[^{18}F]Fluoride and nucleophilic aliphatic substitution

Introduction

1. Aliphatic nucleophilic substitution reactions involving ^{18}F-fluoride or S_N2 are the most common methods for the incorporation of [^{18}F]fluoride onto aliphatic molecules.

2. In contrast to electrophilic reactions, ^{18}F-S_N2 reactions provide access to ^{18}F-tracers in moderate to high yields and high specific activity under relatively mild reaction conditions.

3. ^{18}F-S_N2 reactions provide access to un-activated aromatics, peptides, proteins and other macromolecules through small aliphatic conjugates.

4. Radiolabelling reactions will be presented according to
   - type of leaving group
   - reaction type
   - direct one step fluorination or
   - incorporation via a ^{18}F-fluoride-prosthetic group
   - potential pitfalls

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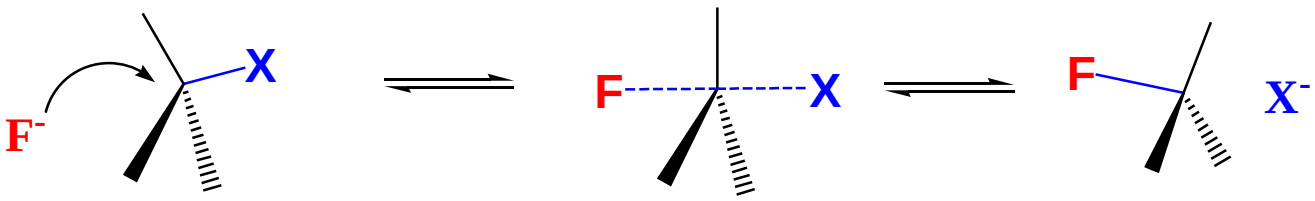
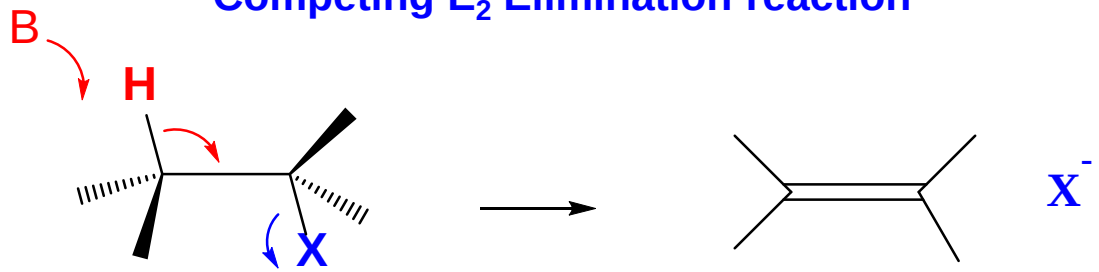
[^{18}F]Fluoride and nucleophilic aliphatic substitution

Mechanism - Aliphatic Nucleophilic Substitution S_N2



- ^{18}F- is a good nucleophile and X must be good leaving group
- Polar solvents are required to moderately solvate ^{18}F- and the emerging X^- leaving group whilst maintaining the nucleophilicity of ^{18}F
- If carbon is chiral, “Walden Inversion” occurs giving product with opposite stereochemistry to that of precursor e.g. ^{18}F-FDG synthesis
- Competing Elimination (E_2) reaction may also occur
- ^{18}F-fluoride can also act as a strong base

Competing E_2 Elimination reaction



X = GLG, Sulfonates, Halogens, ^{18}F

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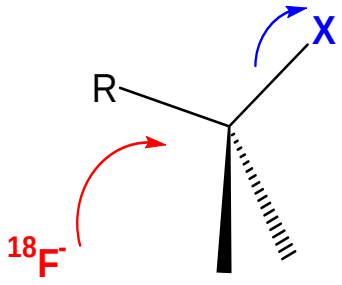
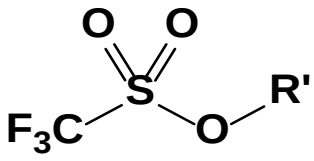
Common Leaving Groups





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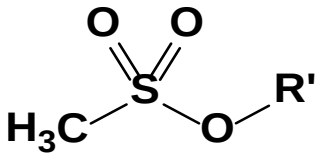

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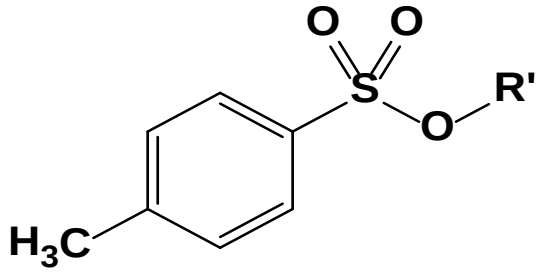
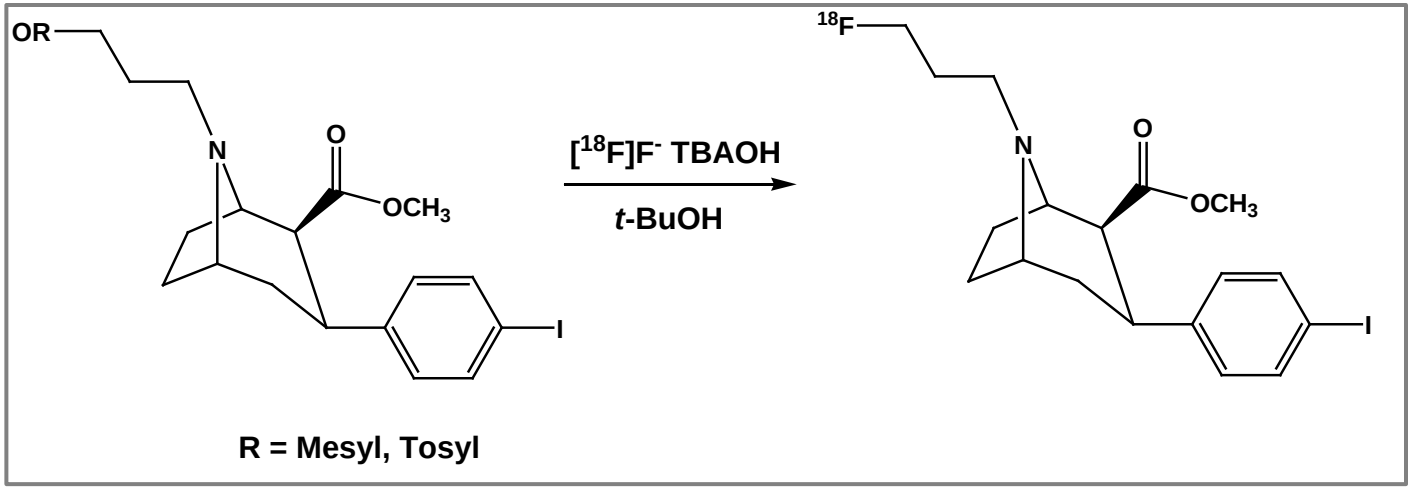
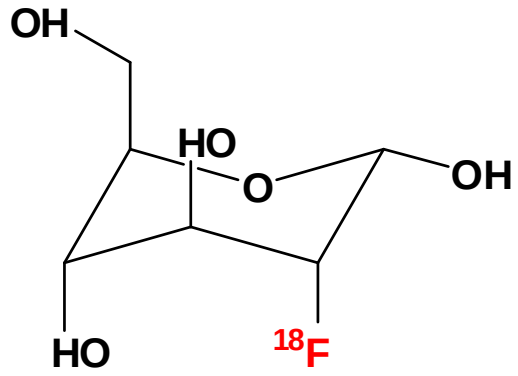


X = Halogen (I, Br > Cl)

X = Sulfonates

OTf **OMs** **OTs**



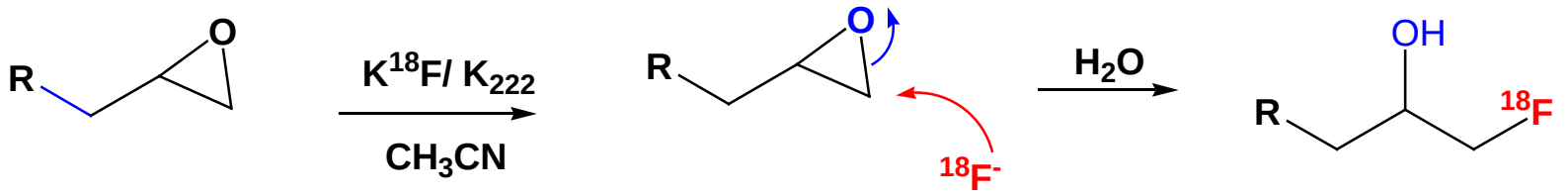


^{18}F-FDG

Lee S.J. *et al.*, Nucl. Med. Biol. 2007, 34, 345-351

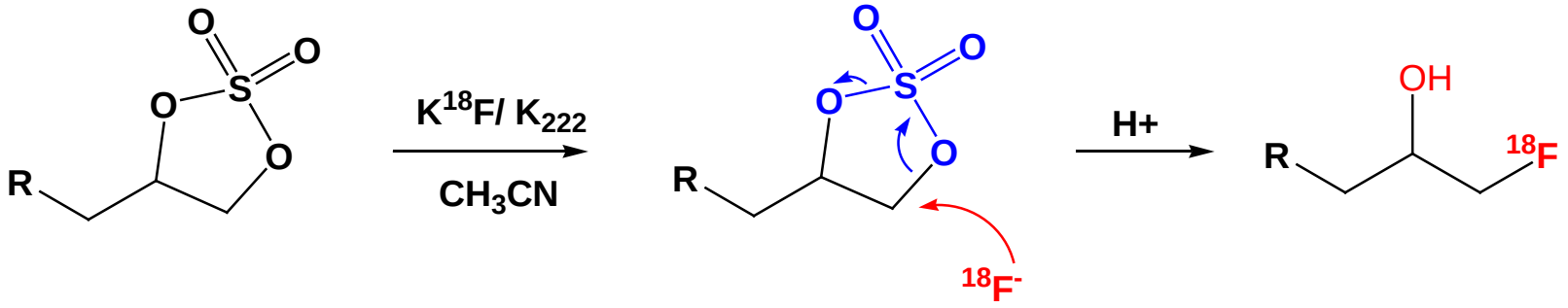
[^{18}F]Fluoride and nucleophilic aliphatic substitution

Cyclic precursors - Epoxides, Sulfonates and Sulfamidates



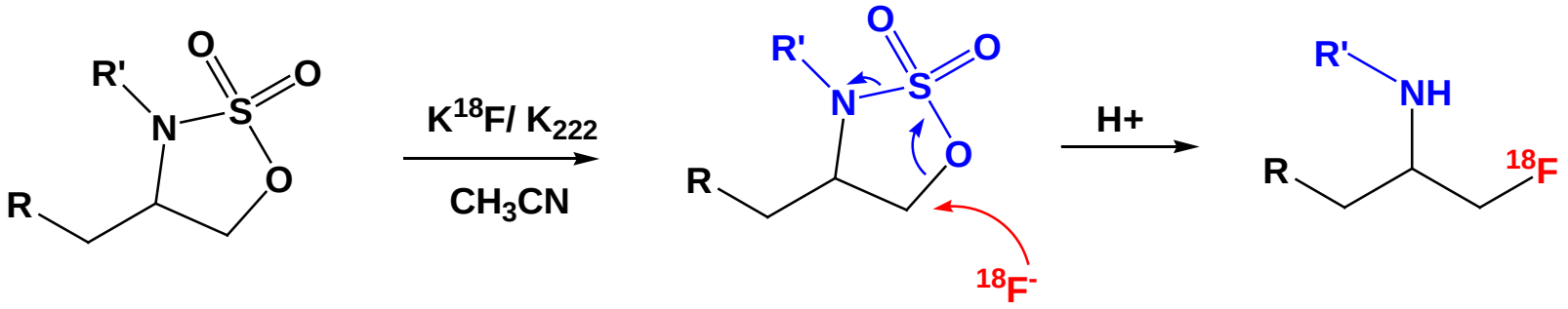
De Groot T.J. *et al.*, Appl. Rad. Isot. 1994, 45, 811

b -^{18}F-fluoroalcohols



Lim J.L. *et al.*, Nucl. Med. Biol. 1996, 23, 911

b -^{18}F-fluoroalcohols



Brady F. *et al.*, Appl. Radiat. Isot. 1989, 40, 325

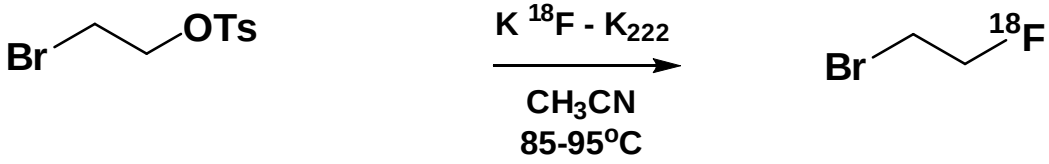
Yu W. *et al.*, J. Med. Chem. 2010, 53, 876-886

b -^{18}F-fluoroamines

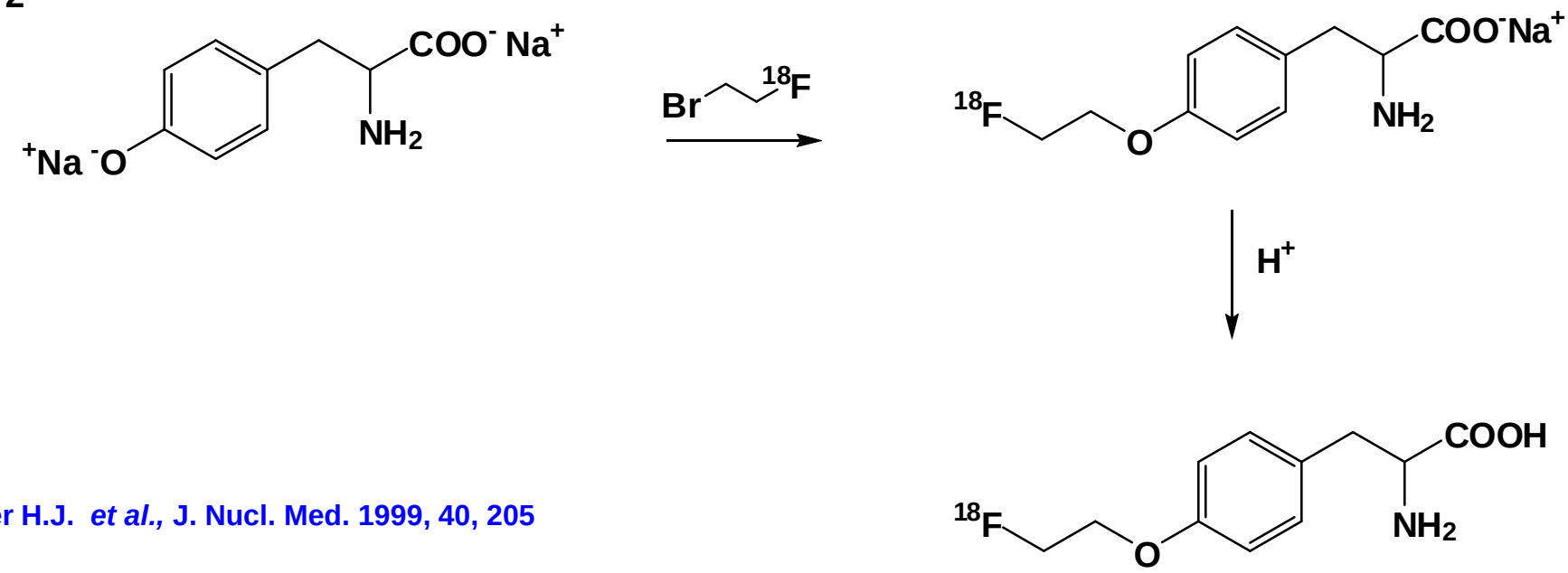
[^{18}F]Fluoride and nucleophilic aliphatic substitution

Two Step ^{18}F-fluoroalkylation - Synthesis of ^{18}F-FET

STEP 1



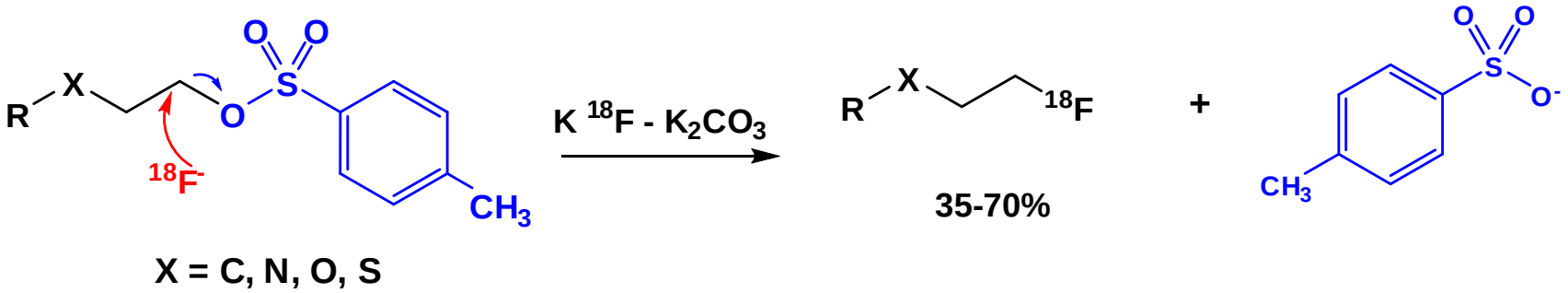
STEP 2



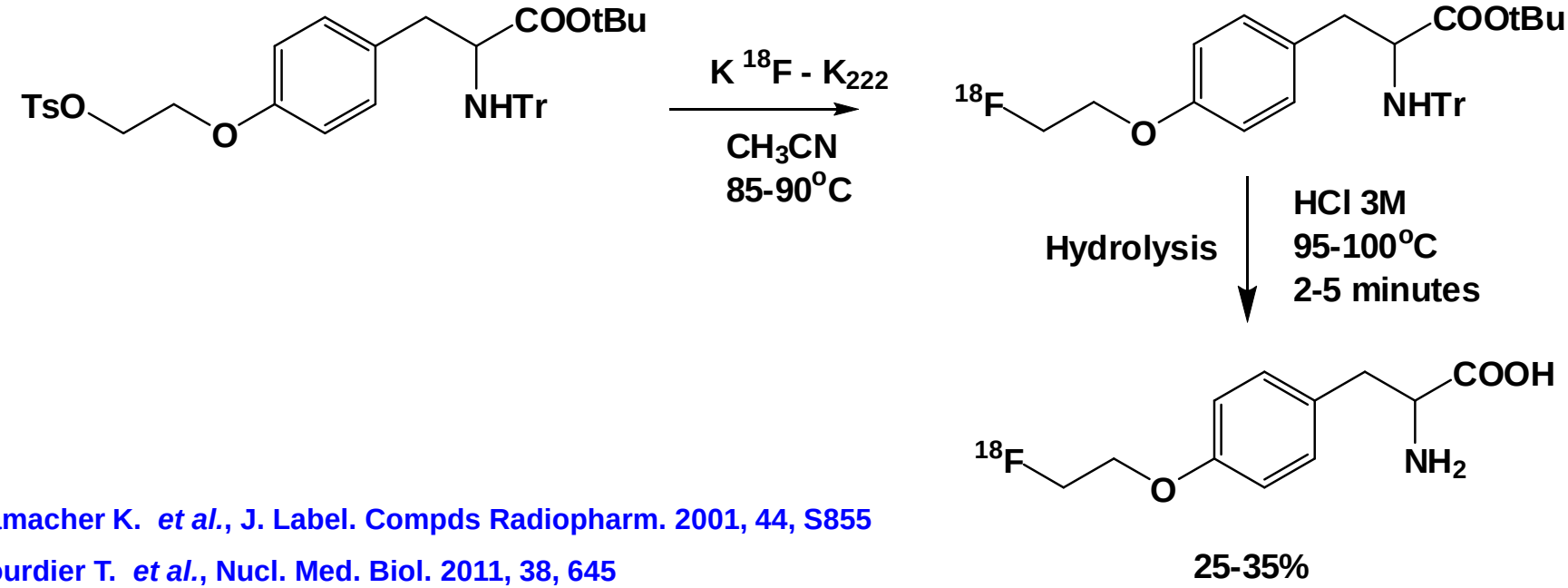
Wester H.J. *et al.*, J. Nucl. Med. 1999, 40, 205

[^{18}F]Fluoride and nucleophilic aliphatic substitution

Direct one-step method ^{18}F-S_N2 substitution - Synthesis of ^{18}F-FET



X = C, N, O, S

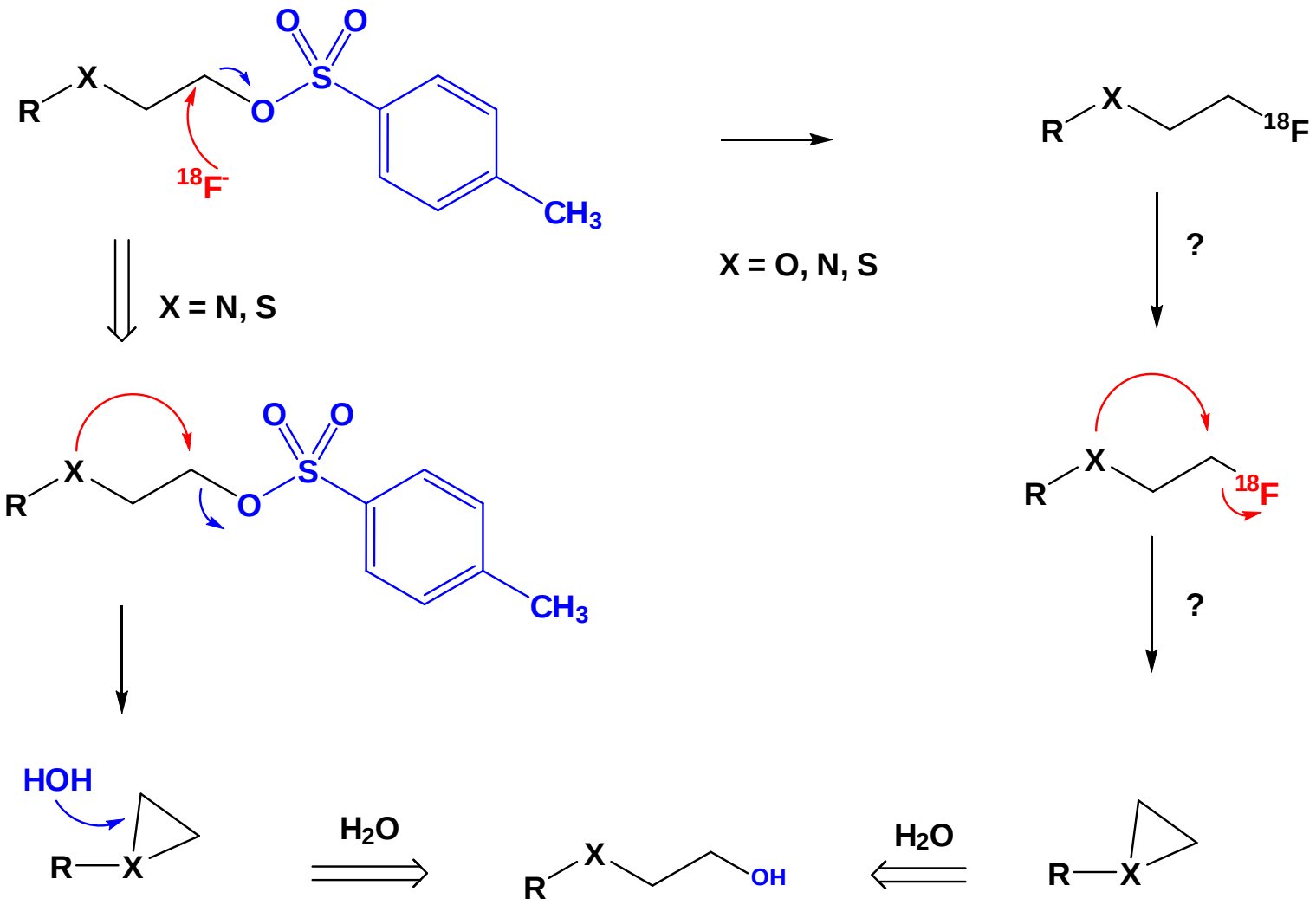


Hamacher K. *et al.*, J. Label. Compds Radiopharm. 2001, 44, S855

Bourdier T. *et al.*, Nucl. Med. Biol. 2011, 38, 645

[^{18}F]Fluoride and nucleophilic aliphatic substitution

Potential Pitfalls in ^{18}F-S_N2 reactions



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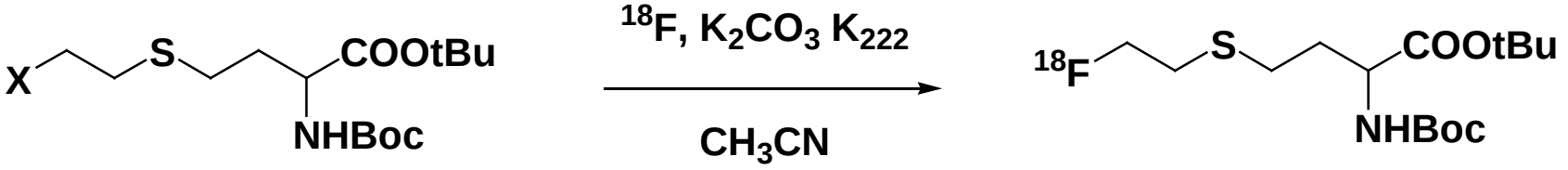
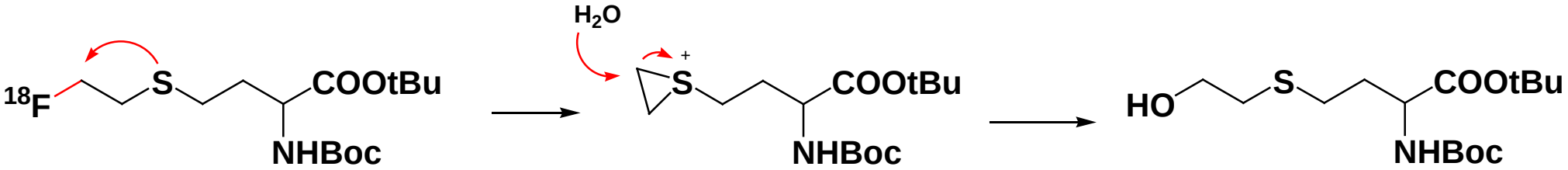
[^{18}F]Fluoride and nucleophilic aliphatic substitution

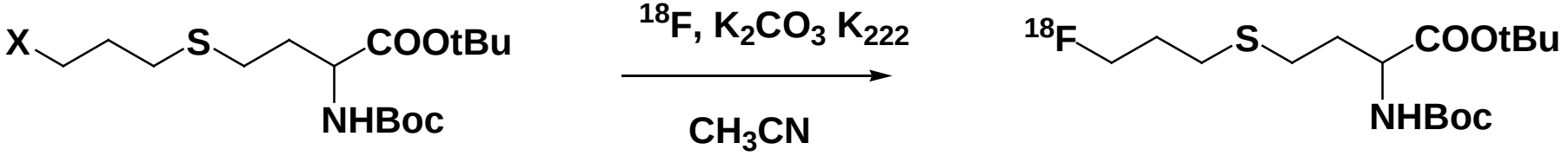
Potential Pitfalls in ^{18}F-S_N2 reactions - Synthesis of ^{18}F-ethyl and propyl methionine



X = OTs, Br, Cl

X = OTs Unstable and could not be isolated
X = Cl Radiochemical yield = 22% after 30 minutes at 100°C
X = Br Radiochemical yield = 40% after 5 minutes at 100°C

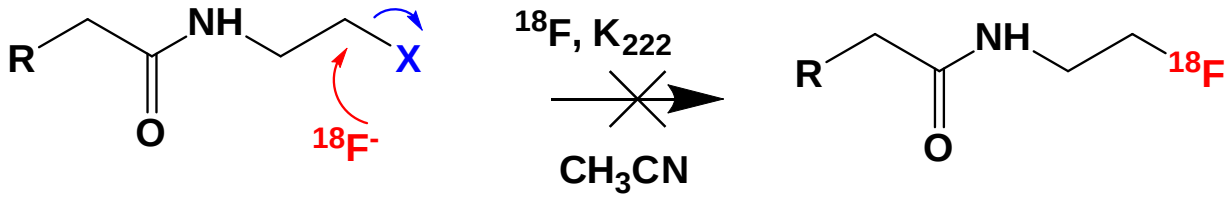




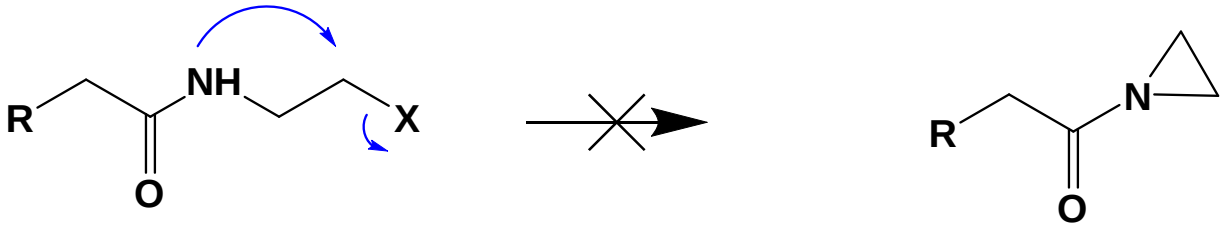
X = Cl Radiochemical yield = 47% after 30 minutes at 100°C
X = Br Radiochemical yield = 76% after 15 minutes at 80°C
X = OTs Radiochemical yield = 82% after 15 minutes at 100°C

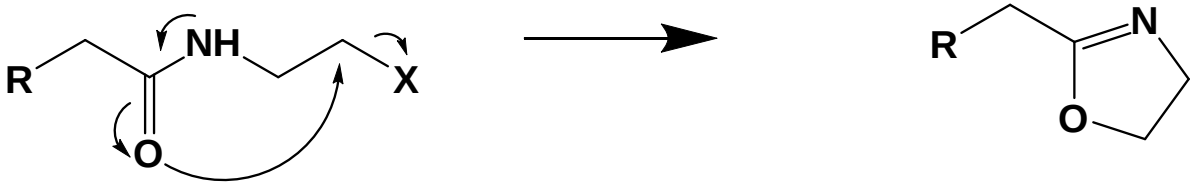
[^{18}F]Fluoride and nucleophilic aliphatic substitution

Pitfalls in S_N2 Amide ^{18}F-Fluorinations



X = OTs, Br, Cl





Reaction favoured due to formation of five-membered ring

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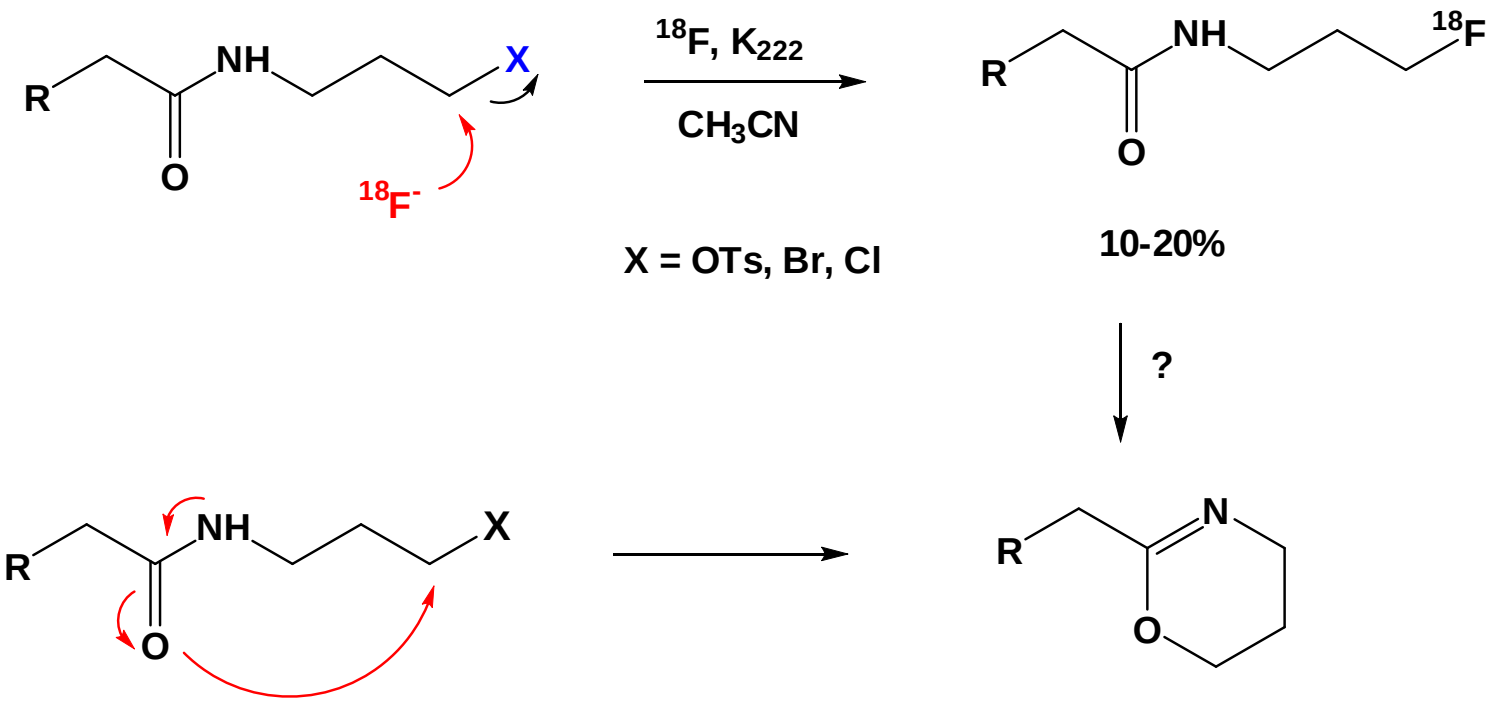
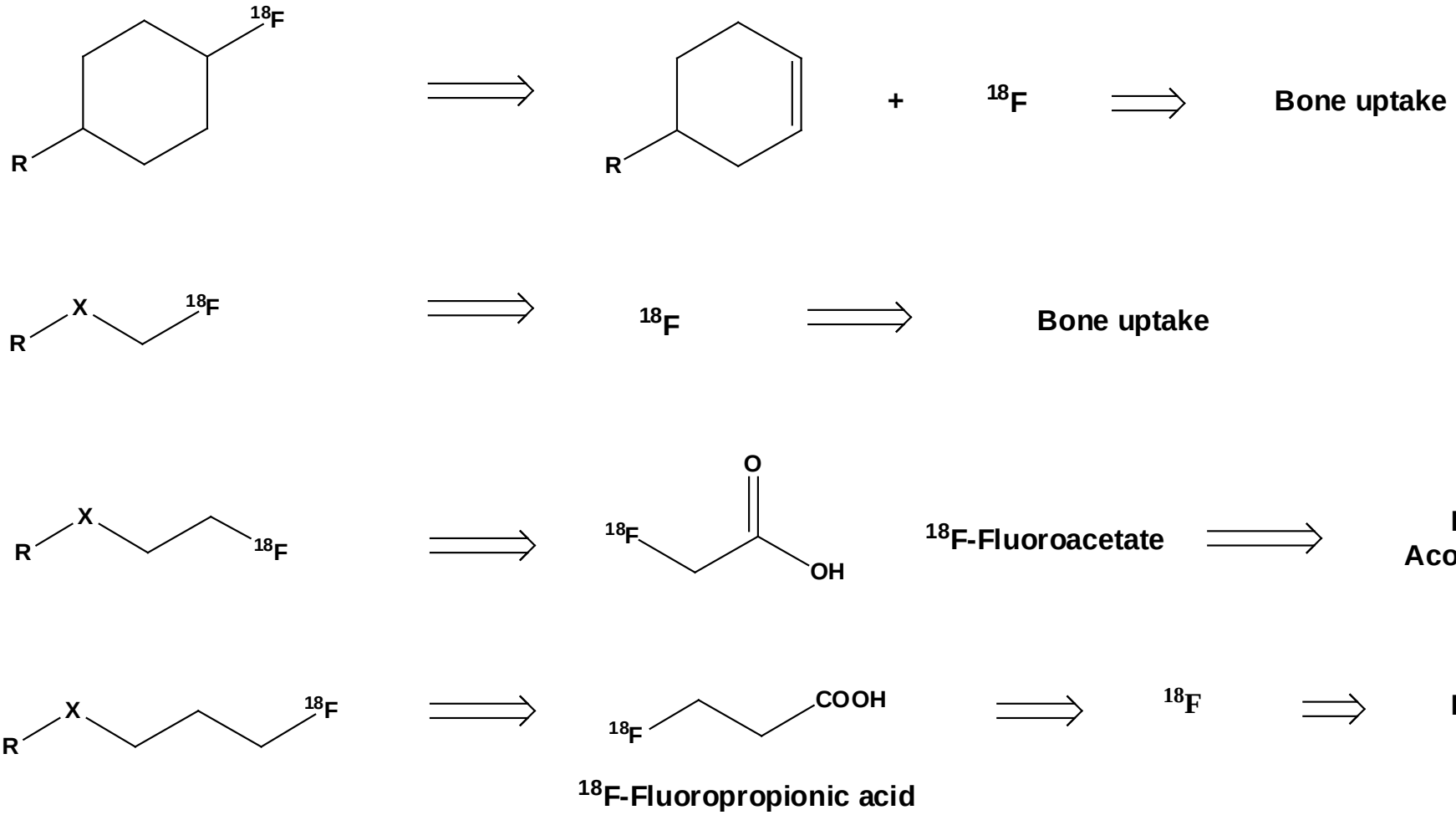
Pitfalls in S_N2 Amide ^{18}F-Fluorinations



Side reaction predominates due to favoured formation of six membered ring

Chemical and *in vivo* stability of 18F-fluoroalkyl based radiopharmaceuticals

18F-Fluoroalkyl groups are prone to defluorination in vivo.
The nature of R and X influences chemical and biological stability



Conclusion

1. Aliphatic Nucleophilic fluorination chemistry is very versatile giving access to a large number of ^{18}F-radiopharmaceuticals either directly or indirectly.
2. Competing reactions including E_2 elimination can reduce the yields of such reactions.
3. Neighbouring group participation can lead to side products.
4. Solvents, base and temperature greatly influence the nucleophilicity and basicity of ^{18}F and hence the fate of S_N2 vs E_2 reactions
5. Stereochemical considerations are critical when a chiral centre is involved

[^{18}F]Fluoride and nucleophilic aliphatic substitution

Considerations and Pitfalls with Aliphatic ^{18}F-S_N2 Reactions

- The most electronegative element, with high charge density renders ^{18}F-fluoride strongly basic.
- Formation of strong hydrogen bonds and stable solvation spheres dramatically decreases its nucleophilicity.
- The insolubility of alkali metal-fluorides in organic solvents can lead to low yields of ^{18}F products necessitating the use of crown ethers, amino poly-ethers or phase transfer catalysts.
- As the presence of water reduces nucleophilicity, extensive drying of quaternary ammonium salts render ^{18}F-fluoride a powerful base, promoting elimination reactions.
- The use of tertiary alcohols (*tert*-butanol) enhances nucleophilicity by decreasing solvation of ^{18}F-fluoride and its basicity, thus increasing fluorination reactions and minimising side reactions.
- ^{18}F-Fluorination reactions are also influenced by unsuspecting, competing nucleophiles (impurities e.g. water, trace halogens, amines, from solvent and reagent). The latter compete in reactions forming analogous hydroxyl, halogenated, amino and other side-products. Competition from ^{19}F-fluoride also leads to low specific activity products.
- Depending on molecular environment ^{18}F-Fluoroalkyl groups are prone to *in vivo* defluorination, or cleavage yielding ^{18}F-fluoride, ^{18}F-fluoroacetate and other fragments.