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

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Liang et al. *Chem. Sci.*, 2016, 7, 4407

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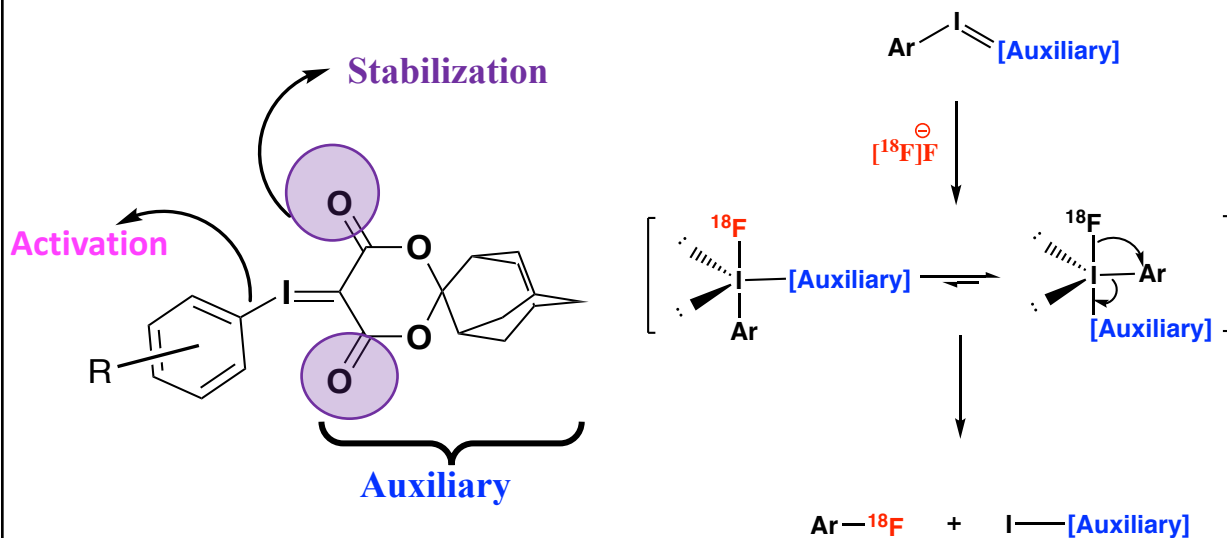
## Outline

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

Background

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## Spirocyclic Iodonium(III) Ylides

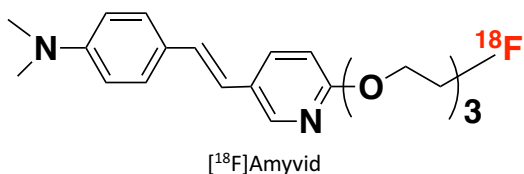
Liang et al. *Nat. Commun.*, 2014, 5, 4365–4371

Background

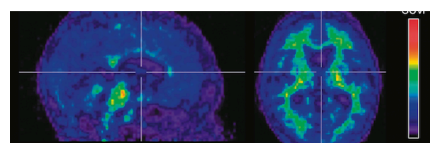
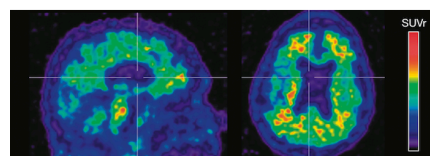
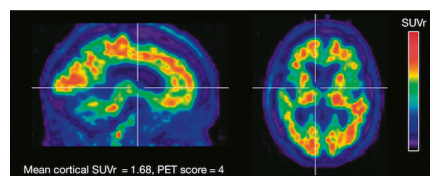
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## Long Term Objective

Development of  $^{18}\text{F}$  based radiotracers

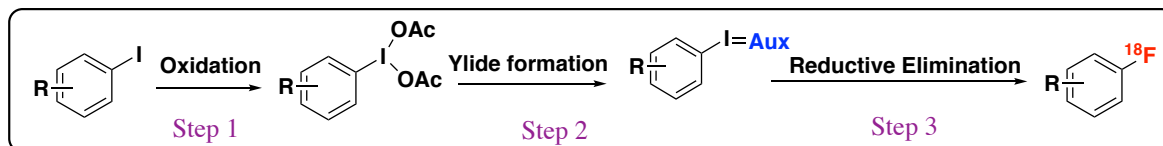


- Half life of  $^{18}\text{F}$  is 109.77 min
- Labeling time < 60 mins

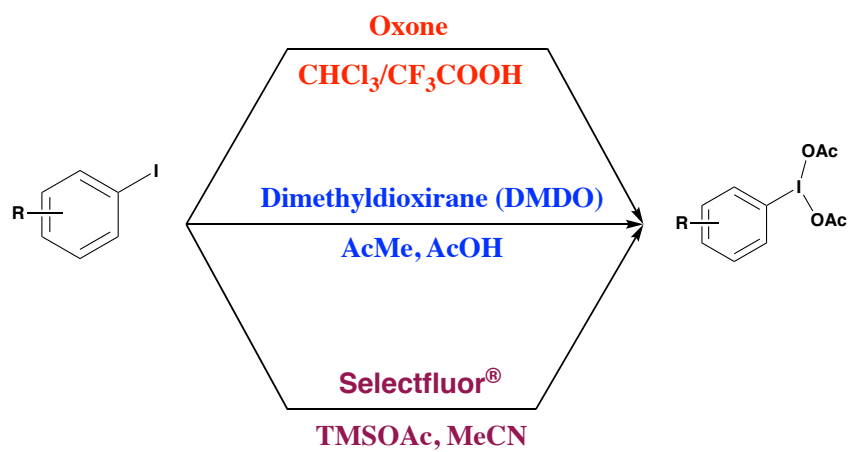
a) No  $\beta$ -amyloid plaquesb) Moderate load of  $\beta$ -amyloid plaquesc) High load of  $\beta$ -amyloid plaquesLin Zhu et al. *Science*, 2013, 342, 429–430



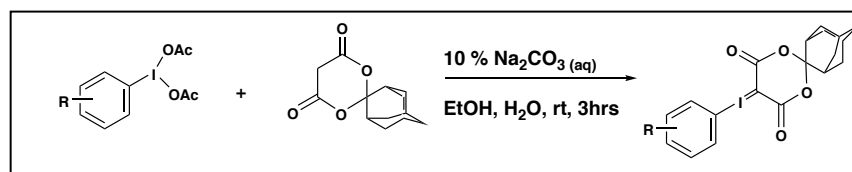
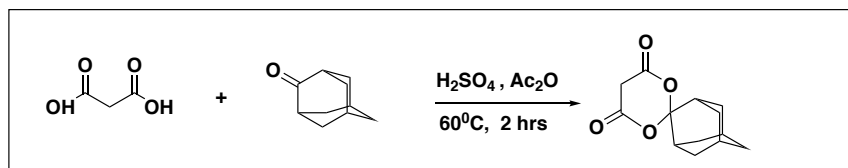
## Reaction Scheme

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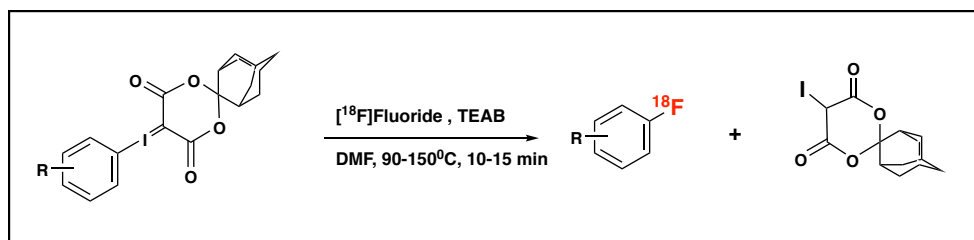
## Step 1: Oxidation

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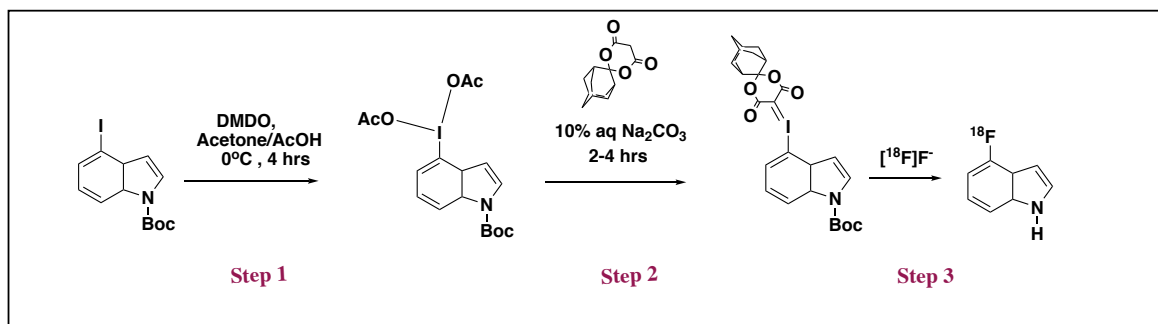
## Step 2: Ylide Formation

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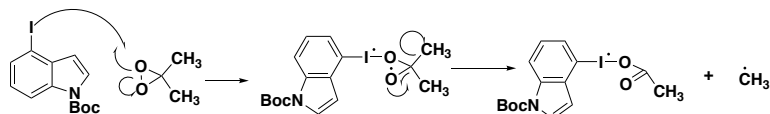
## Step 3: Reductive Elimination

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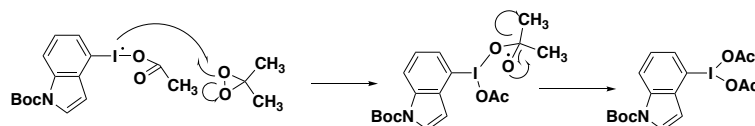
## Synthesis of [ $^{18}\text{F}$ ]Indoles

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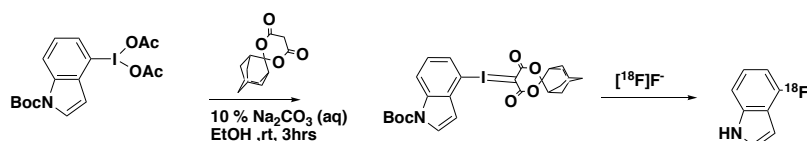
❖ Free radical decomposition of dioxirane leading to generation of methyl radical



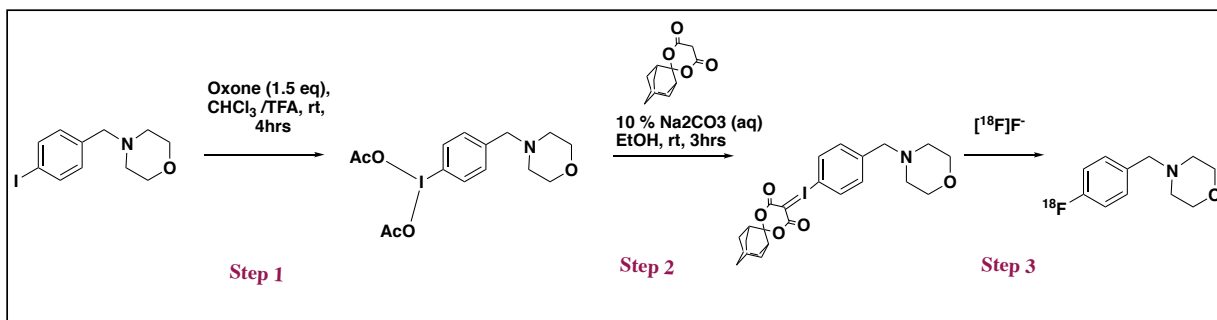
❖ Formation of iodoacetate by using second DMDO equivalent



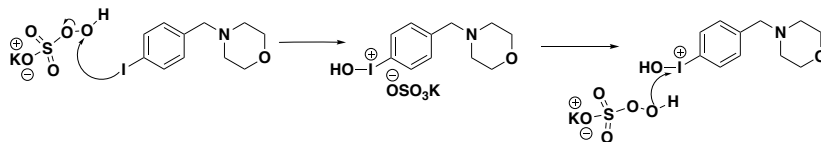
❖ Ylide formation and subsequent reductive elimination

Bravo et al. *Tetrahedron Letters*, 1995, 36, 38, 6945-6948

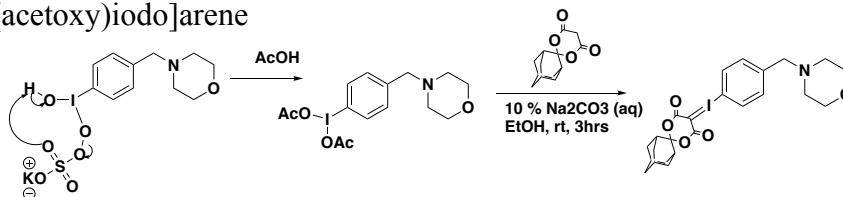
## Synthesis of [ $^{18}\text{F}$ ]Drug Scaffold: Mosapride

Liang et al. *Chem. Sci.*, 2016, 7, 4407

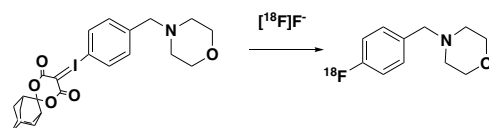
❖ potassium peroxymonosulfate as an oxidizing agent



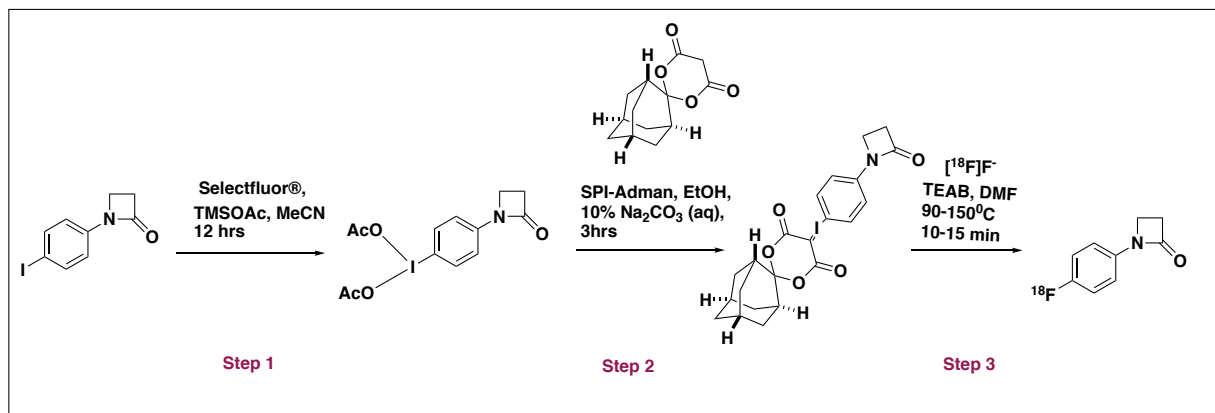
❖ formation of [bis(acetoxy)iodo]arene



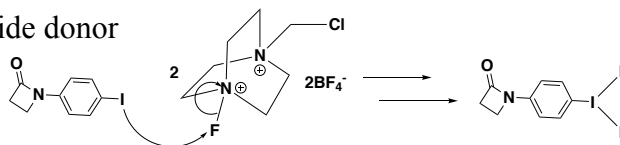
❖  $^{18}\text{F}$  labeling by reductive elimination

Zhdarkin et al. *J. Org. Chem.*, 2010, 75, 2119-2122

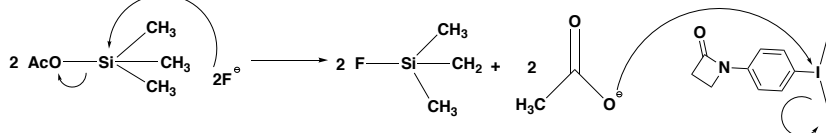
# Synthesis of [ $^{18}\text{F}$ ]Drug Scaffold: Ezetimibe

Liang et al. *Chem. Sci.*, **2016**, 7, 4407

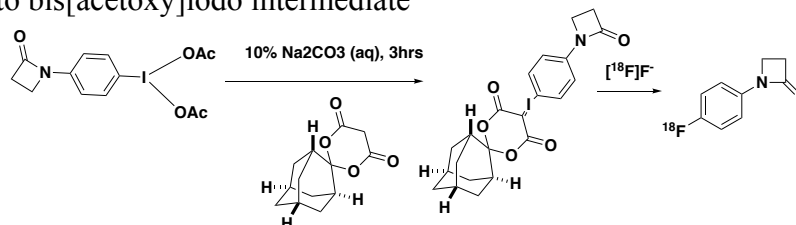
❖ Selectfluor® acts as fluoride donor



❖ TMSOAc acts as Lewis acid to capture fluoride.



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

Linstad et al. *Org. Biomol. Chem.*, **2017**, 15, 2246-2252



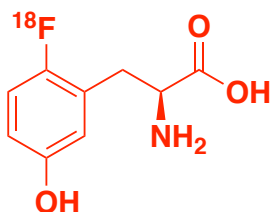
## Results

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

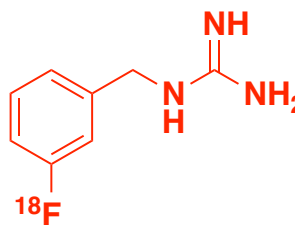
(Cerebral dopamine transport)



Radiochemical yield: 12%

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

(Neuroblastoma)



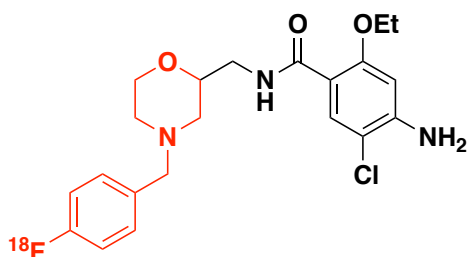
Radiochemical yield: 14%

Results

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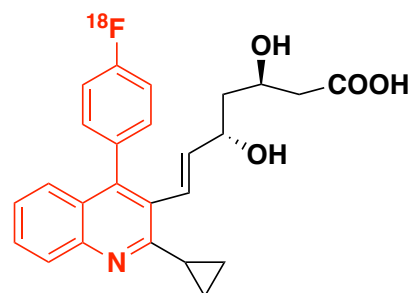
## Mosapride

(Gastric inflammation)

Radiochemical conversion:  $35 \pm 6 \%$ 

## Pitavastatin

(hypocholesterolaemia)

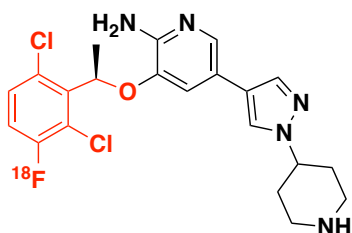
Radiochemical conversion:  $57 \pm 9 \%$ Liang et al. *Chem. Sci.*, 2016, 7, 4407

Results

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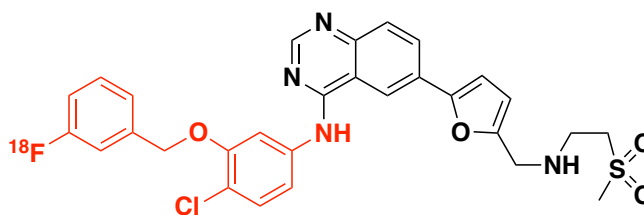
## Crizotinib

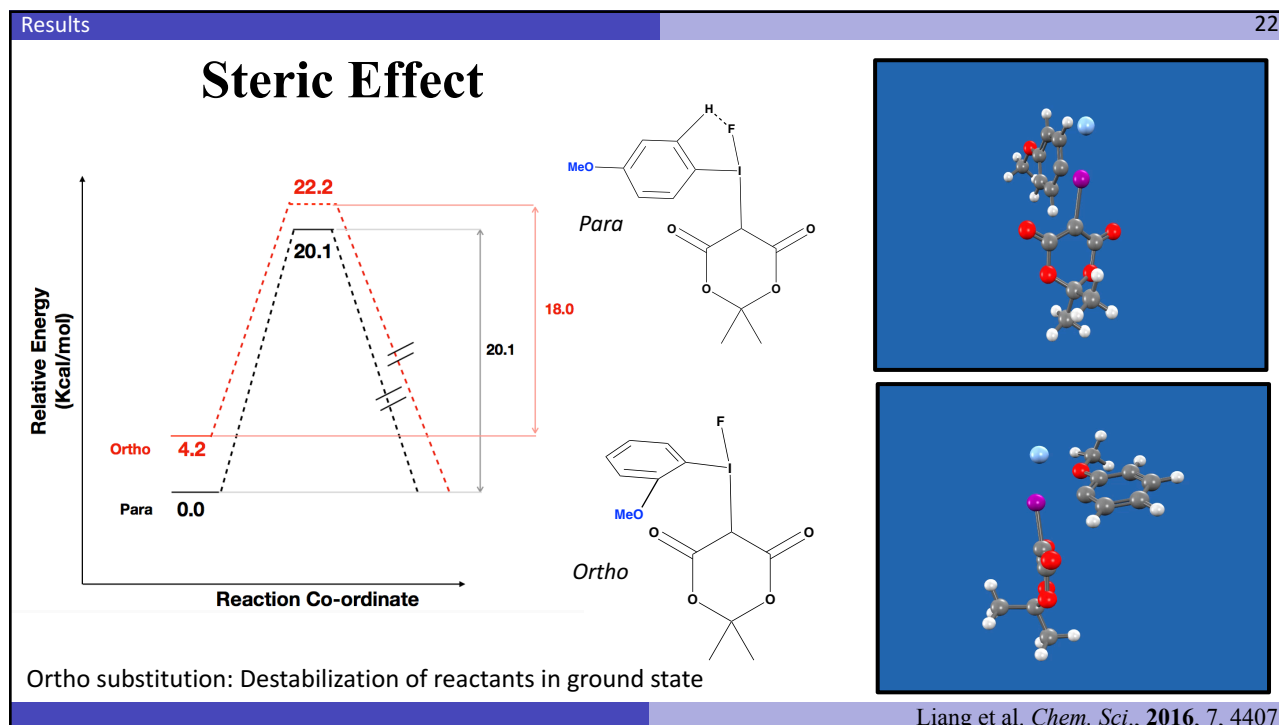
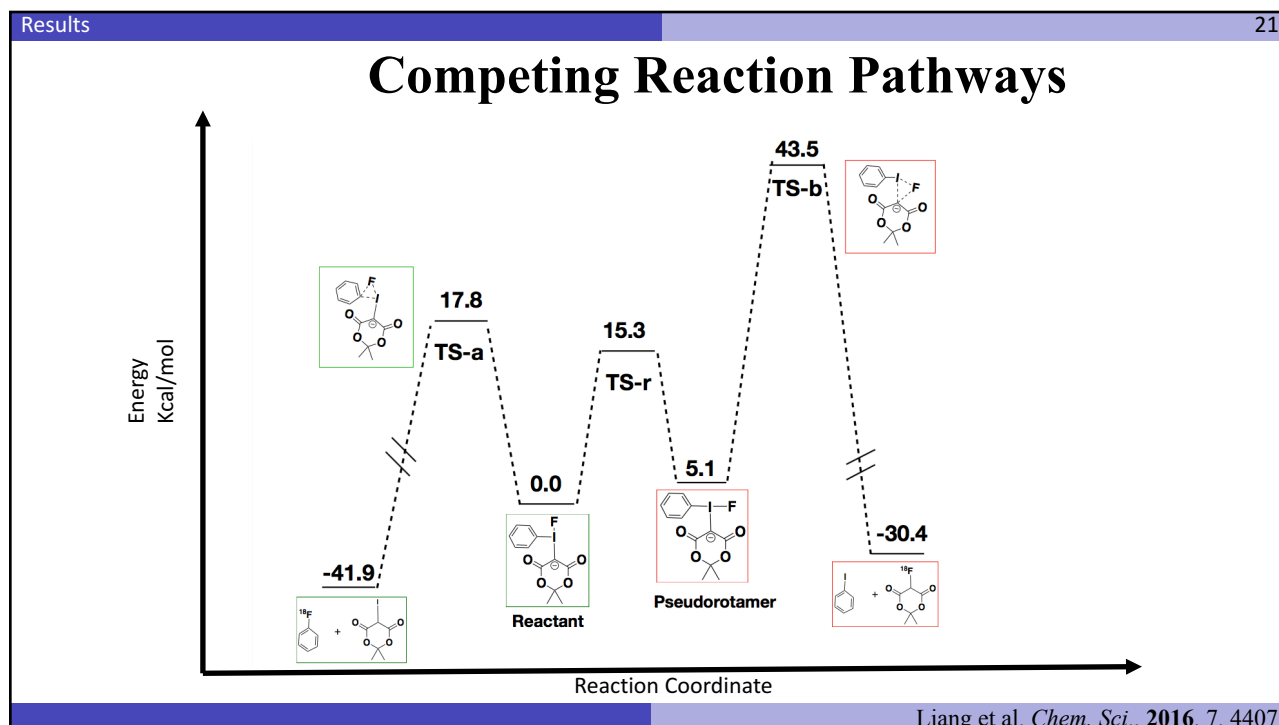
(Non-small cell lung cancer)

Radiochemical conversion:  $82 \pm 6 \%$ 

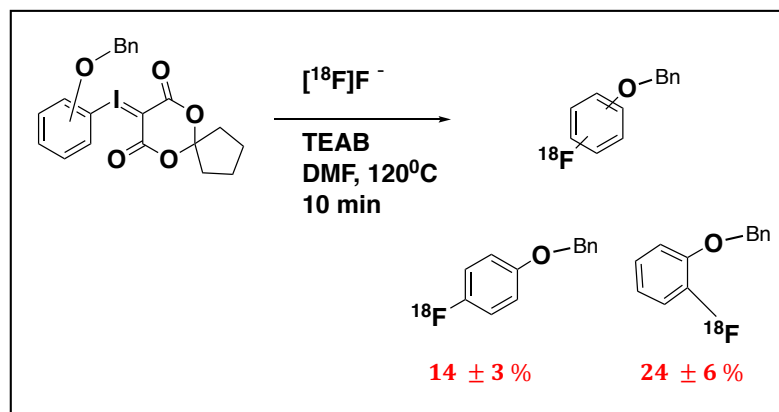
## Ipatinib

(Breast and lung cancer)

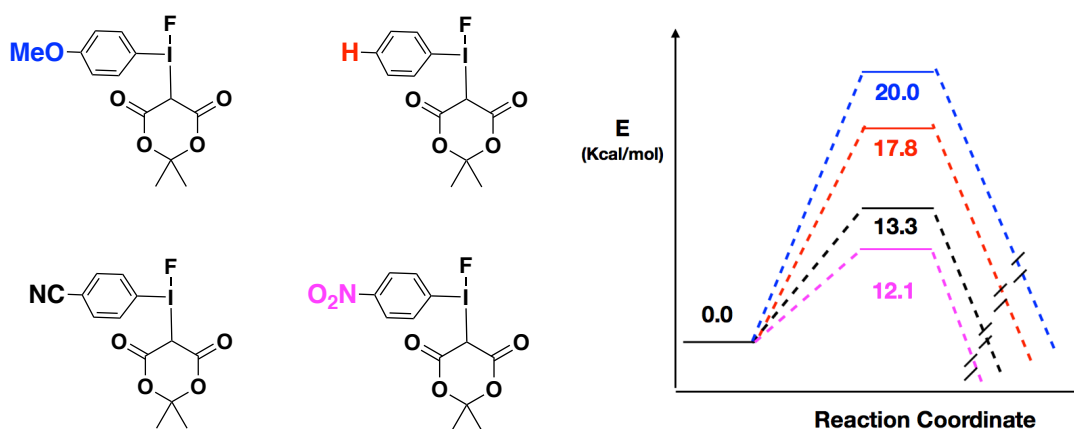
Radiochemical conversion:  $66 \pm 8 \%$ Liang et al. *Chem. Sci.*, 2016, 7, 4407



## Experimental Results for *ortho* Effects

Liang et al. *Chem. Sci.*, 2016, 7, 4407

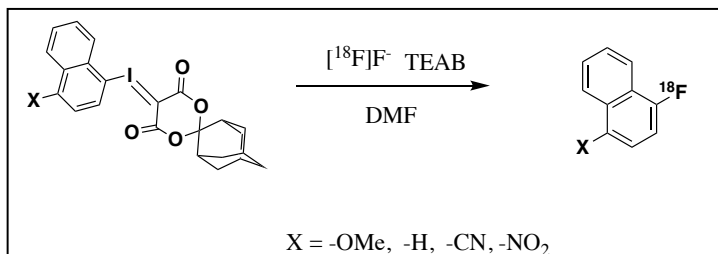
## Electronic Effects of Substitution



Reduction in reductive elimination barrier by EWGs  $\Delta G^\ddagger$   $-\text{NO}_2 < -\text{CN} < -\text{H} < -\text{OMe}$

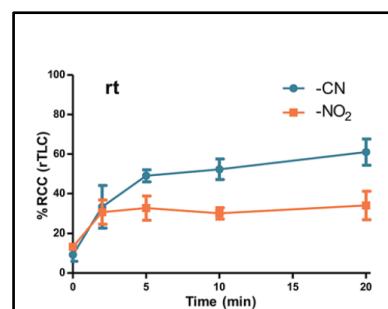
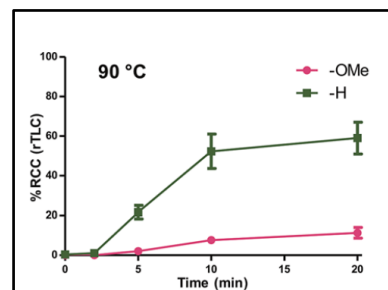
Liang et al. *Chem. Sci.*, 2016, 7, 4407

## Electronic Effects of Substitutions



Factors affected by substitutions:

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



Liang et al. *Chem. Sci.*, 2016, 7, 4407

## Summary

- |   |  |
|---|--|
| 1. Higher PET radiotracers yields                     | 1. Radiation safety                        |
| 2. High Regioselectivity                              | 2. Choice of hazardous reagents            |
| 3. Short reaction times                               | 3. Ylide rearrangement                     |
| 4. Purification of iodonium ylides                    | 4. Clinical trials of designed PET tracers |
| 5. Modulation of $\Delta G^\ddagger$ by substitutions | 5. One-pot oxidation and ylide formation   |



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## Acknowledgments

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

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- Dr. Daniel Glatzhofer

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- Carol Jones
- Nailynn Williams
- Heather Thomson

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- Dr. Ye Mei
- Jingheng Deng
- Zhu Zou
- Eric Gardner
- Tejaswi Bavineni

# Thank you!

## Questions are welcomed!