Iron-Catalyzed Three-Component Synthesis of β-(Radio)fluoroamines

Oaikhena Z. Esezobor,[1] Hannah Le,[1,2] Mark R. Bortolus,[1] Neil Vasdev,[1] Chao Zheng[1,2,3,4]

[1]Azrieli Centre for Neuro-Radiochemistry, Brain Health Imaging Centre, Centre for Addiction and Mental Health, Toronto

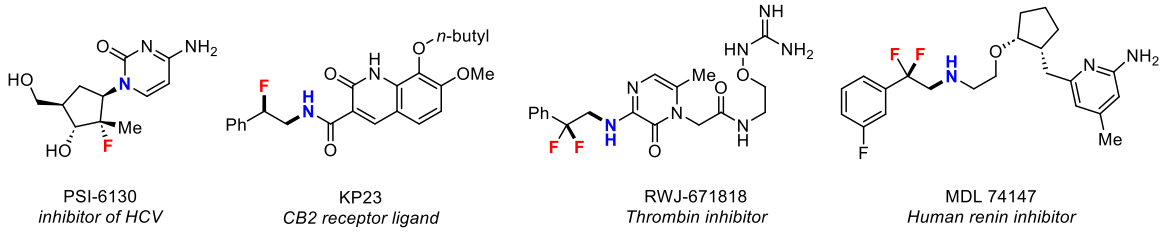
Departments of [2]Pharmacology, [3]Psychiatry, [4]Chemistry, University of Toronto

email: oaikhena.esezobor@camh.ca; chao.zheng@camh.ca

Background

- β-Fluoroamines and β,β-difluoroamines are highly valued in medicinal chemistry.
- Their [^{18}F]-labeled analogues have potentials as positron emission tomography (PET) imaging agents.
- Adjacent fluorine atom attenuates amine basicity, enhances lipophilicity, and modulates hydrogen-bonding capability.[1,2]
- However, direct synthetic access to these compounds remains a persistent challenge.
- We report a mild and direct aminofluorination of alkenes to afford diverse β-fluoroamine and β,β-difluoroamine derivatives.

β-Fluoro- and β,β-difluoroamines in Bioactive Compounds[1,2]



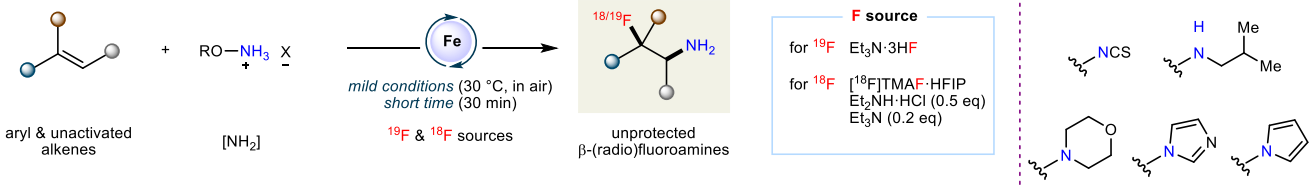
PSI-6130 *inhibitor of HCV*

KP23 *CB2 receptor ligand*

RWJ-671818 *Thrombin inhibitor*

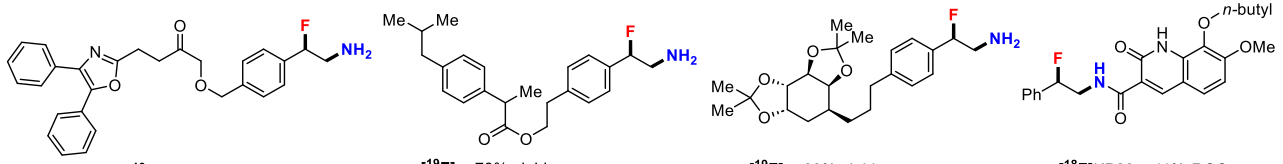
MDL 74147 *Human renin inhibitor*

Amino(radio)fluorination of Alkenes[3]



✔ *first NH_2-involved alkene aminofluorination* ✔ *great synthetic potential* ✔ *key dual roles of $Et_3N{\cdot}_3HF$* ✔ *translatable to ^{18}F-radiochemistry*

Select Substrates:



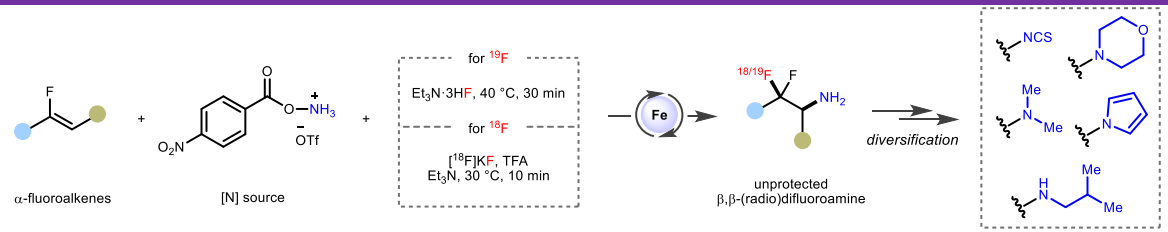
[^{19}F] = 64% yield
[^{18}F] = 8% RCC *(from oxaprozin)*

[^{19}F] = 70% yield
[^{18}F] = 11% RCC *(from Ibuprofen)*

[^{19}F] = 60% yield
from diacetone-D-galactose

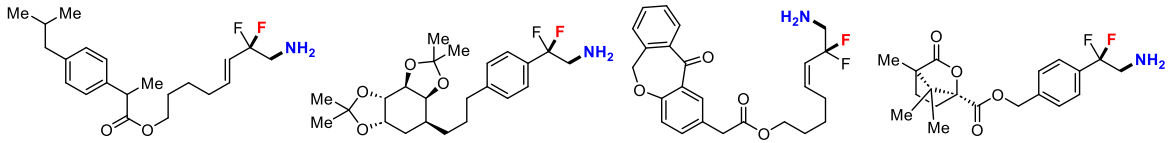
[^{18}F]KP23 = 11% RCC
CB2 receptor ligand

Amino(radio)fluorination of α-Fluoroalkenes[4]



✔ first synthesis of -[^{18}F]CF_2- motifs via alkene difunctionalization ✔ enabling a collective synthesis of structurally diverse β,β-difluorinated *N*-containing compounds

Select Substrates:



[^{19}F] = 58% yield
[^{18}F] = 8% RCC
from Ibuprofen

[^{19}F] = 80% yield
[^{18}F] = 15% RCC
from diacetone-D-galactose

[^{19}F] = 54% yield
[^{18}F] = 12% RCC
from isoxepac

[^{19}F] = 63% yield
[^{18}F] = 8% RCC
from (1S)-(-)-camphanic acid

Proposed Mechanism

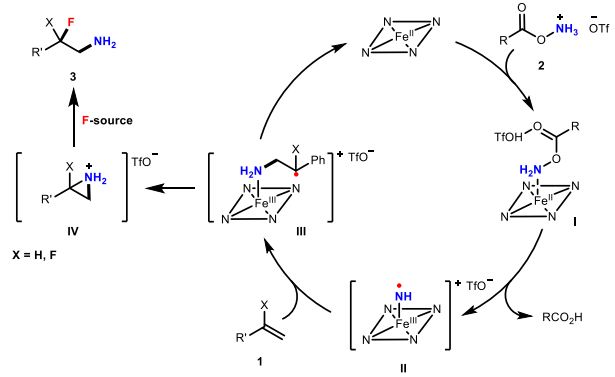


Figure 1. Proposed reaction mechanism

Conclusion

- We developed iron-catalyzed modular and conceptually novel strategies for the synthesis of unprotected *β*-fluoroamines and *β*,*β*-difluoroamines from alkene.
- These strategies were successfully translated into amino(radio)fluorination protocols, offering significant potential for the direct synthesis of PET imaging agents bearing *β*-fluoroamines and *β*,*β*-difluoroamines moieties.

References

[1] Sap *et al.*, *Chem. Soc. Rev.* **2021**, *50*, 8214. [2] Johnson *et al. Med. Chem.* **2020**, *63*, 6315.
[3] Li, Le, and Wang *et al. Nat. Commun.* **2025**, *16*, 10917 [4] Li *et al.*, *ACS Catal.* **2025,** *15*, 20123.