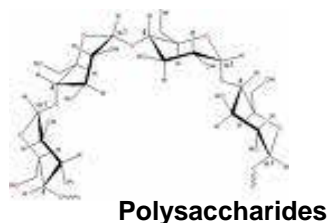
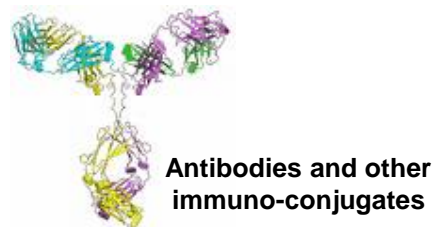
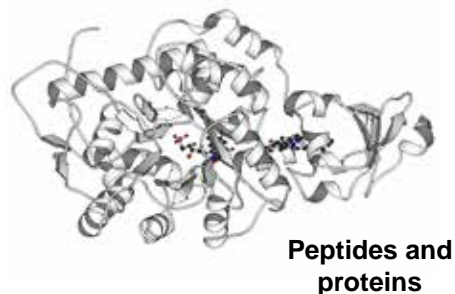


Macromolecules in biosystems: Biopolymers



^{18}F for labeling of biopolymers:

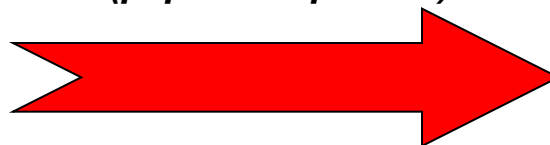
- J Ease of production and highest spatial resolution
- J Meets the needs and experience of clinicians (^{18}F FDG-PET) with instrumentation and interpretation of PET scans

BUT:

- L Still challenging radiochemistry!!!

Biopolymers

*Activation step of ^{18}F
and/or biopolymer
(peptide or protein)*

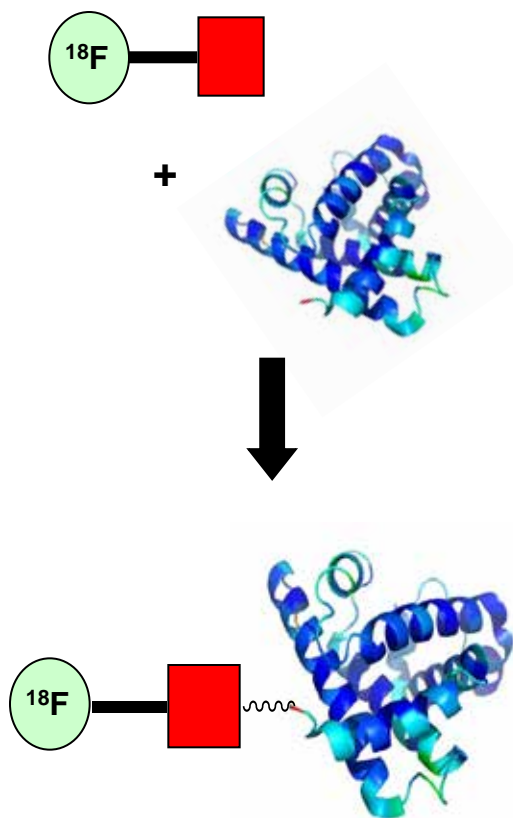


*Bioconjugation
chemistry*

^{18}F -labeled biopolymers

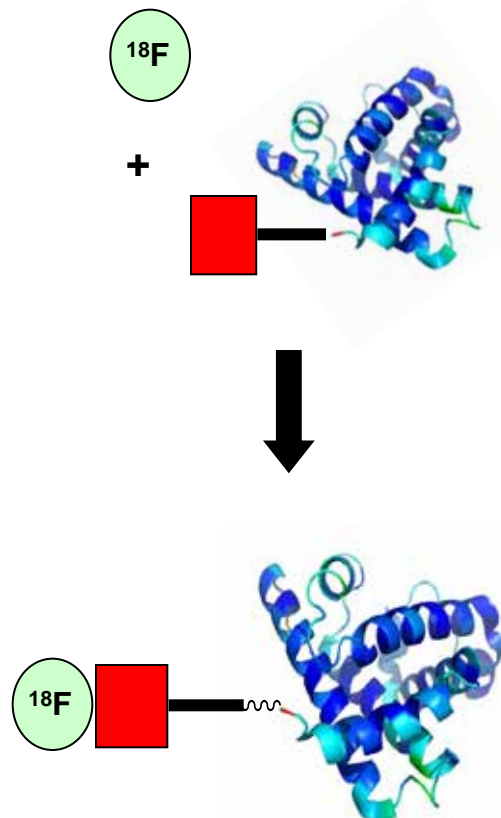
¹⁸F-labeled biopolymers: Basic radiochemistry concepts

Concept 1



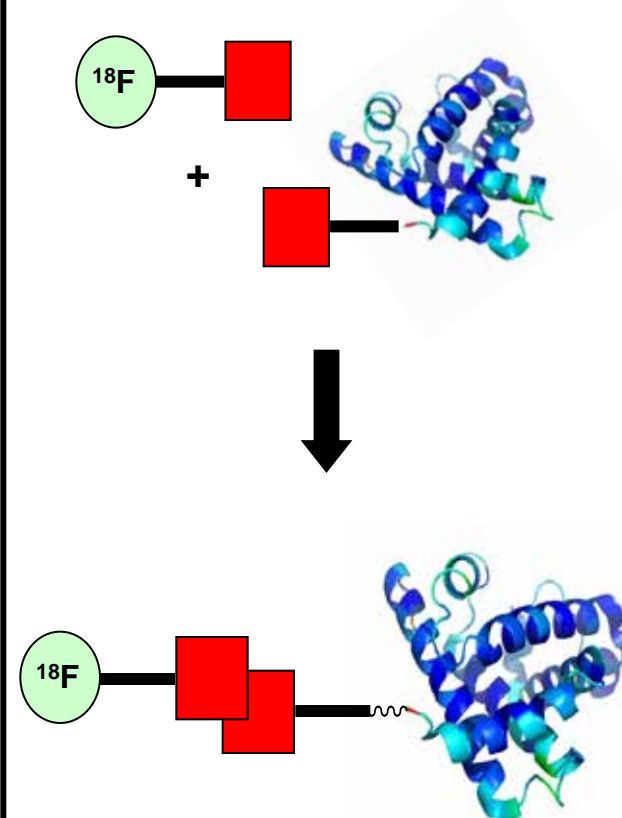
Activation of n.c.a. [¹⁸F]fluoride
followed by conjugation to peptide

Concept 2



Activation/funtionalization of peptide
followed by fixation of n.c.a. [¹⁸F]fluoride

Concept 3



Bioconjugation between activated pep-
tide and activated n.c.a. [¹⁸F]fluoride

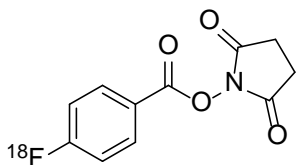
Adopted from: Liu et al. Curr. Org. Syn. 2011, 8, 584-592.

Concept #1: NH_2 - and SH -reactive prosthetic groups

^{18}F -Acylation agents

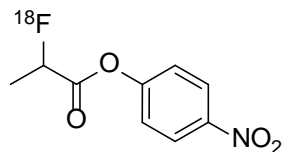
(e.g. *N*-terminal end, lysine residues)

N-Succinimidyl
4- ^{18}F fluorobenzoate



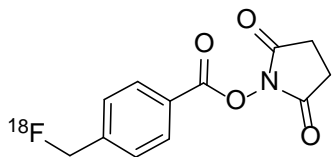
3 steps, 25-60%,
35-100 min

4-Nitrophenyl
2- ^{18}F fluoropropionate



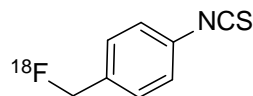
3 steps, 60%,
90 min

N-Succinimidyl
4-([^{18}F]fluoromethyl)benzoate



1 step, 16-21%,
40-50 min

4-([^{18}F]Fluoromethyl)-
phenyl isothiocyanate

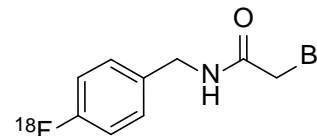


1 step, 23-36%,
25 min

^{18}F -Alkylation agents

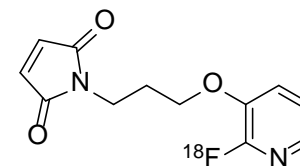
(e.g. cysteine residues)

N-(4-[^{18}F]Fluorobenzyl)-
2-bromoacetamide



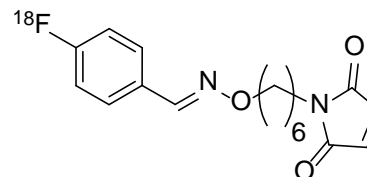
3 steps, 40-45%,
85-95 min

[^{18}F]FPyME



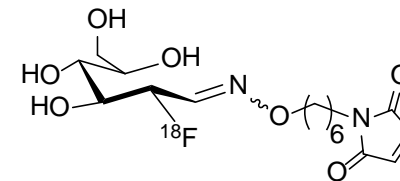
3 steps, 28 %,
110 min

[^{18}F]FBAM



2 steps, 29%,
70 min

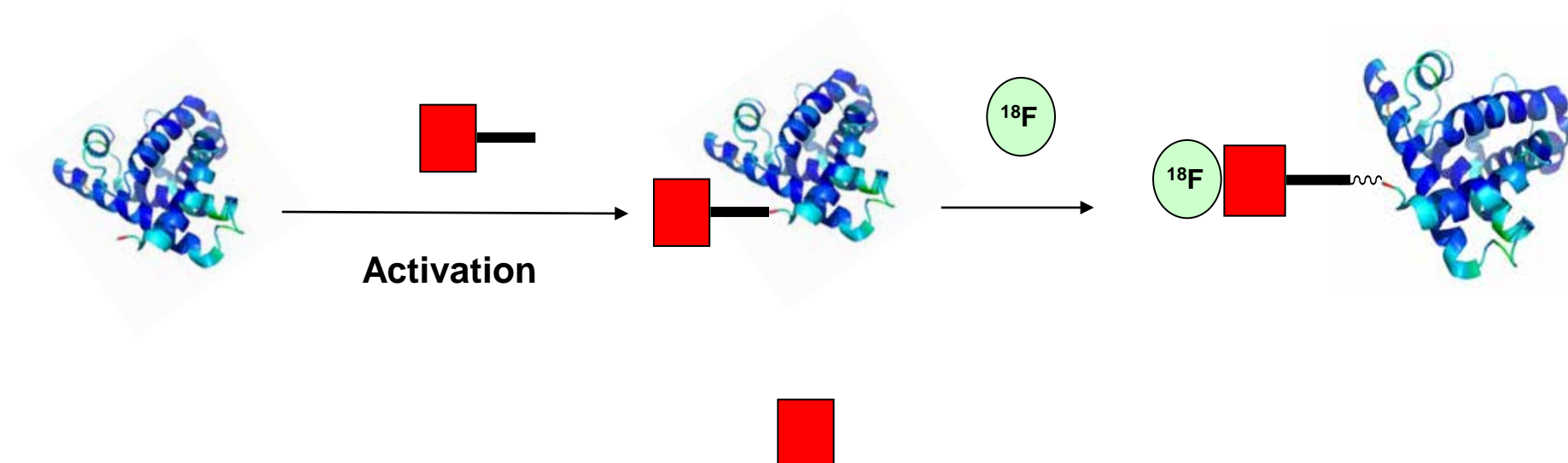
[^{18}F]FDG-MHO



1 step, 45-69%,
45 min

Concept #2: [^{18}F]Fluoride-acceptor chemistry

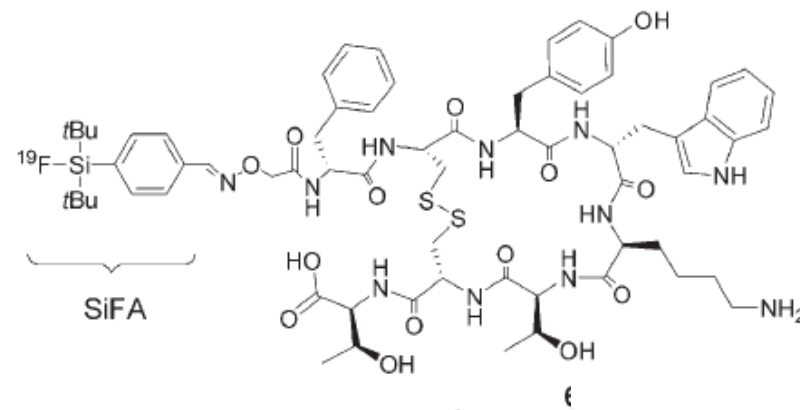
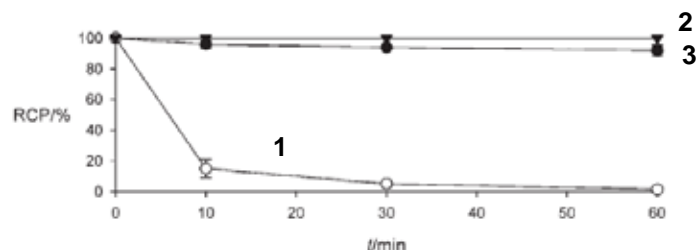
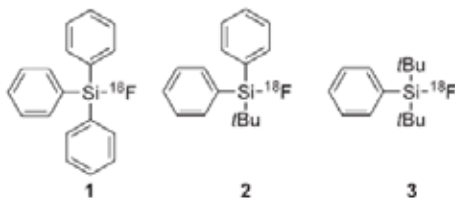
- Formation of stable A- ^{18}F bonds (A = Si, B, Al)
- Strong Lewis acid character of Si, B, Al
- Introduction of [^{18}F]fluoride under mild conditions



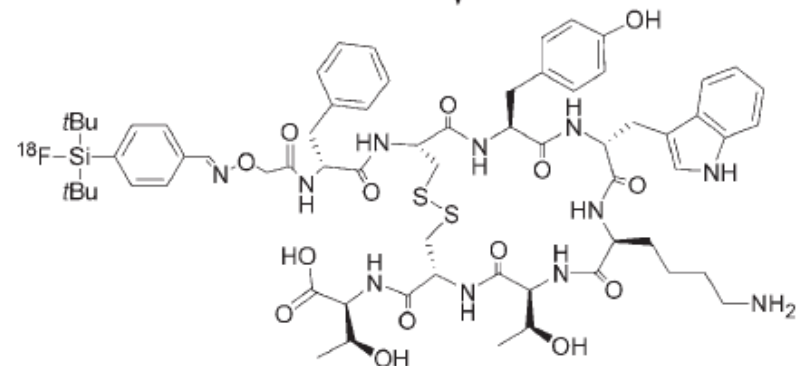
-SiR₃, -BX₃, Al-NOTA

Concept #2: Si-[¹⁸F]Fluoride-acceptor chemistry

- Si-F bond energy (135 kcal/mol)
- Radiolabeling through isotopic ¹⁹F-¹⁸F exchange
- Highly efficient isotopic exchange with very little ¹⁹F precursor (1 mg)
- High specific activity (~200 GBq/mmol)
- In vivo stability depends on substitution pattern of organosilicon-fluorides
 ⇒ di-*tert*-butyl-substituted compounds best



Method A or B
 $+^{18}\text{F}^-$
 $-^{19}\text{F}^-$



A: 95–97 %

B: 70–90 %

Method A: 100 mg peptide, CH₃CN, K₂₂₂/¹⁸F-

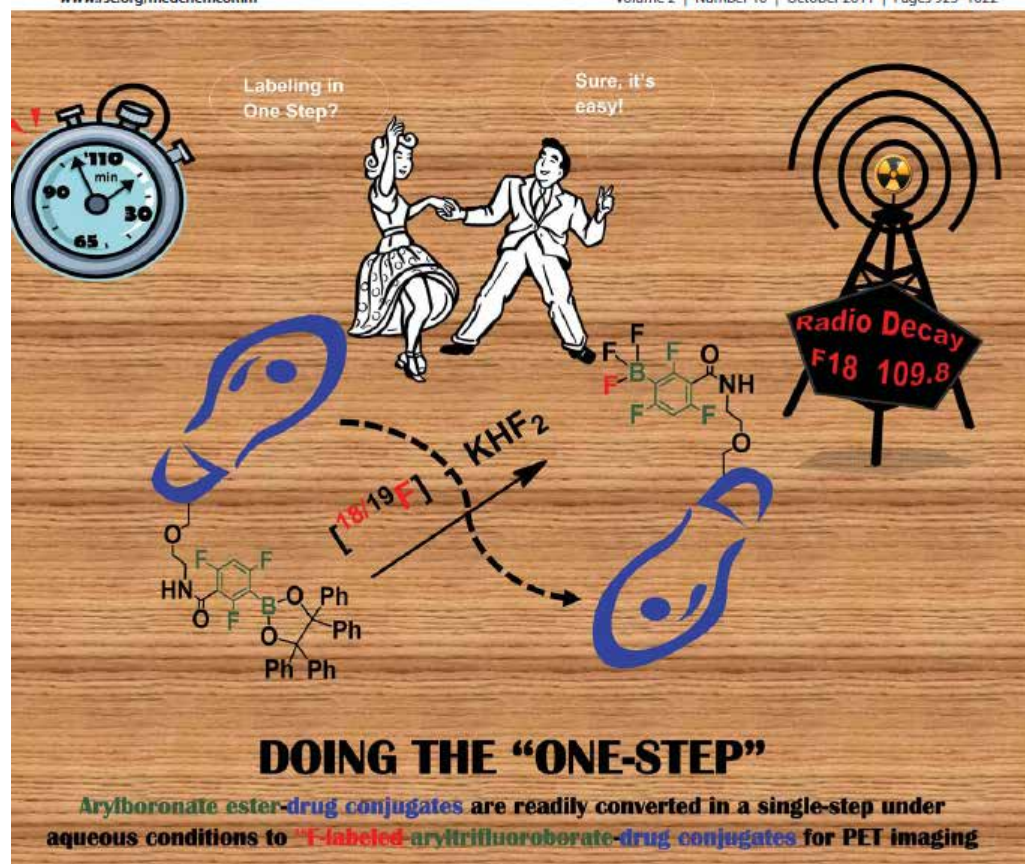
Method B: 100 mg peptide, CH₃CN, H₂O/¹⁸F-

Concept #2: B-[¹⁸F]Fluoride-acceptor chemistry

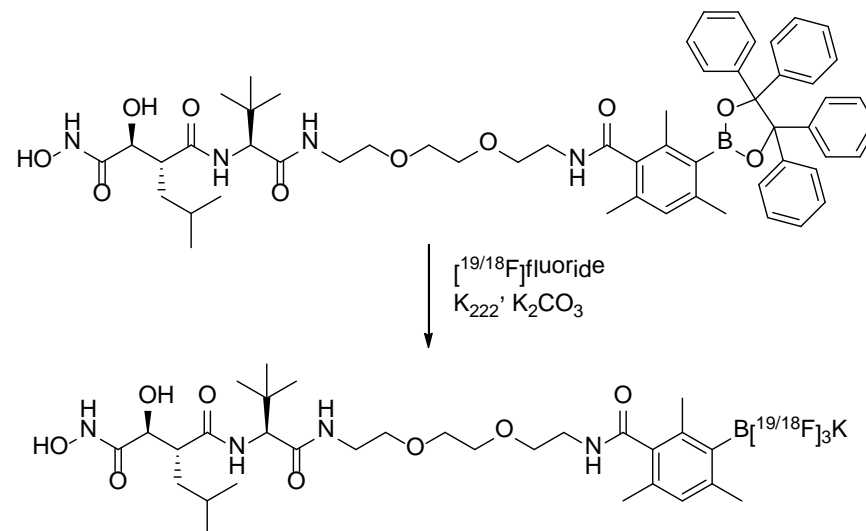
MedChemComm

www.rsc.org/medchemcomm

Volume 2 | Number 10 | October 2011 | Pages 925–1022



Labeling of marimastat boronic acid ester with c.a. [¹⁸F]fluoride for molecular imaging of MMPs in breast cancer



RCY:

50% based upon HPLC
2-3% isolated

Specific activity:

0.2-0.4 Ci/mmol

Synthesis time:

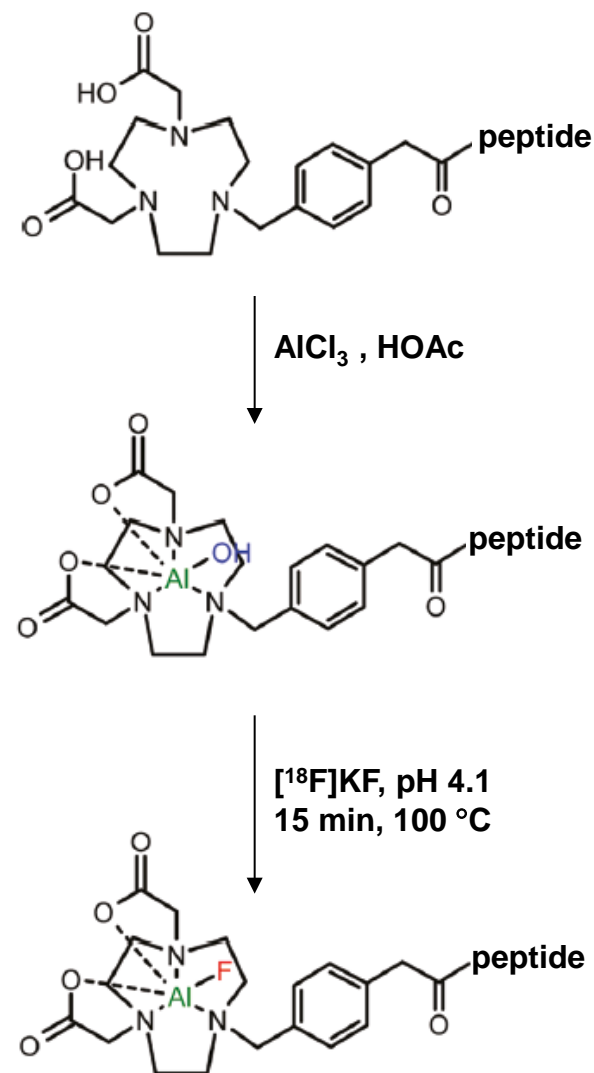
105 min

CHALLENGE:

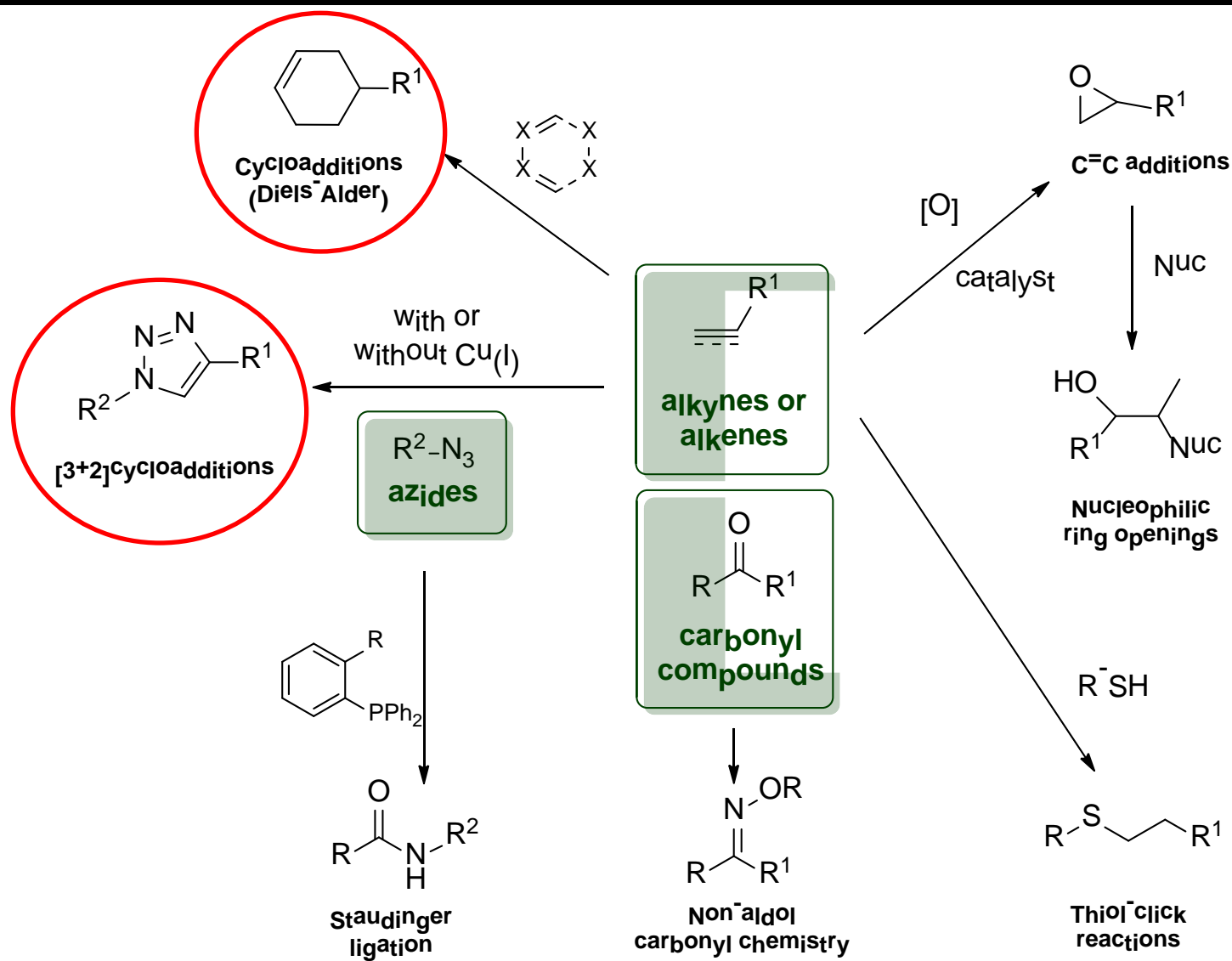
Small volumes used (1.5 mL)

Concept #2: Al- ^{18}F Fluoride-acceptor chemistry

- Al-F bond is among the strongest metal-fluoride bonds
- Chelation of ^{18}F fluoride with Al^{3+} complexed by NOTA
- Elution of ^{18}F fluoride from QMA cartridge and mixing with AlCl_3 and reaction with NOTA-functionalized peptide
- Kit-like preparation of ^{18}F -labeled peptides
- High radiochemical yields (55-89%)
- Stable Al- ^{18}F bond *in vivo* (stable $(\text{AlF})^{2+}$ complex)
- High specific activity (1 Ci/mmol)
- Use of very low peptide amounts (20 nmol)
- Direct labeling \Rightarrow peptides
- Prelabelling \Rightarrow proteins

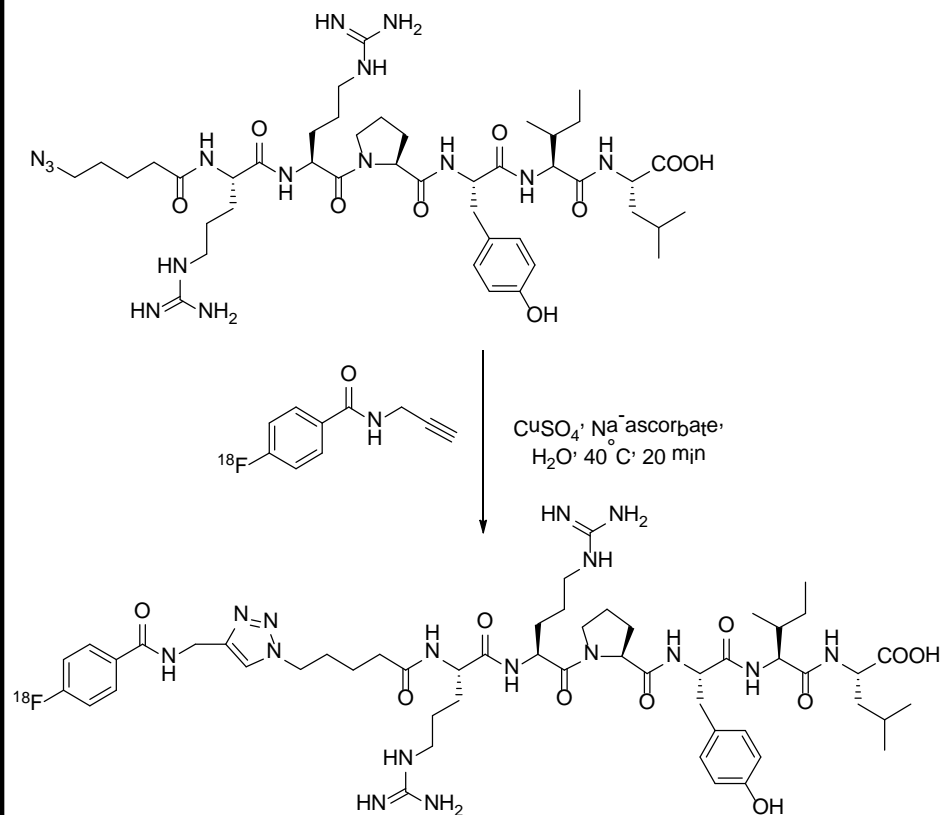


Concept #3: Click chemistry for ^{18}F labeling of biopolymers



Concept #3: Click chemistry for ^{18}F labeling of biopolymers

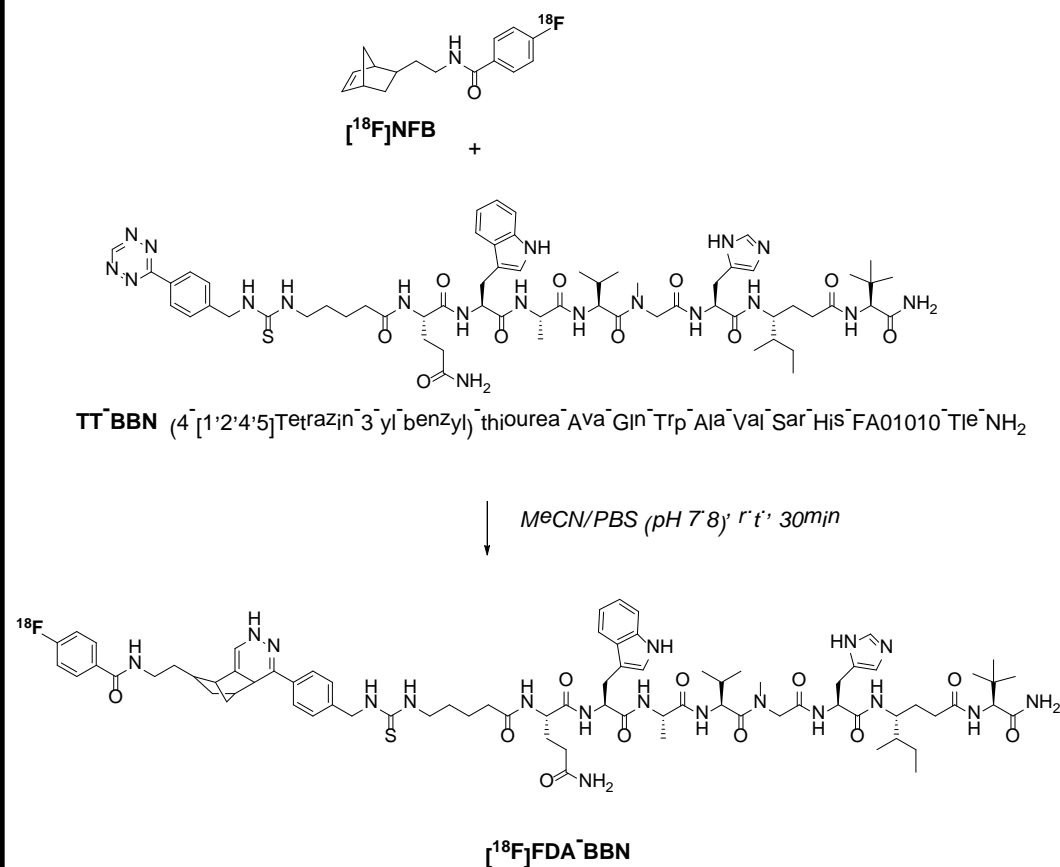
Cu(I)-mediated click chemistry



Peptide amount: 0.5-1 mg

Radiochemical yield: 70%

Cu-free click chemistry



Peptide amount: 0.1 mg

Radiochemical yield: 50%

Selected References

Richter S, Wuest F.

¹⁸F-Labeled Peptides: The Future Is Bright

Molecules 2014, 19, 20536-20556.

Li S, Shen B, Chin FT, Cheng Z.

Recent Progress in Radiofluorination of Peptides for PET Molecular Imaging

Curr. Org. Syn. 2011, 8, 584-592.

Kuhnast B, Dolle F.

The challenge of labelling macromolecules with fluorine-18: Three decades of research.

Curr Radiopharm. 2010, 3, 174-201

Wu Z, Kandeel F.

¹⁸F-labeled proteins.

Curr Pharm Biotechnol. 2010, 11, 572-80.

Mamat C, Ramenda T, Wuest F.

Recent advances of click chemistry for the synthesis of radiotracers for molecular imaging.

Mini-Rev Org Chem. 2009, 6, 21-34.

Wester HJ, Schottelius M.

Fluorine-18 labeling of peptides and proteins.

Ernst Schering Res Found Workshop. 2007; 62, 79-111.