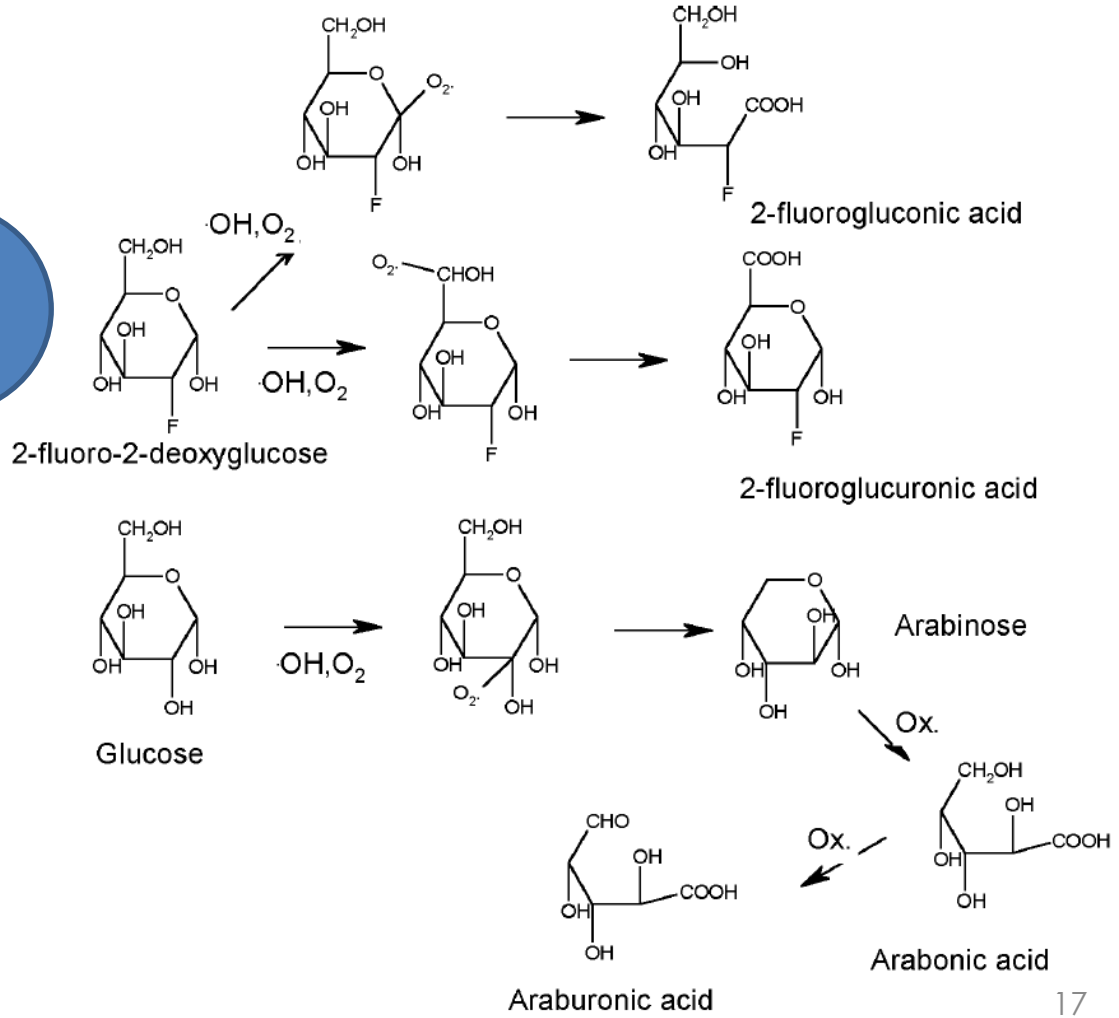
Conclusion: Toxic, unstable side products form by the presence of the higher energy positron in a concentrated solution

Only in Radiochemistry

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield

Each ^{18}F decay ($T_{1/2}$=109.8 mins, $E_{max\beta+}$ = 0.69 MeV) → releases positrons (β^+) particles of 0.23 MeV

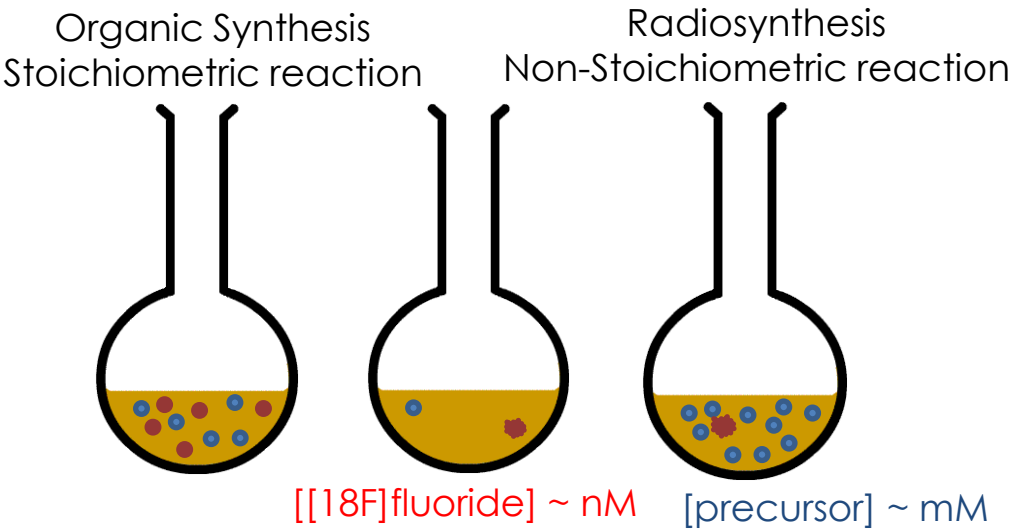




Buriova E et al., J Radioanalytical and Nucl Chem. **2005**, 264, 595-602

General requirements of synthesis of short-lived radioisotopes

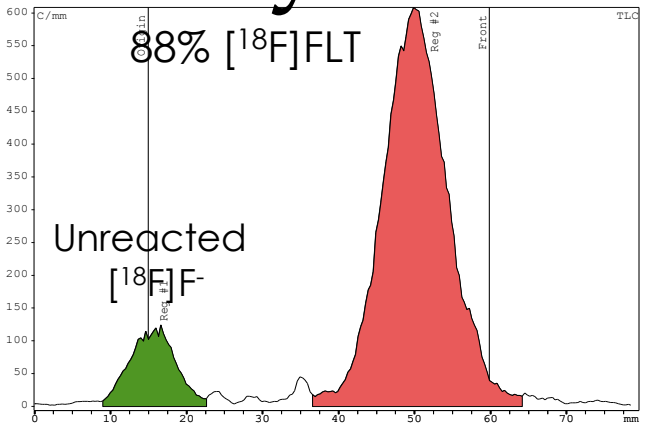
1. Fast, fast and fast. Rule of thumb: 3 half-life. For F18 <6 hours.
2. Non-stoichiometry reactions. Large excess of reagents/precursors to increase the reaction rates



3. High temperatures to increase the reaction rates
4. Optimization of reaction conditions (time, temperature, solvents, concentrations)

Only in Radiochemistry

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield (RCY)



Definition RCY:

(1) Fluorination efficiency (radio-TLC or radio-HPLC) **** THIS IS NOT RCY!**

(2) RCY yield= Percentage of (purified product/starting radioactivity)

- Decay corrected (corrected to (EOB, EOS)
- Non decay corrected
- Which one is more useful?
- Eg: decay corrected RCY = 20% with a synthesis time of 90 mins→ Non decay corrected RCY ~ 11%

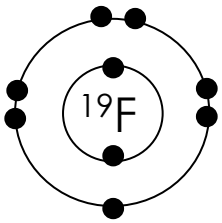
(3) For reaction optimization/research and development

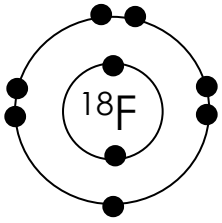
- Crude RCY %= [Total radioactivity collected x (conversion by radio-TLC)]/(total starting radioactivity)
- ** important – losses as volatile side radioactive products; reoptimize conditions.

F18 LABELING METHOD

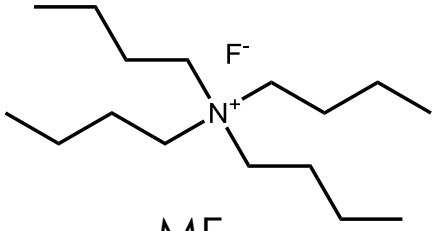
Fluorine Chemistry

1s2 2s2 2p5



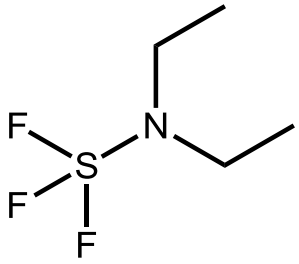


Fluorinating agents



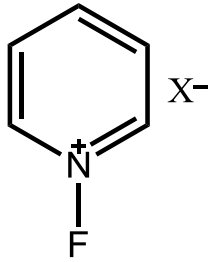
MF

HF



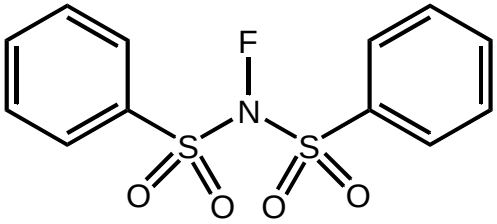
Diethylaminosulfur Trifluoride (DAST)

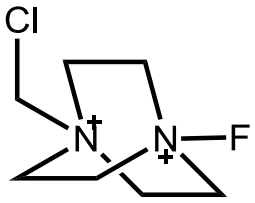
XeF_2



Pyridine hydrofluoride

Fluorobenzenesulfonimide (NFSI)





Selectfluor

Table 4. Currently used methods of ^{18}F production

Nuclear reaction	Target material	Beam energy (MeV)	Product	Specific radioactivity
$^{20}Ne(d, \alpha)^{18}F$	0.1 % F_2/Ne	18 or 23	$[^{18}F]F_2$	30 – 370 MBq µmol^{-1}
$^{20}Ne(d, \alpha)^{18}F$	15 % H_2/Ne	14	$[^{18}F]HF$	0.1 – 1 TBq µmol^{-1}
$^{18}O(p, n)^{18}F$	$H_2{}^{18}O$	15	$[^{18}F]F^-$	0.01 – 7 TBq µmol^{-1}

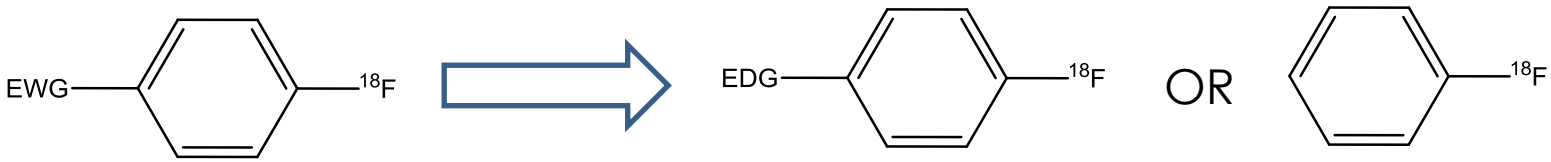
[^{18}F]F-Labeling Methods

1. Direct labeling

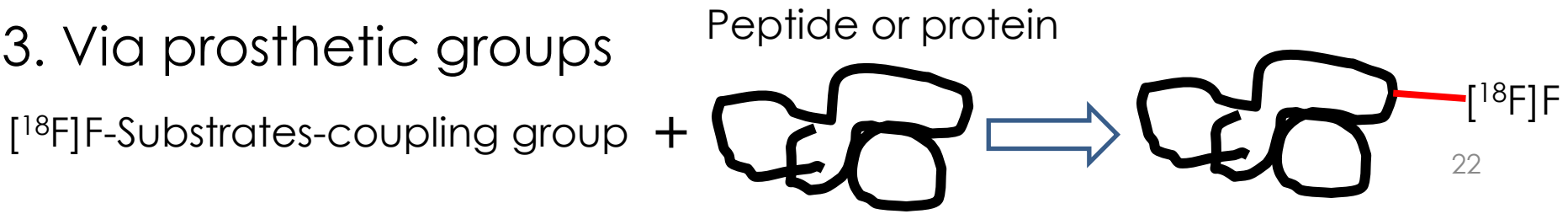
(i) Electrophilic Substitution

(ii) Nucleophilic Substitution

2. Via built-up procedures

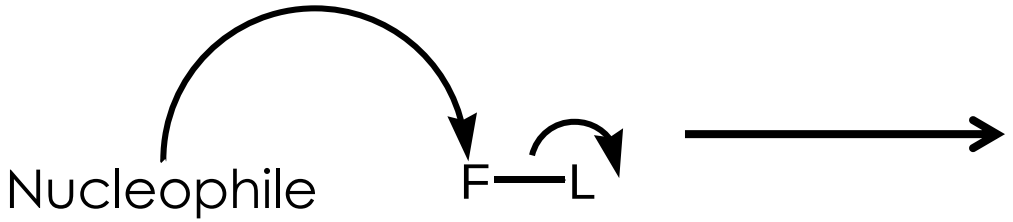


3. Via prosthetic groups

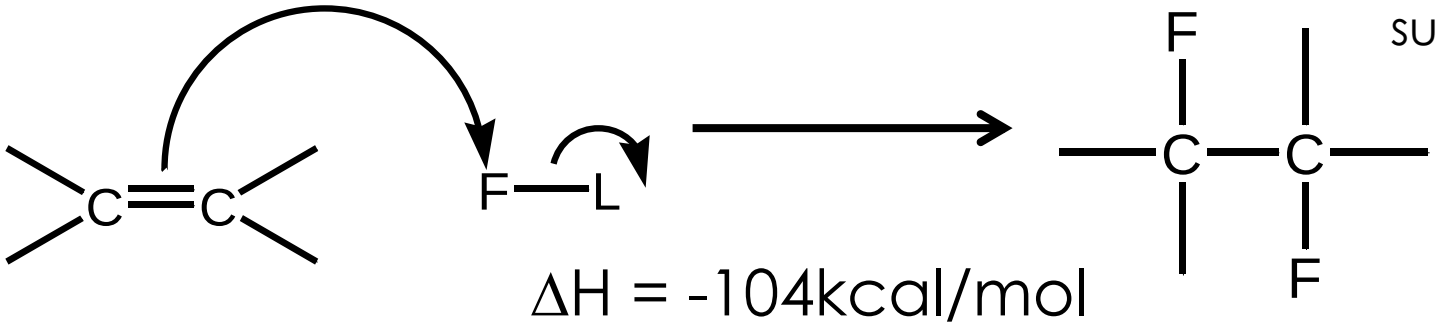


ELECTROPHILIC FLUORINATION

Mechanism Electrophilic Fluorination

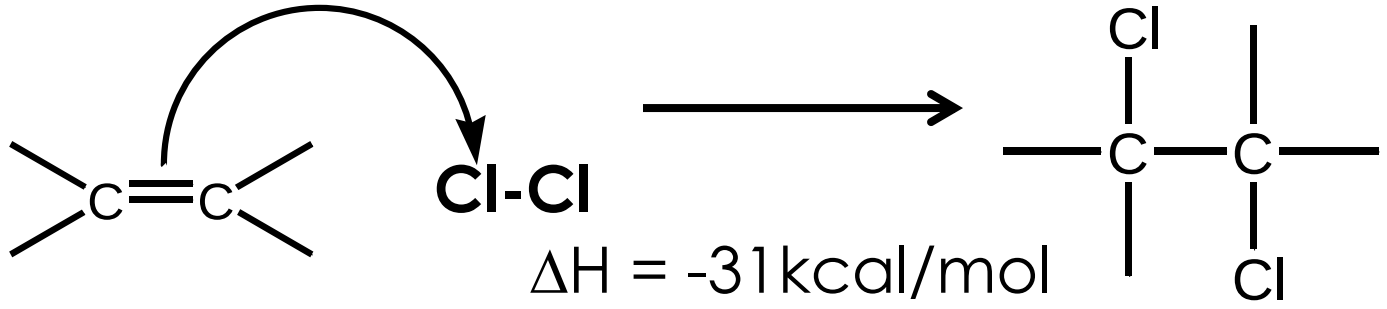


- Very reactive
- Mechanism(?)
- Highly exothermic
- Electron rich substrate



ΔH = -104kcal/mol

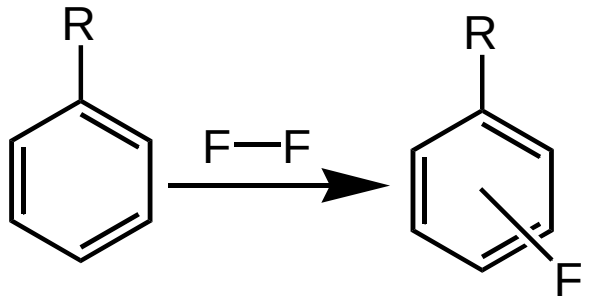
F-F, $FClO_3$, XeF_2, CF_3OF and $CsSO_4F$

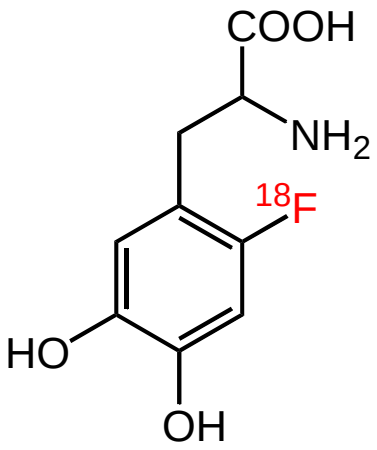


ΔH = -31kcal/mol

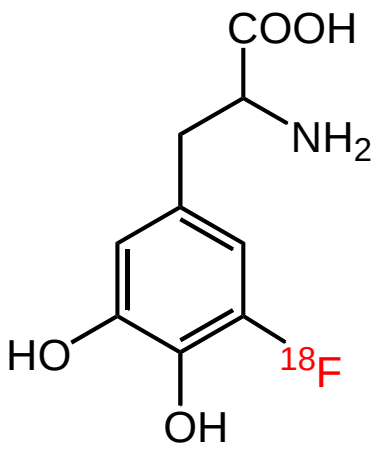
Electrophilic Fluorination

1. Non selective (F_2, XeF_2, CH_3COOF source)

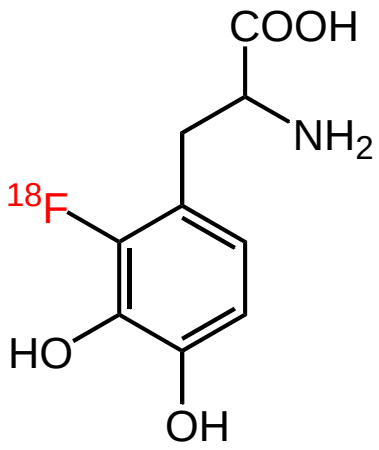




12%

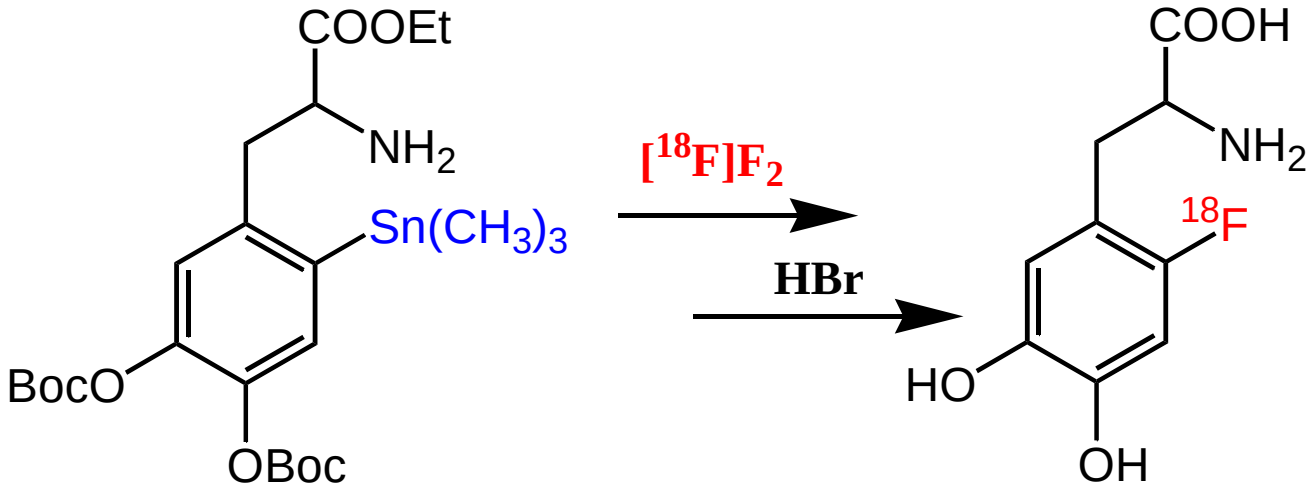


1.7%



21%

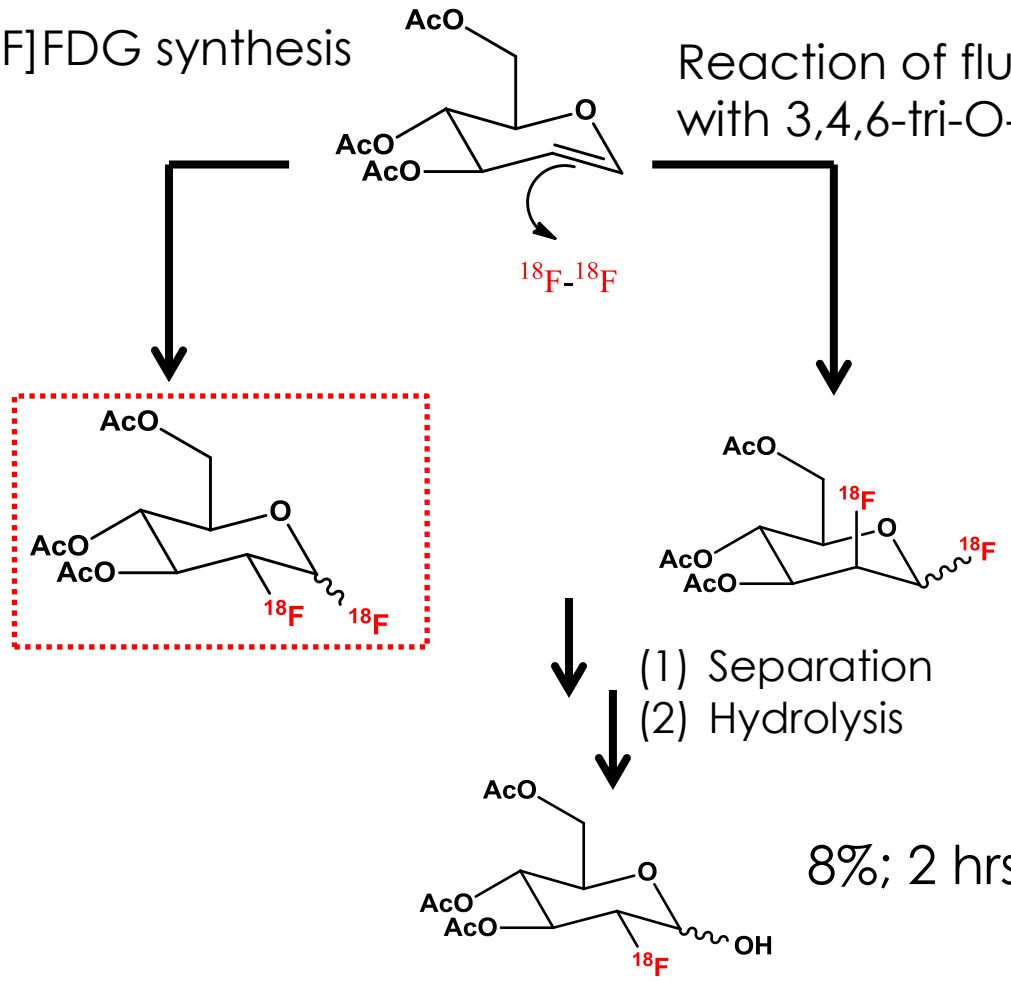
2. Selective precursor ($HgOCOCF_3$ or $Sn(CH_3)_3$)



Electrophilic fluorination

1976: First synthesis of [^{18}F]FDG at Brookhaven National Lab.
→ U of Pennsylvania, the 1st [^{18}F]FDG PET imaging of the brain
1978: Preclinical studies of [18F]FDG for myocardial metabolism
1980: Preclinical studies of [18F]FDG for tumor metabolism

[^{18}F]FDG synthesis



Reaction of fluorine gas with 3,4,6-tri-O-acetylglucal

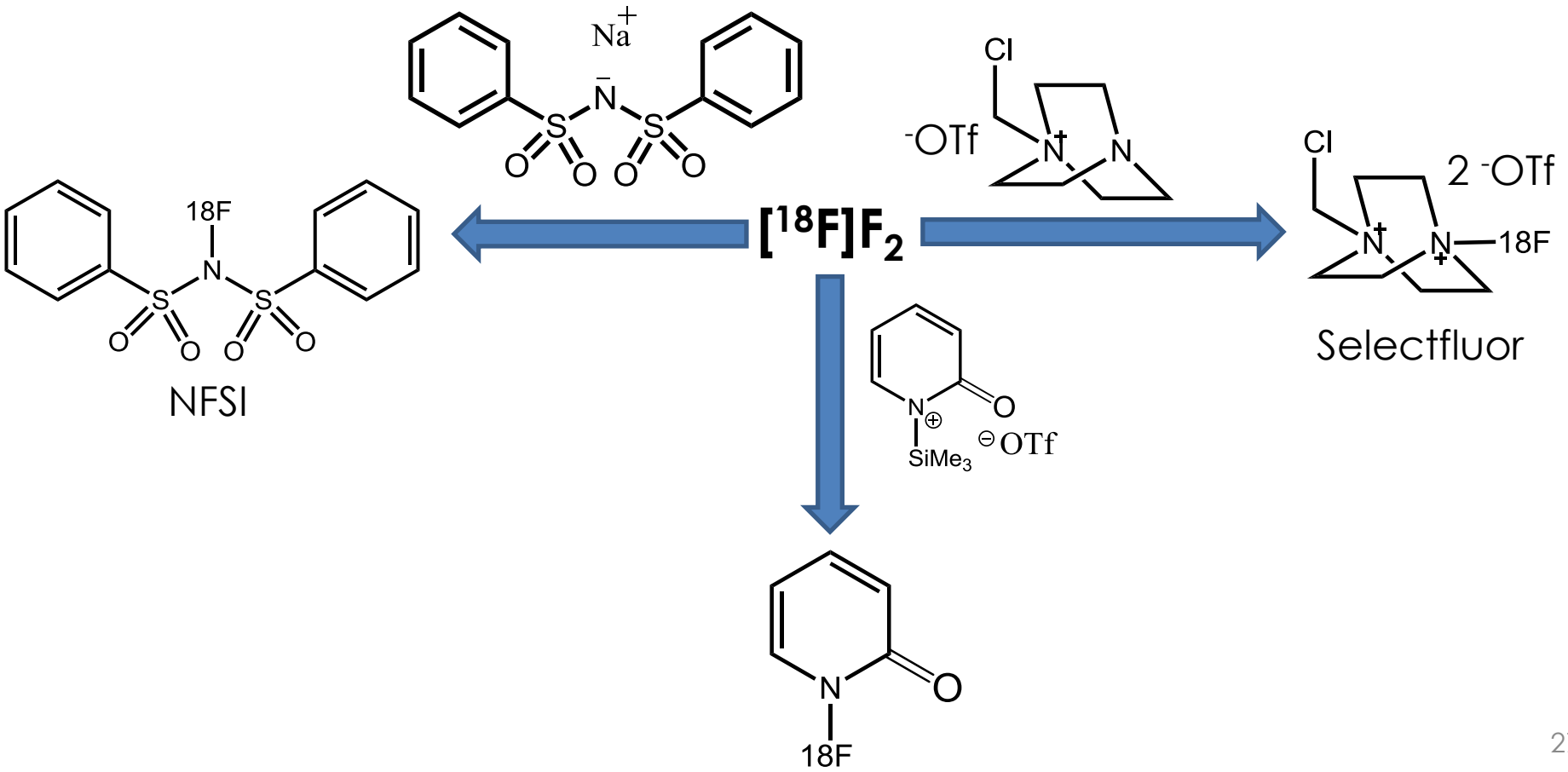
Poor stereoselectivity→2-FDM (3:1 ratio)
Poor RCY; only 25% (max) is labeled
Low specific activity- [^{18}F]F_2 gas doped with F_2

8%; 2 hrs

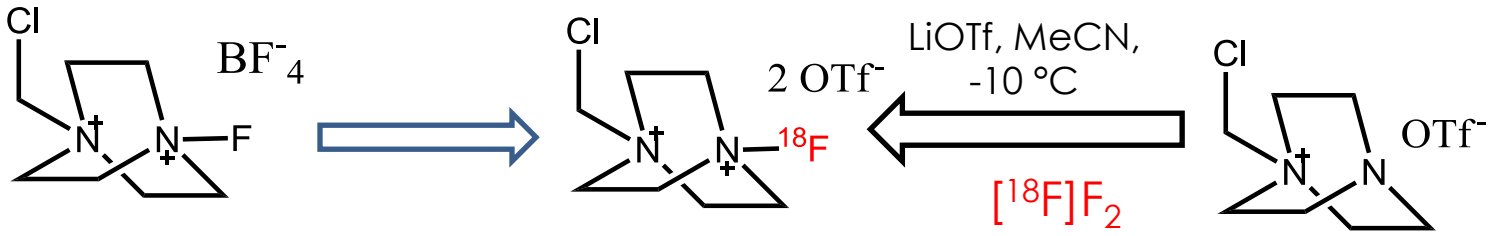
N-[^{18}F]F Radiofluorination

Gouverneur, V. et al, Angew Chemie Int Ed. 2012, 51, 2-14

Electrophilic fluorination agent
Reactive, but more ***selective***
Easier to handle –solid, liquid
Not as corrosive as F_2 gas.

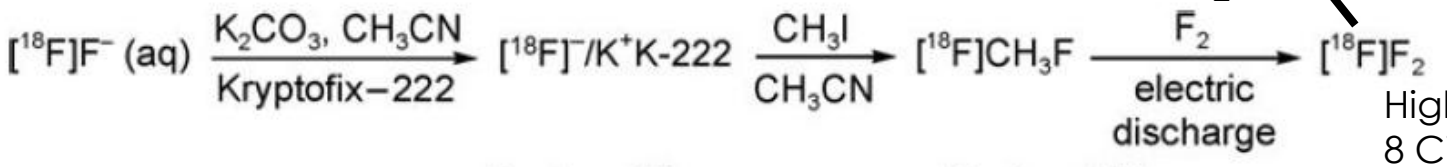


[^{18}F]Selectfluor bis(triflate)



Isotopic exchange with BF^-_4

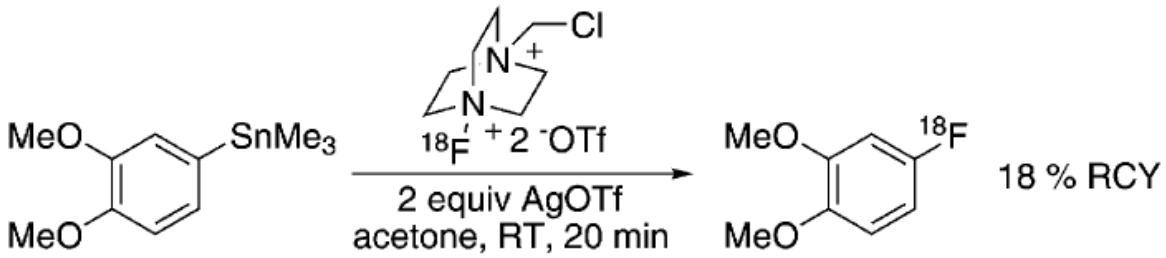
Electrical discharge methodology: Higher SA of [^{18}F]F_2



Higher SA
8 Ci/μmole

	Protocol II	Protocol III
target irradiation	15 min	60 min
beam current	40 μA	40 μA
F_2 carrier added	1200 nmol	600 nmol

Synthesis of [^{18}F]fluoroveratrole



18 % RCY

Gouverneur, V. et al. Angew Chem Int Ed. 2010, 49, 6821

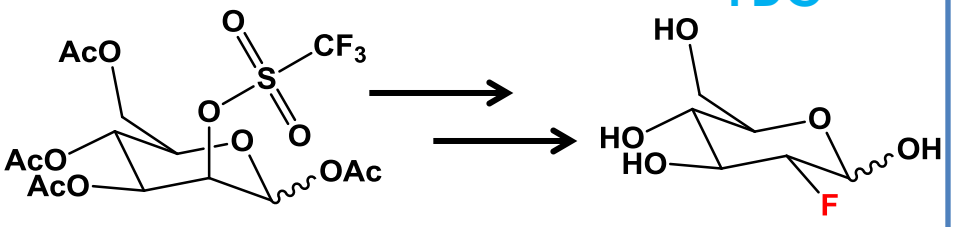
Summary Electrophilic Fluorination

1. [18F]F_2 gas:
   i. Gaseous, difficult to handle
   ii. Low specific activity, doped with F_2 gas
   iii. Need dedicated cyclotron and radiochemistry lab
2. Extremely reactive.
3. Aromatic substrates (electron rich substrates)
4. New, milder, and more selective N-[18F] fluorination agent
5. Improve specific activity of [18F]F_2 by gas discharge method (SA

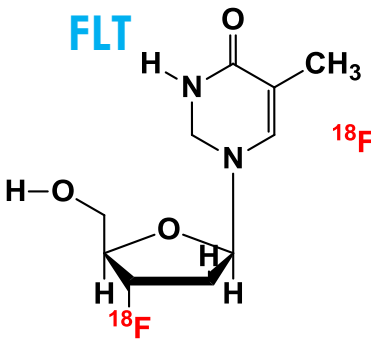
NUCLEOPHILIC FLUORINATION

PET Probes from Nucleophilic Fluorination

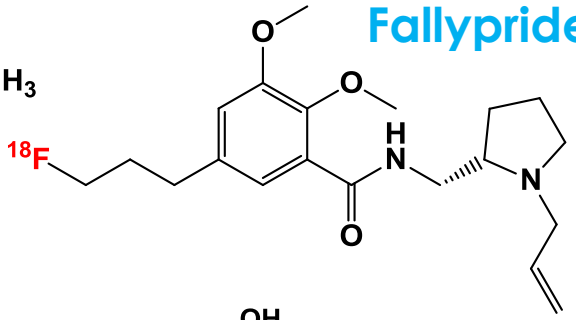
Aliphatic



FDG

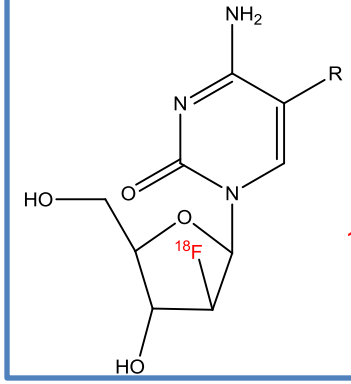


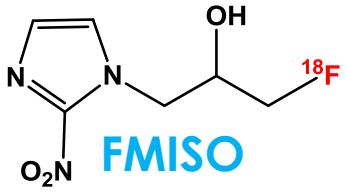
FLT



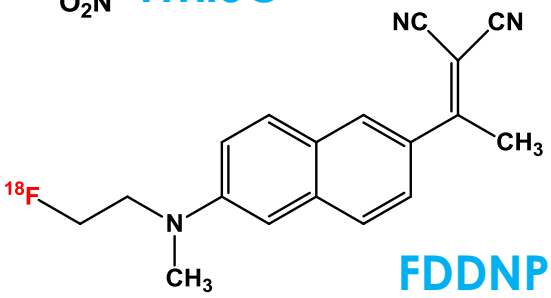
Fallypride

FAC family



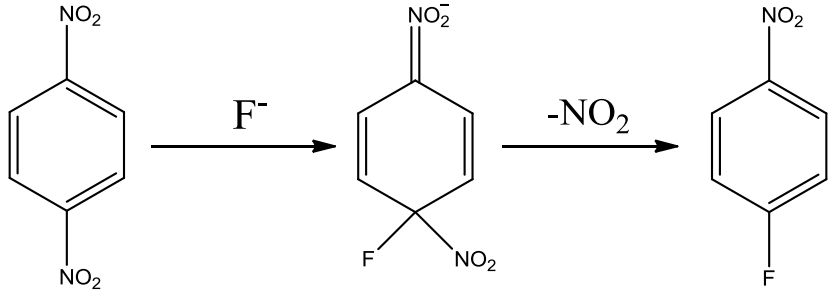


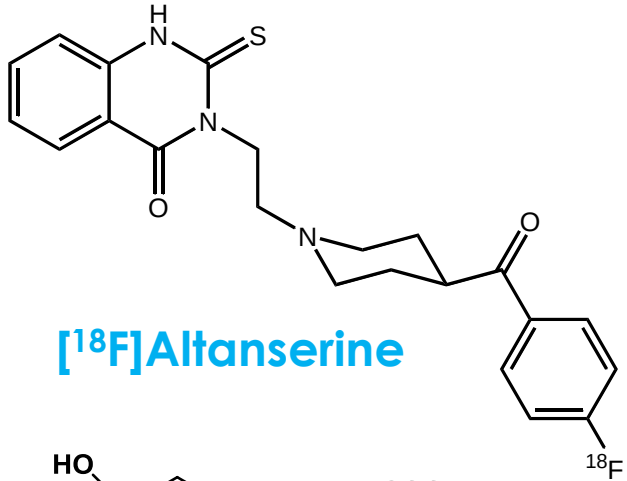
FMISO



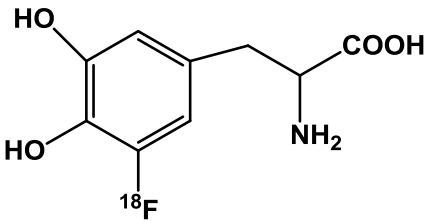
FDDNP

Aromatic



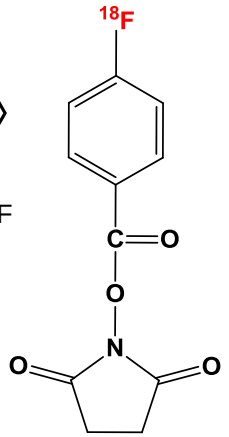


[18F]Altanserine



FDOPA

SFB



[18F]F Nucleophilic Sources

Alkaline metal fluoride

(1) MF (M: K, Cs, Ag)

Common alkali metal fluorides

Increasing ionic strength

LiF < NaF < KF < CsF

Increasing nucleophilicity
Increasing solubility

Metal cations that render nucleophilicity

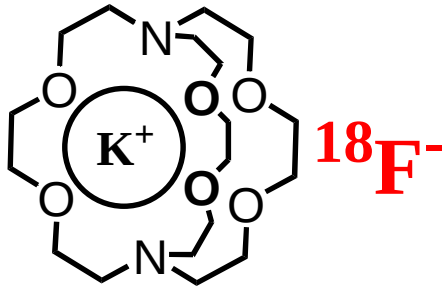
Al, In, Ni, Cu, Zn, Ca, Na

(2) HF

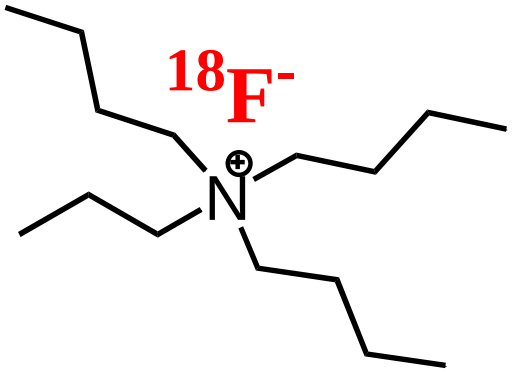
$[^{18}F]$fluoride ion/$[^{18}O]H_2O$

$K_{2.2.2}$/ K_2CO_3
or
TBAOH/$TBAHCO_3$

KF/Cryptand



Tetraalkylammonium fluoride

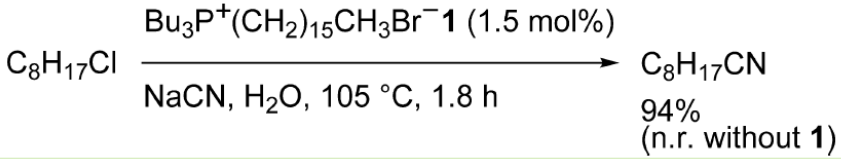


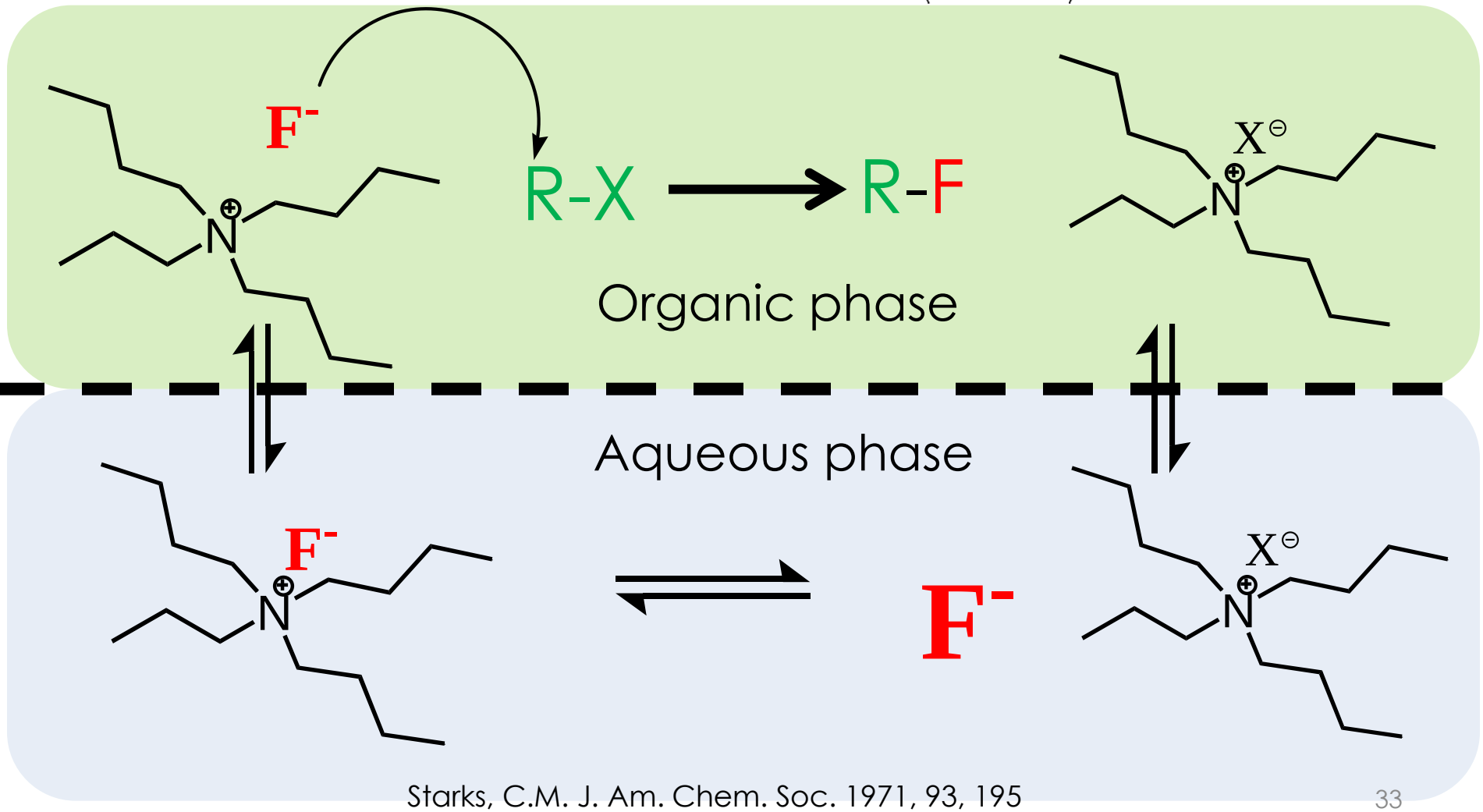
(1) Role of PTC?

(2) Role of base?

Phase Transfer Catalyst (PTC)

Role of Cryptand and tetraalkylammonium salt?





Starks, C.M. J. Am. Chem. Soc. 1971, 93, 195

Which PTC or Base?

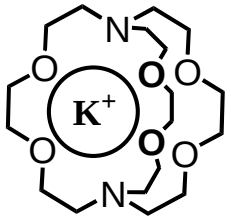
1. Solubility, (2) Stability, (4) Hygroscopic (likes water)

$[^{18}F]$fluoride ion/$[^{18}O]H_2O$

Kryptofix ($K_{2.2.2}$)
K_2CO_3

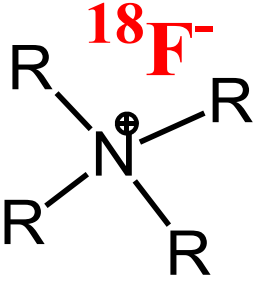
Tetrabutylammonium carbonate or bicarbonate

Cesium carbonate or bicarbonate



$^{18}F^-$

KF/Cryptand

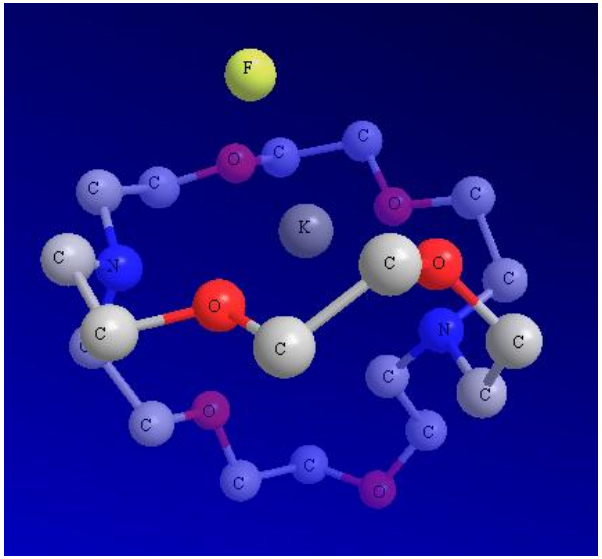


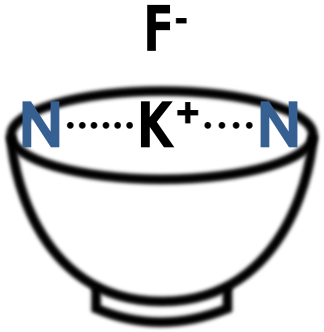
$^{18}F^-$

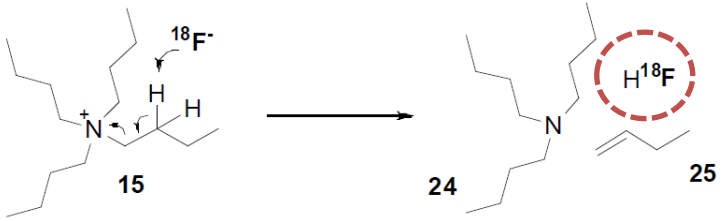
CsF

Tetraalkylammonium fluoride

R = methyl, ethyl, butyl







Thermal decomposition of TBAF

Role of Base

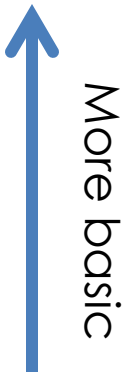
Role of base

(1) Prevent formation of H[18F]F → volatile, lost radioactivity
(2) Counter ion for [18F]fluoride ion complexation– phase transfer
(3) Side reactions and decomposition of PTC
(4) Base hydrolysis of precursor (base sensitive)
(5) Base catalyzed side reactions

Molar ratio Kryptofix >base (K_2CO_3 and $KHCO_3$)- decomposition, and 2 K^+

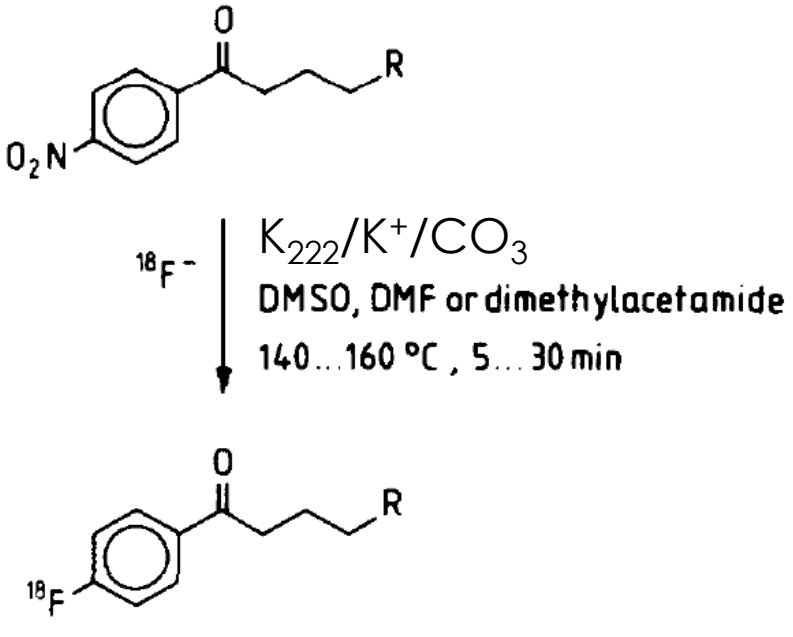
Choice of base

Base	pKb
K_2CO_3	3.8
$KHCO_3$	7.6
K^+ oxalate	10
H_2O	14



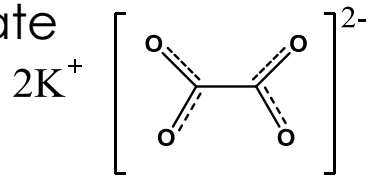
Kryptofix/K/oxalate system **ALONE**- resulted in 30% loss of radioactivity as H[18F]F
Add 30-50 ug of K_2CO_3 to prevent radioactivity losses during drying

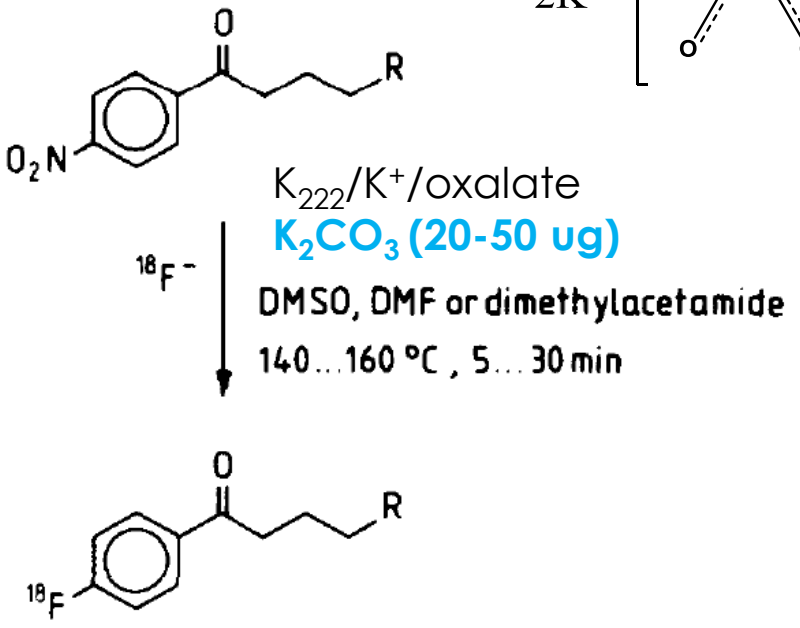
Literature example, the role of base



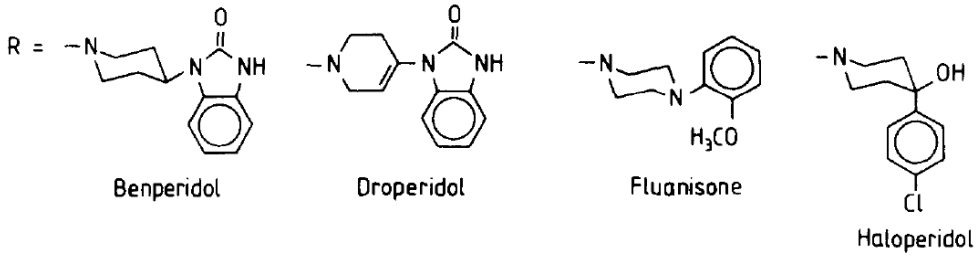
Radiochemical yield ~ 1%

Potassium oxalate





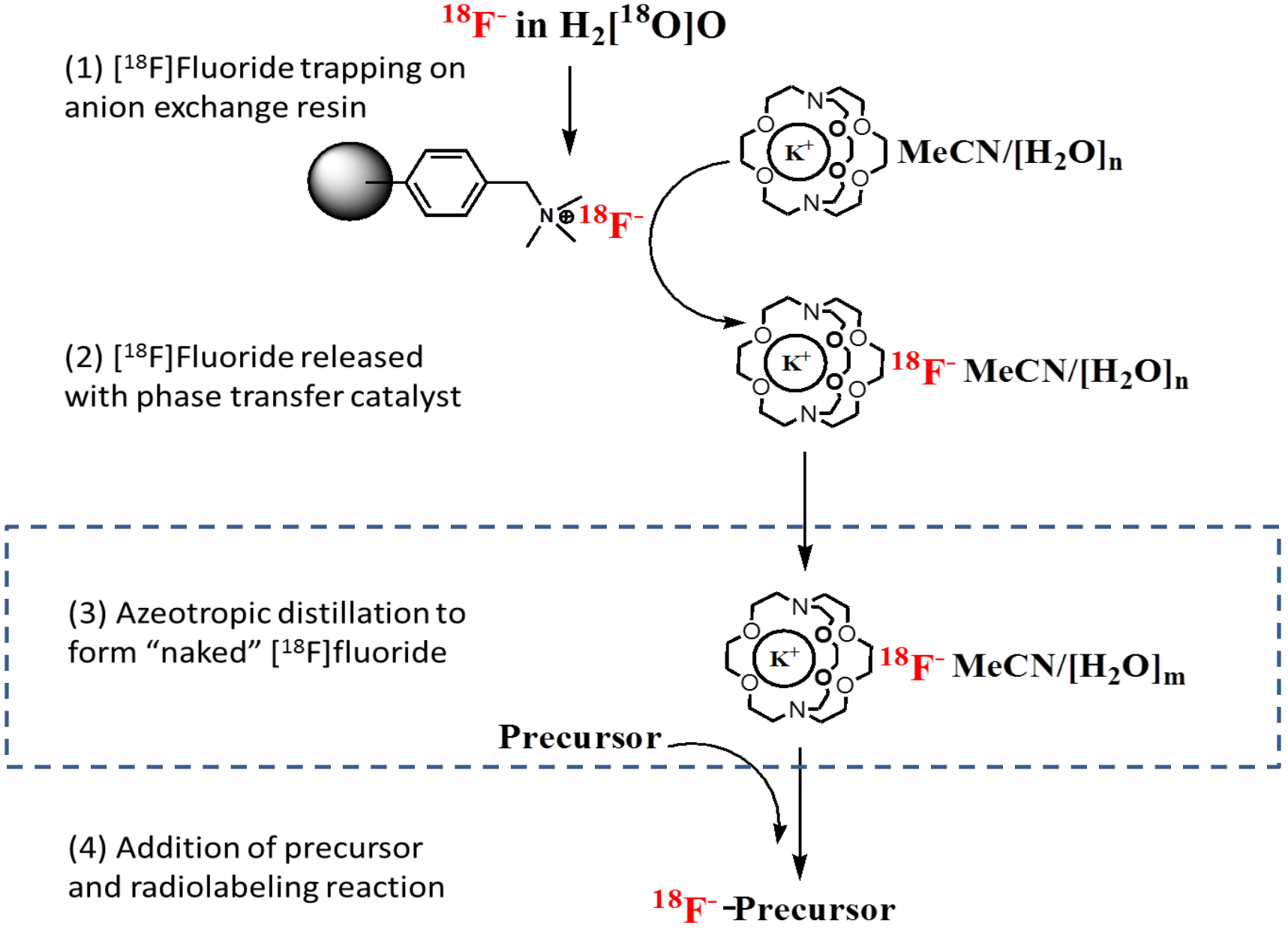
Radiochemical yield 25... 35%



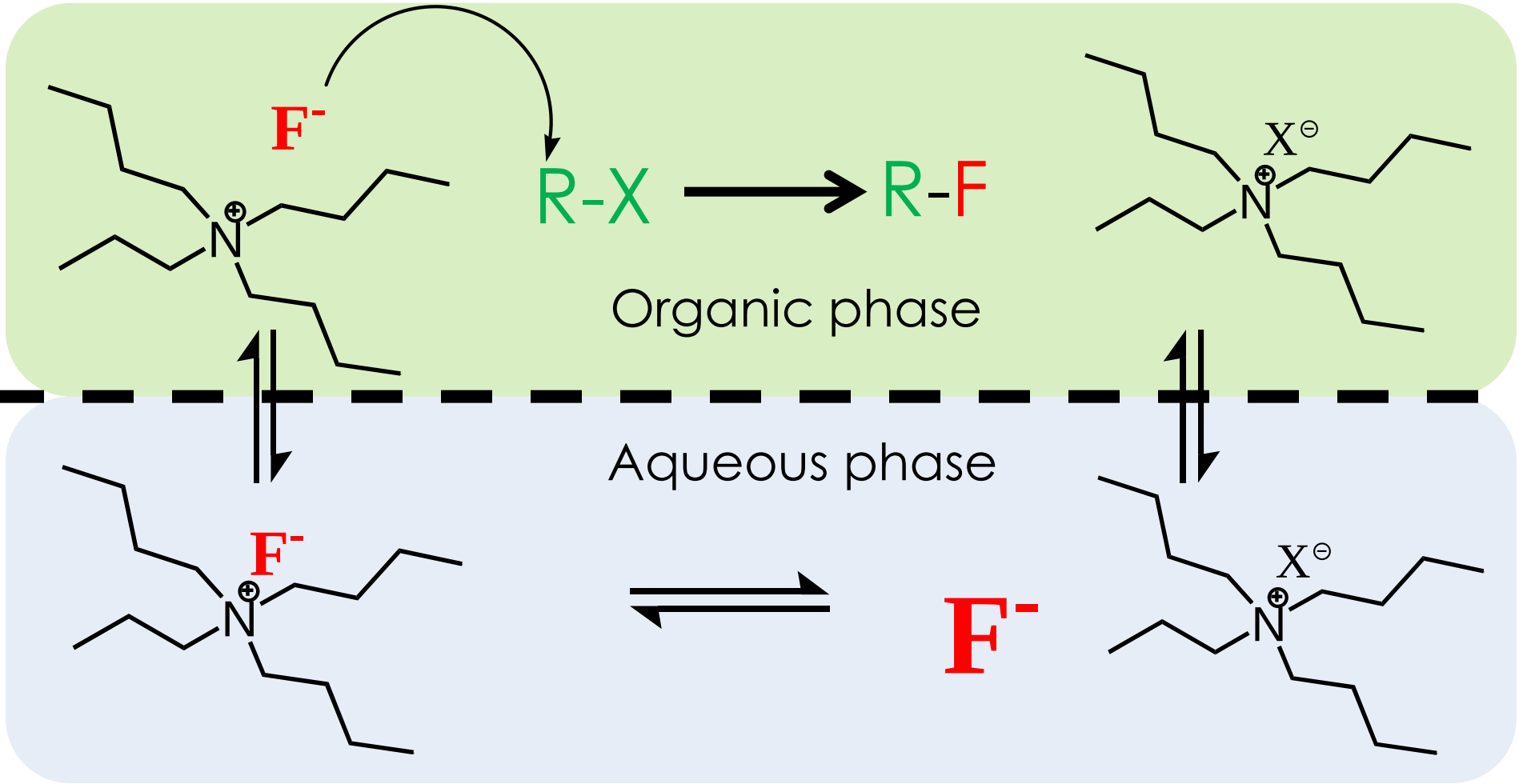
Direct nucleophilic fluorination of butyrophenone neuroleptics

Katsifis, A. et al. Appl Radiat Isot. 1993, 44, 1015

Typical workflow of F18 ion radiochemistry

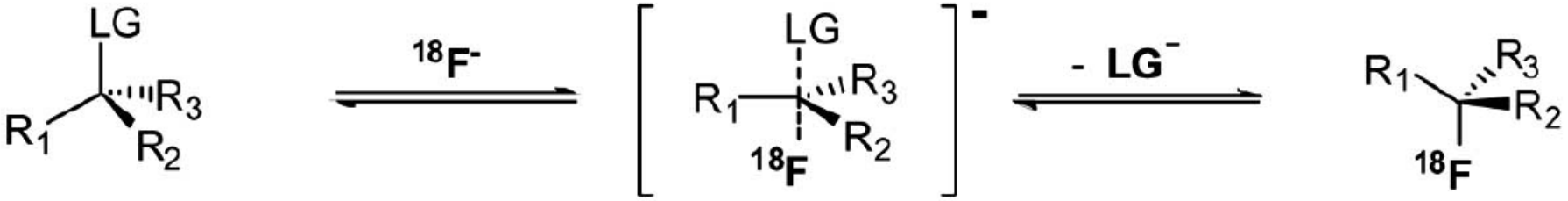


Phase Transfer Catalysis and azeotropic distillation in Radiochemistry?



Nucleophilic Aliphatic Substitution

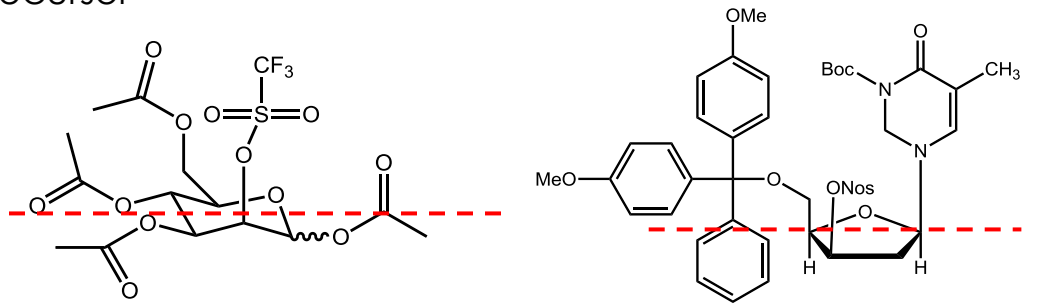
(1) S_N2 substitution mechanism → Radiolabelled product



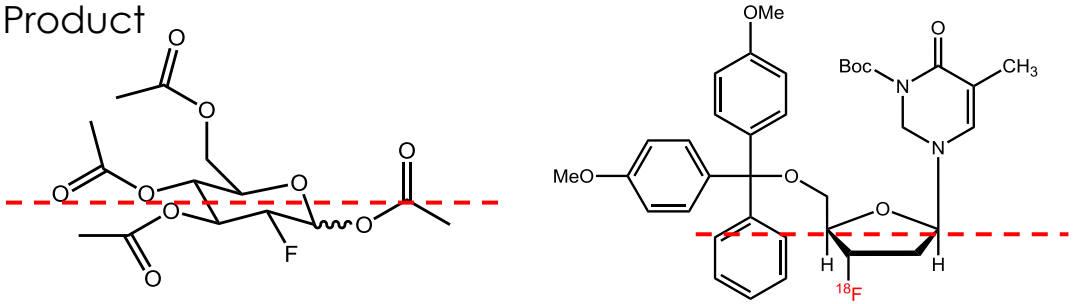
transition state

Inversion of stereochemistry

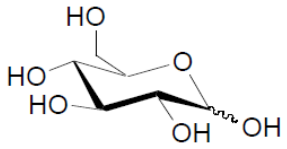
Precursor



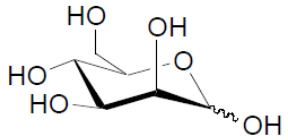
Product



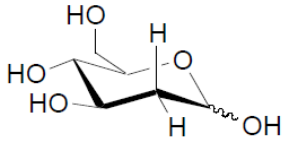
Stereochemical Consequences



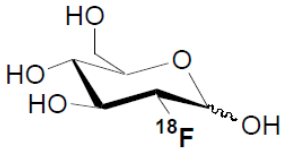
34, D-glucose



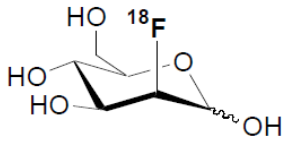
35, D-mannose



36 2-deoxy-D-glucose
2-deoxy-D-mannose

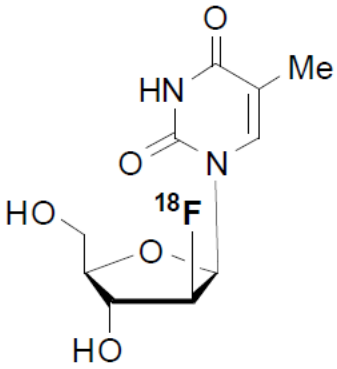


2-[^{18}F]fluoro-2-deoxy-D-glucose
(**23**, [^{18}F]FDG)

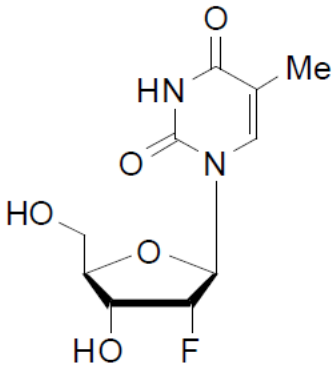


2-[^{18}F]fluoro-2-deoxy-D-mannose
(**37**, [^{18}F]FDM)

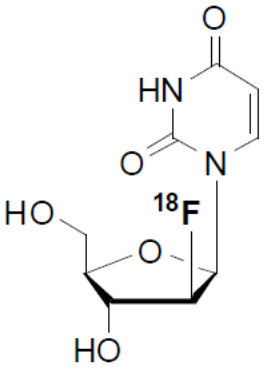
Kinetic differences of cell uptake



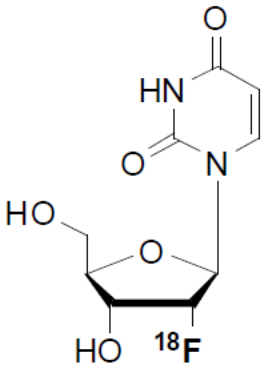
38, [^{18}F]FMAU



39, FTdR



40, [^{18}F]FAU



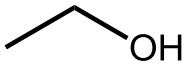
10, [^{18}F]FUdR

Chemo/Stereo consequences Probe different biological functions

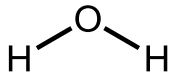
Nucleophilic Aliphatic Substitution

3. Solvents (Dielectric constant? acidic H? H-bonding?)

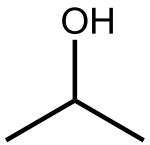
Polar Protic



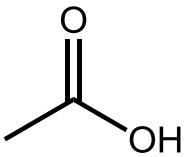
ethanol



water



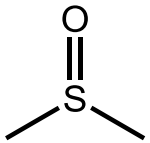
propan-2-ol



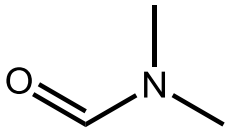
acetic acid

Polar aprotic

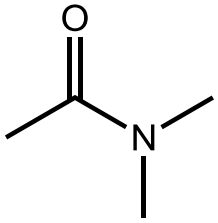
acetonitrile



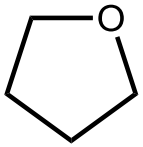
Dimethylsulfoxide



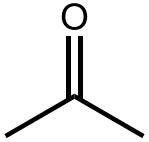
N,*N*-dimethylformamide



N,*N*-dimethylacetamide



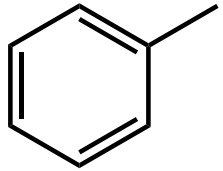
tetrahydrofuran

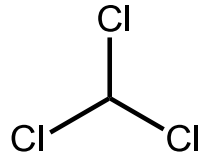


Acetone

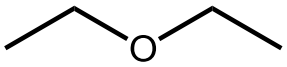
Non-polar


hexane


toluene



chloroform



ethoxyethane

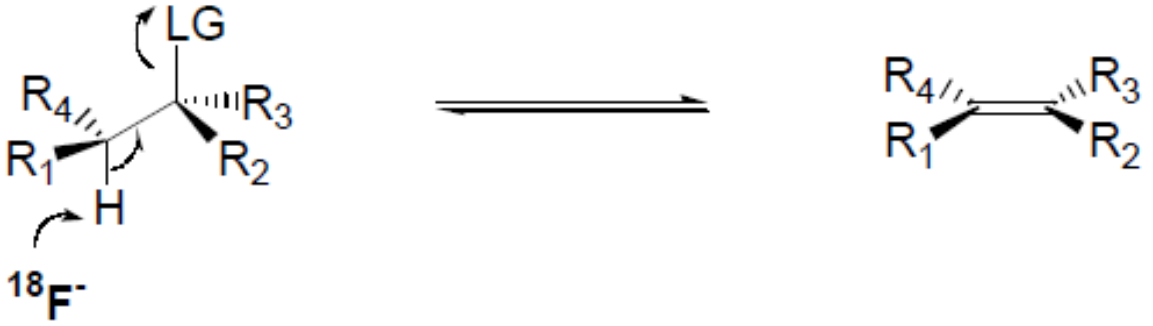
Choice: Solubility, boiling point, dielectric constant

Nucleophilic Aliphatic Substitution

2. Side reactions

(1) Undesirable reaction: E2 elimination mechanism→ Side product

Antiperiplanar

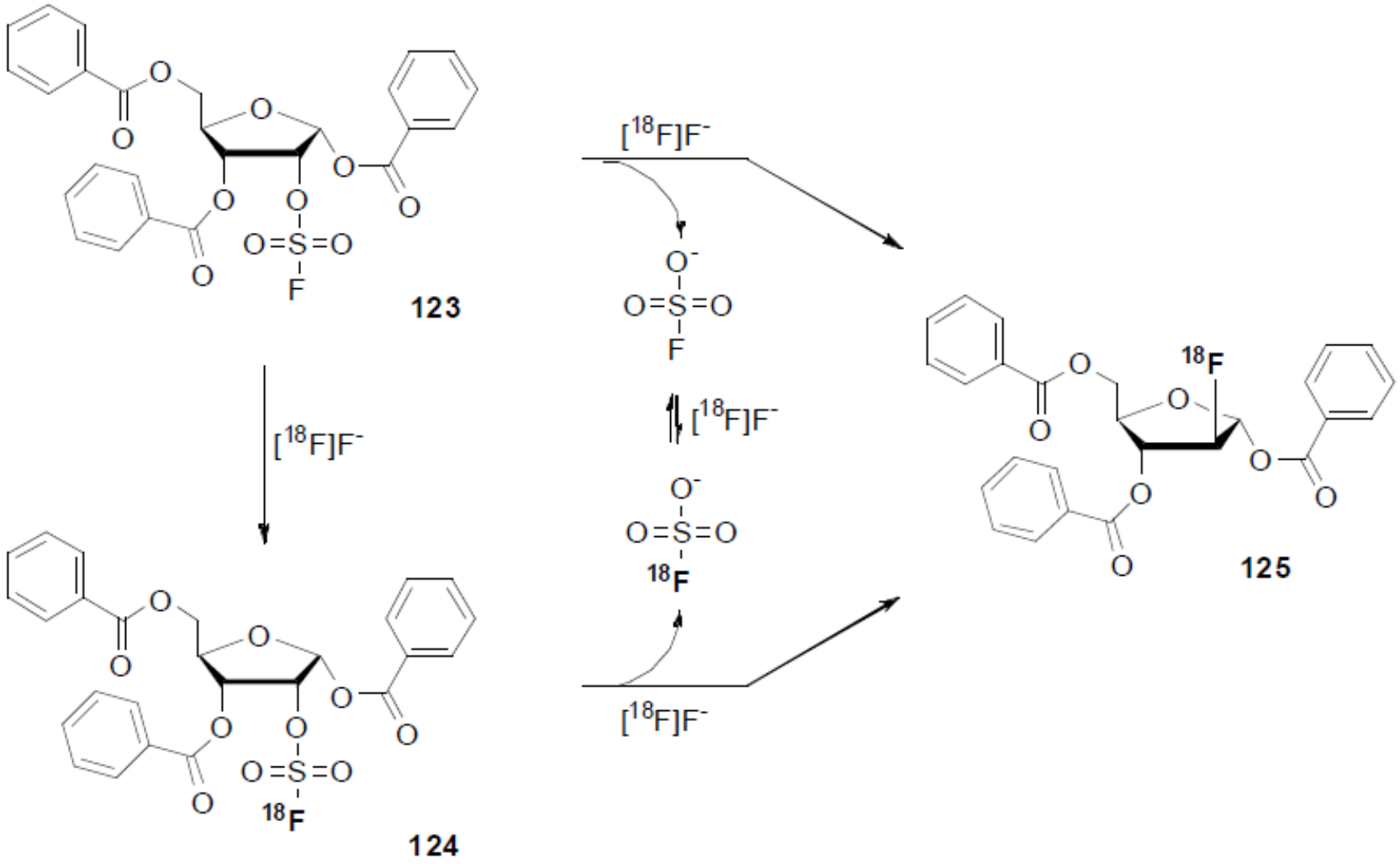


or other base (K_2CO_3, Kryptofix, $KHCO_3$, $TBAHCO_3$…etc)

i. Optimal ratio of phase transfer *catalyst:base:precursor*
ii. Choice of base eg: potassium oxalate
iii. Higher temperature → higher elimination byproducts
iv. Better leaving group are more sensitive to elimination side reaction, especially with increasing temperatures
v. Elimination rate in 2° LG >> 1° LG

F18-F19 exchange

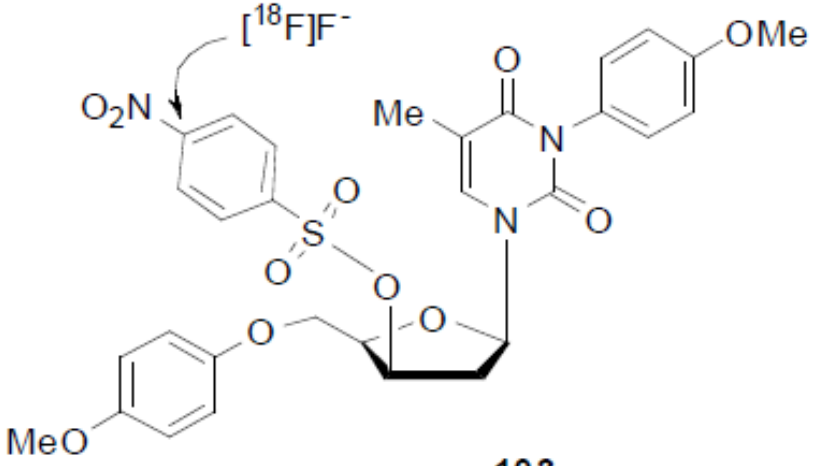
Side reaction



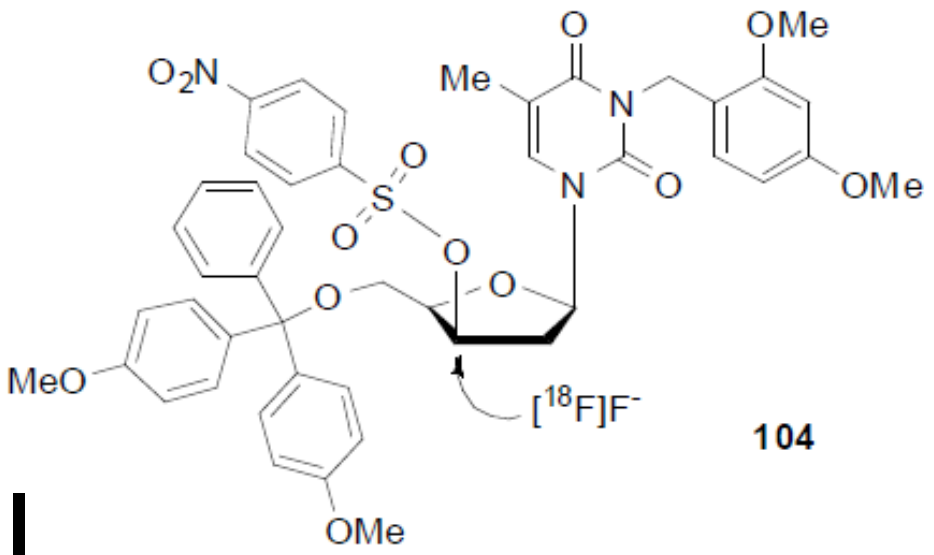
Lowers RCY. Importance of leaving group. Less reactive LG (mesylate) → 0 yield

Roeda D. et al., Current Radiopharm. 2010, 3, 81-108

Side reaction with leaving group

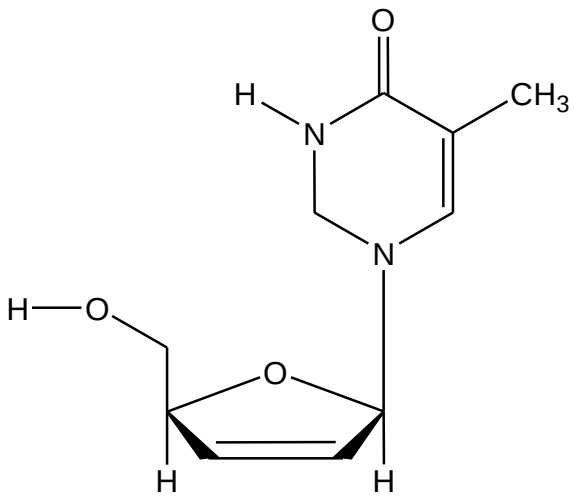


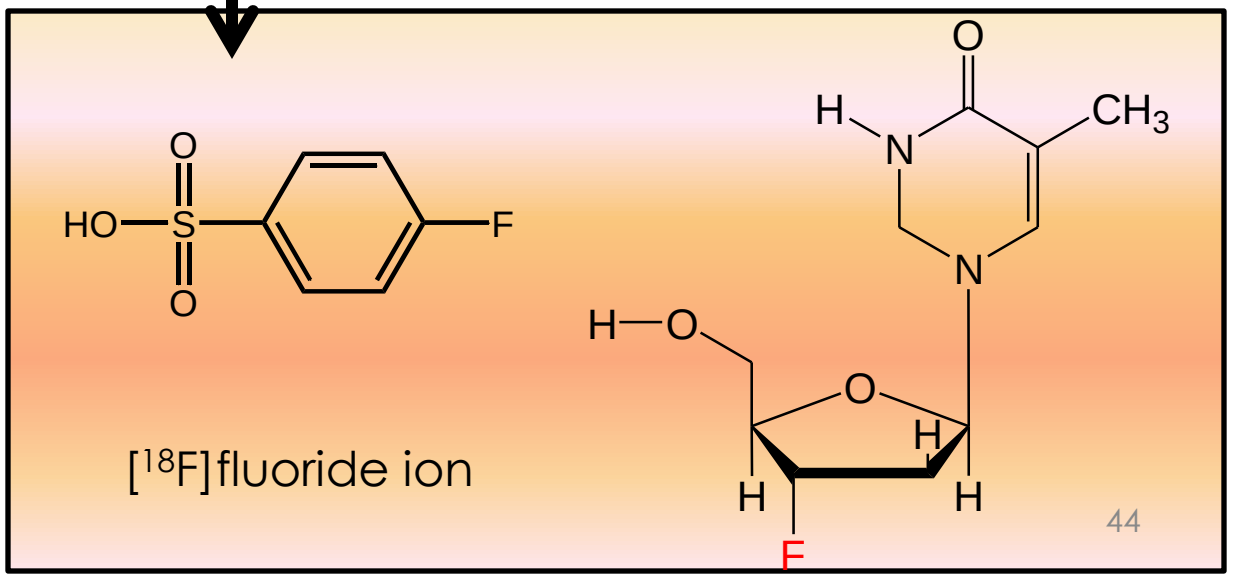
103



104

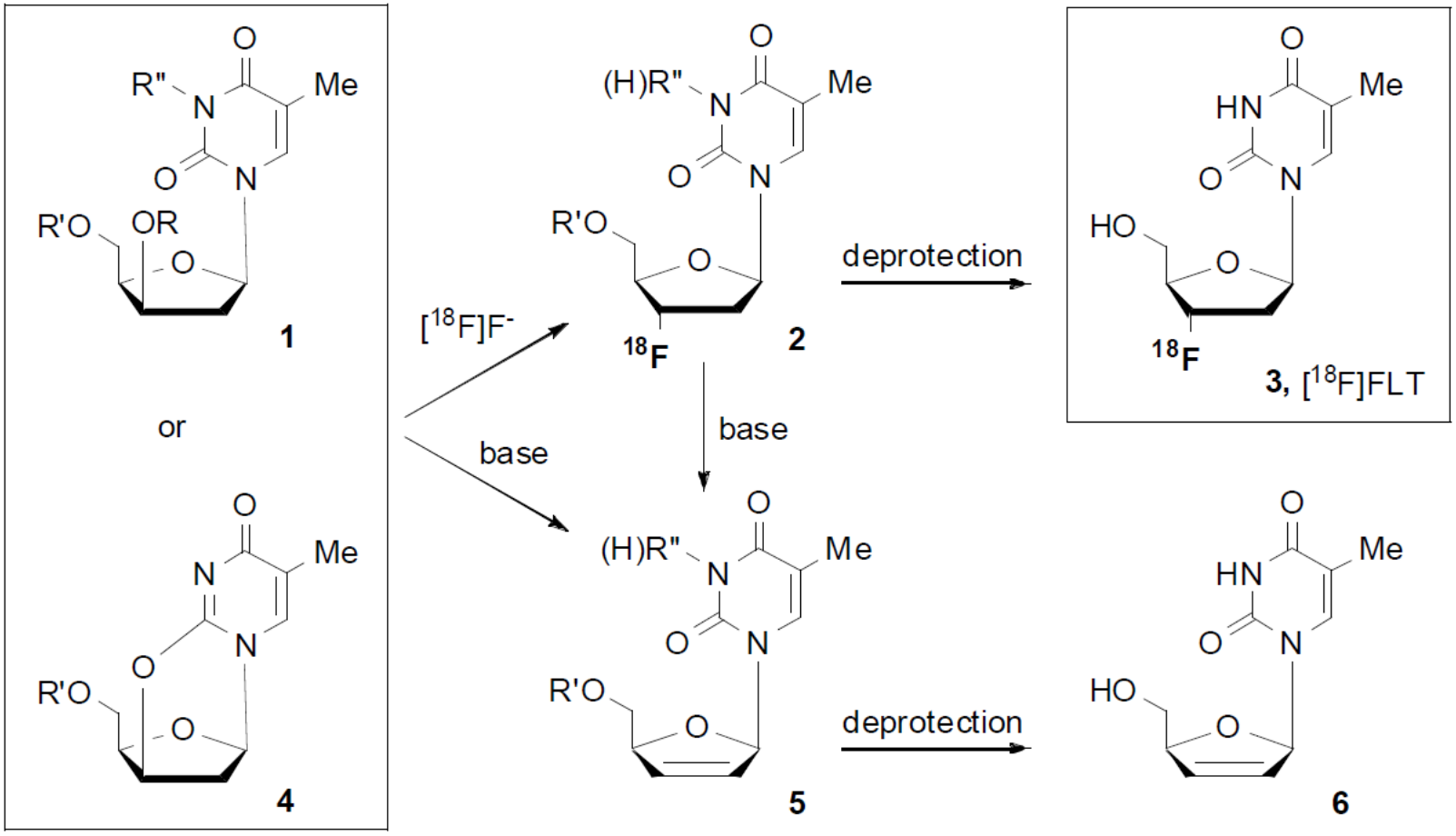
HCl





Nucleophilic Aliphatic Substitution

Example: Side reaction in [^{18}F]FLT

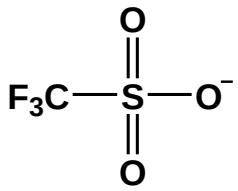
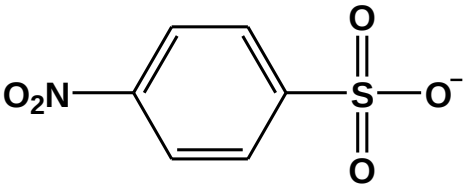
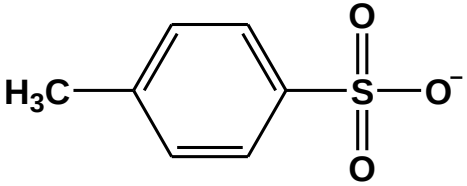
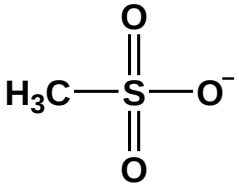


Roeda D. et al., Current Radiopharm. 2010, 3, 81-108

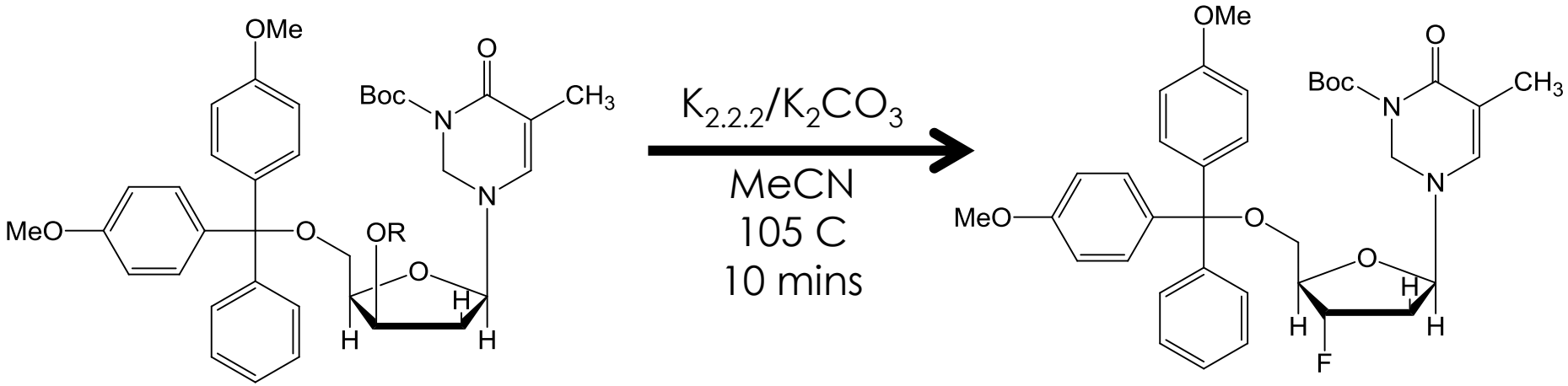
Nucleophilic Aliphatic Substitution

4. Precursor design: Leaving group

reactivity

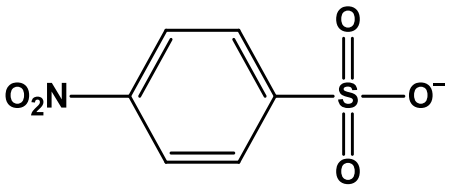
	K_{rel}
 Triflate (Tf)	1.4×10^8
 Nosylate (Ns)	4.4×10^5
 Tosylate (Ts)	3.7×10^4
 Mesylate (Ms)	3.0×10^4
I^-	91
Br^-	14
$CF_3CO_2^-$	2.1
Cl^-	1
F^-	9×10^{-6}
p-nitrobenzoate	5.5×10^{-6}
$CH_3CO_2^-$	1.4×10^{-6}

Literature Survey: FLT synthesis

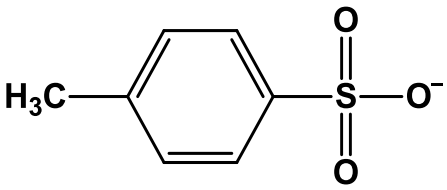


reactivity

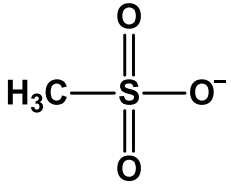
Leaving group, R =



Nosylate (Ns)



Tosylate (Ts)



Mesylate (Ms)

Fluorination yield
19.8
7.8
5.3

Eisenhut, M. et al. Nuc Med Biol. 2002, 263-273

The n.c.a. [^{18}F]FDG synthesis

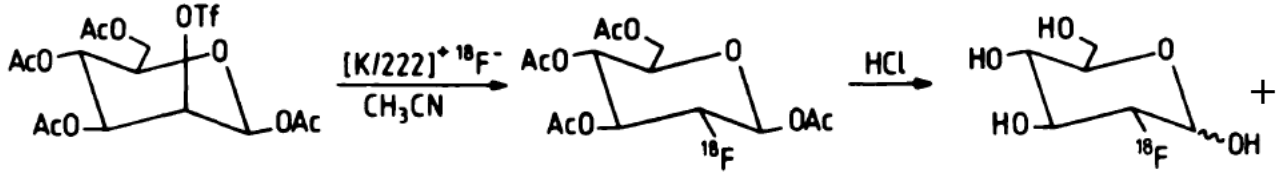
Efficient Stereospecific Synthesis of No-Carrier-Added 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose Using Aminopolyether Supported Nucleophilic Substitution

K. Hamacher, H. H. Coenen, and G. Stöcklin

Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, Jülich, FRG

An aminopolyether mediated synthesis of fluorine-18 (^{18}F) 2-fluoro-2-deoxy-D-glucose (FDG) has been developed. The nucleophilic fluorination with accelerator-produced [^{18}F]fluoride works at the no-carrier-added level and gives epimerically pure 2-^{18}FDG with an uncorrected radiochemical yield of a maximum 50% in a synthesis time of ~ 50 min from EOB.

J Nucl Med 27:235–238, 1986



1 2 3

Tf = $-SO_2CF_3$

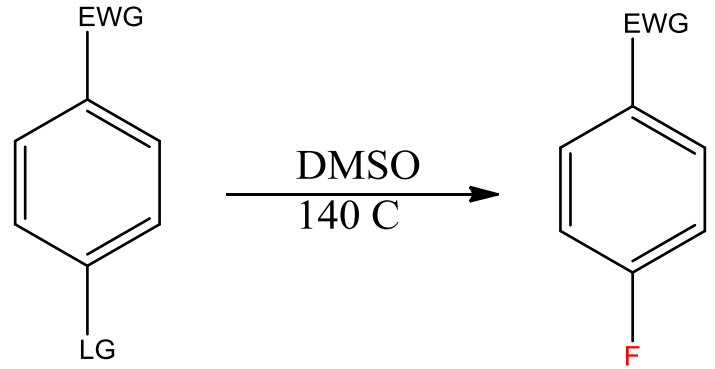
+ glucose

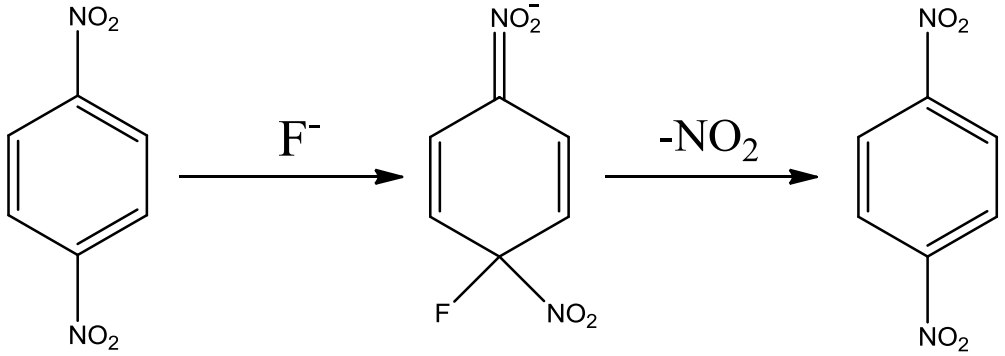
No other side products!

NUCLEOPHILIC AROMATIC SUBSTITUTION

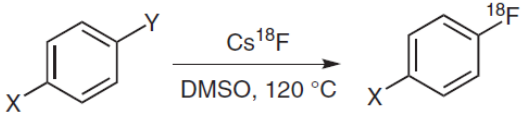
Precursor Requirements

(a) Activating effect: EWG: 3-NO_2 < 4-CH_3CO < 4-CN < 4-NO_2





Effect of activating (X) and leaving groups (Y) on nucleophilic aromatic fluorination



X	Y	k_{rel} (80 °C)	k_{rel} (120 °C)
NO_2	NMe_3ClO_4	400	30000
NO_2	NO_2	40	420
CN	NMe_3ClO_4	16	100
COMe	NMe_3ClO_4	8	33
CN	NO_2	1	1

Meisenheimer complex; delocalization electron onto EWG

(b) Leaving group: I < Br < Cl <F < NO_2 < N^+Me_3

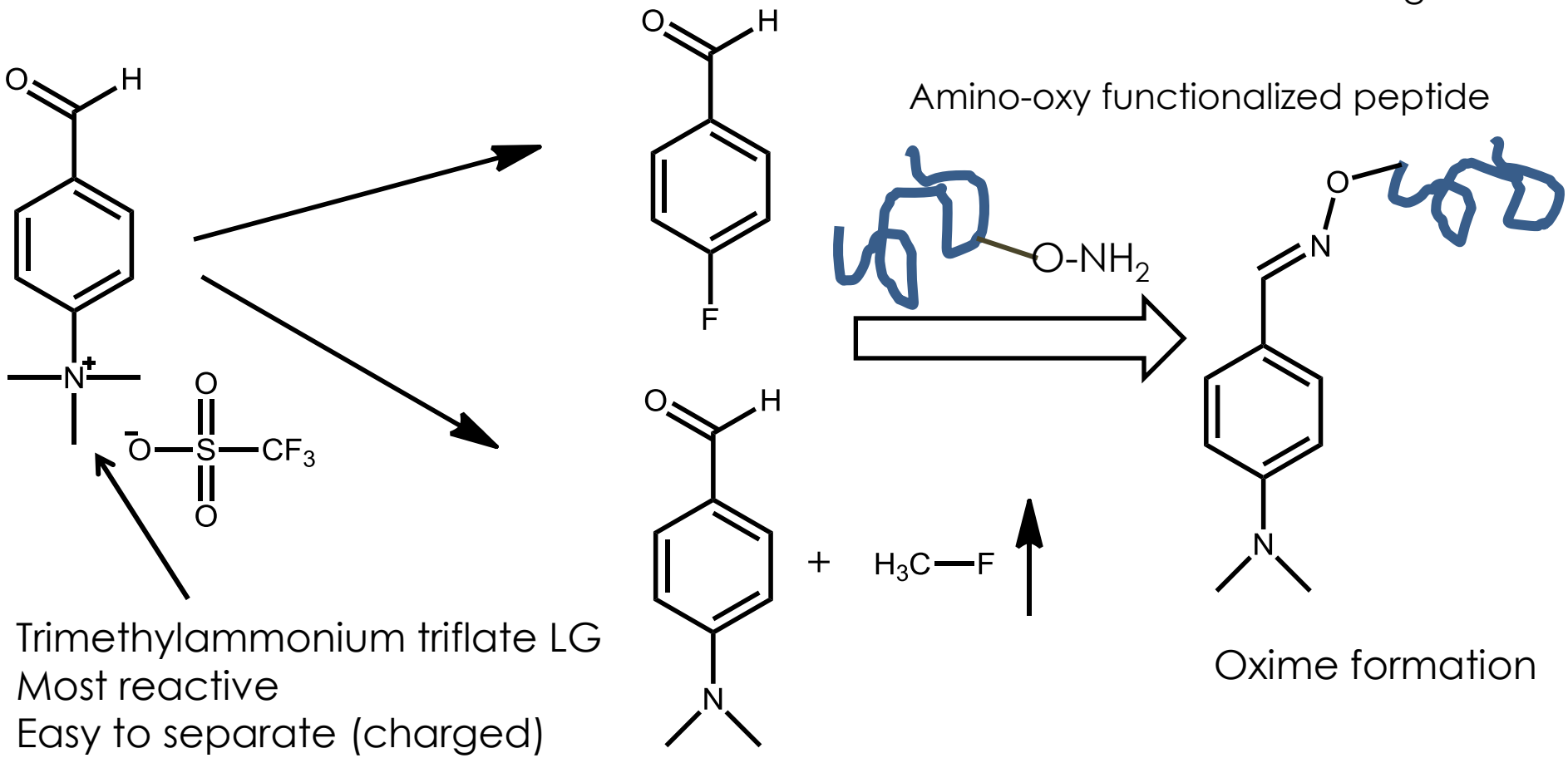
(C-F bond making is RLS. Polar effects favors addition step)

(c) Solvent effect: DMSO > DMAc (N,N,-dimethylacetamide) > sulfolane >> acetonitrile

Side Reactions in S_{NAr}

Side reactions

Fluorobenzaldehyde → site specific peptide conjugation; away from the binding sites
(Prosthetic group)



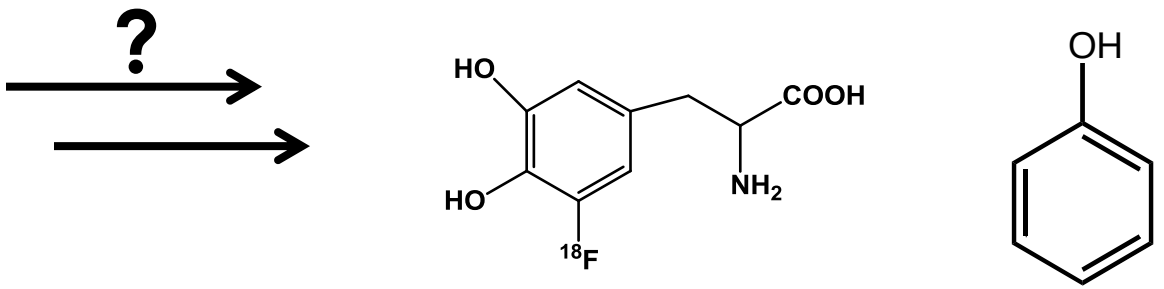
Trimethylammonium triflate LG
Most reactive
Easy to separate (charged)

Oxime formation

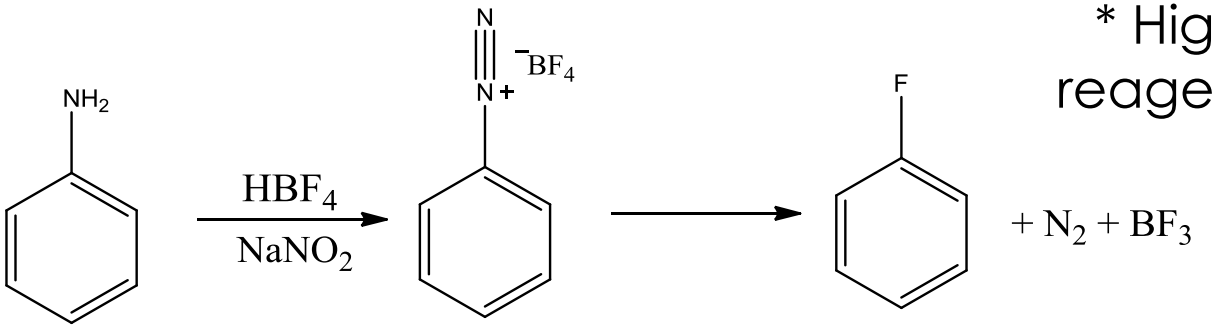
Li, X. et al. Bioconjugate Chem. 2008, 19, 1684-1688
Solin, O. et al. J Fluorine Chemistry, 2012, 143, 49-56

Nucleophilic Aromatic Substitution

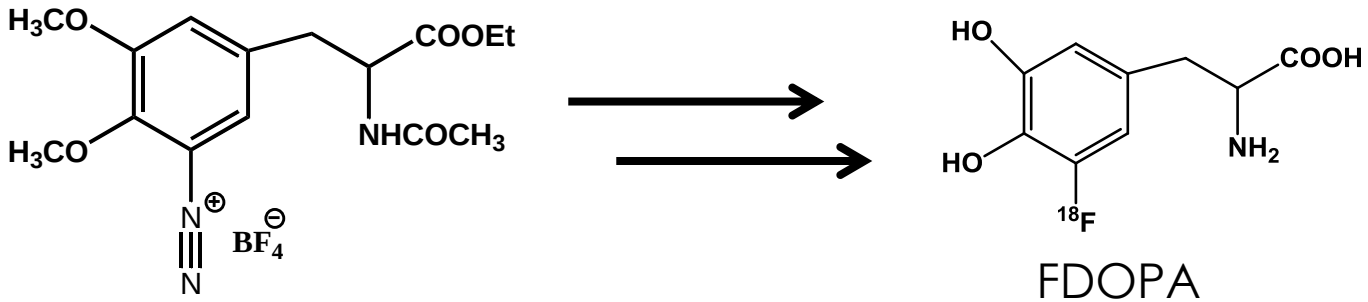
of substrate without EWG?



Balz-Shciemann reaction



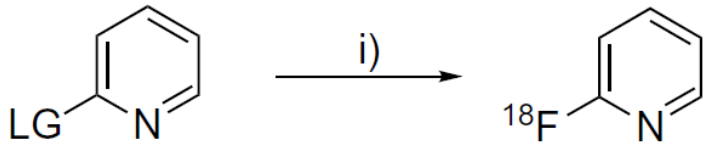
* High temperature, harsh reagent, corrosive, explosive
Low yield



FDOPA

[^{18}F]F-Nucleophilic Heteroaromatic Substitution

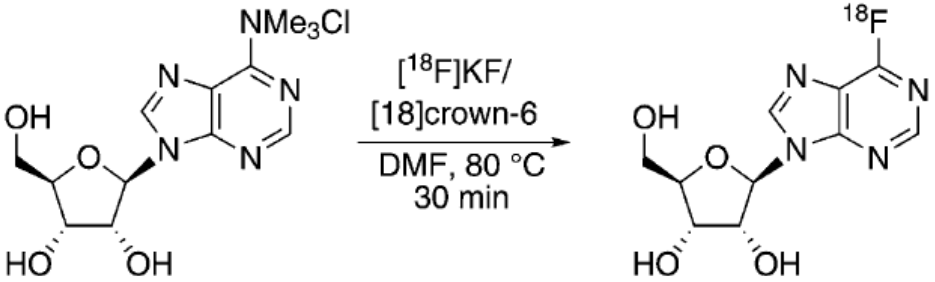
LUMO of pyridine at ortho and para position lower than benzene
No need activating group



Coenen, H.H. 2007. Basic Fluorine-18 Labeling Methods

LG	150 °C RCY (%)	180 °C RCY (%)
I	1	19
Cl	23	57
Br	25	87
NO_2	92	89
$(CH_3)_3N^+CF_3SO_3^-$	90	92

Scheme 46. i) ^{18}F]F$^-$/K_2CO_3/K_{222}, DMSO



6-[^{18}F]fluoro-9-β-D-ribofuranosylpurine
63 % RCY

Irie, T. et al. App Radiat Isot. 1982. 33 445.

TABLE 2. Temperature dependence of the radiochemical yields of ^{18}F-(IV)

Reaction temp. (°C)	Radiochemical yield (%)[1]
room temp	55–66
50–60	68–75
80–90	0.4–1.4

[1] Yields from the reaction for 20 min of 15 μmol of (II) with the solubilized K^{18}F (1.2 μmol) in DMF-CE solution before addition of (II).

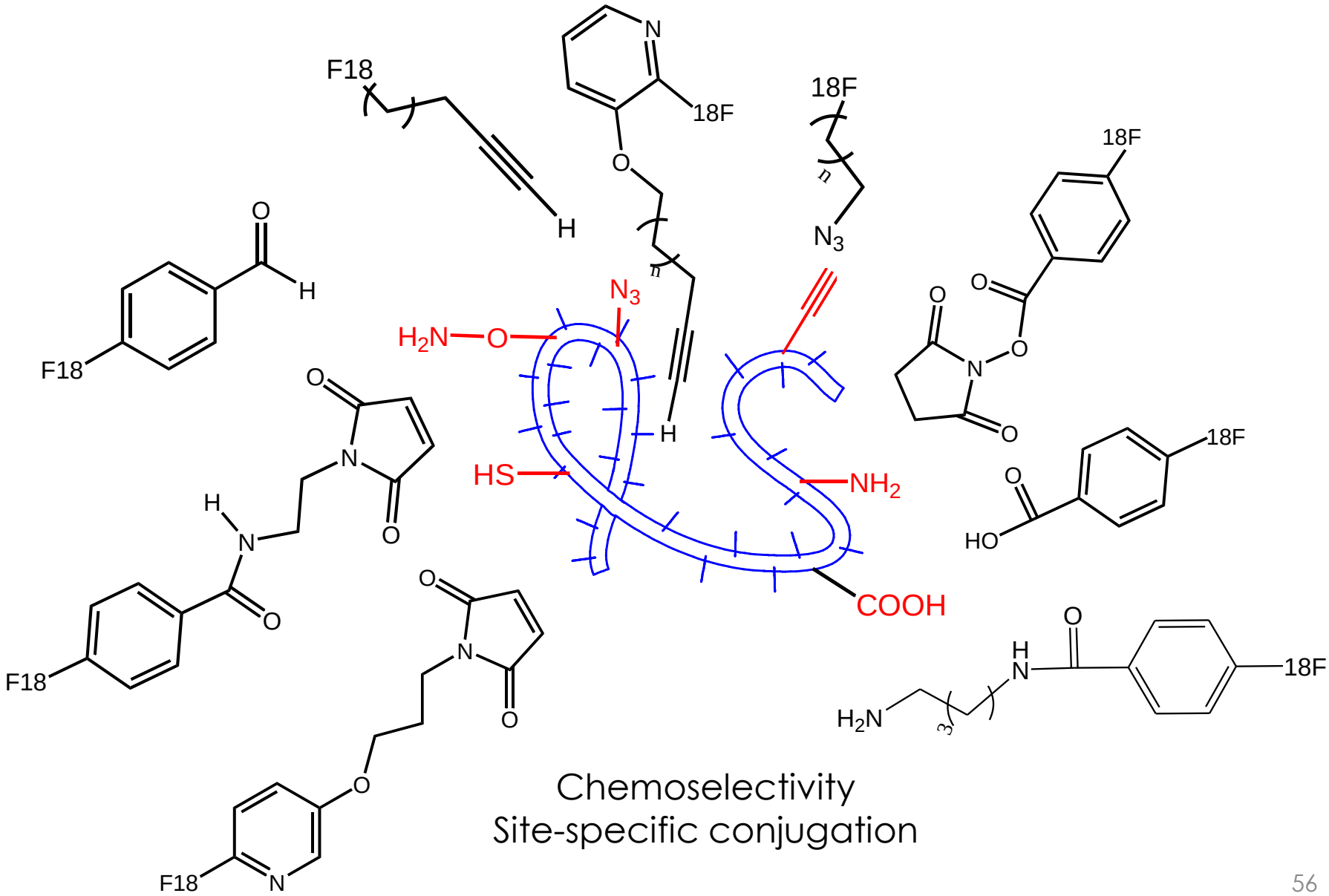
Gouverneur, V. et al. Angew Chem Int Ed. 2012, 51, 2-14

Summary Nucleophilic Substitution

1. Preferred method
2. High specific activity of $[18F]F^-$ vs $[18F]F_2$ (1740 Ci/umole vs 0.1 Ci/umole)
3. Easy to handle (liquid vs gas)
4. $[^{18}F]F^-$ Can be transported and distributed to nearby imaging clinicic (Decentralized model of PET probe production)
5. S_N2, leaving group, solvent, phase transfer catalyst and base
6. Side reactions, optimization
7. Activated substrate and good leaving group for S_{NAr}

INDIRECT F18-LABELING

Commonly used [18F]Prosthetic groups



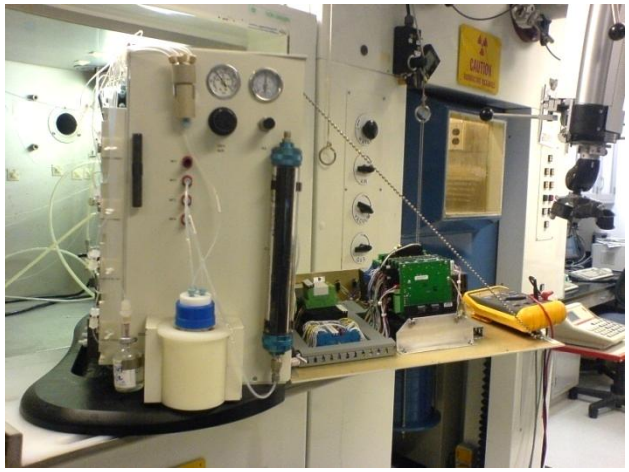
Chemoselectivity
Site-specific conjugation

Banister et al. Current Radiopharm, 2010, 3, 68-80

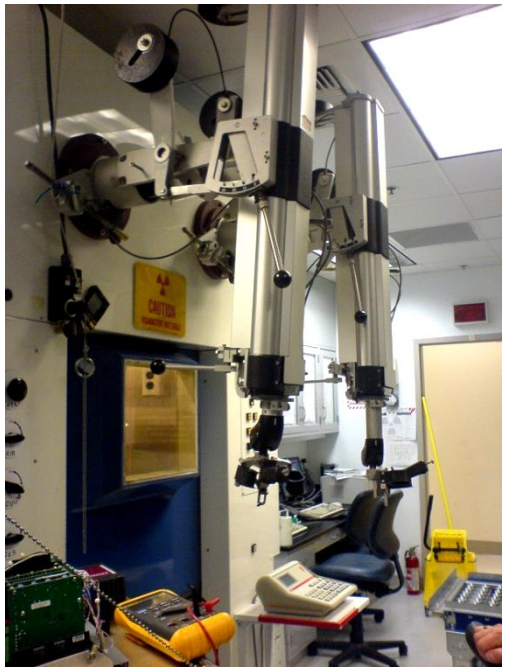
CHALLENGES IN F18 RADIOCHEMISTRY

Radiochemistry Requirements

Hot cells. Pb shielding



Automation



Robotic arms

Expensive, bulky synthesizer
1-synthesizer, 1-probe workflow

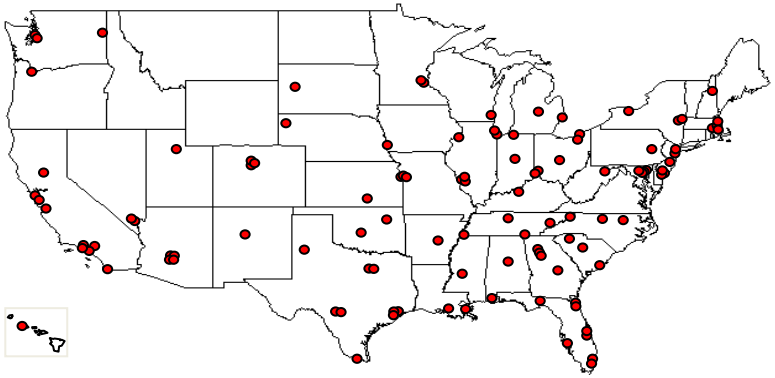
Dedicated radiochemistry lab

- **High-cost**
- **Low-throughput**
- **Bulky**
- **Complicated**
- **Need skillful personnel**
- **Limited flexibility**

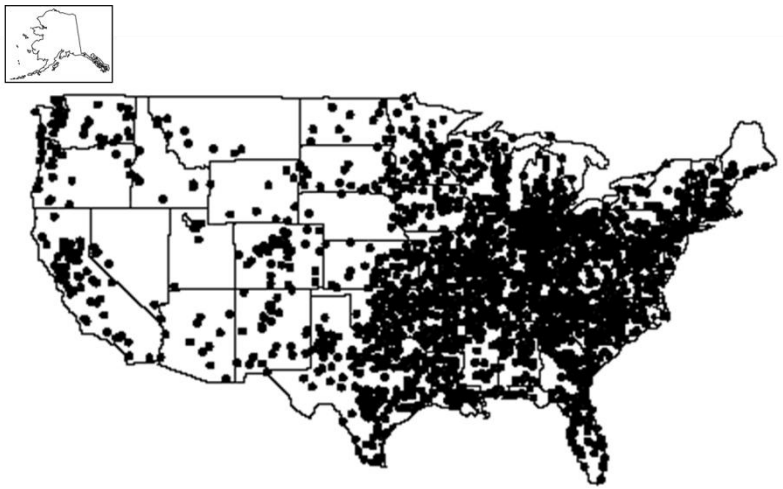
Slide adapted from Clifton Shen M248

A Typical Workflow of PET imaging

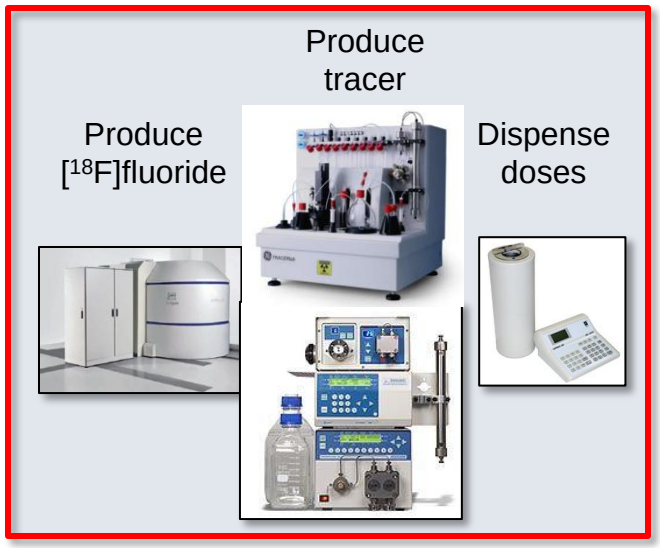
Centralized PET probes production



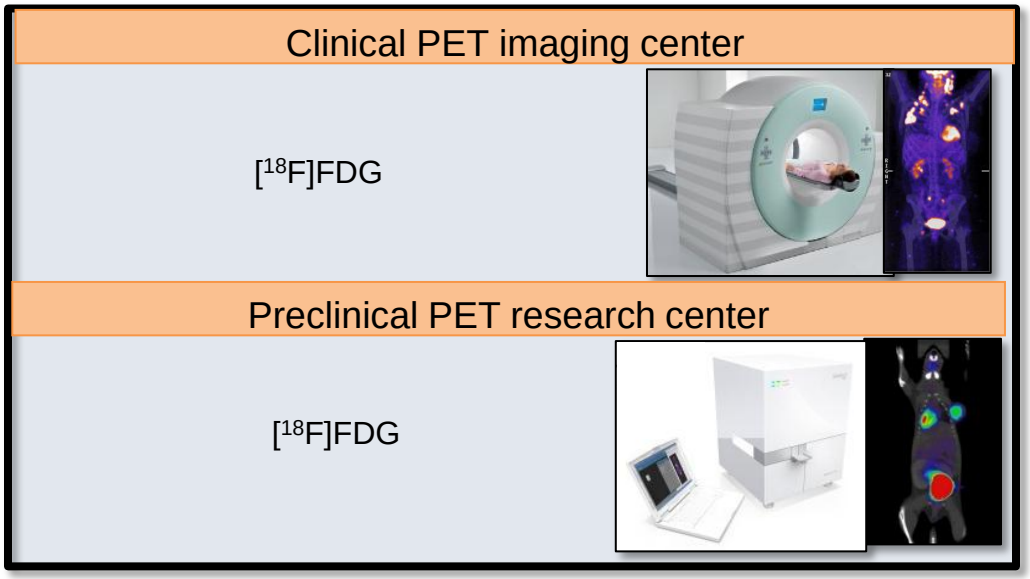
- PET radiopharmacies



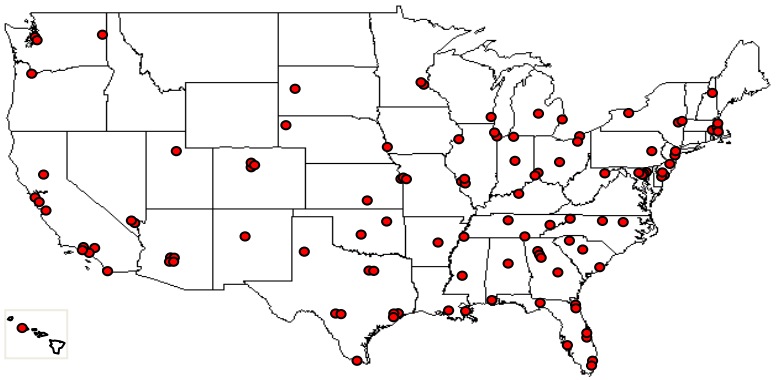
- PET/CT imaging clinics



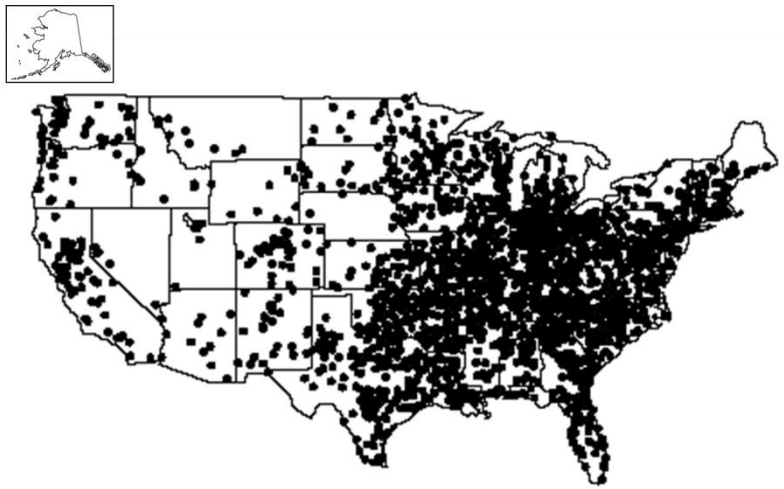
[18F]FDG



DeCentralized Production of PET Probes



● PET radiopharmacies



● PET/CT imaging clinics

Produce $[^{18}F]$fluoride

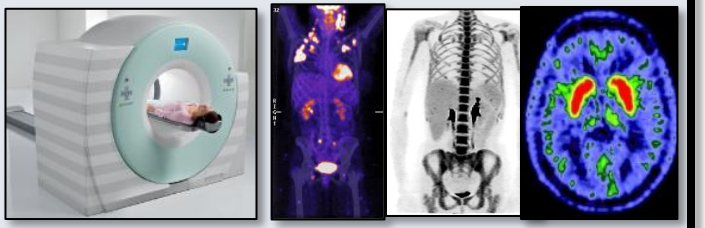
Dispense doses

$[^{18}F]F^-$ ion

Clinical PET imaging center

Produce tracer

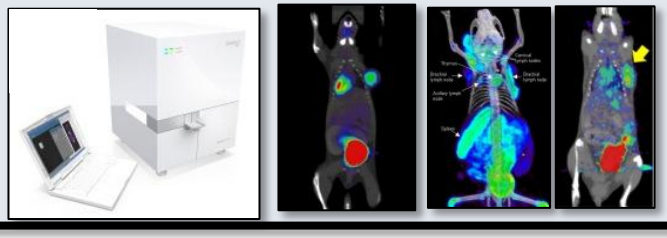
$[^{18}F]$FDG
$[^{18}F]$FLT
$[^{18}F]$FDOPA



Preclinical PET research center

Produce tracer

$[^{18}F]$FDG
$[^{18}F]$FAC
$[^{18}F]$SFB-Db



New technologies, simplified chemistry, higher kinetics, higher reaction selectivity

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