Chemical Science

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Mechanistic studies and radiofluorination of structurally diverse pharmaceuticals with spirocyclic iodonium(III) ylides

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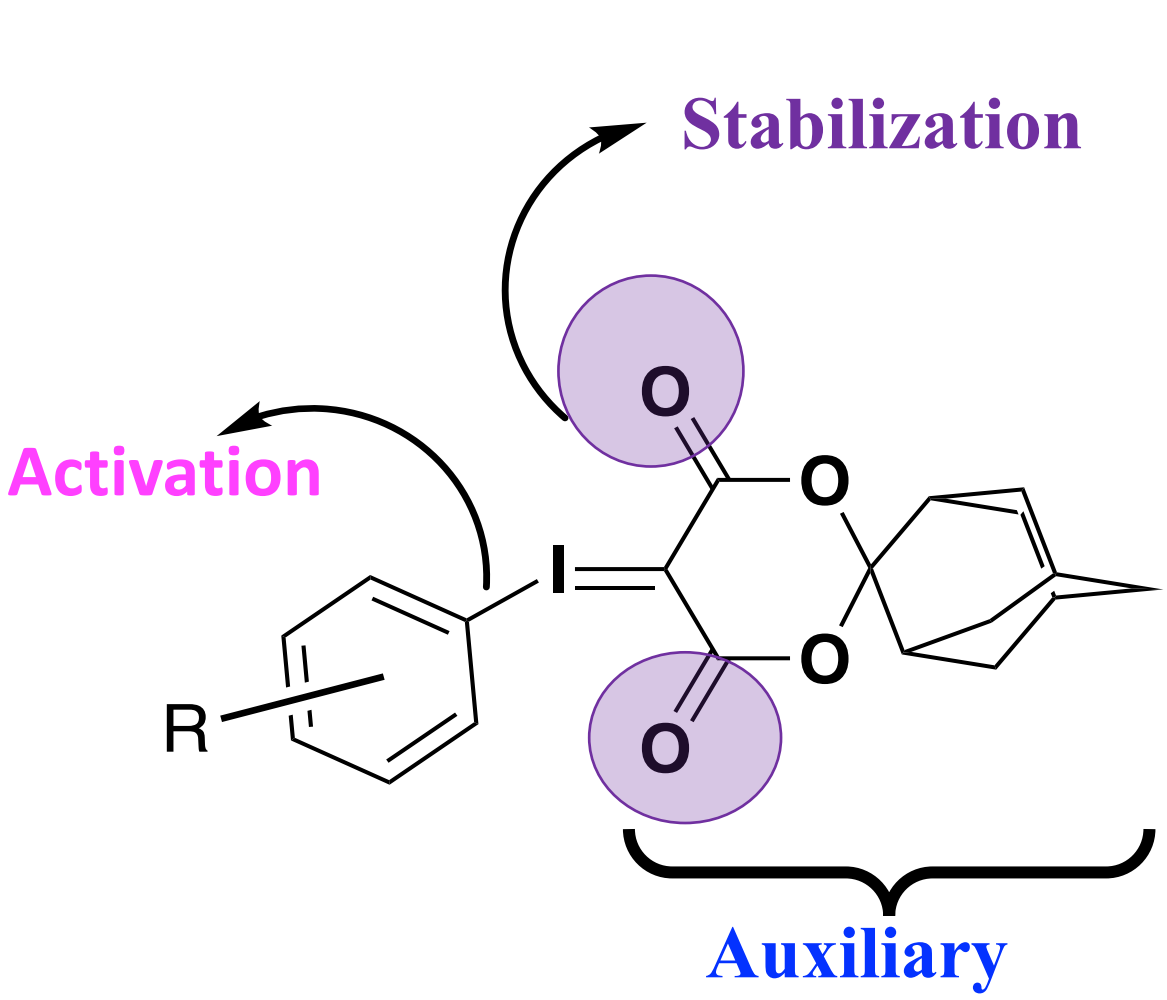
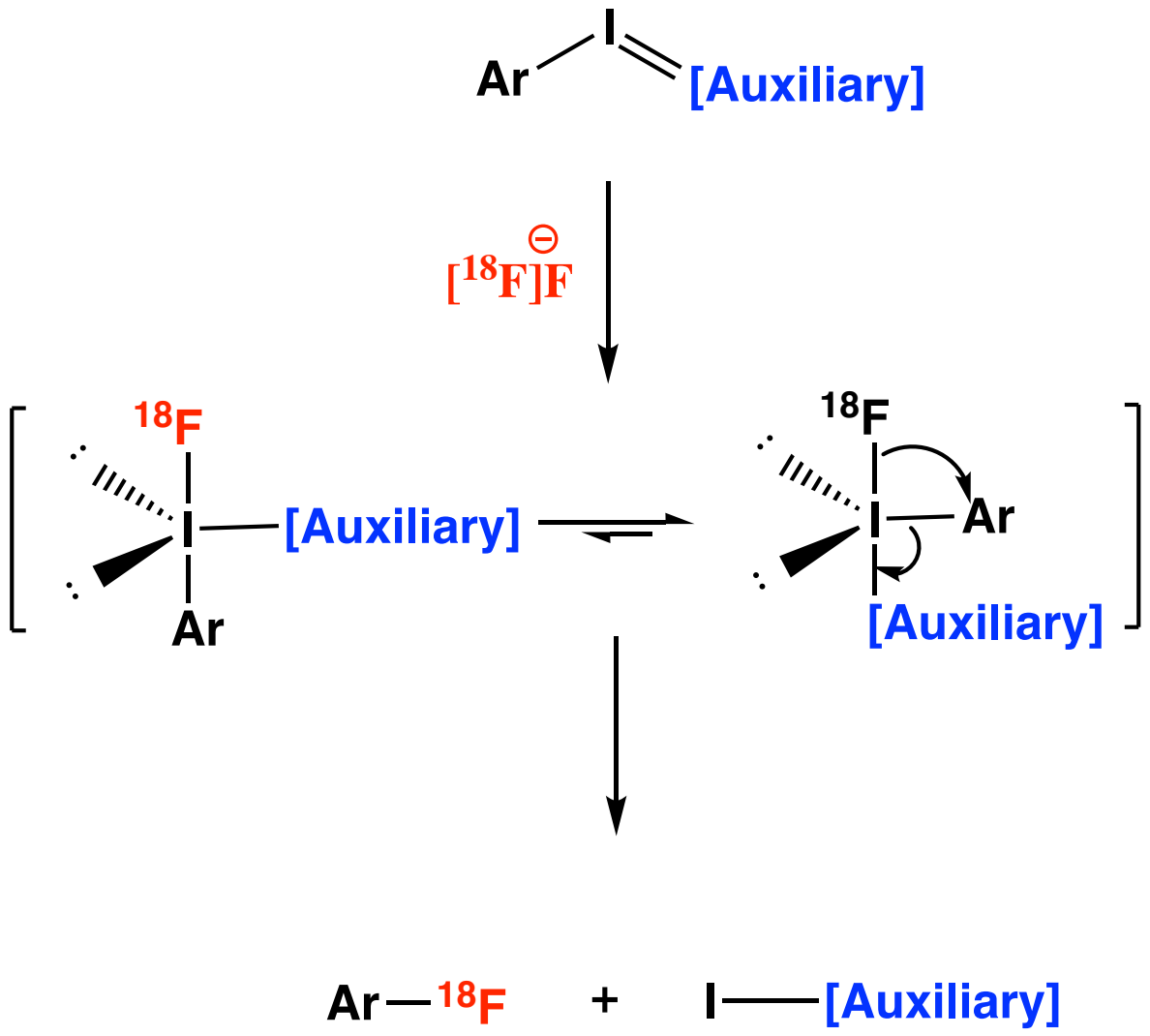
Outline

1. Background
2. Reaction schemes and mechanisms
3. Results
4. Summary

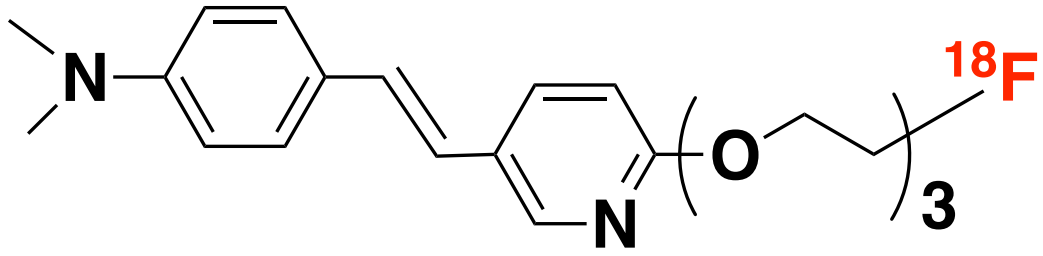
Spirocyclic Iodonium(III) Ylides





Long Term Objective

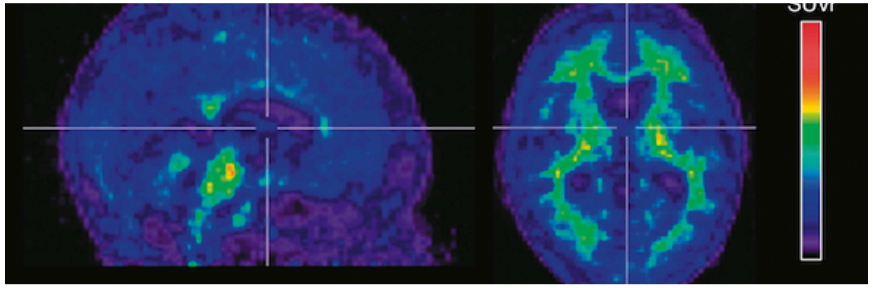
Development of [^{18}F] based radiotracers



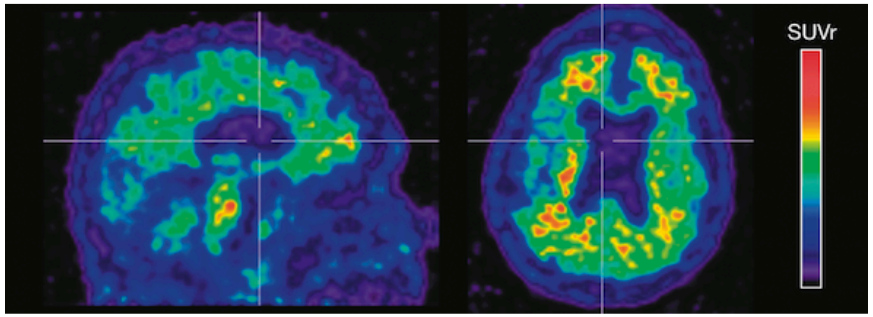
[^{18}F]Amyvid

- Half life of ^{18}F is 109.77 min
- Labeling time < 60 mins

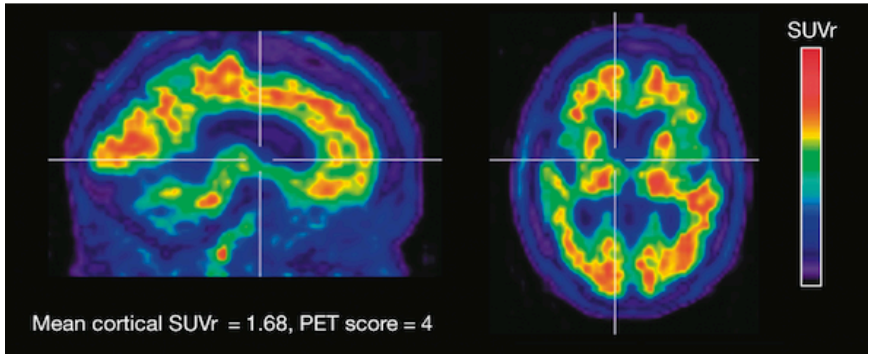
a) No β-amyloid plaques



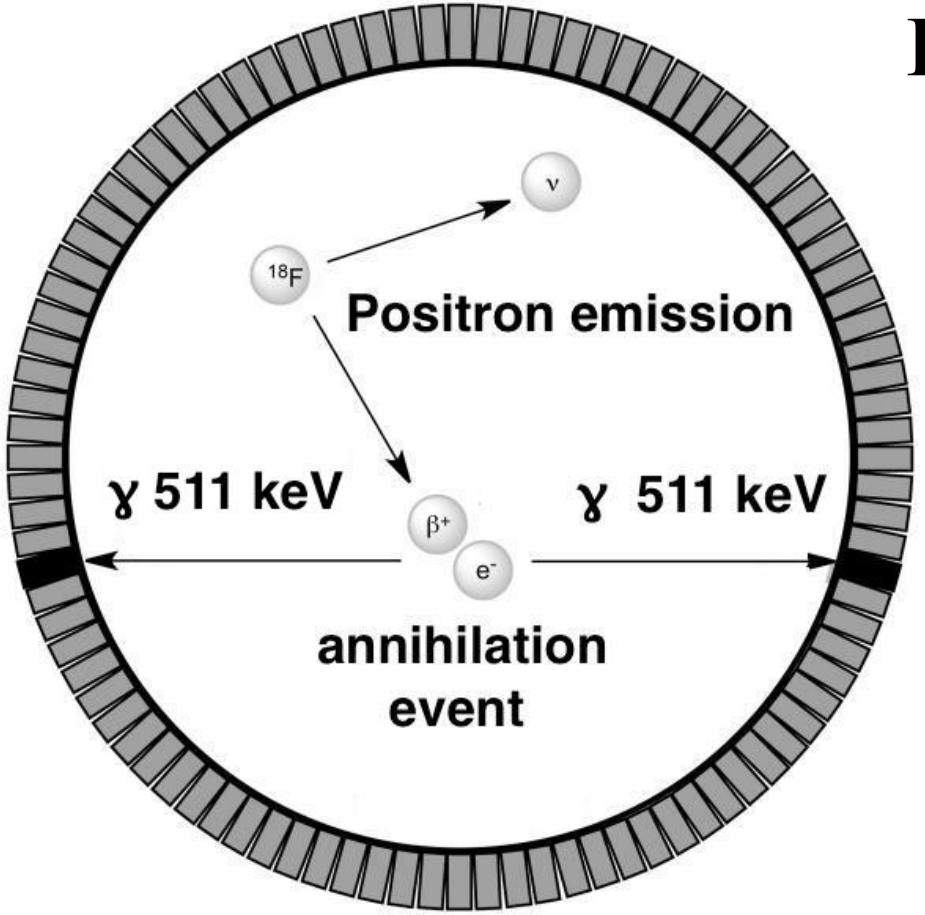
b) Moderate load of β-amyloid plaques



c) High load of β-amyloid plaques



Positron Emission Tomography (PET)



1. $^{18}F \longrightarrow {}^{18}O + \beta^{+} + \nu_e$
2. $\beta^{+} + e^{-} \longrightarrow 2\gamma$

Decay of radionuclide

⇩

Positron (β^{+}) emission

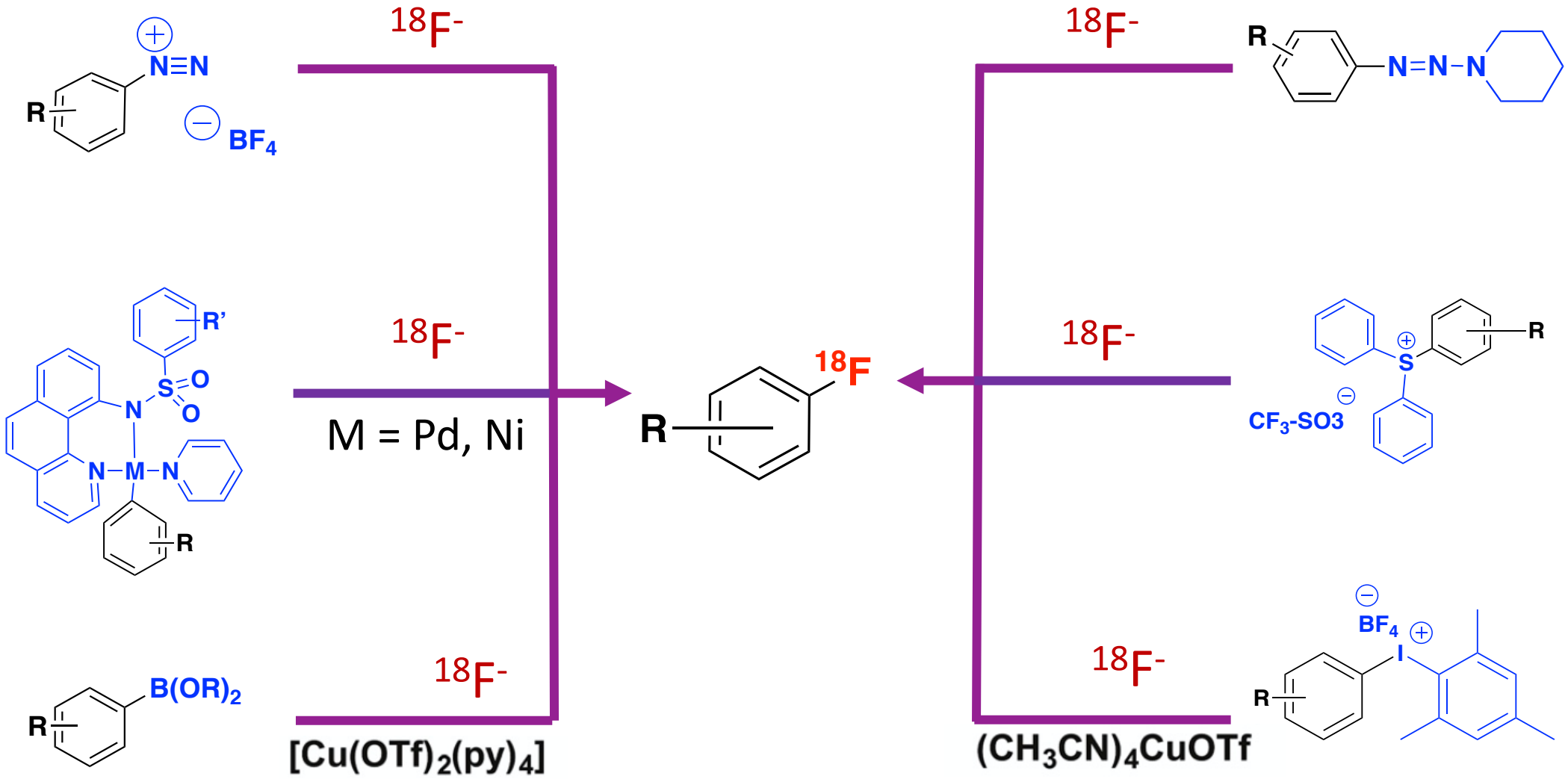
⇩

Annihilation with e^{-}

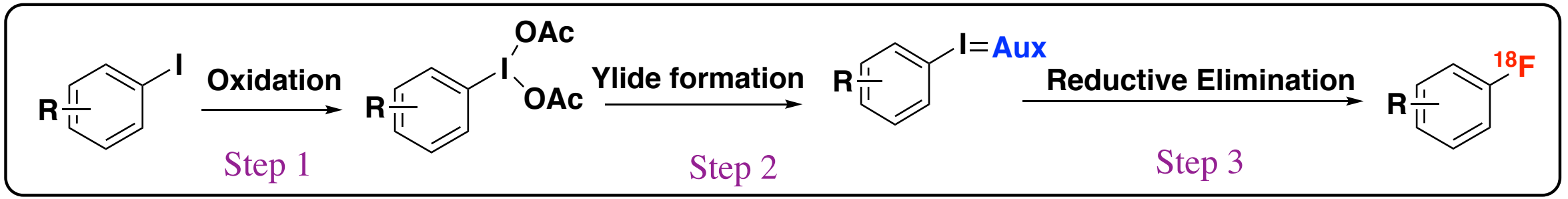
⇩

Detection of γ rays

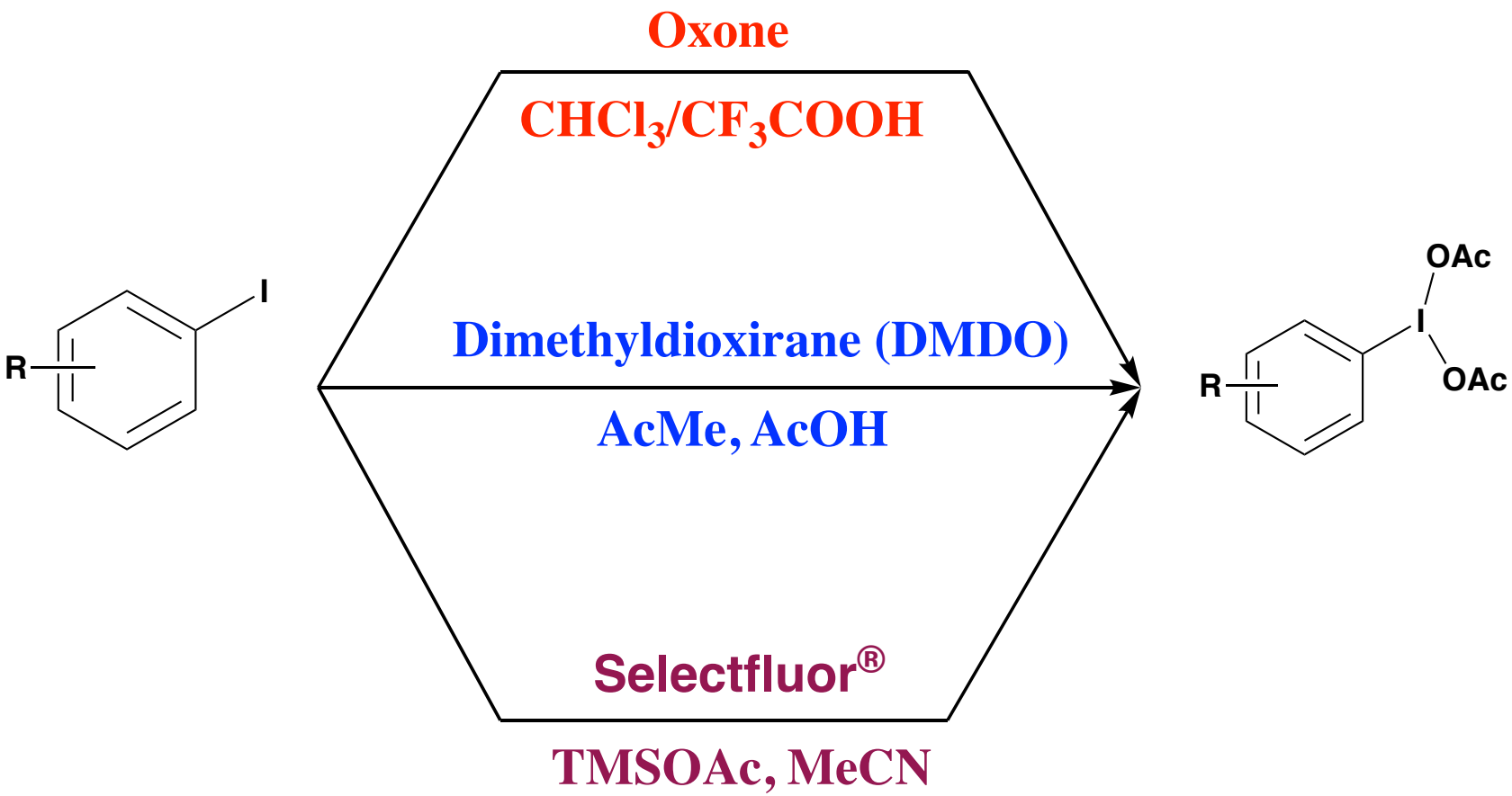
Previous ^{18}F Labeling Routes



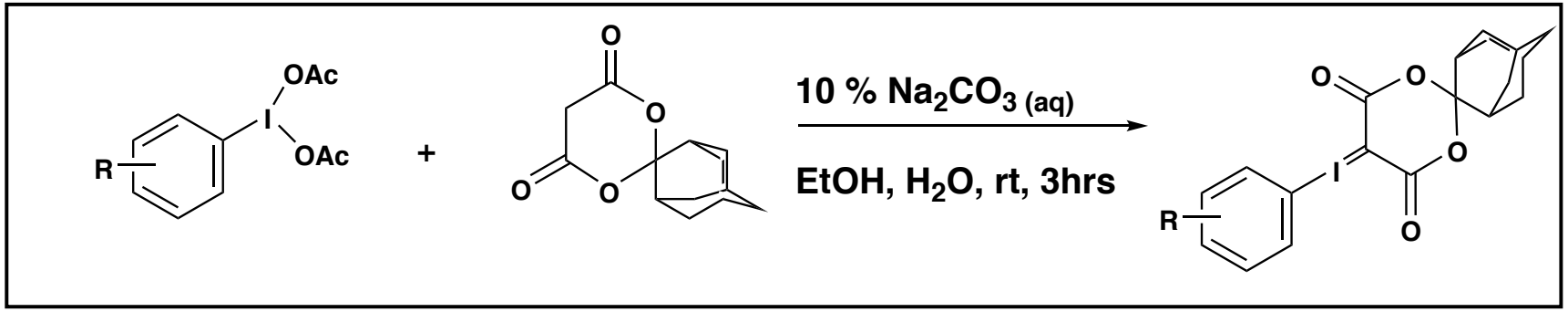
Reaction Scheme



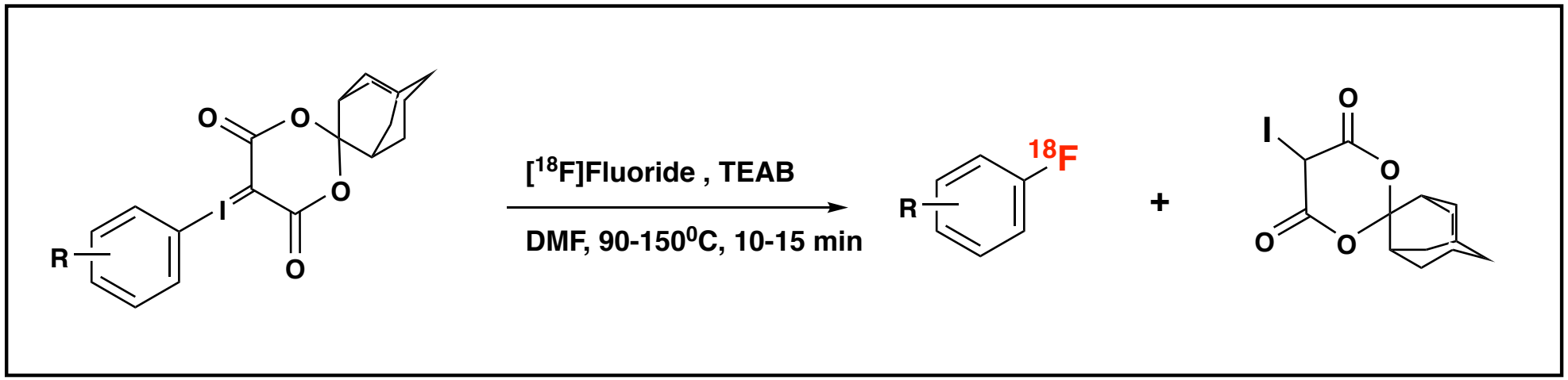
Step 1: Oxidation



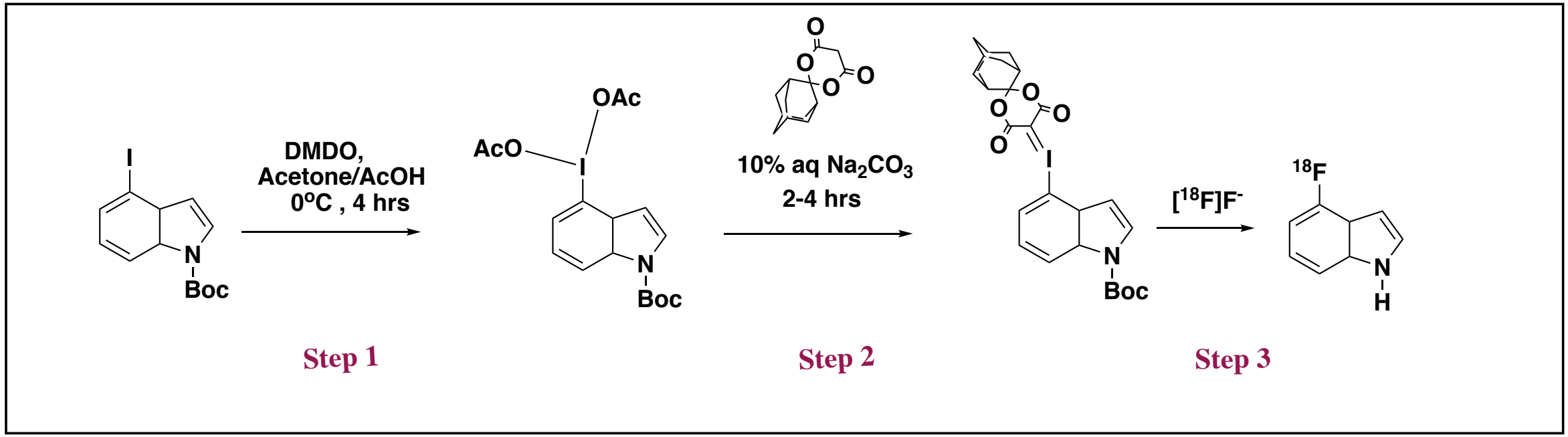
Step 2: Ylide Formation



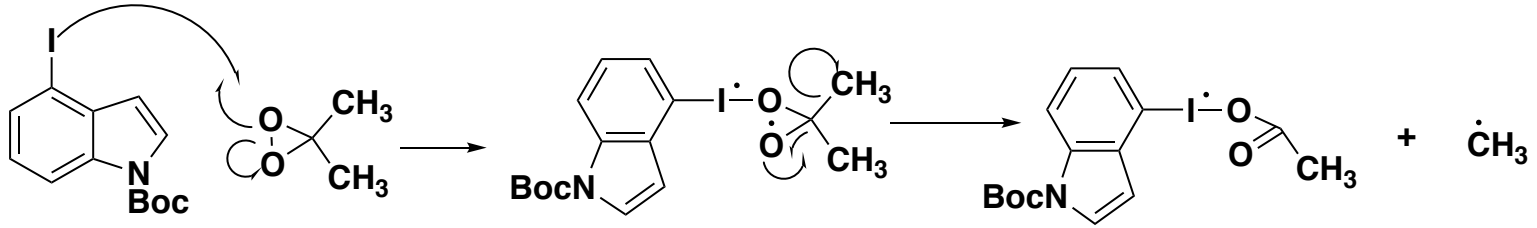
Step 3: Reductive Elimination



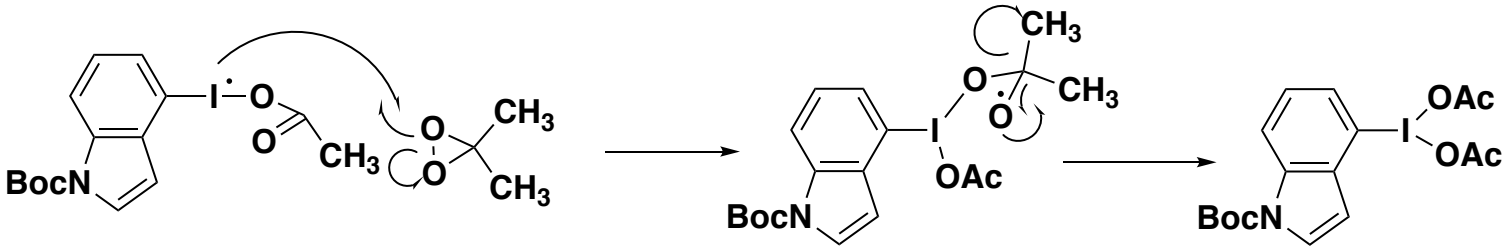
Synthesis of [^{18}F]Indoles



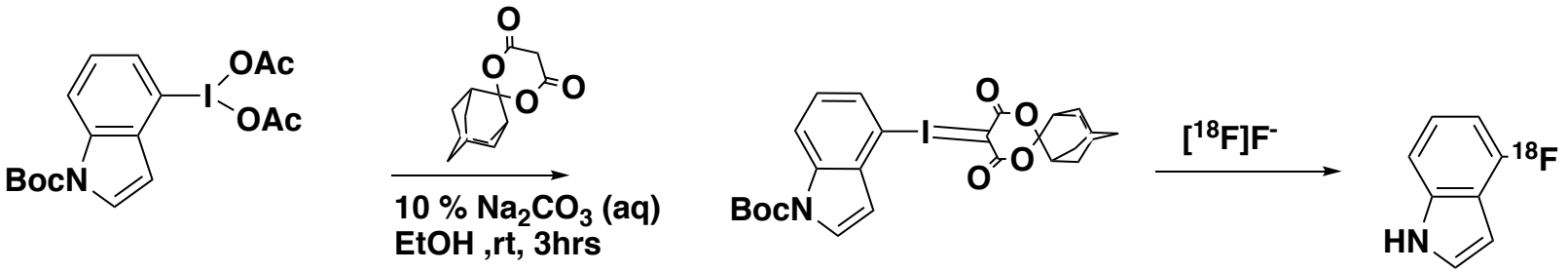
❖ Free radical decomposition of dioxirane leading to generation of methyl radical



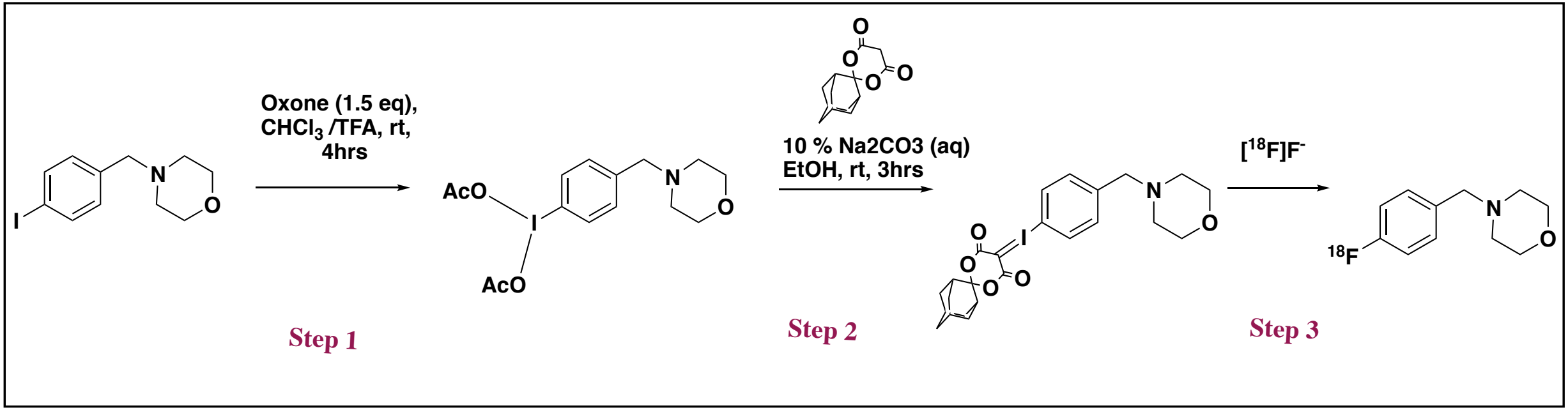
❖ Formation of iodosoacetate by using second DMDO equivalent



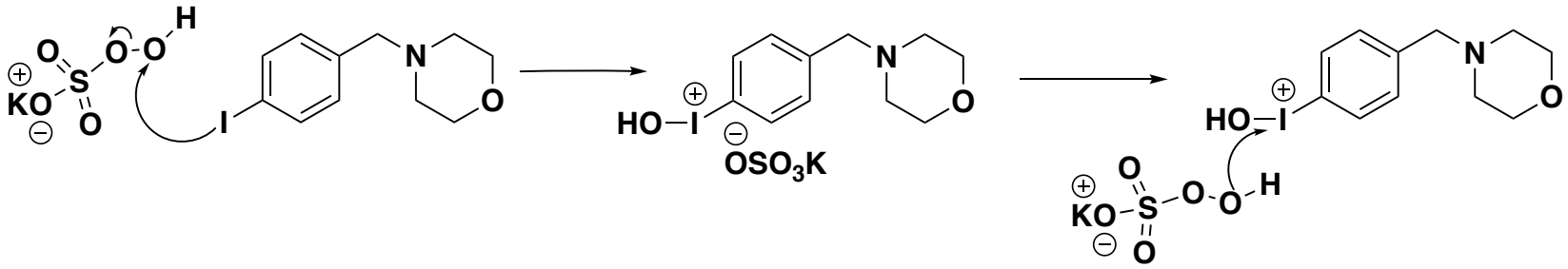
❖ Ylide formation and subsequent reductive elimination



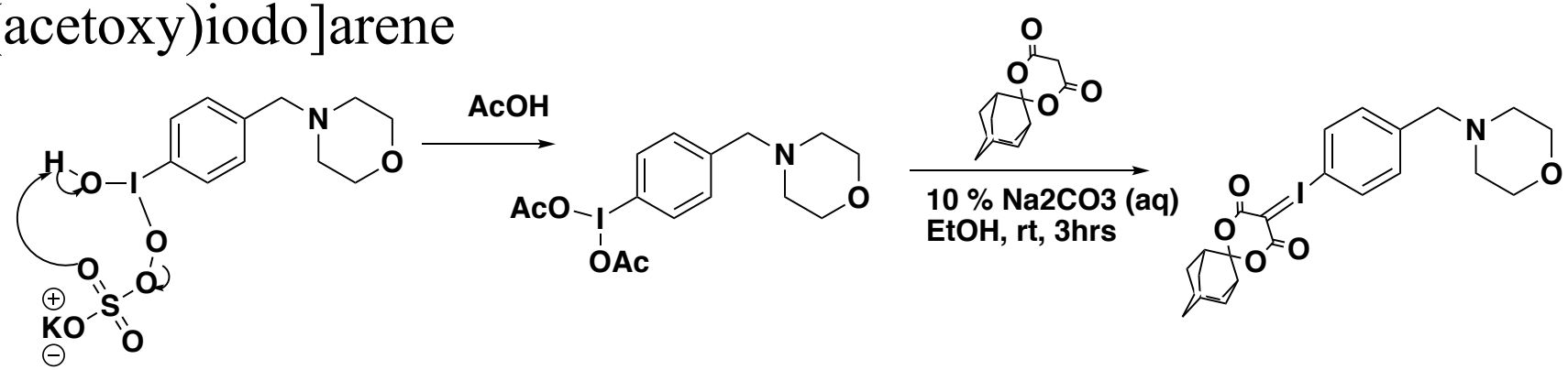
Synthesis of [^{18}F]Drug Scaffold: Mosapride



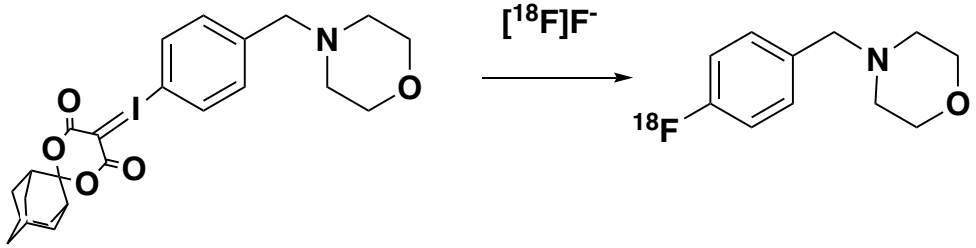
❖ potassium peroxymonosulfate as an oxidizing agent



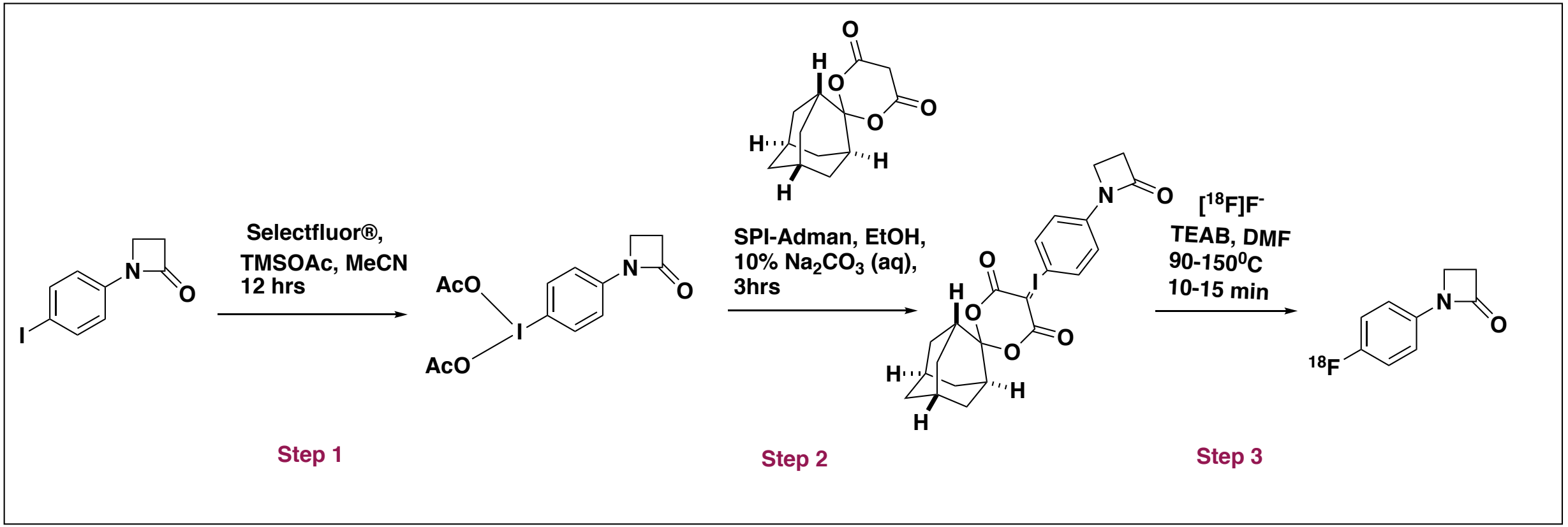
❖ formation of [bis(acetoxy)iodo]arene



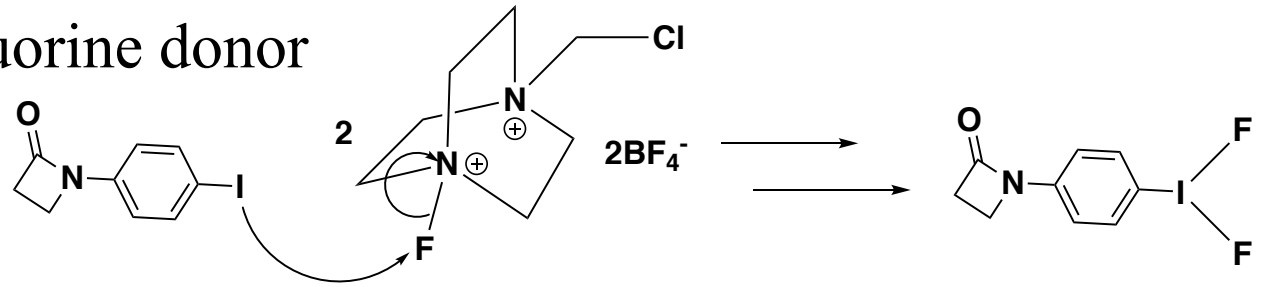
❖ ^{18}F labeling by reductive elimination



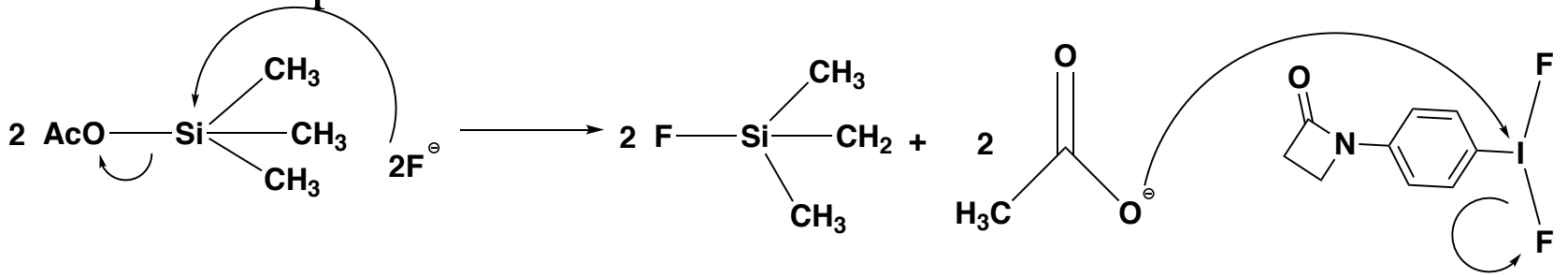
Synthesis of [^{18}F]Drug Scaffold: Ezetimibe



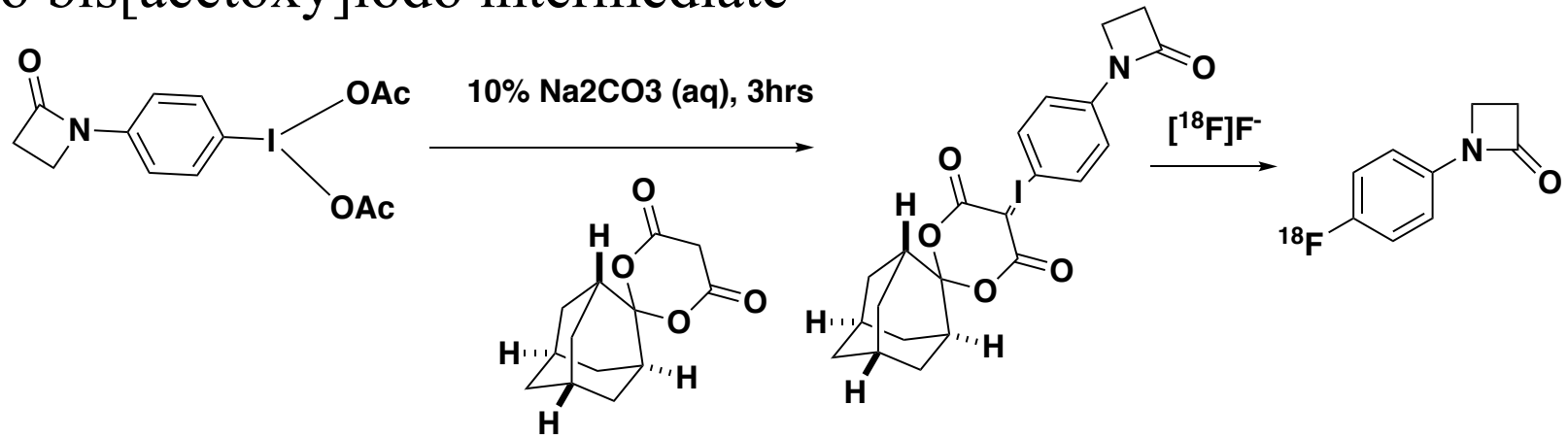
❖ Selectfluor® acts as an fluorine donor



❖ TMSOAc acts an an lewis acid to capture fluoride.



❖ Conversion of Ar-IF_2 into bis[acetoxy]iodo intermediate



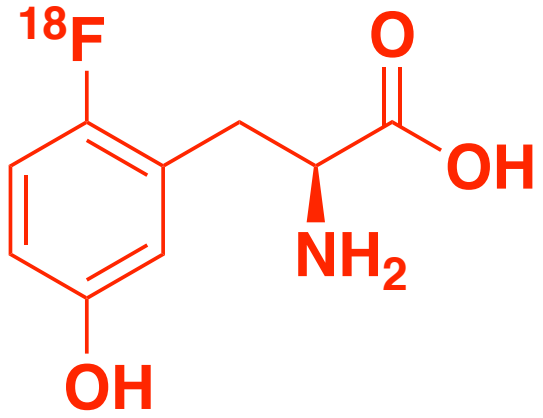
Results

1. PET radiopharmaceuticals
2. Competing reaction pathways
3. Steric effect of substituents
4. Electronic effect of substituents

PET Radiopharmaceuticals

[^{18}F]fluoro-meta-tyrosine

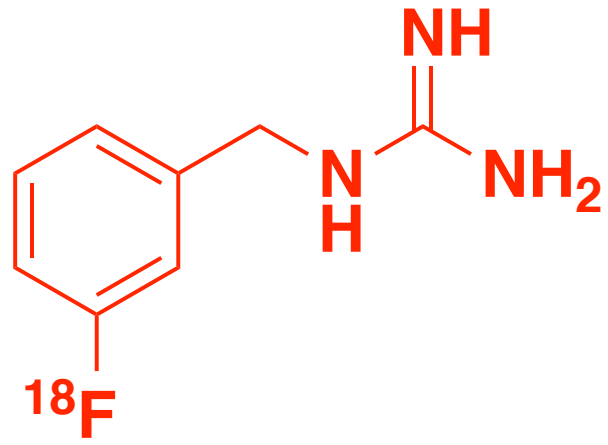
(Cerebral dopamine transport)



Radiochemical yield: 12%

meta-[^{18}F]fluorobenzylguanidine

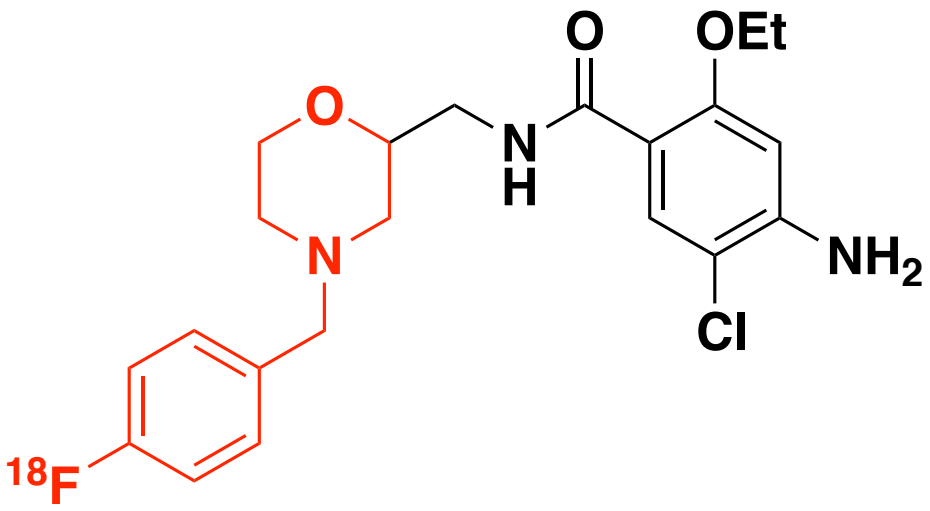
(Neuroblastoma)



Radiochemical yield: 14%

Mosapride

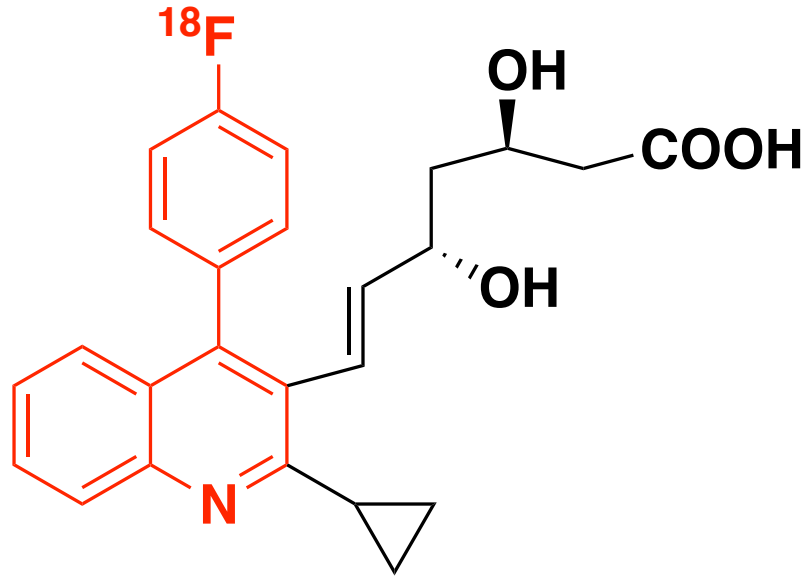
(Gastric inflammation)



Radiochemical conversion: 35 ± 6 %

Pitavastatin

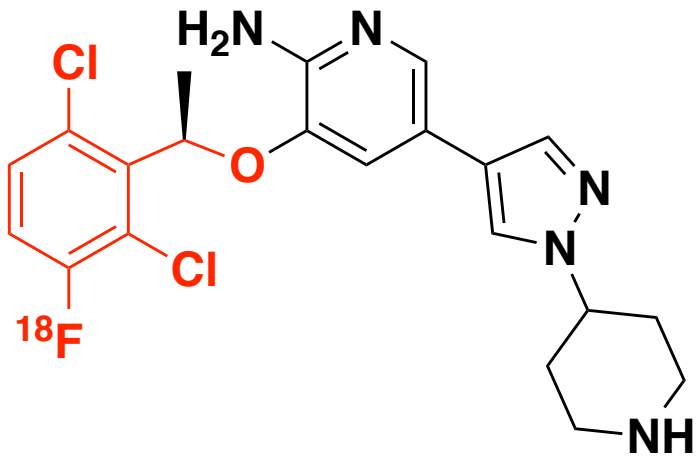
(hypocholestrolaemia)



Radiochemical conversion: 57 ± 9 %

Crizotinib

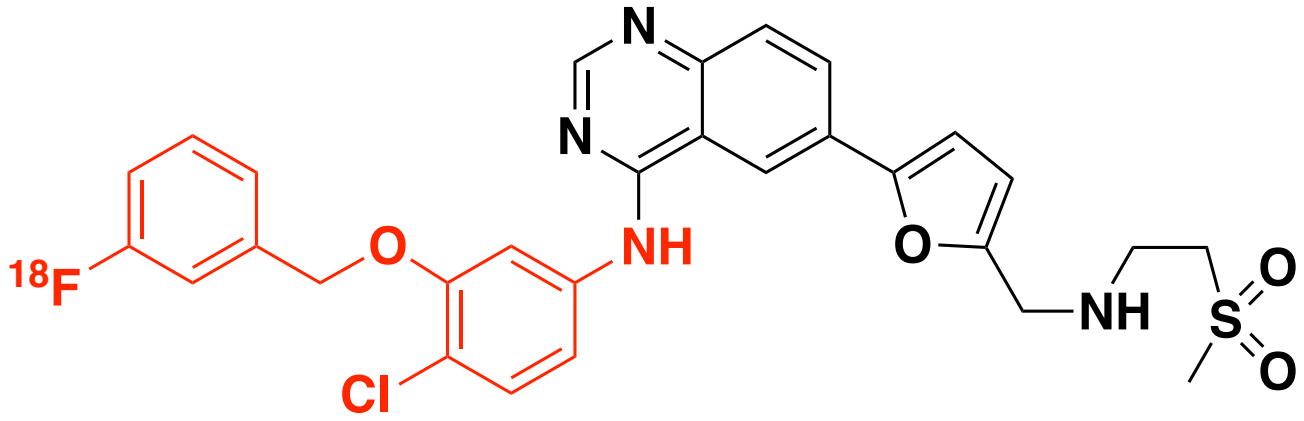
(Non-small cell lung cancer)



Radiochemical conversion: 82 ± 6 %

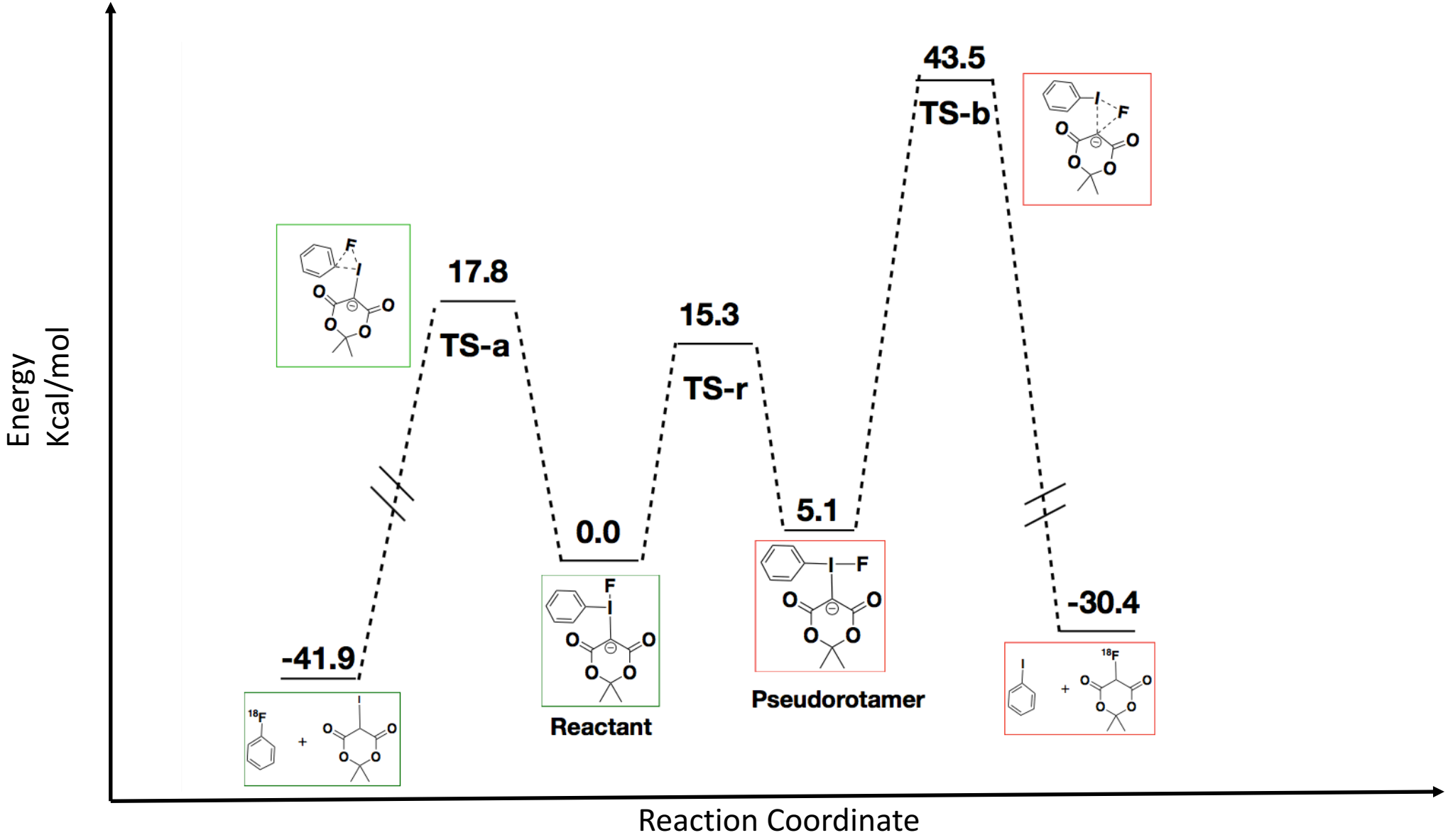
Ipatinib

(Breast and lung cancer)

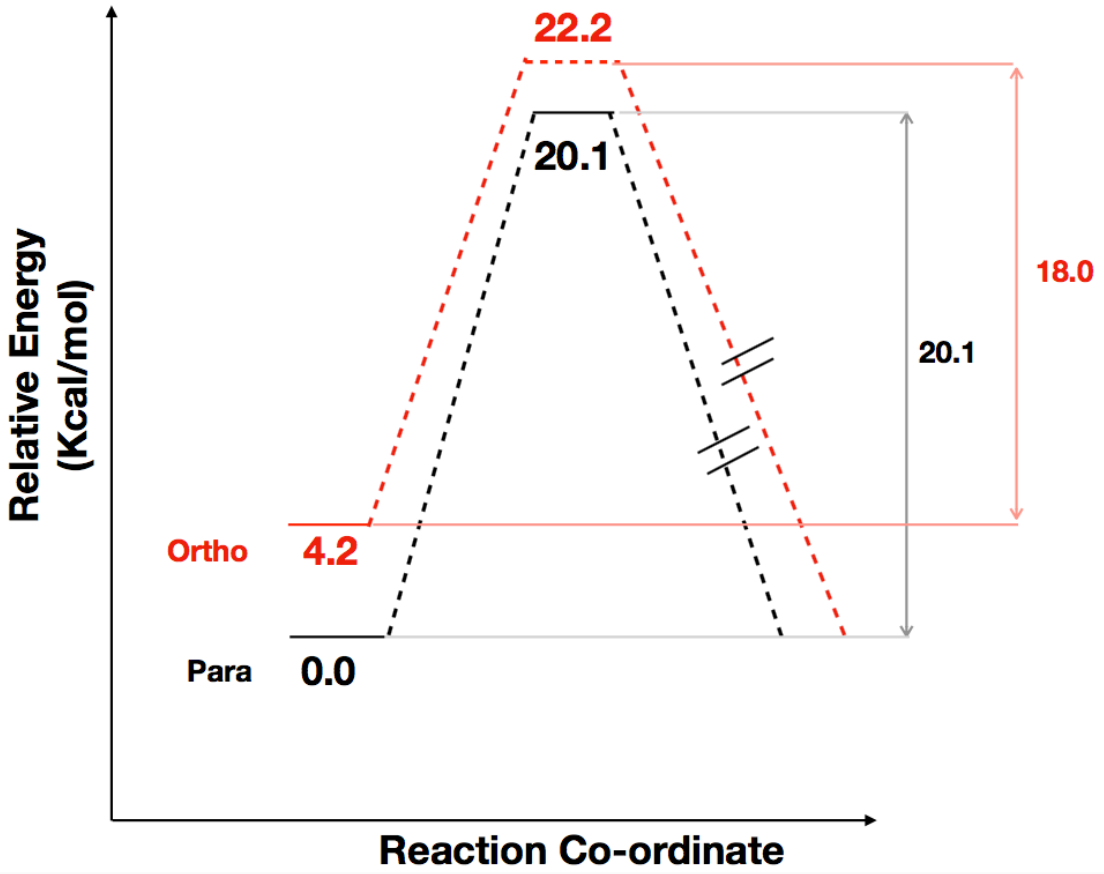


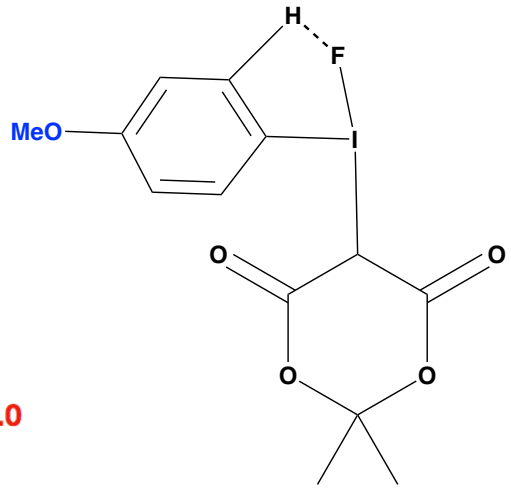
Radiochemical conversion: 66 ± 8 %

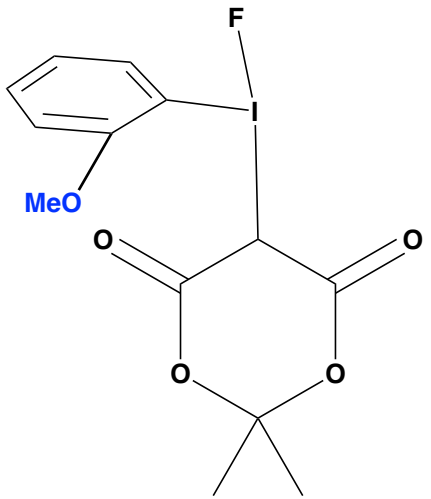
Competing Reaction Pathways

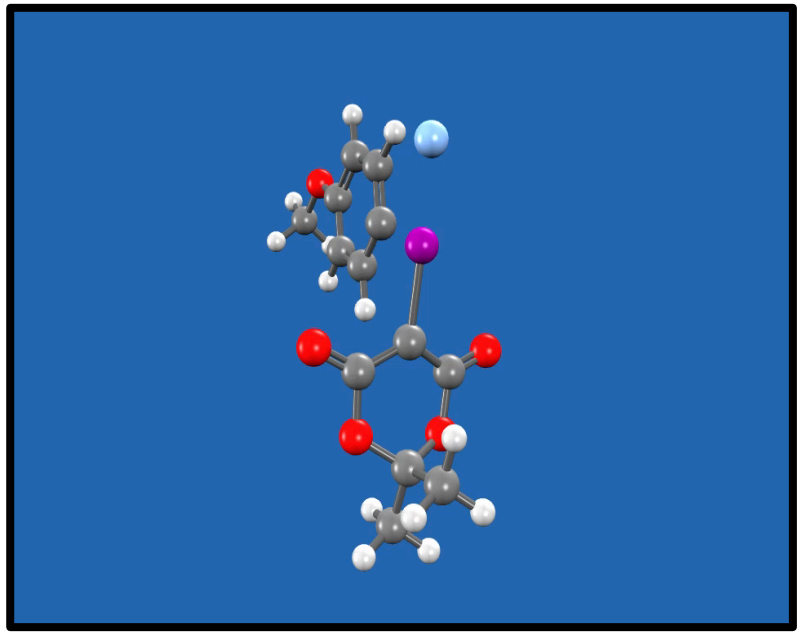


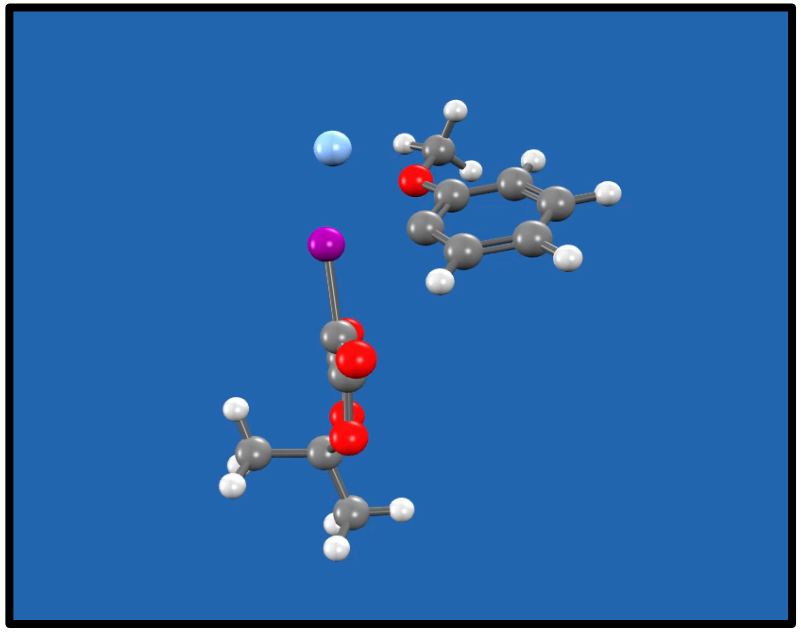
Steric Effect





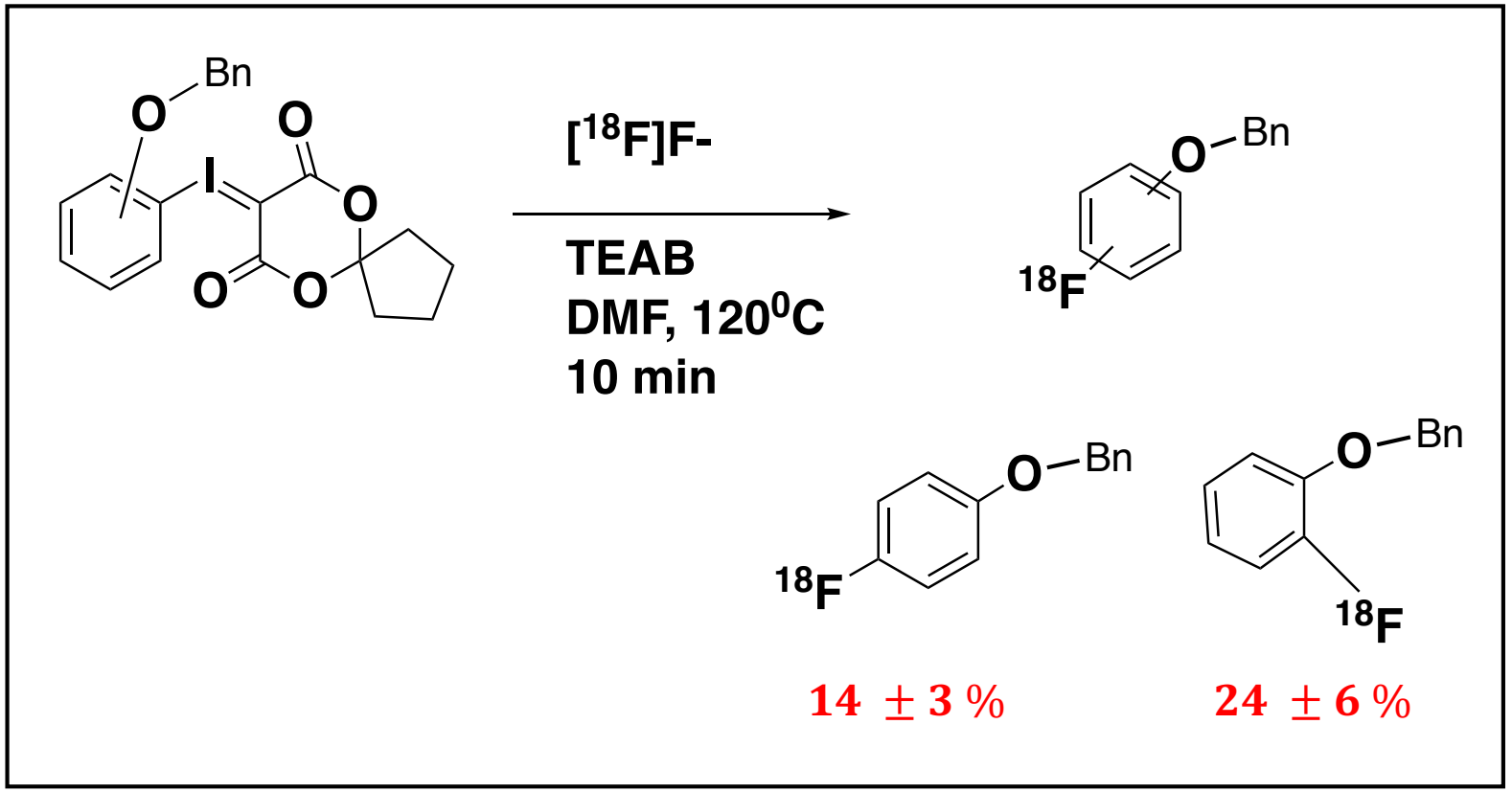




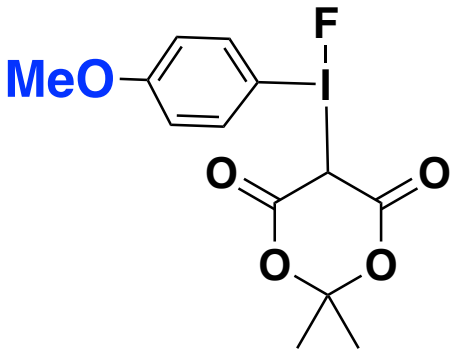


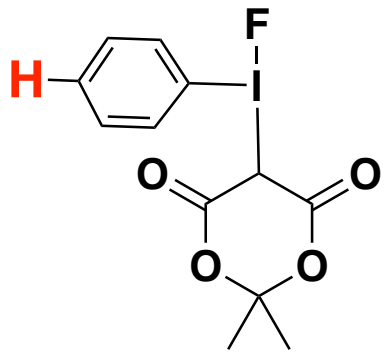
Ortho substitution: Destabilization of reactants in ground state

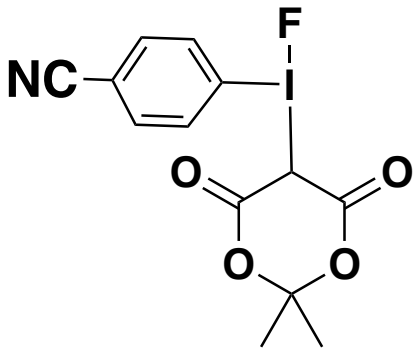
Experimental Results for *ortho* Effects

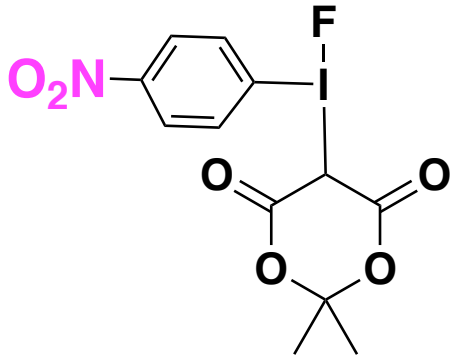


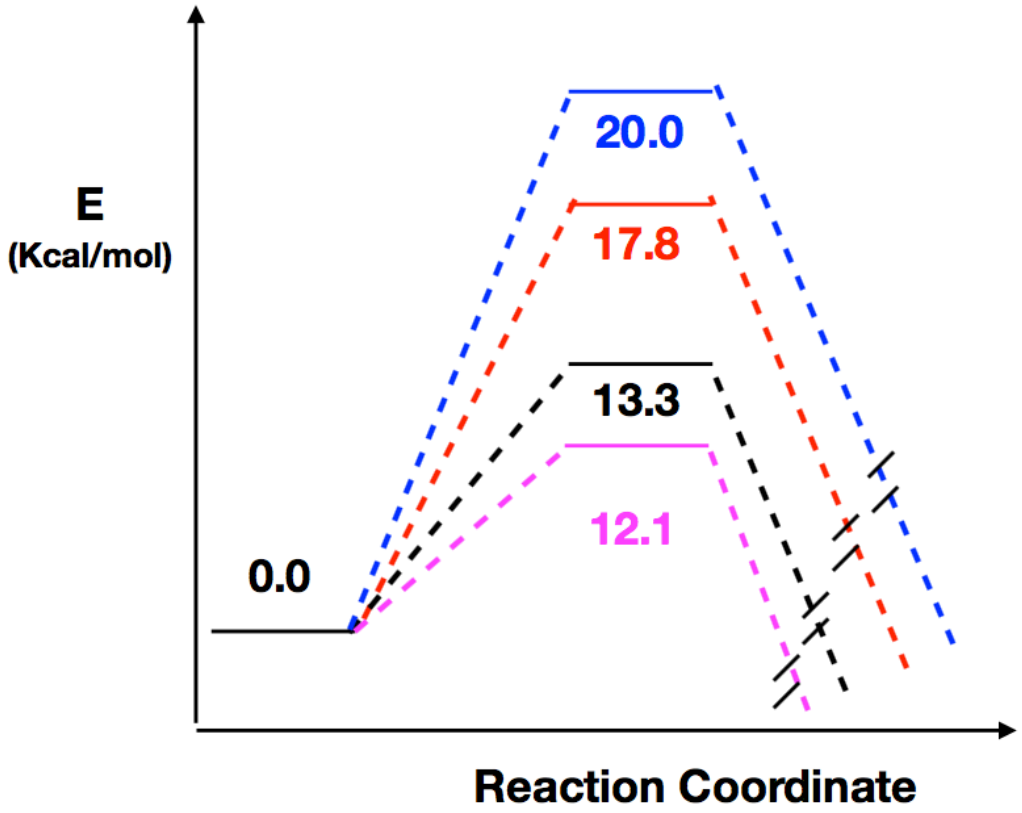
Electronic Effects of Substitution





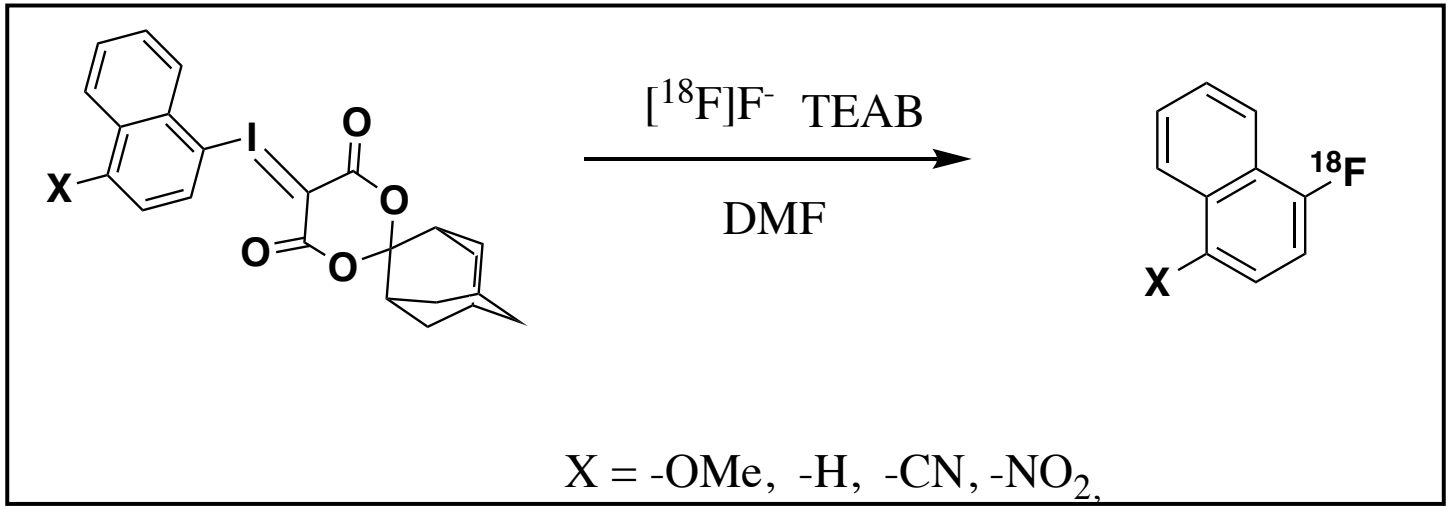


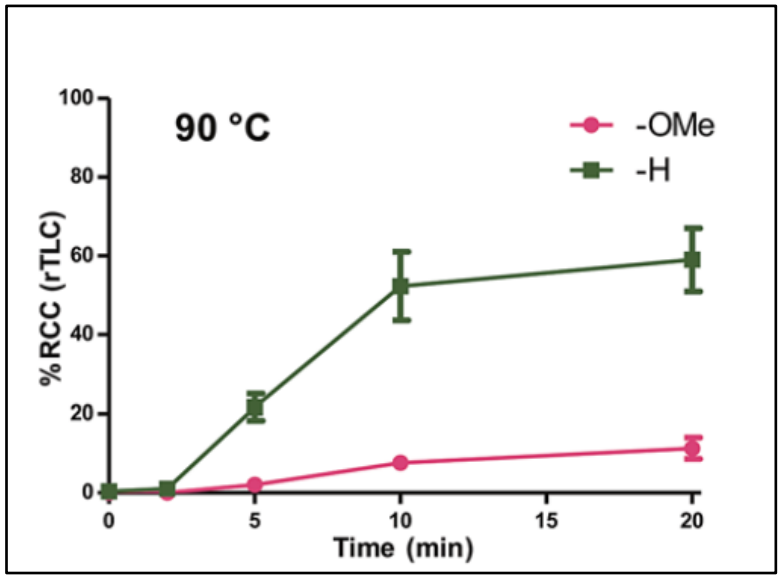




Reduction in reductive elimination barrier by EWGs $\Delta G^{\ddagger}$ $-NO_2 < -CN < -H < -OMe$

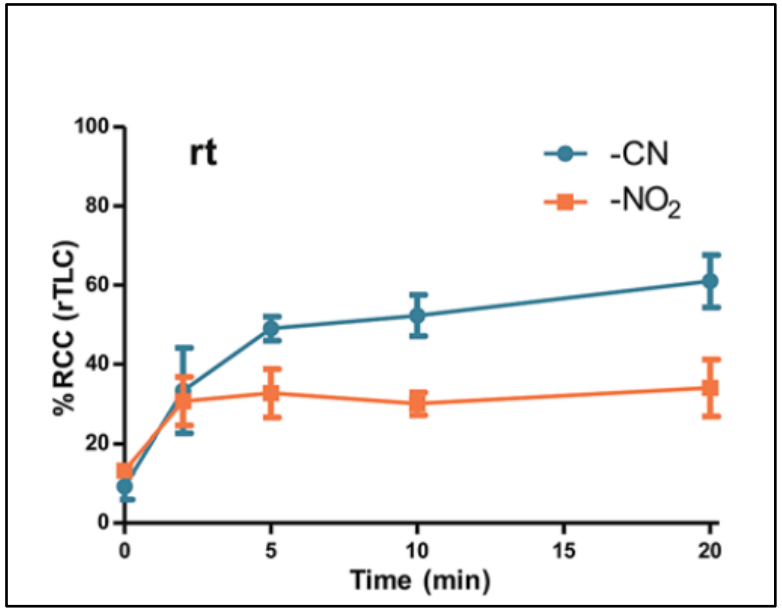
Electronic Effects of Substitutions





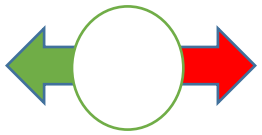
Factors affected by substitutions:

1. Rate of conversion
2. Temperature of the reaction
3. Reductive elimination barrier



Summary

1. Higher PET radiotracers yields
2. High Regioselectivity
3. Short reaction times
4. Purification of iodonium ylides
5. Modulation of $\Delta G^{\ddagger}$ by substitutions



1. Radiation safety
2. Choice of hazardous reagents
3. Ylide rearrangement
4. Clinical trials of designed PET tracers
5. One-pot oxidation and ylide formation

Acknowledgments

Graduate committee members:

- Dr. Yihan Shao
- Dr. Anthony Burgett
- Dr. Bing Wang
- Dr. George Richter-Addo
- Dr. Wai Tak Yip

Chemistry faculty

- Dr. Ronald Halterman
- Dr. Daniel Glatzhofer

OU support staff

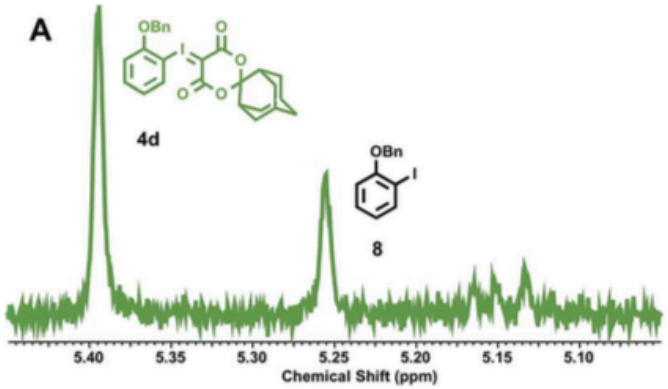
- Kelsi Nulnee
- Carol Jones
- Nailynn Williams
- Heather Thomson

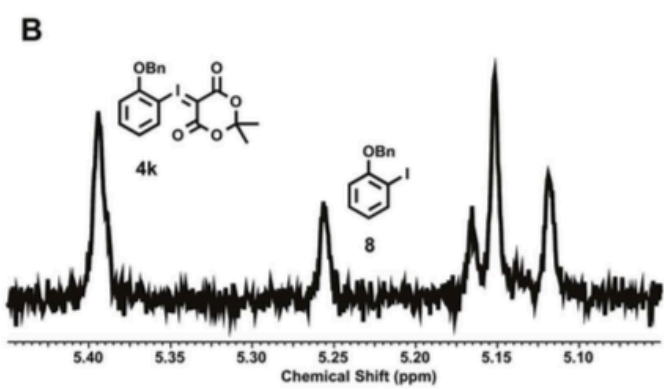
Lab mates and colleagues

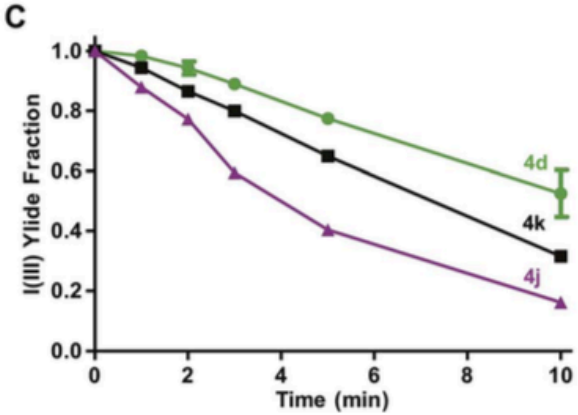
- Dr. Xiaoliang Pan
- Dr. Gengwei Zhang
- Dr. Ye Mei
- Jingheng Deng
- Zhu Zou
- Eric Gardner
- Tejaswi Bavineni

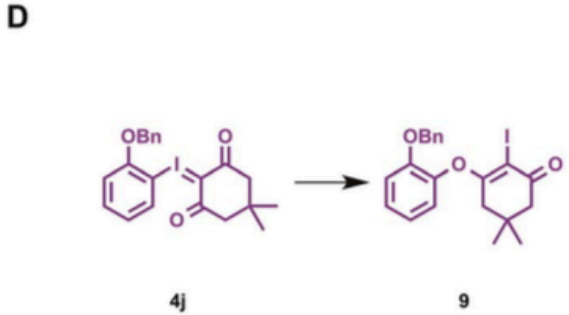
supplementary slides

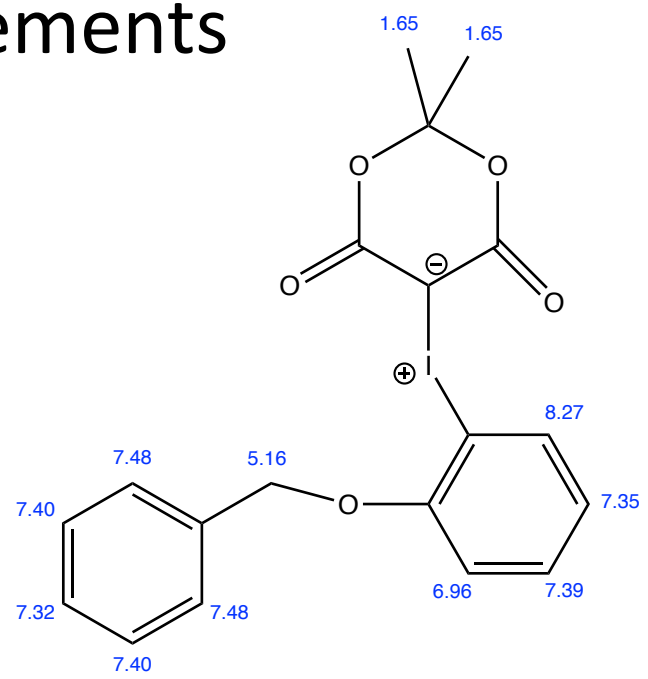
Possible rearrangements



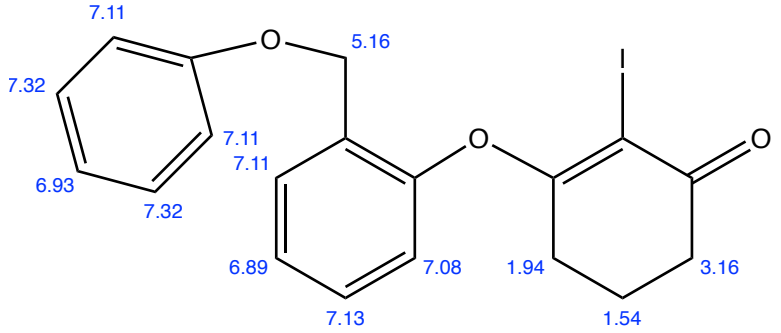






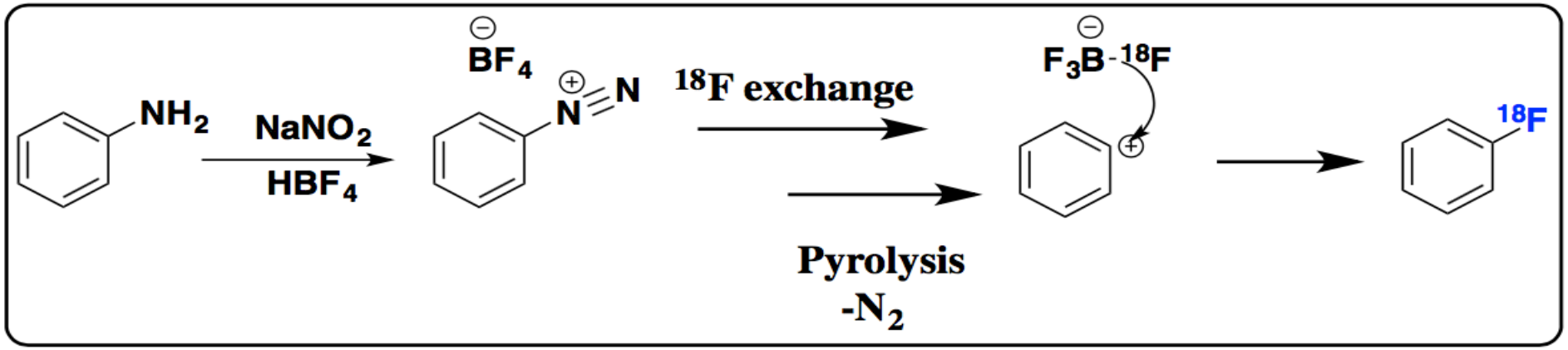


4K

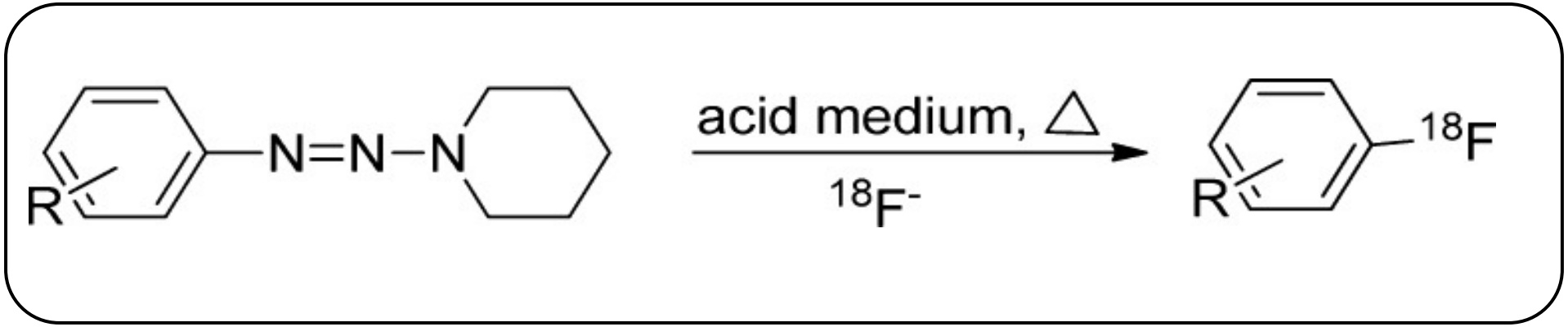


9

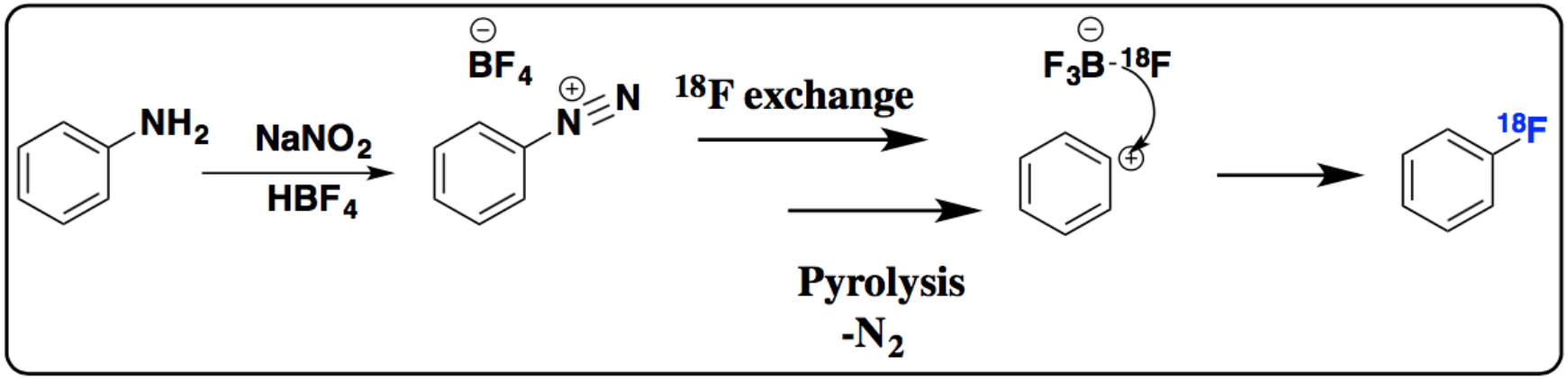
- Balz-Schiemann reaction:



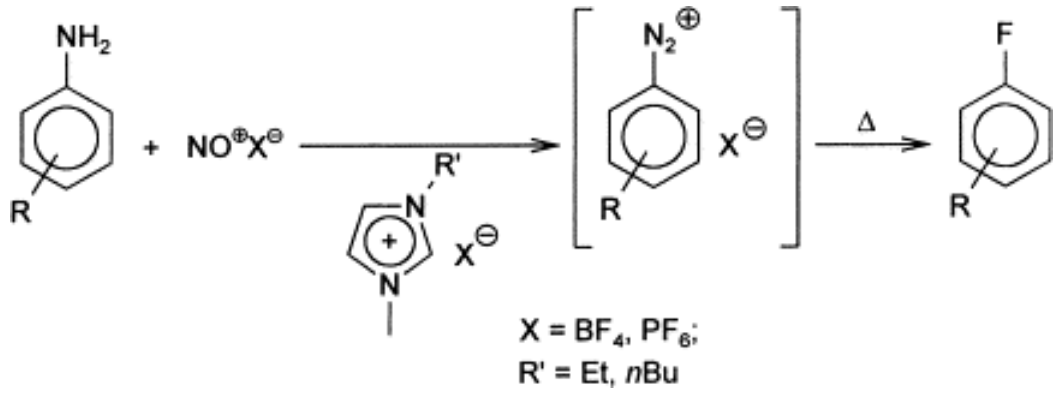
- Wallach reaction:

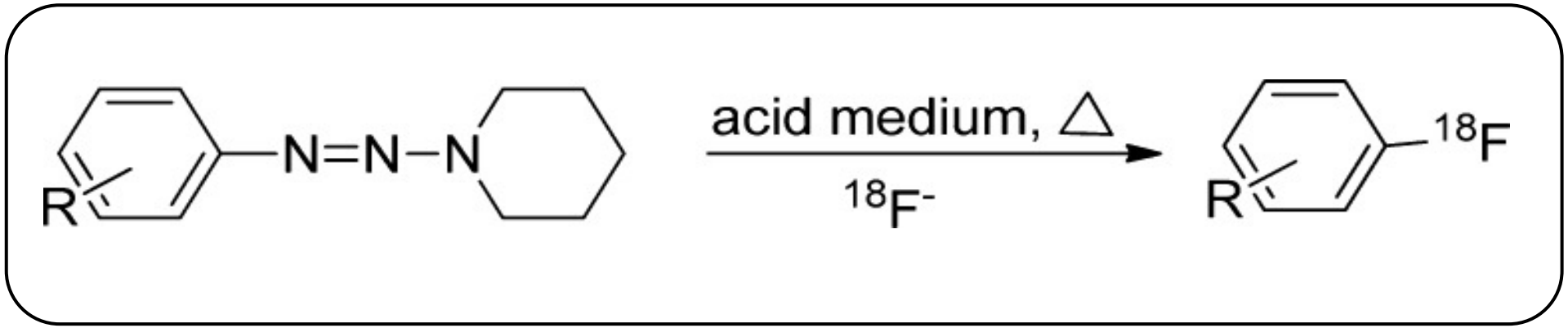


- Balz-Schiemann reaction:

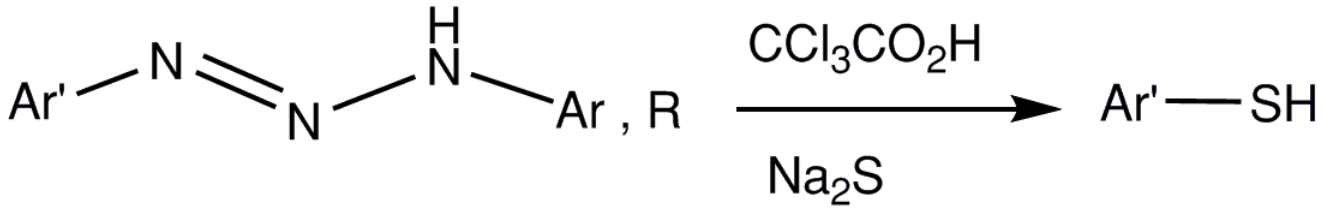


- Balz-Schiemann reaction with ionic liquids:

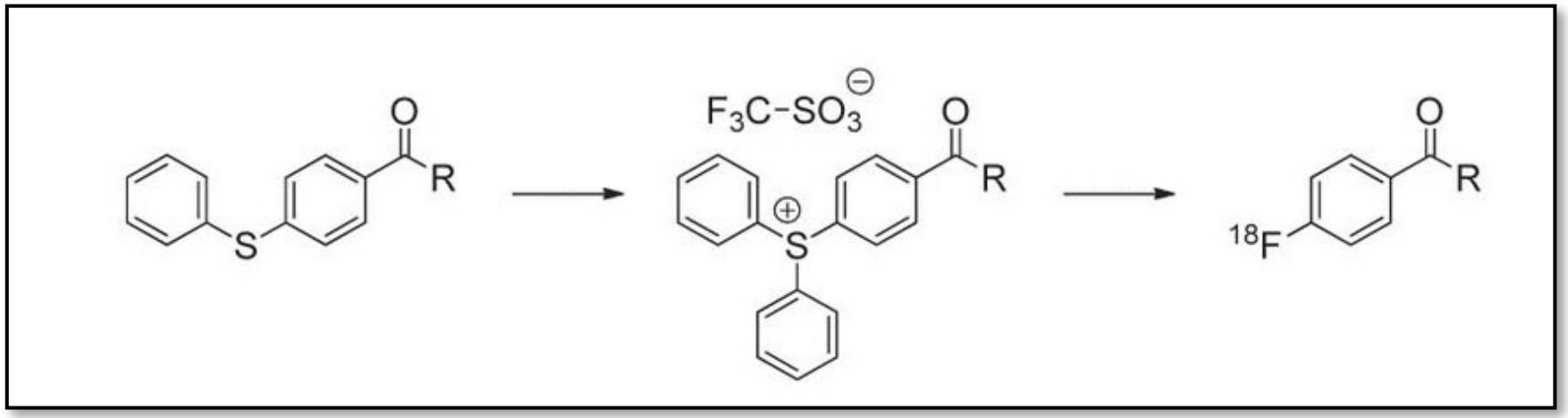




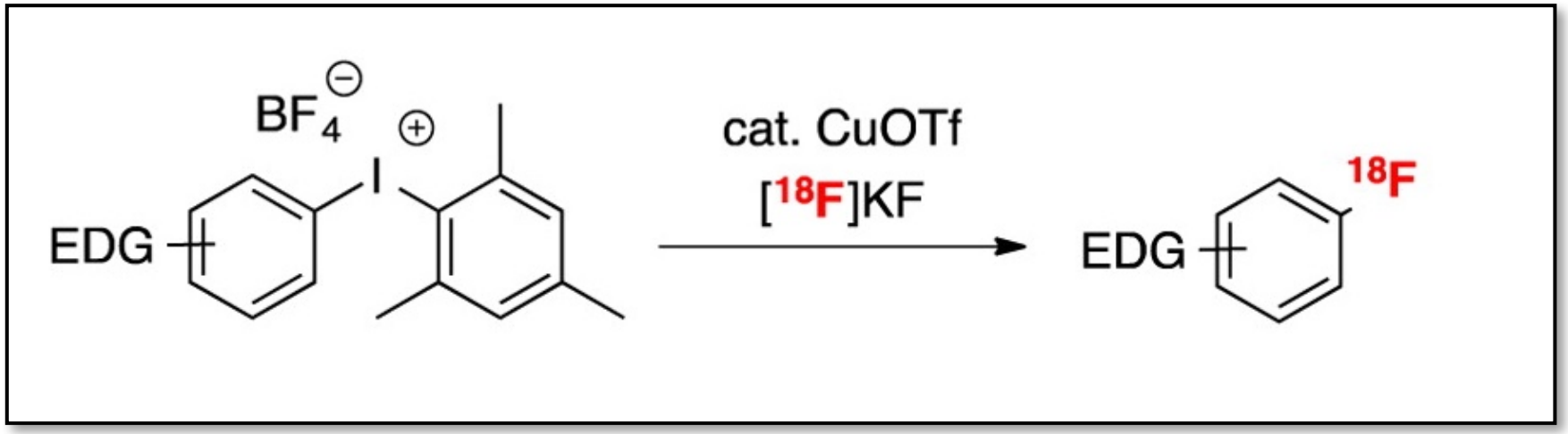
$$ArNH_2 + HNO_2 \longrightarrow ArN_2^+ \xrightarrow[Na_2CO_3]{HNR_2} Ar{-}N = N{-}NR_2$$



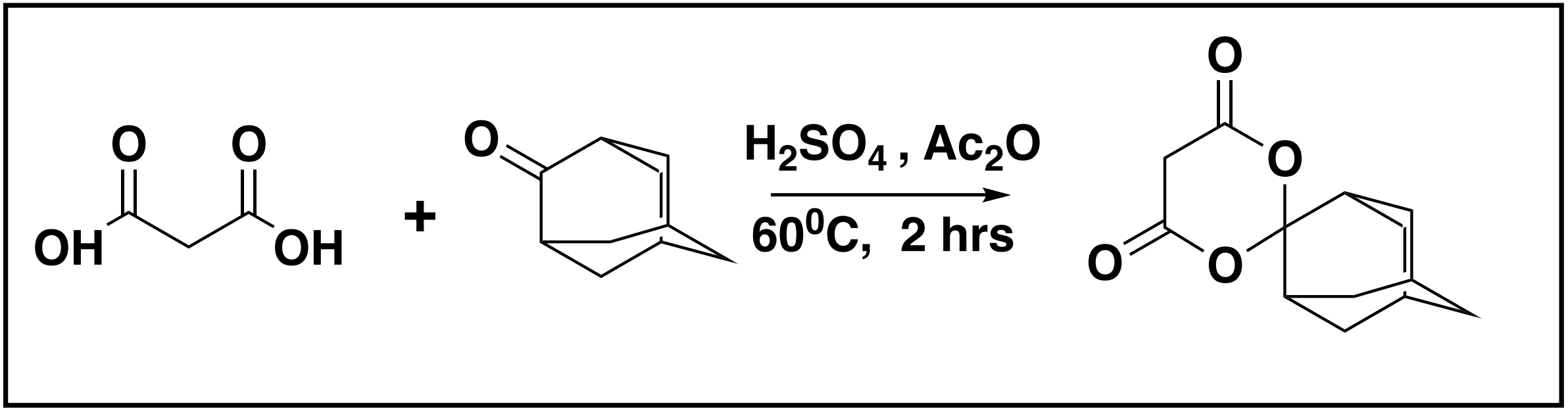
- Triarylsulfonium salts



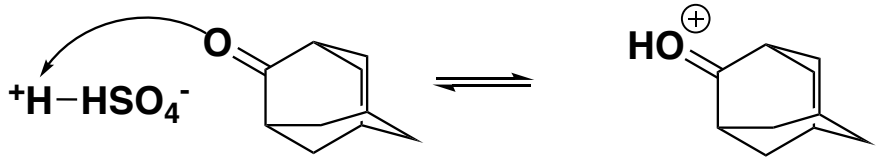
- Diaryliodonium salts



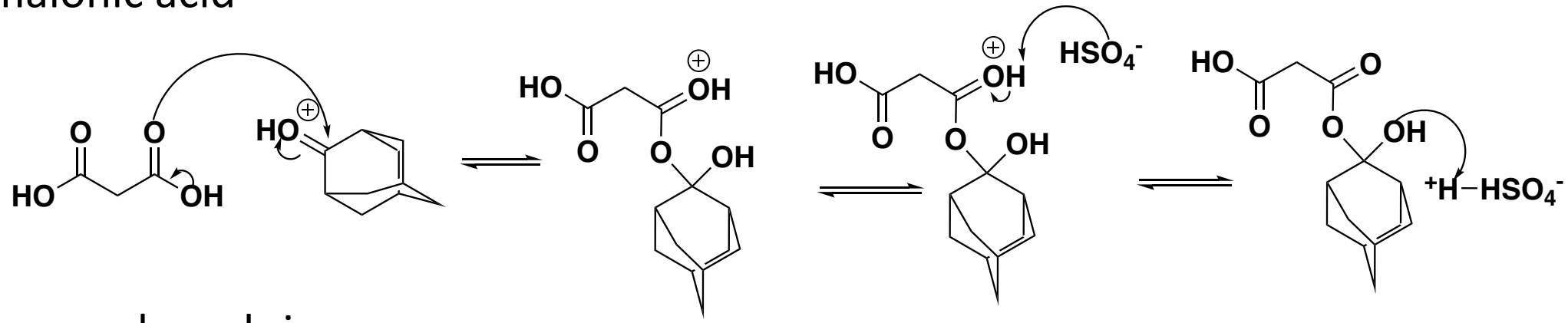
SPIAd Synthesis



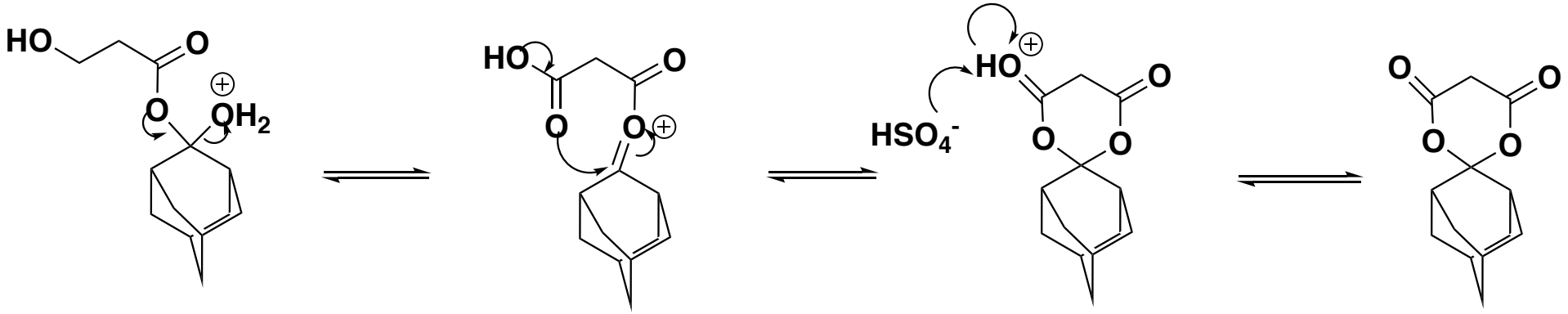
❖ protonation of ketone in acidic medium:



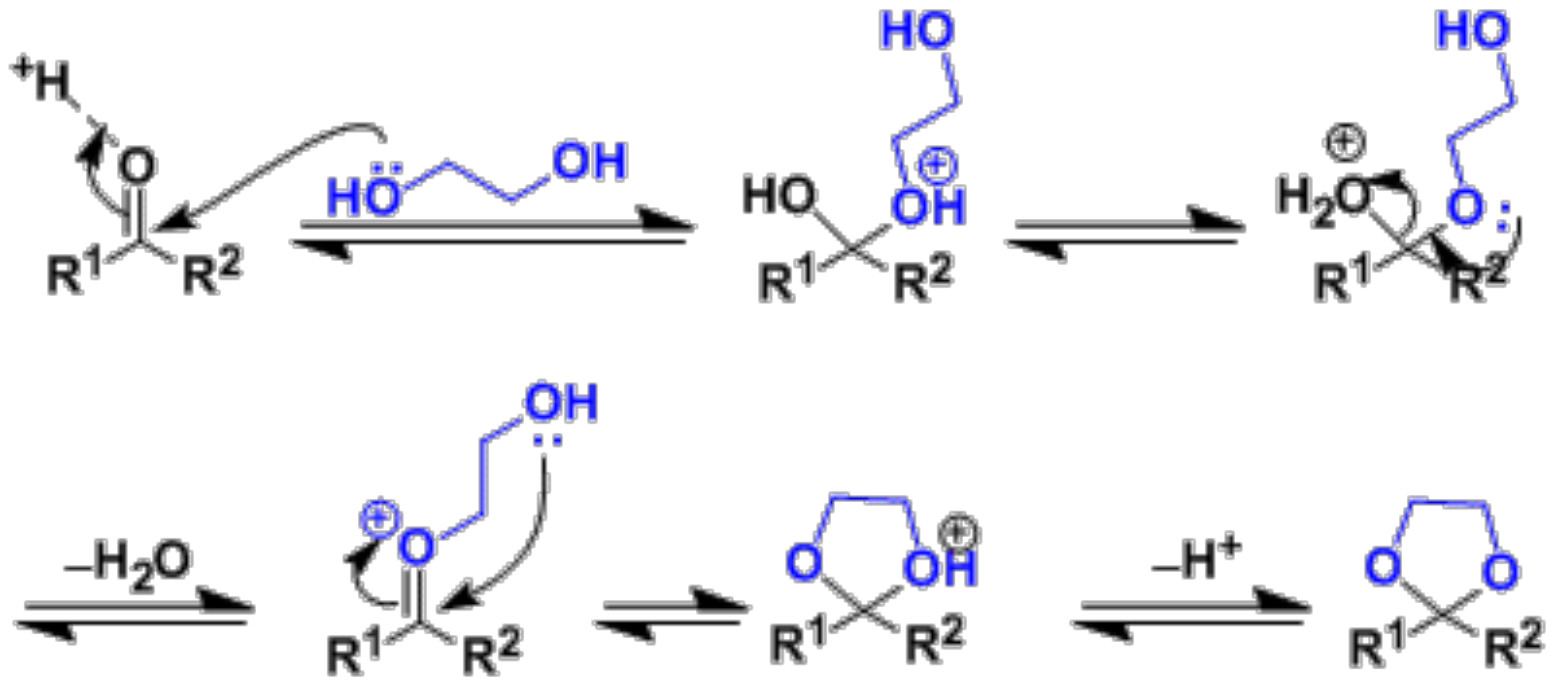
❖ reaction with malonic acid



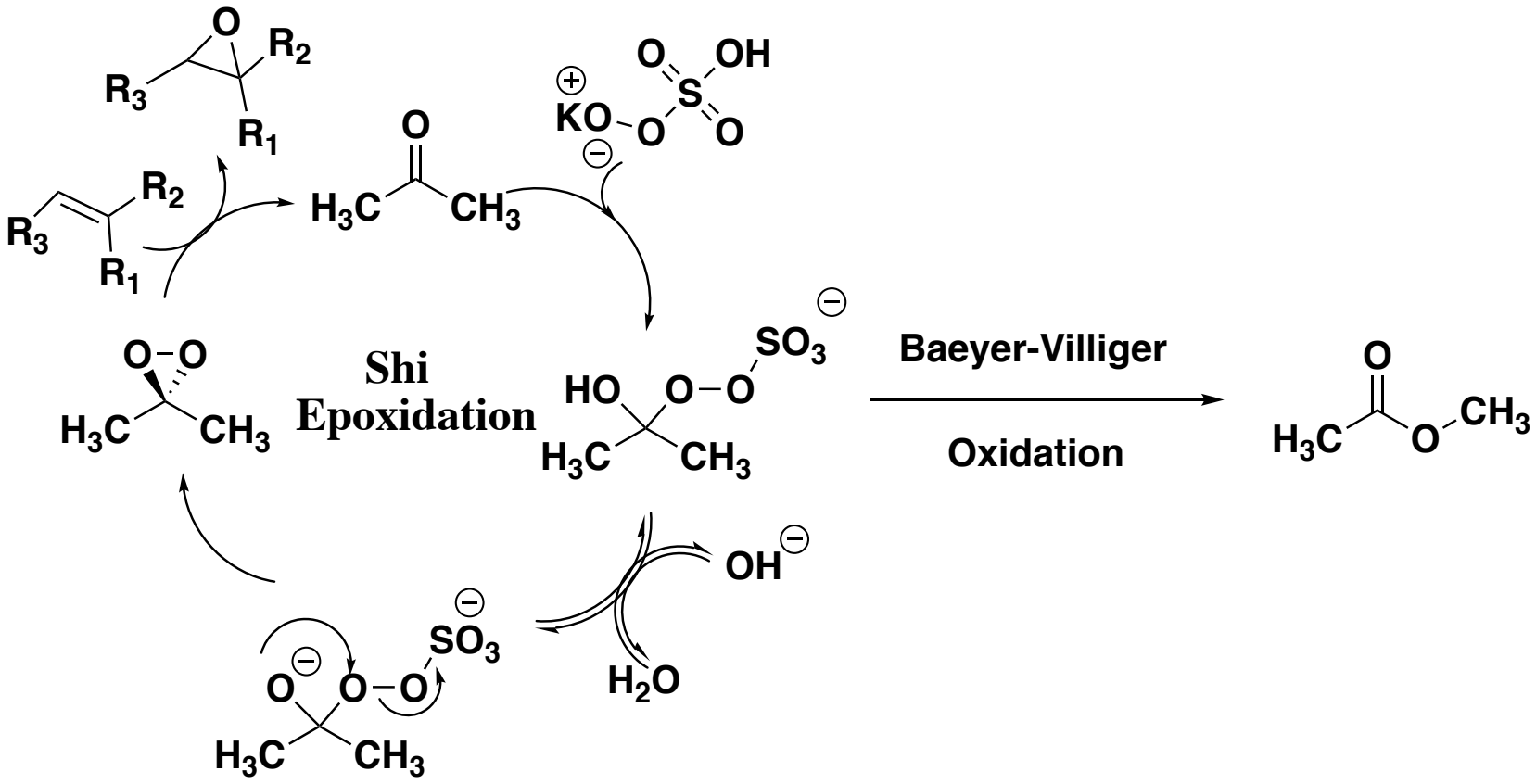
❖ formation of six-membered ring



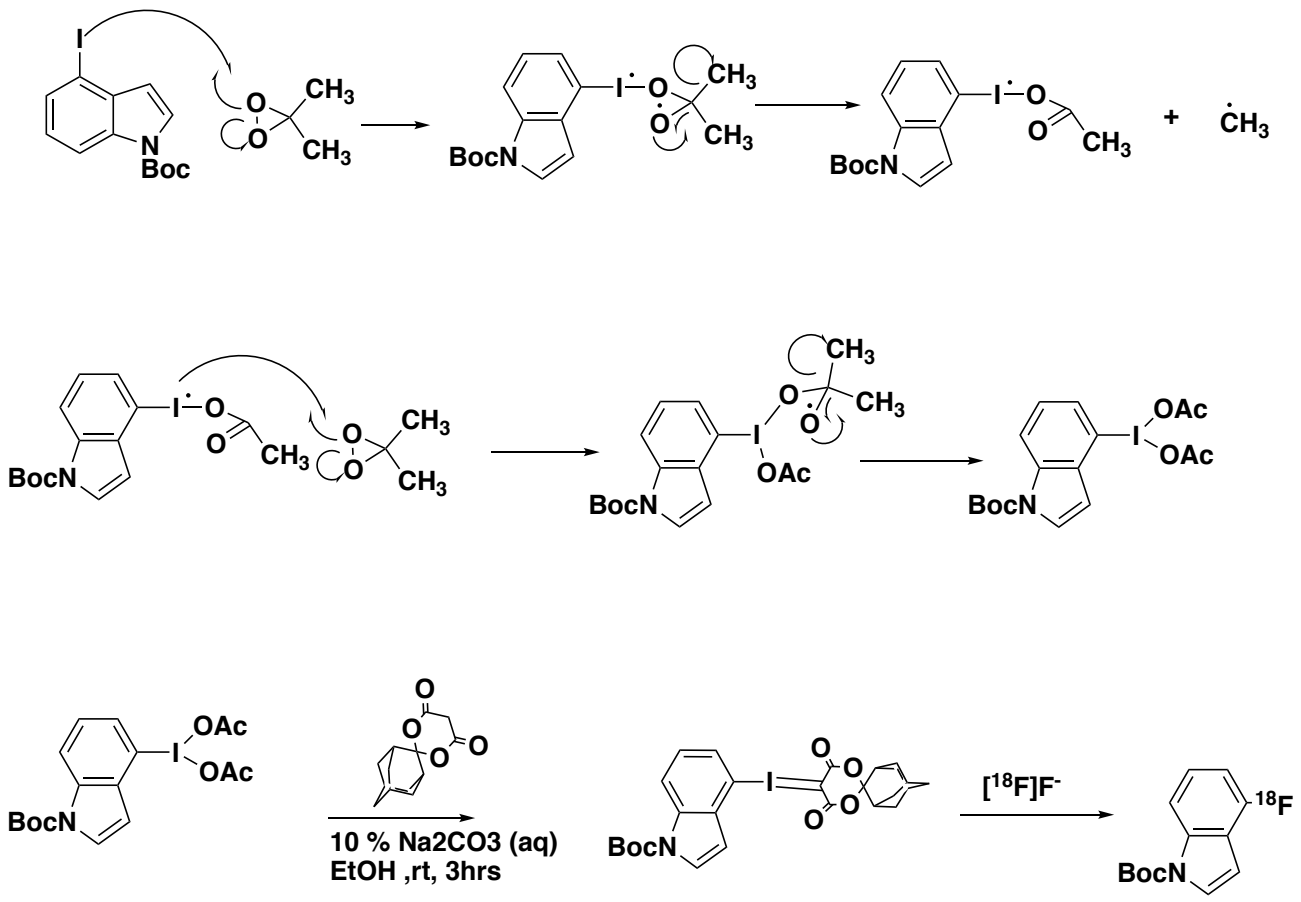
Similar to SPIAD Reaction mechanism



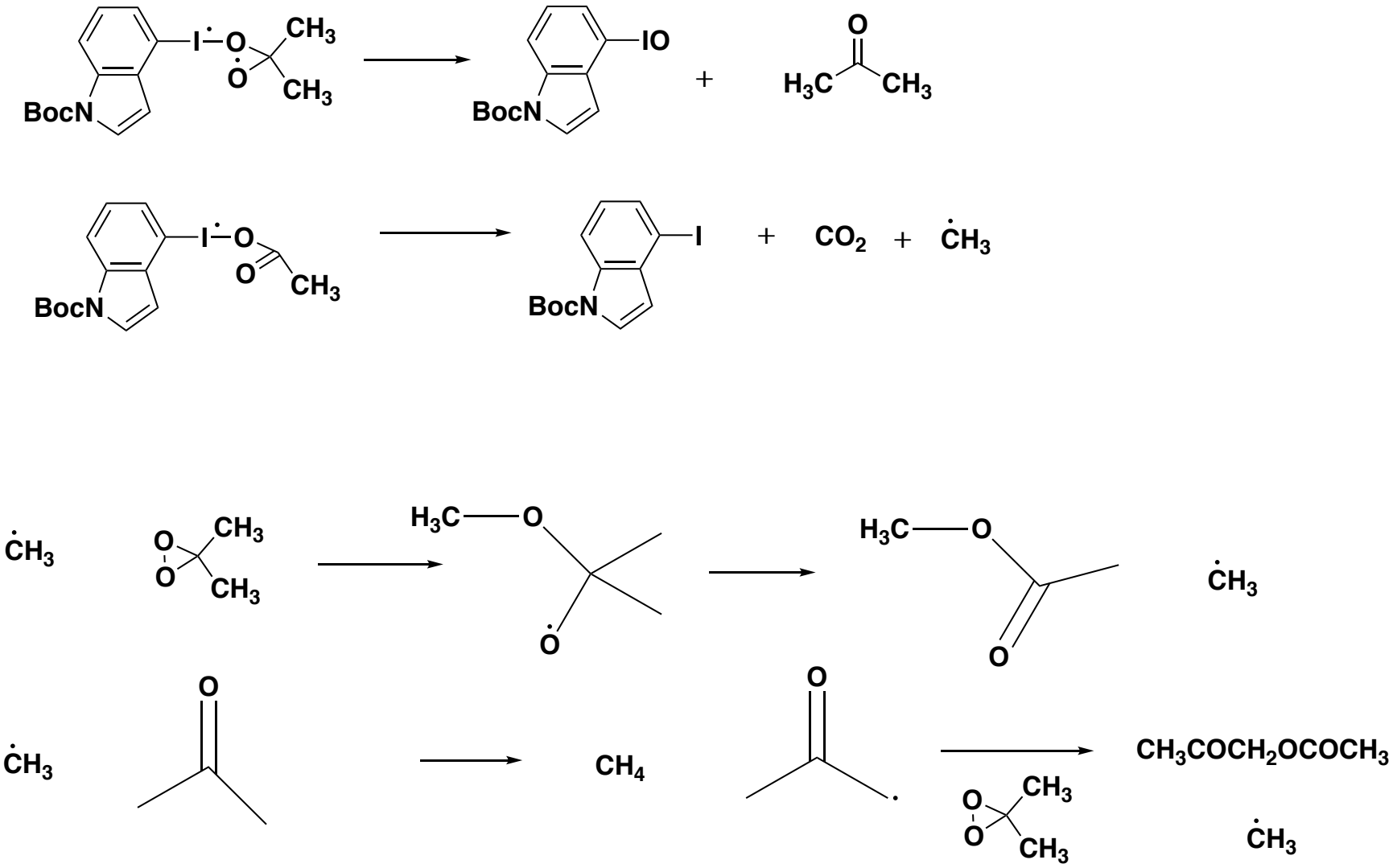
DMDO Generation: Shi epoxidation



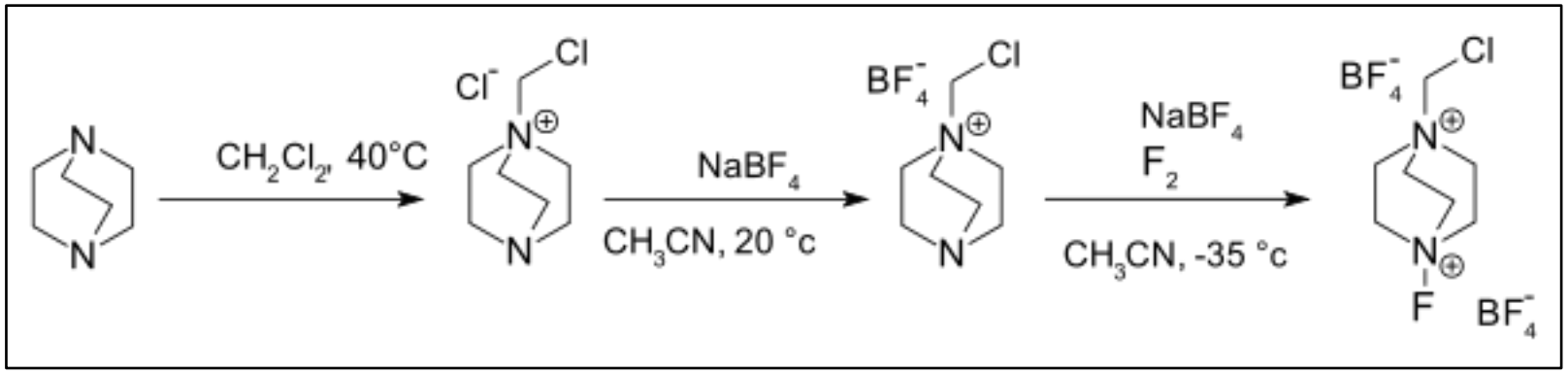
DMDO Mechanism

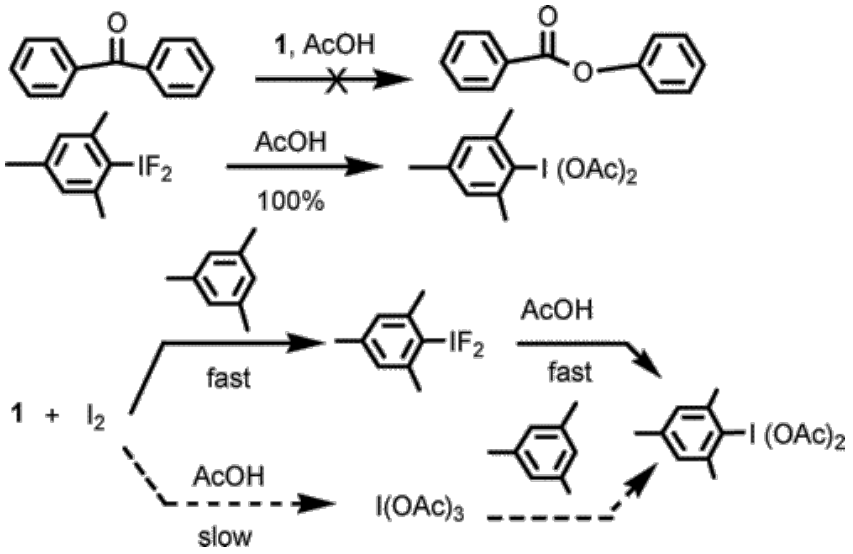


DMDO Side reactions

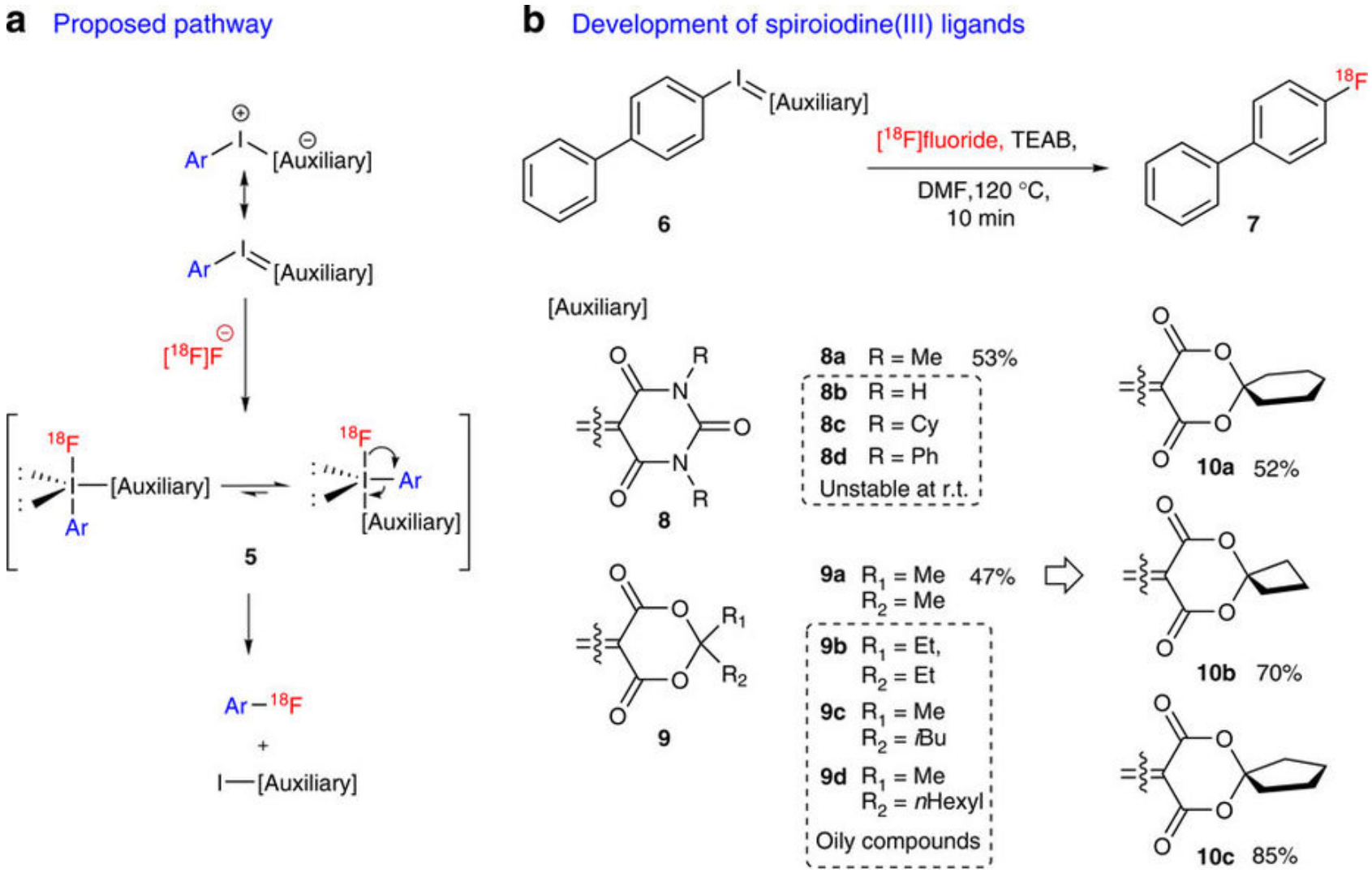


Synthesis of Selectfluor

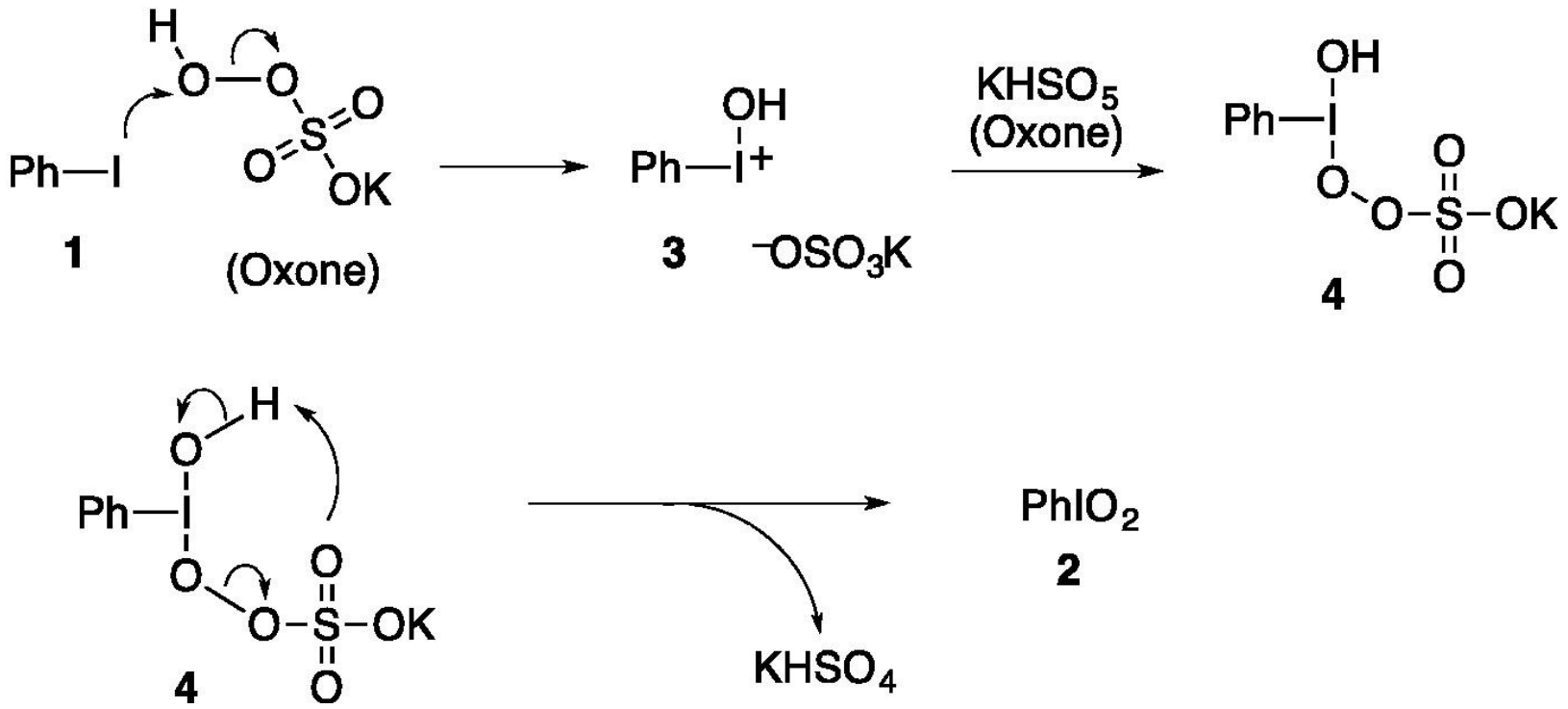




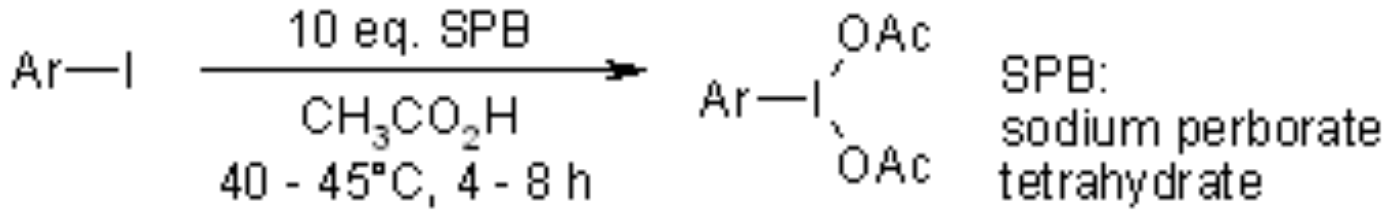
Development of Auxiliary

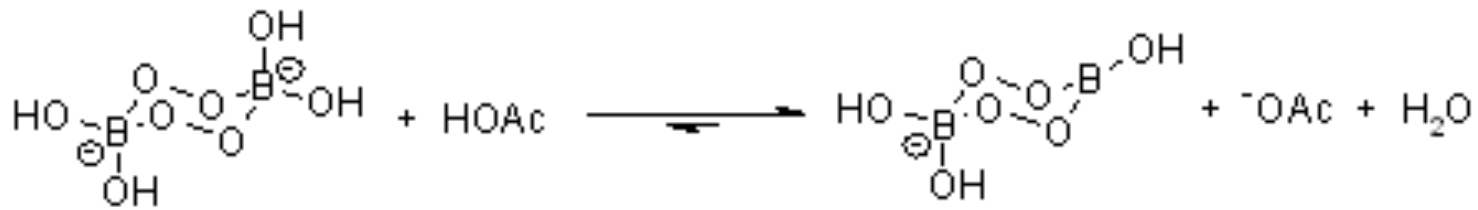


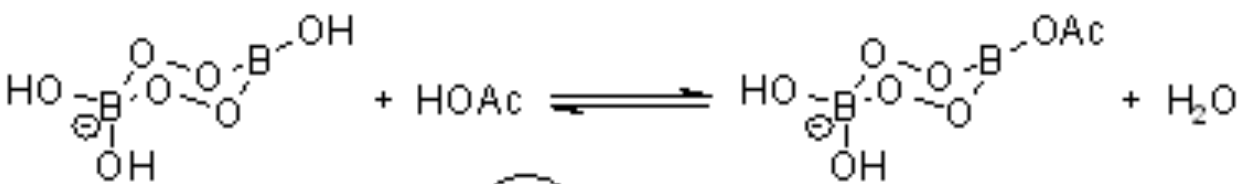
Oxone+ Iodoarenes

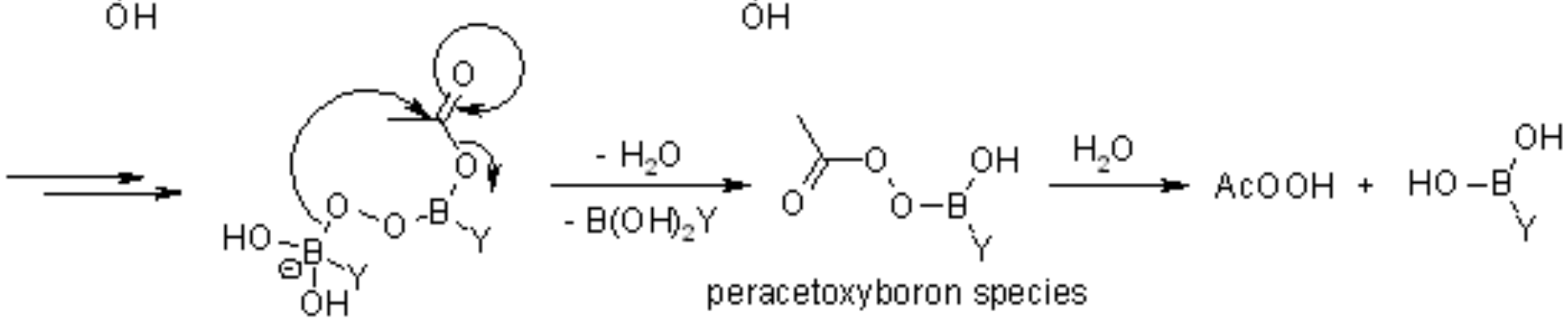


Perborate Mechanism

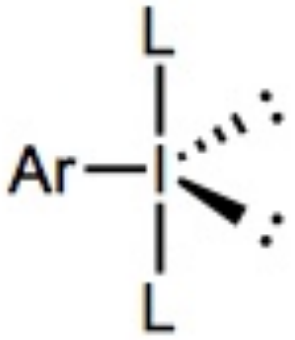






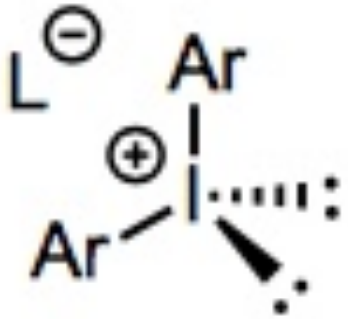


Hypervalent Iodine



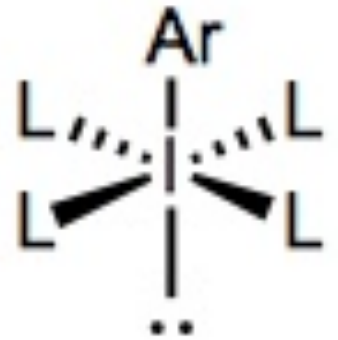
$\lambda^3 - Iodanes$

[10-I-3]



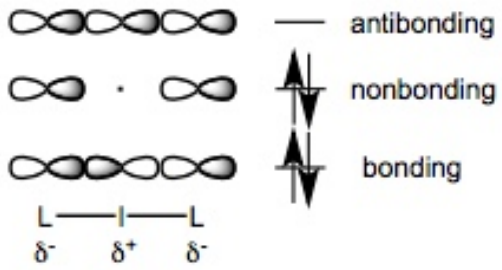
$\lambda^3 - Iodanes$

[8-I-2]



$\lambda^5 - Iodanes$

[12-I-5]

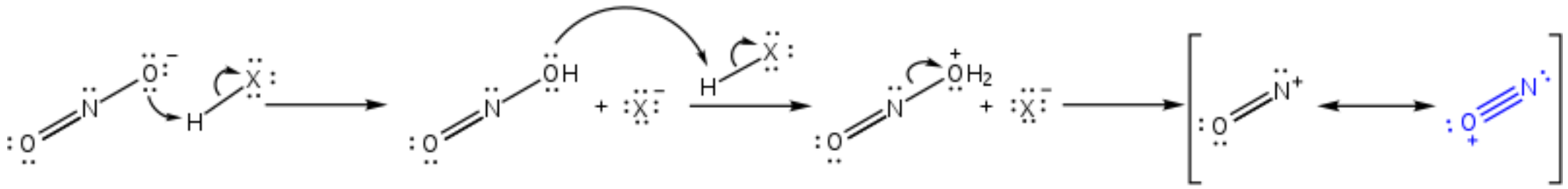


Problems related to Radiolabeling

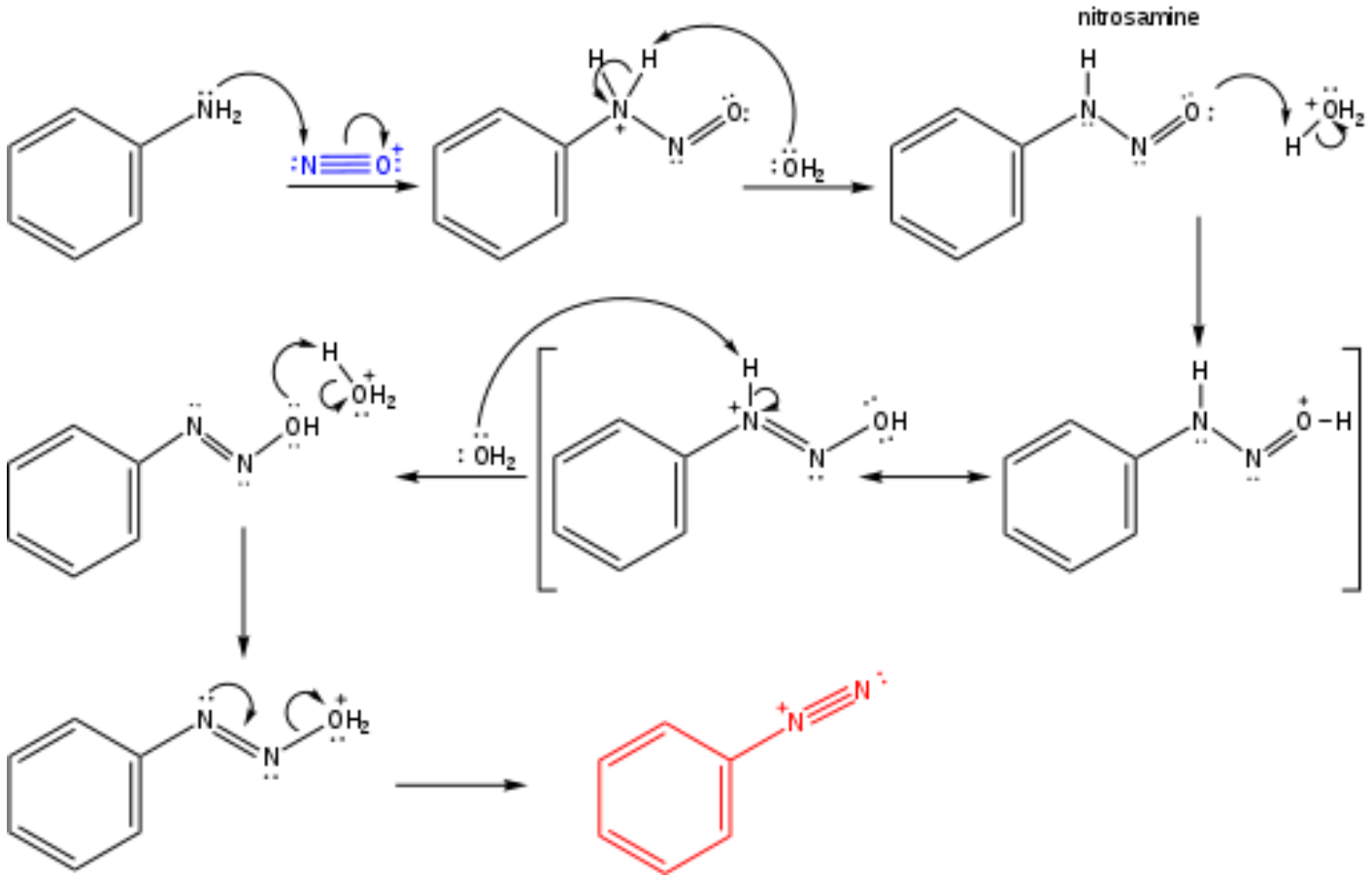
1. Several radiosynthetic steps, sensitive functionalities to be labeled. Thus, in spite of the many ^{18}F-fluorination methods available, a rational design of a labeling concept cannot be set up.

2. Synthesis protocols enabling the large-scale production of ^{18}F-labeled PET with pharmaceutical quality are required as current commercially available synthesis apparatus are not well suited for complex multistep radiosyntheses.

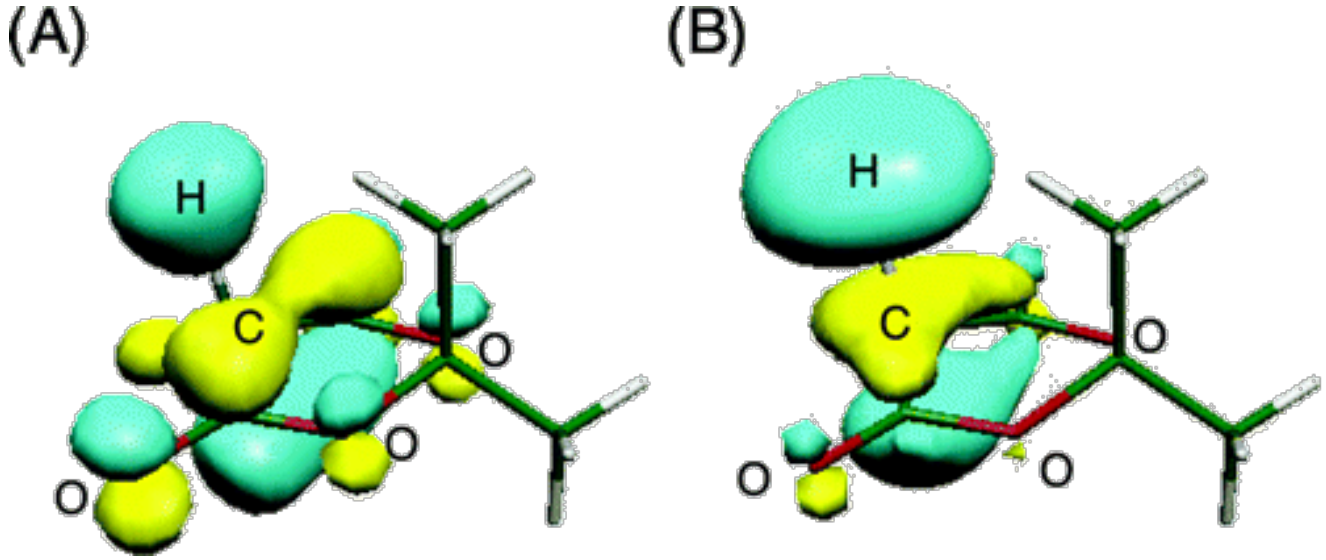
3. The widespread availability of medium half-life (3 h to 4 d) positron emitting radionuclides widens the potential clinical useful positron emitting radiopharmaceuticals compete against ^{18}F radionuclide.



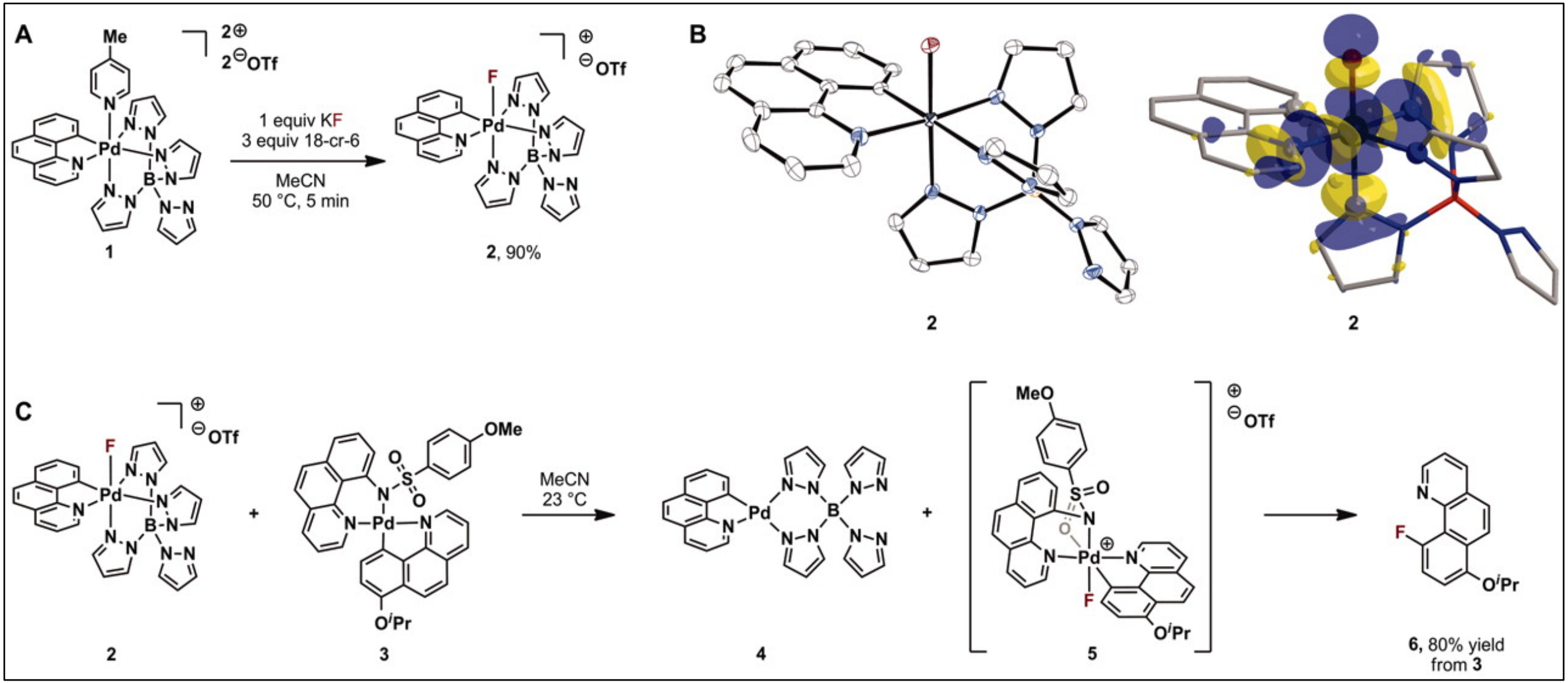
- Nitrous acid is prepared by sodium nitrite
- Nitrosonium ion: an electrophile
- Nitrosamine intermediate



Meldrum’s Acid: pKa = 4.83

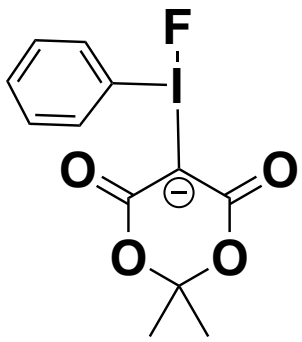


Transition metal mediated reactions

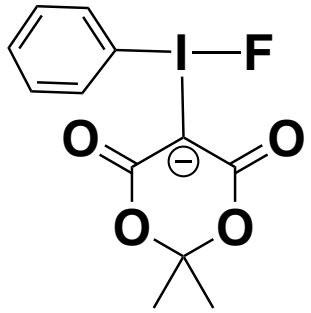


Reaction pathways

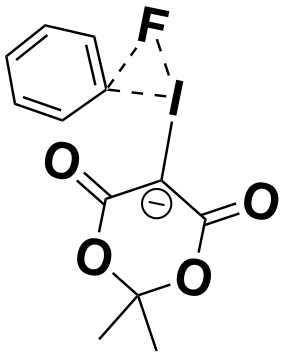
Ia



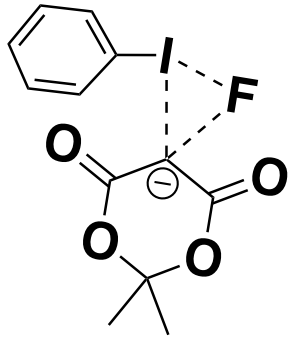
Ib

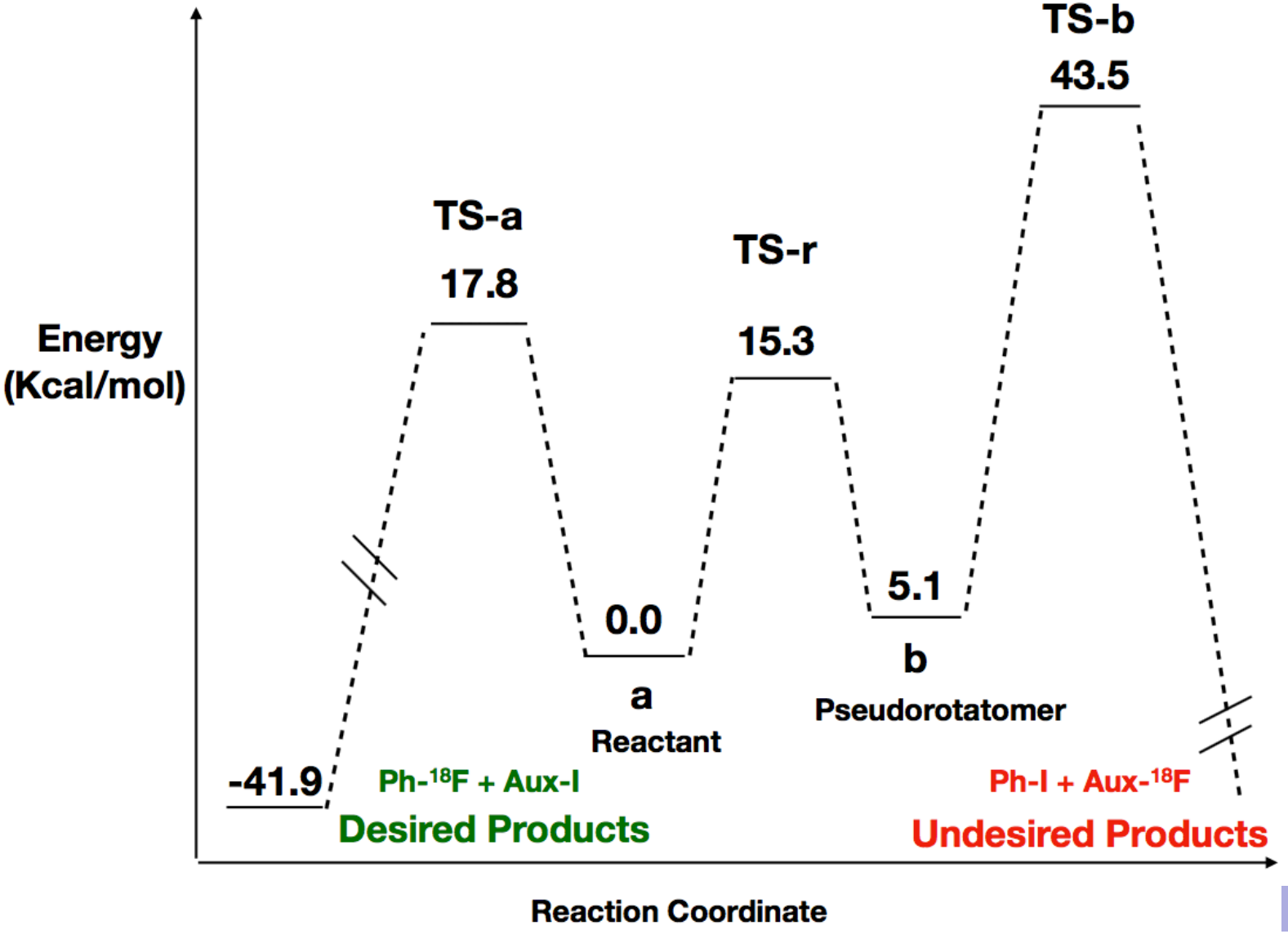


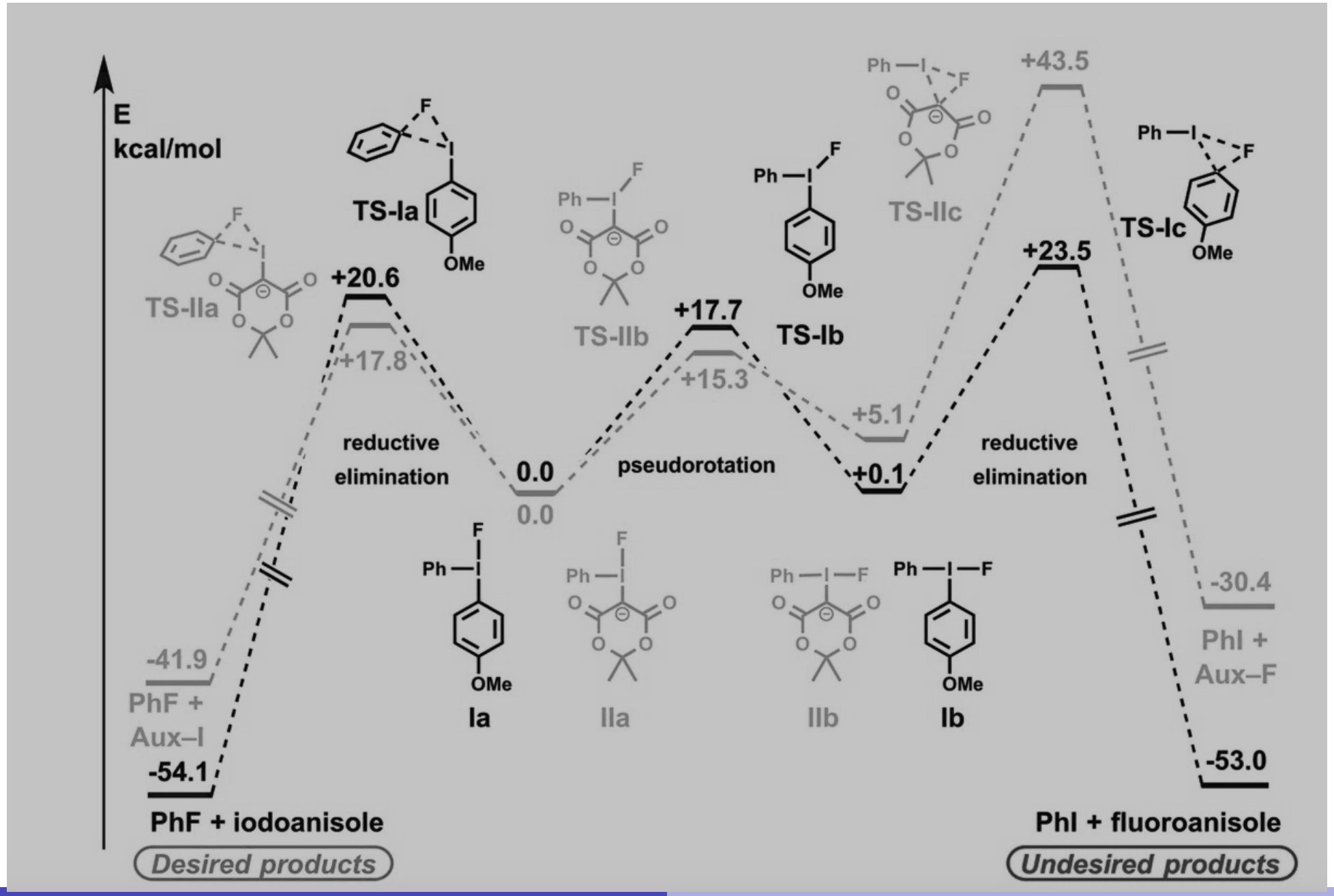
TS-a

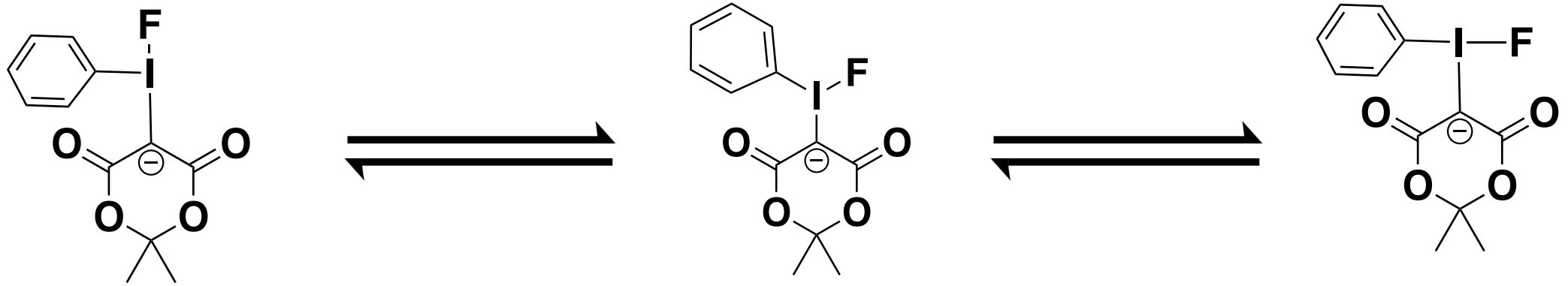


TS-Ib






E
kcal/mol
TS-IIa
TS-Ia
OMe
+20.6
+17.8
TS-IIb
+17.7
+15.3
TS-Ib
TS-IIc
+43.5
+5.1
+23.5
TS-Ic
OMe
reductive
elimination
0.0
0.0
pseudorotation
+0.1
reductive
elimination
-41.9
PhF +
Aux–I
-54.1
PhF + iodoanisole
Desired products
Ia
IIa
IIb
Ib
-30.4
PhI +
Aux–F
-53.0
PhI + fluoroanisole
Undesired products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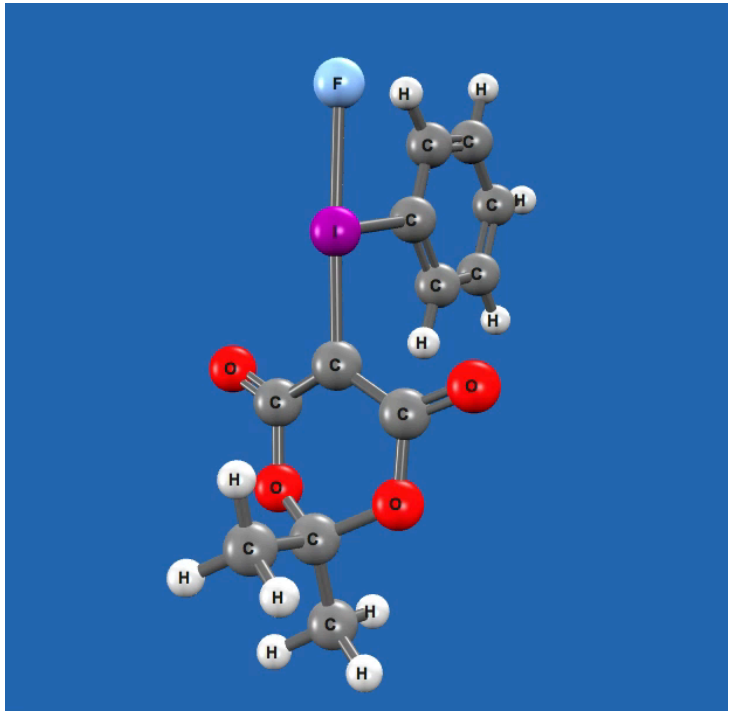
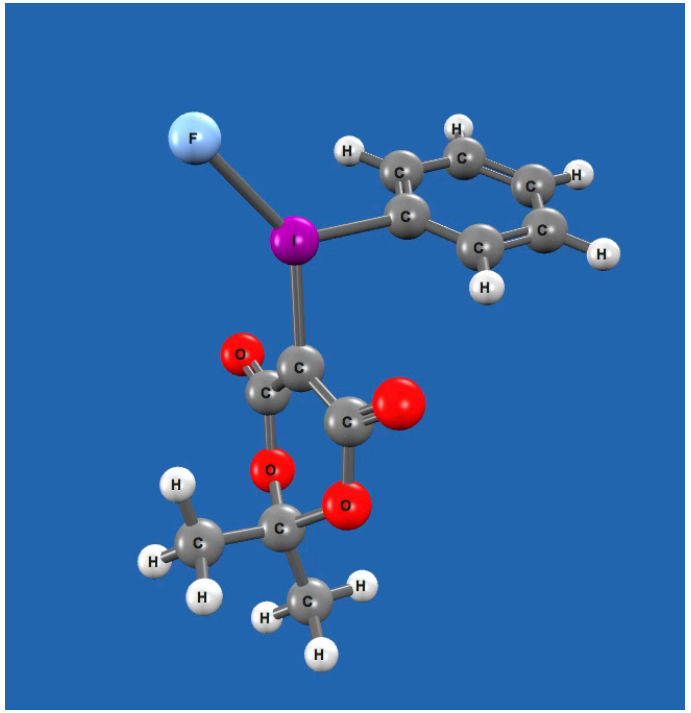
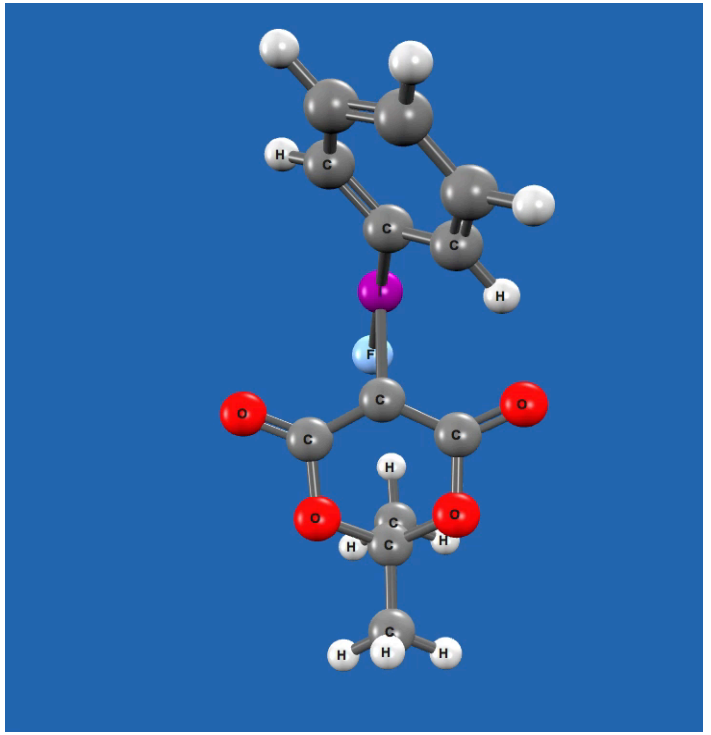
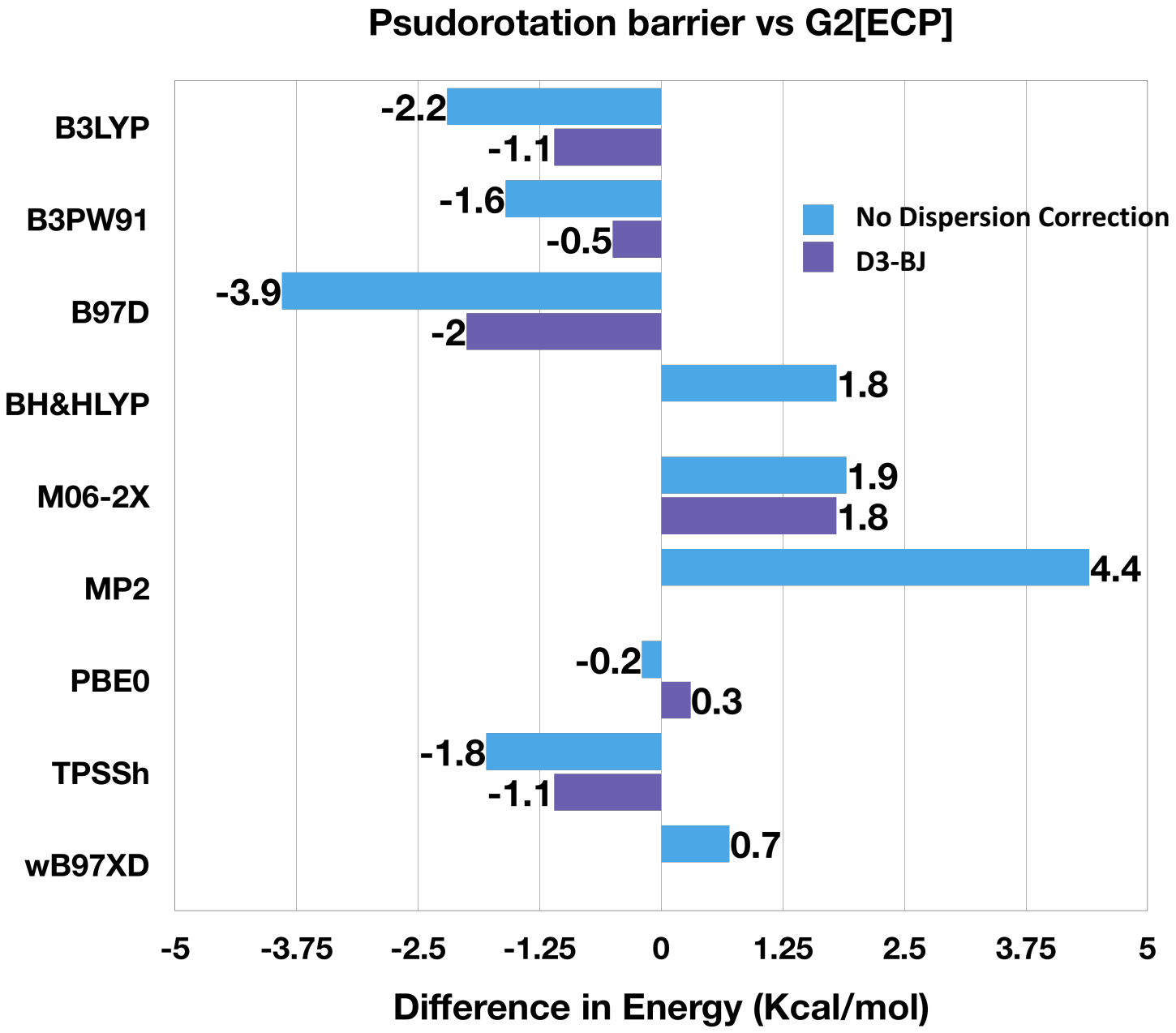






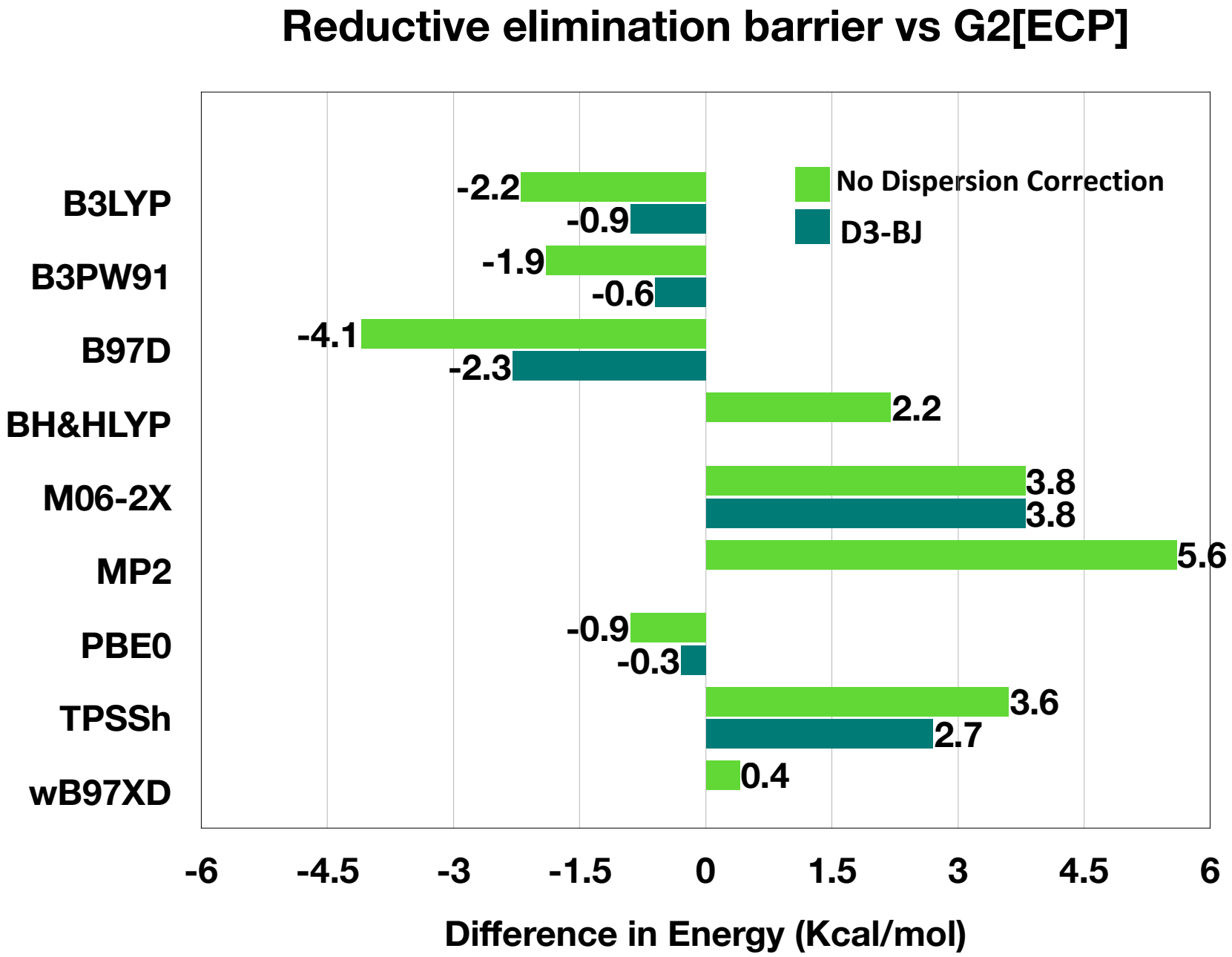


Computational Details

- Geometry Optimization
- B3LYP/6-31G(d) /LANL2DZ(I)/PCM(DMF)

- Single point energies
- PBE0/aug-cc-pVTZ /SDB-aug-cc-pVTZ(I)

- BJ-damped D3 dispersion correction
- Comparison of G2[ECP] vs DFT



Computational Details

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^{18}F Production

- $^{18}O(p,n)^{18}F$

- $^{20}Ne(p,2n)^{18}F$
- $^{20}Ne(d,\alpha)^{18}F$
- $^{20}Ne(^{3}He,n)^{18}Ne, ^{18}Ne\text{-}^{18}F$

- $^{16}O(\alpha,pn)^{18}F$
- $^{16}O(^{3}He,p)^{18}F$
- $^{6}Li(n,\alpha)3H$, $^{16}O(^{3}H,n)^{18}F$

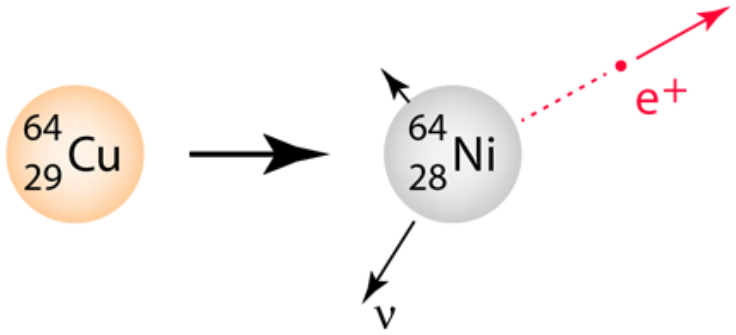
Radioisotopes for PET imaging

Nuclide	$T_{1/2}$ (min)	Decay	Max Energy (MeV)	Theoretical SA (GBq/μmol)	Decay Product
18_F	109.77	β^+ (97 %); EC (3 %)	0.64	6.3×10^4	18_O
11_C	20.38	β^+ (99 %)	0.97	3.4×10^5	11_B
13_N	9.96	β^+ (100 %)	1.20	7.0×10^5	13_C
15_O	2.03	β^+ (100 %)	1.74	3.4×10^6	15_N

Radioactive decay in PET

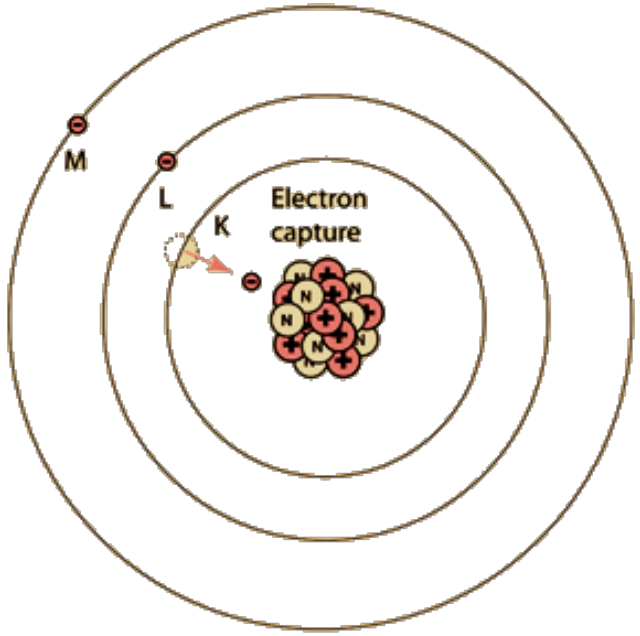
A. Positron emission

$$p \rightarrow n + \beta^{+} + \nu_e$$



B. Electron capture

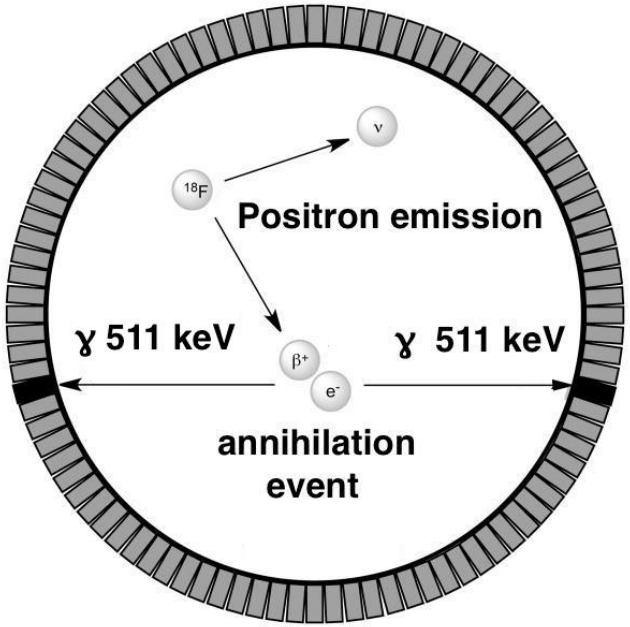
$$p + e^{-} \rightarrow n + \nu_e$$

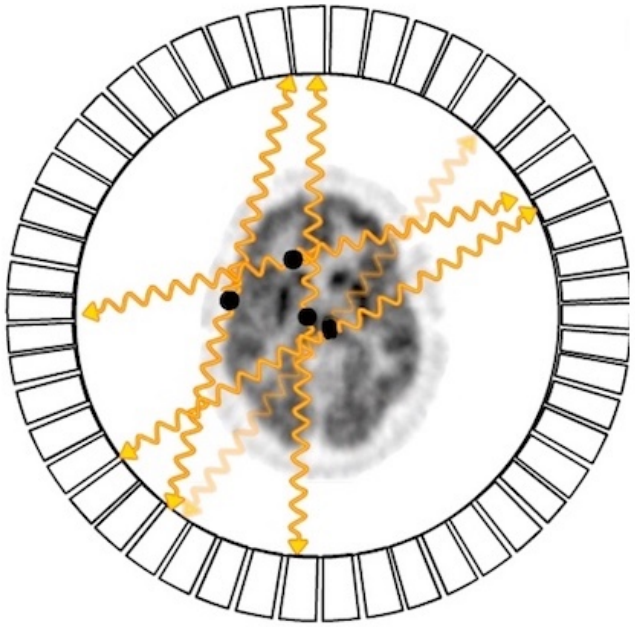


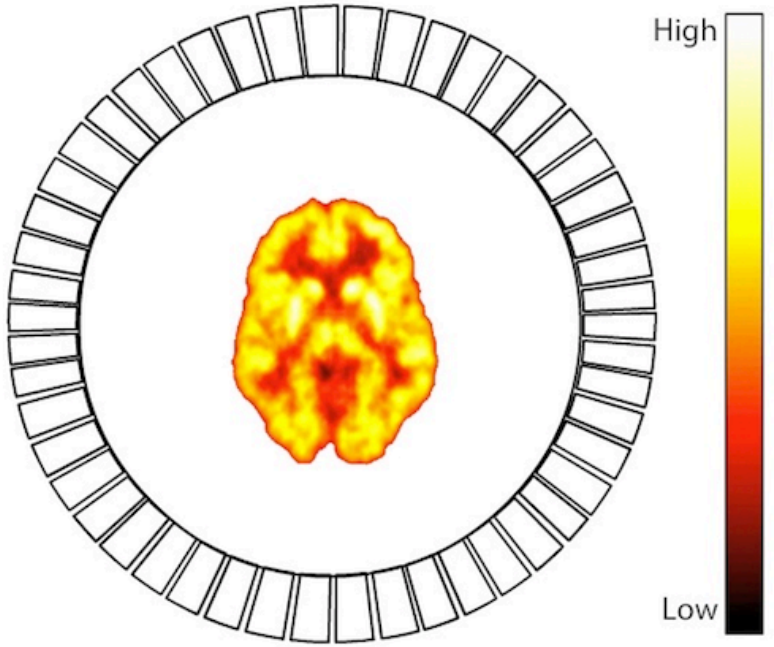
Examples

$${}^{A}_{Z}\mathrm{X}_{N} \rightarrow {}^{A}_{Z-1}\mathrm{X}_{N+1}$$

- ${}^{18}_{9}\mathrm{F}_{9} \rightarrow {}^{18}_{8}\mathrm{O}_{10}$
- ${}^{15}_{8}\mathrm{O}_{7} \rightarrow {}^{15}_{7}\mathrm{N}_{8}$
- ${}^{11}_{6}\mathrm{C}_{5} \rightarrow {}^{11}_{5}\mathrm{B}_{6}$

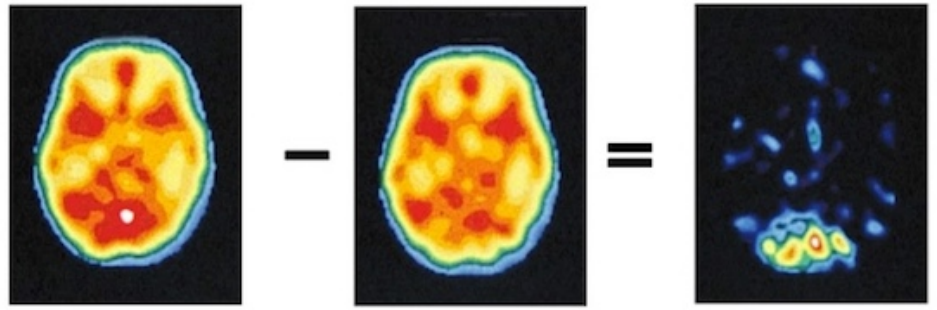






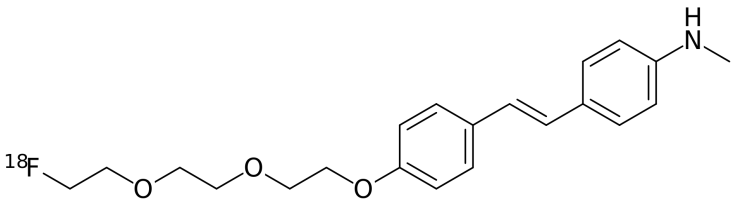
- Speed of light: 3.00×10^{8} m/s
- Mass of an electron/positron: 9.11×10^{-31} Kg
- $E = mc^2$
- $E = 9.11 \times 10^{-31} \times (3.00 \times 10^{8})^2 / 1.60 \times 10^{-19}$ eV

➔ 511 keV × 2

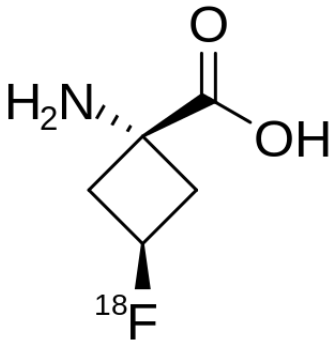


Experiment **Control** **Difference**

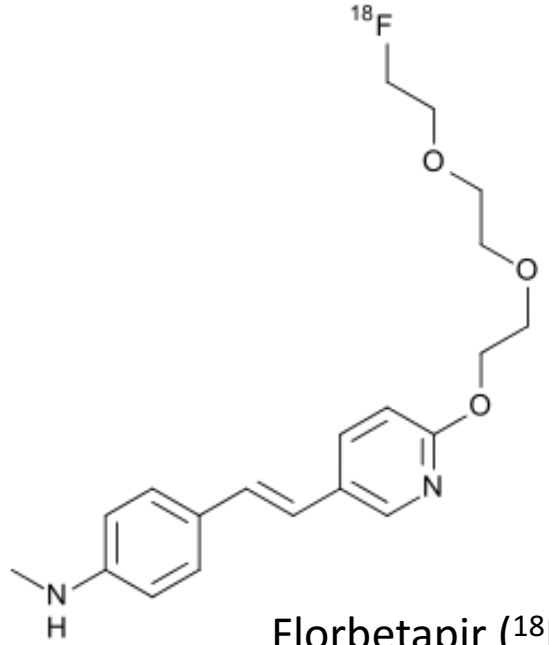
FDA approved radiotracers



Florbetaben (^{18}F)

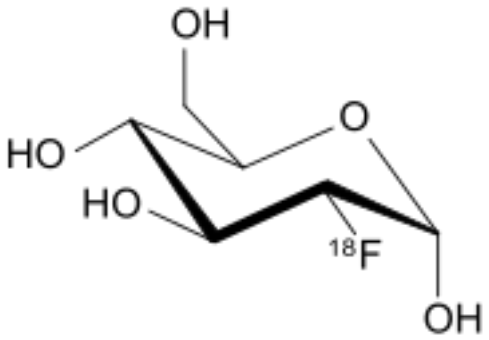


Fluciclovine

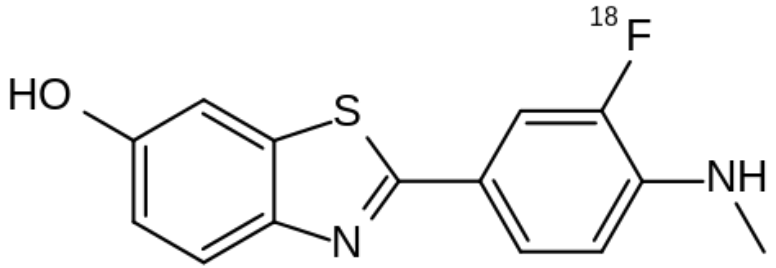


Florbetapir (^{18}F)

NaF^{18}

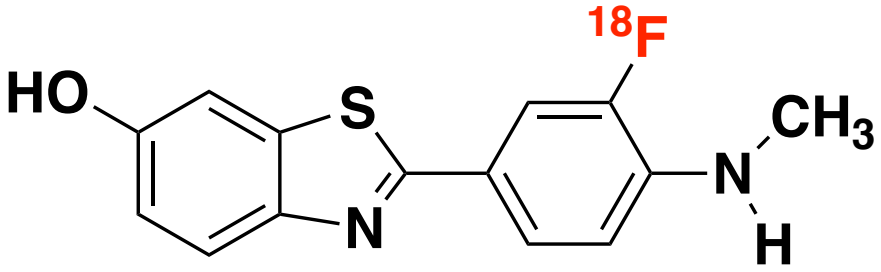


^{18}FDG



Flutemetamol

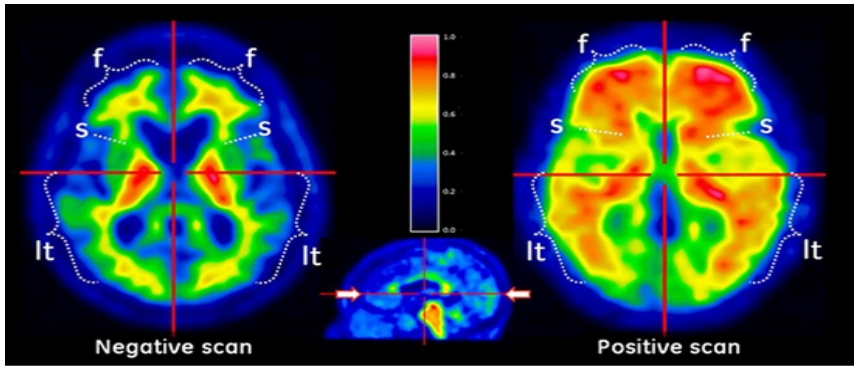
Biomedical Imaging



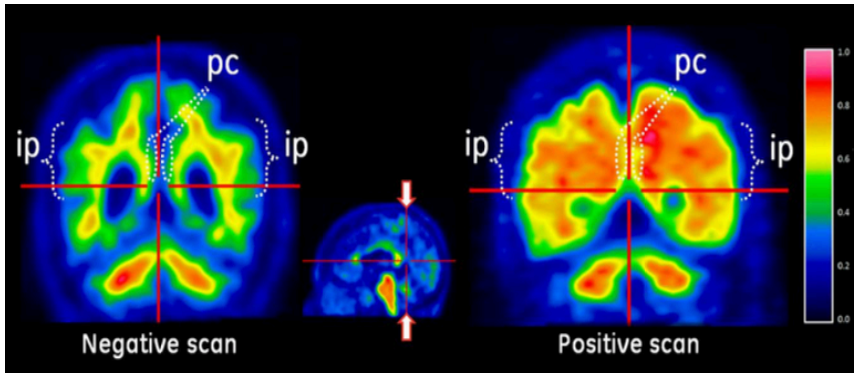
[^{18}F]Flutemetamol

- Half life of ^{18}F is 109.77 mins
- Labeling time < 60 mins
- Intravenous dose at PET-CT site

Axial View



Coronal View



Sagittal View