San Diego State University Georgia, Tbilisi, Georgia
Faculty of Chemistry

Synthetic strategies to obtain [^{18}F]radiolabeled compounds

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Desirable properties of radiotracers

Minimal difference in biological activity from the ordinary biomolecule

Stability of attachment between radionuclei and biological molecules.

Labeling compounds with ^{18}F nuclei is attractive due to its several advantageous properties

- Lowest energy positron emission leads to greatest spatial resolution of PET and decrease of risk for patient.
- Half-life of 109.8 min allows for synthesis and delivery from external site to the PET centers and finds a balance to allow for a minimized dose of radioactive substance to a patient.
- Strong bond between fluorine and carbon.
- Usually minimal effect on the biological activity of the compound to be labeled, C-F bond usually mimics C-O bond quite well.

Radionuclide	Mode of Decay	Half-life	Emax (mean)
^{18}F	β^+	109.8 min	0.63 MeV
^{68}Ga	β^+	68 min	1.90 MeV
^{99m}Tc	IC	6.02 h	0.14 MeV
^{111}In	EC	2.8 d	0.24 MeV
^{123}I	EC	13.2 h	0.16 MeV

Desirable properties of chemical reactions

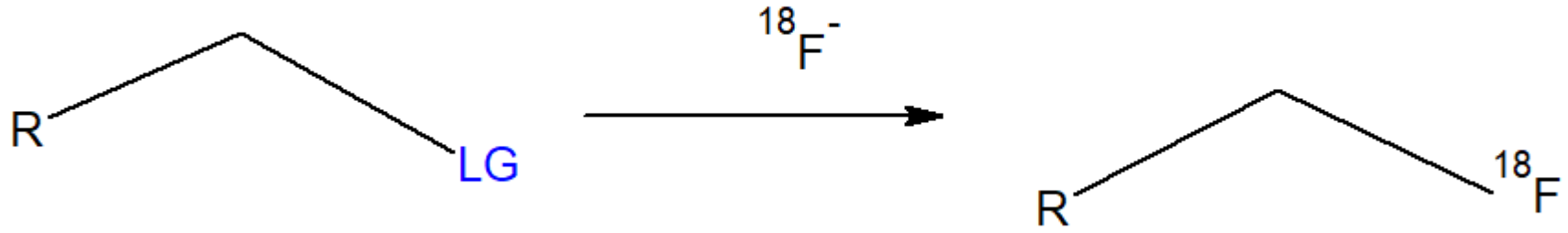
- Chemo- and regioselectivity
- As quick a reaction as possible –^{18}F decays, therefore it is desirable to put the ^{18}F on the very last stage (or withing trivial and fast transformations)
- Ease of product purification

There are several strategies and modifications of the labeling compounds with ^{18}F

- ❑Most common reactions are nucleophilic substitutions:
  - Nucleophilic substitution at saturated carbons – S_N2
  - Nucleophilic substitution in aromatic ring- S_NAr
- ❑Electrophilic aliphatic/aromatic reactions with $^{18}F_2$
- ❑Organometallic chemistry can be used
  - Catalysis or organometallic substrates
  - Coordination complexes can be used for labeling some metabolites readily
- ❑Electrochemical routes have been proposed and shown to work
- ❑Prosthetic groups can be used for indirect incorporation of ^{18}F

Nucleophilic substitution at saturated carbons – S_N2. Putting ^{18}F in the molecule.

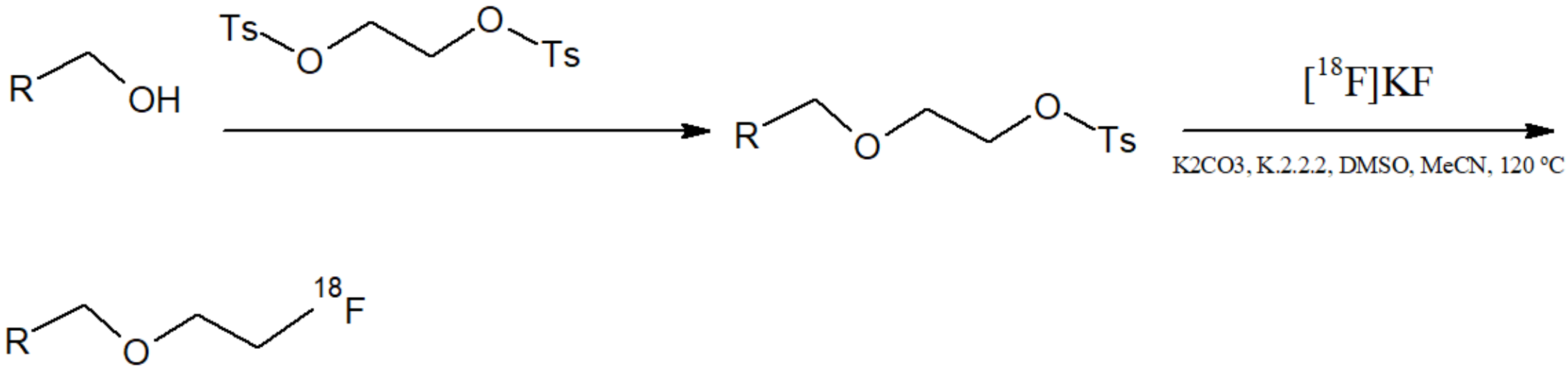
General Reaction



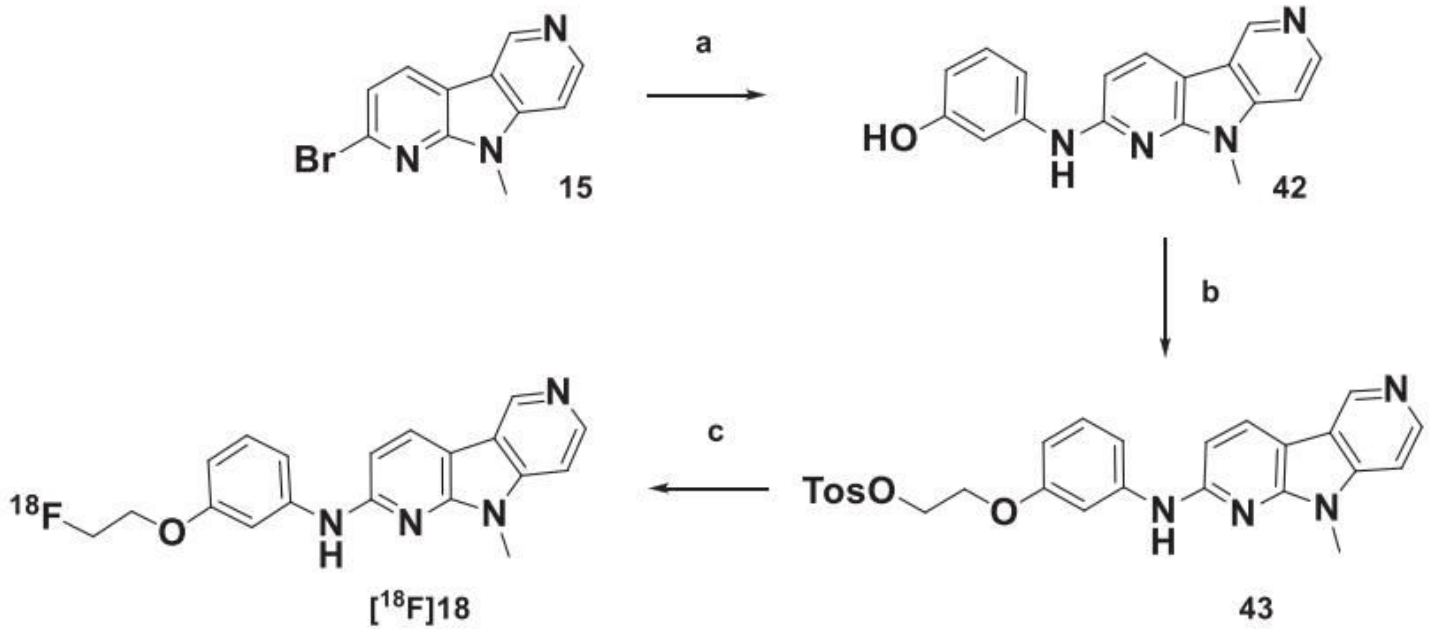
Applied conditions:

- Kryptofix 2.2.2
- Polar aprotic solvents
- Weak, non-nucleophilic base, K_2CO_3 or Cs_2CO_3
- Elevated temperatures, usually 100 – 150 ºC

Common schemes



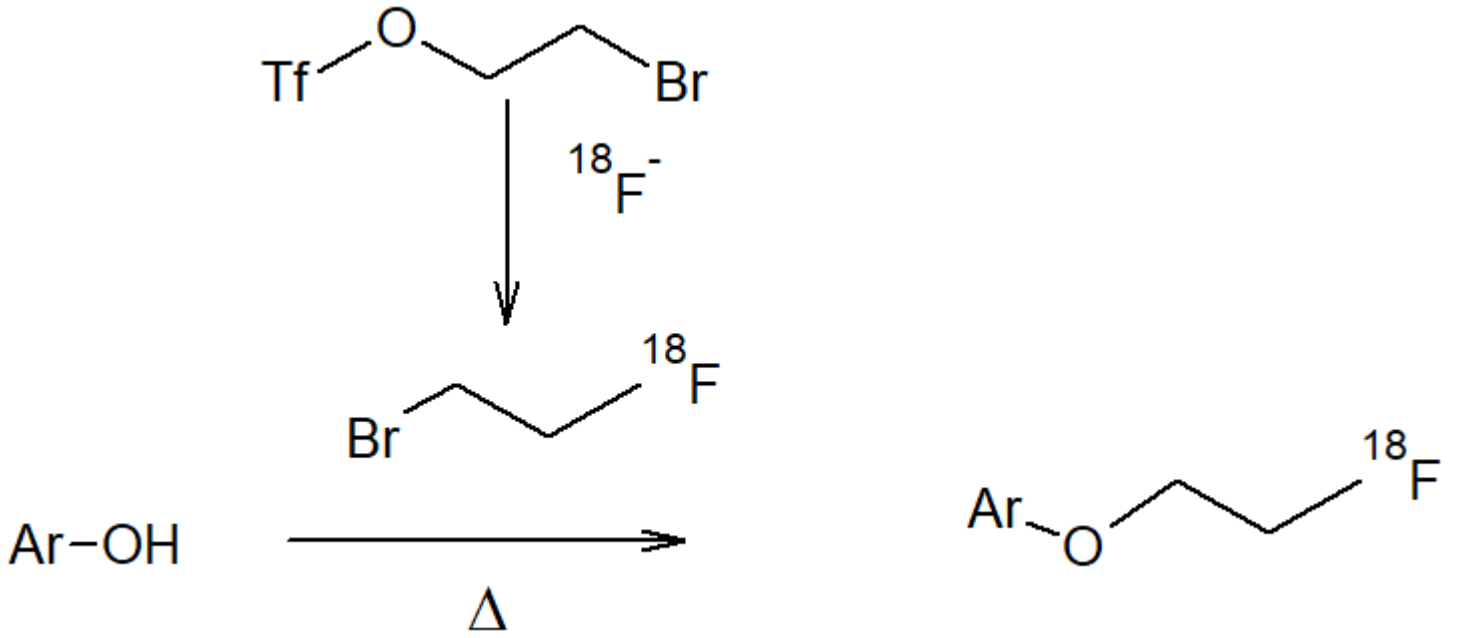
Exemplification

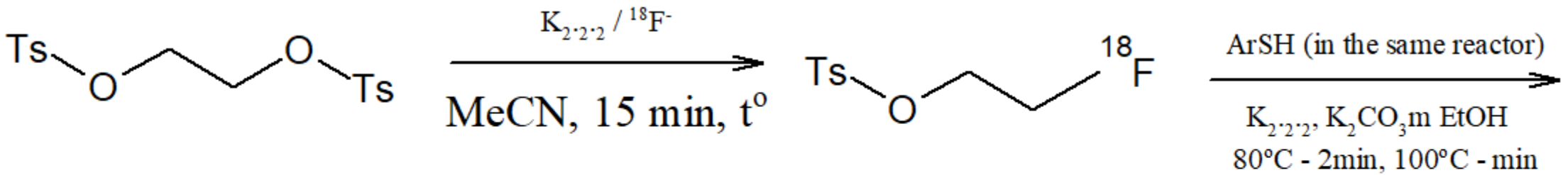


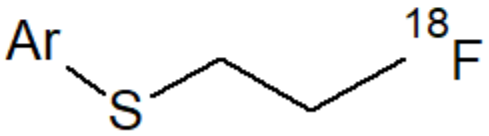
Scheme 7. Reagents and conditions: (a) $Pd(OAc)_2$, XantPhos, Cs_2CO_3, 3-aminophenol, 1,4-dioxane, 110 °C, 3 h, 74%. (b) Cs_2CO_3, ethane-1,2-diyl bis(4-methylbenzenesulfonate) DMF, 80 °C, 5 h, 20%. (c) [^{18}F]fluoride, K_2CO_3, Kryptofix®222, MeCN, DMSO, 120 °C, 15 min, 3% (d.c.).

Reference [1]

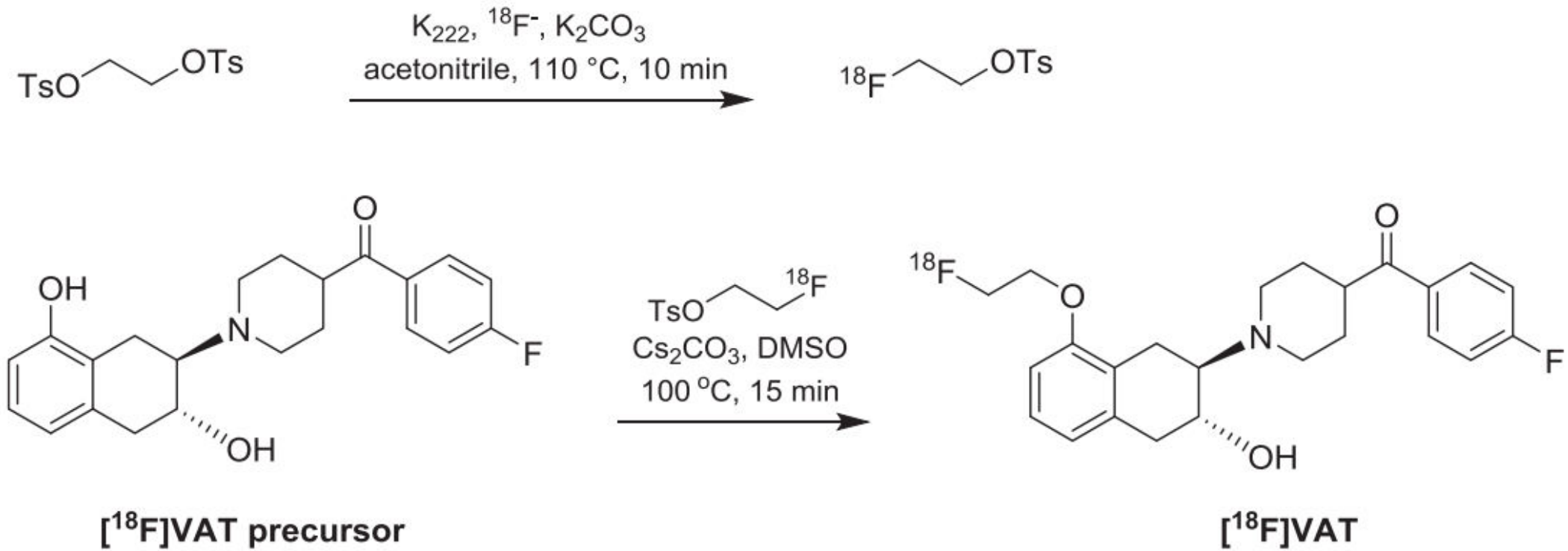
Common Schemes







Exemplification



Scheme 1. Radiosynthesis of [^{18}F]VAT using a two-step procedure.

Reference [2]

Exemplifications

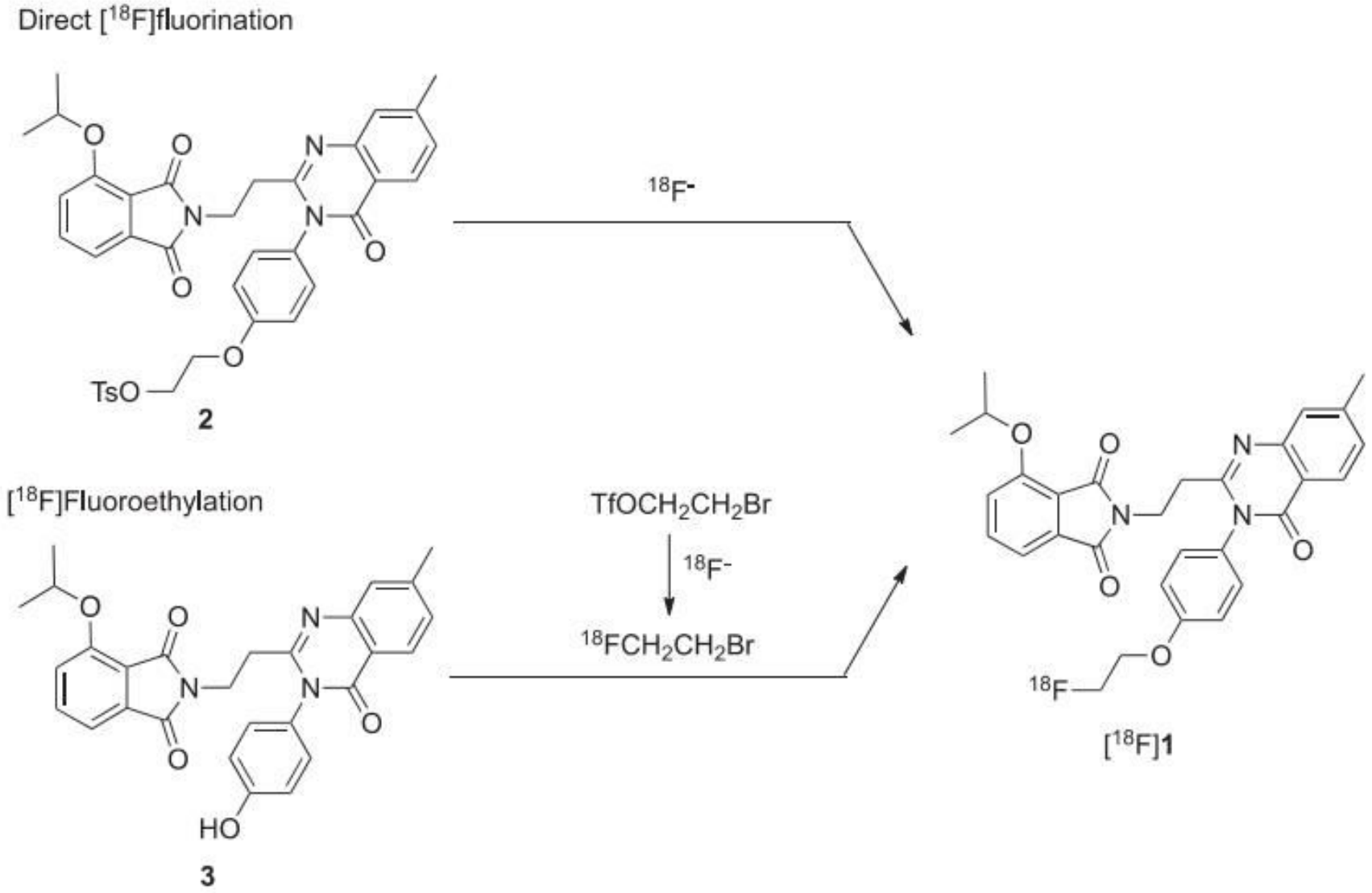


Fig. 2. Radiosynthesis of [^{18}F]**1** by [^{18}F]fluorination of tosylate precursor **2** with [^{18}F]F$^-$ and [^{18}F]fluoroethylation of phenol precursor **3** with [^{18}F]FEtBr in this study.

Reference [3]

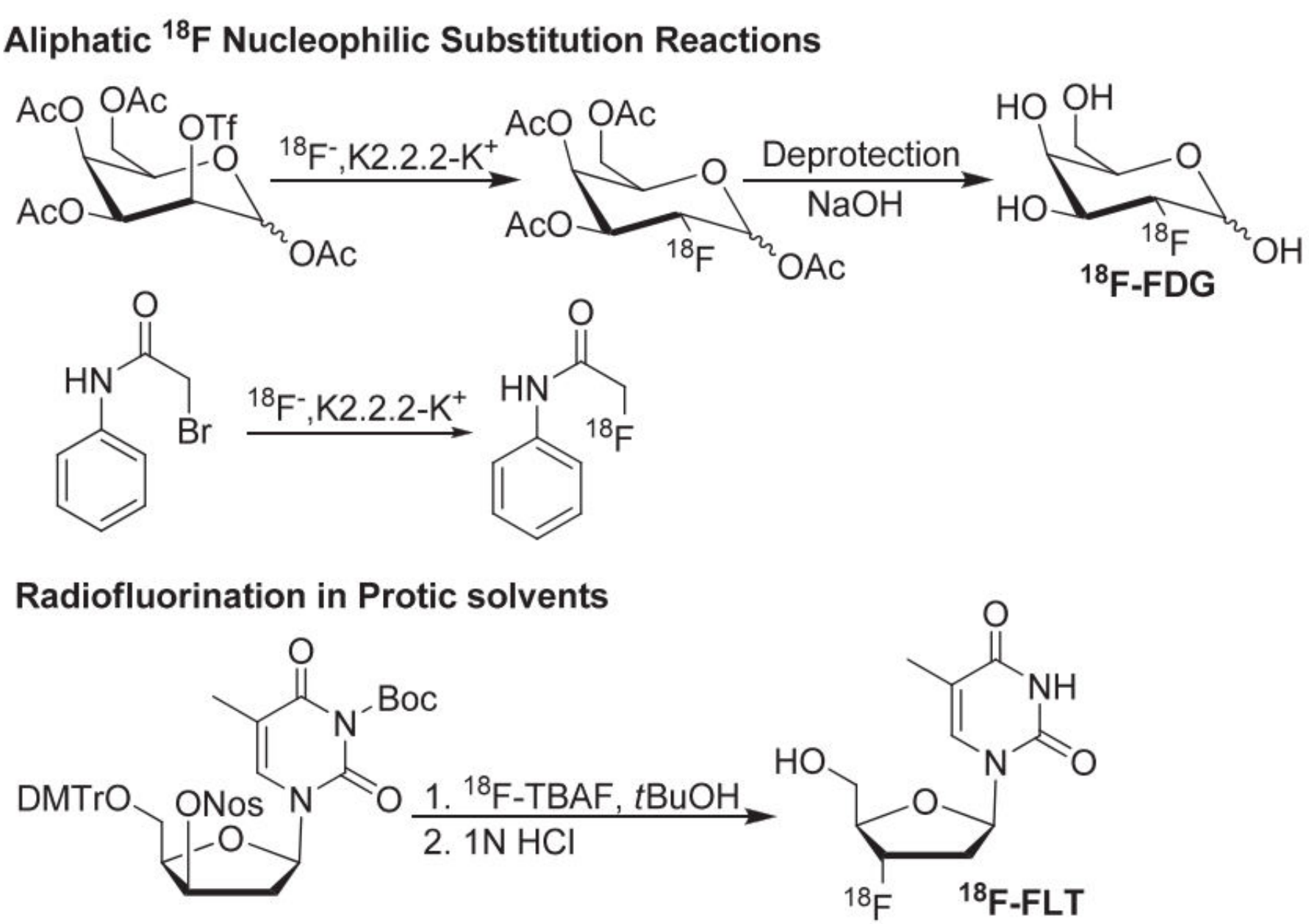
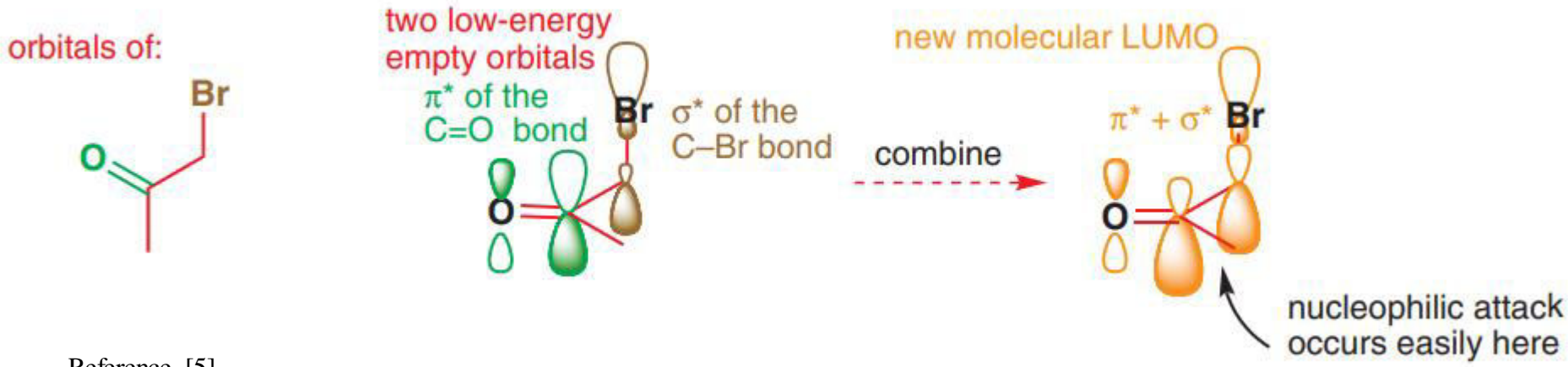


Fig. 15. Aliphatic ^{18}F nucleophilic substitution reactions.

Reference [4]

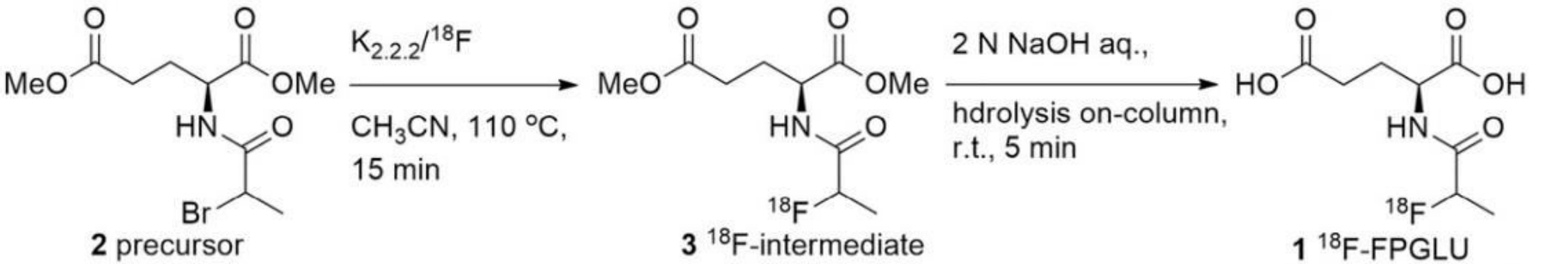
α-carbon substitutions (rate enhanced due to orbital reasons)

Nucleophiles attack α-carbon rather than carbonyl carbon if carbonyl group is compatible, in this case, even if fluoride attacked carbonyl, this attack is reversible, while attack on saturated carbon is not.



Reference [5]

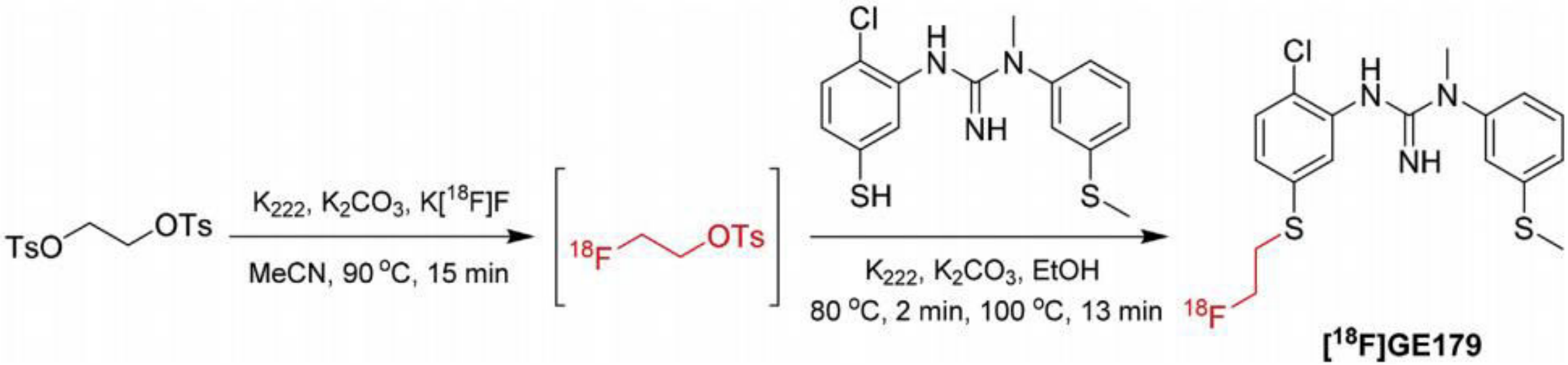
Application of α-carbon substitution



Scheme 2. The two-step route of ^{18}F-FPGLU radiosynthesis.

Reference [6]

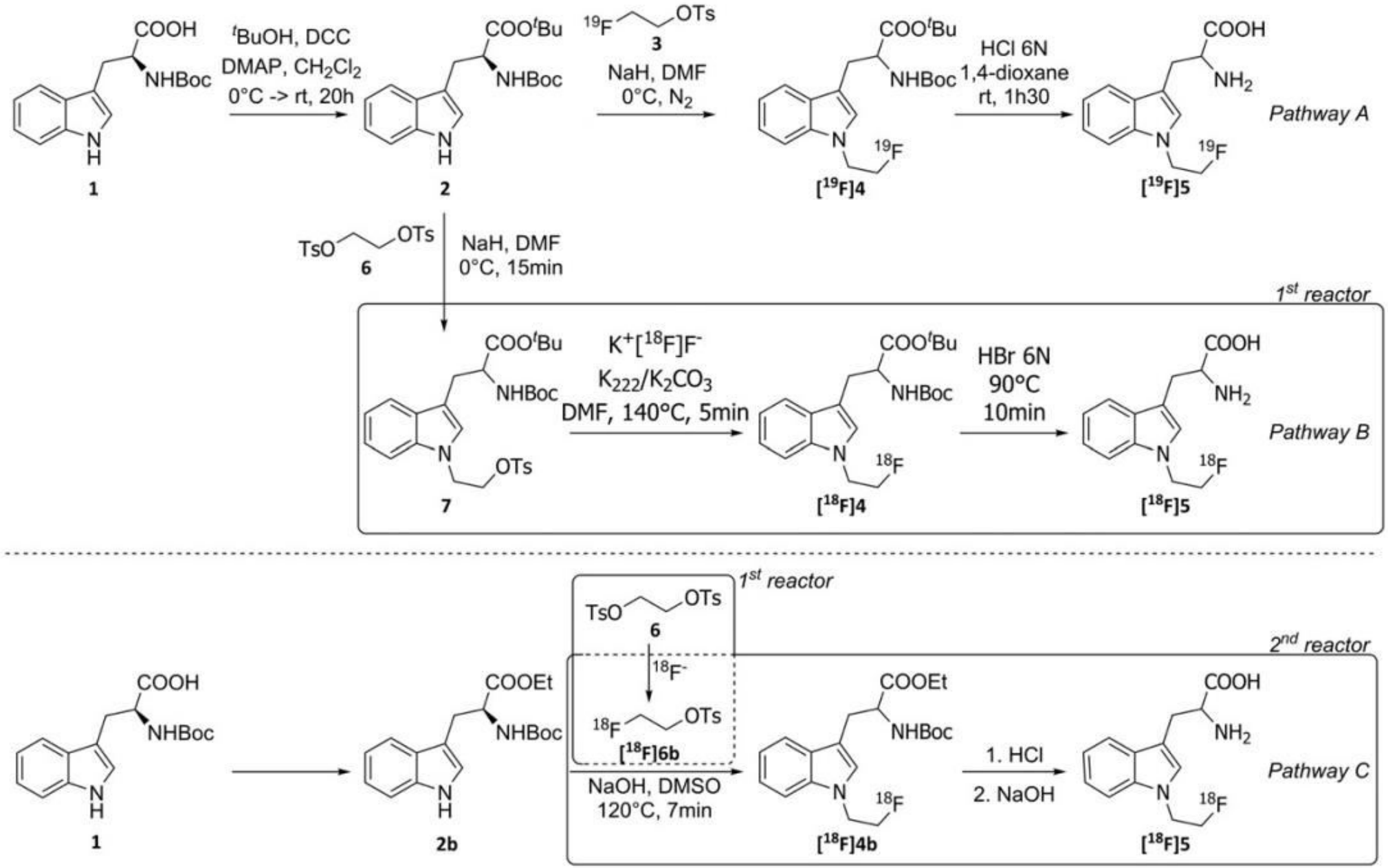
Automation of process



Scheme 1. One-pot two-step radiosynthesis of [^{18}F]GE179 in the PETCHEM automated module.

Total process time 110 min with a radiochemical yield of 12 ± 6% (n = 4, decay corrected), radiochemical purity > 95%, molar activity of 146 ± 32 GBq/μmol (at the end of synthesis), an average mass of GE179 at 2.2 μg/batch, and total impurities less than 0.5 μg/batch (n = 4)

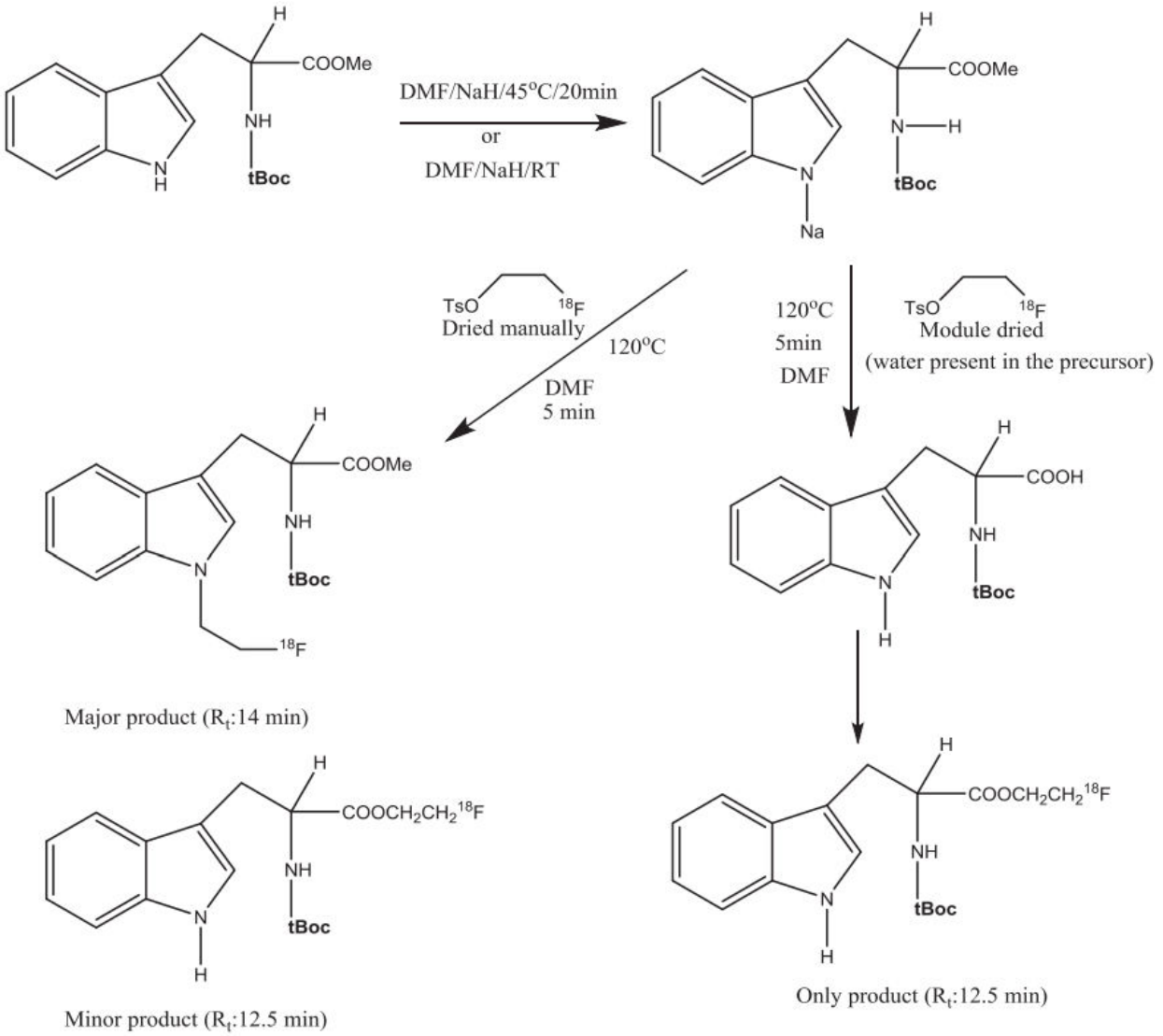
Reference [7]



Scheme 1. General scheme for the synthesis of 1-(2-[**19F**]fluoroethyl)-tryptophan (DL-[**19F**]**5**) (Pathway A), the radiosynthesis of 1-(2-[**18F**]fluoroethyl)-tryptophan (DL-[**18F**]**5**) following our strategy (Pathway B), or following the strategy involved by Sun & al. (Pathway C) [9]. Reactions carried out in the same reactor are framed together in the pathways above.

Reference [8]

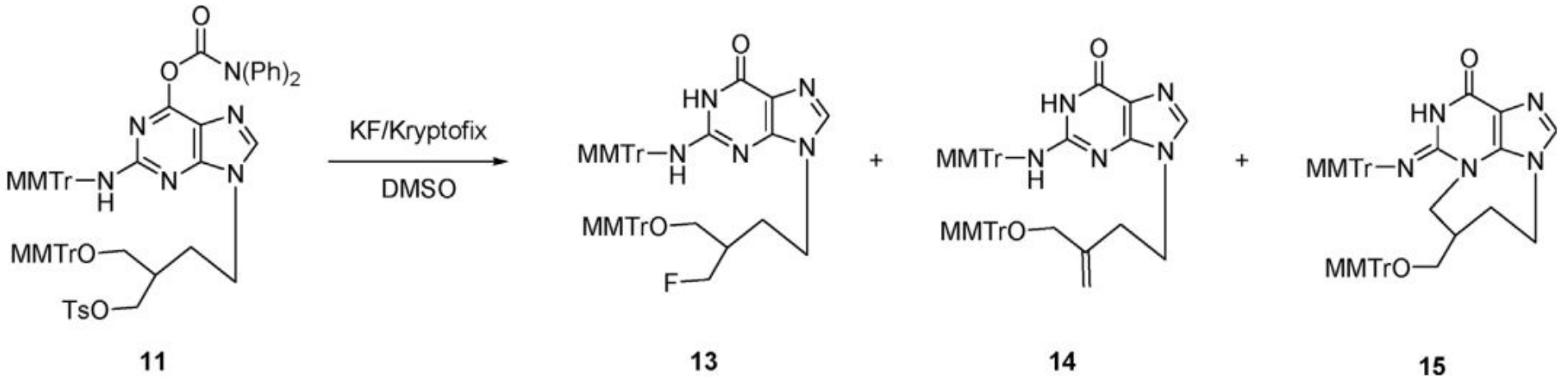
Challenges with automation



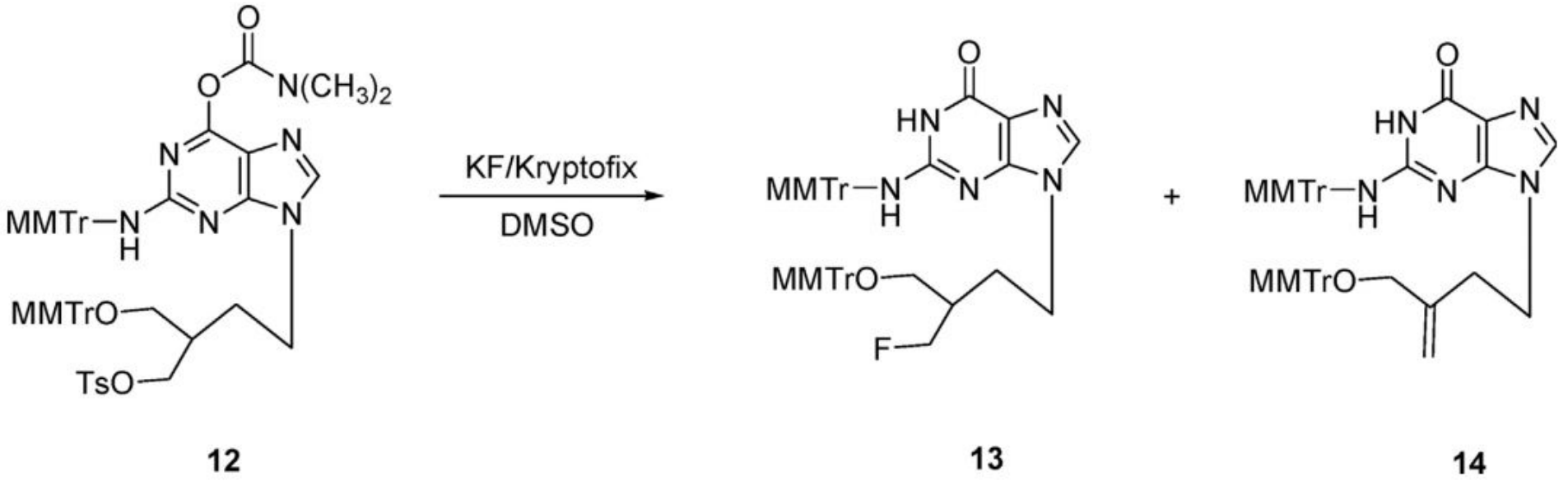
Scheme 3. Synthesis of [^{18}F]-1-N-fluoroethyl-tBoc-tryptophan methyl ester.

Reference [9]

Challenges with labeling via S_N2 reaction



Scheme 3. Nucleophilic fluorination reaction of diphenylcarbamoyl-protected penciclovir derivative.



Scheme 4. Reaction of dimethylcarbamoyl-protected penciclovir analog with the fluoride ion.

Reference [10]

Eliminations and, sometimes, hydrolysis can happen

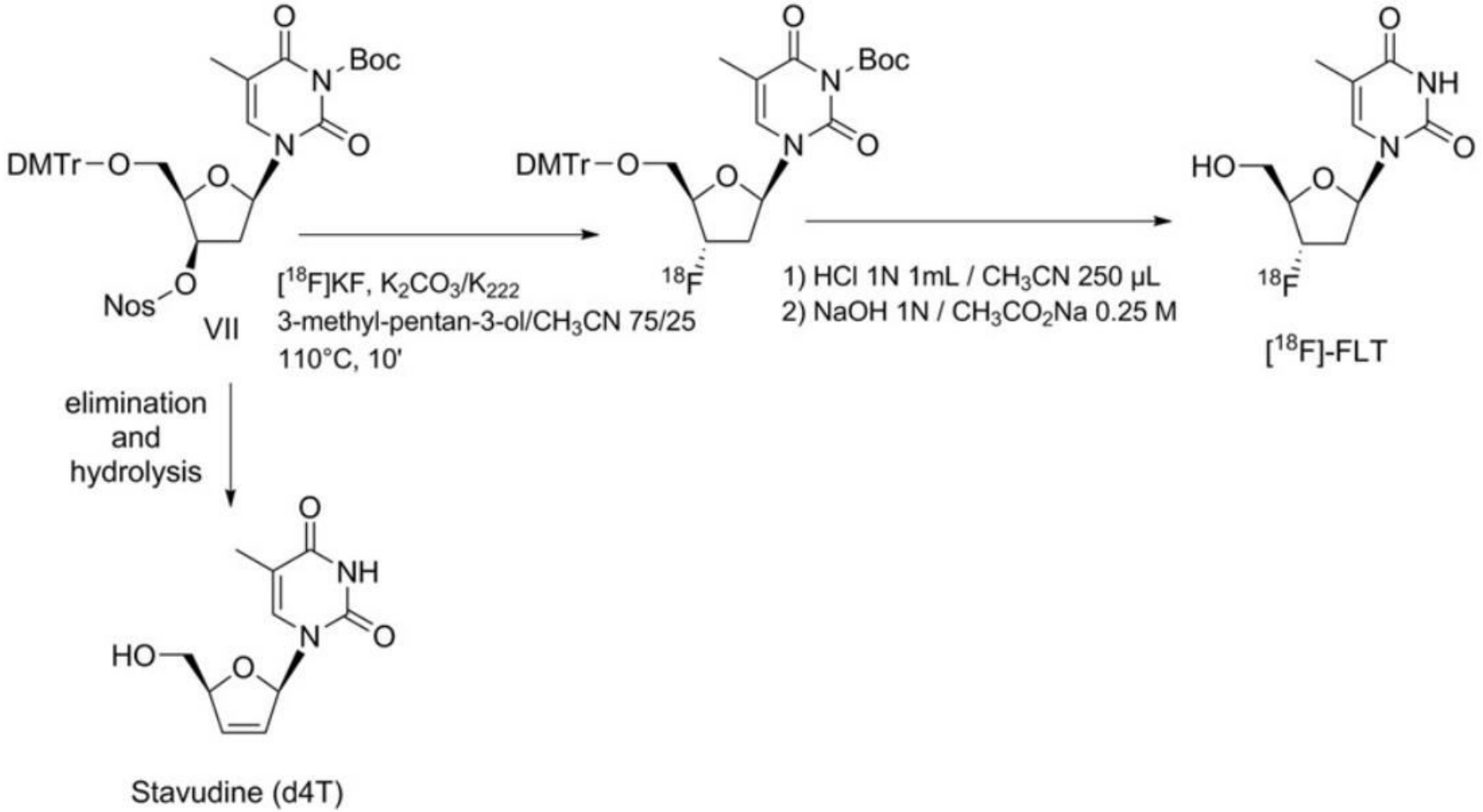


Fig. 2. Radiosynthesis of [^{18}F]FLT and formation of stavudine (d4T).

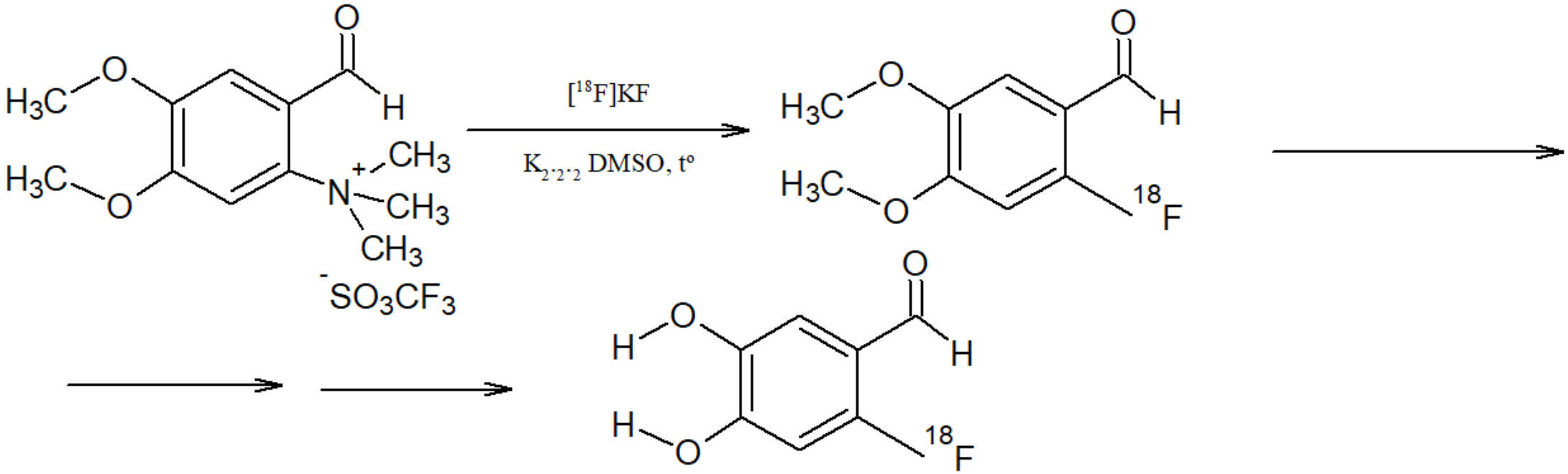
Reference [11]

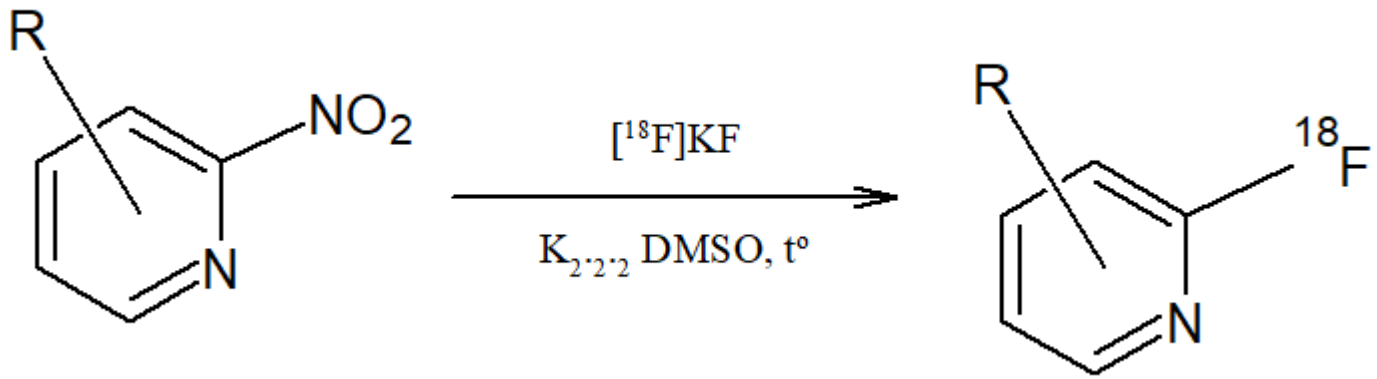
Nucleophilic substitution reaction in aromatic ring- S_NAr

- Pyridines and pyrimidines
- Benzene rings with strongly electrowithdrawing groups

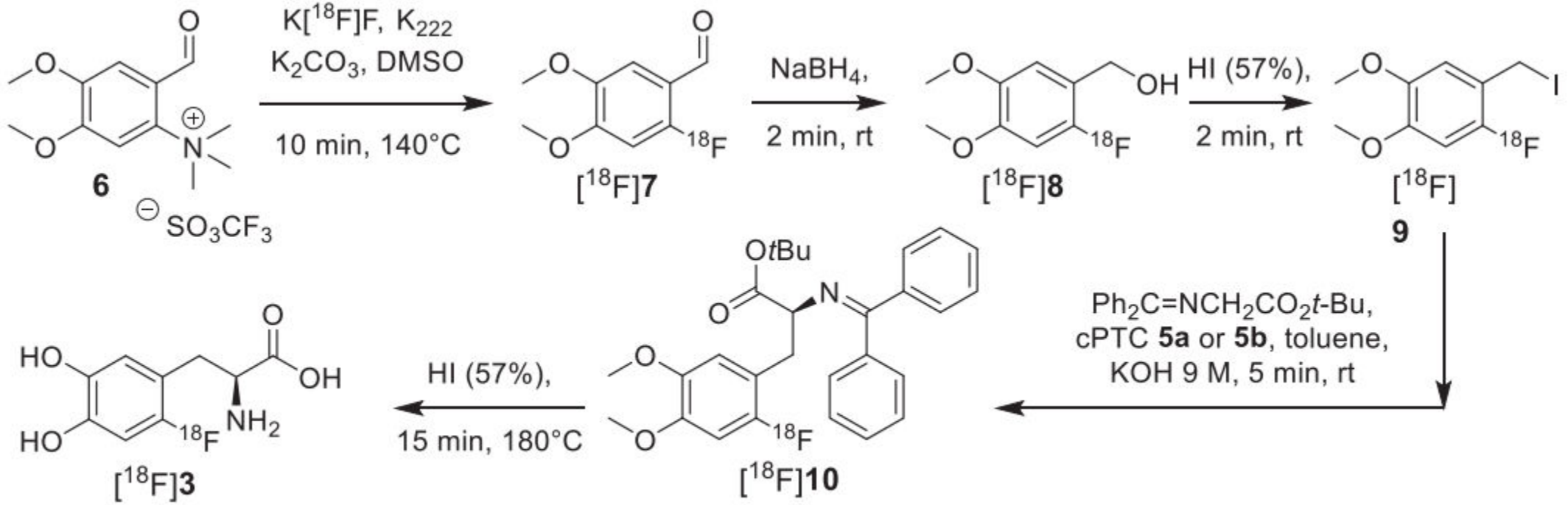
Variety of activating (electrowithdrawing) and leaving groups

Common schemes for S_NAr substitutions



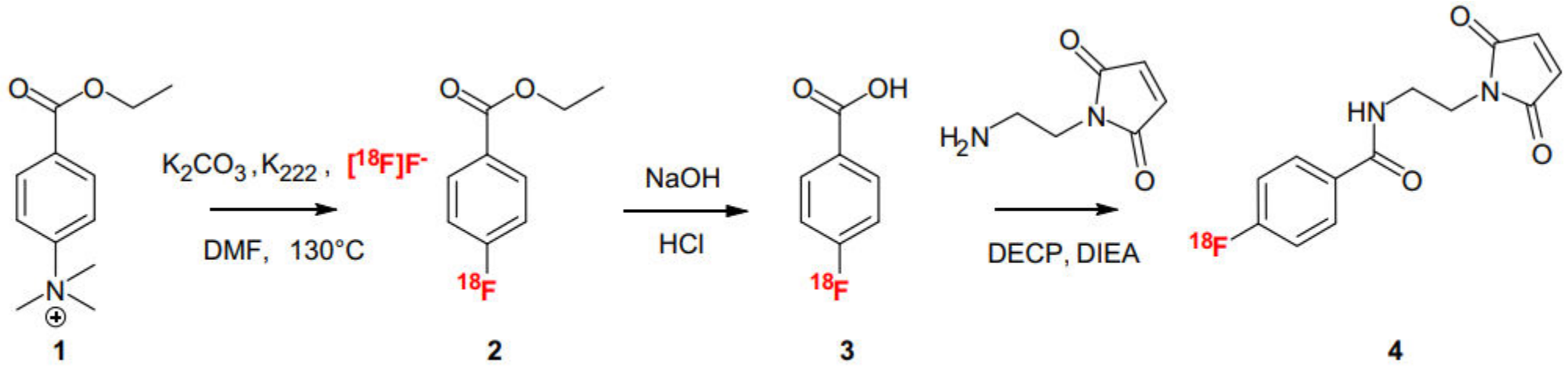


Synthetic pathways for S_NAr



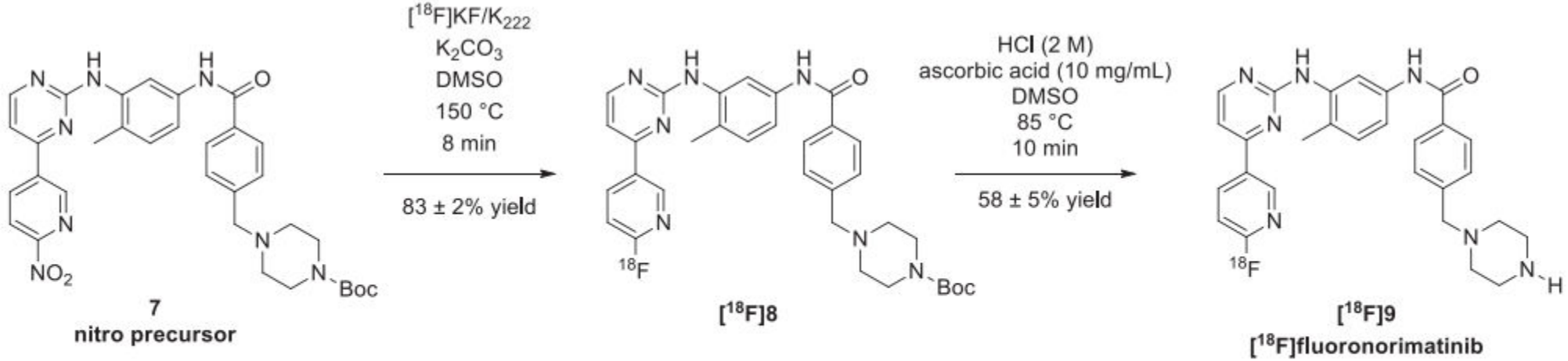
Scheme 2. Schematic depiction of the automated synthesis pathway using the chiral phase-transfer catalysts **5a**/**b** [41].

Reference [12]



Reference [13]

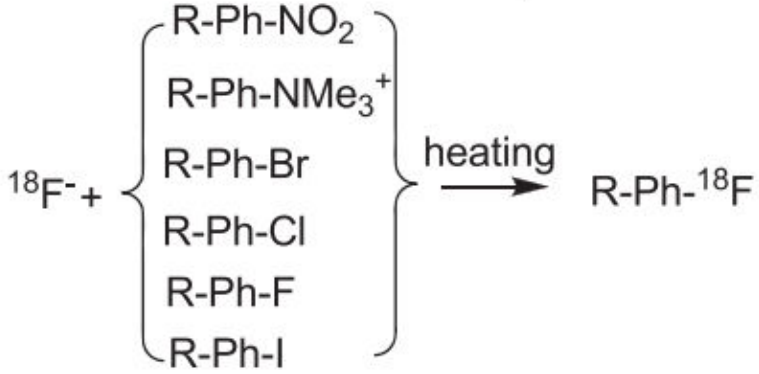
Scheme 1. Radiosynthesis of [^{18}F]FBEM.



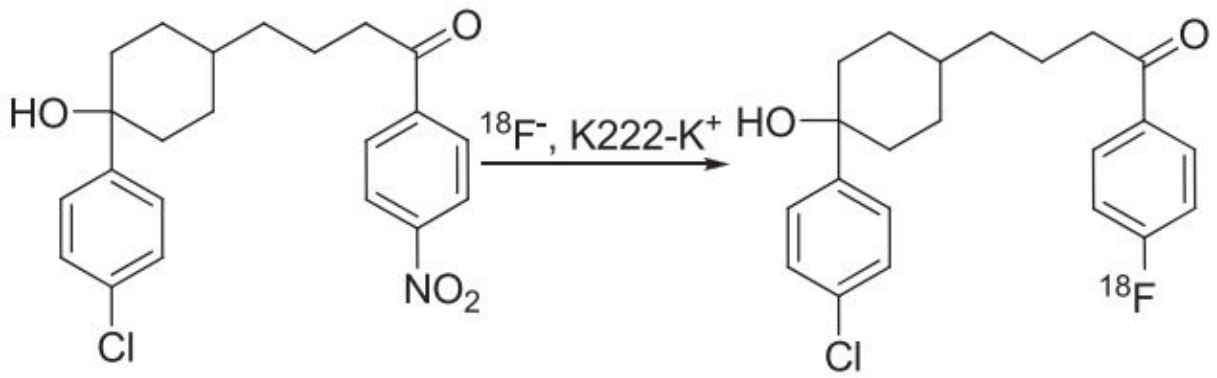
Scheme 3. Two-step radiosynthesis towards [^{18}F]**9** starting from precursor **7**: incorporation of [^{18}F]fluoride, followed by deprotection and purification. Total yield of the radiosynthesis: 22 ± 3% after 90 min overall synthesis time.

Reference [12]

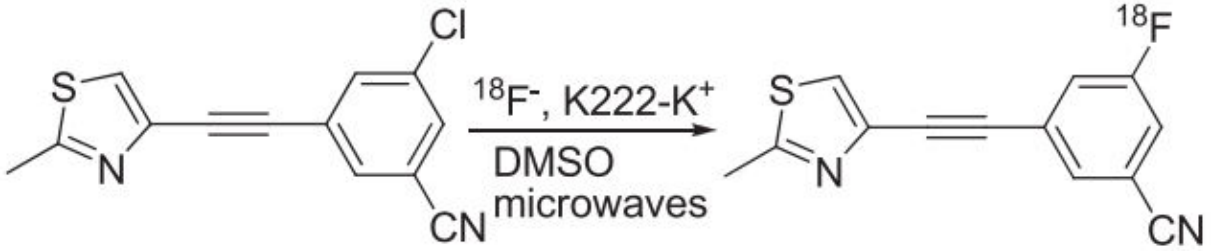
Direct Aromatic ^{18}F Nucleophilic Reactions



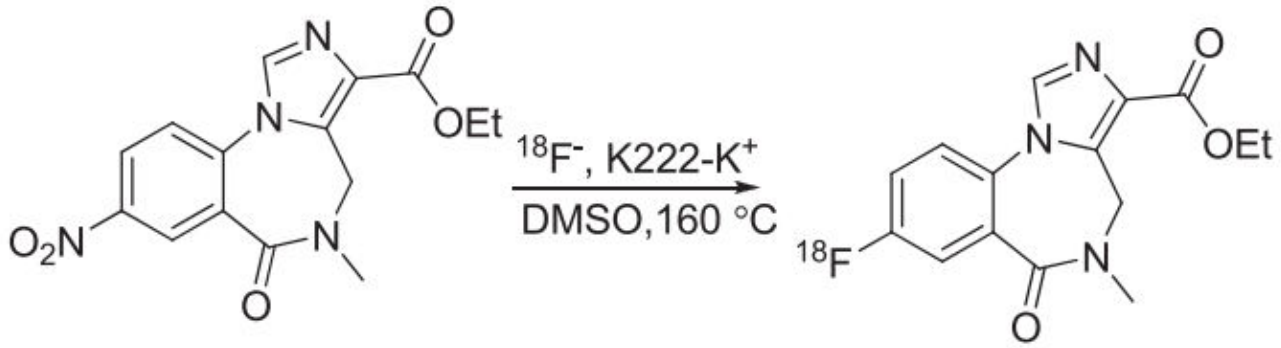
Direct synthesis of ^{18}F-haloperidol



^{18}F Nucleophilic Reaction with electron-withdrawing group at *m*-position

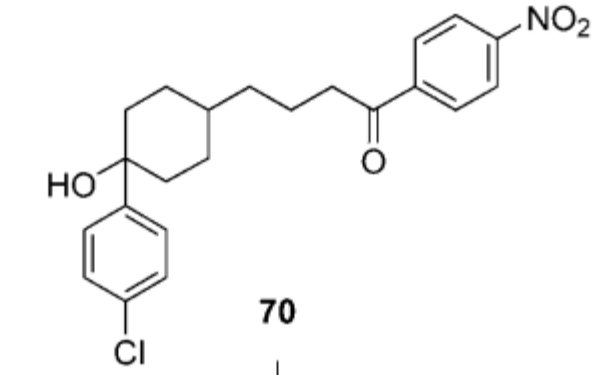


^{18}F Nucleophilic Reaction on weakly activated compound



Reference [4]

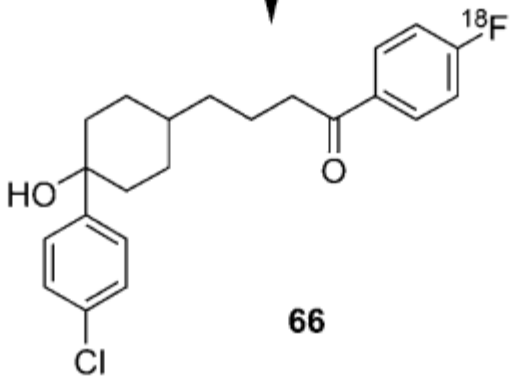
Fig. 12. Direct aromatic ^{18}F nucleophilic reactions.



70

$[^{18}F]KF \cdot K_{222}$

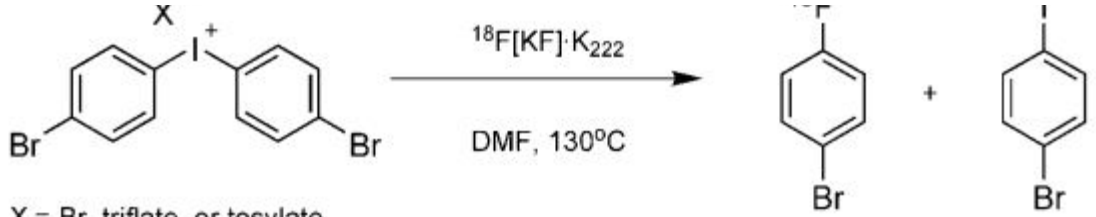
Direct Nucleophilic ^{18}F Substitution



66

Reference [14]

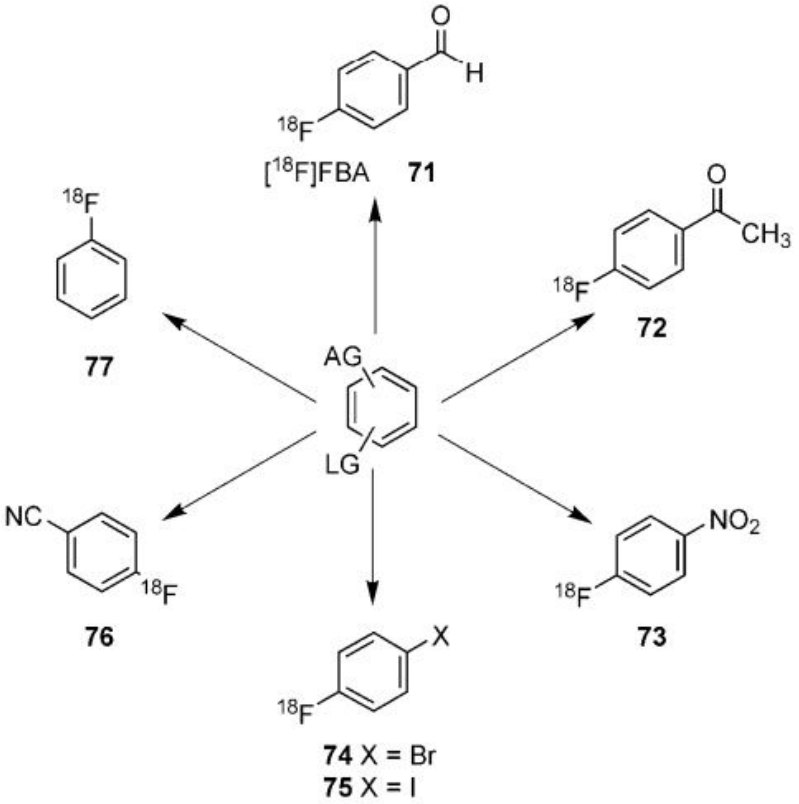
Scheme 37. Direct synthesis of [^{18}F]haloperidol (**66**) from the corresponding nitro precursor **70**.



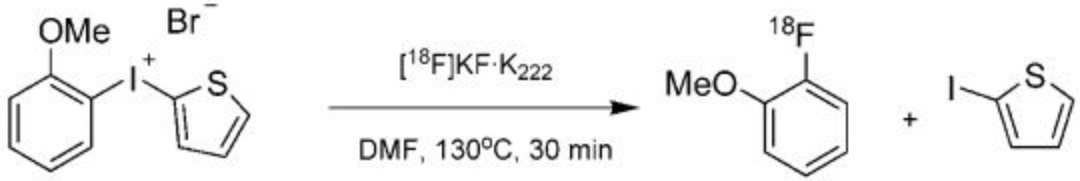
X = Br, triflate, or tosylate

74

Scheme 40. One-step synthesis of **74** from bis(4-bromophenyl)iodonium salts.



Scheme 38. Synthesis of simple [^{18}F]fluoroaromatic precursors by direct nucleophilic ^{18}F substitution. AG = activating group (NO_2, nitrile, or carbonyl). LG = leaving group (NO_2, halide, triflate, tosylate, mesylate, trialkylamonium halide, or iodonium salt). X = halide I or Br.



78 79

Scheme 41. Synthesis of *ortho*-[^{18}F]fluoroanisole (**79**) using the heteroaromatic iodonium salt **78**.

Electrophilic aliphatic/aromatic reactions with $^{18}F_2$ or [^{18}F] acetyl hypofluorite.

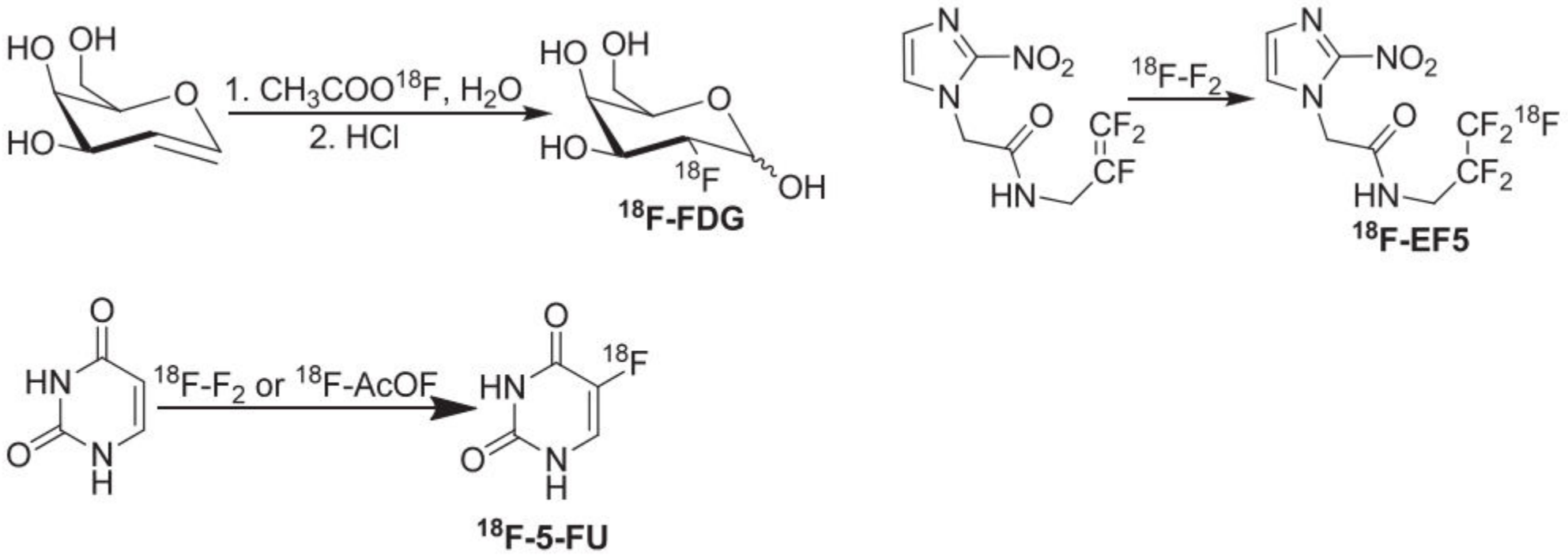
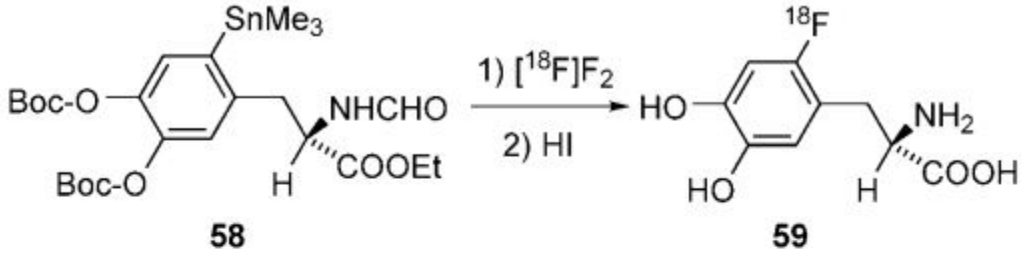


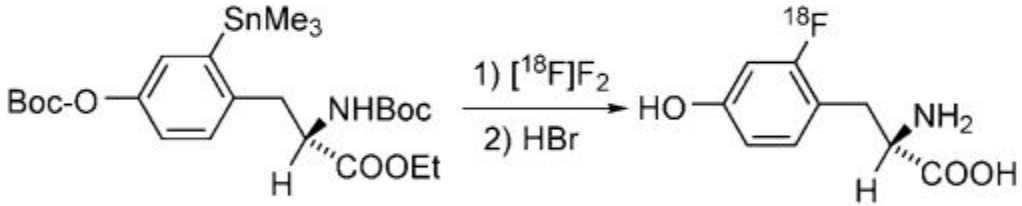
Fig. 10. Direct electrophilic fluorination for PET probe construction.

Reference [4]

Organometallic reactions

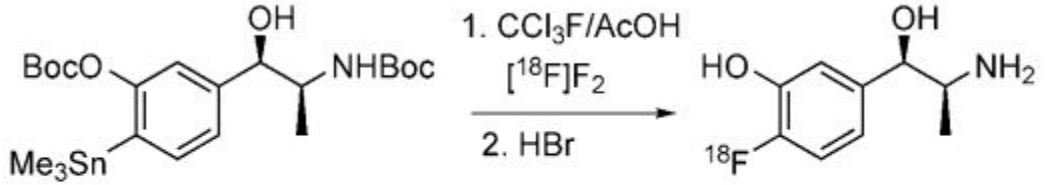


58 59



60 61

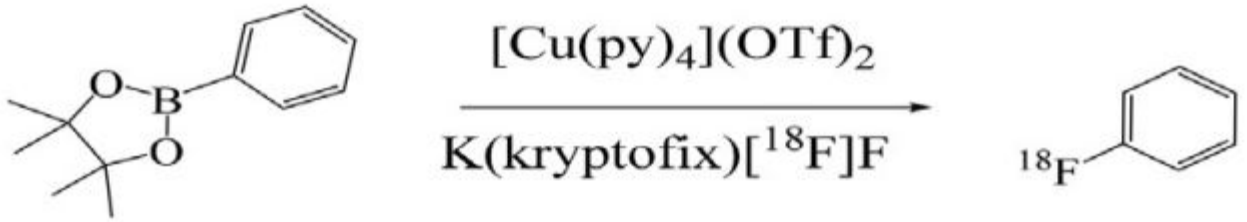
Scheme 34. Synthesis of [^{18}F]fluoro-L-DOPA (**59**) and 2-[^{18}F]fluoro-L-tyrosine (**61**) from their corresponding organotin precursors by direct fluorination with [^{18}F]F_2.



62 63

Scheme 35. Preparation of **63**, with improved specific activities, by reaction of the corresponding organotin reagent with [^{18}F]F_2.

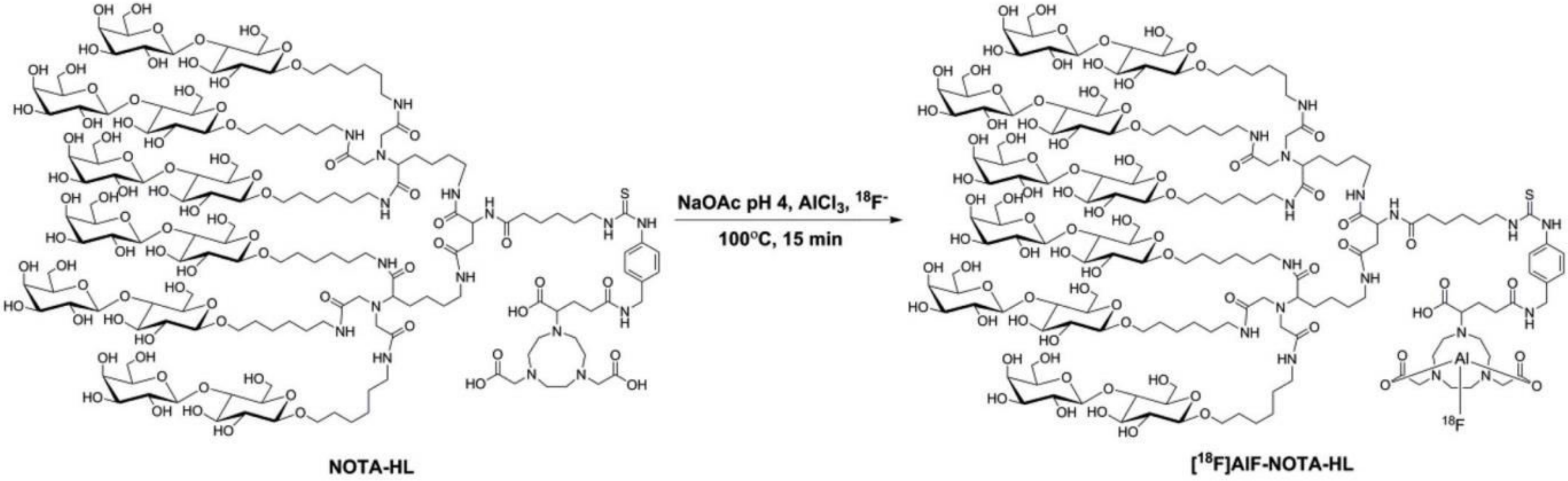
Reference [14]



Scheme 3. Radiosynthetic route of [^{18}F]fluorobenzene *via* copper-mediated nucleophilic [^{18}F]fluorination method.

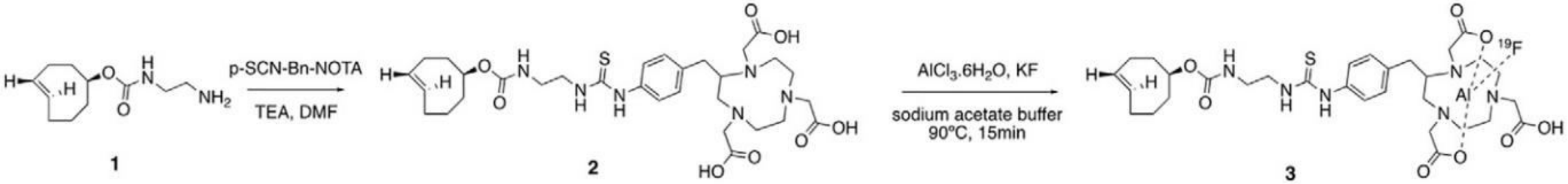
Reference [15]

Coordination complexes can be made



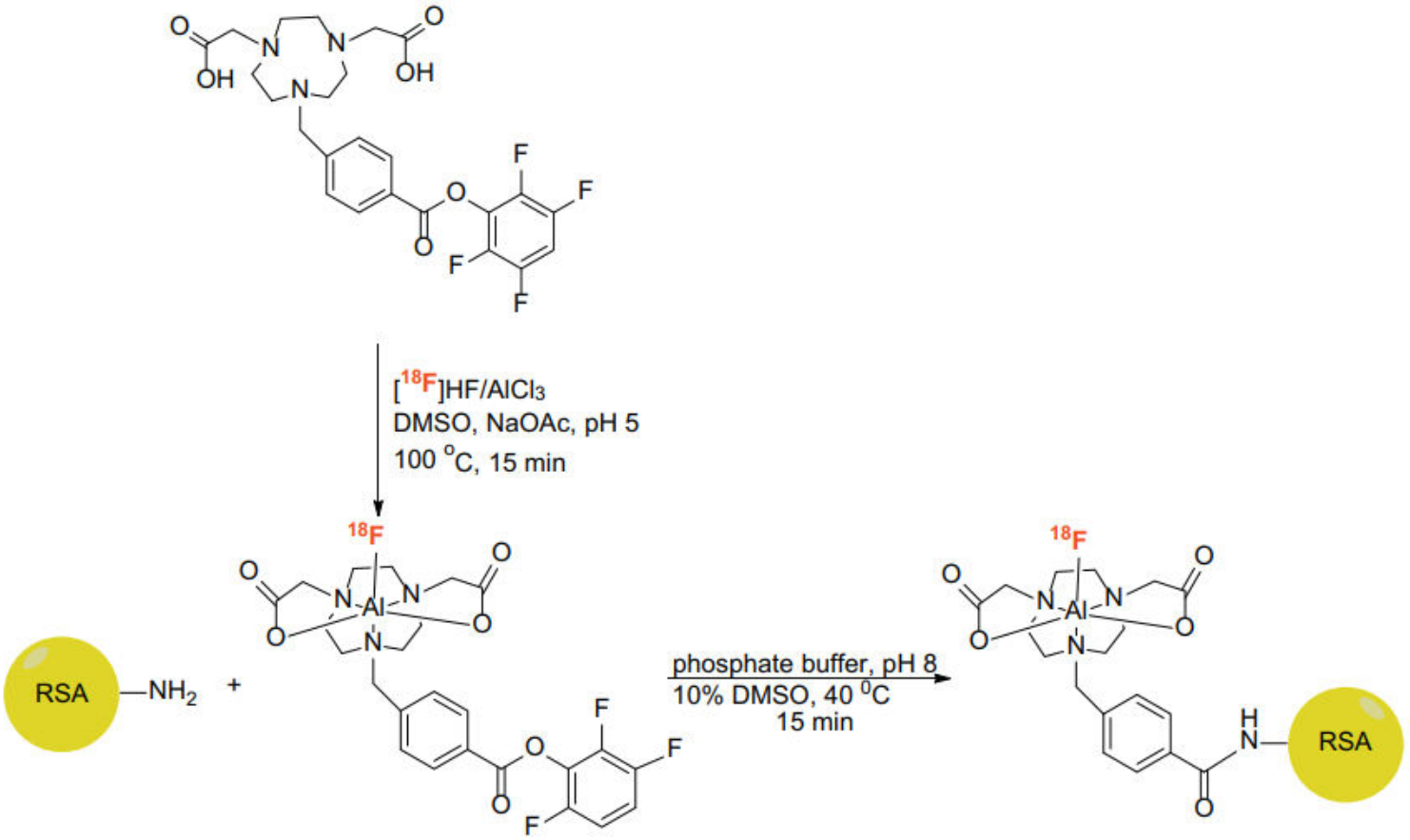
Reference [16]

Fig. 1. The [^{18}F]AlF labeling of NOTA-HL.



Reference [17]

Scheme 1. Synthesis of TCO-NOTA precursor and cold reference.



Reference [18]

Scheme 2. Preparation of [^{18}F]AlF-NODA-Bz-TFPE and [^{18}F]RSA-AlF.

Electrochemical methods have been proposed

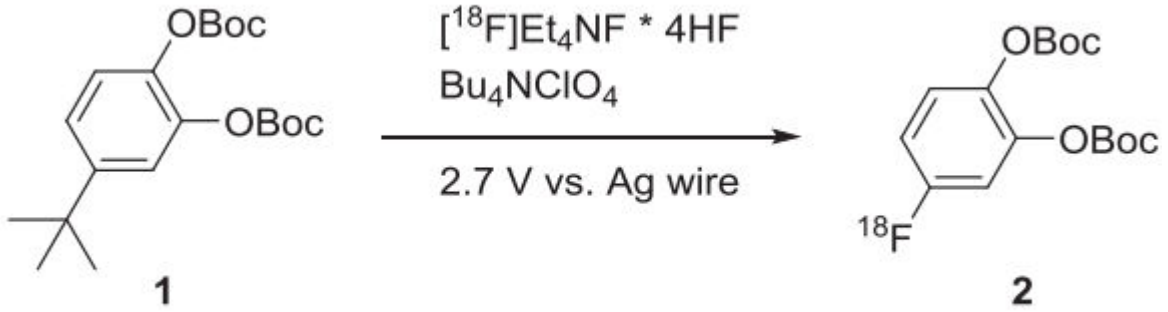


Fig. 1. Electrochemical ^{18}F-fluorination described by He et al.

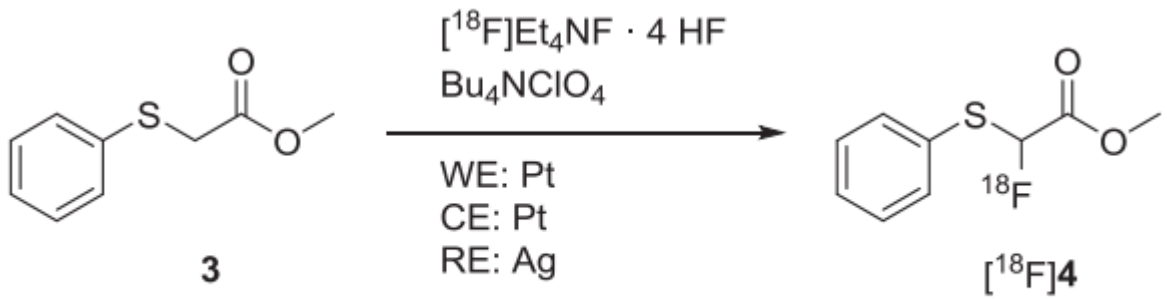
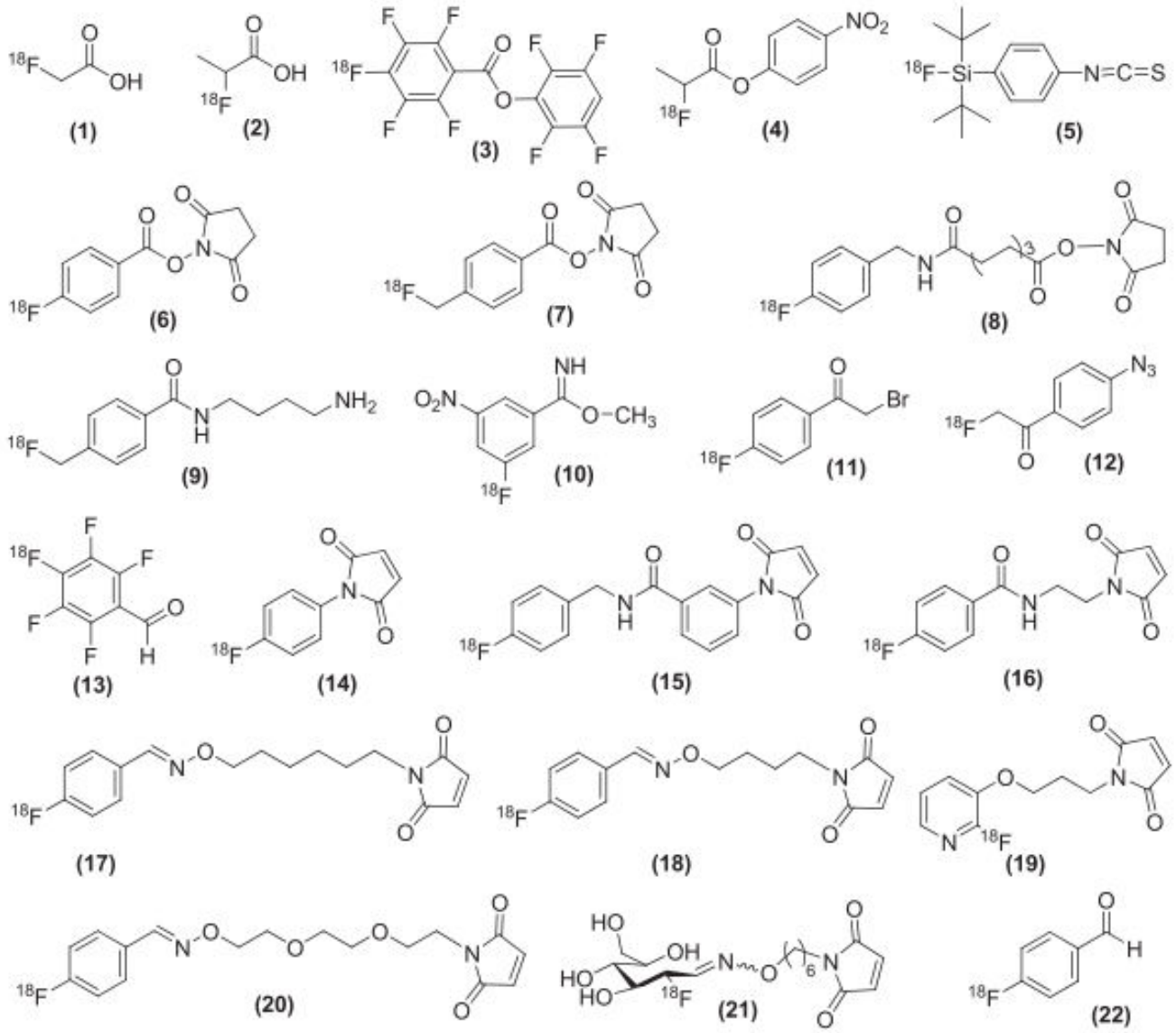


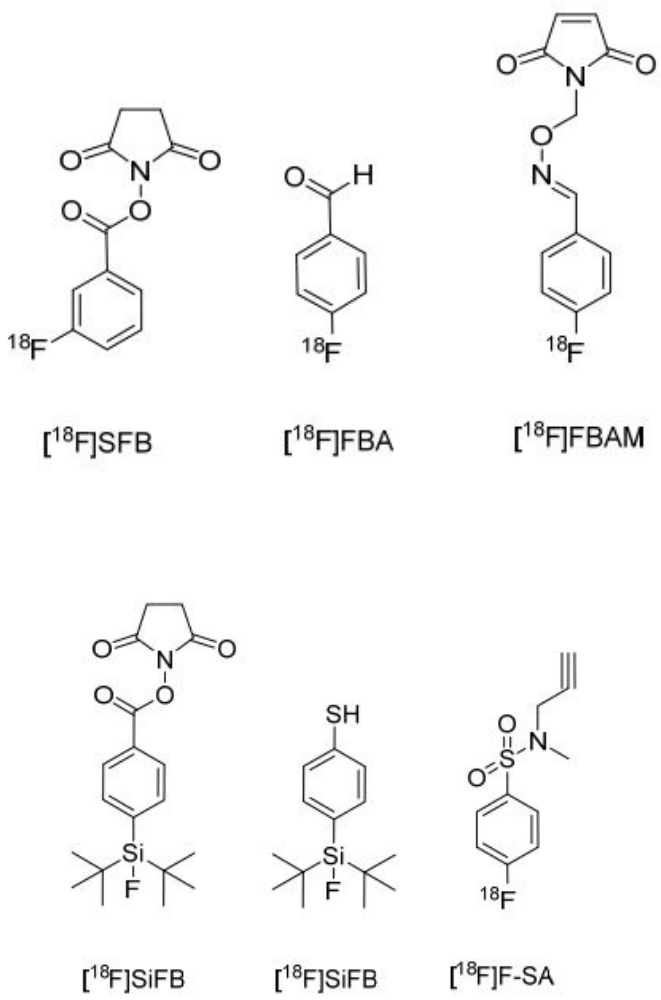
Fig. 2. Carrier-added ^{18}F-fluorination of methyl 2-(phenylthio)acetate (**3**).

Reference [19]

Prosthetic groups can be used for ^{18}F incorporation



Reference [4]



Reference [20]

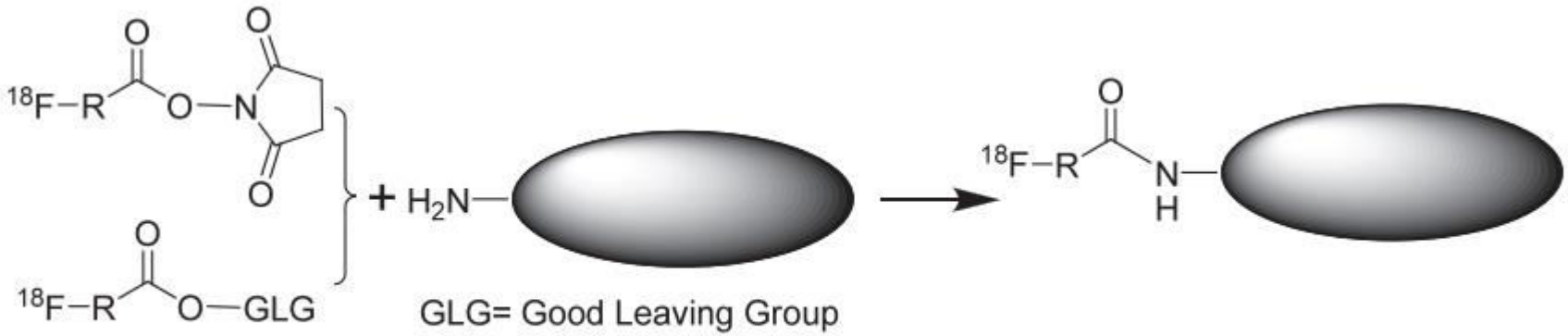
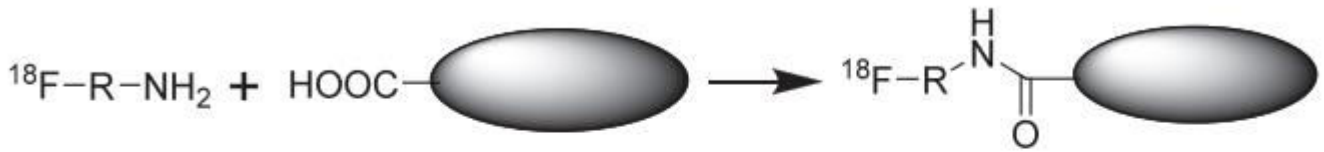


Fig. 17. ^{18}F labeling through amine reactive prosthetic groups.

^{18}F labeling through Carboxylic acid reactive prosthetic groups



^{18}F labeling through Thiol-reactive prosthetic groups

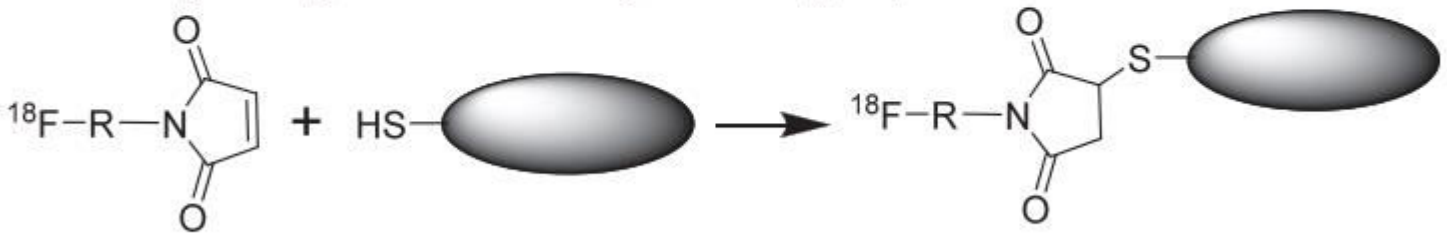
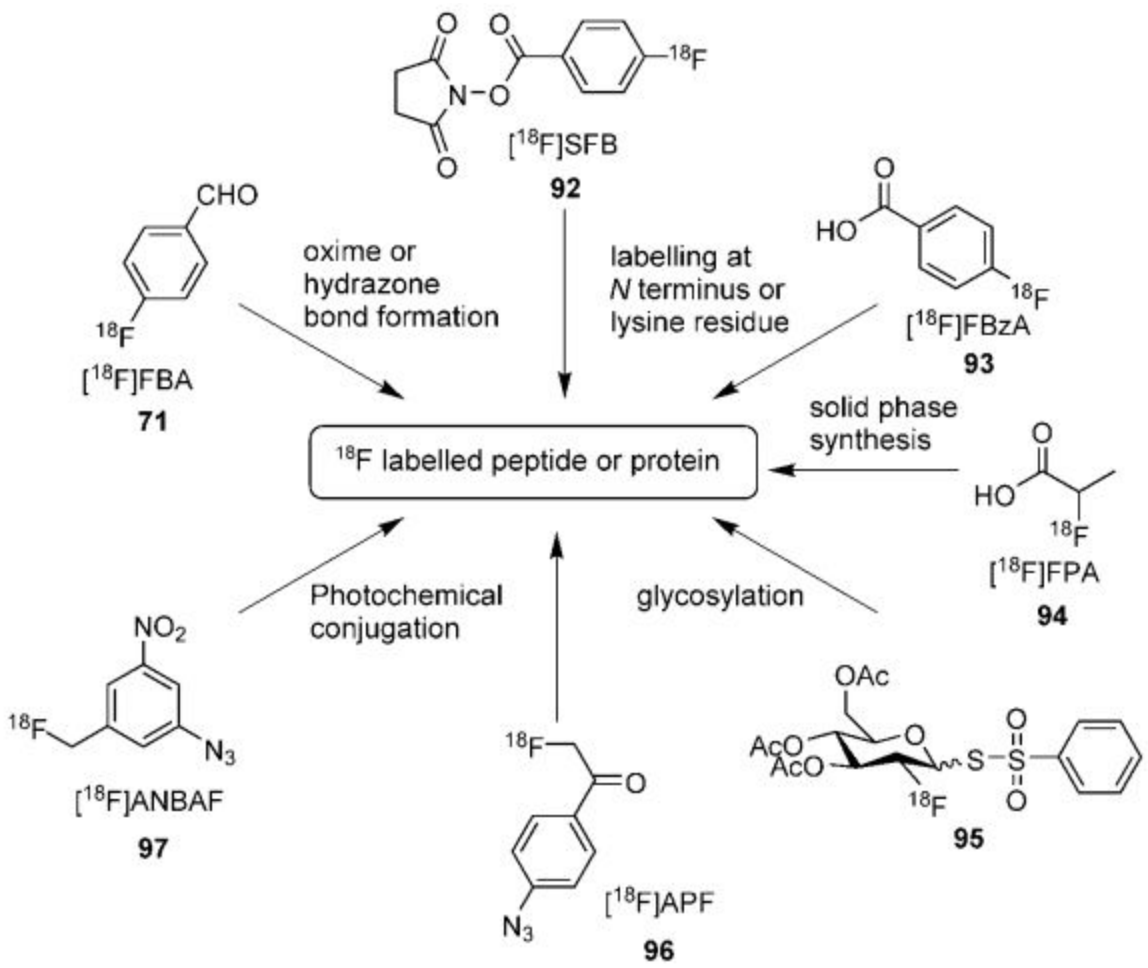
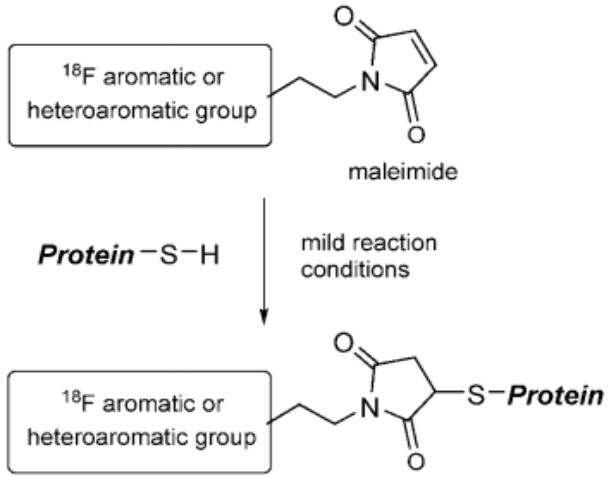


Fig. 18. ^{18}F labeling through Carboxylic acid reactive and Thiol-reactive prosthetic groups.

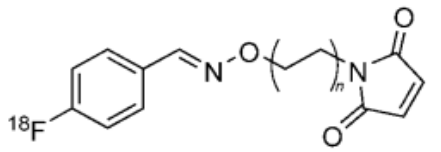
Reference [4]



Scheme 51. Reagents for the ^{18}F labeling of proteins, peptides, and oligonucleotides.

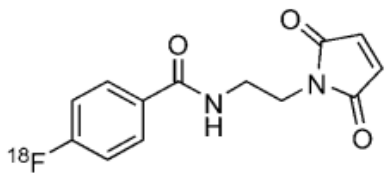


Scheme 52. Synthesis of ^{18}F-labeled proteins by reaction of [^{18}F]maleimides and free thiol groups.



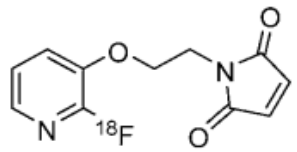
[^{18}F]FBAM (n = 3) [^{18}F]FBABM (n = 2)

98 **99**



[^{18}F]FBEM

100



[^{18}F]FPyME

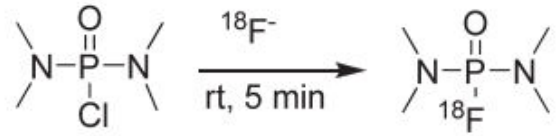
101

Scheme 53. [^{18}F]Malemide reagents that react with thiol groups for peptide and protein labeling.

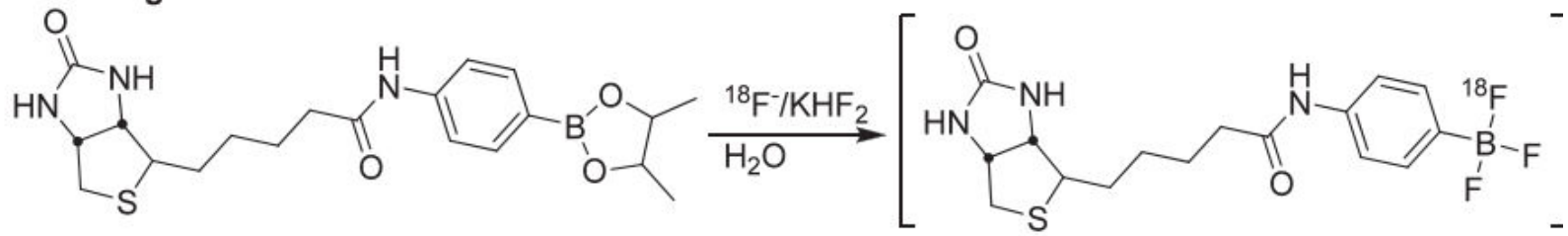
Reference [15]

Synthetic Ingenuity and various methods

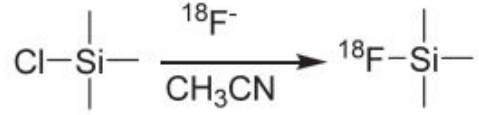
^{18}F labeling via phosphorous-^{18}F bond formation

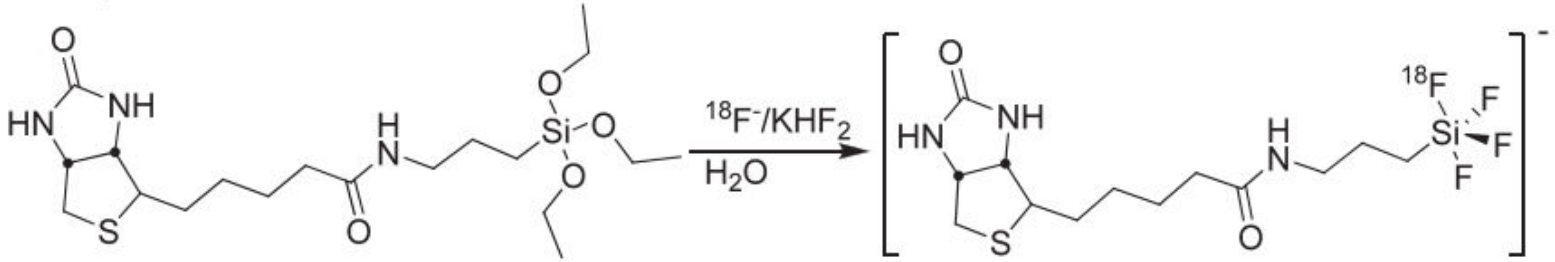


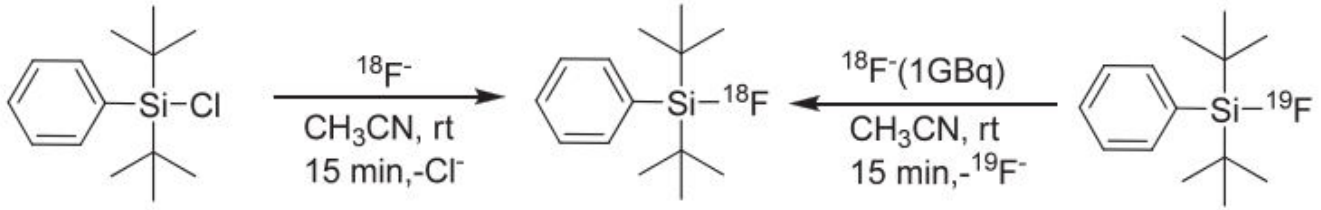
^{18}F labeling via boron-^{18}F bond formation



^{18}F labeling via silicon-^{18}F bond formation







Reference [4]

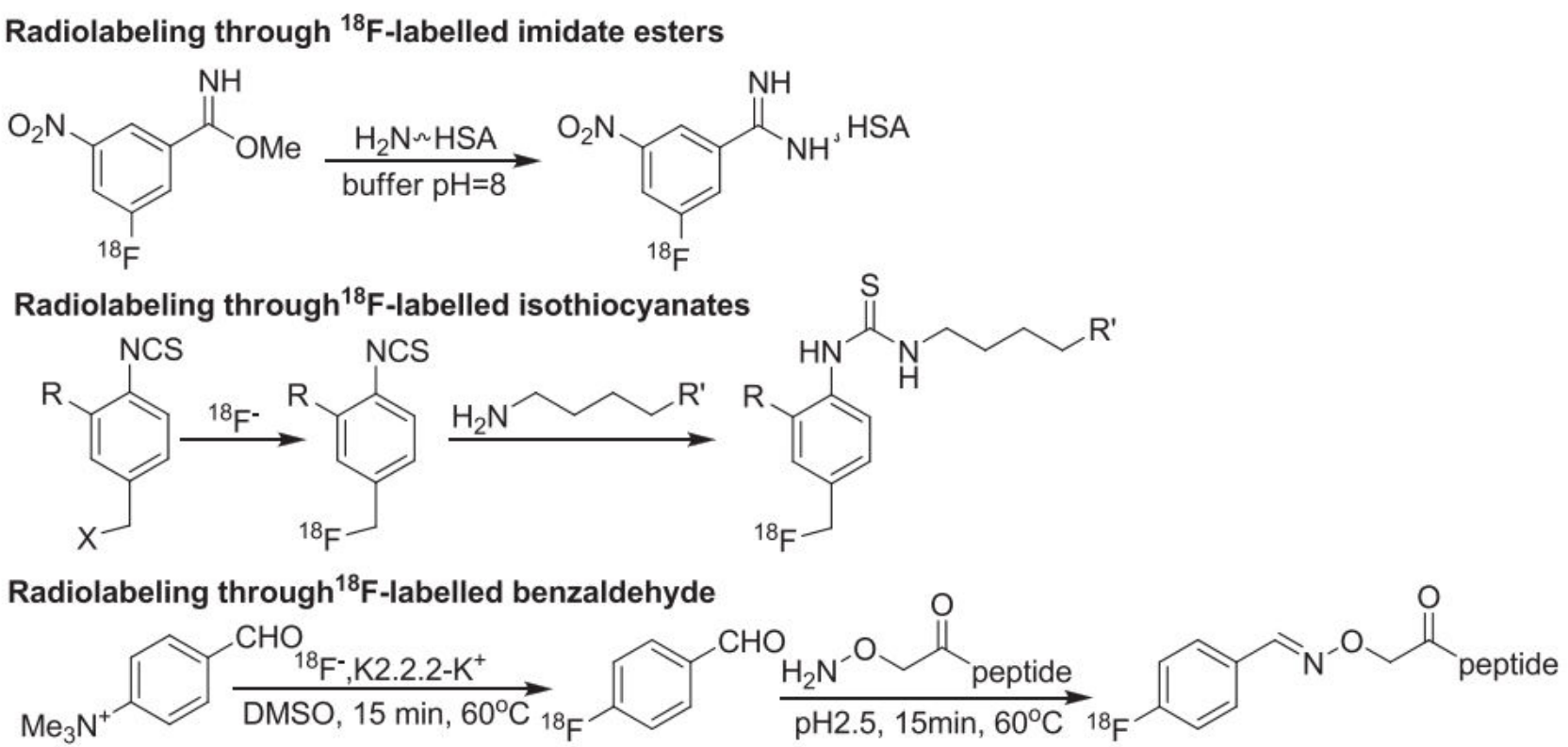


Fig. 19. Radiolabeling through ^{18}F-labeled imidate esters, isothiocyanates, and benzaldehyde.

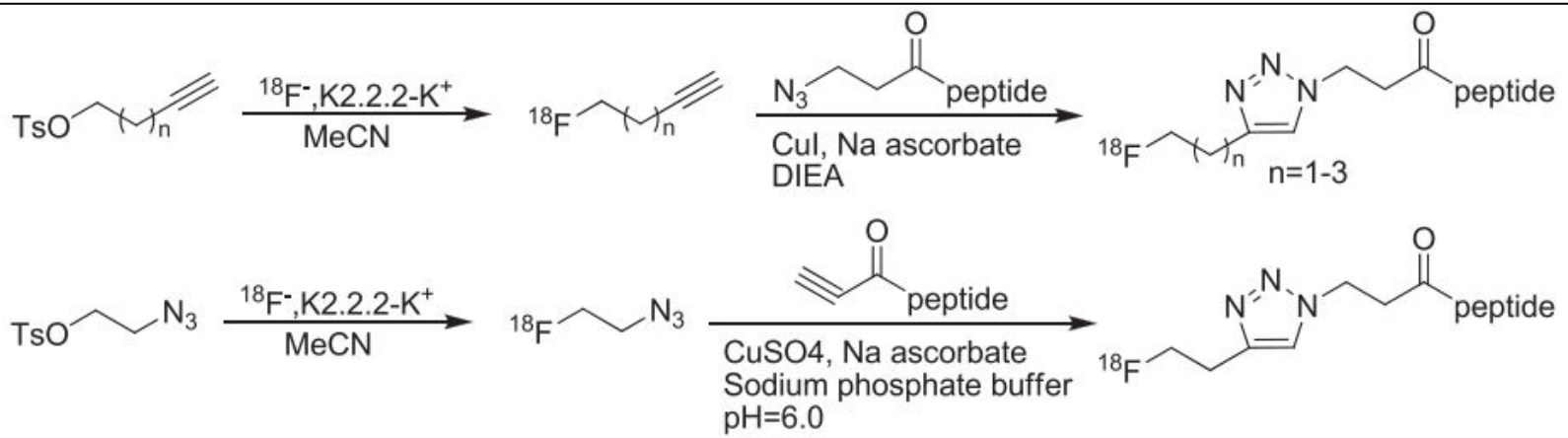


Fig. 20. The use of "click" reaction for PET probe construction.

Reference [4]

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