Chemical Science

EDGE ARTICLE

View Article Online
View Journal

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

Benjamin H. Rotstein,[‡ab] Lu Wang,[‡a] Richard Y. Liu,[c] Jon Patteson,[a] Eugene E. Kwan,[c] Neil Vasdev[*ab] and Steven H. Liang[*ab]

Accepted 24th March 2016

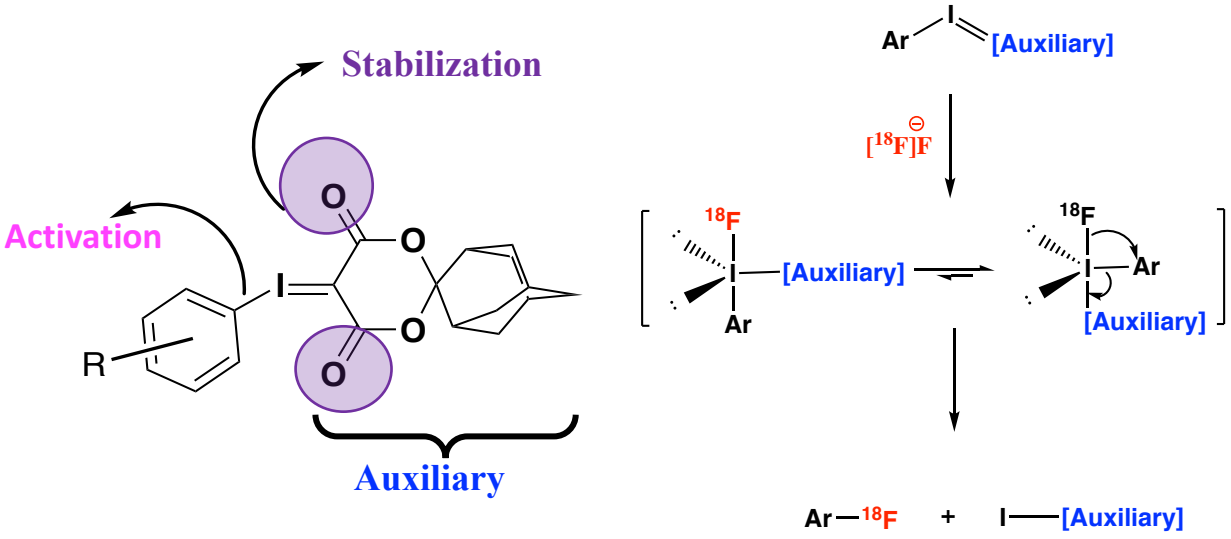
a. Division of Nuclear Medicine and Molecular Imaging & Gordon Center for Medical Imaging, Massachusetts General Hospital
b. Department of Radiology, Harvard Medical School
c. Department of Chemistry and Chemical Biology, Harvard University

DOI: 10.1039/c6sc00197a

Outline

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

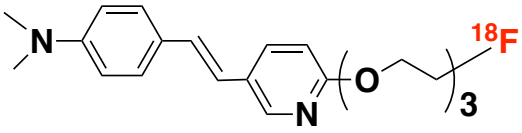
Spirocyclic Iodonium(III) Ylides



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

Long Term Objective

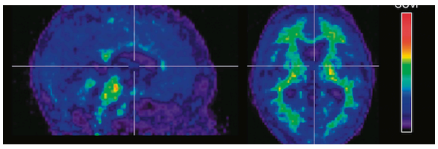
Development of [^{18}F] based radiotracers



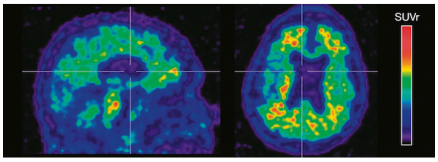
[^{18}F]Amyvid

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

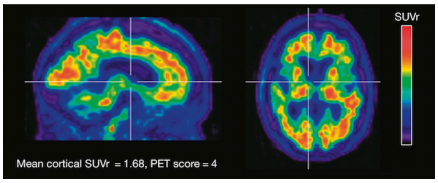
a) No β-amyloid plaques



b) Moderate load of β-amyloid plaques

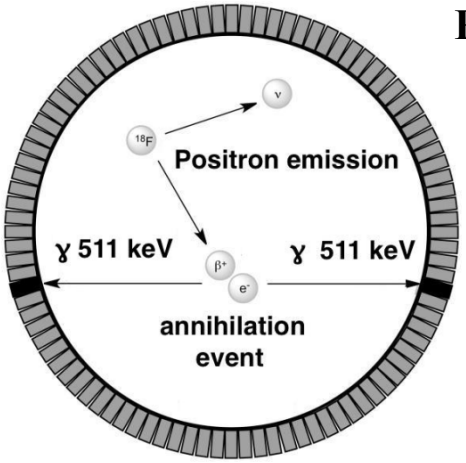


c) High load of β-amyloid plaques



Lin Zhu et al. *Science*, **2013**, 342, 429-430

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

↓

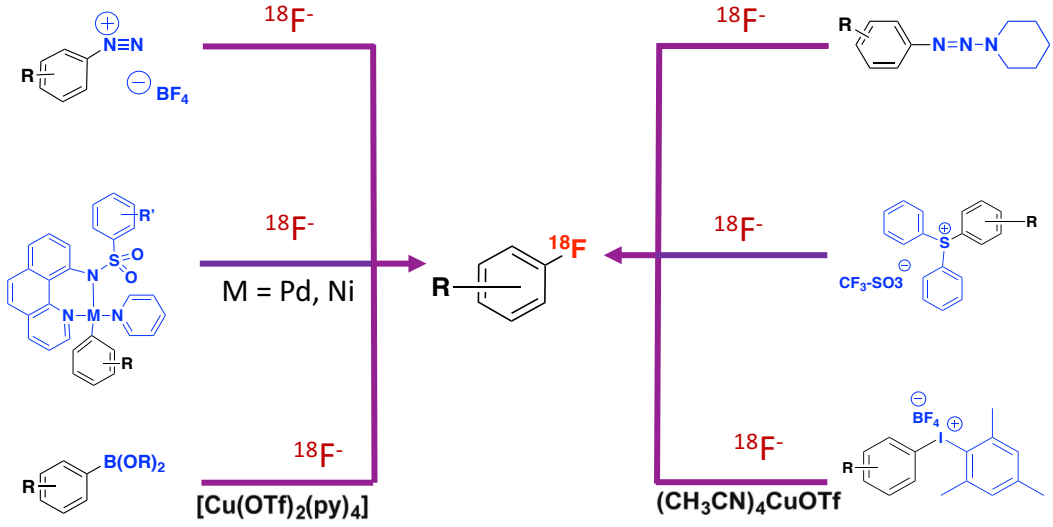
Annihilation with e^{-}

↓

Detection of γ rays

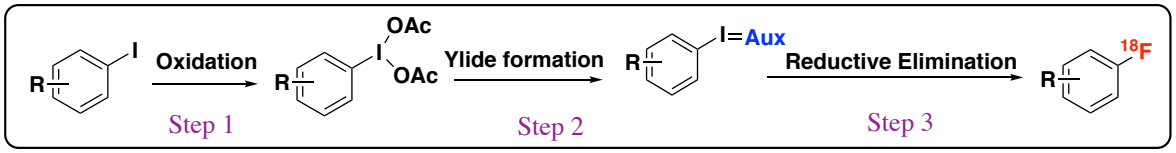
Scott et al. *Curr Top Med Chem.*, **2014**, 14(7), 875–900

Previous ^{18}F Labeling Routes

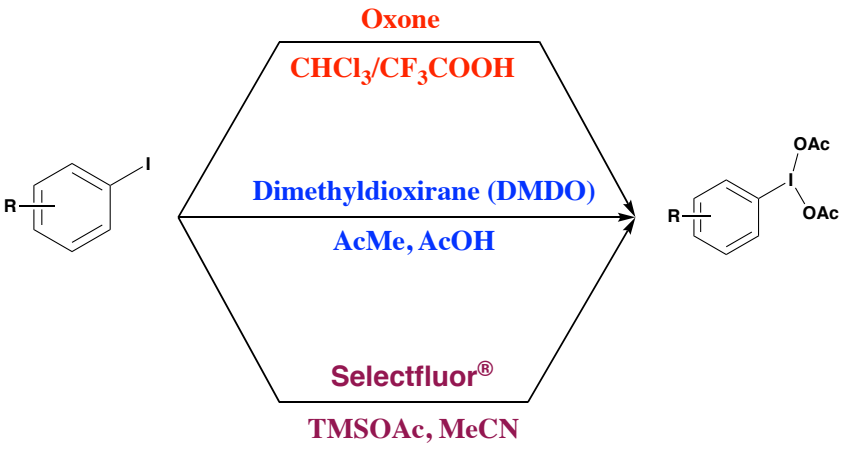


Chen et al. *Bioconjugate Chem.*, **2015**, 26, 1−18

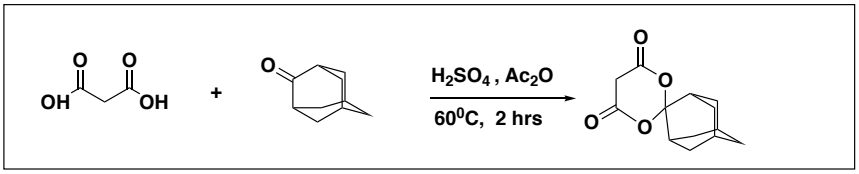
Reaction Scheme

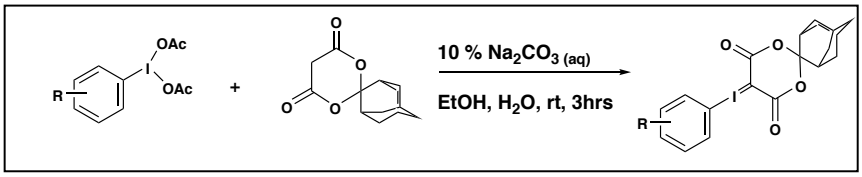


Step 1: Oxidation



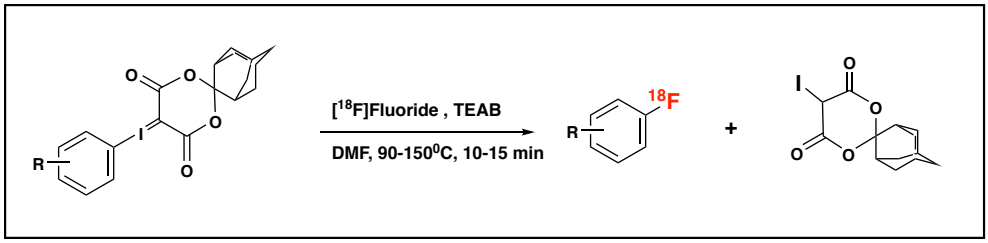
Step 2: Ylide Formation





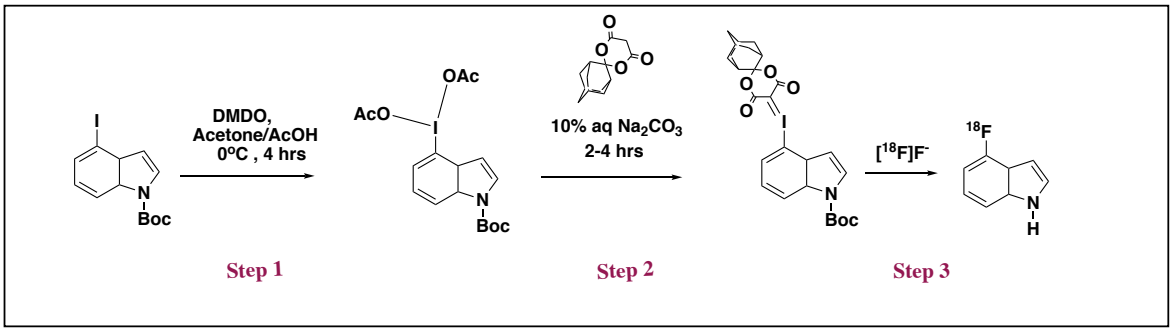
Liang et al. *Chem. Sci.*, **2016**, 7, 4407

Step 3: Reductive Elimination



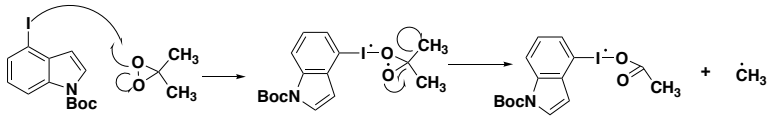
Liang et al. *Chem. Sci.*, **2016**, 7, 4407

Synthesis of [^{18}F]Indoles

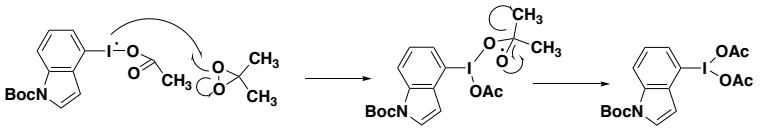


Liang et al. *Chem. Sci.*, **2016**, 7, 4407

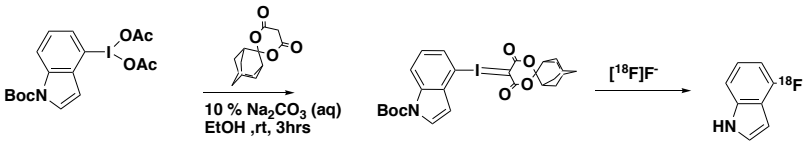
❖Free radical decomposition of dioxirane leading to generation of methyl radical



❖Formation of iodosoacetate by using second DMDO equivalent

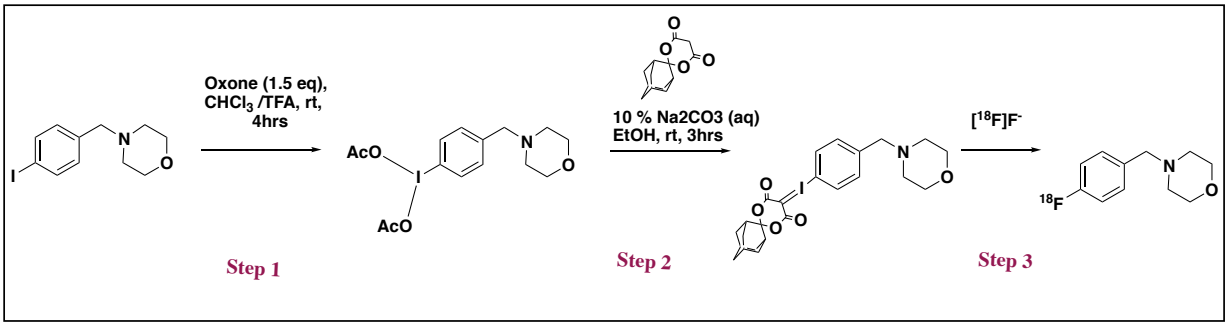


❖Ylide formation and subsequent reductive elimination



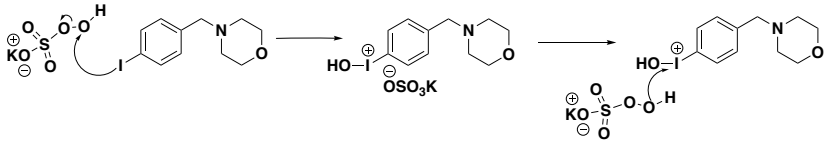
Bravo et al. *Tetrahedron Letters*, **1995**, 36, 38, 6945-6948

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

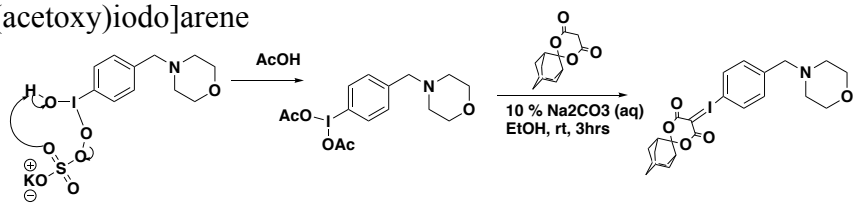


Liang et al. *Chem. Sci.*, **2016**, 7, 4407

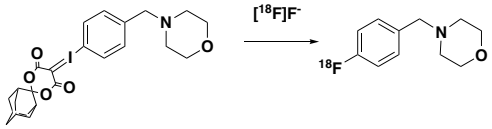
❖ potassium peroxymonosulfate as an oxidizing agent



❖ formation of [bis(acetoxy)iodo]arene

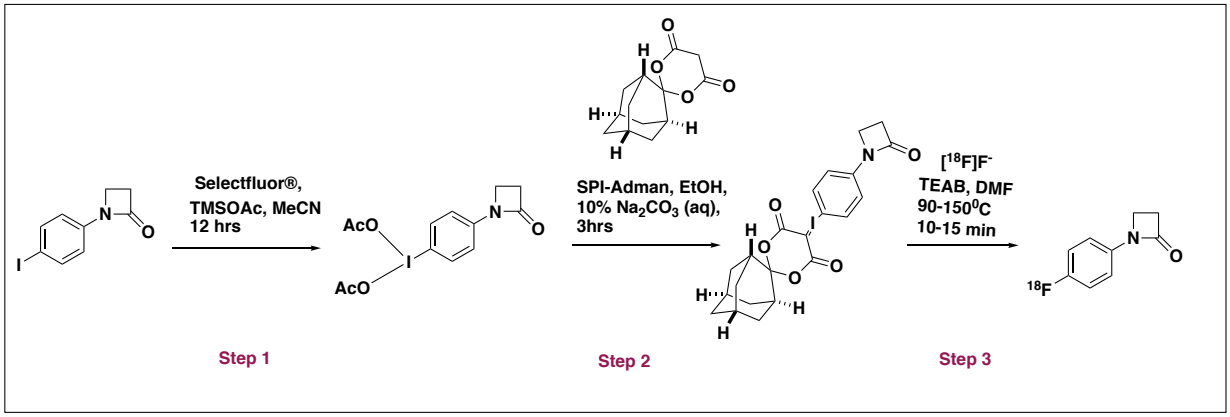


❖ ^{18}F labeling by reductive elimination



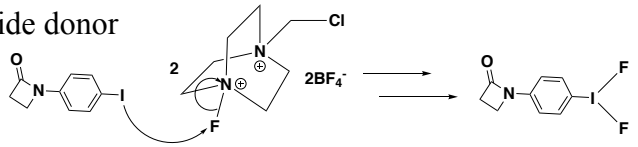
Zhdankin et al. *J.Org. Chem.*, **2010**, 75, 2119-2122

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

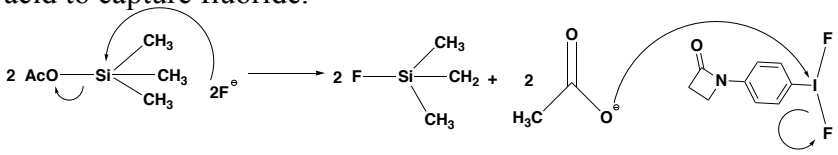


Liang et al. *Chem. Sci.*, **2016**, 7, 4407

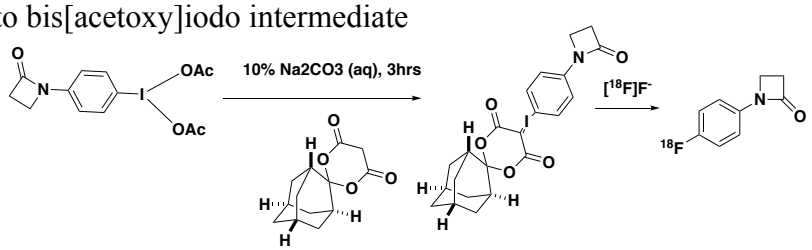
❖ Selectfluor® acts as fluoride donor



❖ TMSOAc acts as lewis acid to capture fluoride.



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



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

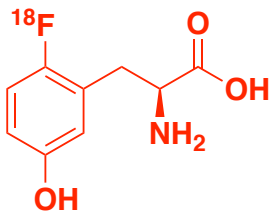
Results

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

PET Radiopharmaceuticals

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

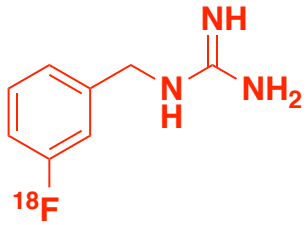
(Cerebral dopamine transport)



Radiochemical yield: 12%

meta-[^{18}F]fluorobenzylguanidine

(Neuroblastoma)

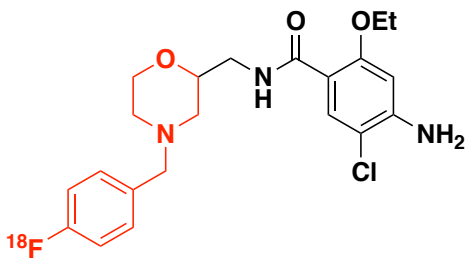


Radiochemical yield: 14%

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

Mosapride

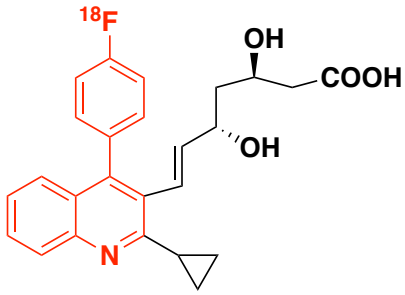
(Gastric inflammation)



Radiochemical conversion: 35 ± 6 %

Pitavastatin

(hypocholestrolaemia)

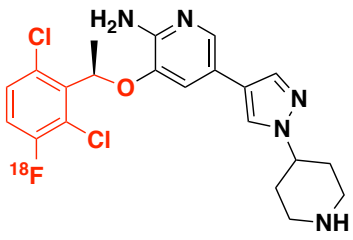


Radiochemical conversion: 57 ± 9 %

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

Crizotinib

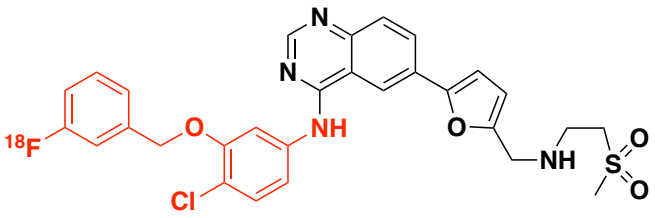
(Non-small cell lung cancer)



Radiochemical conversion: 82 ± 6 %

Ipatinib

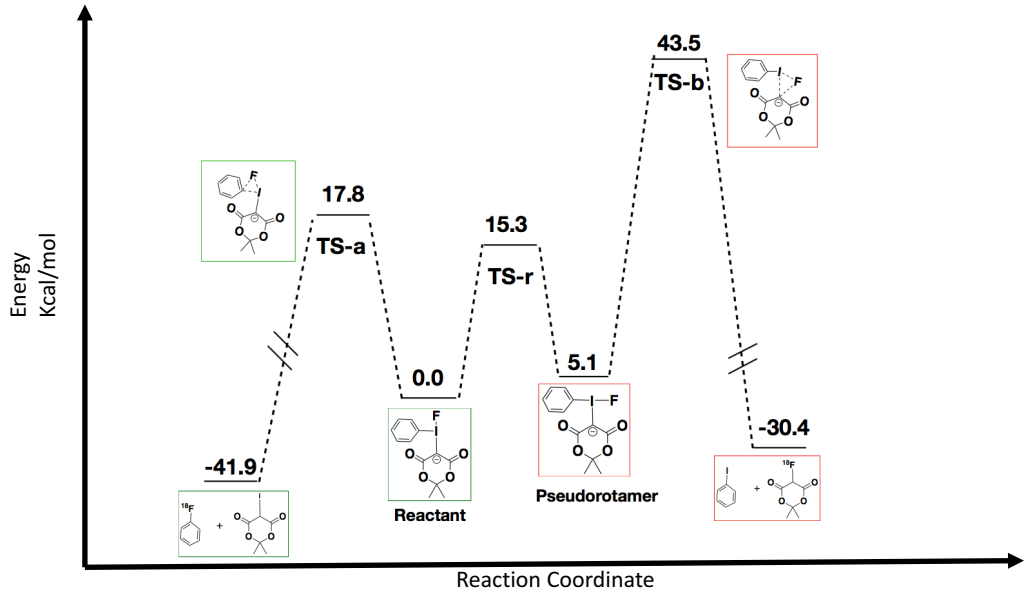
(Breast and lung cancer)



Radiochemical conversion: 66 ± 8 %

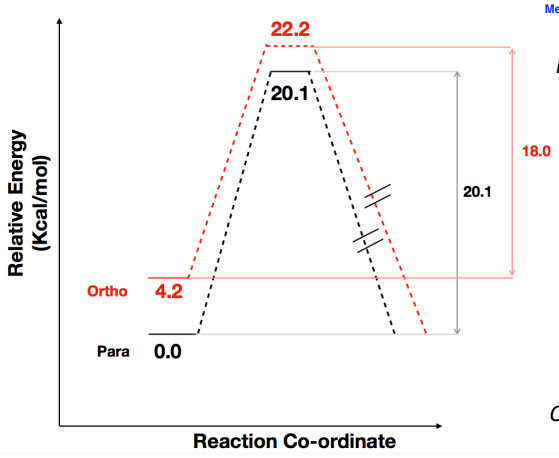
Liang et al. *Chem. Sci.*, **2016**, 7, 4407

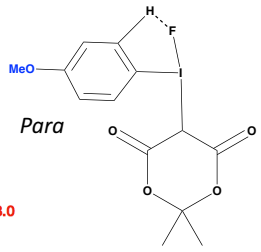
Competing Reaction Pathways

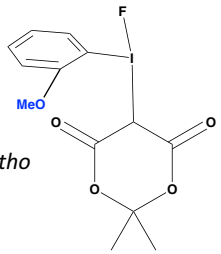


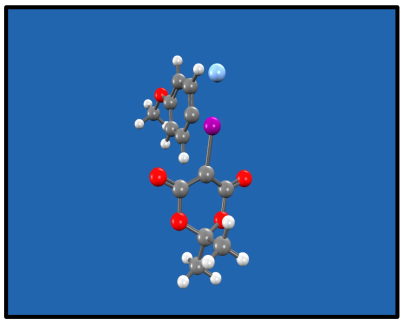
Liang et al. *Chem. Sci.*, **2016**, 7, 4407

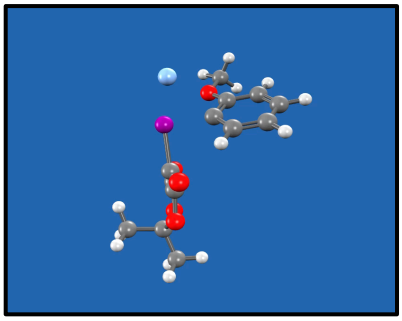
Steric Effect







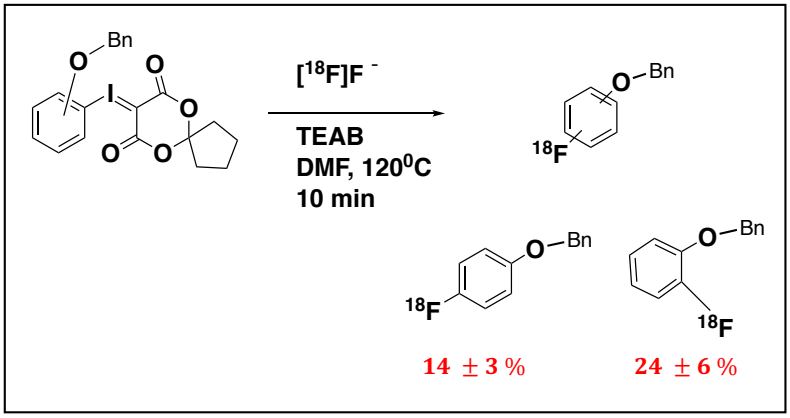




Ortho substitution: Destabilization of reactants in ground state

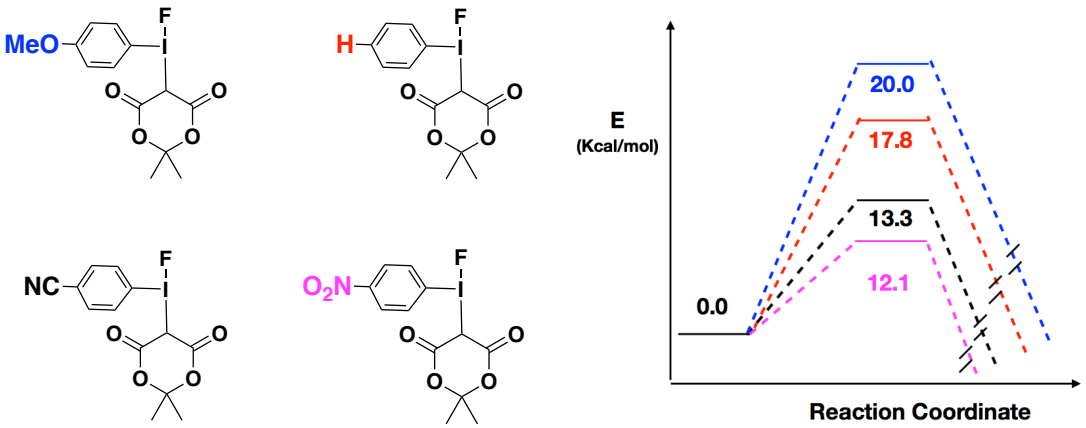
Liang et al. *Chem. Sci.*, **2016**, 7, 4407

Experimental Results for *ortho* Effects



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

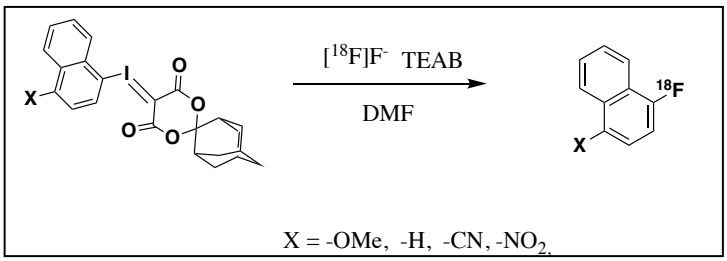
Electronic Effects of Substitution

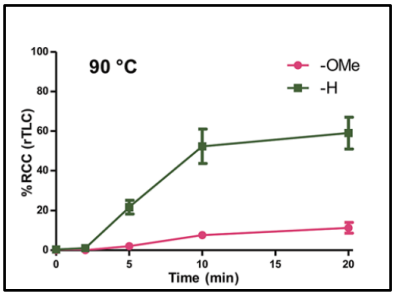


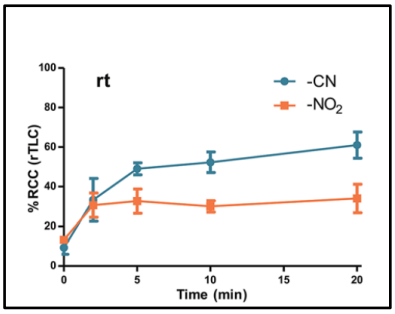
Reduction in reductive elimination barrier by EWGs $\Delta G^{\ddagger}$ $-NO_2 < -CN < -H < -OMe$

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
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

Thank you!

Questions are welcomed!