

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

**Benjamin H. Rotstein,<sup>‡ab</sup> Lu Wang,<sup>‡a</sup> Richard Y. Liu,<sup>c</sup> Jon Patteson,<sup>a</sup>  
Eugene E. Kwan,<sup>c</sup> Neil Vasdev<sup>\*ab</sup> and Steven H. Liang<sup>\*ab</sup>**

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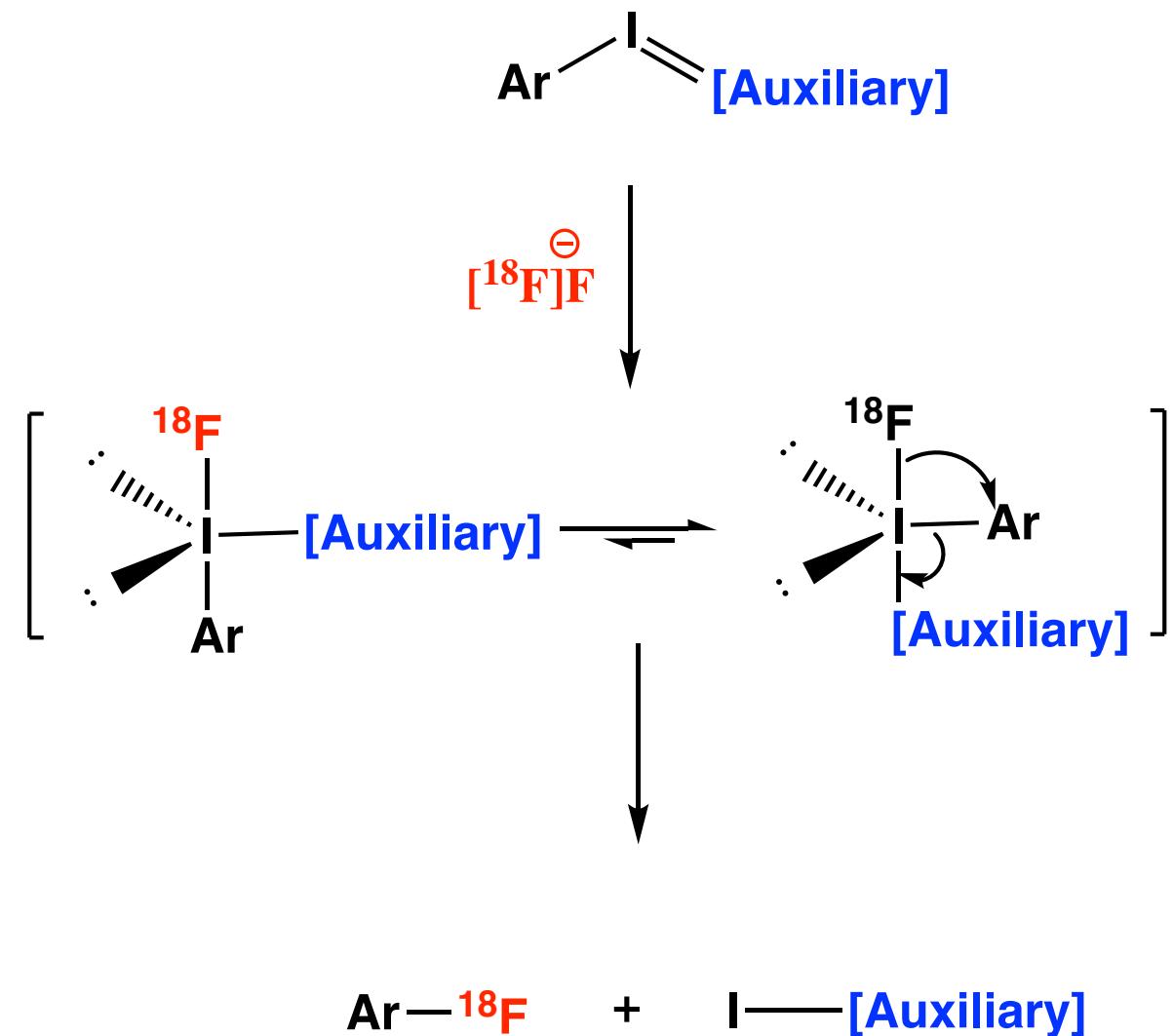
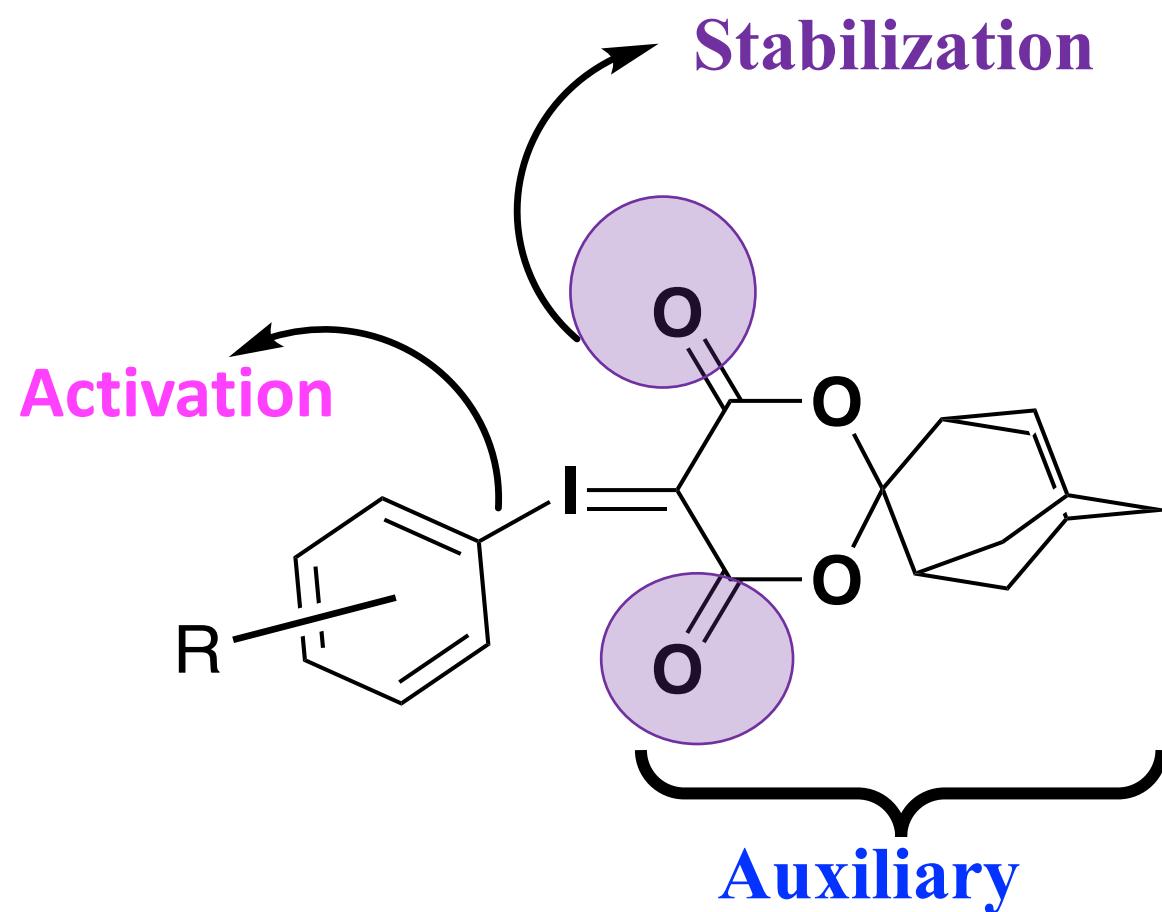
- a. Division of Nuclear Medicine and Molecular Imaging & Gordon Center for Medical Imaging, Massachusetts General Hospital  
b. Department of Radiology, Harvard Medical School  
c. Department of Chemistry and Chemical Biology, Harvard University

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# Outline

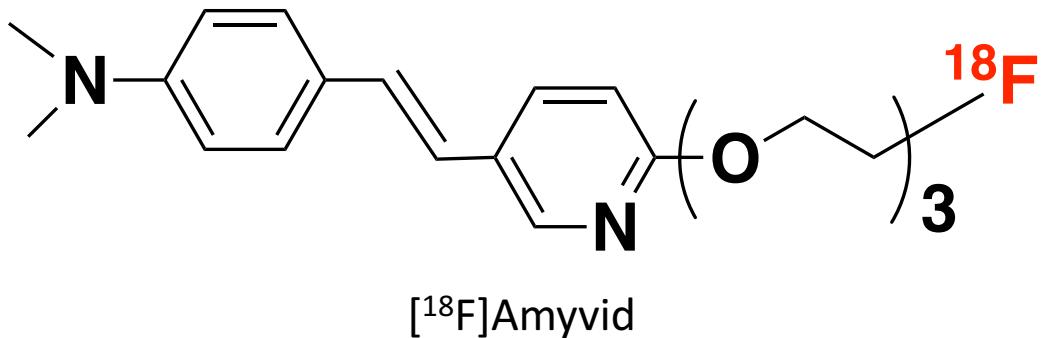
1. Background
2. Reaction schemes and mechanisms
3. Results
4. Conclusions

# Spirocyclic iodonium(III) ylides



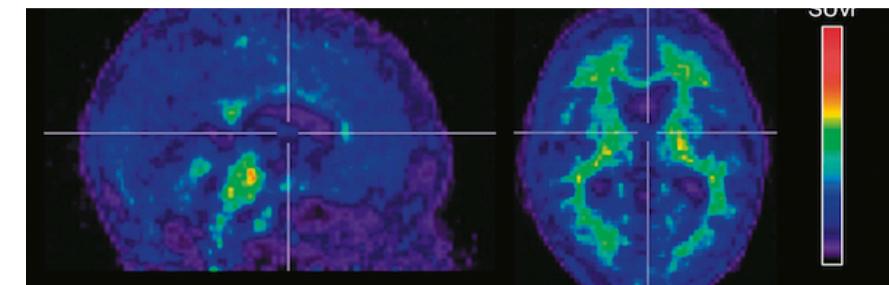
# Long term objectives

Development of [<sup>18</sup>F] based radiotracers

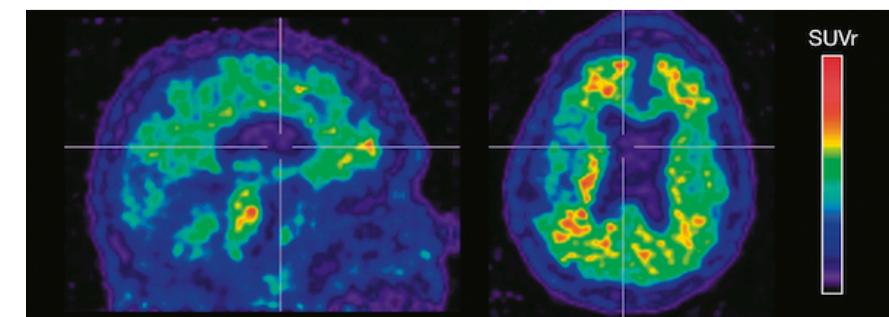


- Half life of <sup>18</sup>F is 109.77 min
- Labeling time < 60 mins

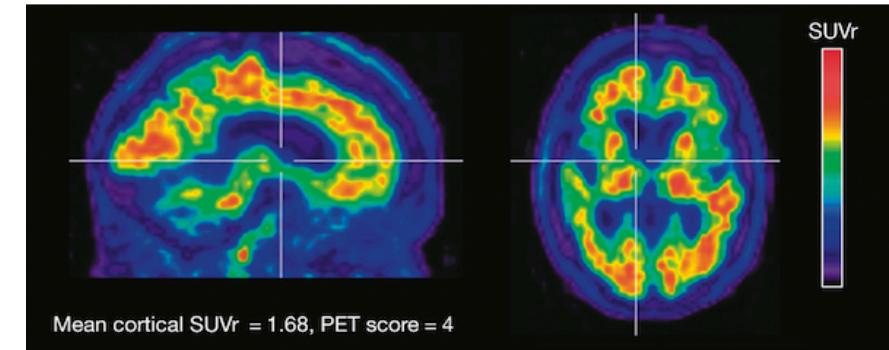
a) No  $\beta$ -amyloid plaques



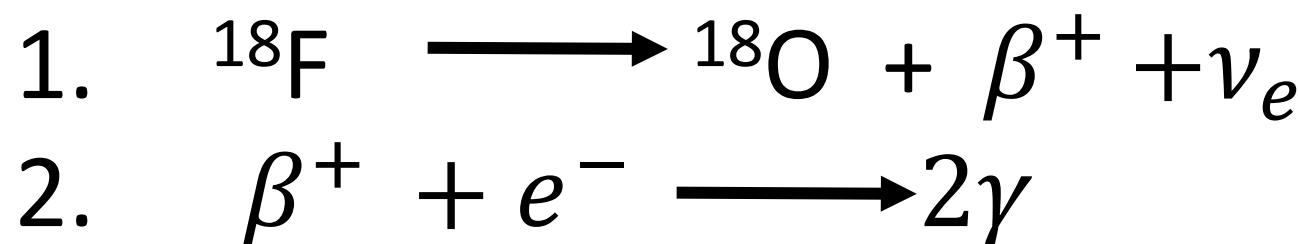
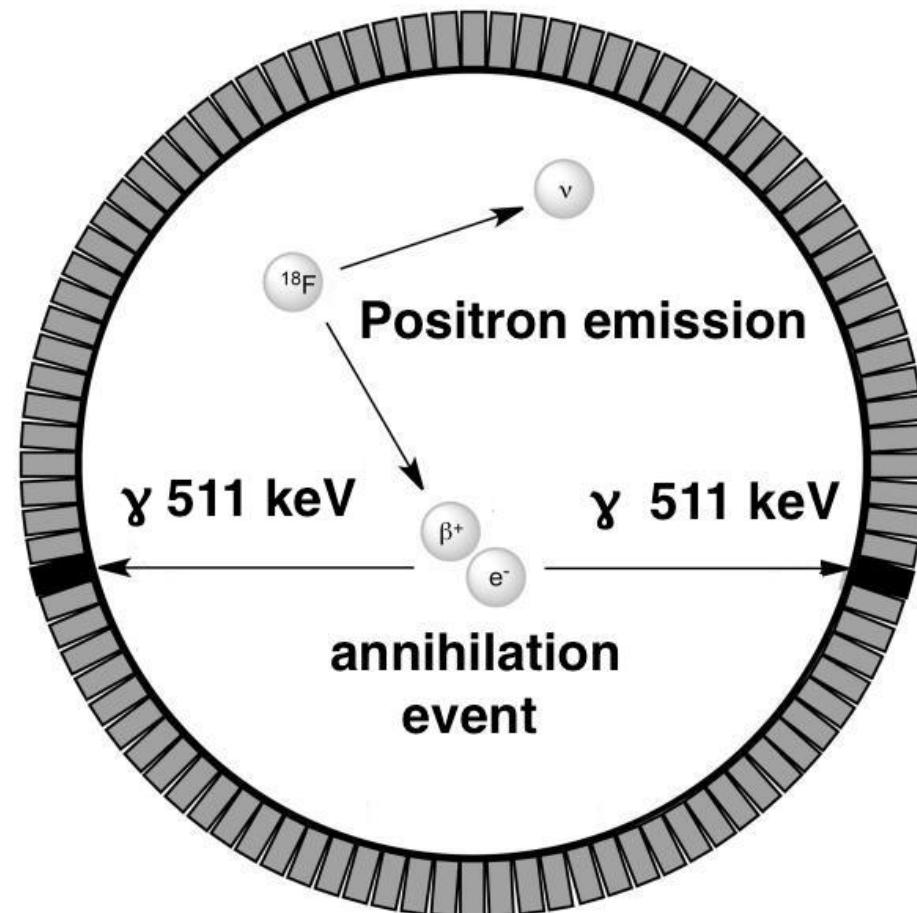
b) Moderate load of  $\beta$ -amyloid plaques



c) High load of  $\beta$ -amyloid plaques



# Positron Emission Tomography (PET)



Decay of radionuclide



Positron ( $\beta^+$ ) emission

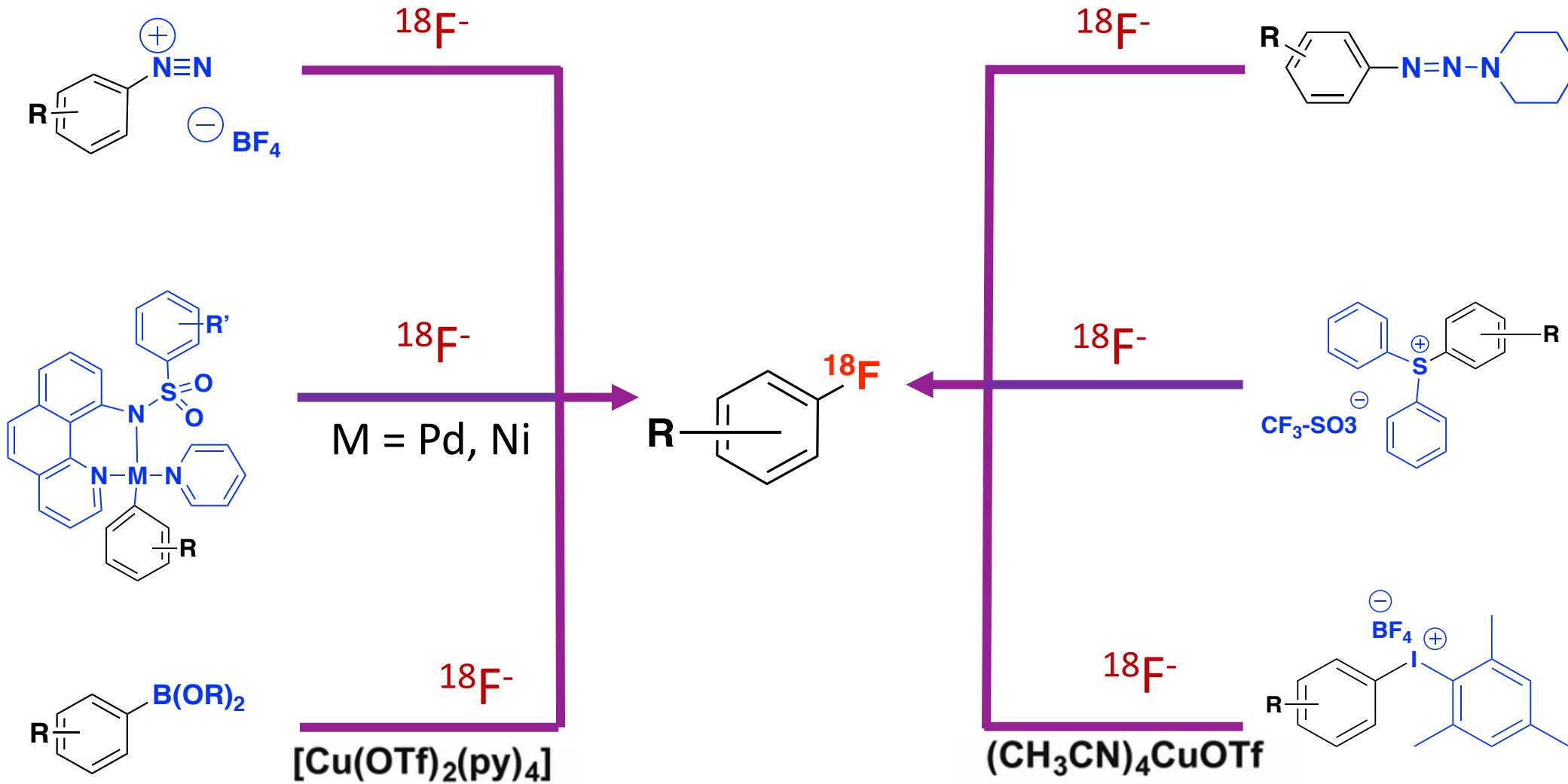


Annihilation with  $e^-$

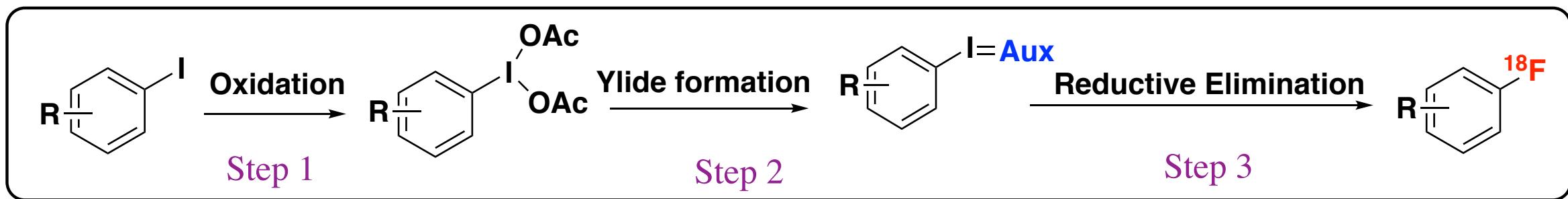


Detection of  $\gamma$  rays

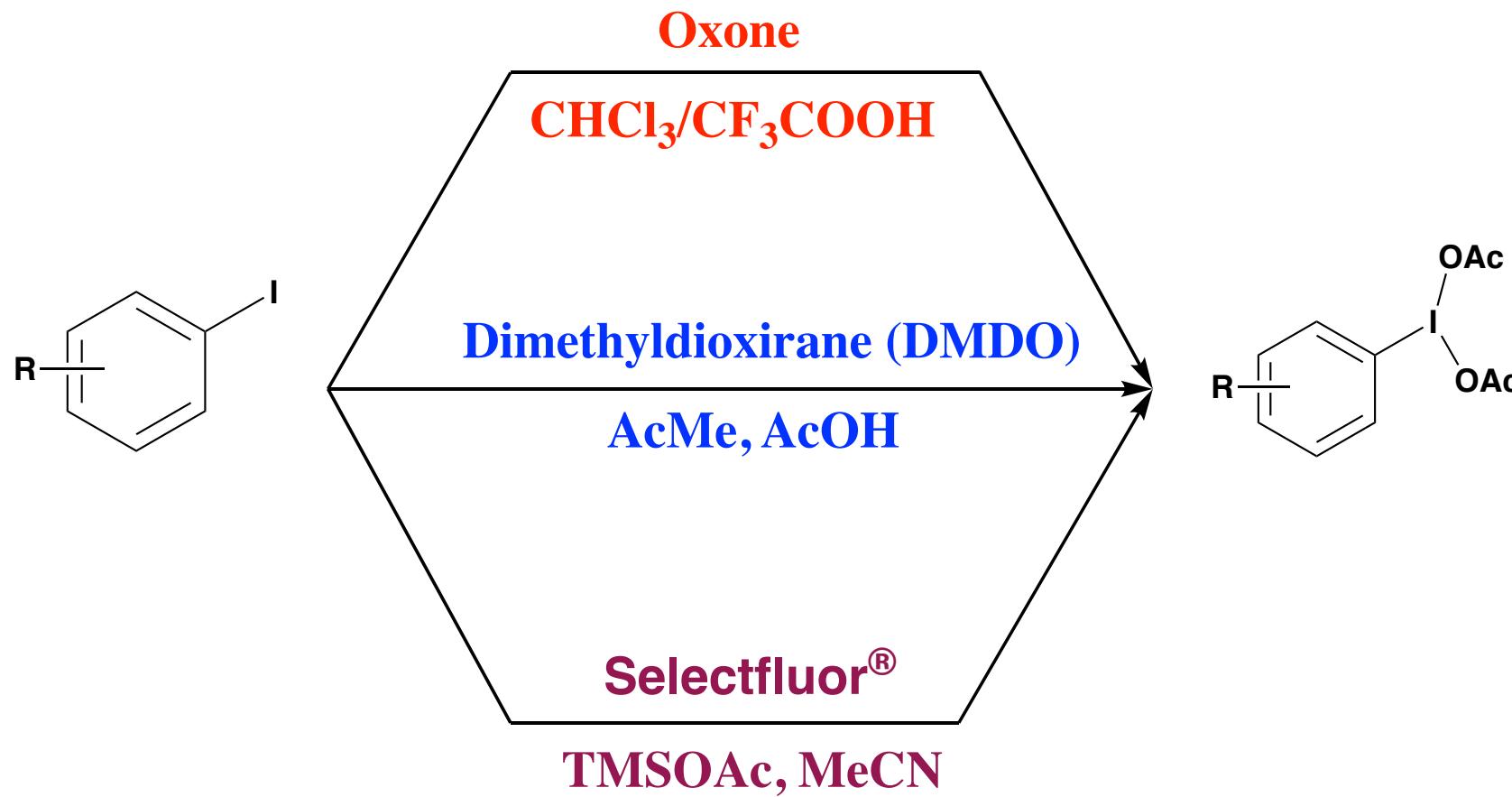
# Previous $^{18}\text{F}$ labeling routes



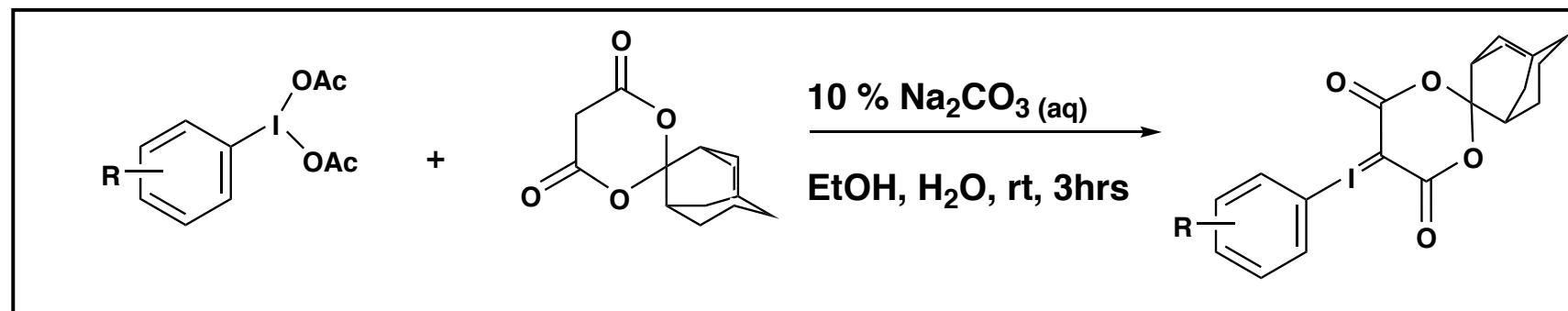
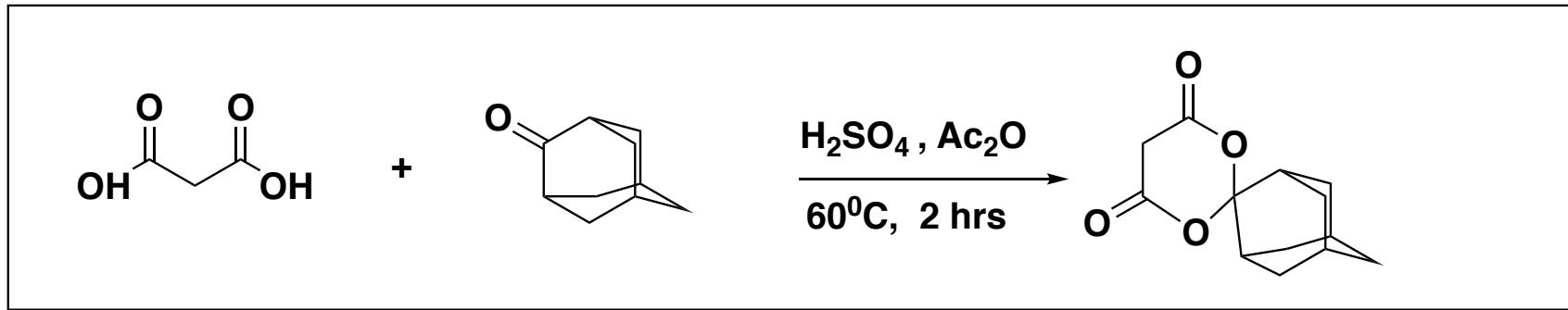
# Reaction Scheme



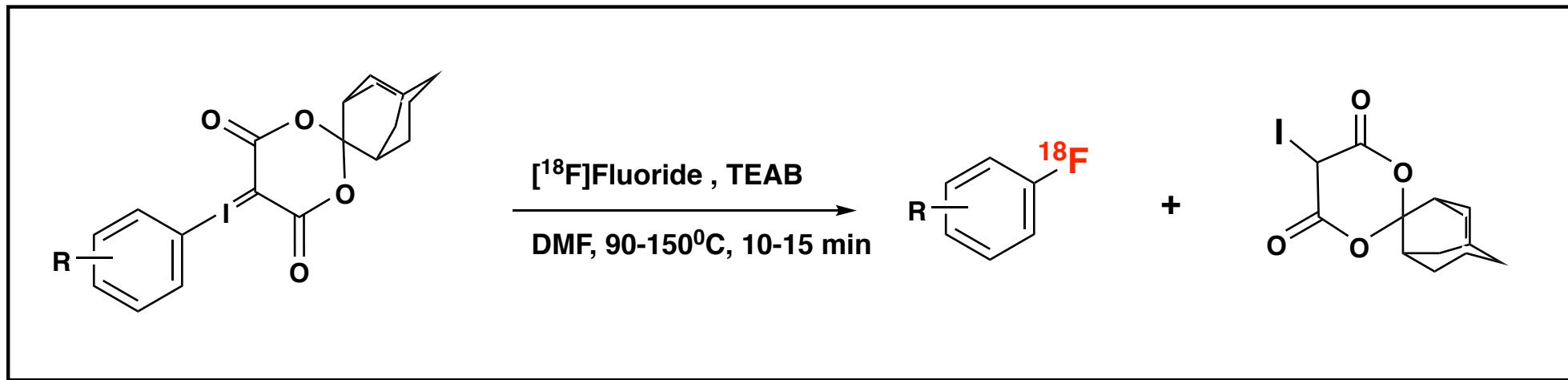
# Step 1: Oxidation



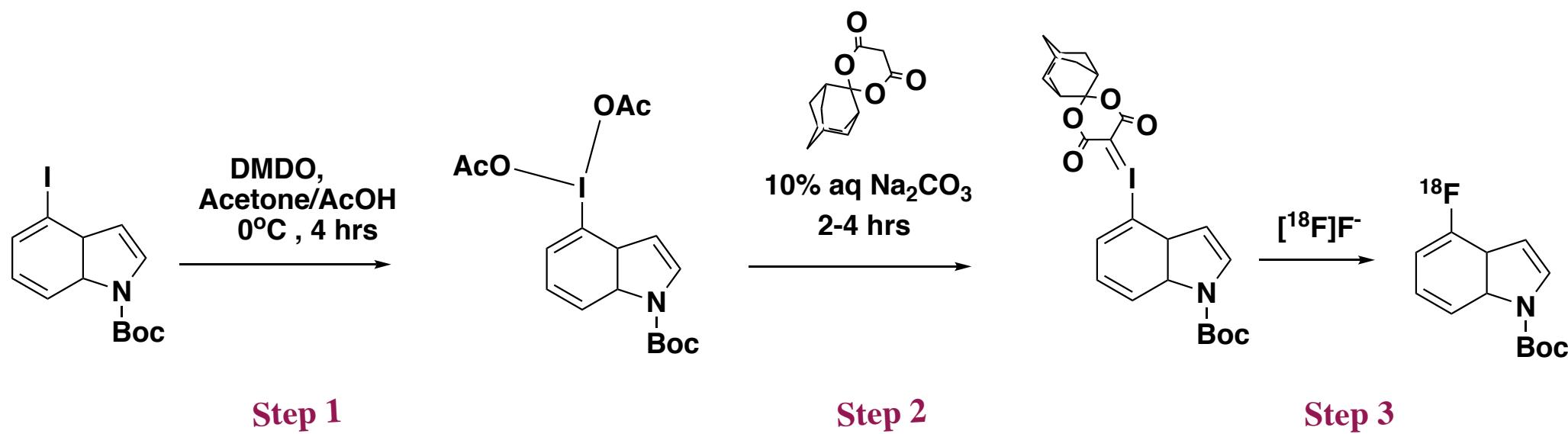
## Step 2: Ylide formation



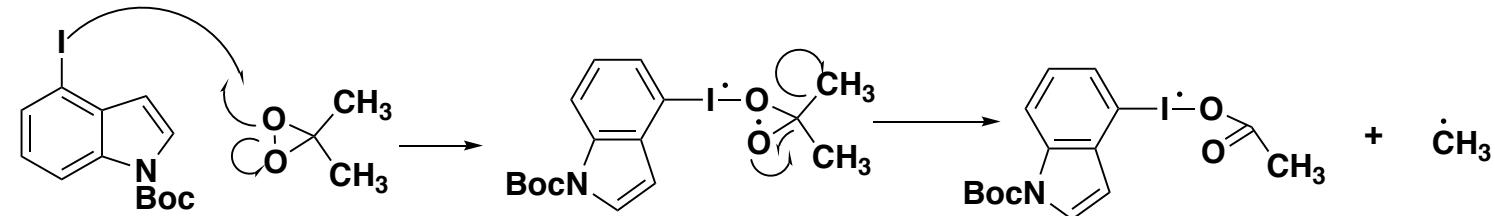
# Step 3: Reductive Elimination



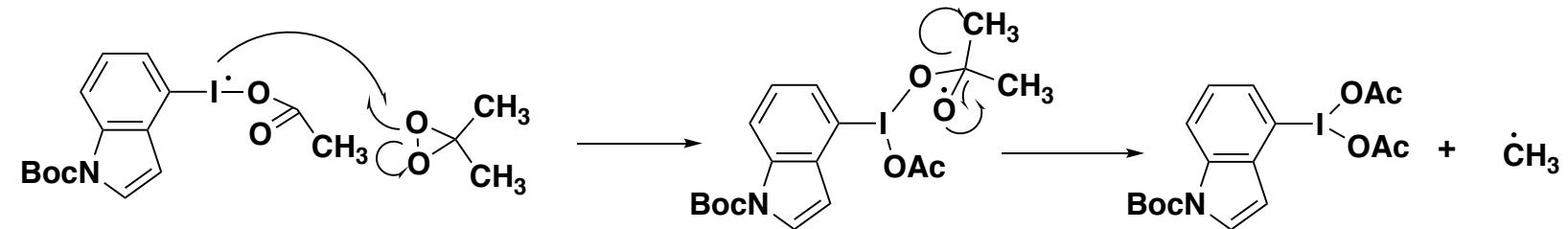
# Synthesis of [<sup>18</sup>F]Indoles



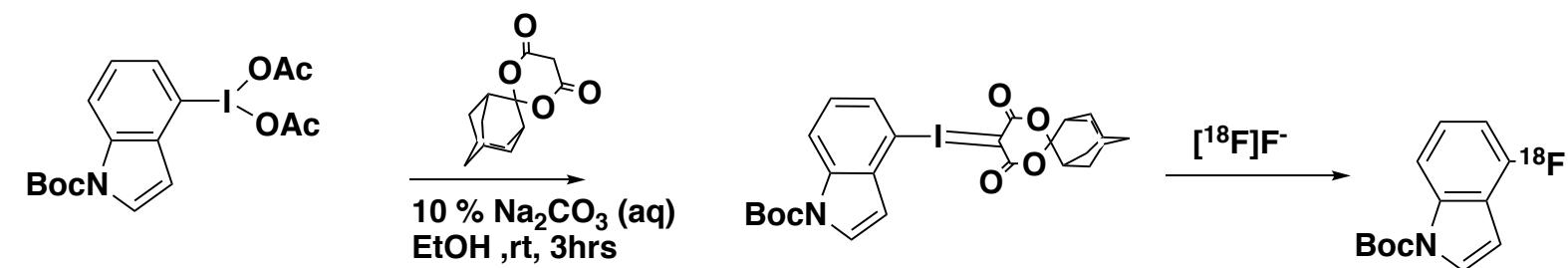
❖ Free radical decomposition of dioxirane leading to generation of methyl radical



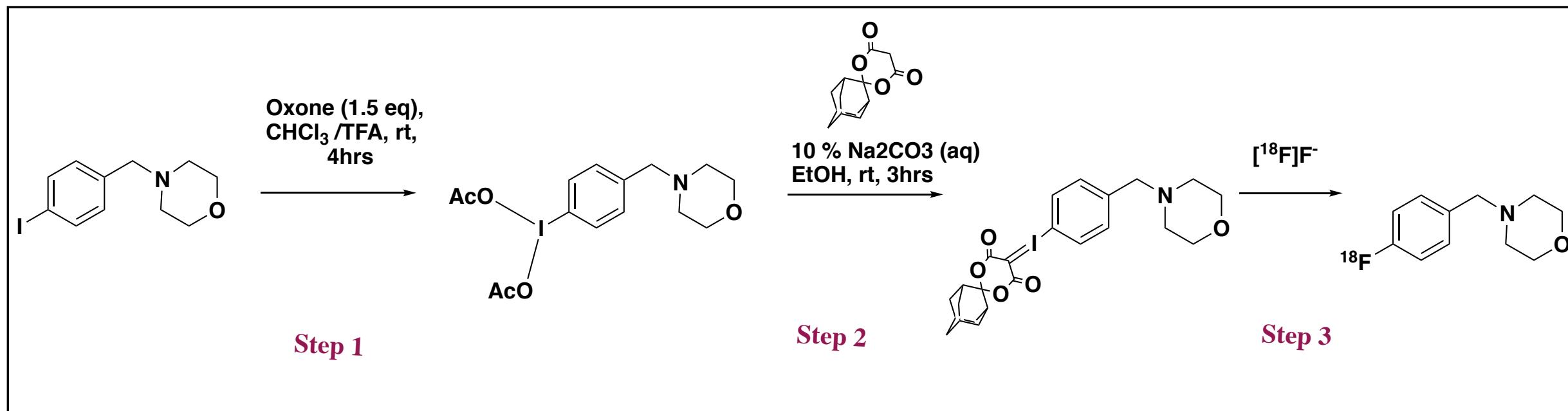
❖ Formation of iodosoacetate by using second DMDO equivalent



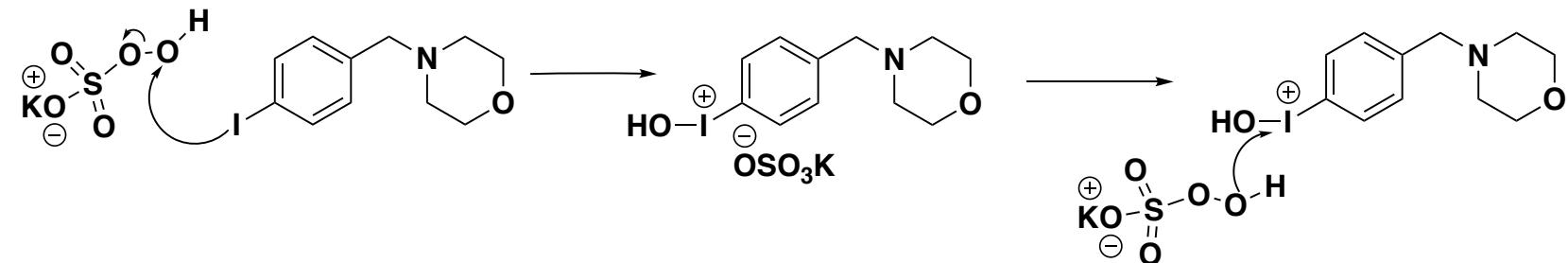
❖ Ylide formation and subsequent reductive elimination



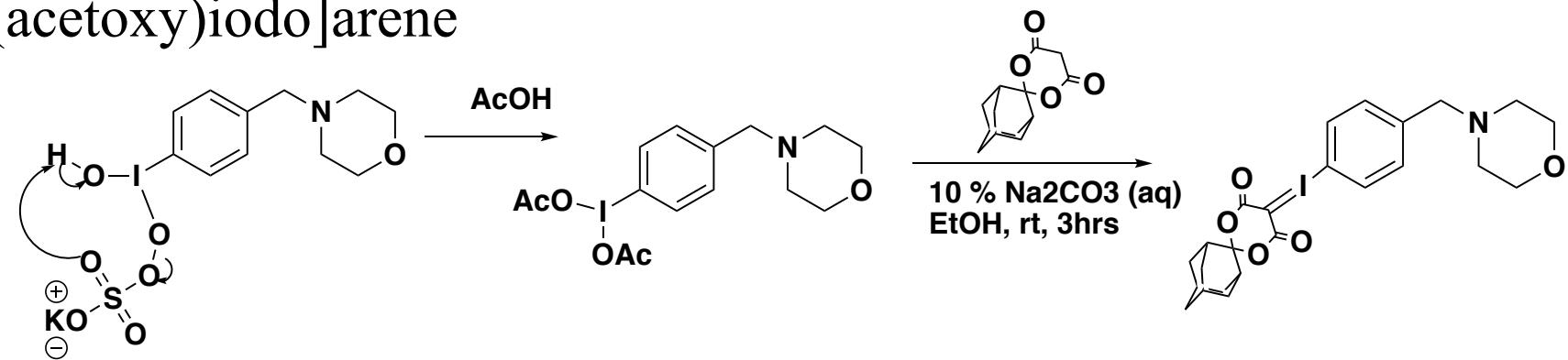
# Synthesis of [<sup>18</sup>F]drug scaffold: Mosapride



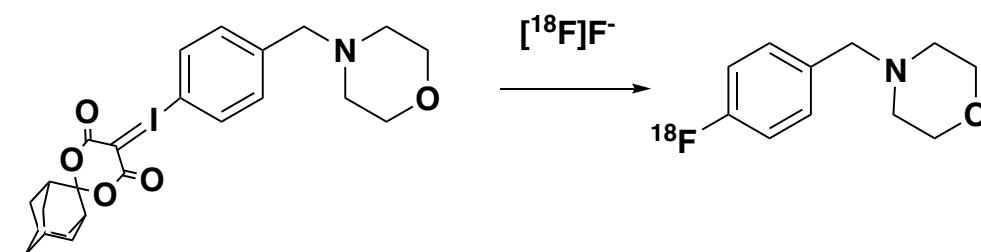
❖ potassium peroxymonosulfate as an oxidizing agent



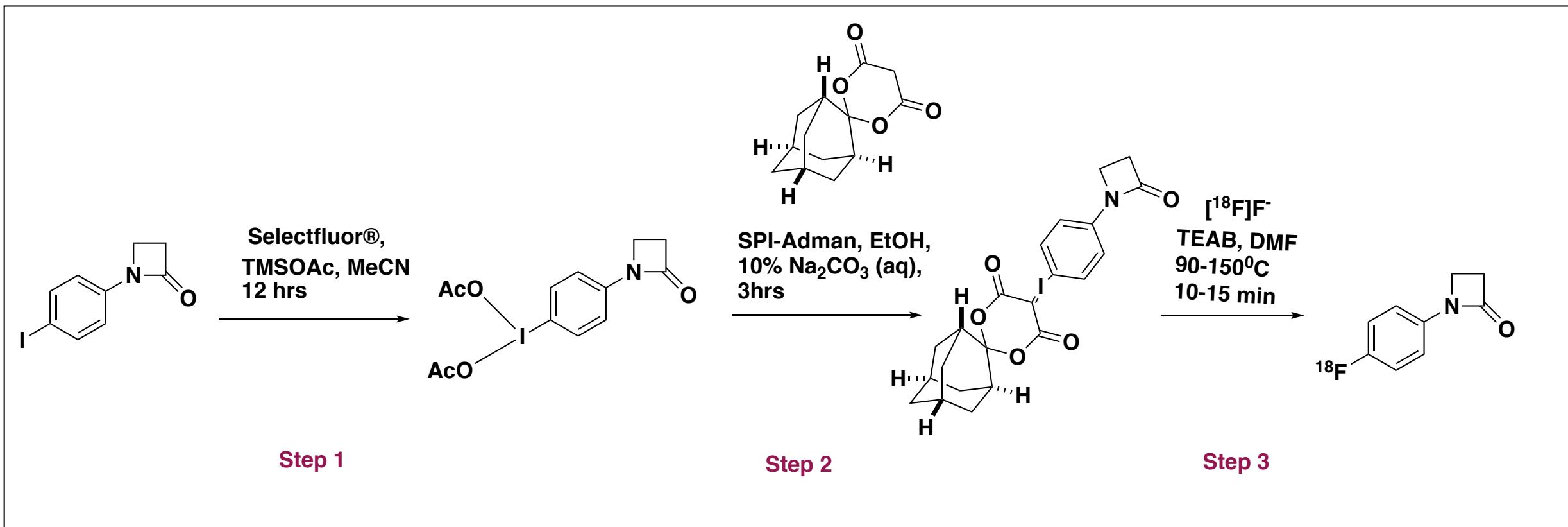
❖ formation of [bis(acetoxy)iodo]arene



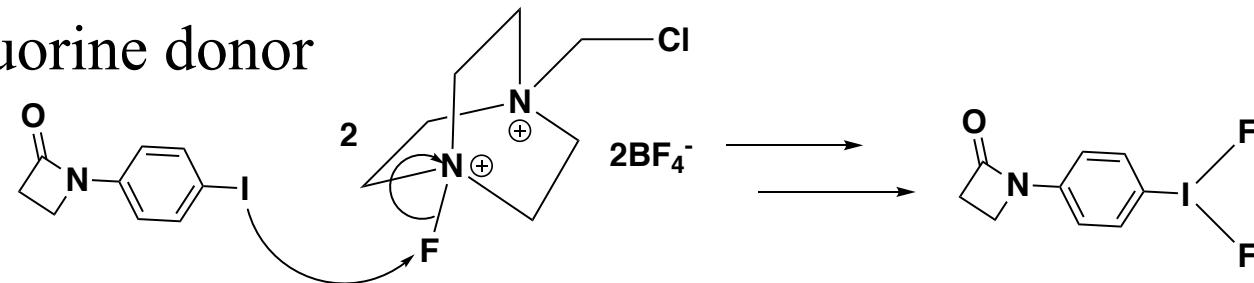
❖  $^{18}\text{F}$  labeling by reductive elimination



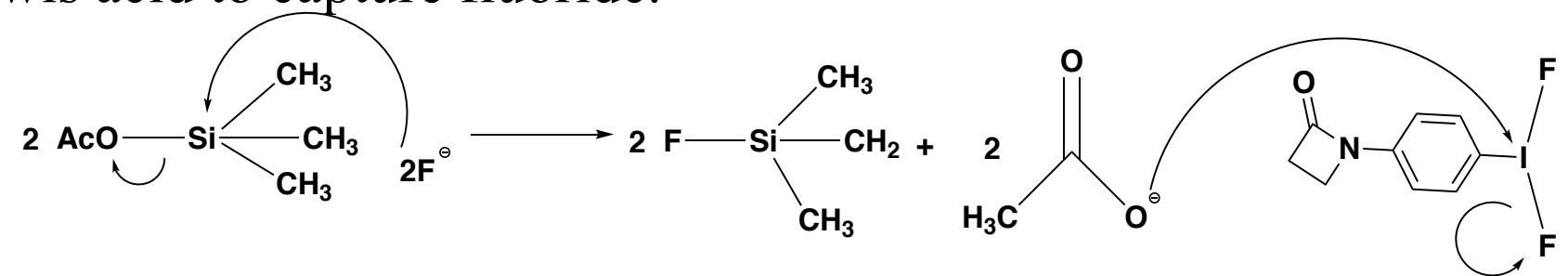
# Synthesis of [<sup>18</sup>F] drug scaffold: Ezetimibe



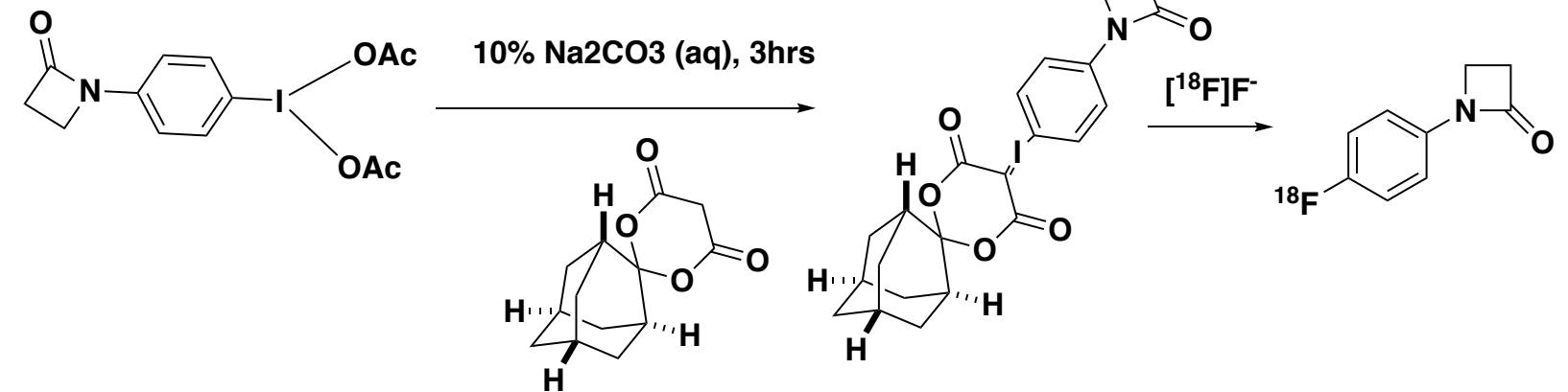
❖ Selectfluor® acts as an fluorine donor



❖ TMSOAc acts as a lewis acid to capture fluoride.



❖ Conversion of Ar-IF<sub>2</sub> into bis[acetoxy]iodo intermediate



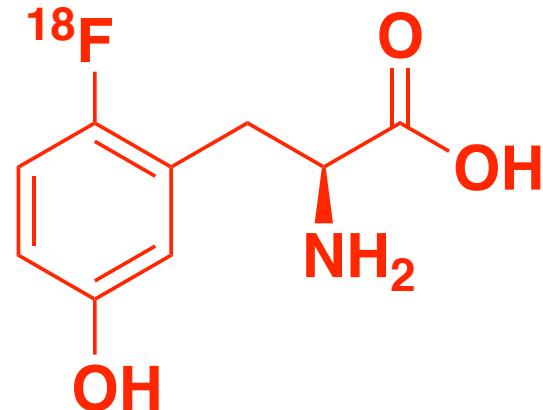
# Results

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

# PET radiopharmaceuticals

[<sup>18</sup>F]fluoro-meta-tyrosine

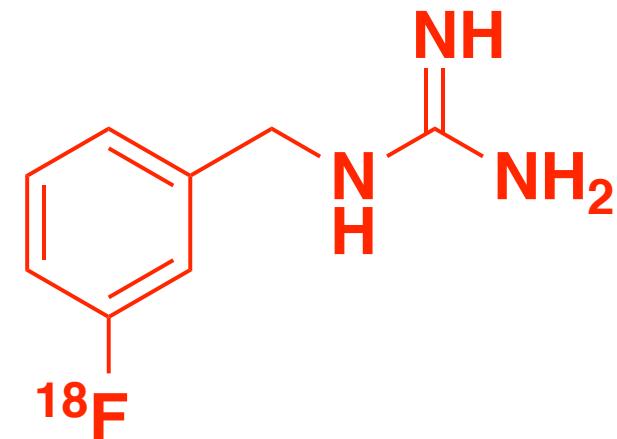
(Cerebral dopamine transport)



Radiochemical yield: 12%

meta-[<sup>18</sup>F]fluorobenzylguanidine

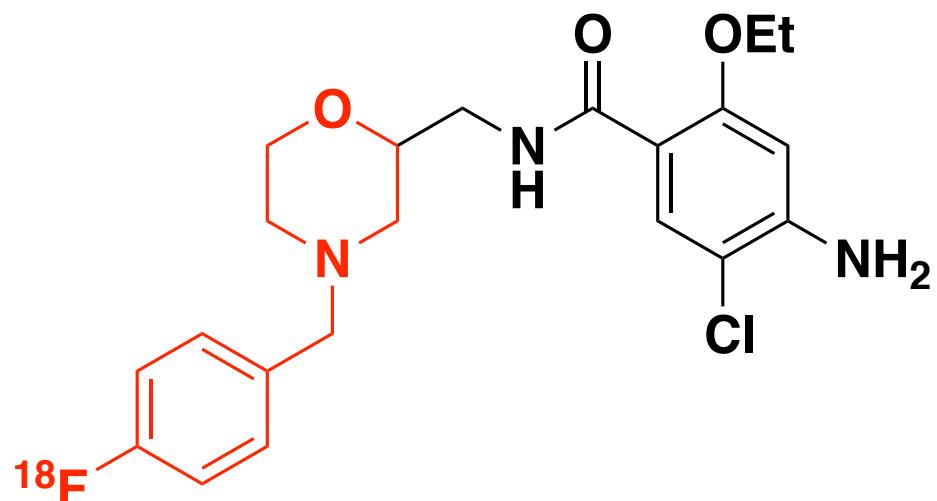
(Neuroblastoma)



Radiochemical yield: 14%

# Mosapride

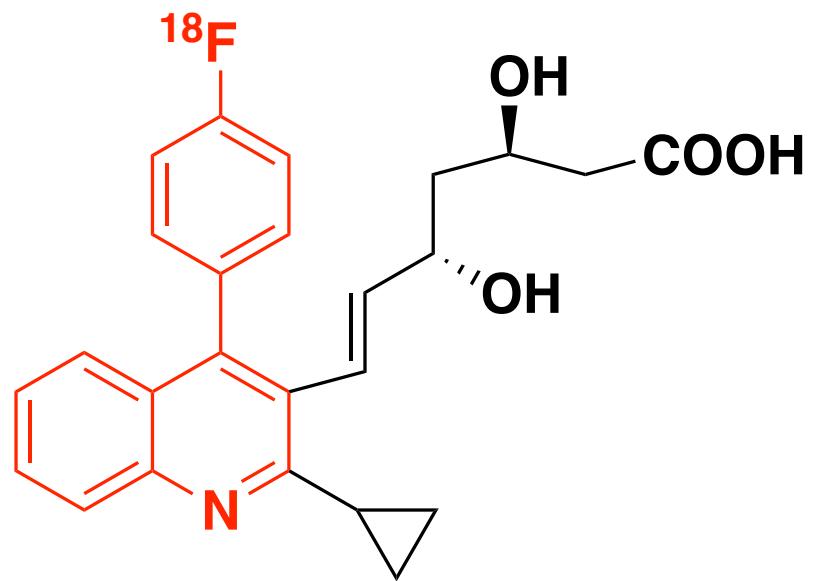
(Gastric inflammation)



Radiochemical conversion:  $35 \pm 6\%$

# Pitavastatin

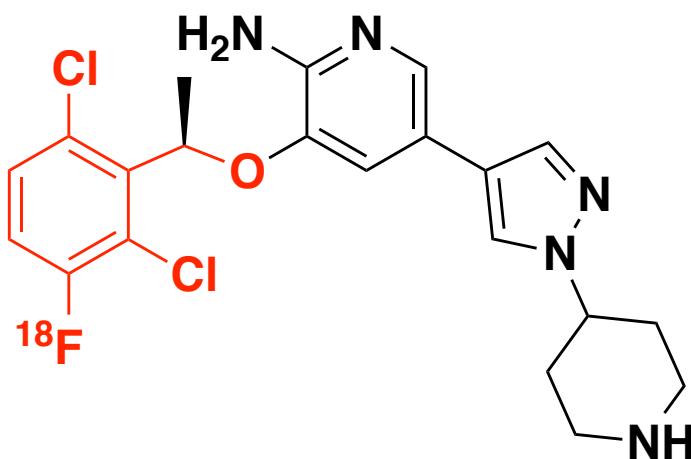
(hypcholesterolæmia)



Radiochemical conversion:  $57 \pm 9\%$

# Crizotinib

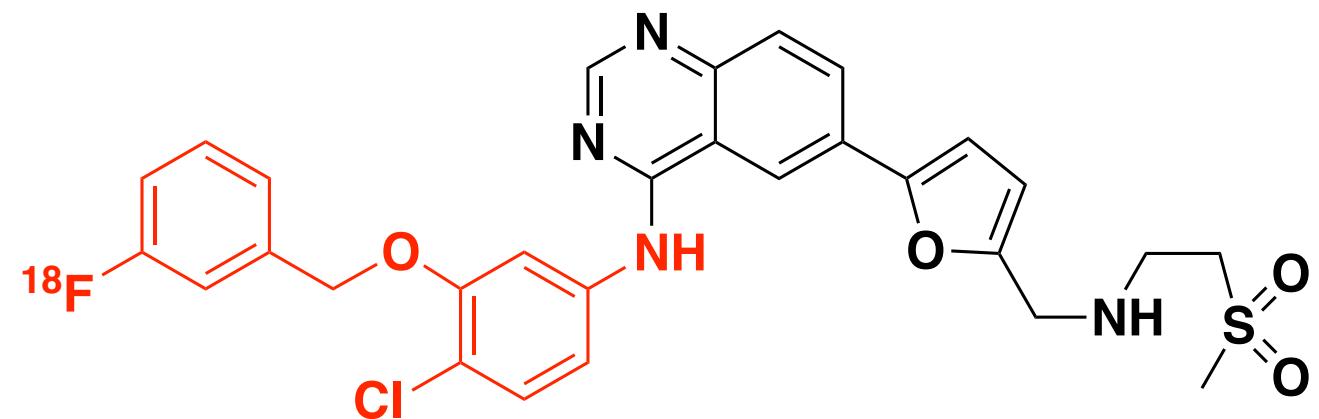
(Non-small cell lung cancer)



Radiochemical conversion:  $82 \pm 6\%$

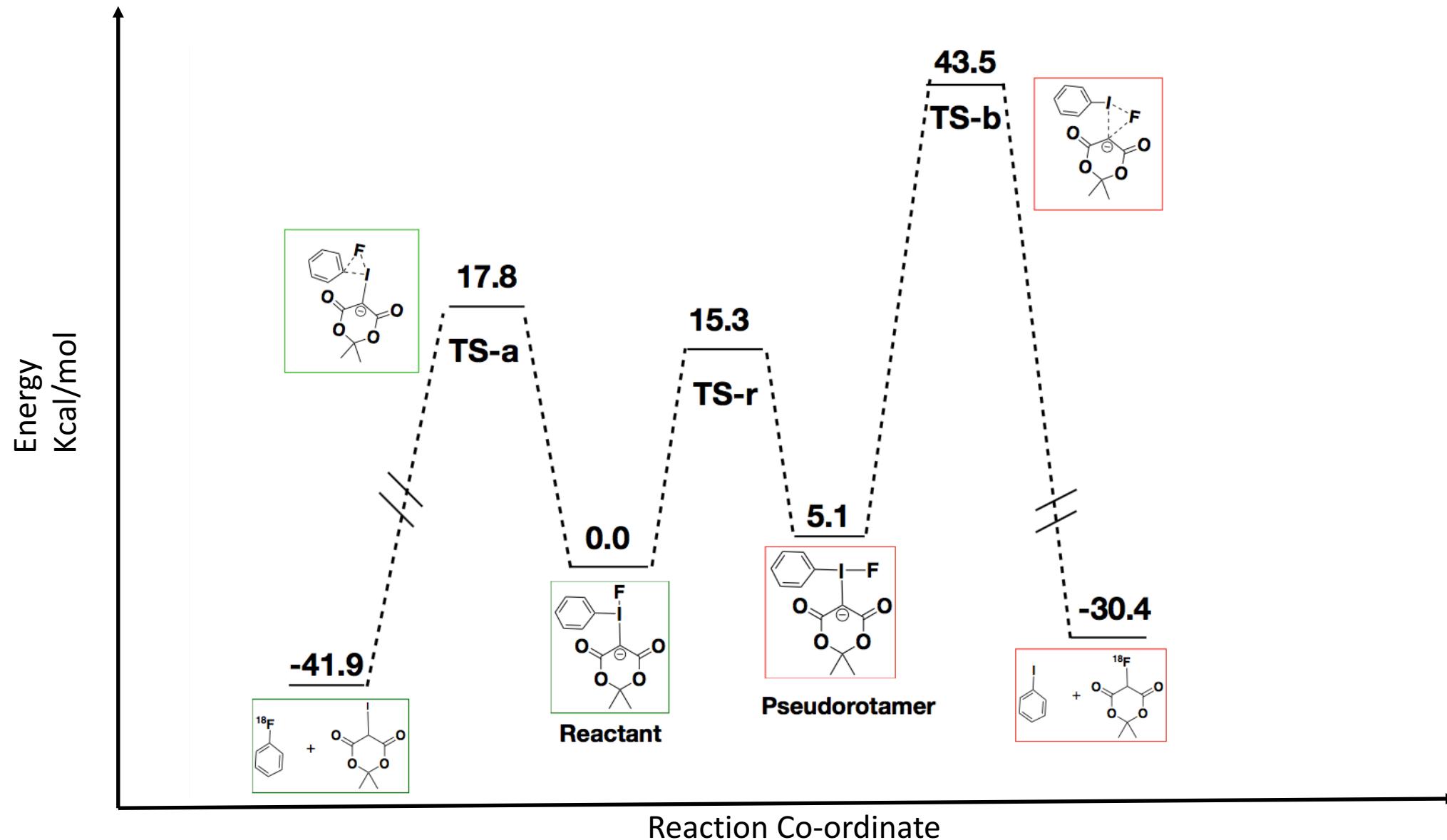
# Ipatinib

(Breast and lung cancer)

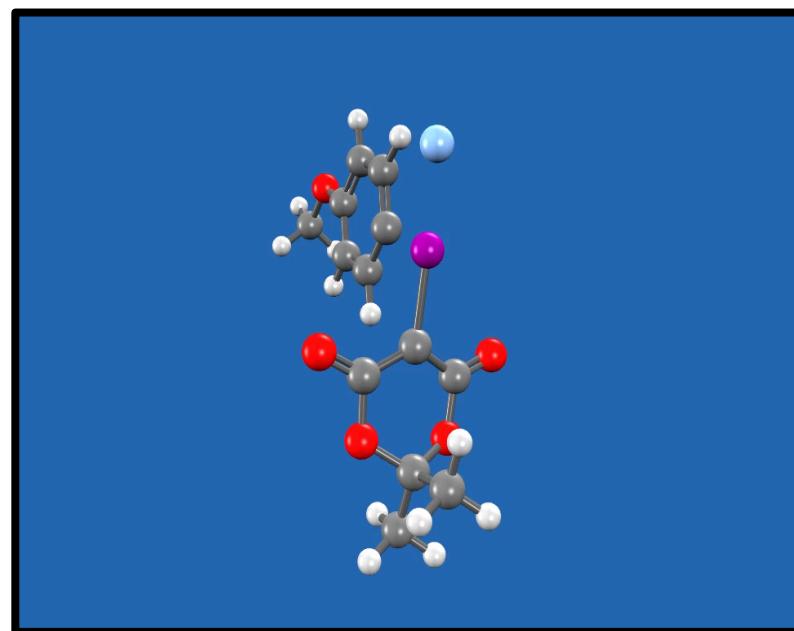
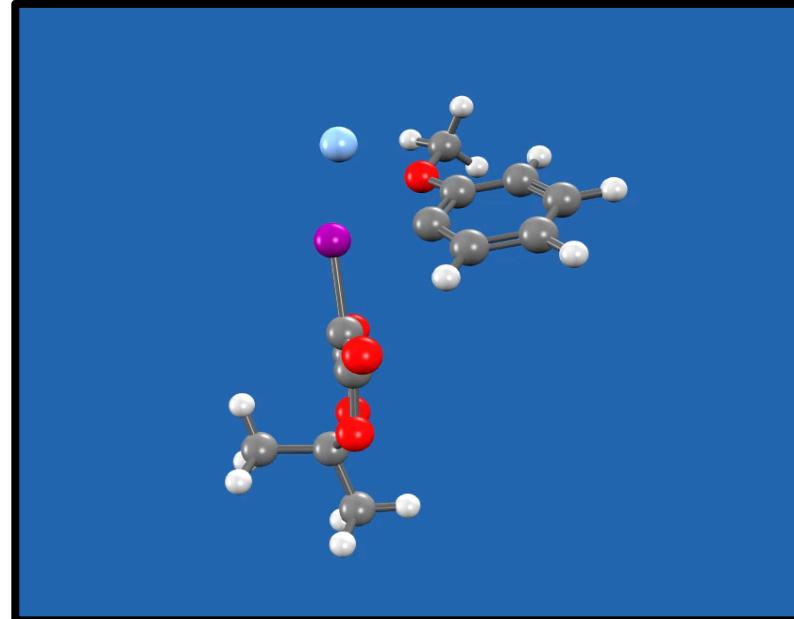
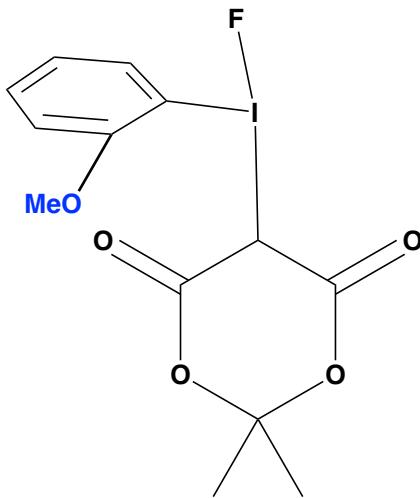
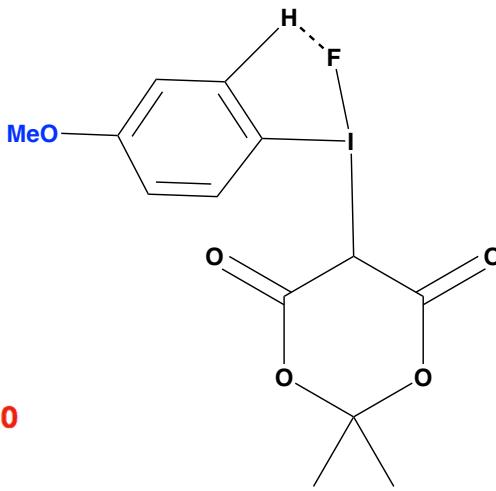
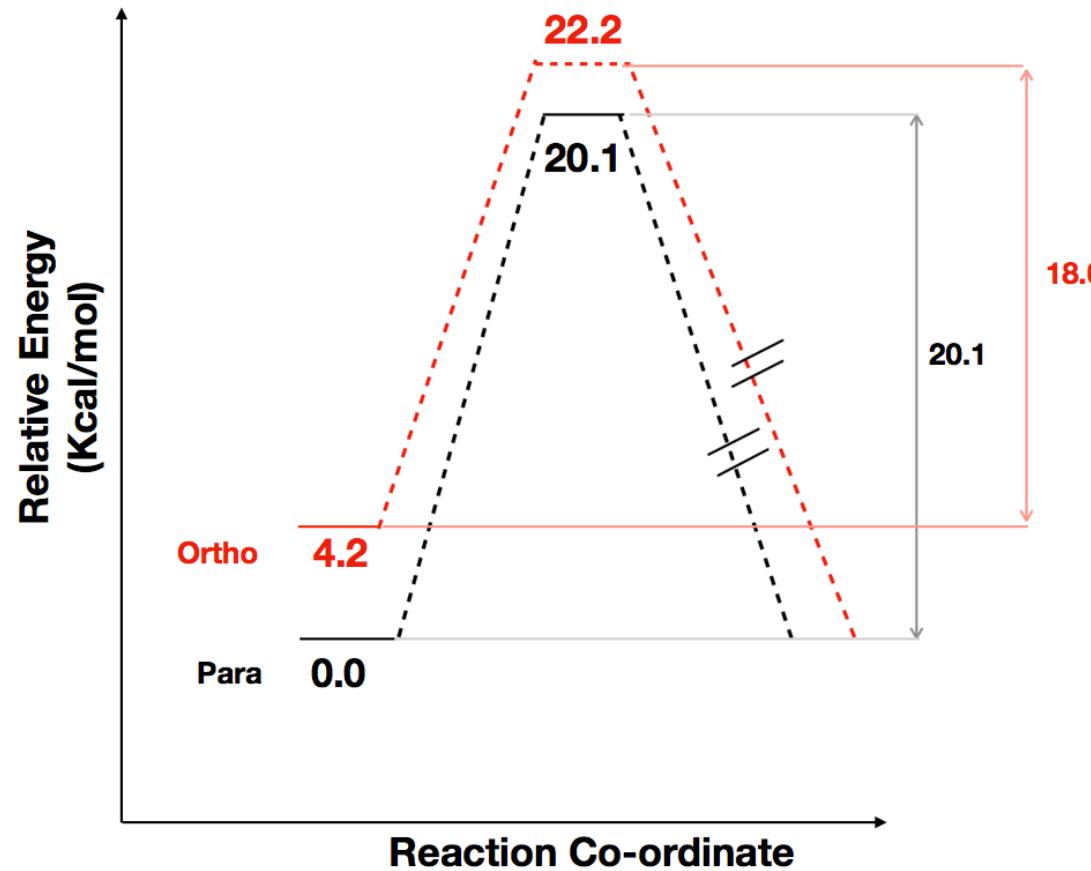


Radiochemical conversion:  $66 \pm 8\%$

# Competing Reaction pathways

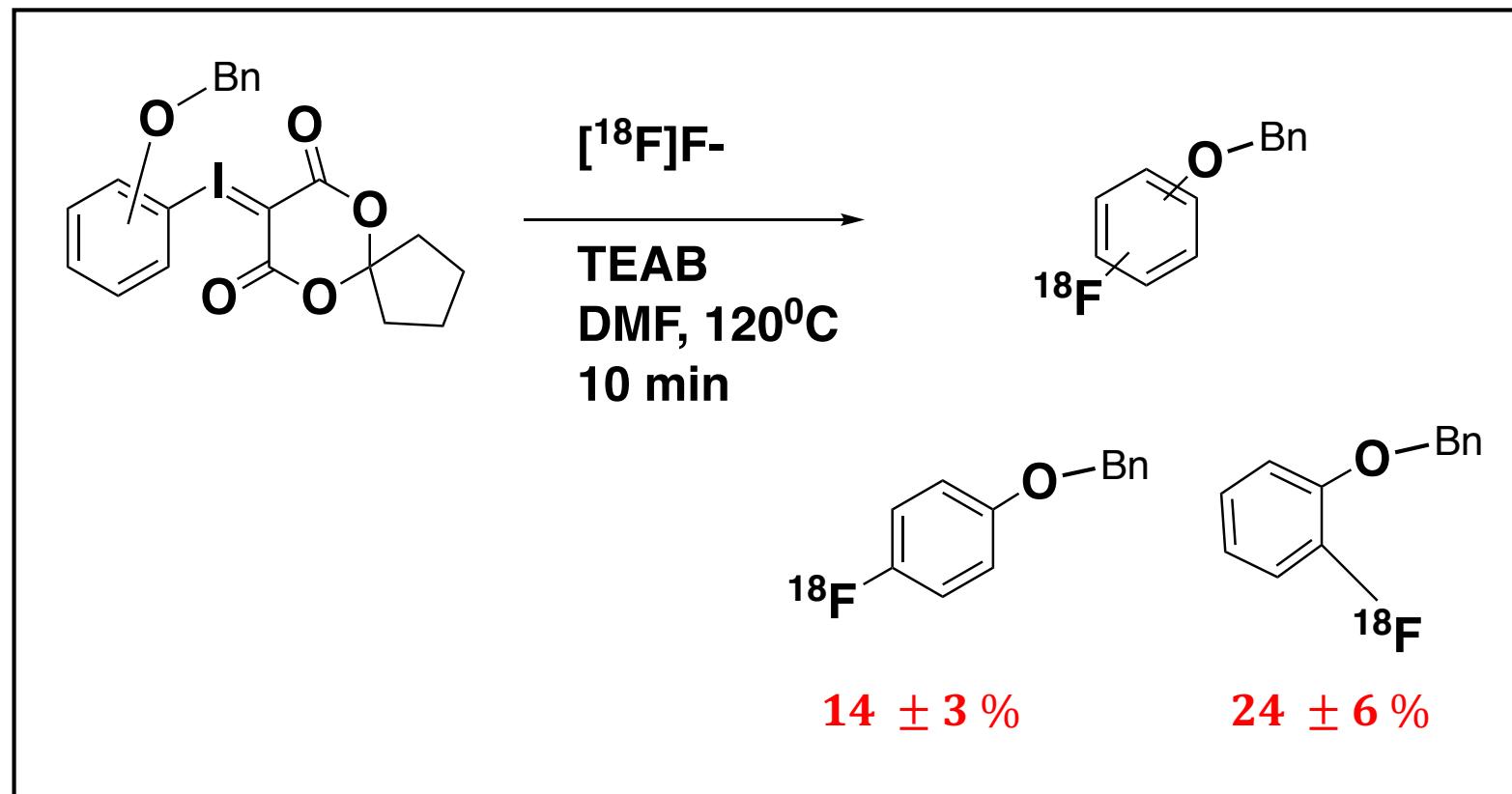


# Steric Effect

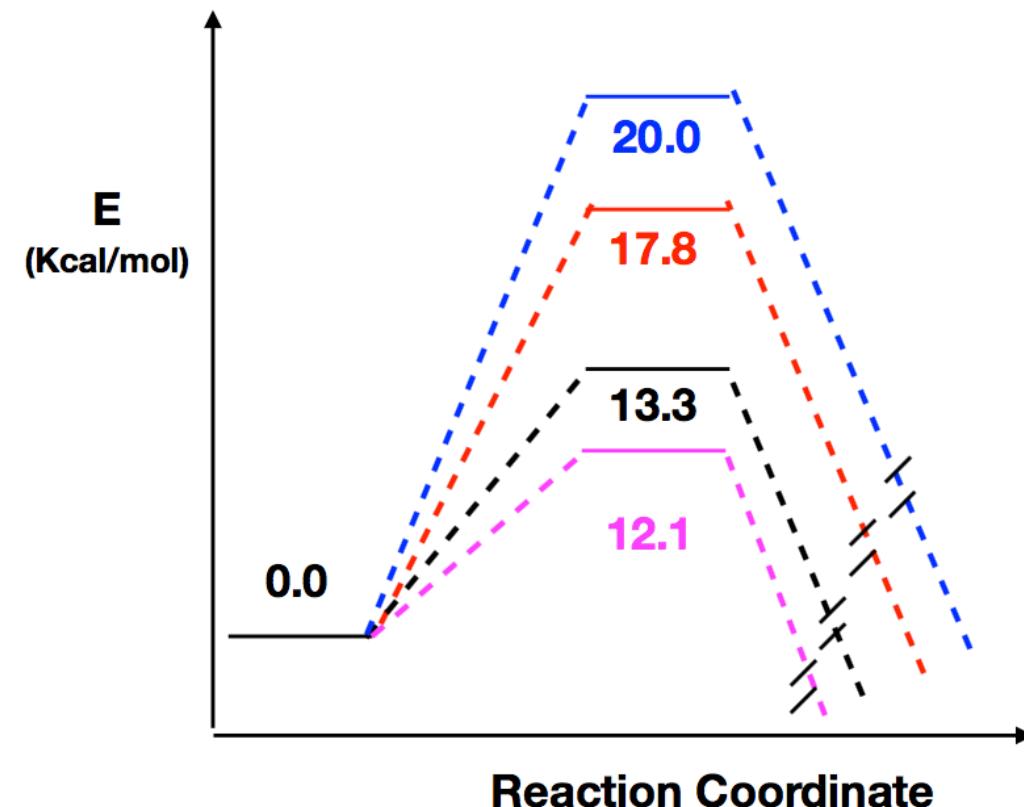
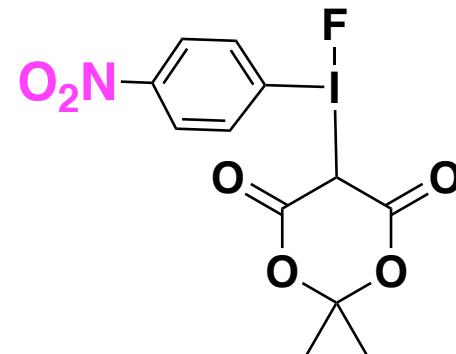
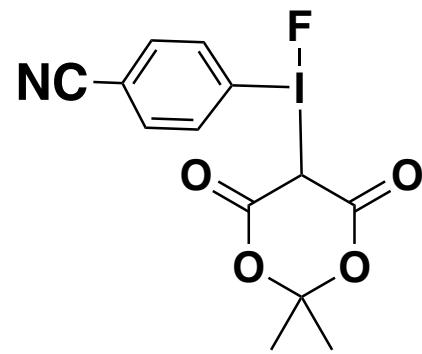
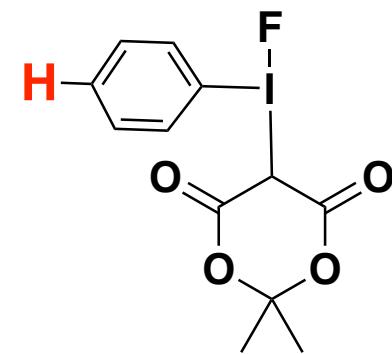
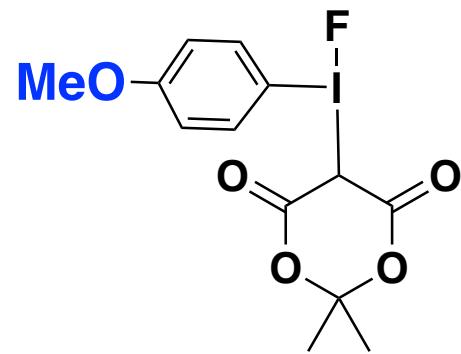


Ortho substitution: Destabilization of reactants in ground state

# Experimental Results for *ortho* effects



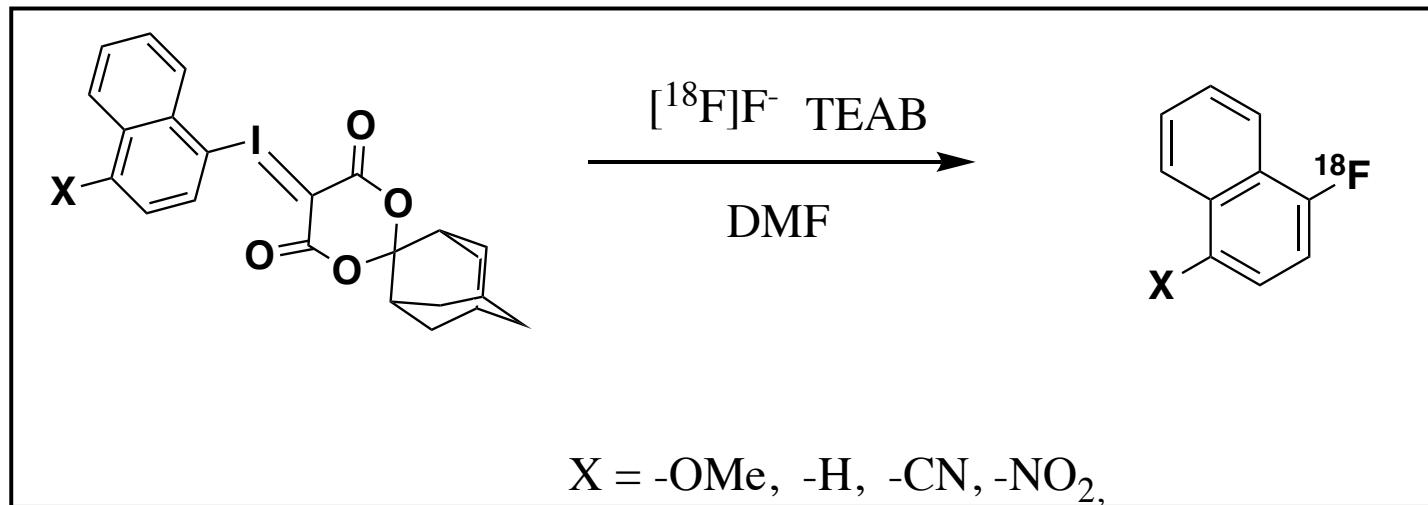
# Electronic Effects of substitution



Reduction in reductive elimination barrier by EWGs

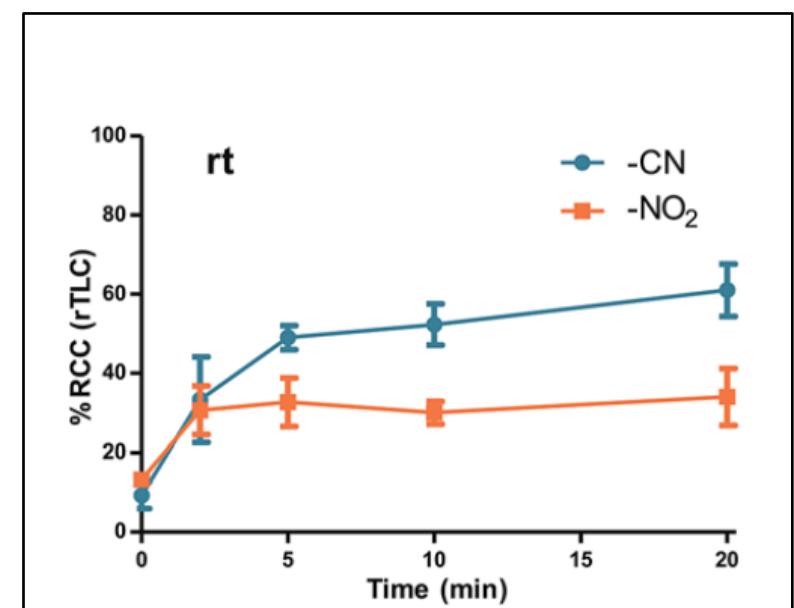
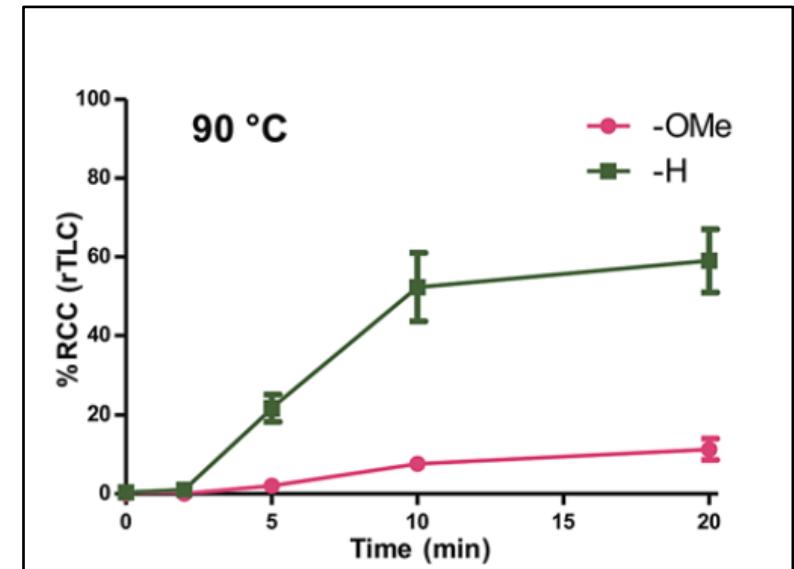
$$\Delta G^\ddagger \quad -NO_2 < -CN < -H < -OMe$$

# Electronic Effects of substitutions

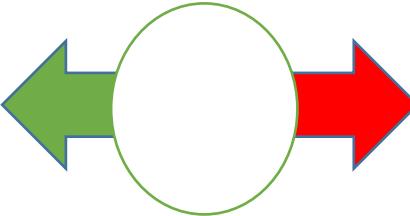


Factors affected by substitutions:

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



# Conclusions

- 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 formations

# Acknowledgments

Graduate Committee members:

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

Chemistry faculty

- Dr. Ronald Halterman
- Dr. Daniel Glatzhofer
- Dr. Ye Mei

Our support staff

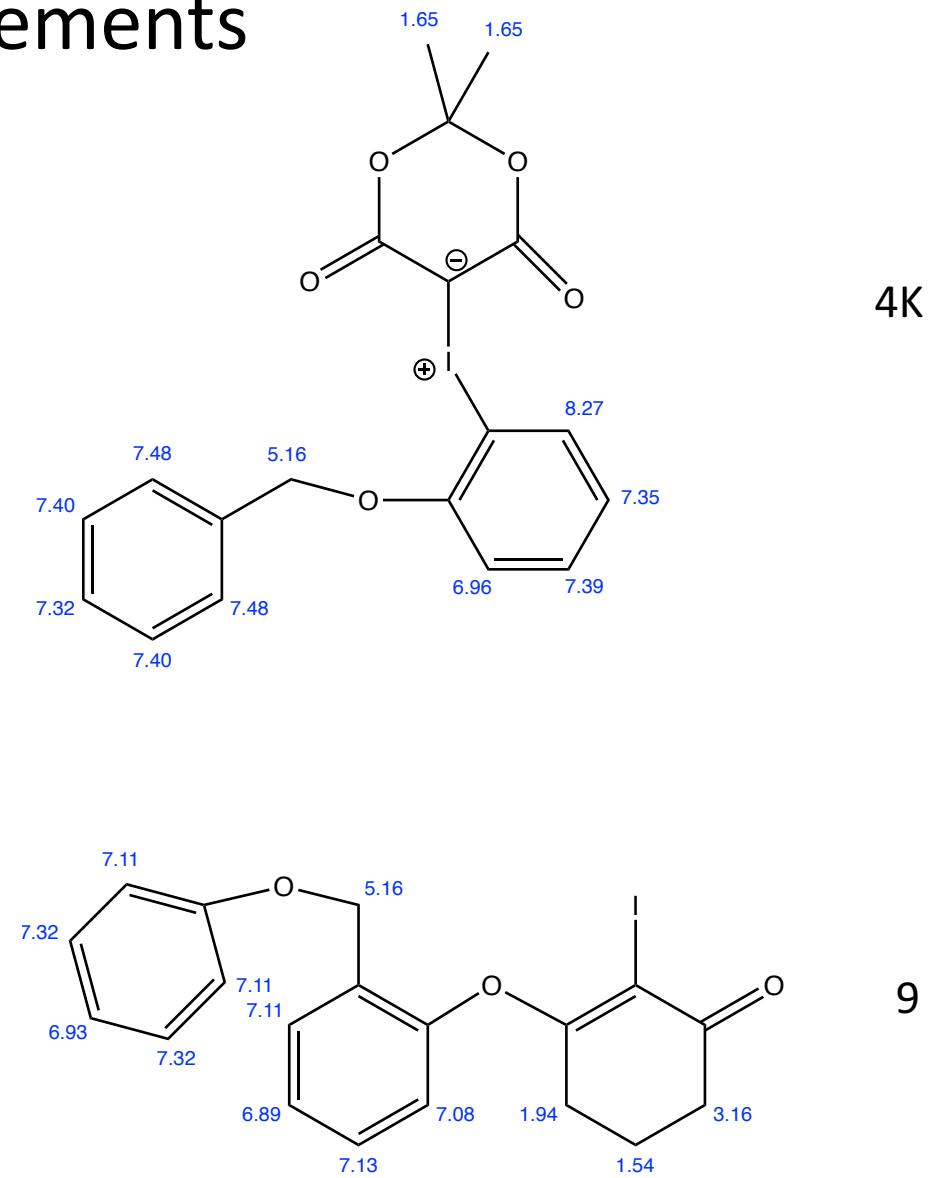
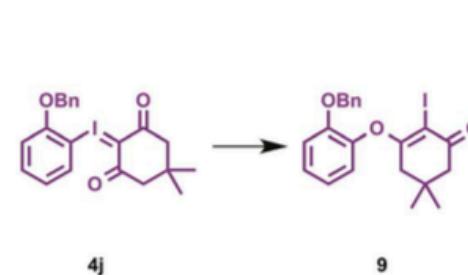
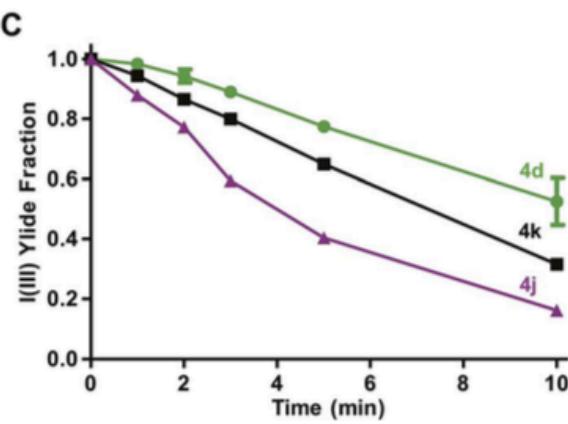
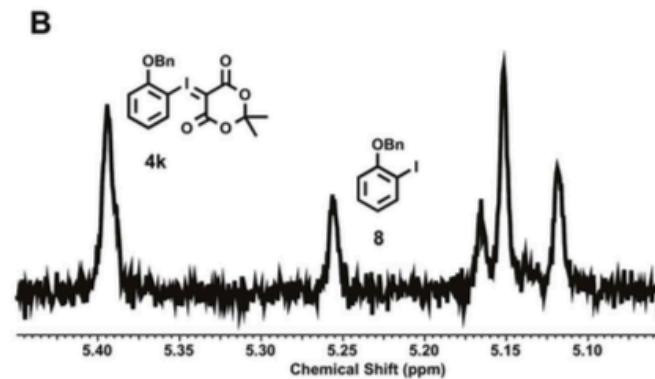
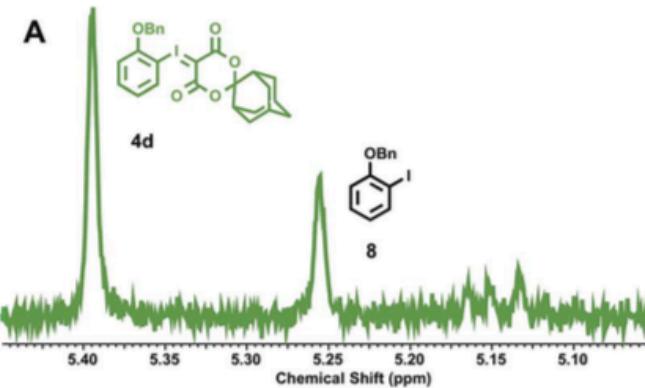
- Kelsi Nulnee
- Carol Jones
- Nailynn Williams
- Heather

Lab mates and colleges

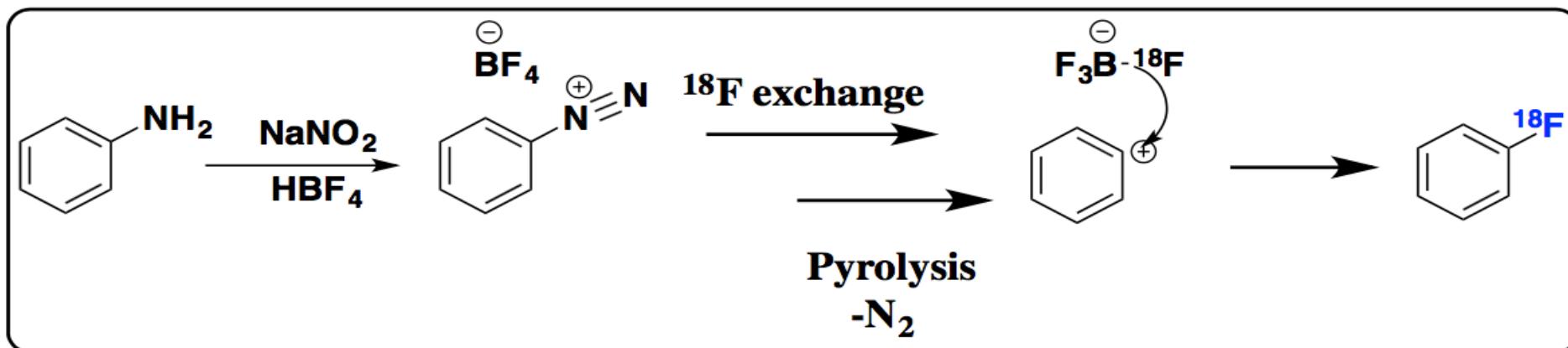
- Xiaoliang Pan
- Gengwei Zhang
- Jingheng Deng
- Zhou zou
- Eric Gardner
- Tejaswi Bavineni

# supplementary slides

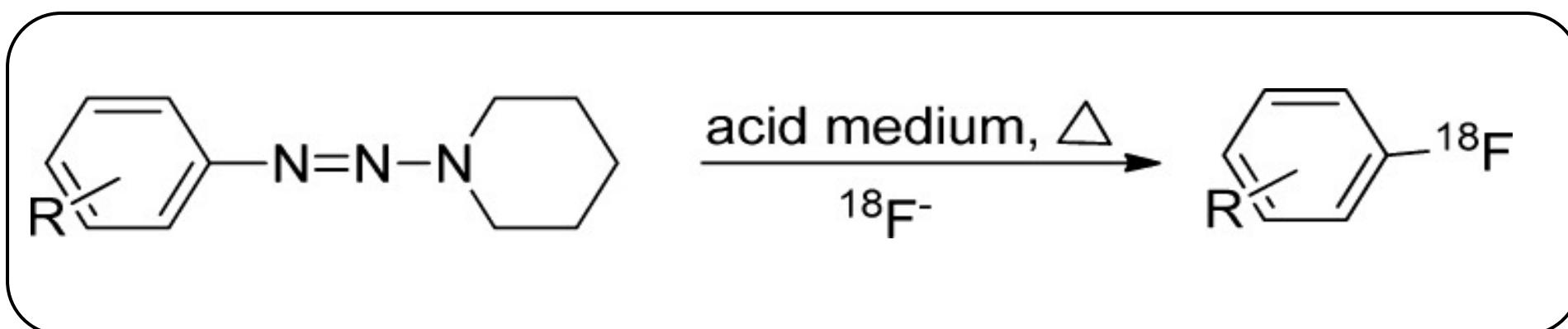
# Possible rearrangements



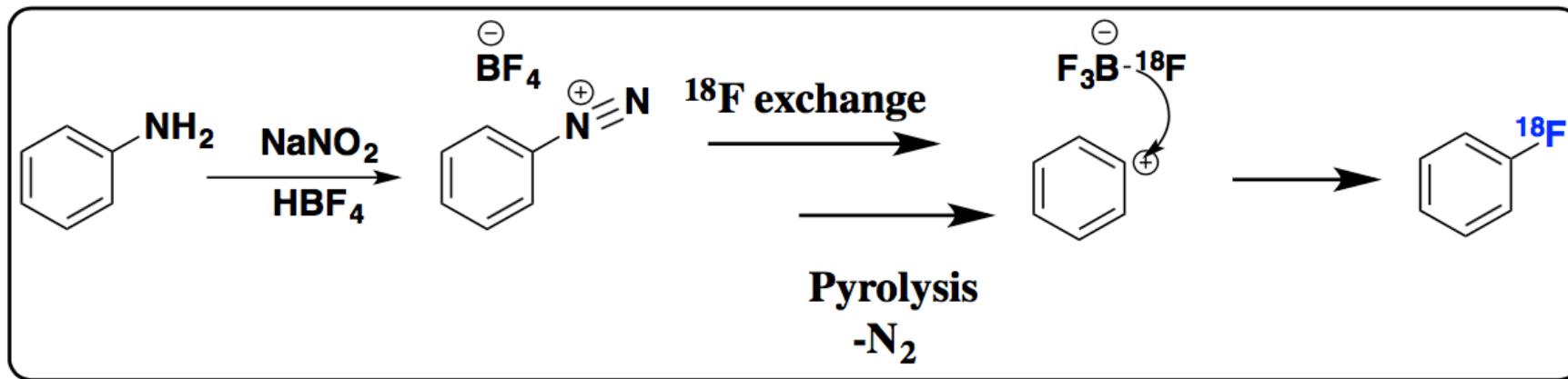
- Balz-Schiemann reaction:



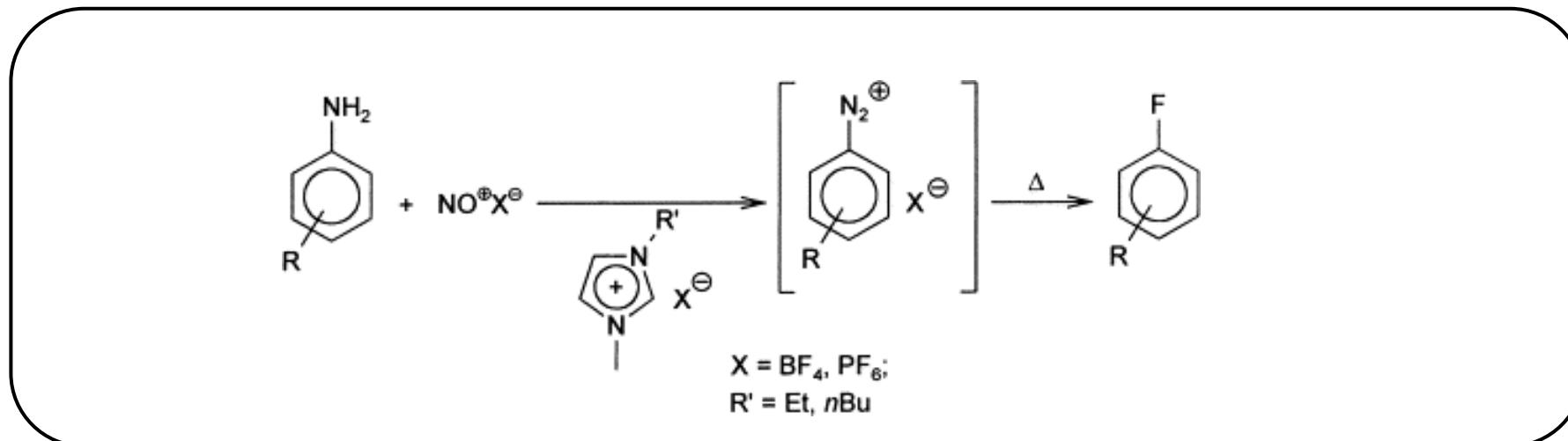
- Wallach reaction:

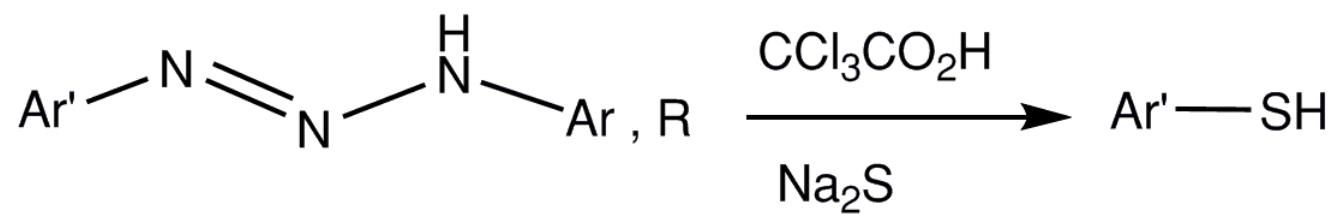
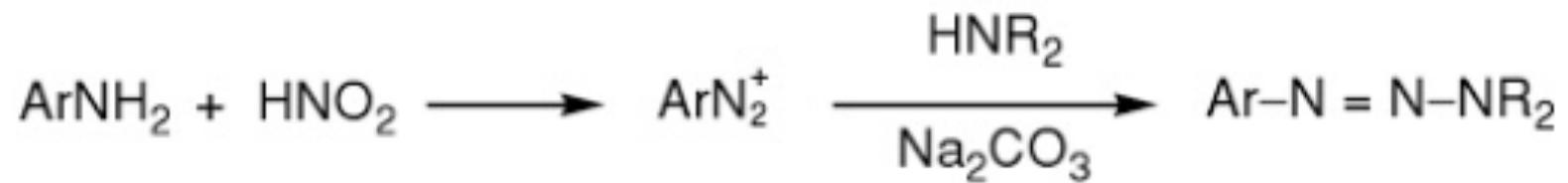
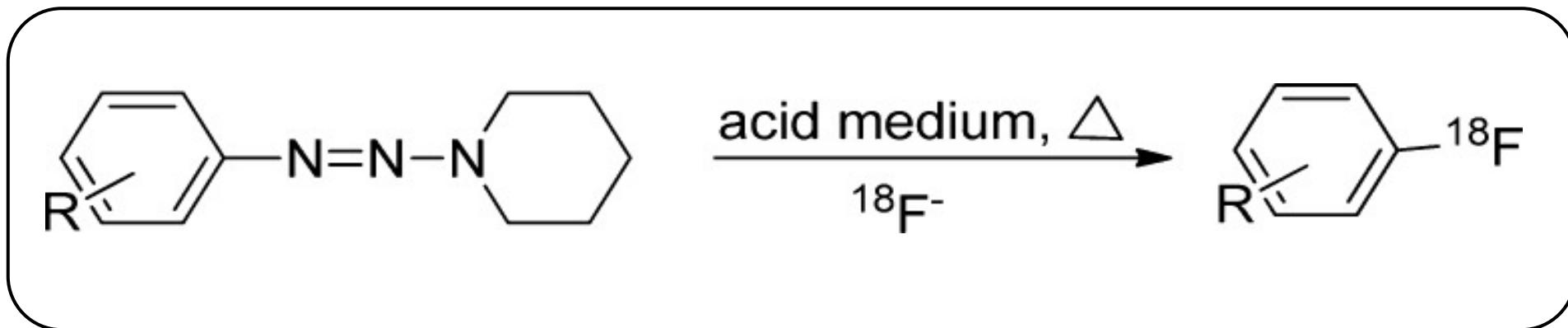


- Balz-Schiemann reaction:

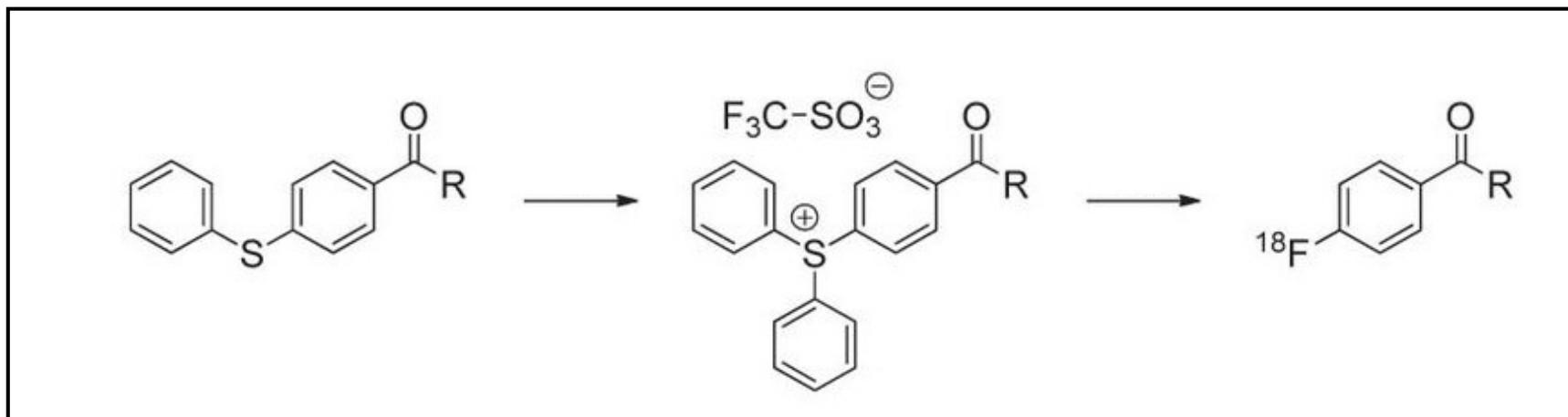


- Balz-Schiemann reaction with ionic liquids:

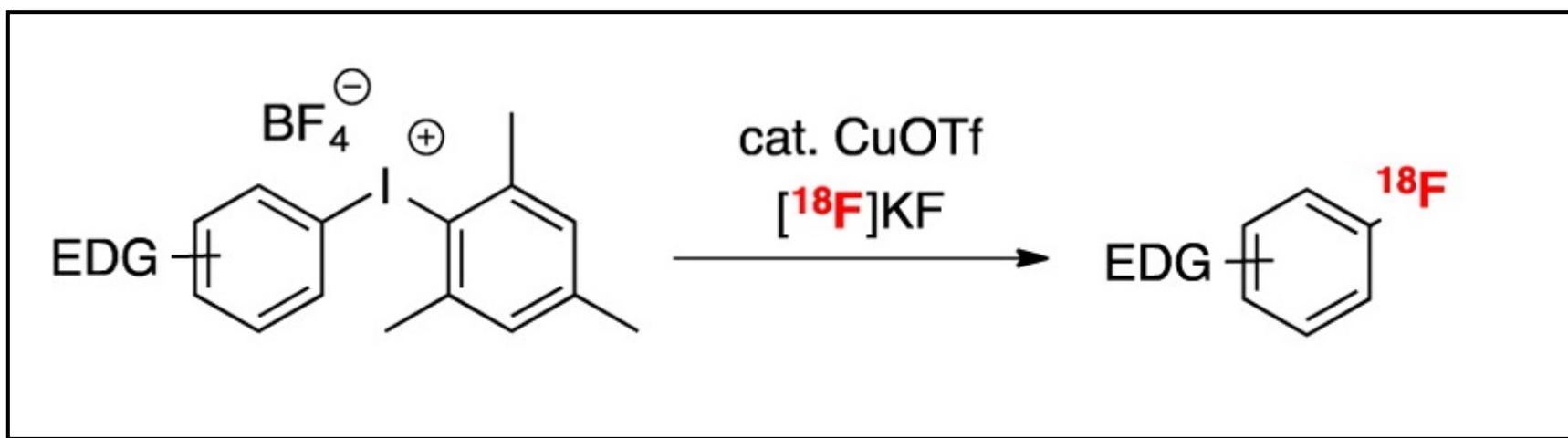




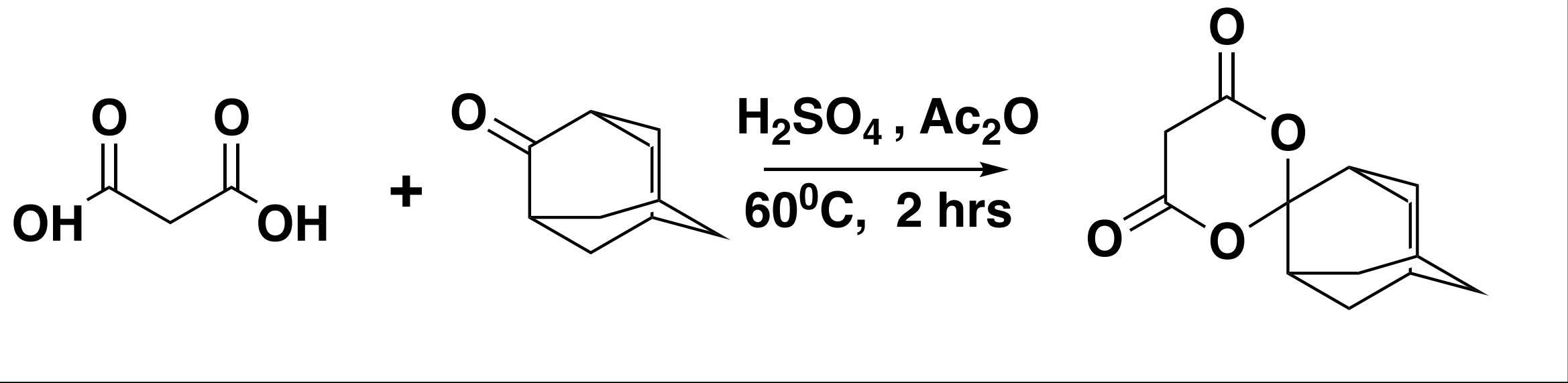
- Triarylsulfonium salts



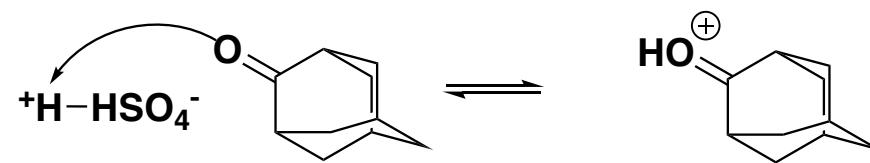
- Diaryliodonium salts



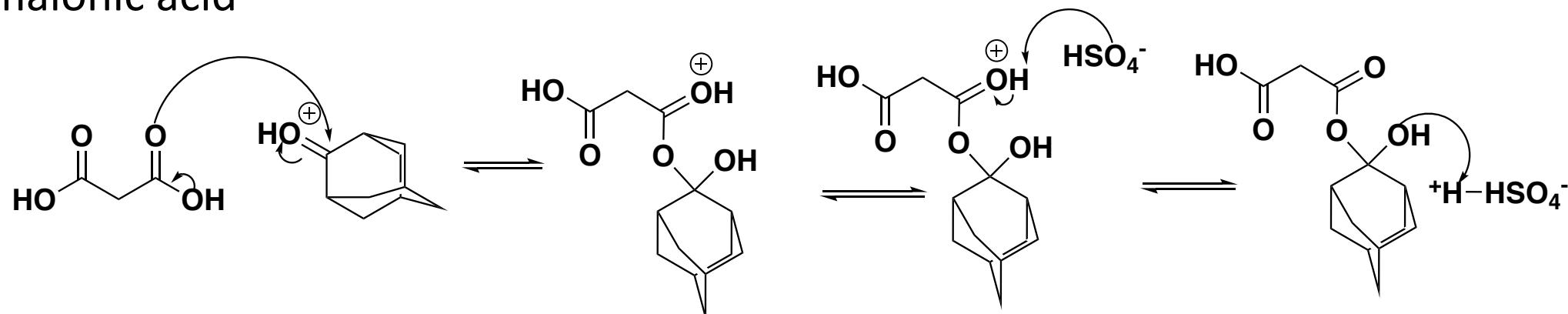
# SPIAd Synthesis



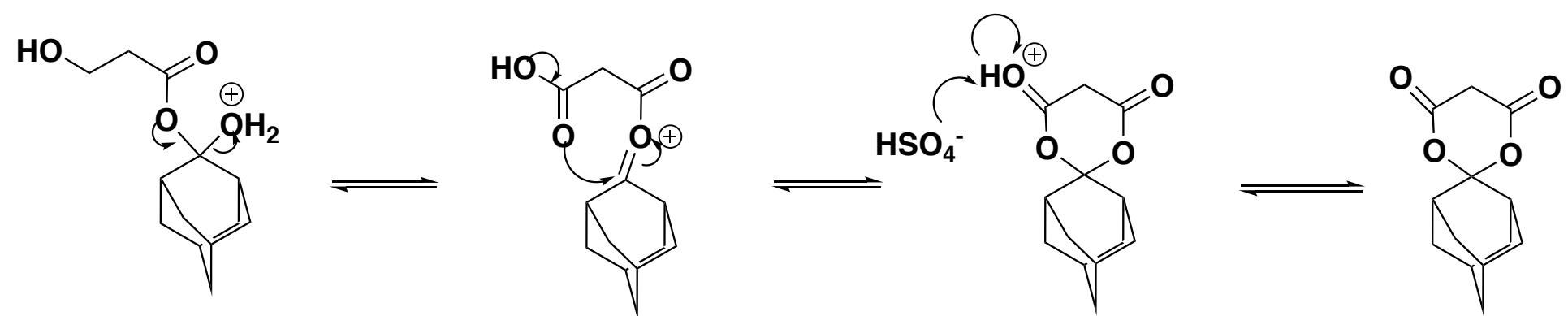
❖ protonation of ketone in acidic medium:



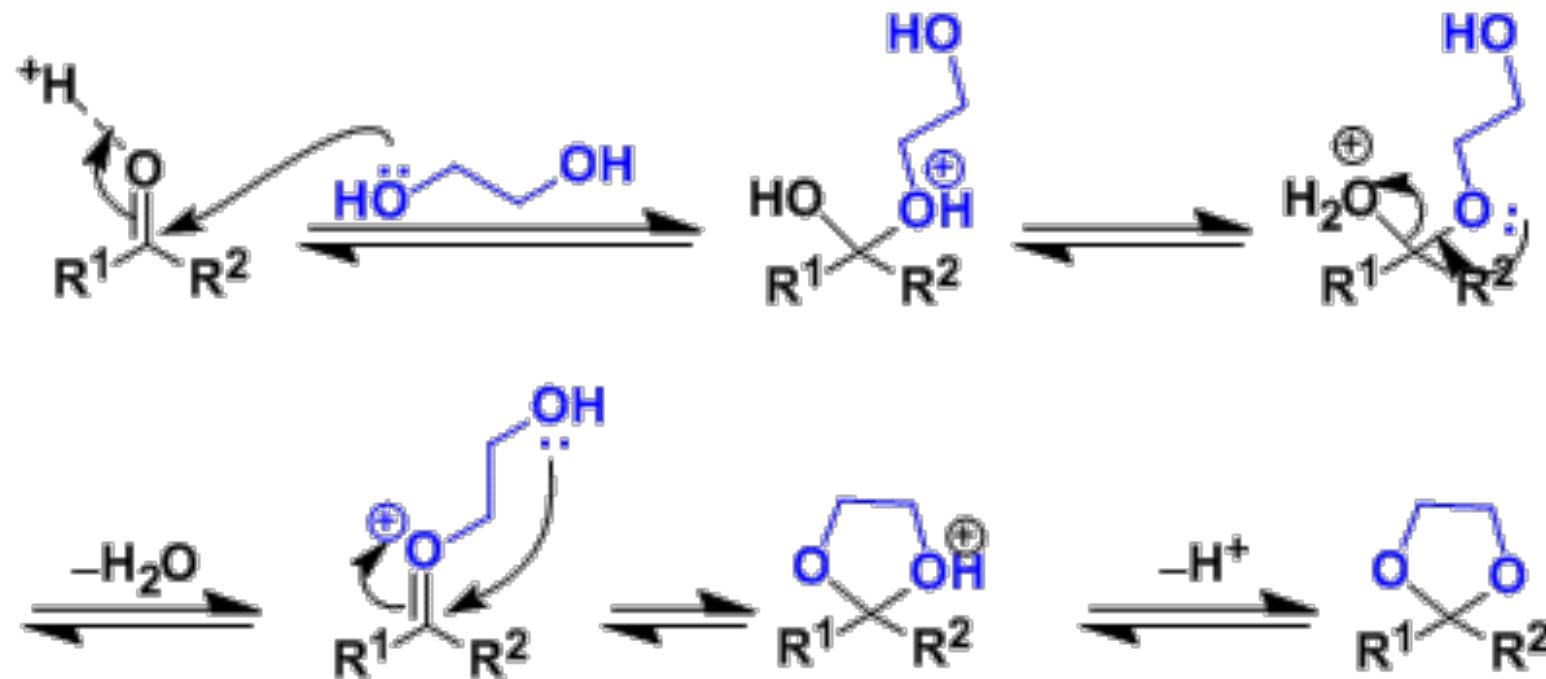
❖ reaction with malonic acid



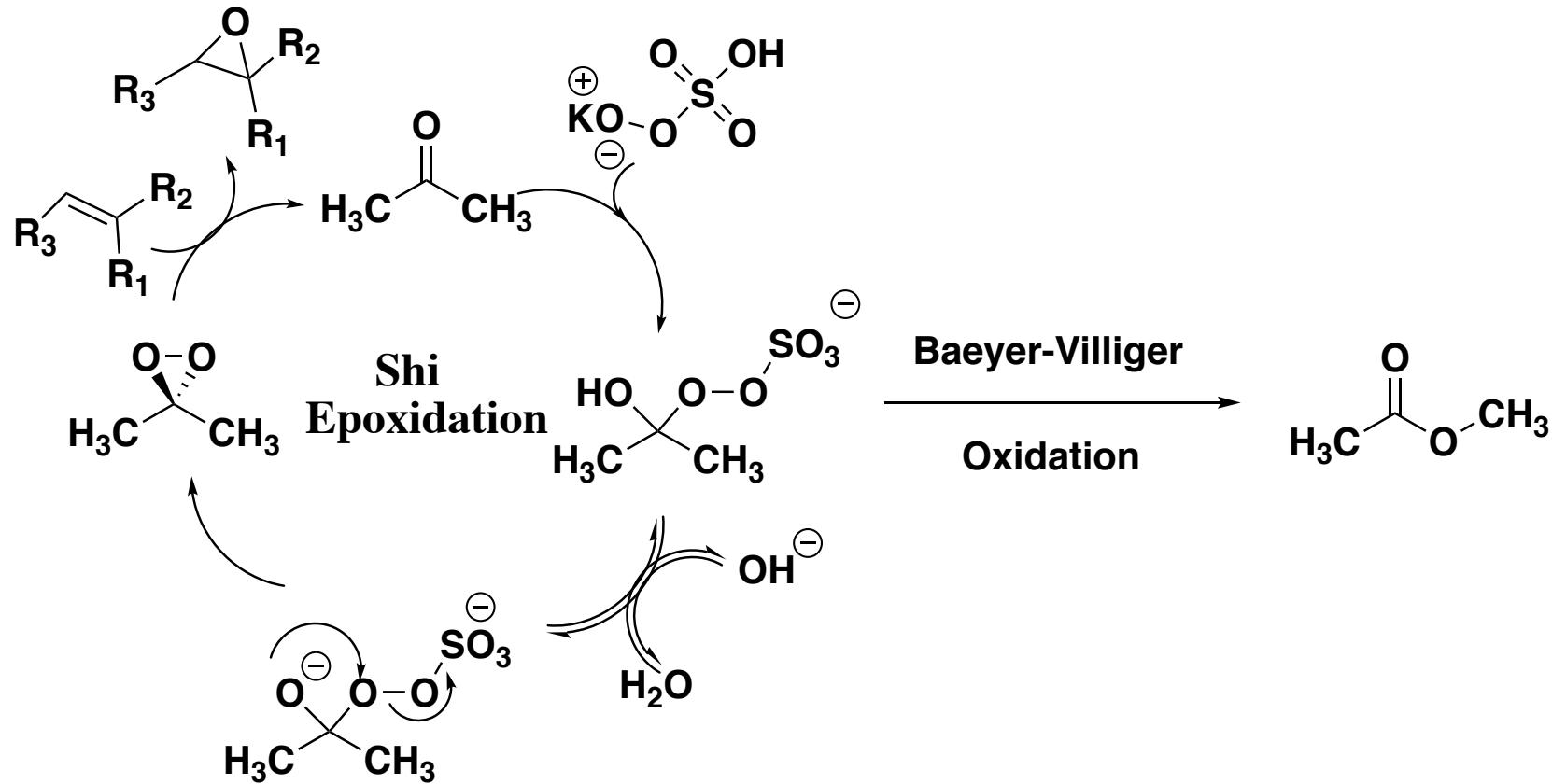
❖ formation of six-membered ring



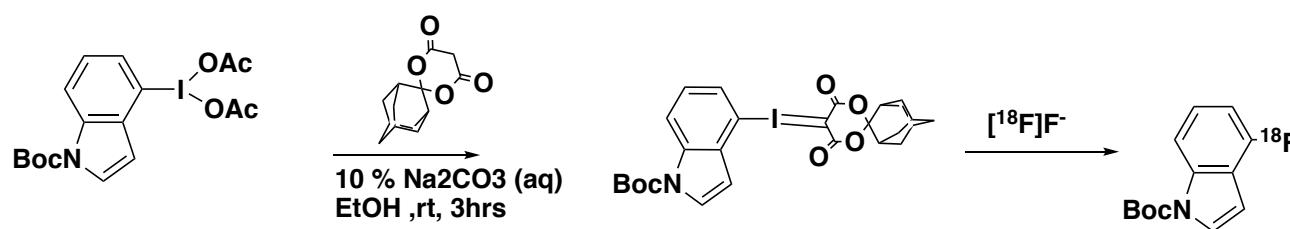
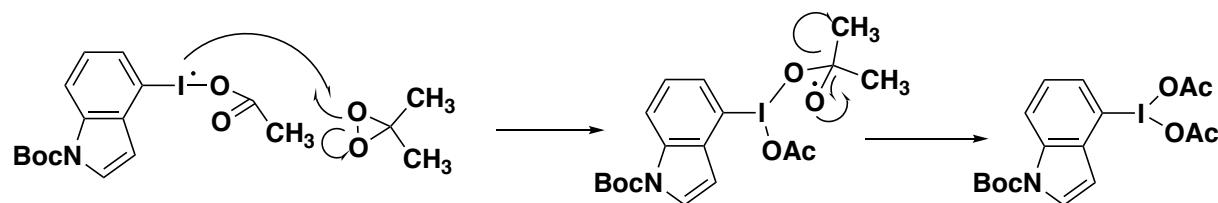
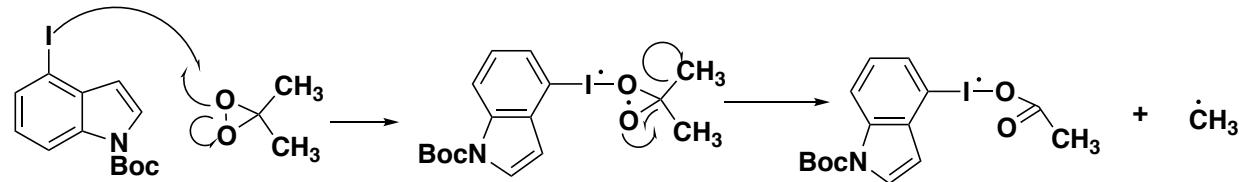
Similar to SPIAD Reaction mechanism



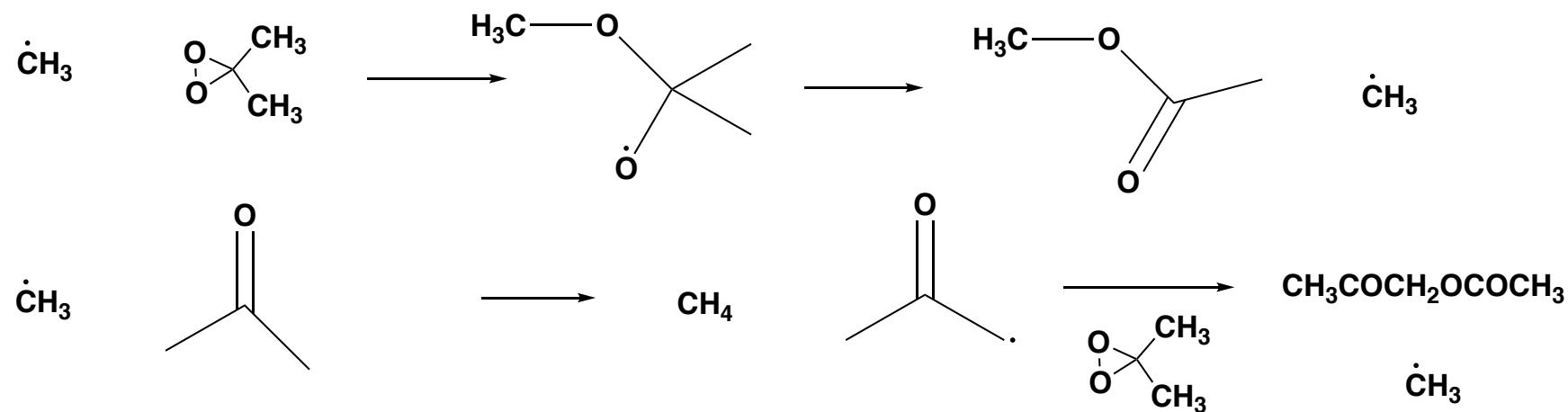
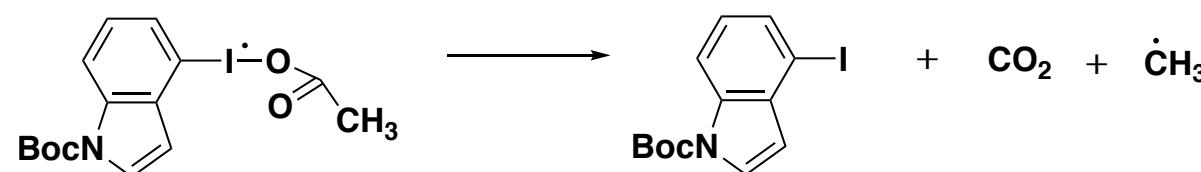
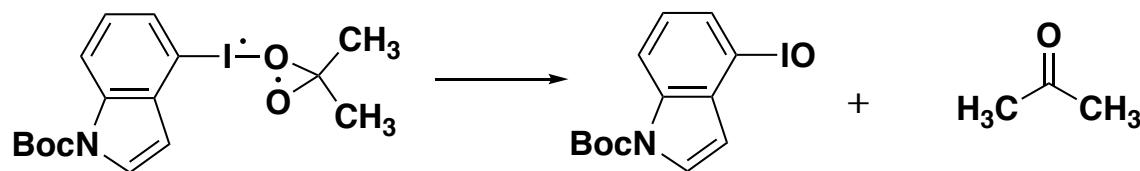
## DMDO Generation: Shi epoxidation



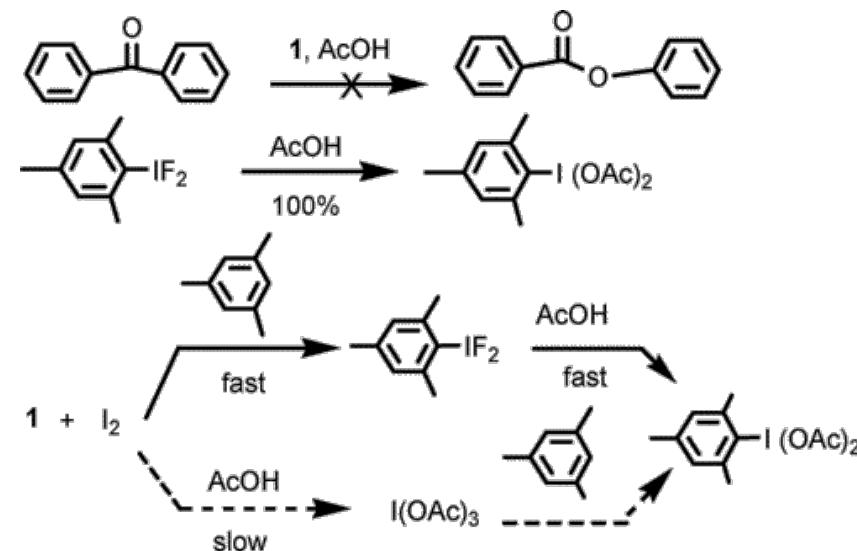
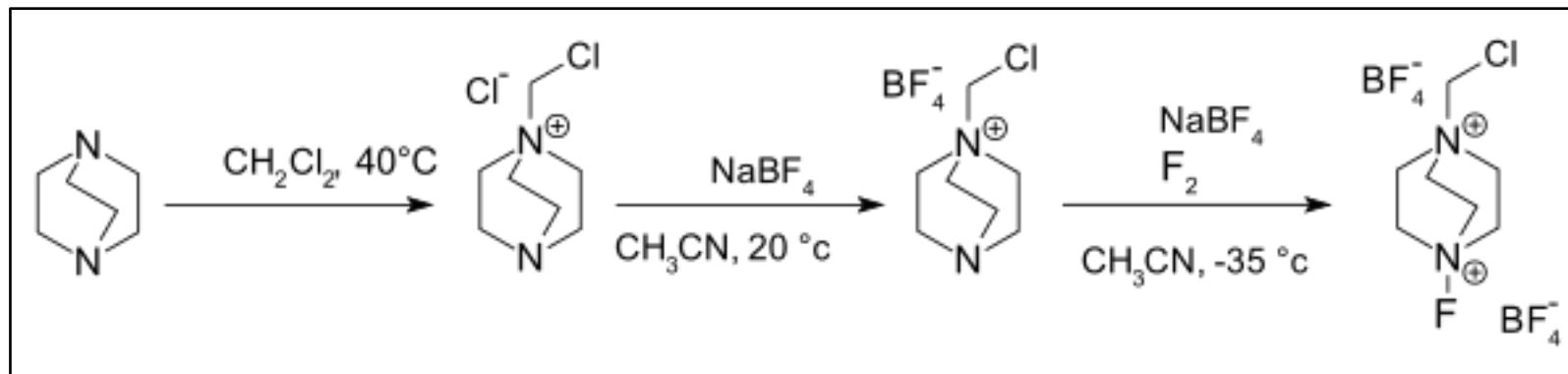
## DMDO Mechanism



## DMDO Side reactions

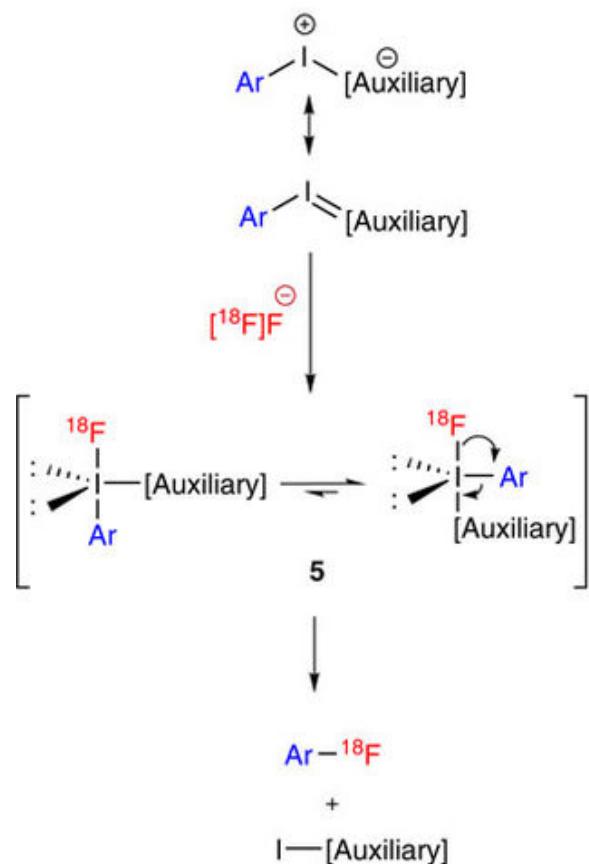


# Synthesis of Selectfluor

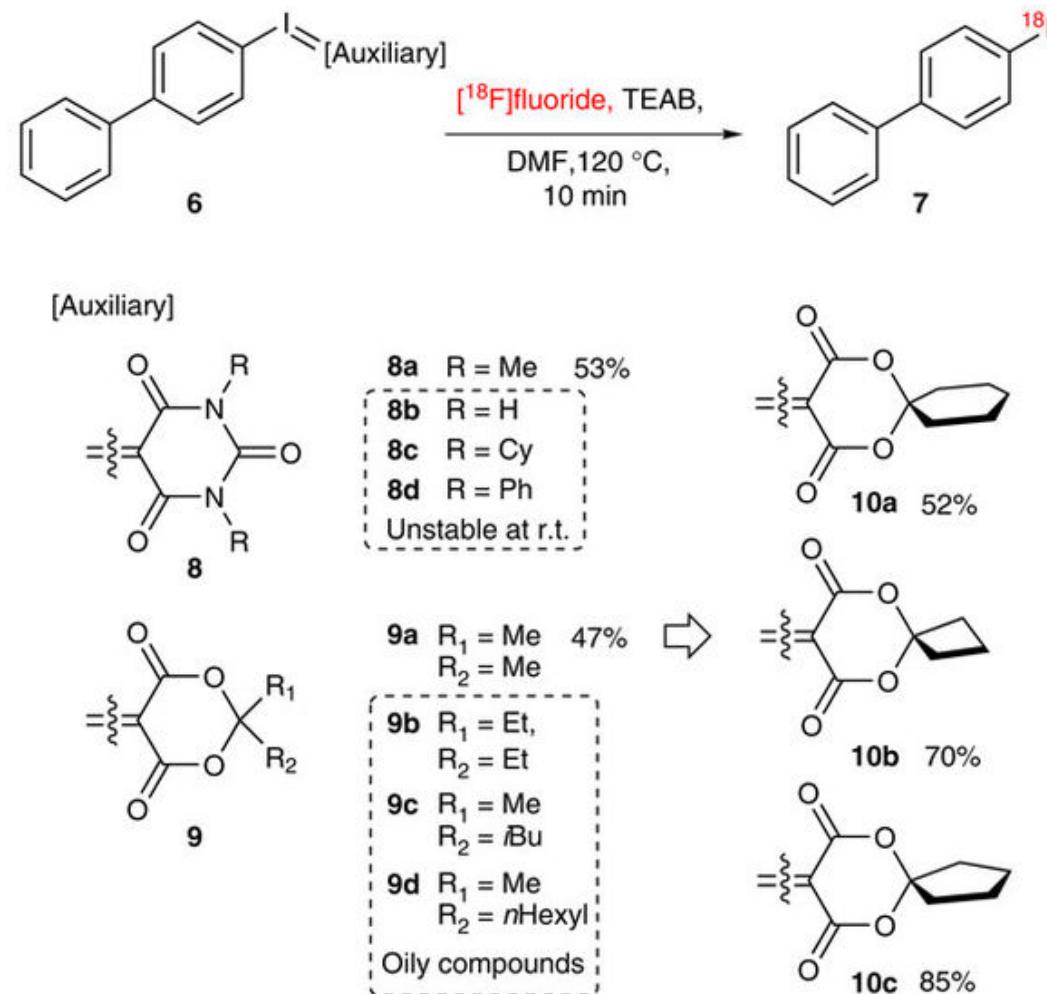


# Development of Auxiliary

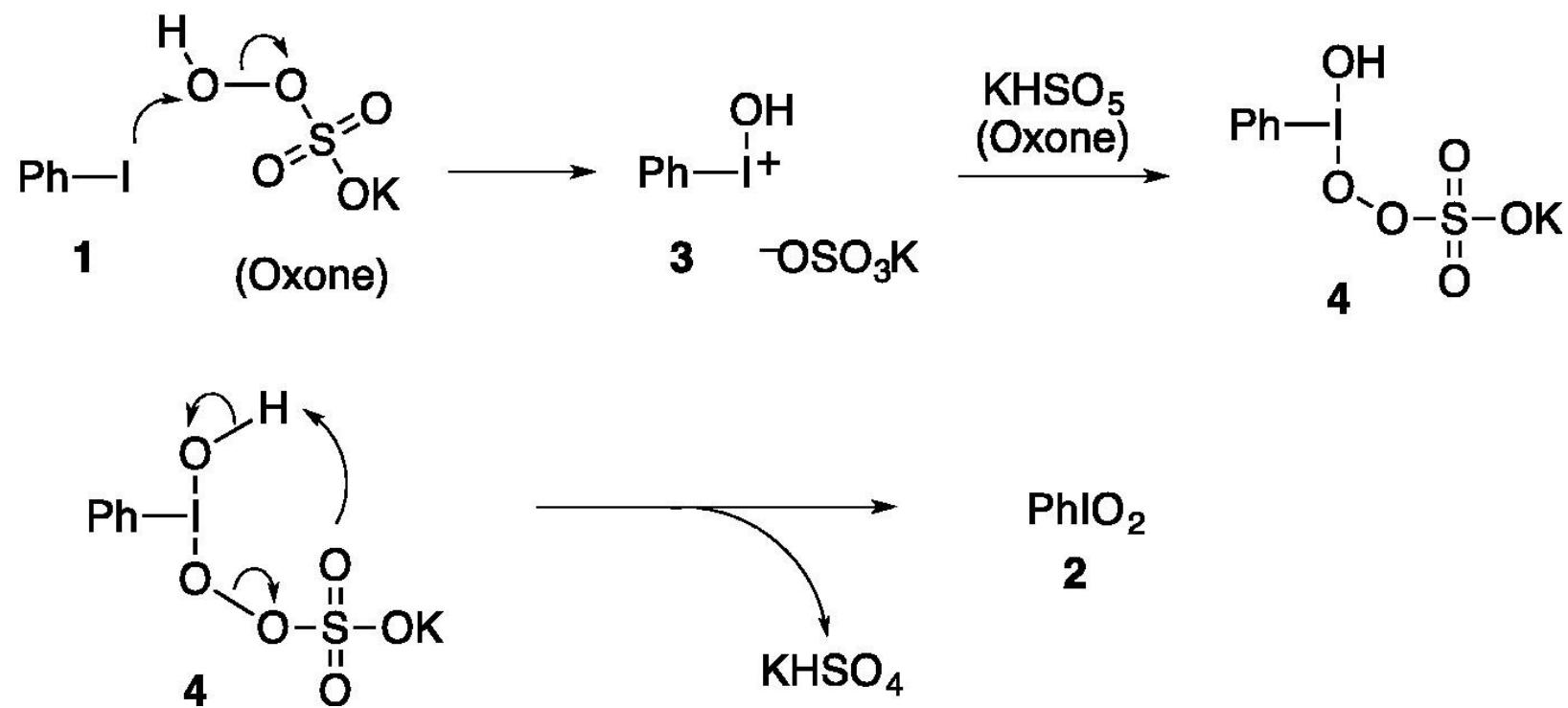
**a** Proposed pathway



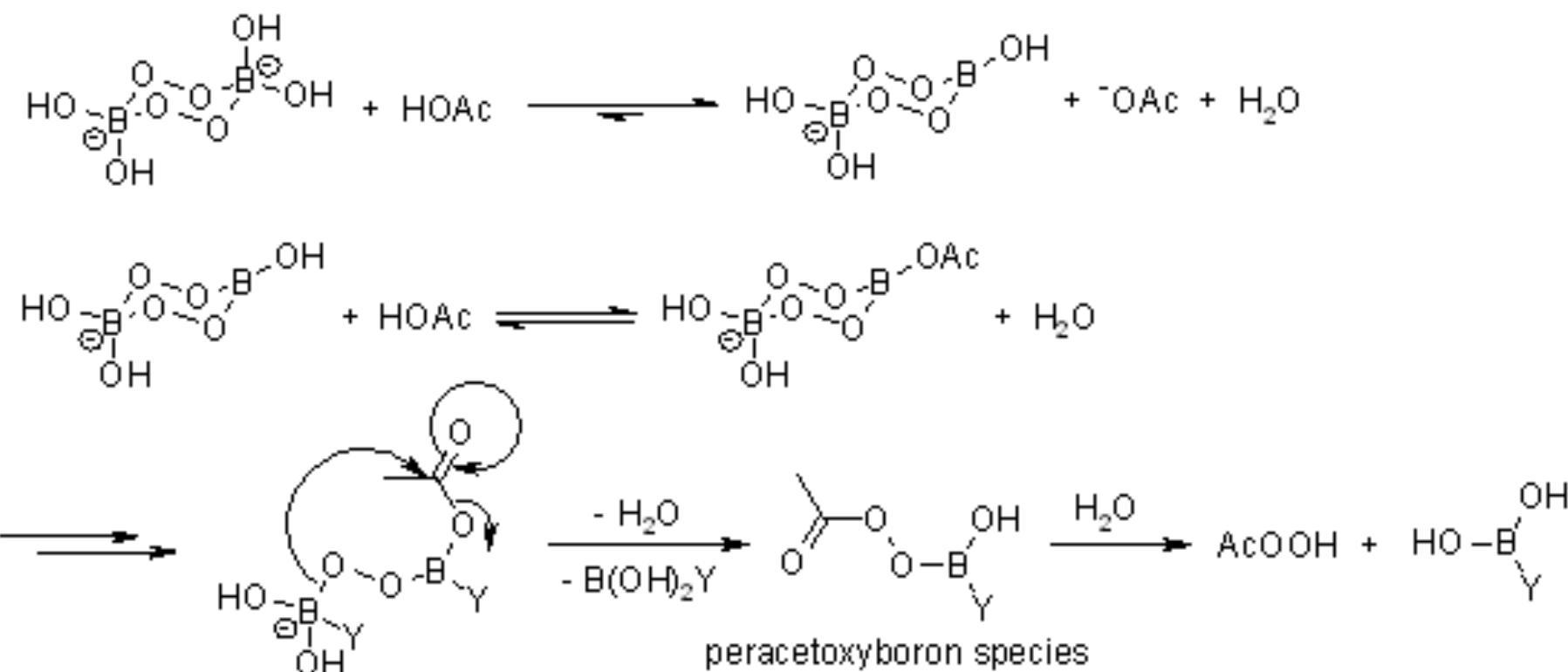
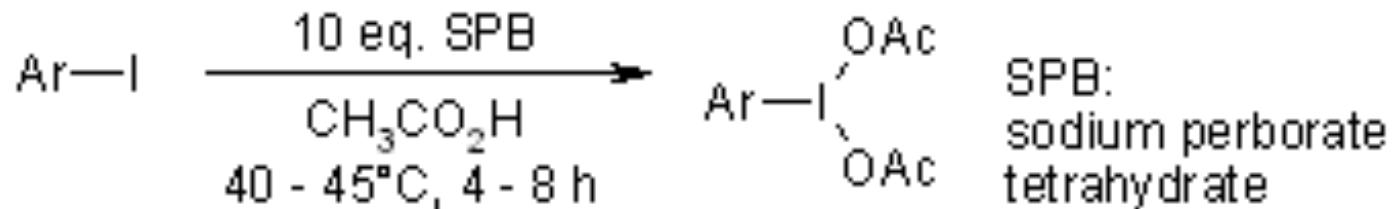
**b** Development of spiroiodine(III) ligands



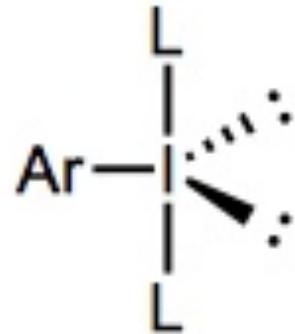
## Oxone+ Iodoarenes



## Perborate Mechanism

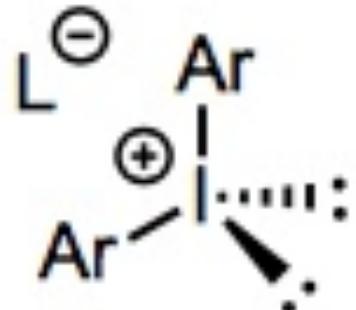


# Hypervalent Iodine



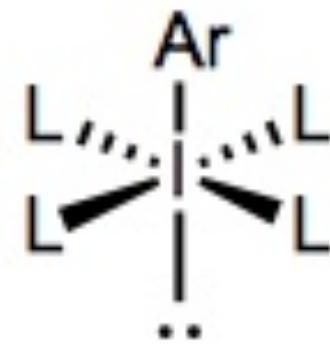
$\lambda^3 - Iodanes$

[10-I-3]



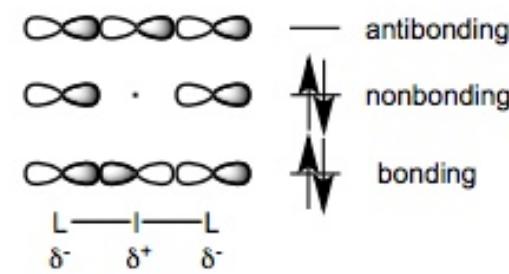
$\lambda^3 - Iodanes$

[8-I-2]



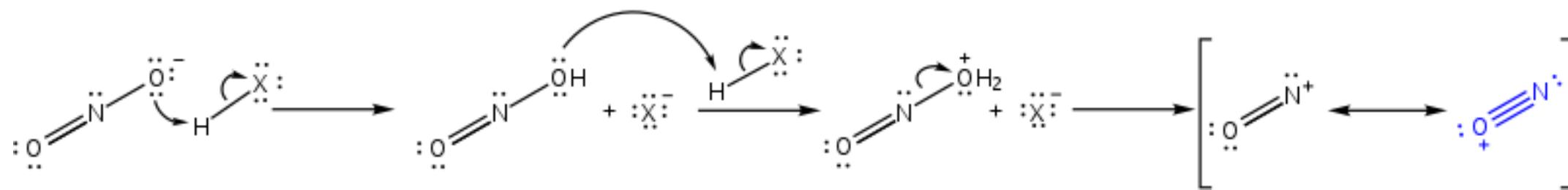
$\lambda^5 - Iodanes$

[12-I-5]

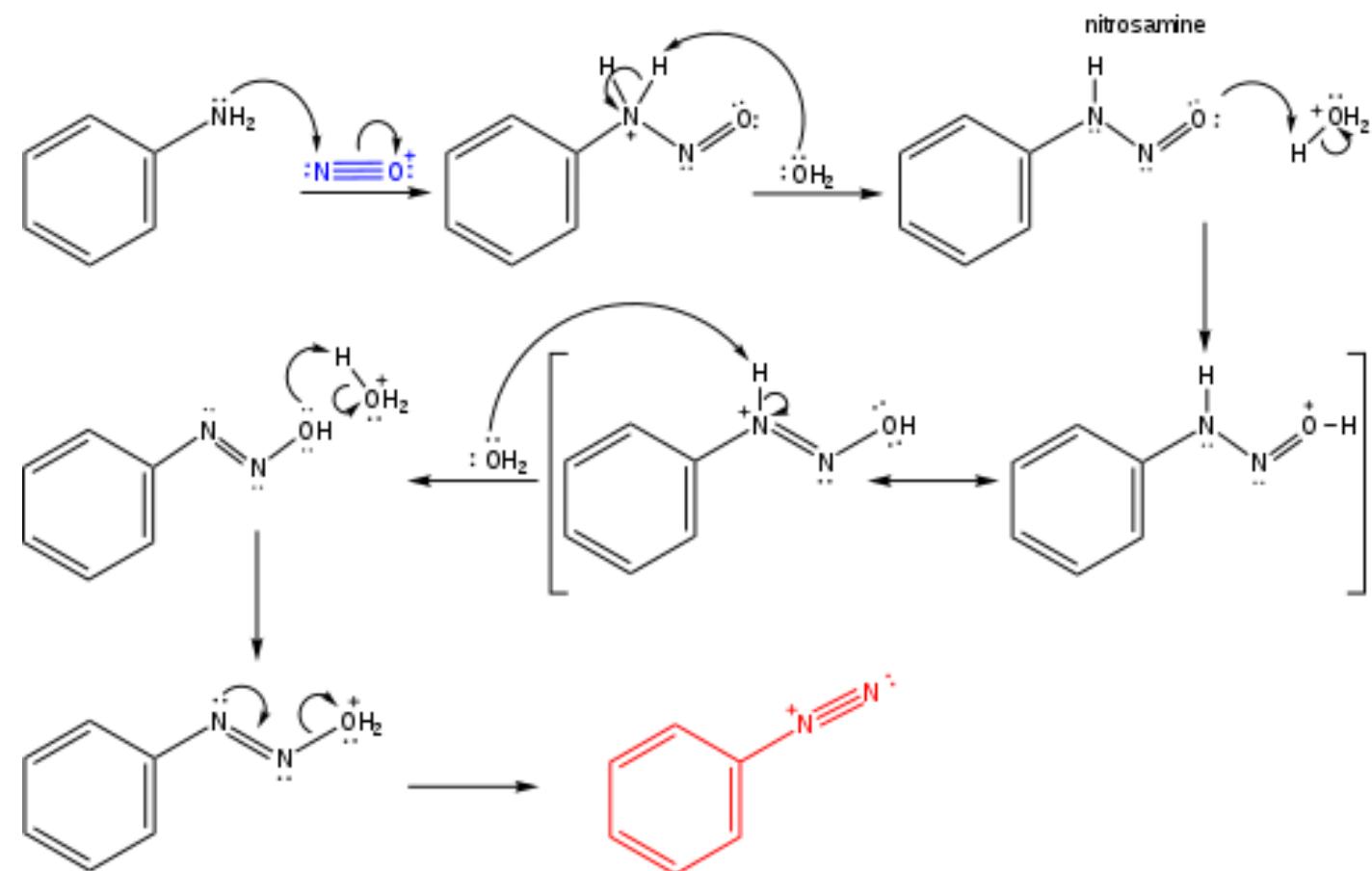


## Problems related to Radiolabeling

1. Several radiosynthetic steps, sensitive functionalities to be labeled. Thus, in spite of the many  $^{18}\text{F}$ -fluorination methods available, a rational design of a labeling concept cannot be set up.
2. Synthesis protocols enabling the large-scale production of  $^{18}\text{F}$ -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  $^{18}\text{F}$  radionuclide.

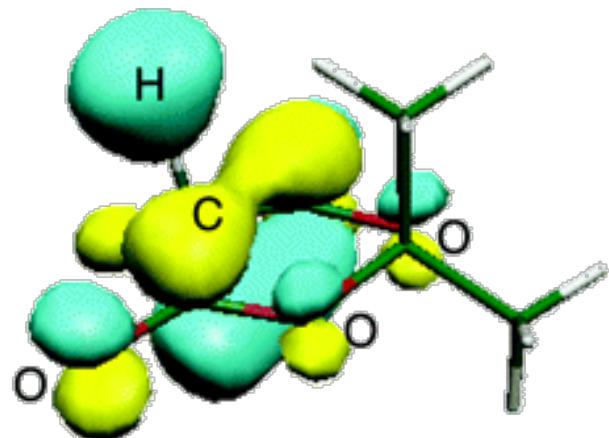


- Nitrous acid is prepared by sodium nitrite
- Nitrosonium ion: an electrophile
- Nitrosamine intermediate

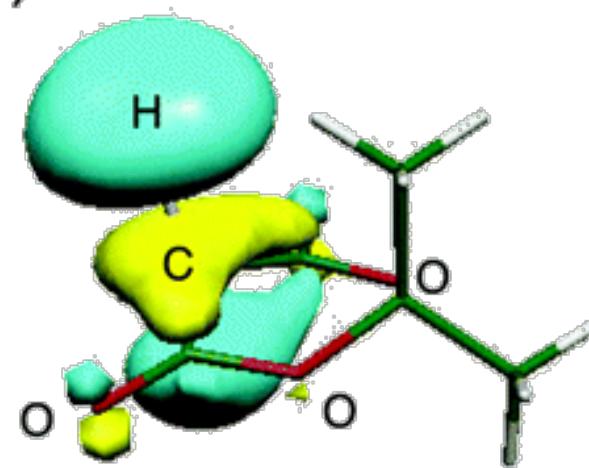


# Meldrum's Acid: $pK_a = 4.83$

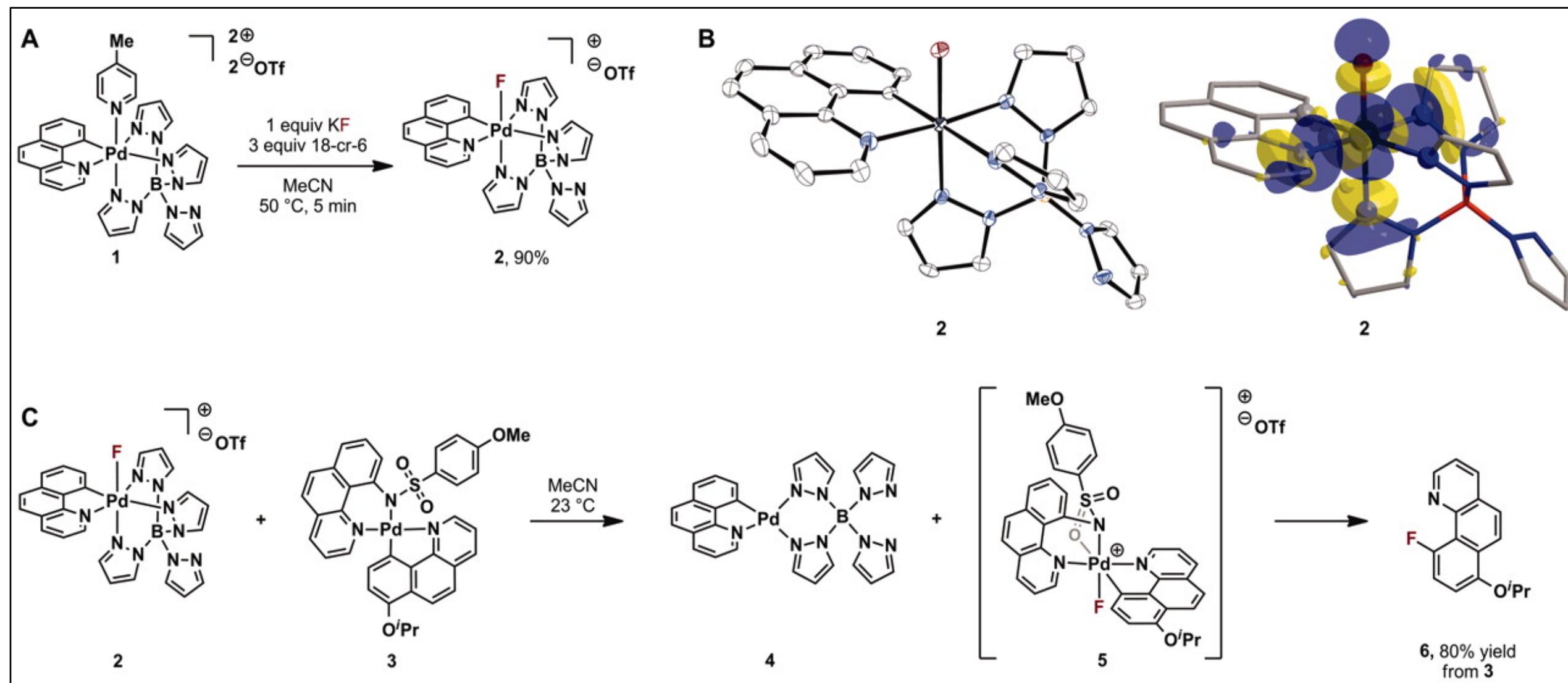
(A)



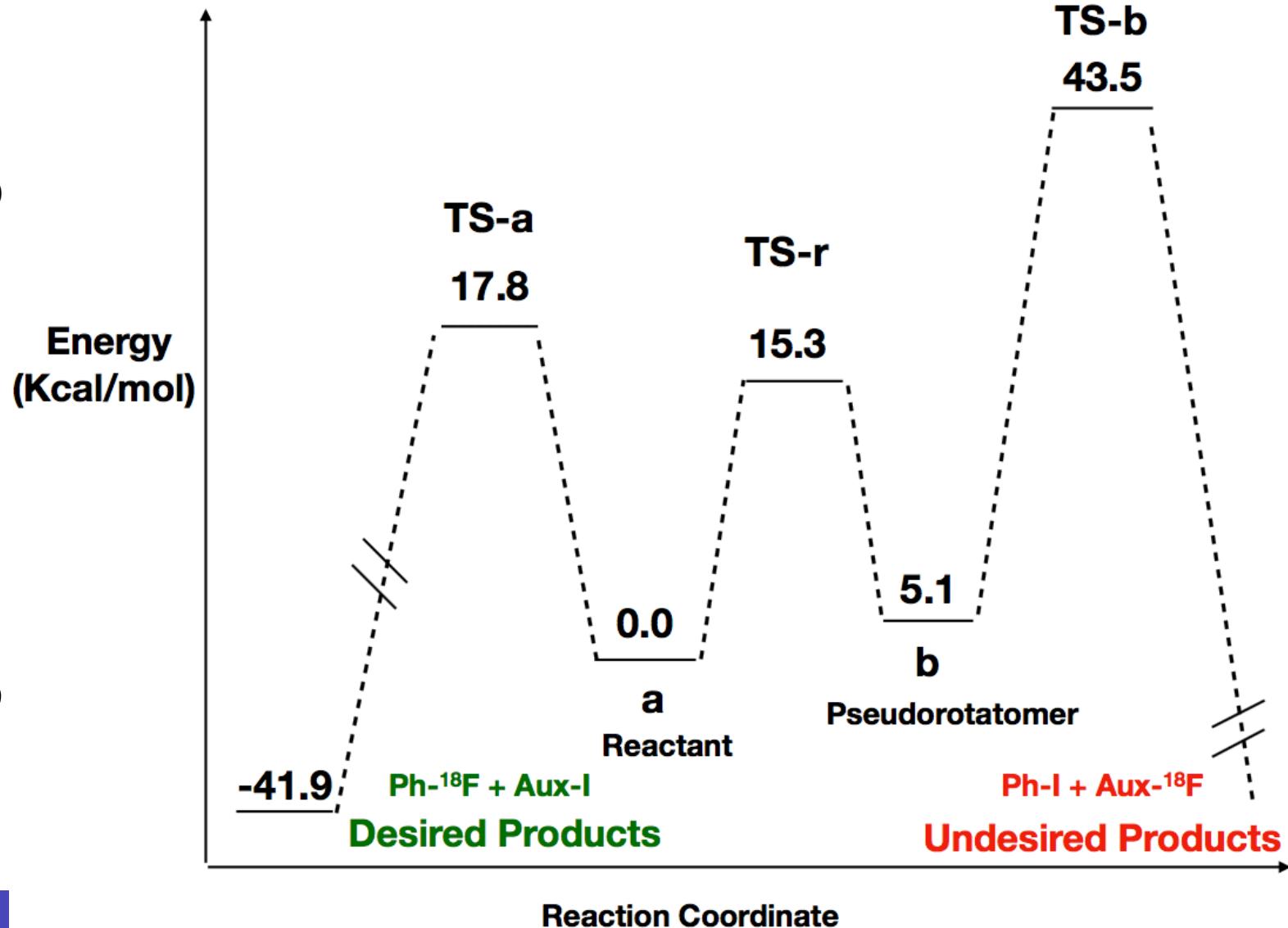
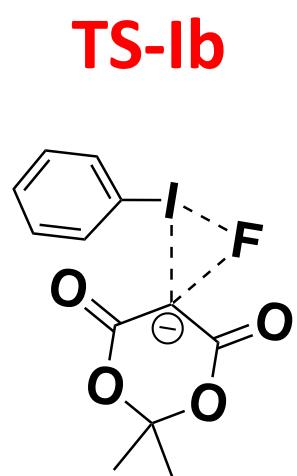
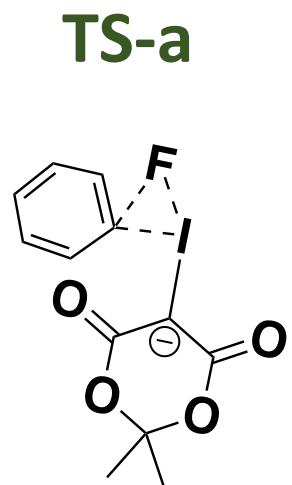
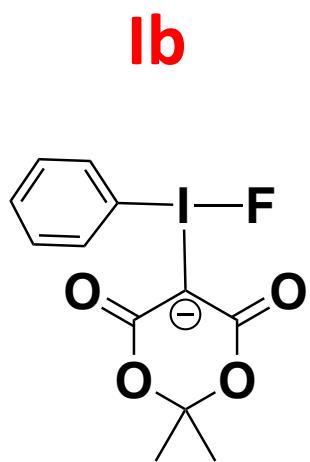
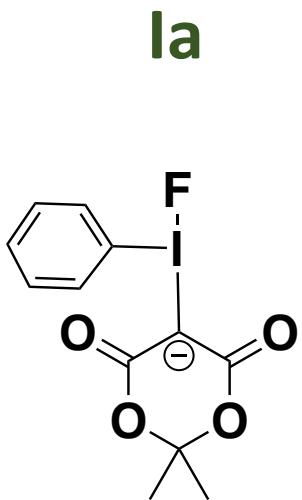
(B)

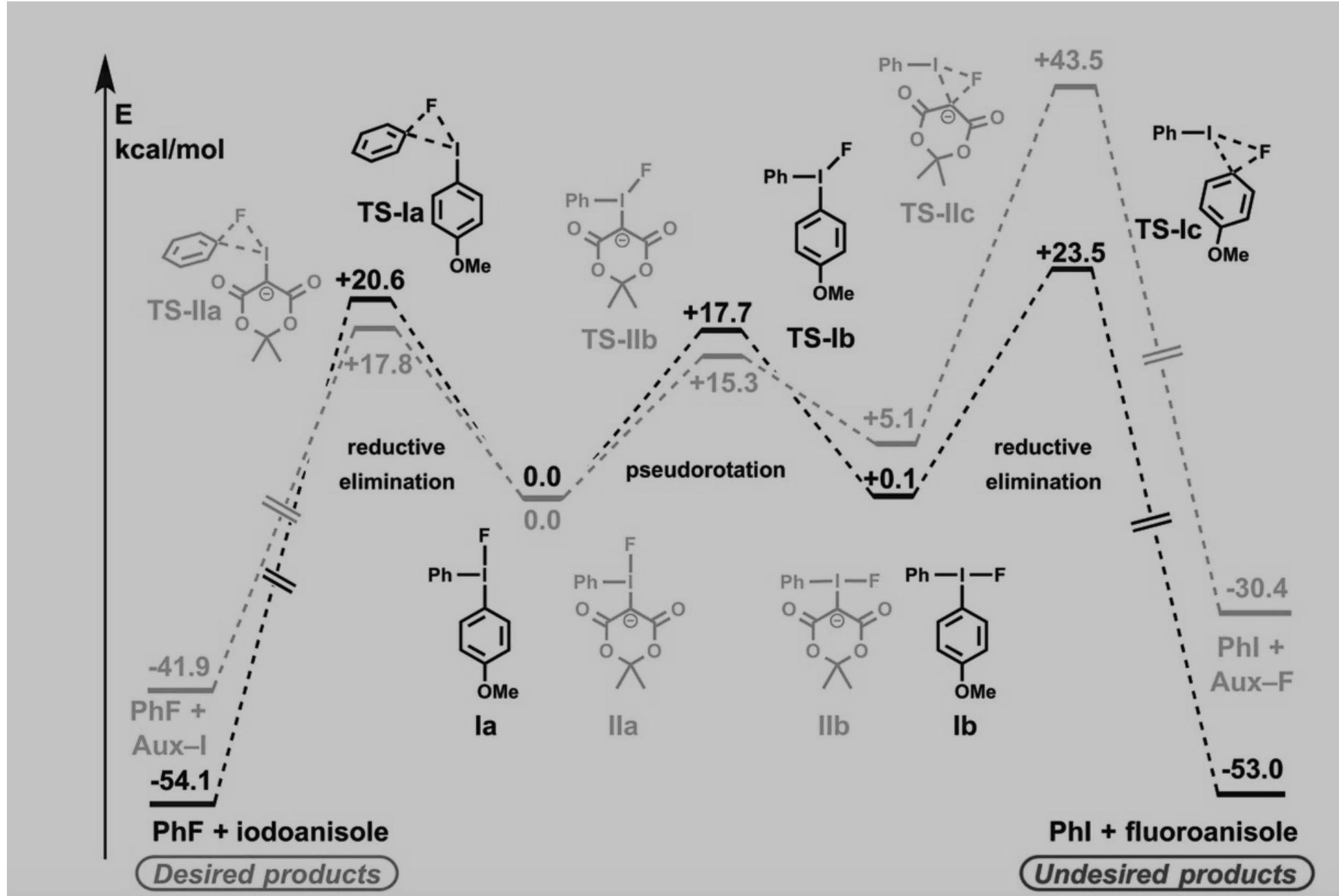


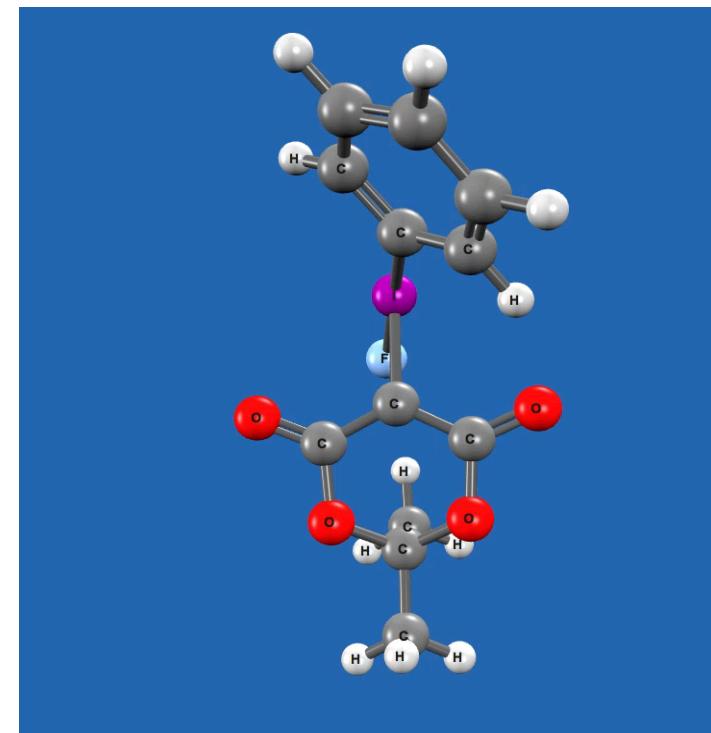
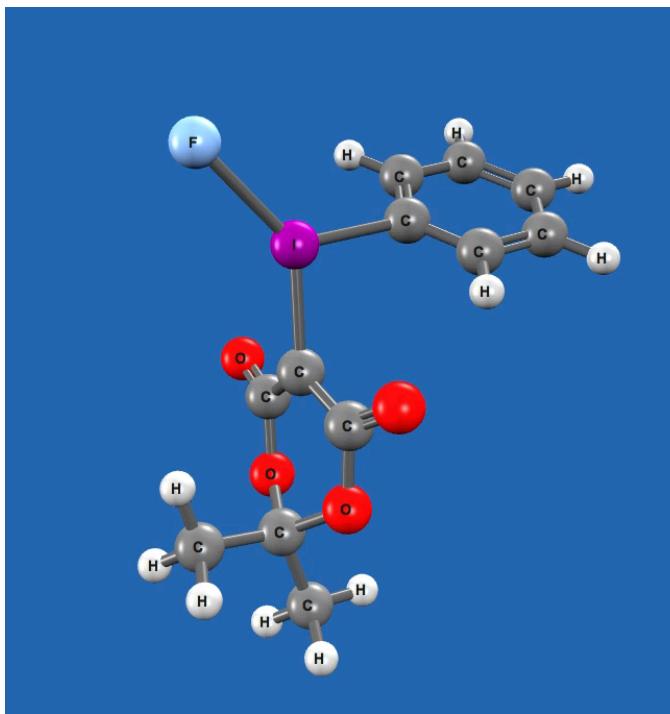
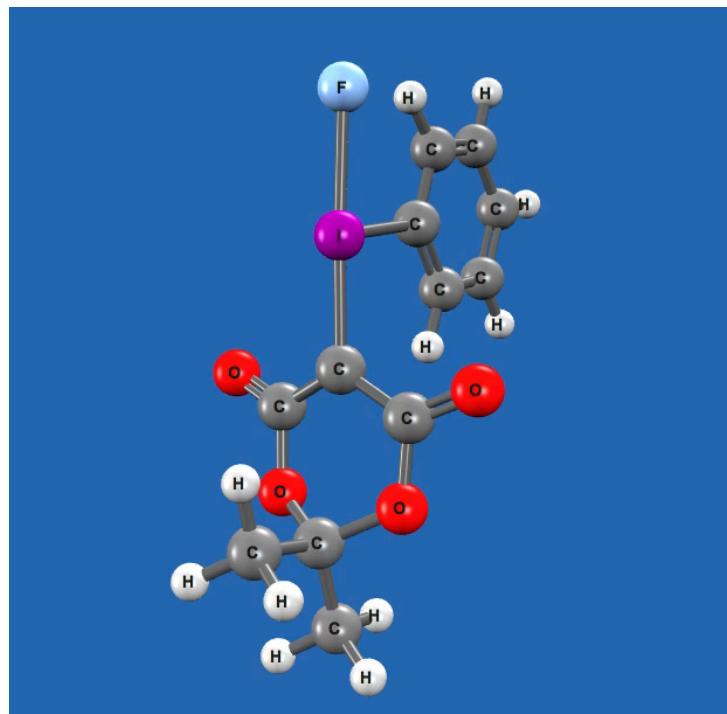
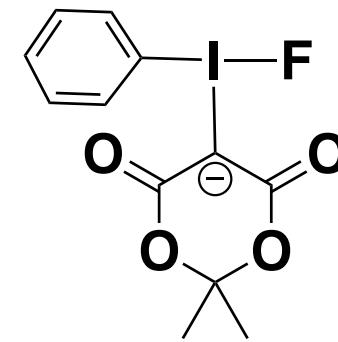
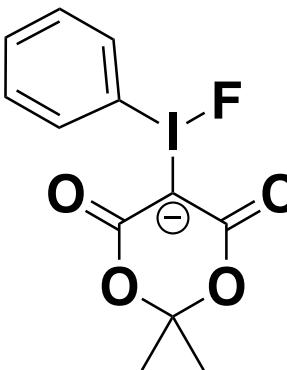
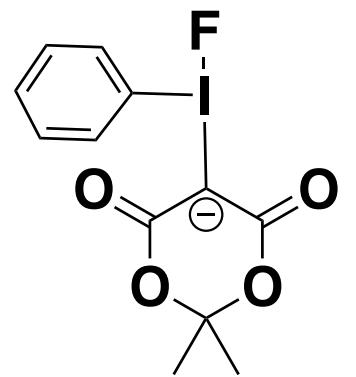
# Transition metal mediated reactions



# Reaction pathways



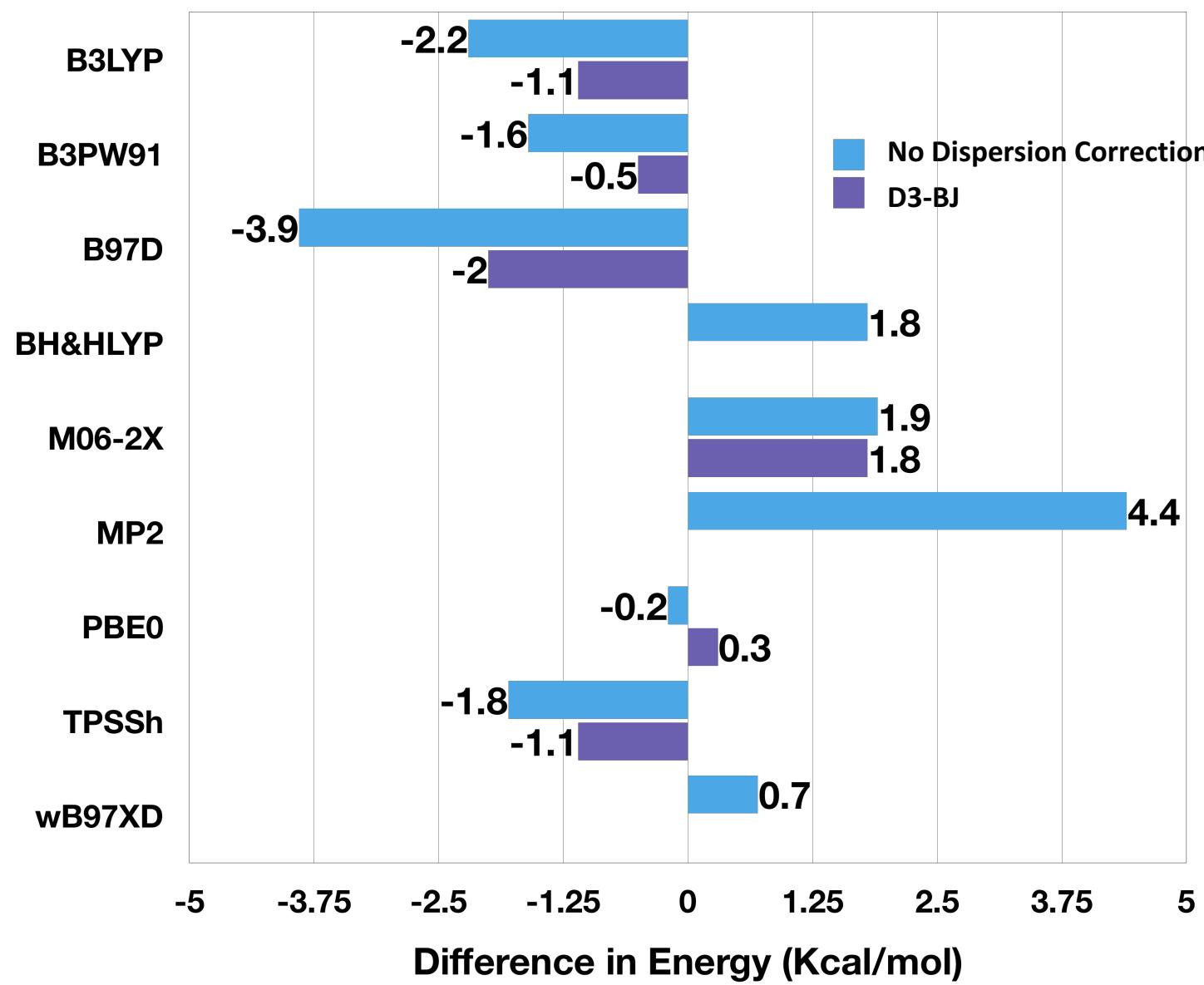




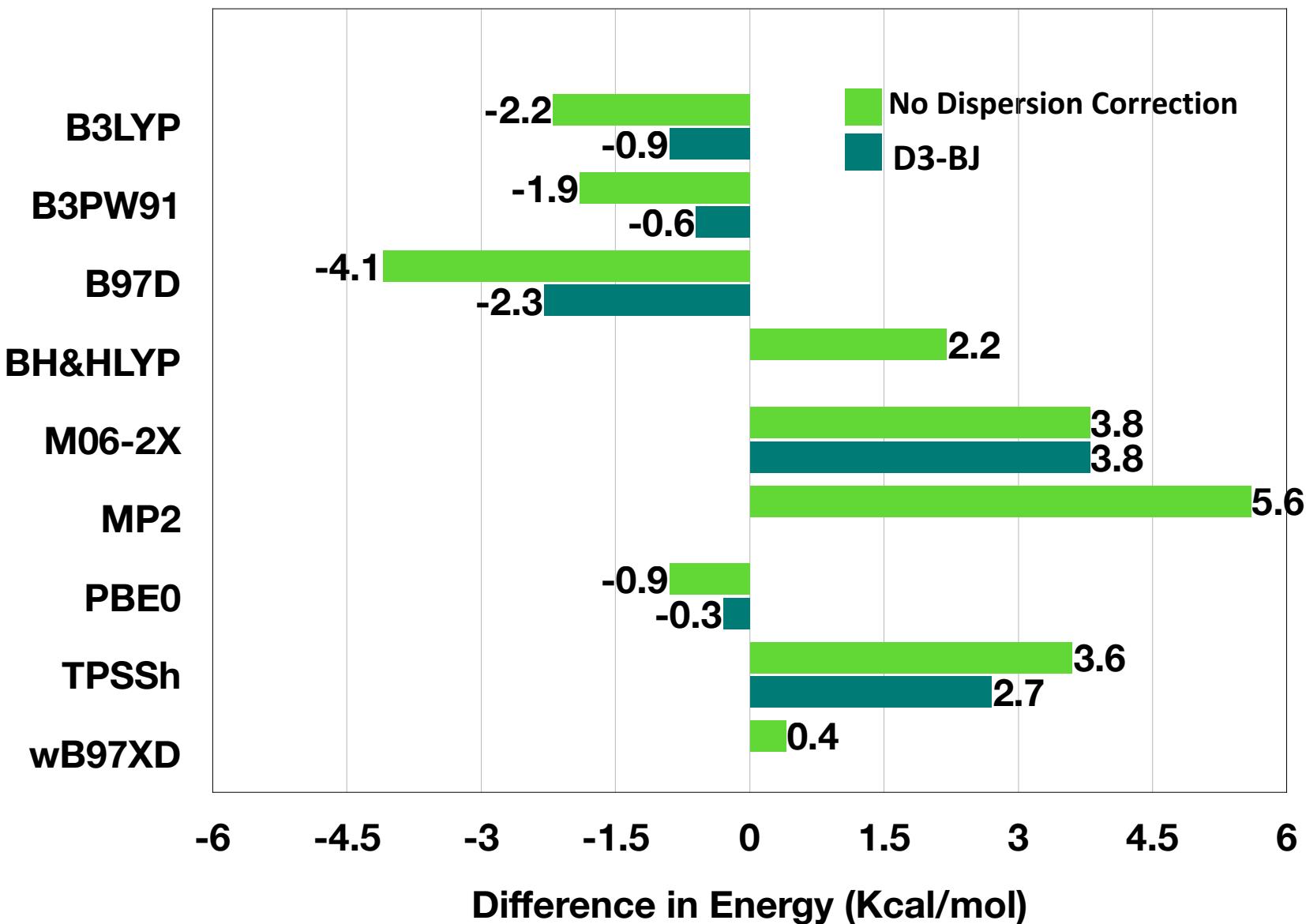
# Computational Details

- 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

Pseudorotation barrier vs G2[ECP]



## Reductive elimination barrier vs G2[ECP]



## 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

# $^{18}\text{F}$ Production

- $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$
- $^{20}\text{Ne}(\text{p},2\text{n})^{18}\text{F}$
- $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$
- $^{20}\text{Ne}(3\text{He},\text{n})^{18}\text{Ne}, ^{18}\text{Ne}-^{18}\text{F}$
- $^{16}\text{O}(\alpha,\text{pn})^{18}\text{F}$
- $^{16}\text{O}(^3\text{He},\text{p})^{18}\text{F}$
- $^6\text{Li}(\text{n},\alpha)^3\text{H}, ^{16}\text{O}(^3\text{H},\text{n})^{18}\text{F}$

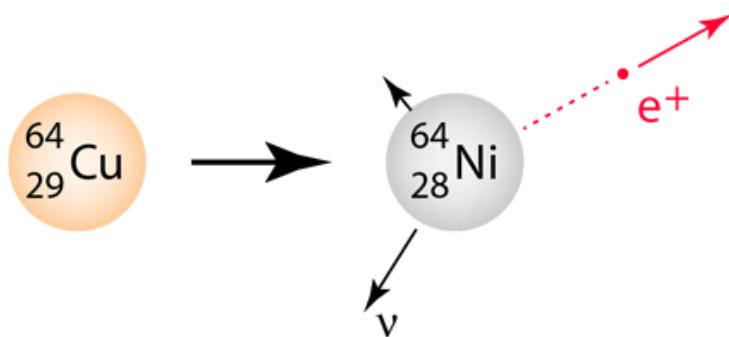
# Radioisotopes for PET imaging

Nuclide	$T_{1/2}$ (min)	Decay	Max Energy (MeV)	Theoretical SA (GBq/ $\mu$ mol)	Decay Product
$^{18}F$	<b>109.77</b>	$\beta^+$ (97 %); EC (3 %)	<b>0.64</b>	$6.3 \times 10^4$	$^{18}O$
$^{11}C$	20.38	$\beta^+$ (99 %)	0.97	$3.4 \times 10^5$	$^{11}B$
$^{13}N$	9.96	$\beta^+$ (100 %)	1.20	$7.0 \times 10^5$	$^{13}C$
$^{15}O$	2.03	$\beta^+$ (100 %)	1.74	$3.4 \times 10^6$	$^{15}N$

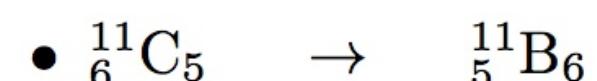
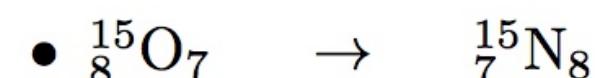
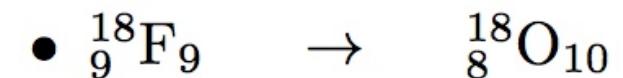
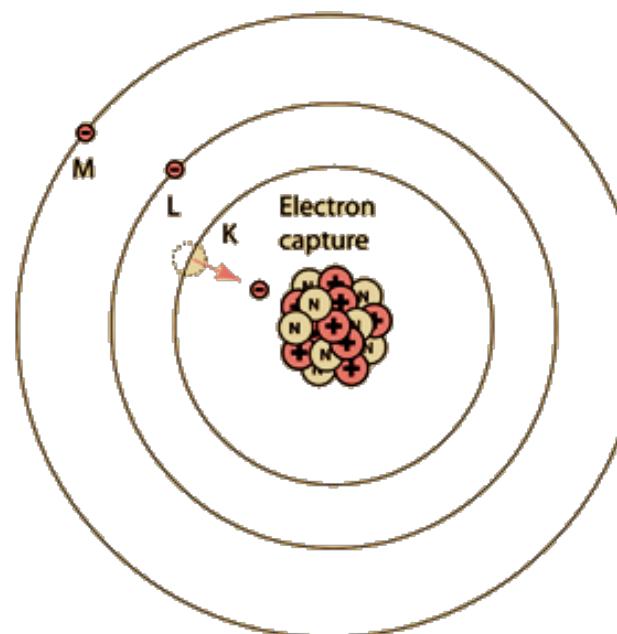
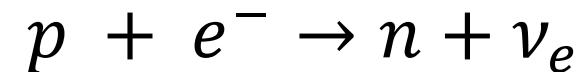
# Radioactive decay in PET

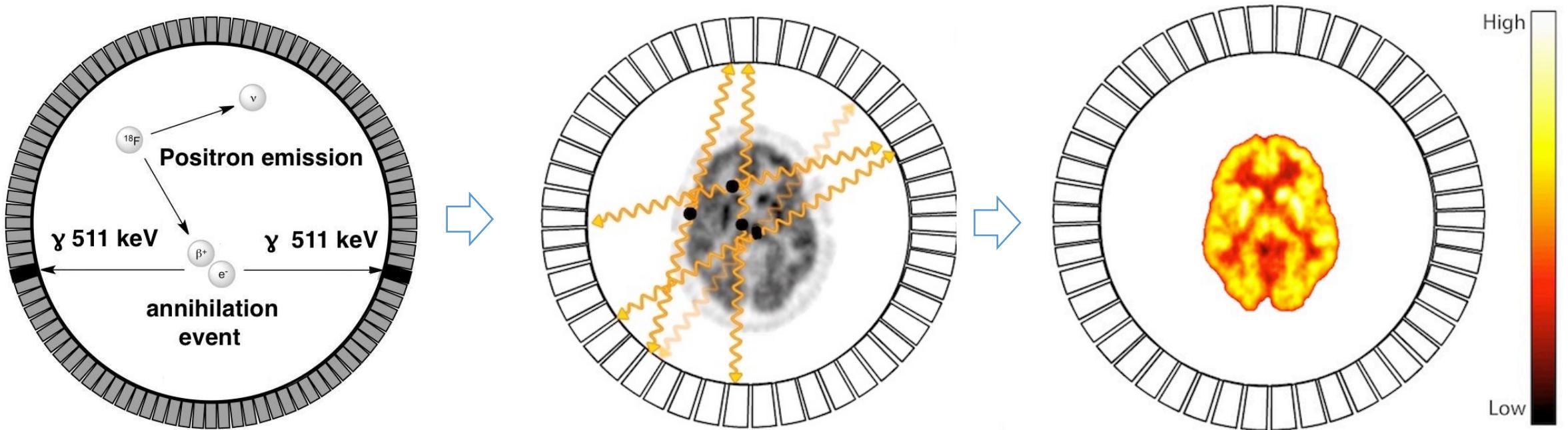
## Examples

### A. Positron emission

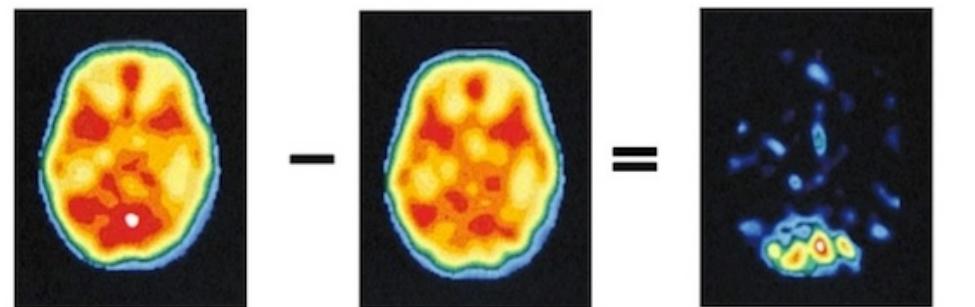


### B. Electron capture



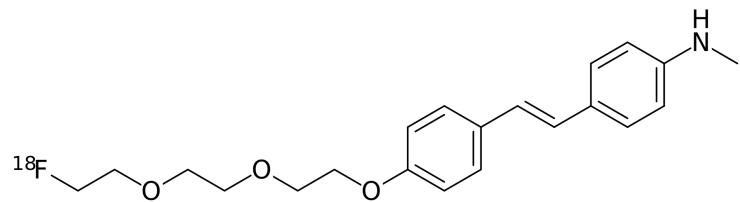


- Speed of light:  $3.00 \times 10^8 \text{ m/s}$
- Mass of an electron/positron:  $9.11 \times 10^{-31} \text{ Kg}$
- $E = mc^2$
- $E = 9.11 \times 10^{-31} \times (3.00 \times 10^8)^2 / 1.60 \times 10^{-19} \text{ eV}$
- ➔  $511 \text{ keV} \times 2$

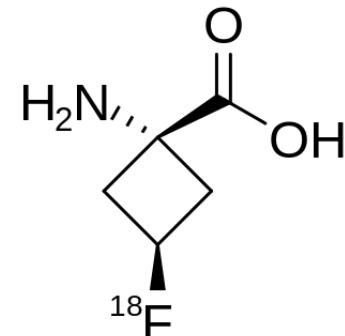


Experiment      Control      Difference

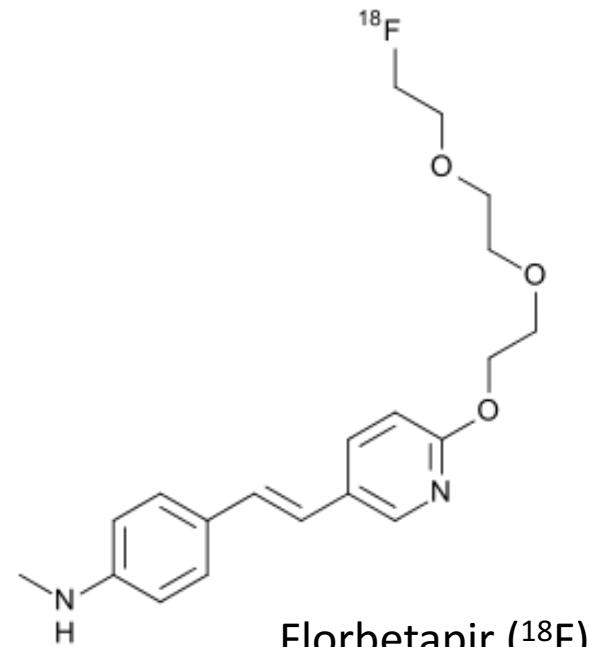
# FDA approved radiotracers



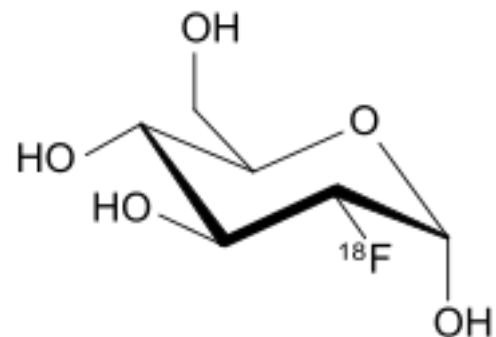
Florbetaben (<sup>18</sup>F)



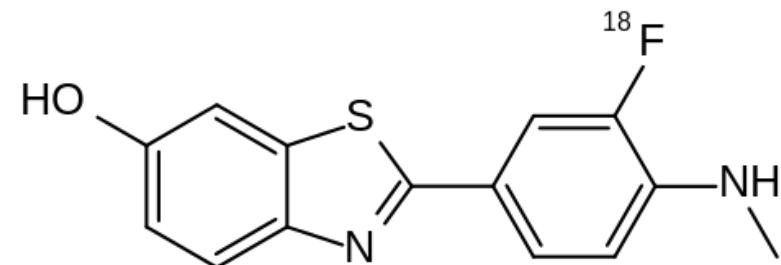
Fluciclovine



Florbetapir (<sup>18</sup>F)

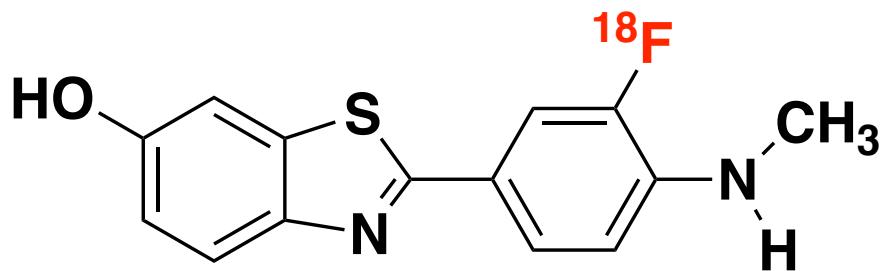


<sup>18</sup>FDG



Flutemetamol

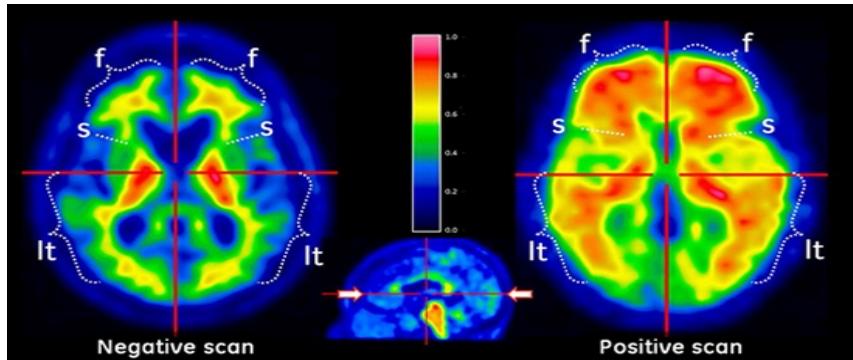
# Biomedical Imaging



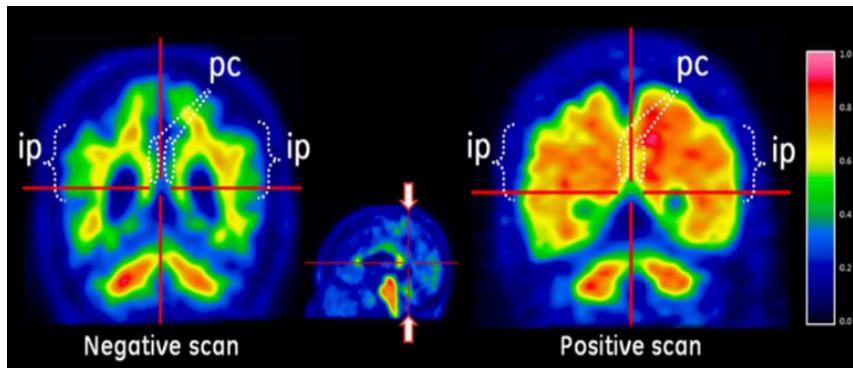
[<sup>18</sup>F]Flutemetamol

- Half life of <sup>18</sup>F is 109.77 mins
- Labeling time < 60 mins
- Intravenous dose at PET-CT site

Axial View



Coronal View



Sagittal View

