

Late-Stage Functionalizations

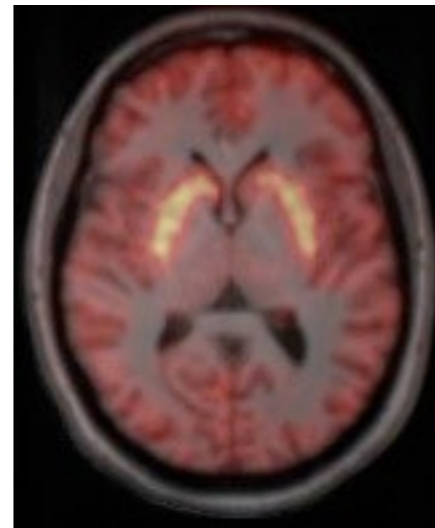
Tobias Ritter

Max-Planck-Institut für Kohlenforschung
RWTH Aachen University
Massachusetts General Hospital

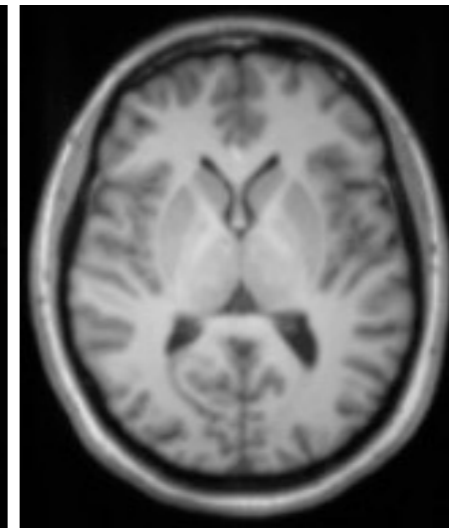


Positron Emission Tomography

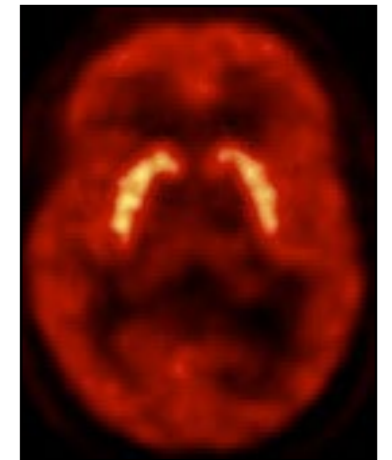
- non-invasive
- functional imaging modality
- ^{18}F is nuclide of choice
- Half life of ^{18}F is 110 min



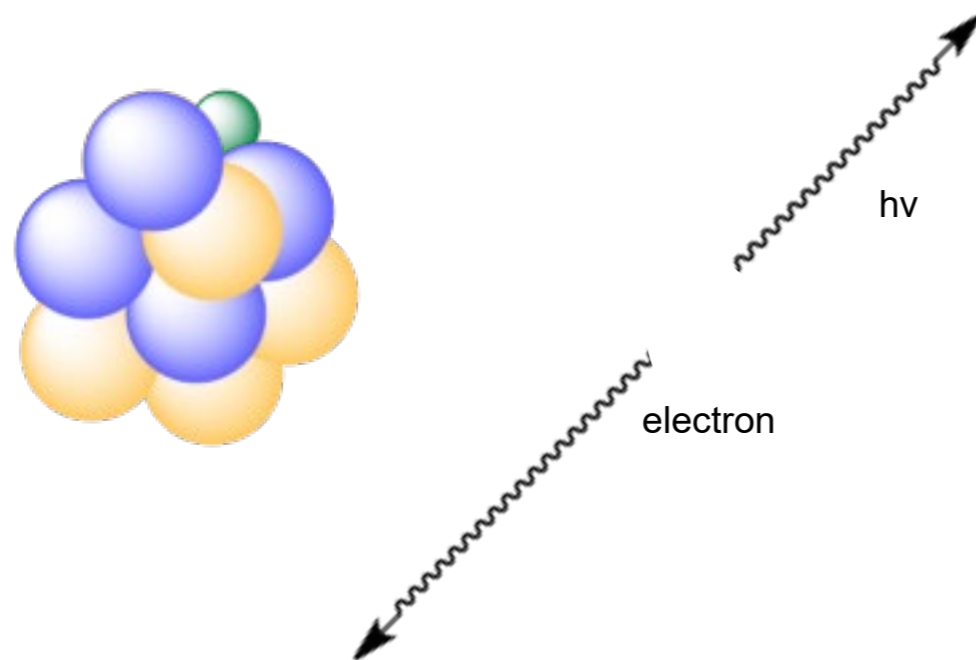
PET-MR



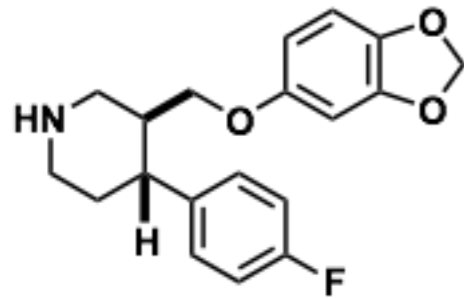
MR



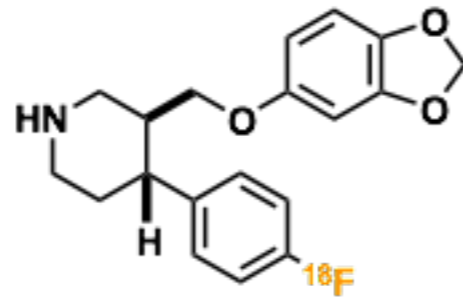
PET



Biodistribution of Paroxetine

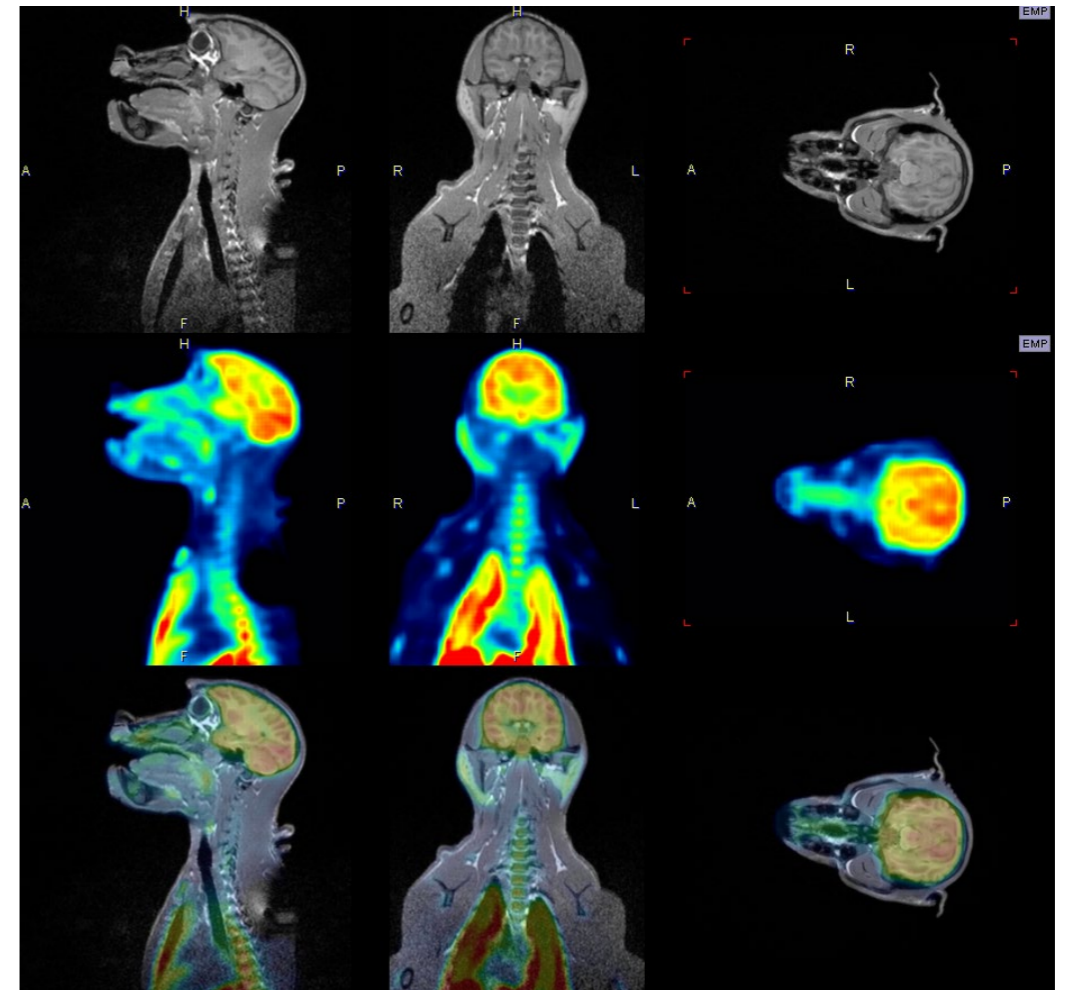
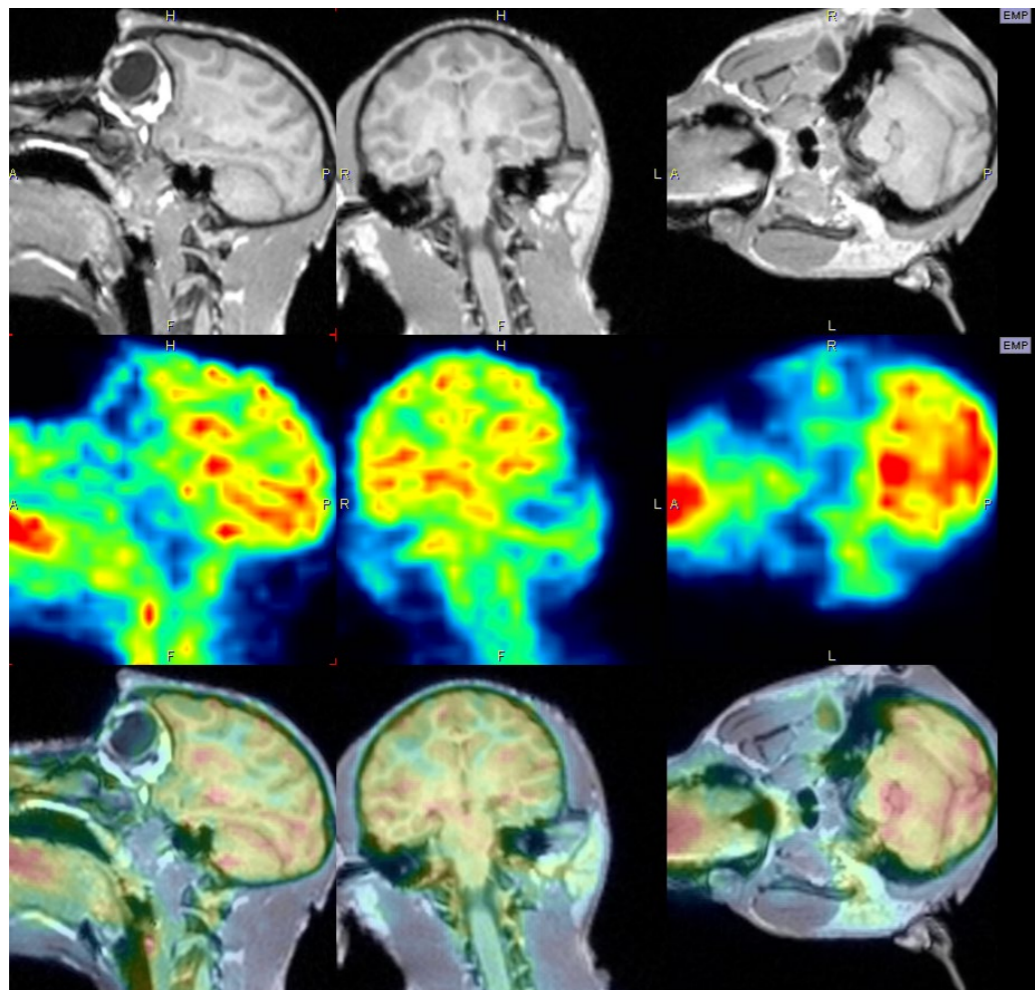
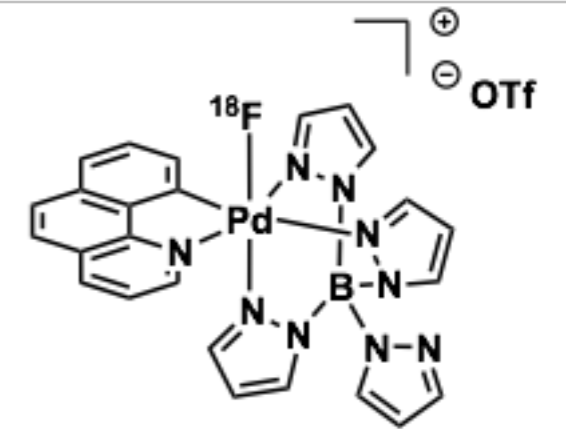


Paxil

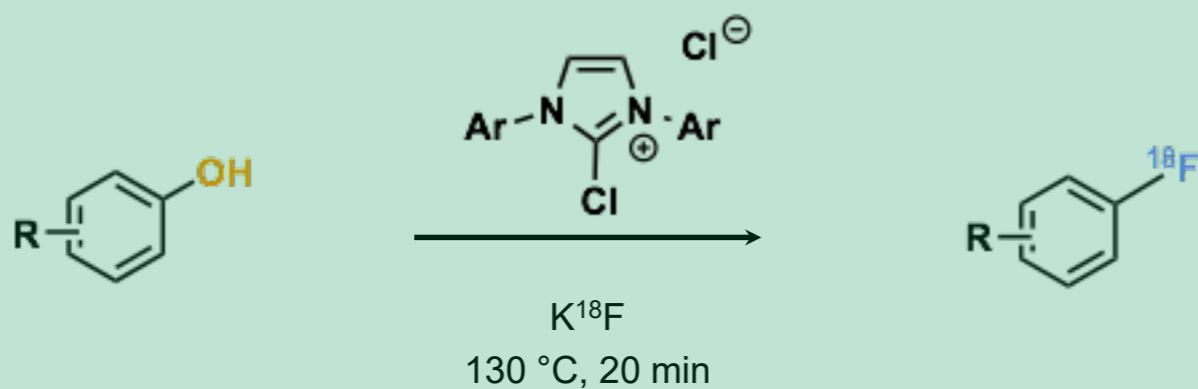


[¹⁸F]Paxil

22 ± 4% RCY
> 13 Ci / μmol
> 10 mCi prepared



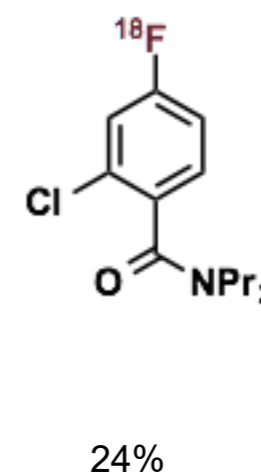
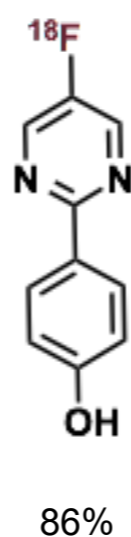
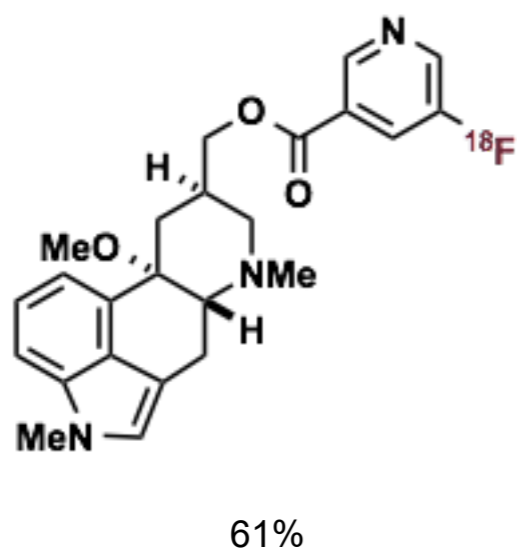
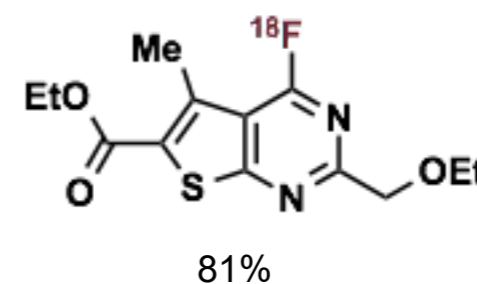
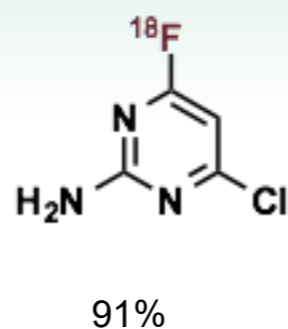
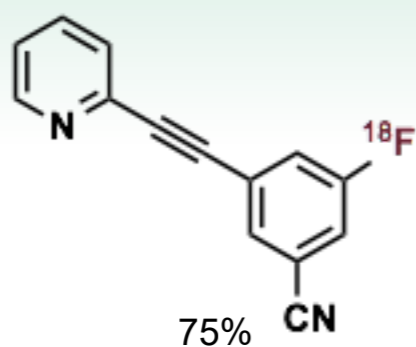
Practical ^{18}F Fluorination



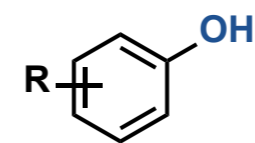
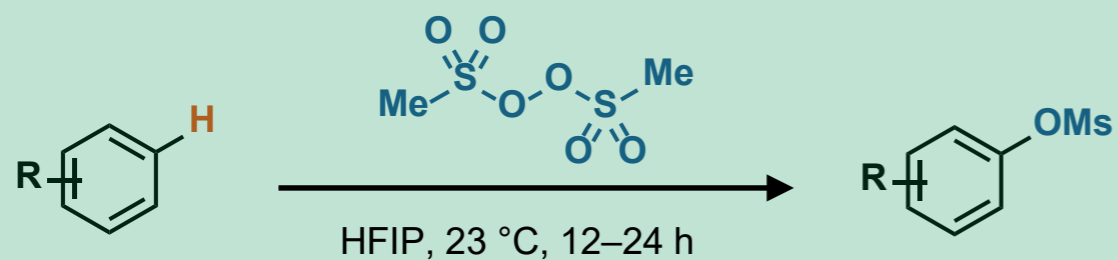
heteroarenes

basic and protic
functional groups

9.3 mCi from 34 mCi ^{18}F fluoride
 $3.03\text{ Ci} \times \mu\text{mol}^{-1}$

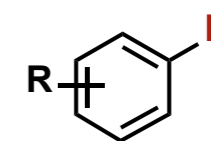


Late-Stage Arene Hydroxylation



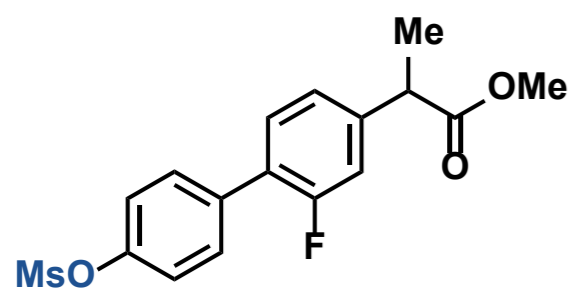
metabolite

LDA, -78 °C or TBAF, 0 °C

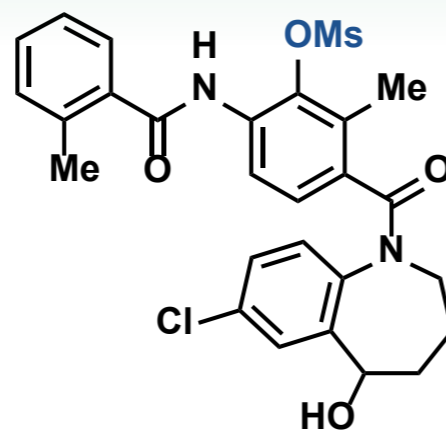


metabolism blocked

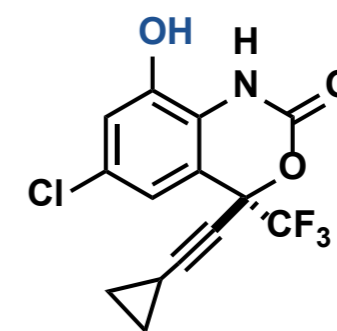
PhenoFluorMix, 110 °C



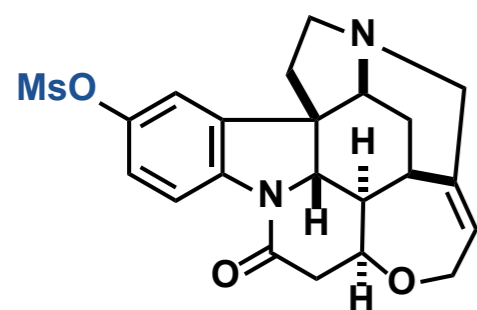
flurbiprofen, 77%



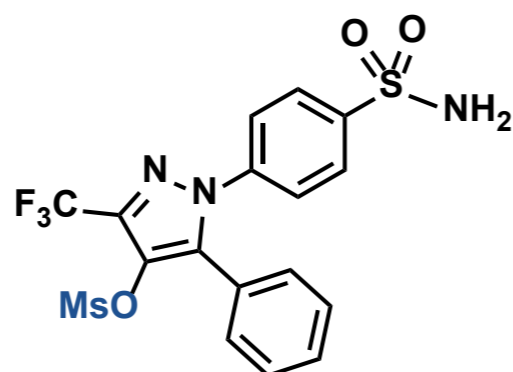
tolvaptan, 41%



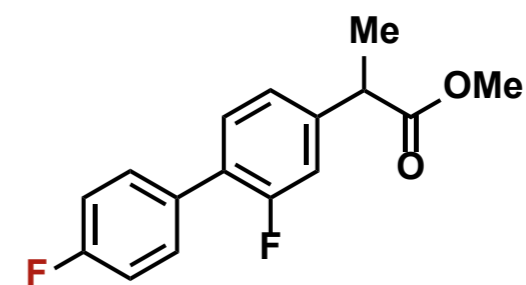
efavirenz, 80%



strychnine, 61%

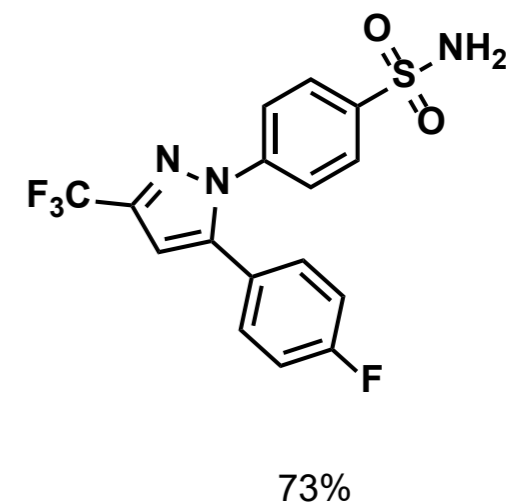
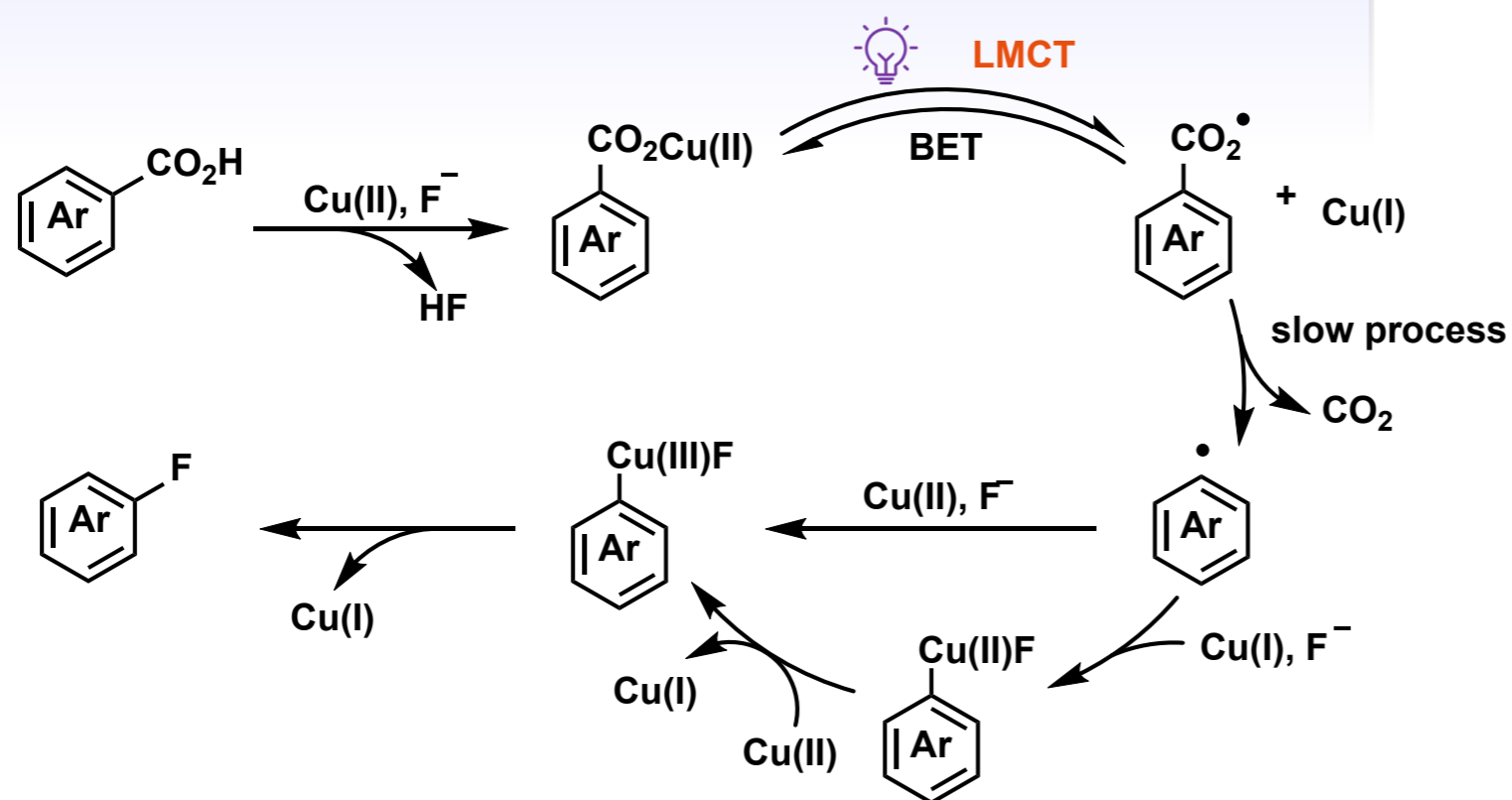
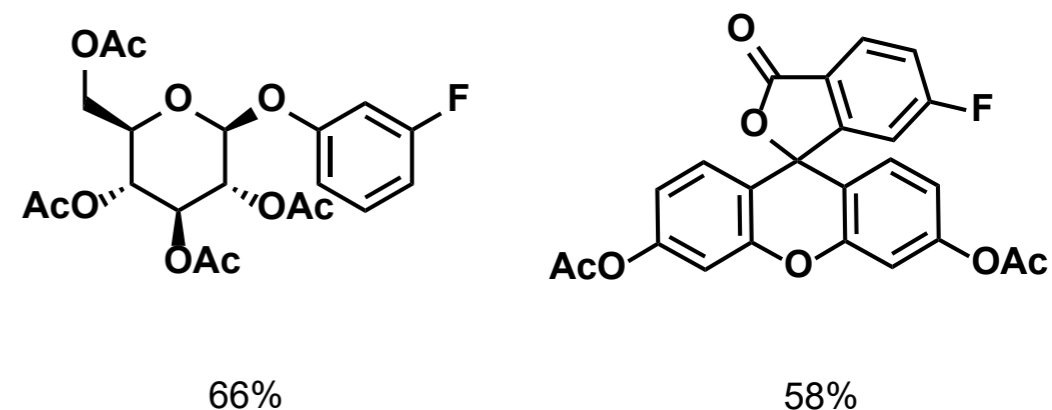
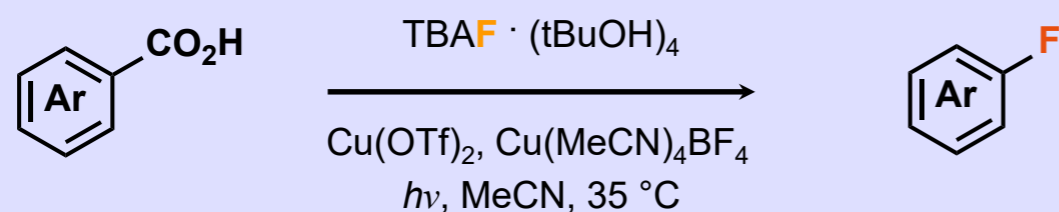


celecoxib, 61%

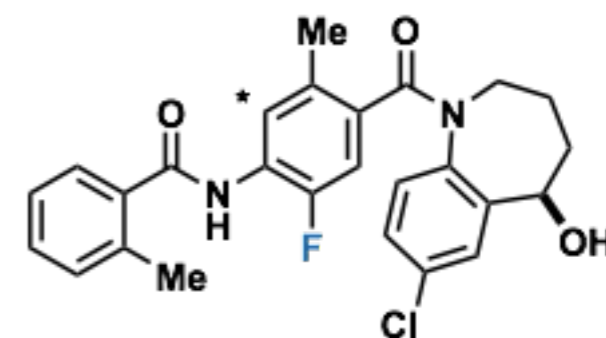
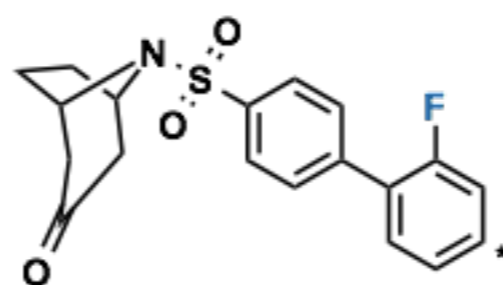
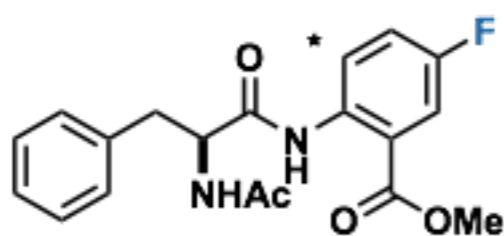
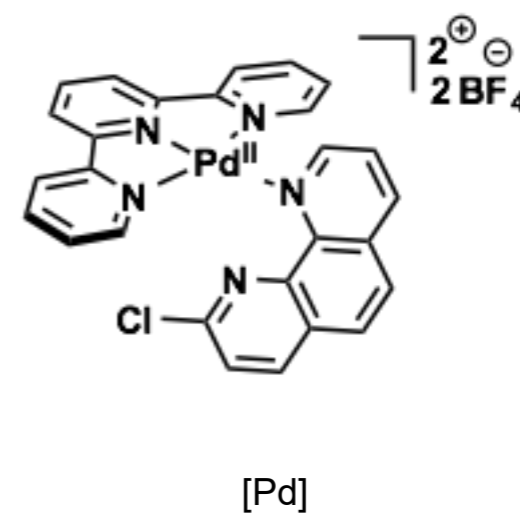
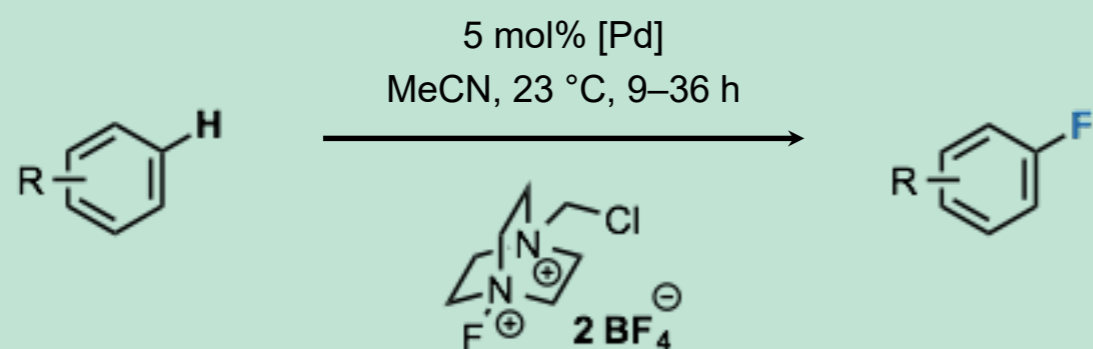


fluoroflurbiprofen, 56%

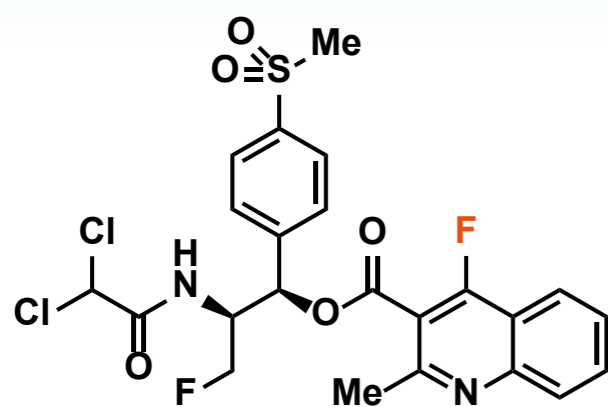
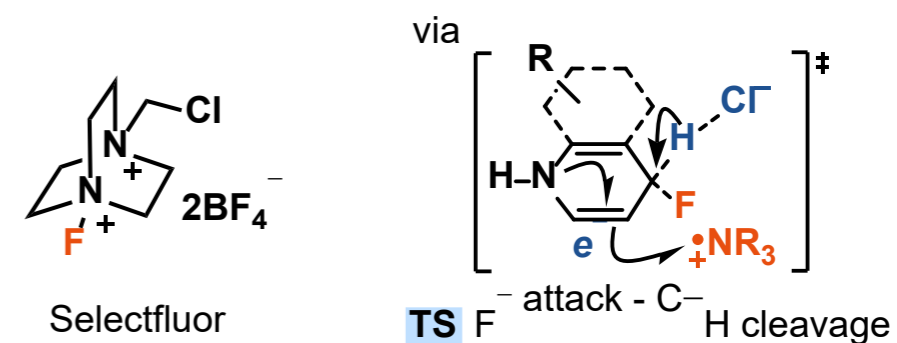
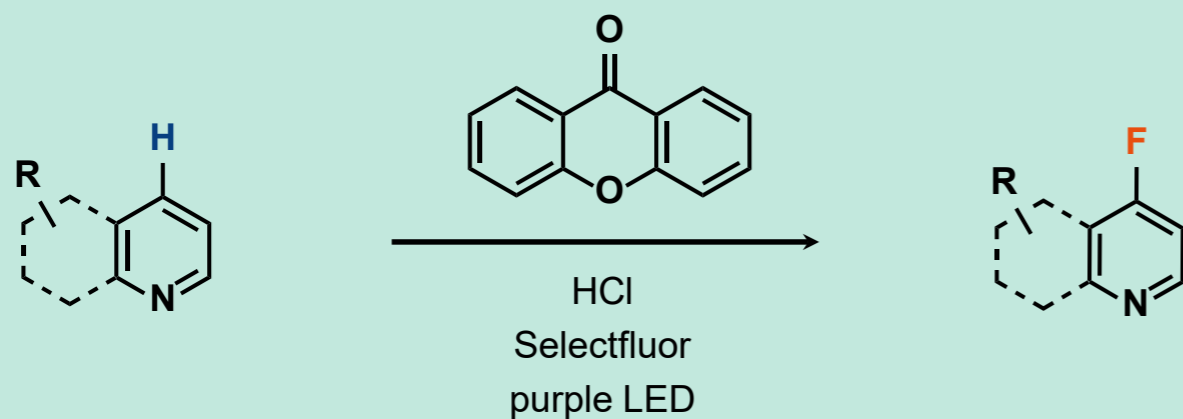
Aromatic Decarboxylative Fluorination



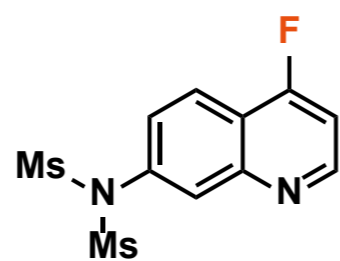
Direct C–H Fluorination



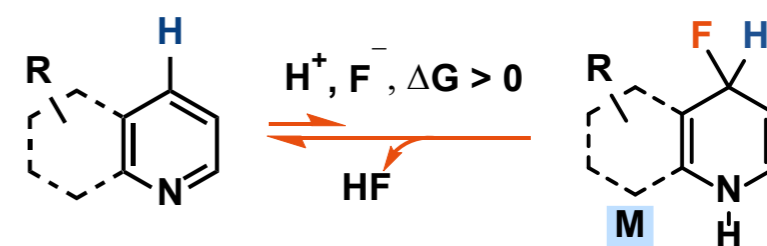
Azaarene C–H Fluorination



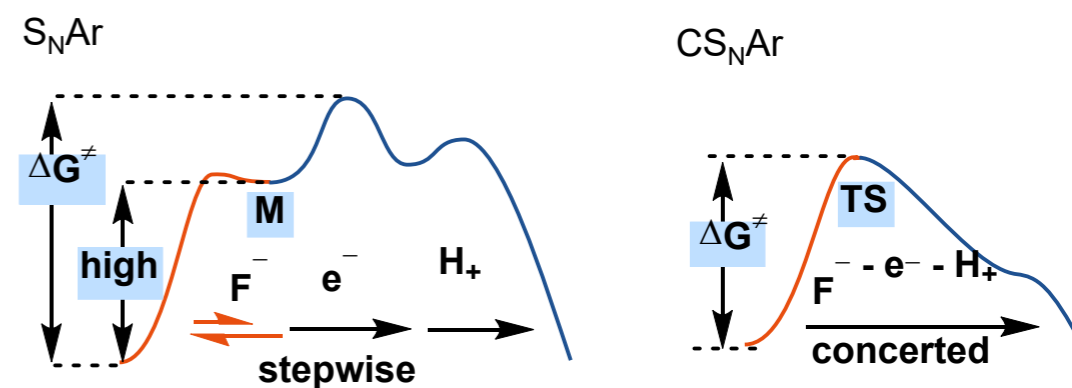
49%



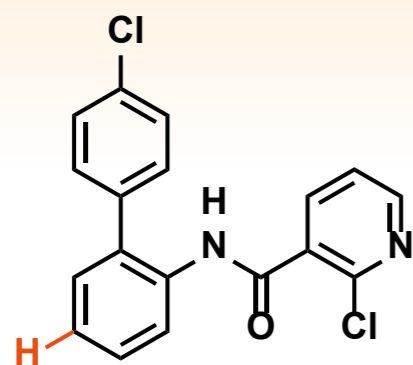
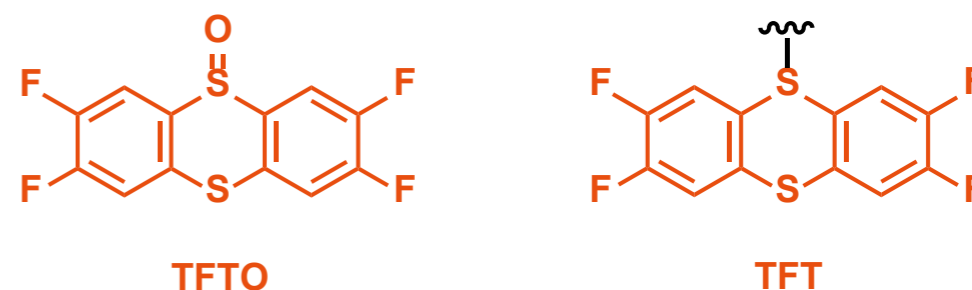
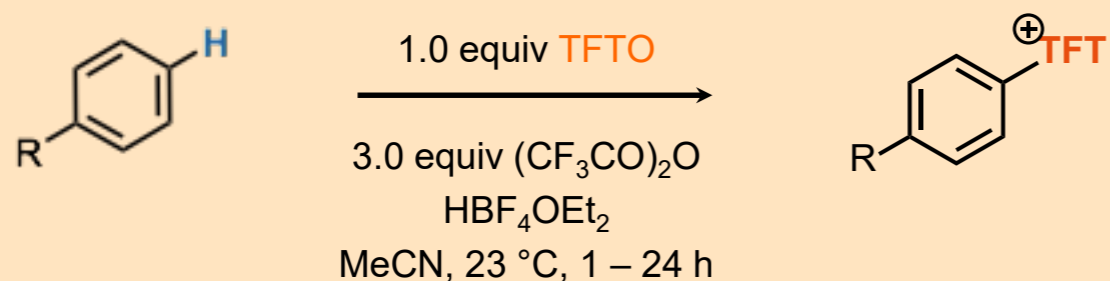
53% (C4:C2 = 4:1)



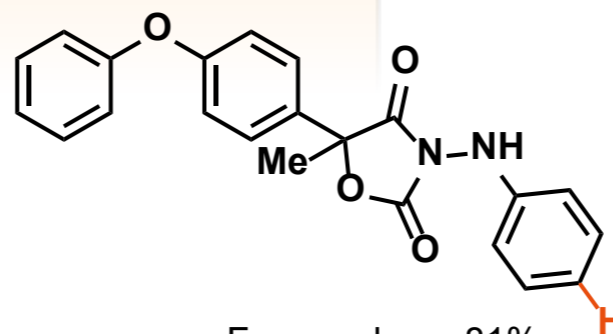
high-energy Meisenheimer int.



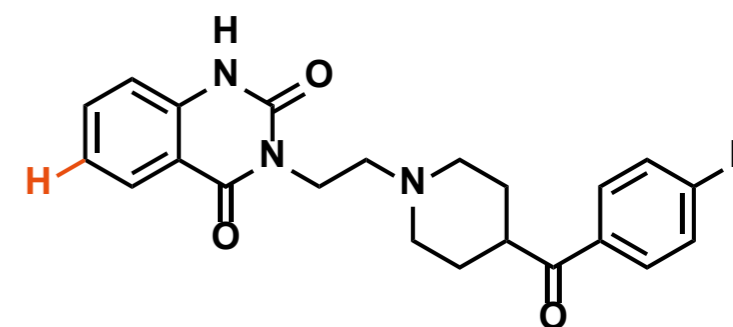
Site-Selective C–H Thianthrenation



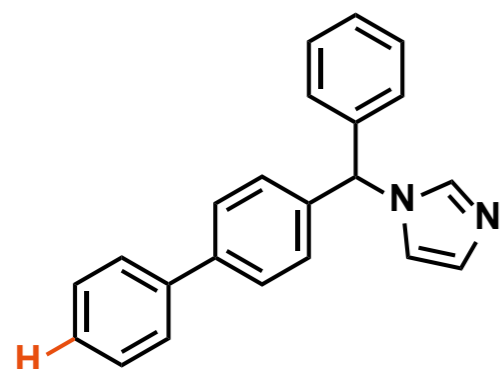
Boscalid, 95%



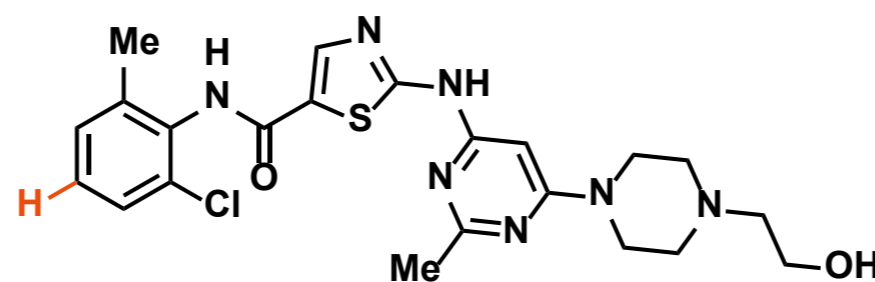
Famoxadone, 81%



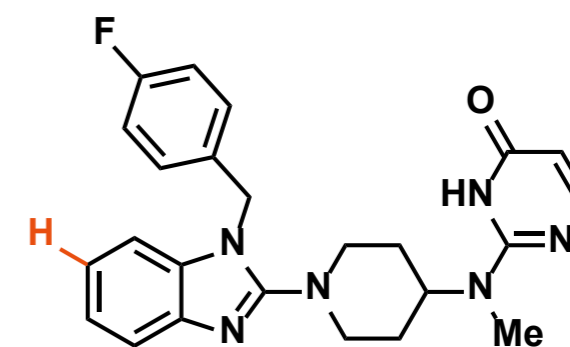
Ketanserin, 60%



Bifonazole, 87%

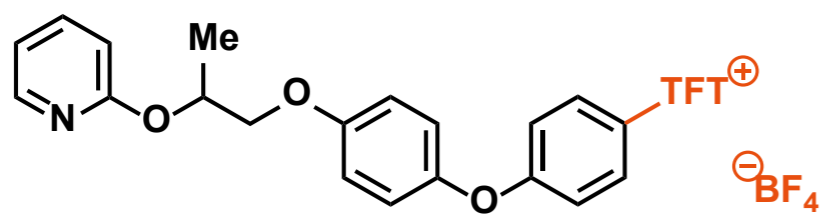


Dasatinib, 80%

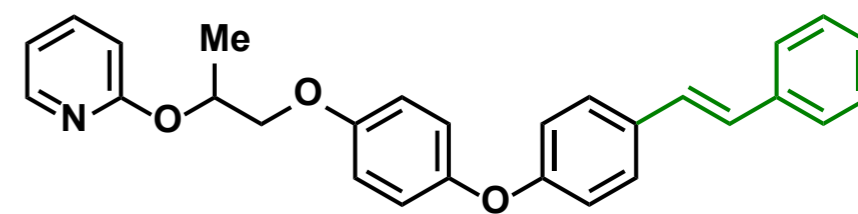


Misolastine, 62%

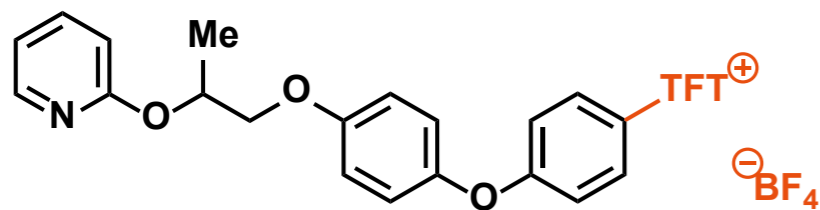
TFT as a Useful Linchpin



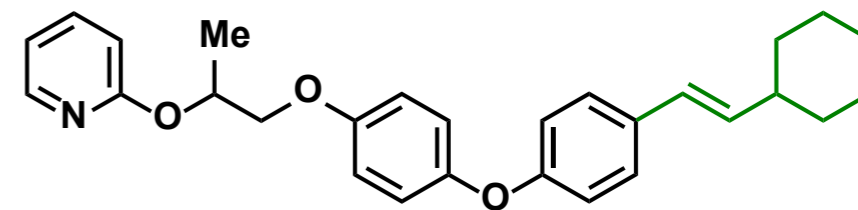
Heck



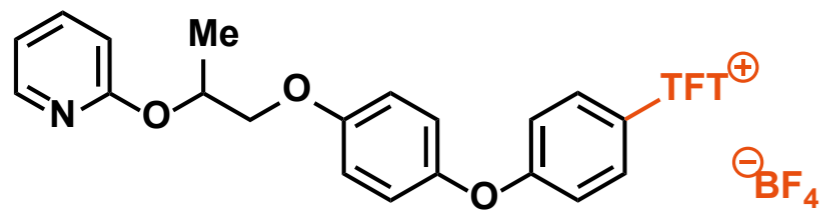
86%



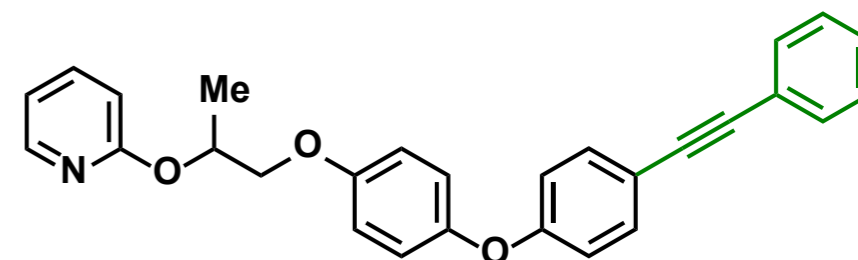
Suzuki



90%

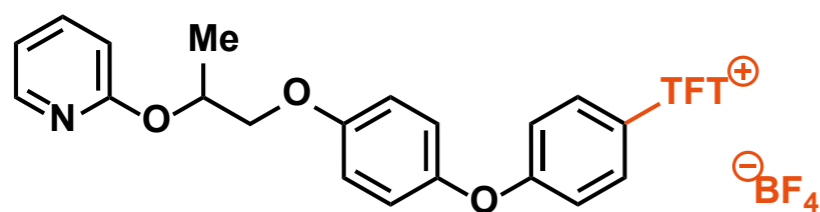


Sonogashira

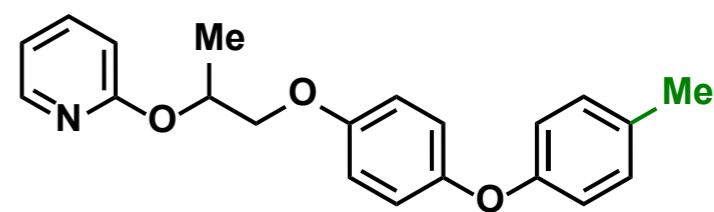


95%

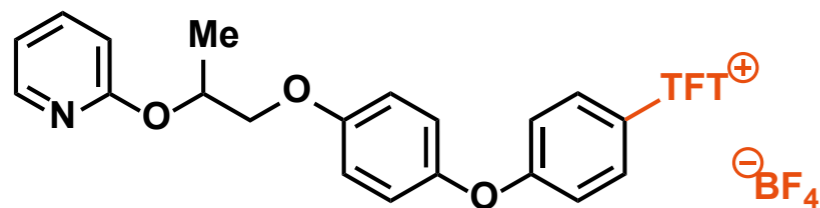
Versatile C–H Functionalization



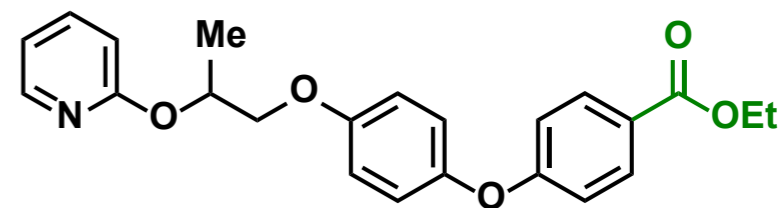
Negishi



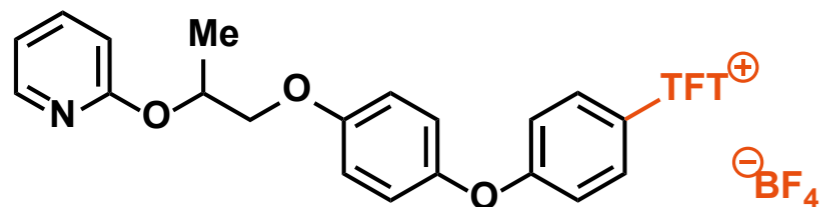
78%



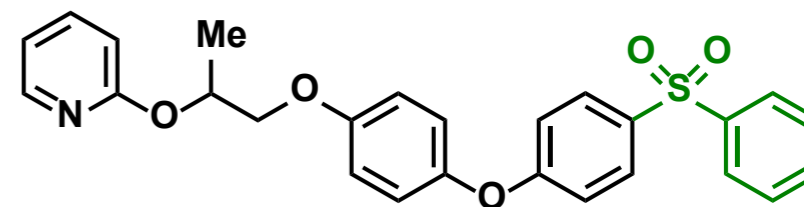
Carbonylation



91%

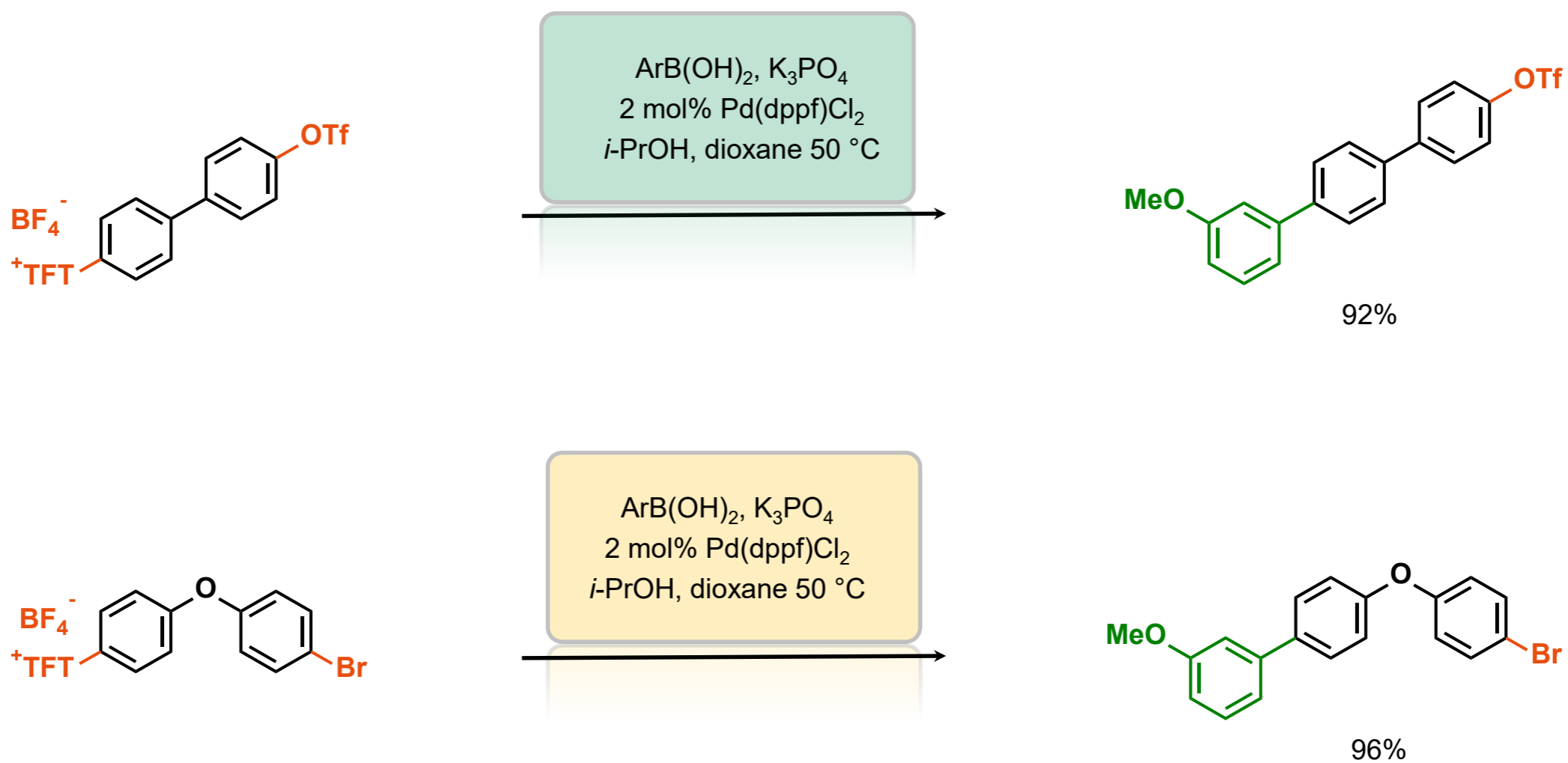


Sulfonylation

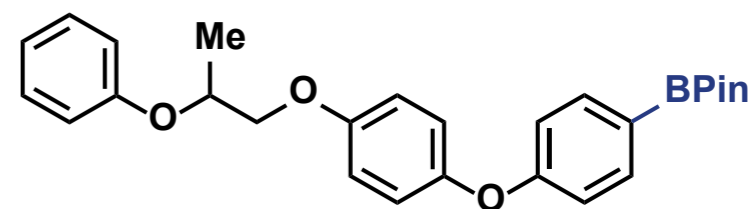
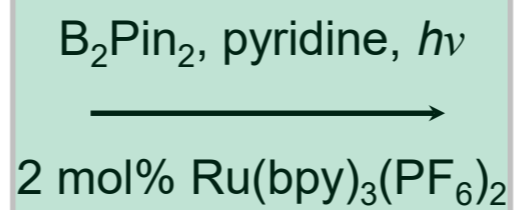
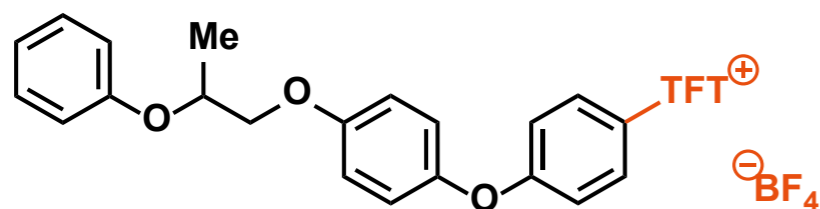


78%

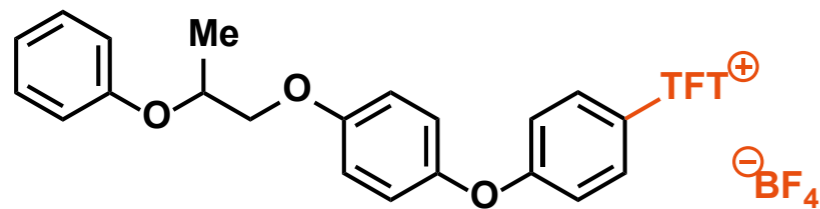
TFT in Conventional Cross Coupling



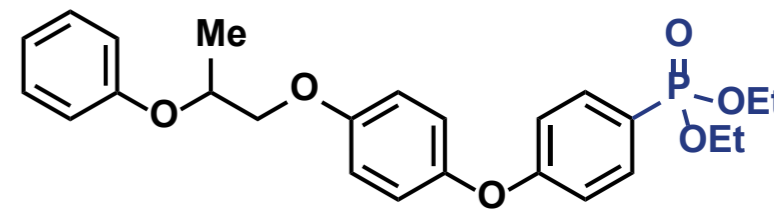
TFT in Photoredox Catalysis



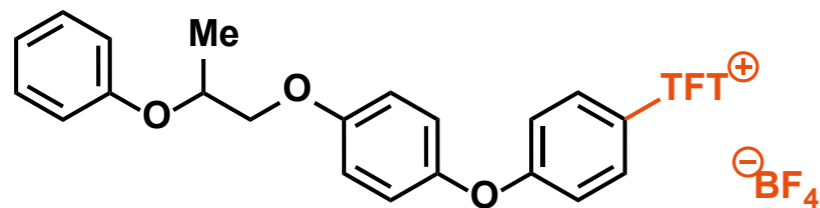
76%



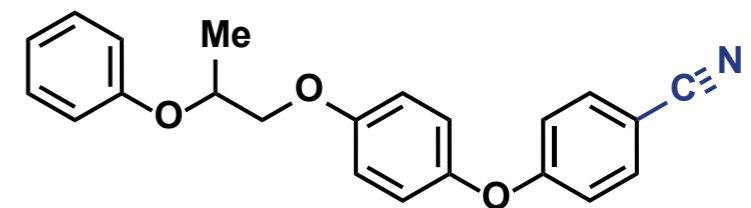
Phosphonylation



58%

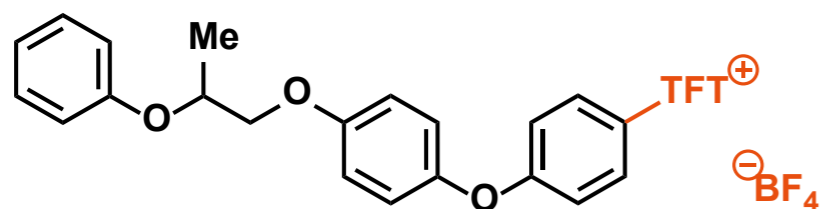


Cyanation

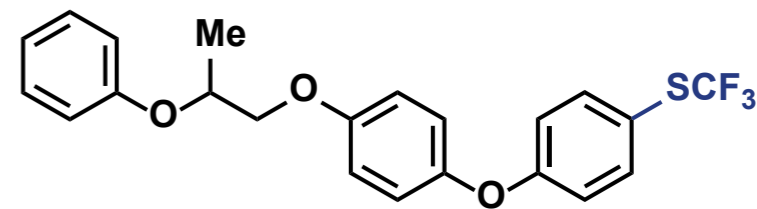


69%

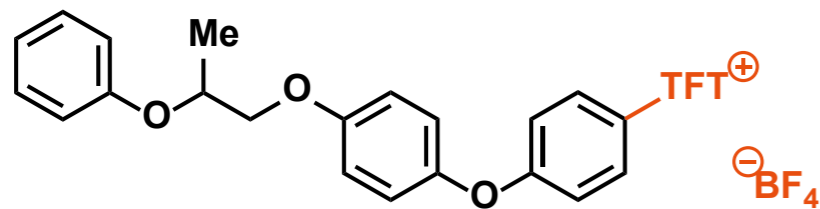
TFT in Photoredox Catalysis



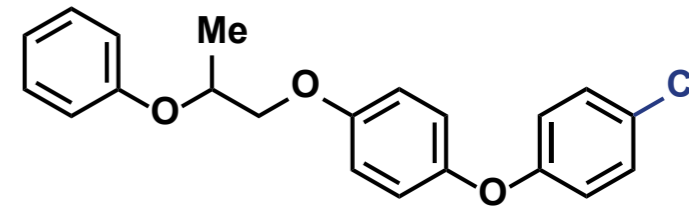
Trifluoromethyl
thiolation



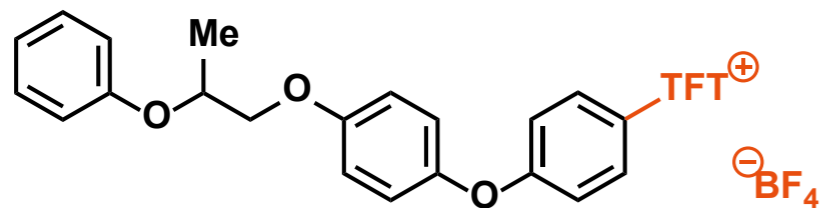
53%



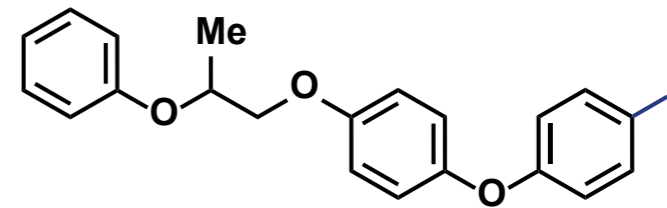
Chlorination



53%

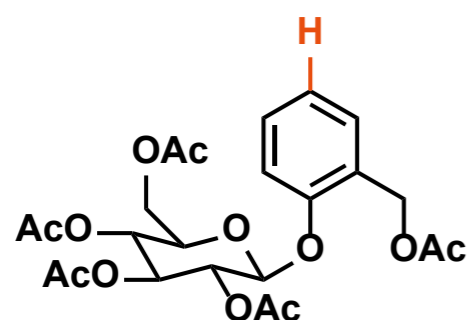


Iodination

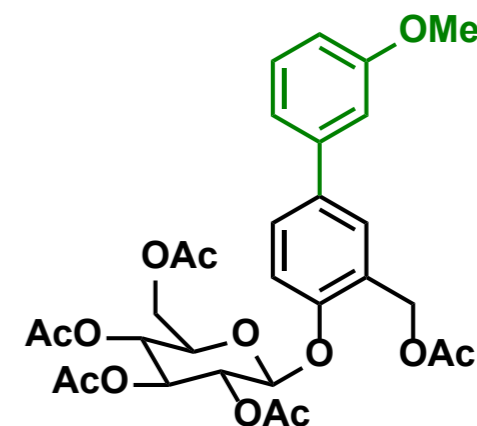


66%

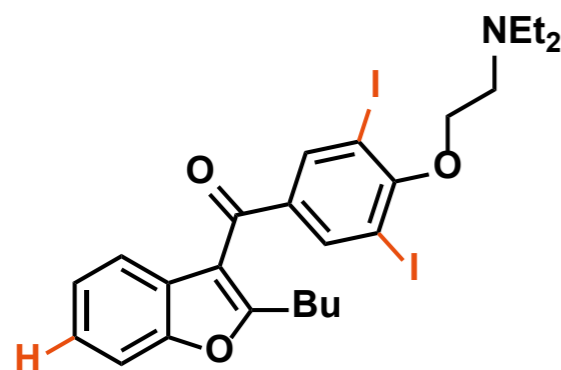
Selective Late-Stage C-H Functionalization



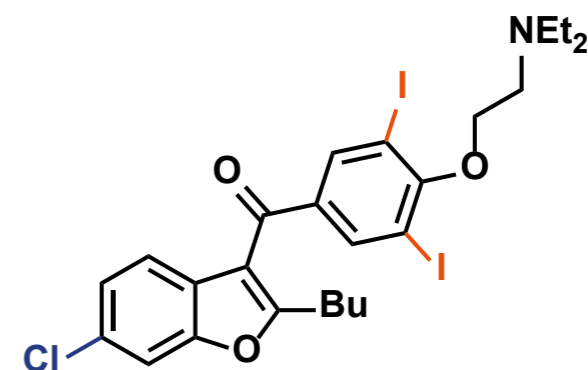
- 1) Thianthrenation
- 2) Conventional Suzuki Cross coupling



75%, 2 steps
76% TFT recovered
25 g scale

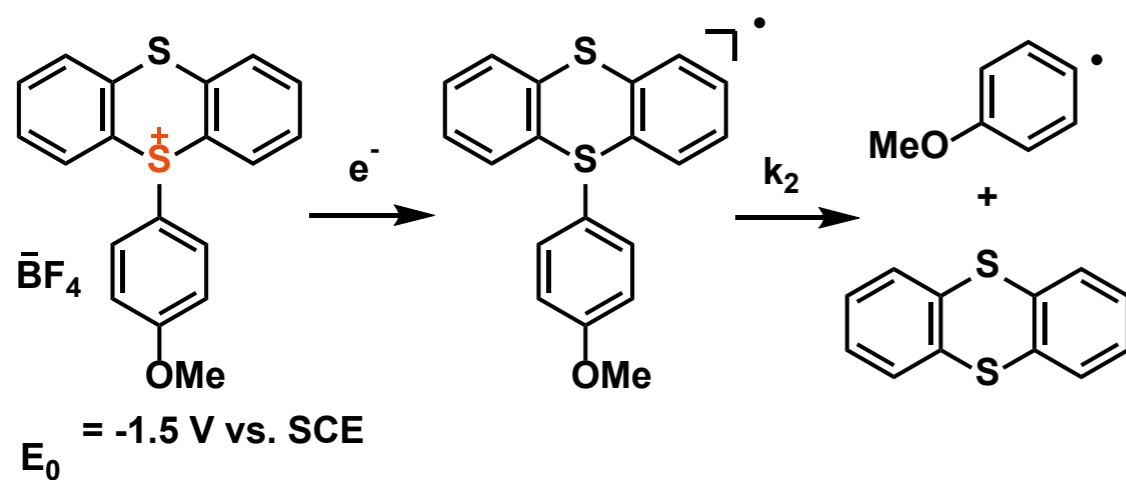
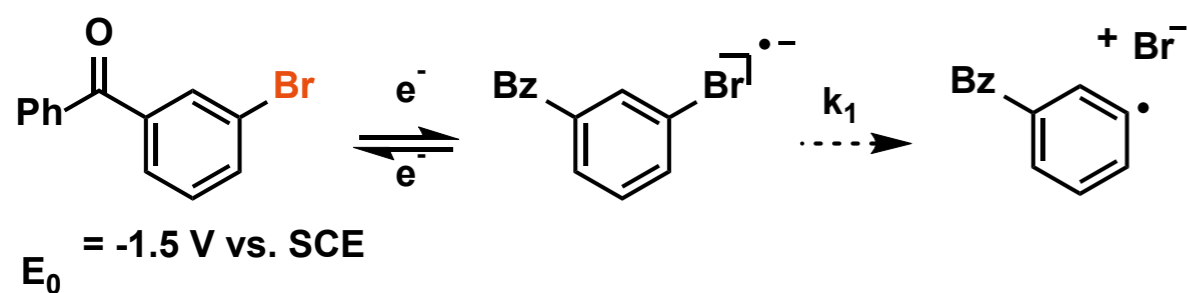


- 1) Thianthrenation
- 2) Photoredox chlorination

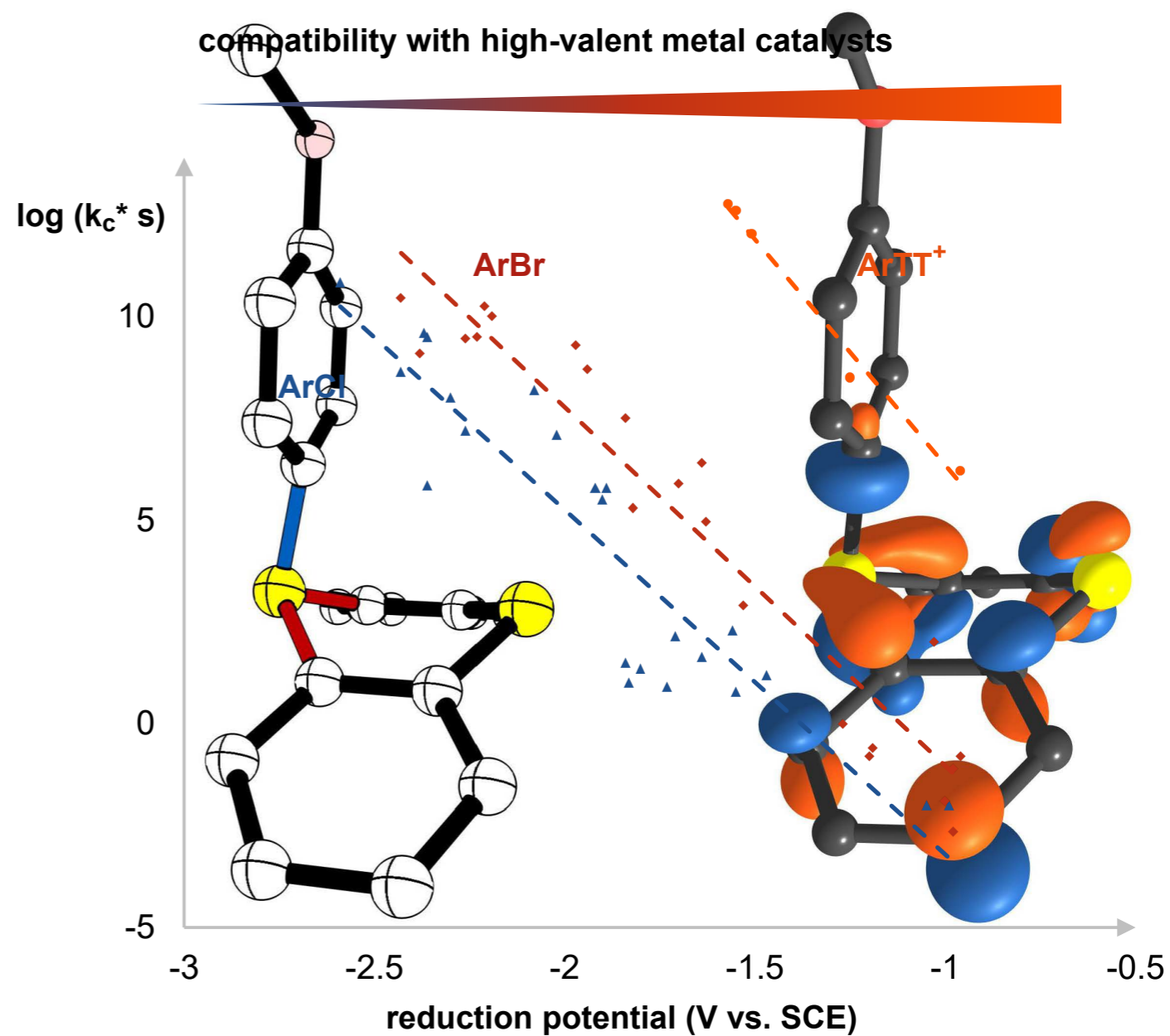


50%, 2 steps

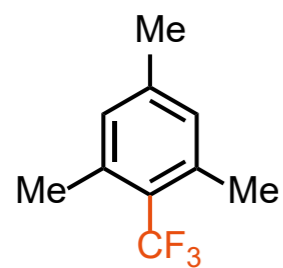
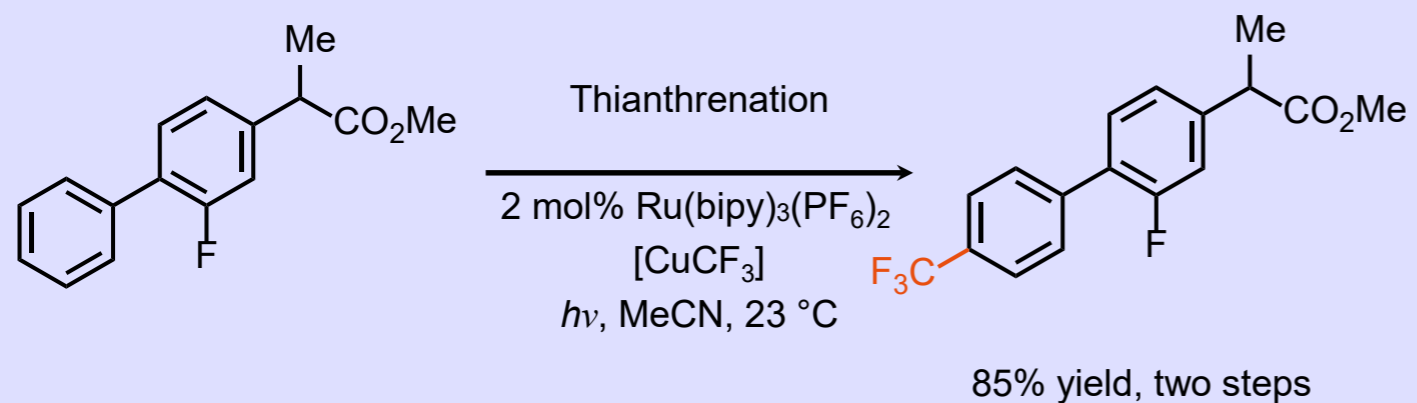
Arylsulfoniums desirable in Photoredox Catalysis



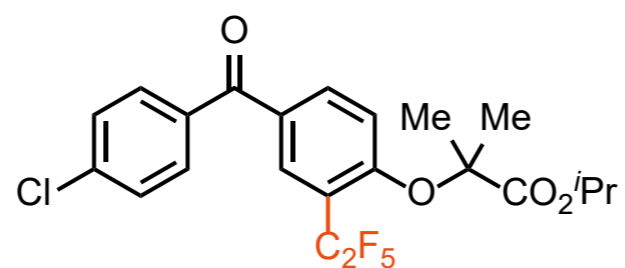
$$k_2/k_1 > 10^{10}$$



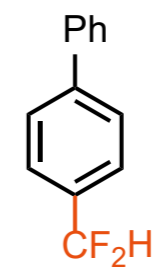
Site-selective Trifluoromethylation



41%

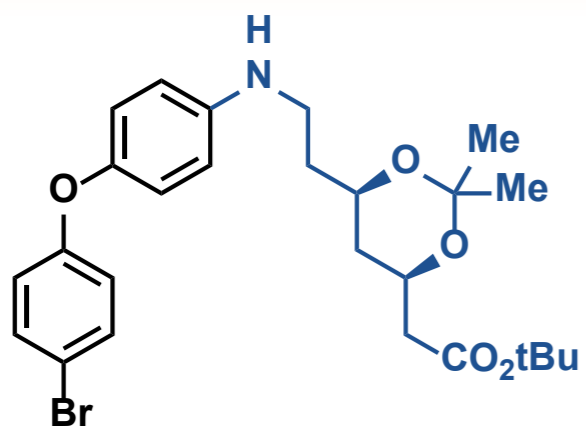
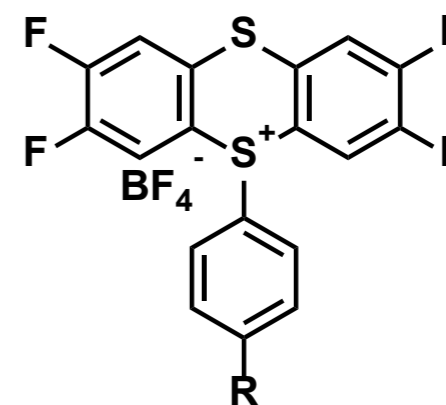
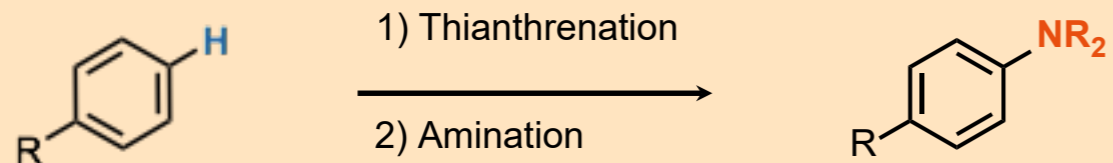


70%

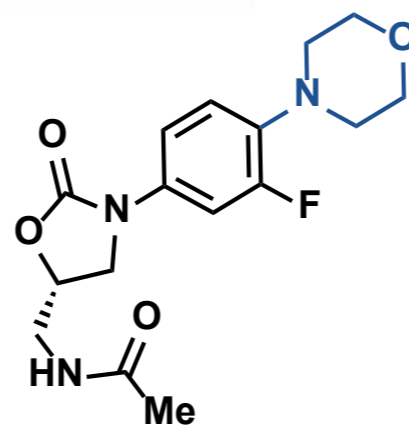


38%

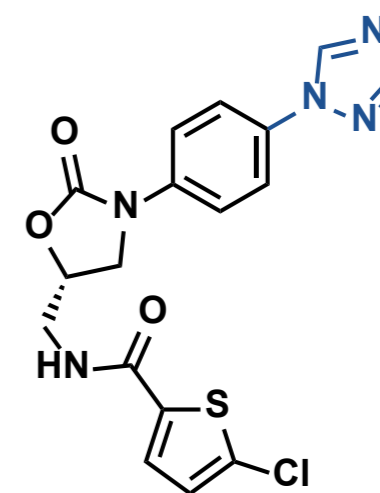
Site-Selective Amination



58%

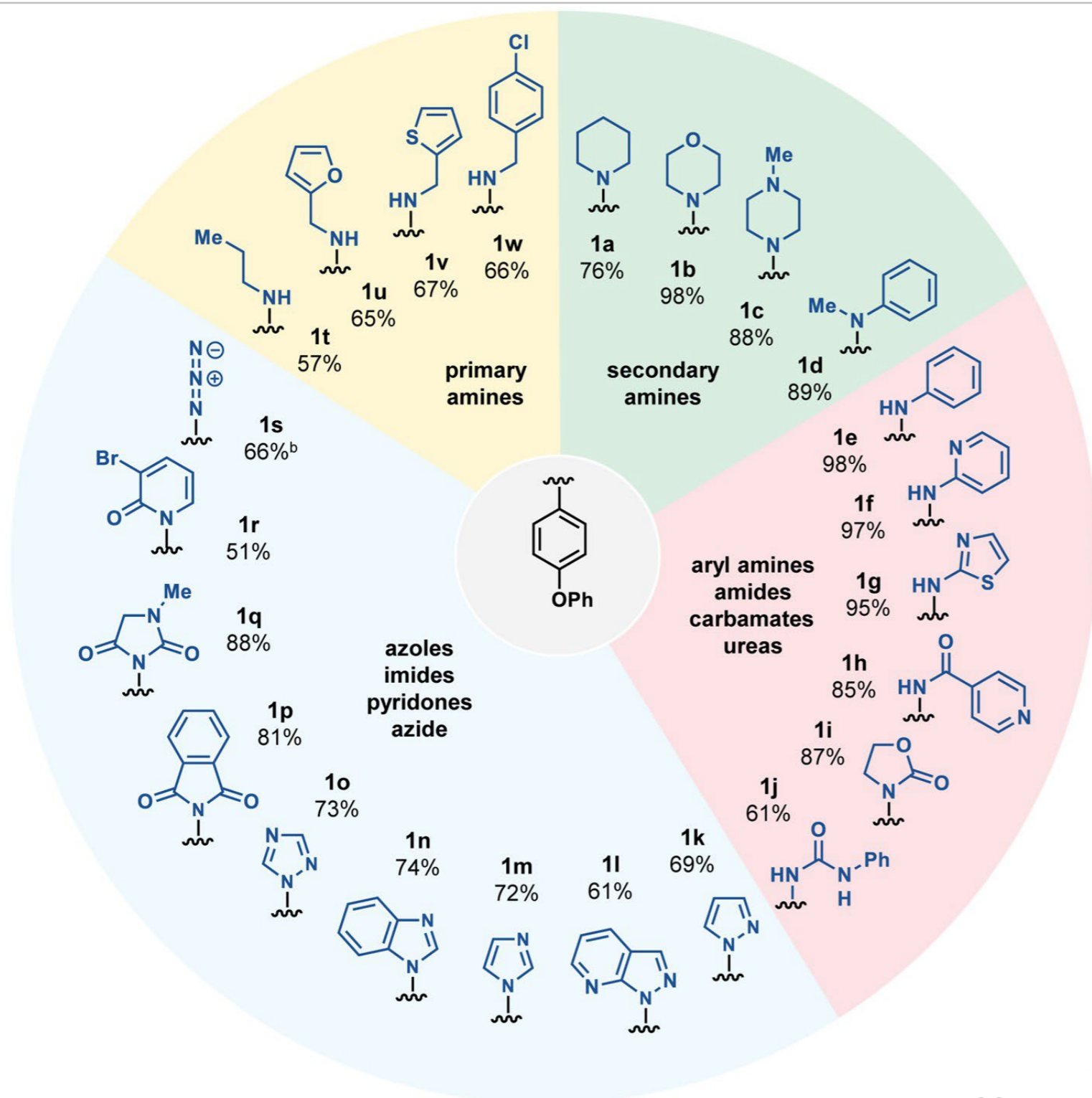


36%



55%

Site-Selective Amination



Method A

1 mol% $[\text{Pd}_2(\text{dba})_3]$
 2 mol% RuPhos
 1.5 equiv. HNR^2R^3
 2 equiv. Cs_2CO_3
 DMF, 90 °C, 20 h

Method B

1 mol% $[(\text{PdAlPhos})_2\text{COD}]$
 1.5 equiv. HNR^2R^3
 2 equiv. DBU
 THF, 70 °C, 16 h

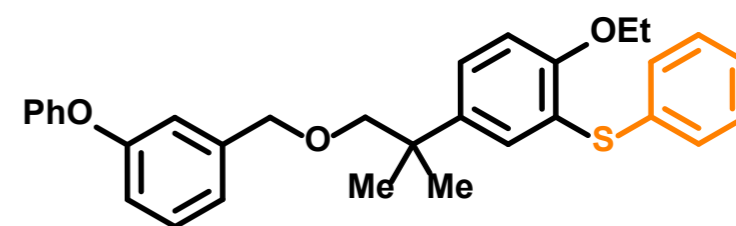
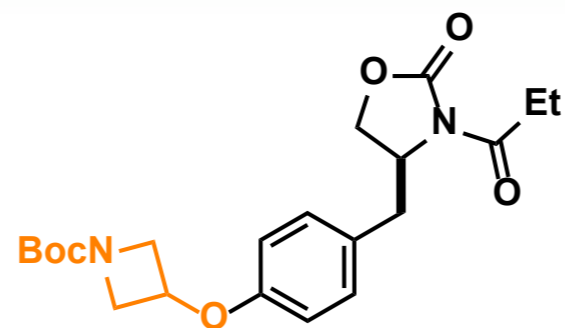
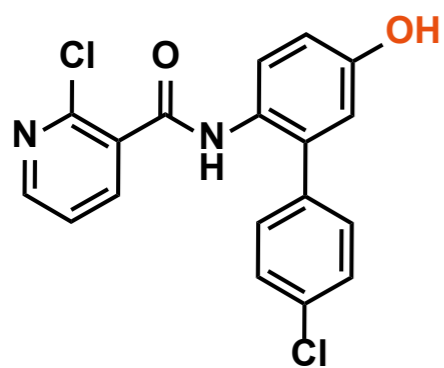
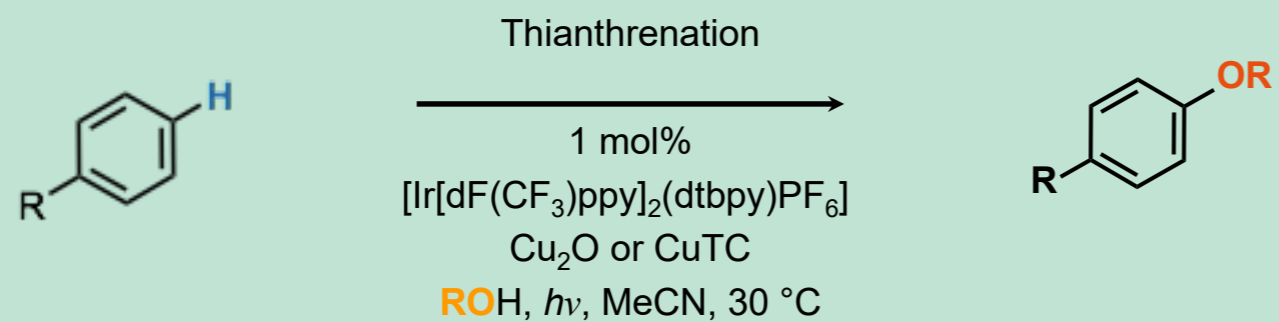
Method C

5 mol% $[\text{Ru}(\text{bipy})_3](\text{PF}_6)_2$
 1 equiv. $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$
 3 equiv. HNR^2R^3
 3 equiv. NMe_4OH or NaH
 MeCN:DMSO (1:1)
 blue LED (60W), 15 °C, 8 h

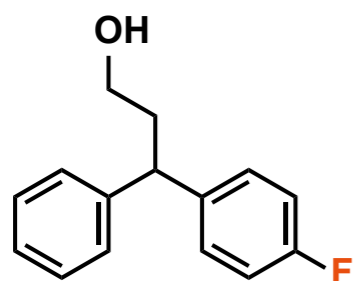
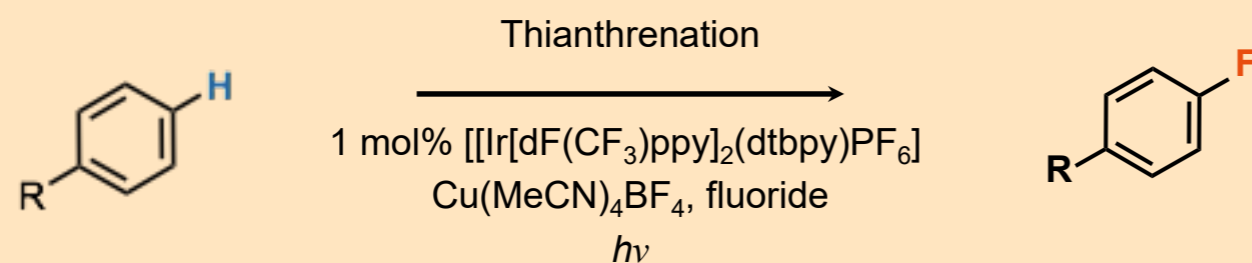
Method D

3 mol% $[\text{Ir}(\text{ppy})_3]$
 1 equiv. $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$
 1.5 equiv. HNR^2R^3
 2 equiv. K_2CO_3
 MeCN, blue LED (60W)
 15 °C, 8 h

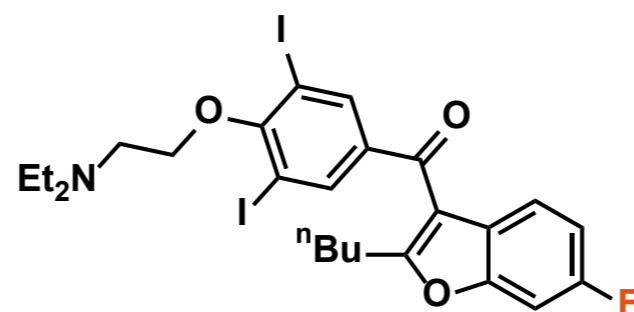
Site-selective Chalcogenation



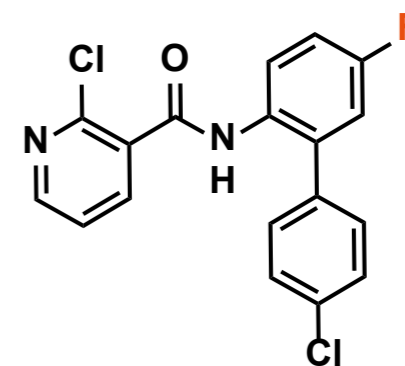
Site-selective Fluorination



78%

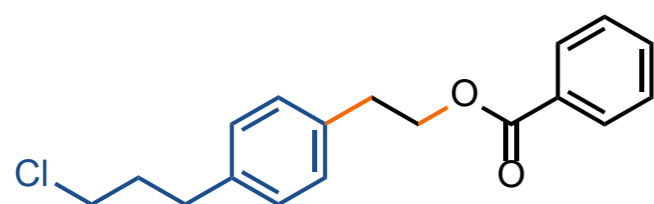
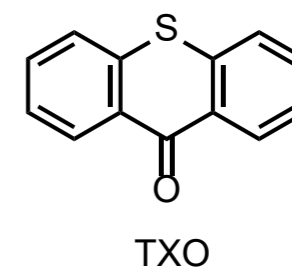
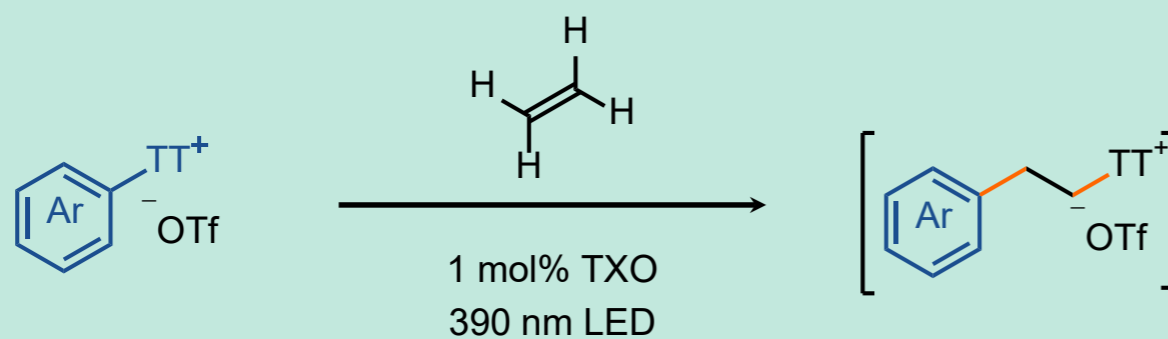


35%

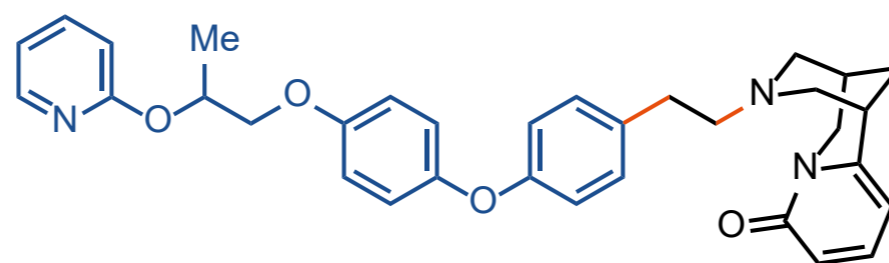


80%

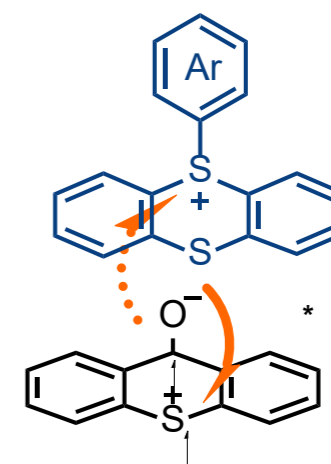
Energy Transfer to Aryl TT Salts



63%

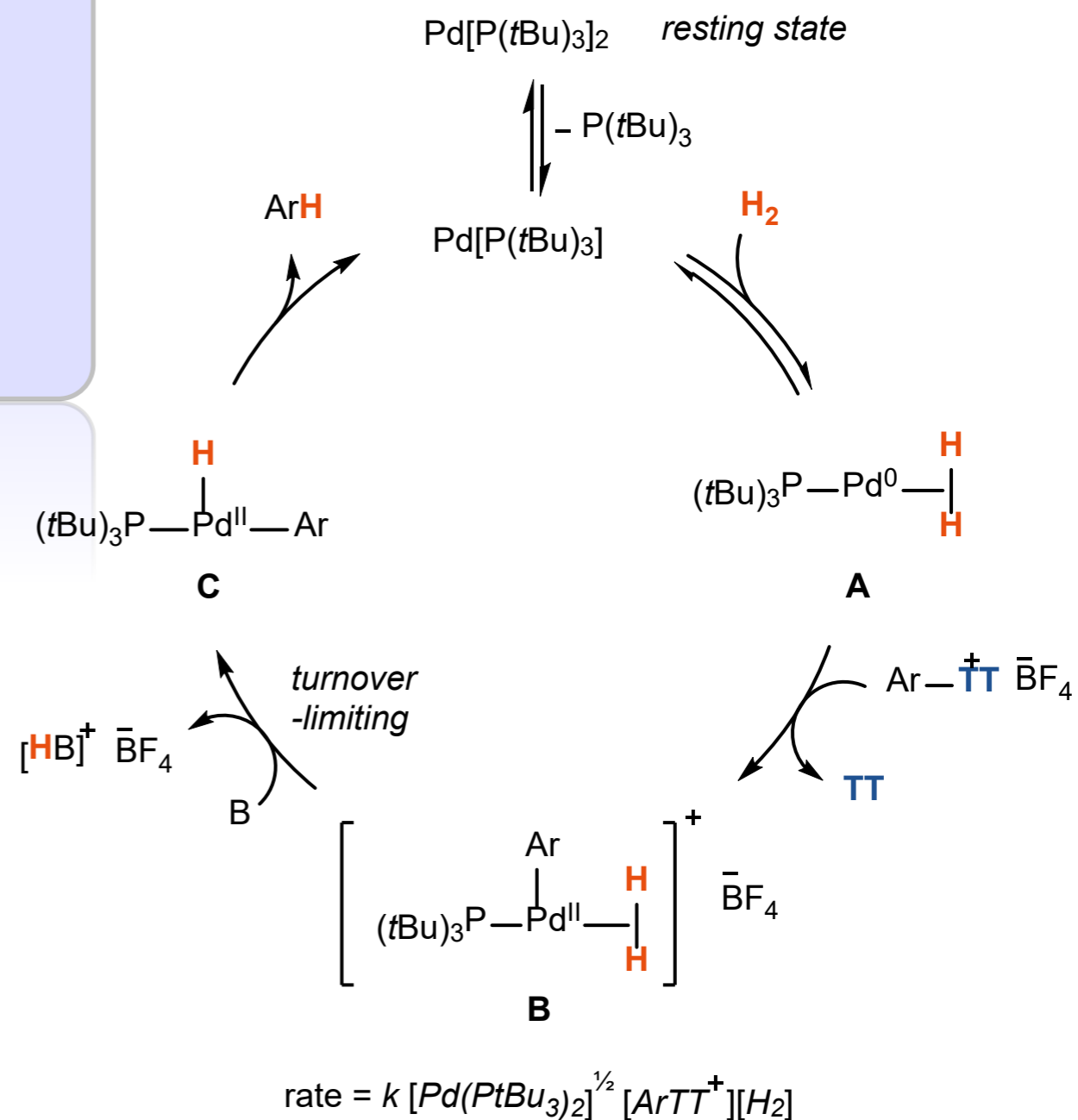
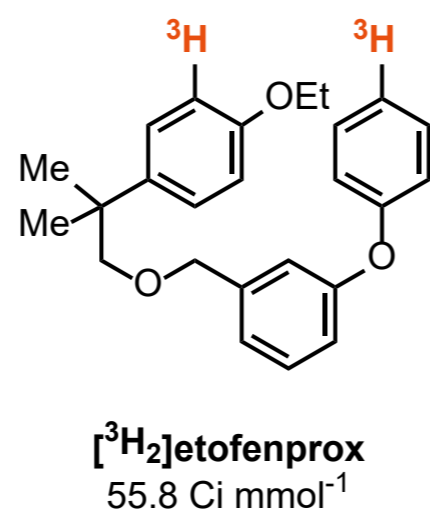
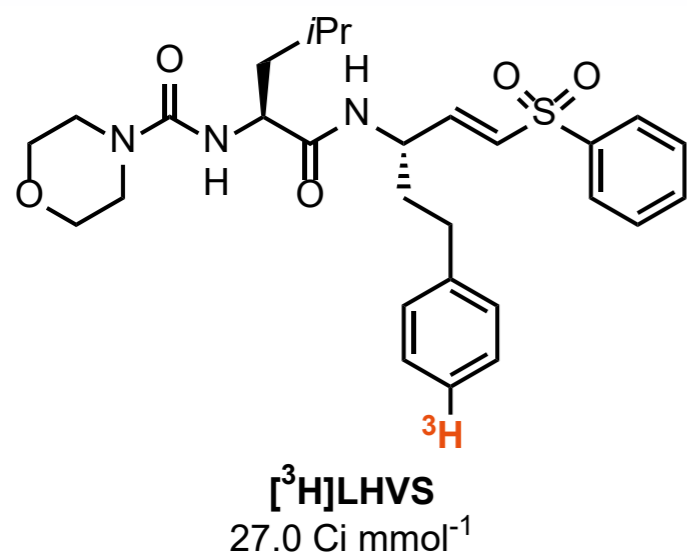
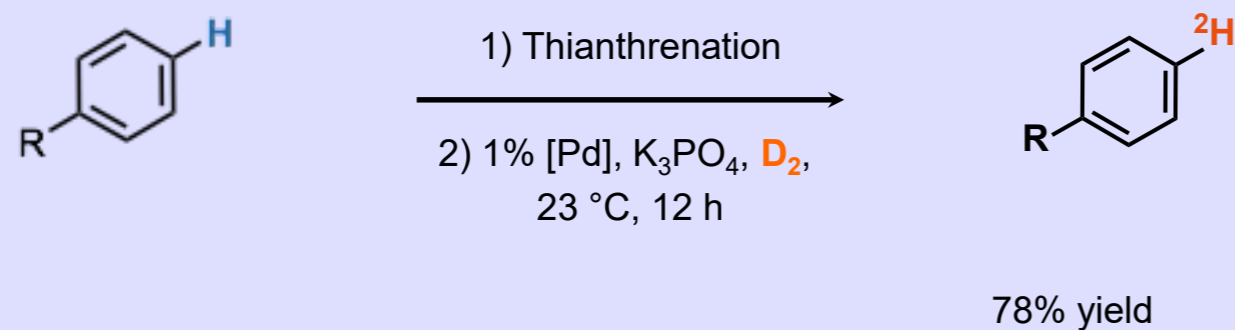


63%

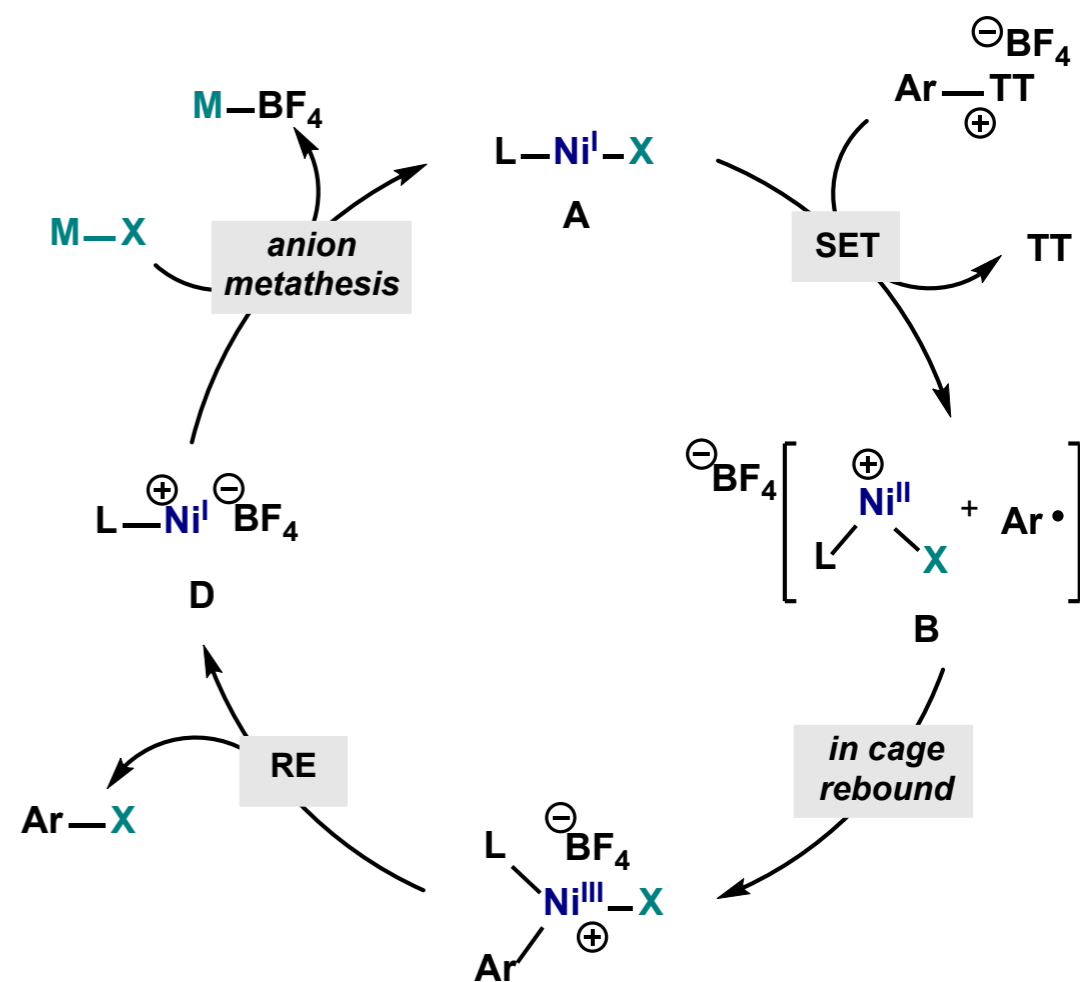
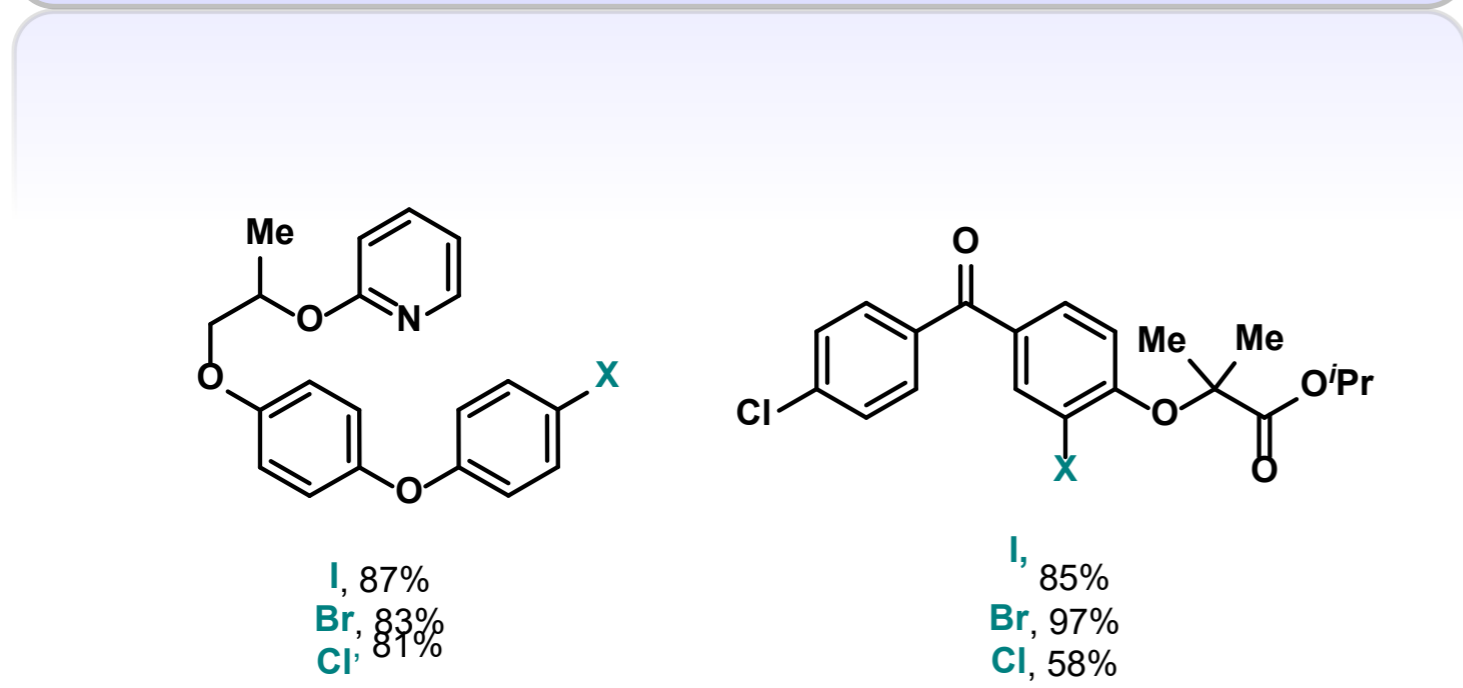
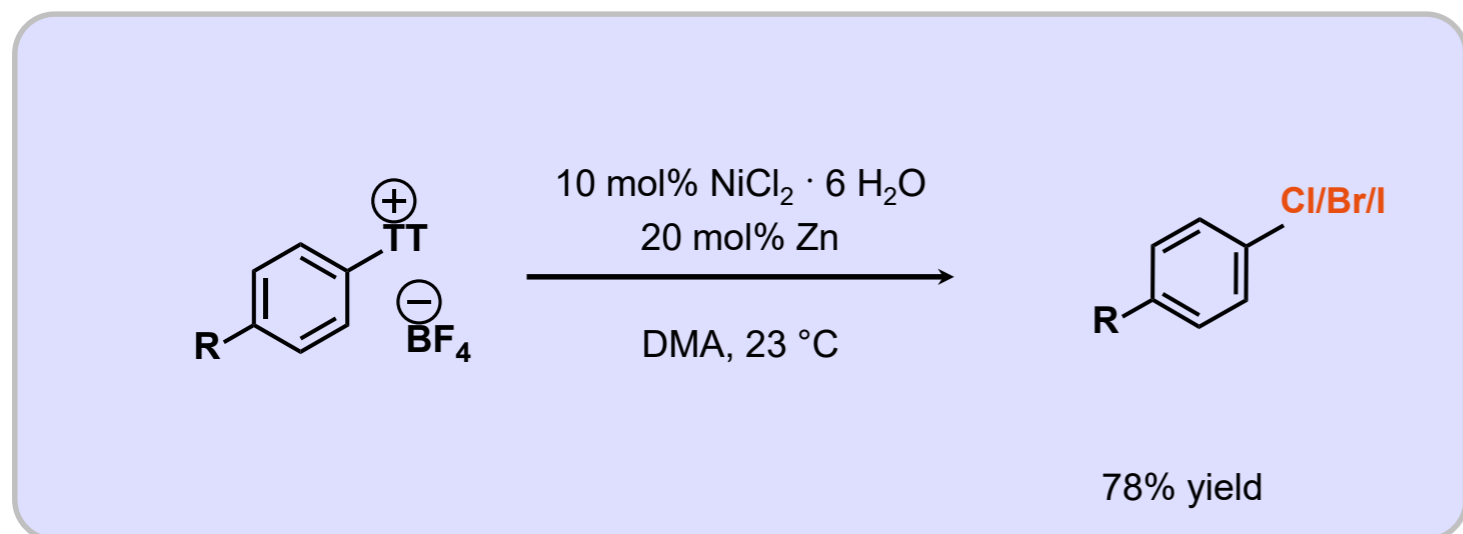


Dexter
Energy transfer

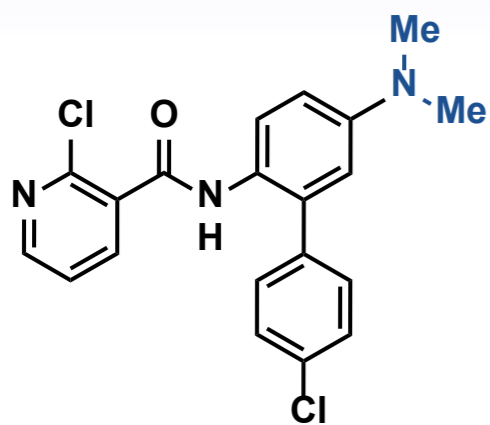
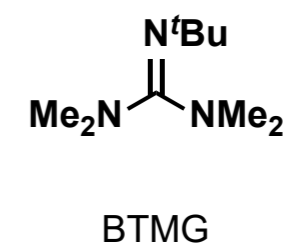
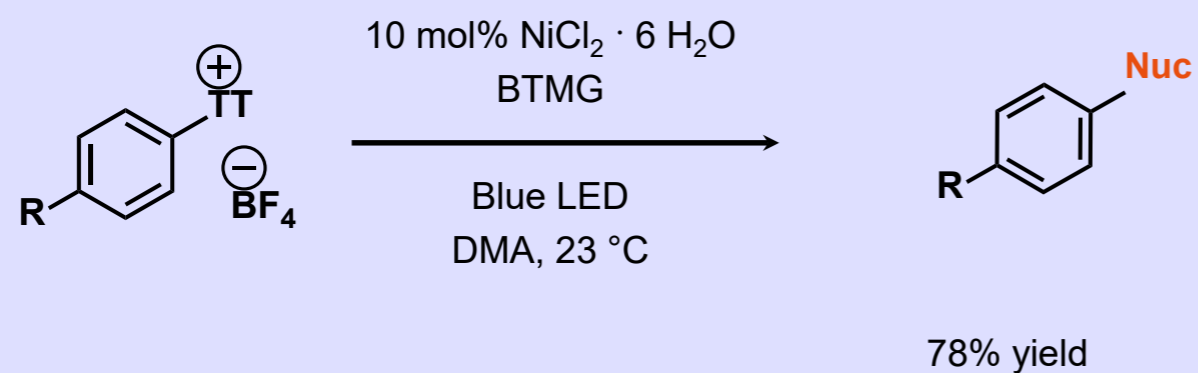
Homogeneous Aryl pseudohalide Hydrogenolysis



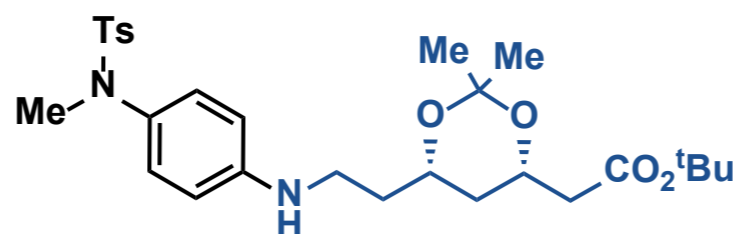
Homogeneous Ni(I)/(III) Catalysis



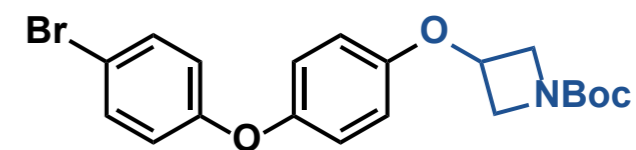
Homogeneous Ni(I)/(III) Catalysis



42%

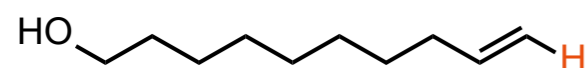
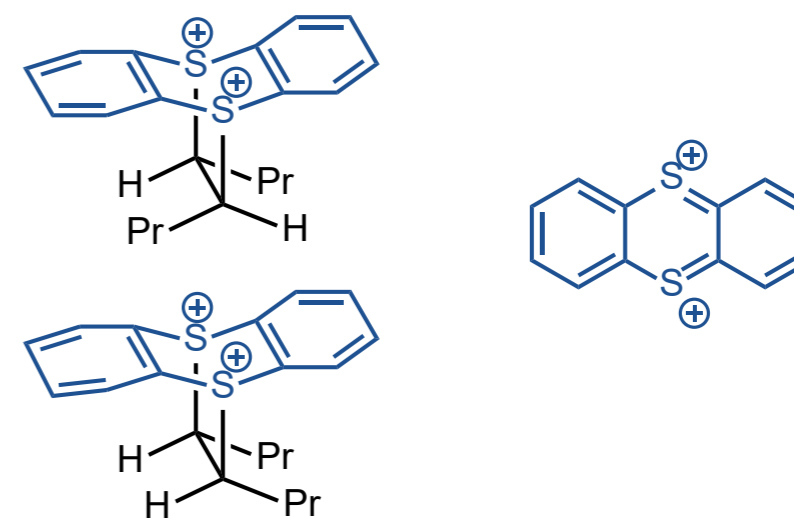
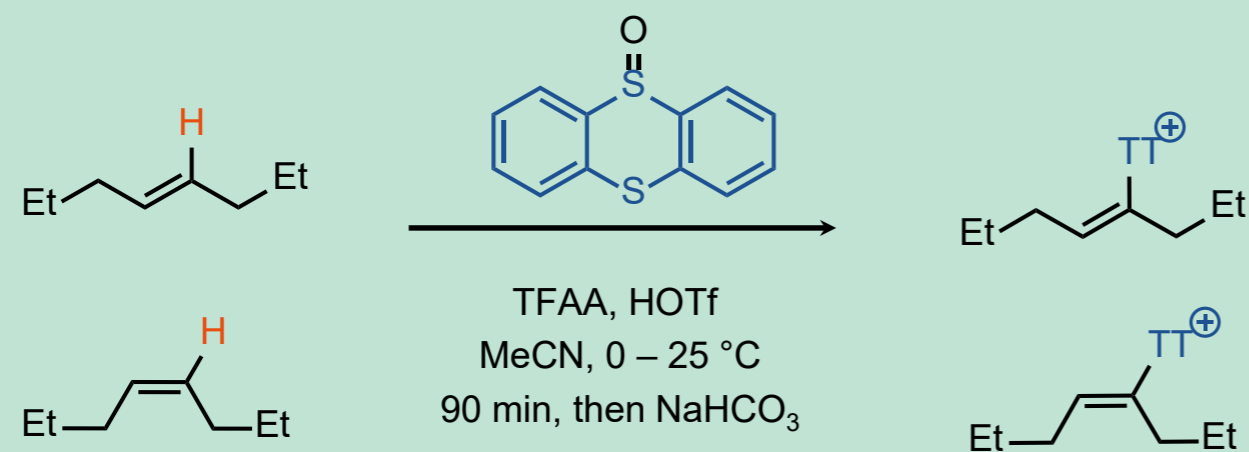


64%

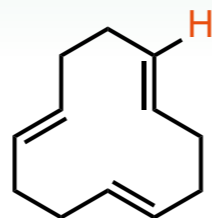


51%

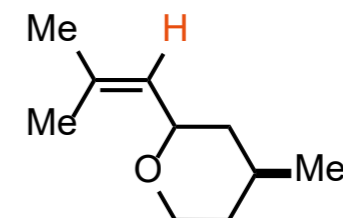
Stereoselective Olefin Functionalization



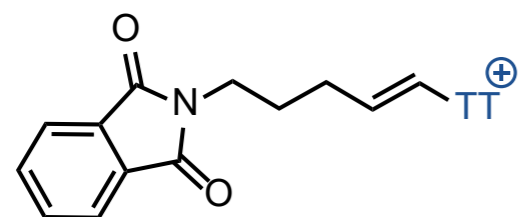
71%



68%

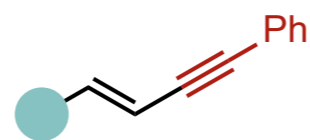


75%

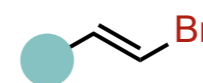


[Pd] or [Ru]

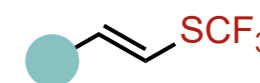
catalysis



95%

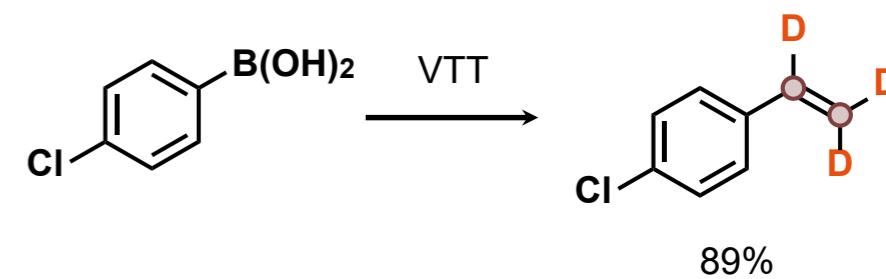
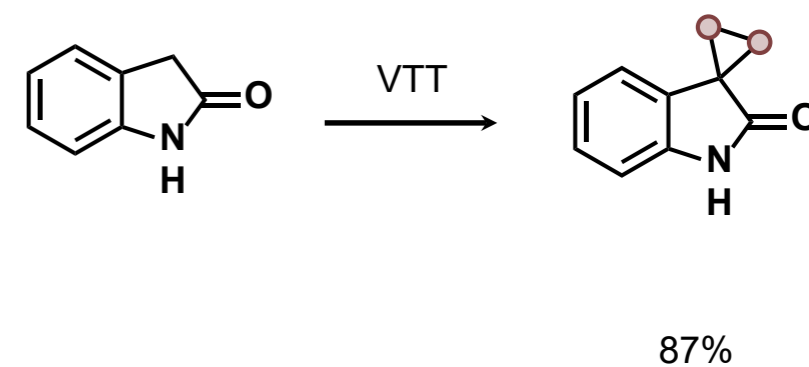
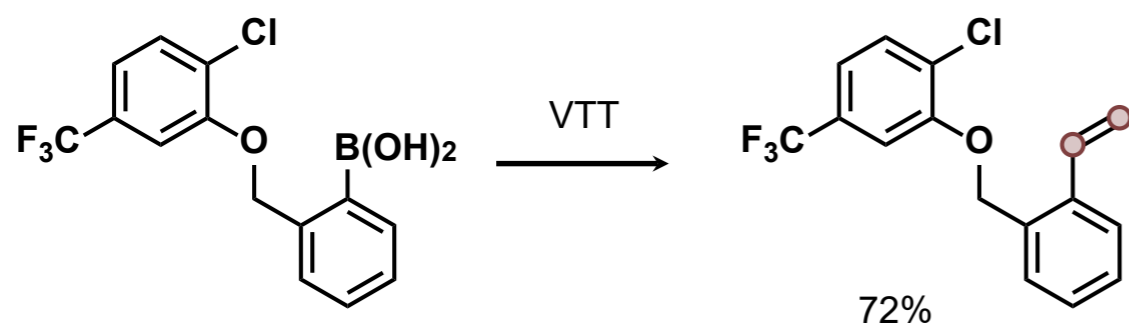
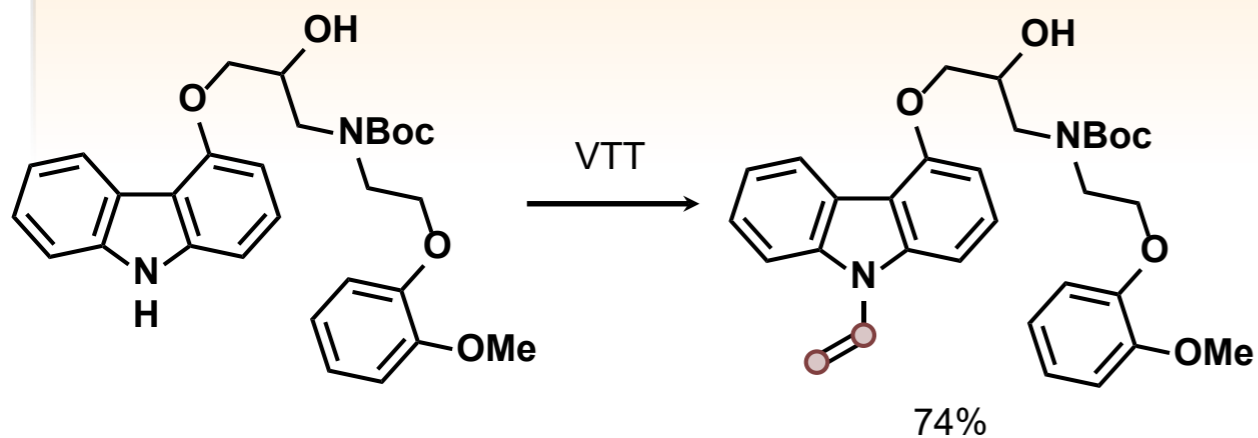
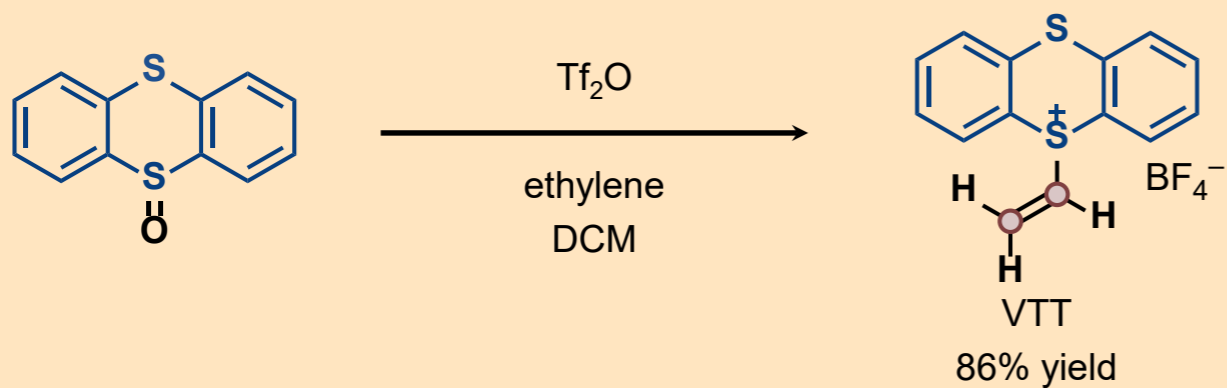


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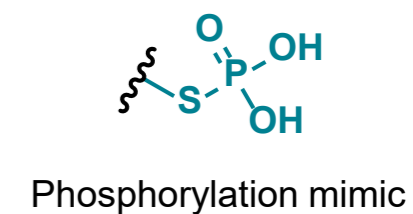
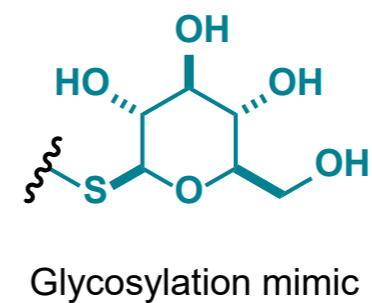
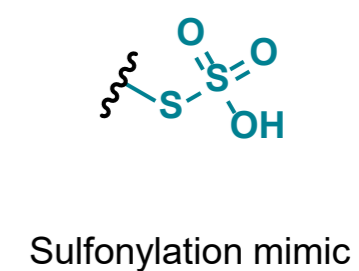
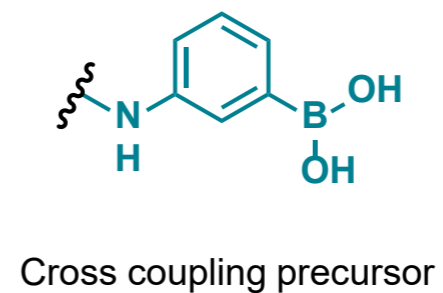
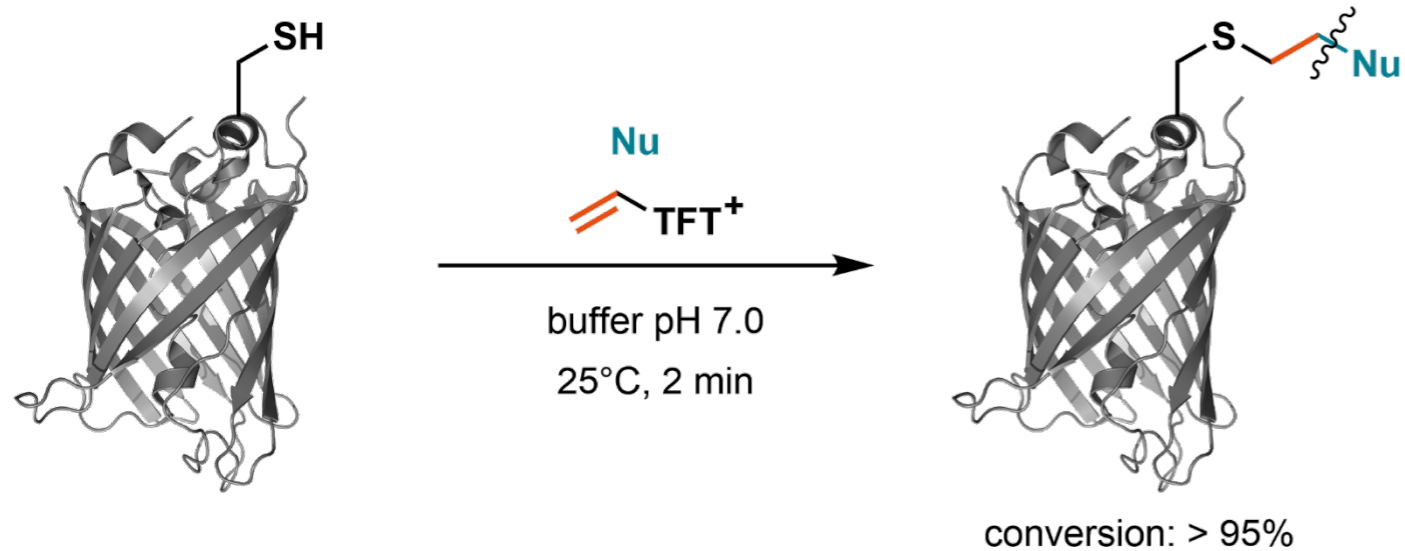
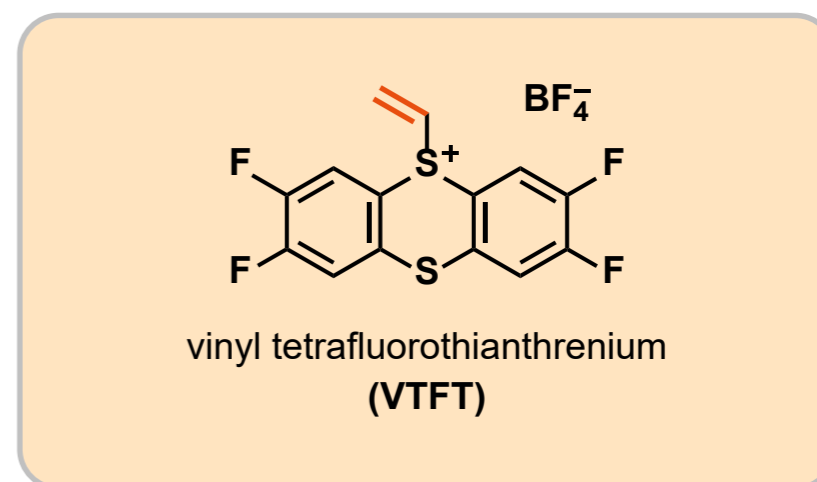
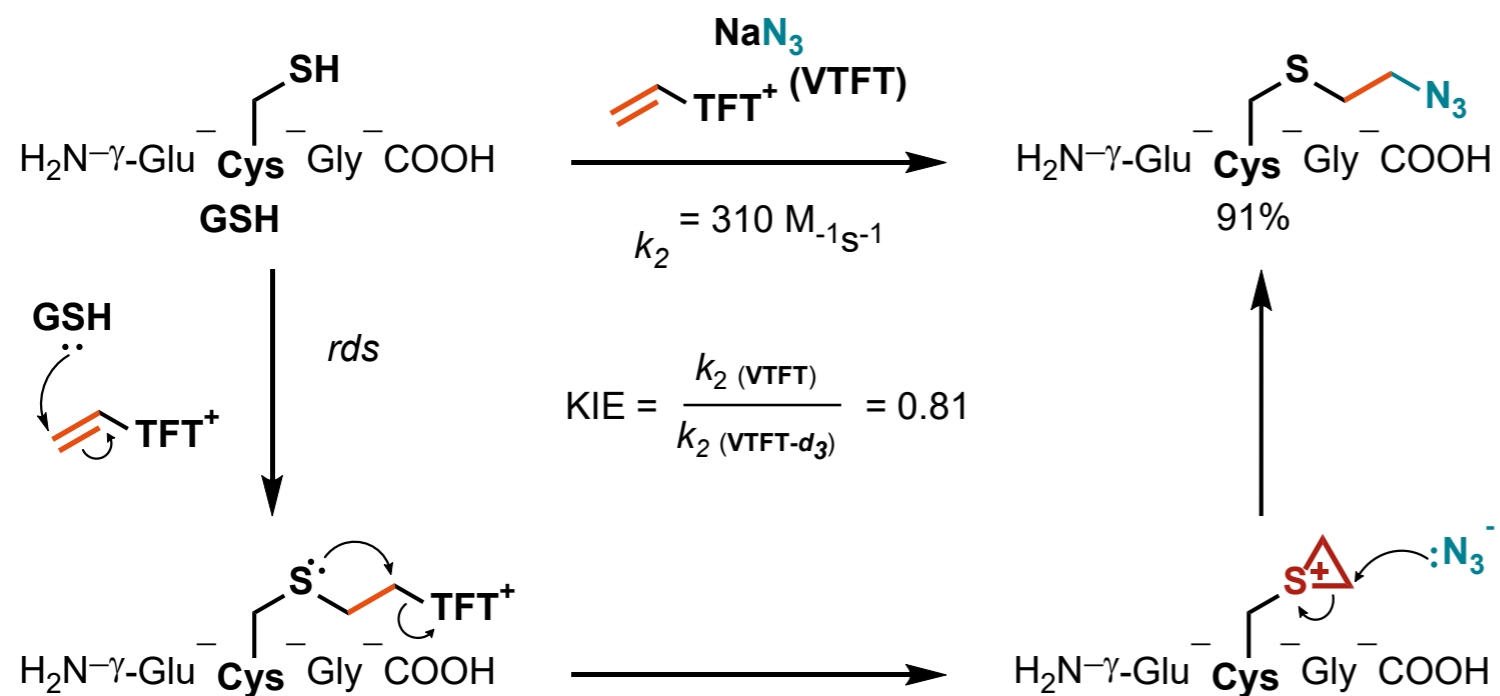


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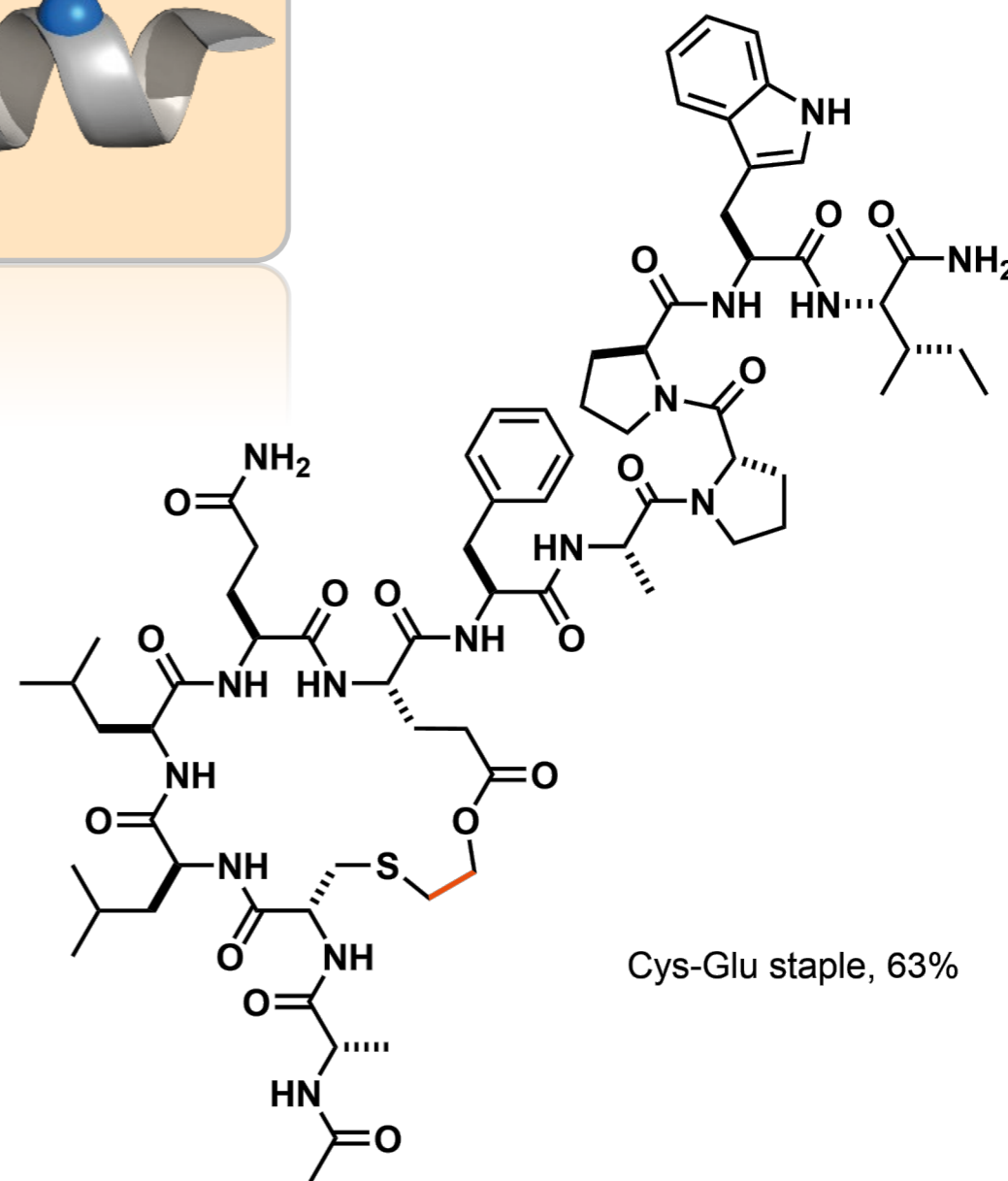
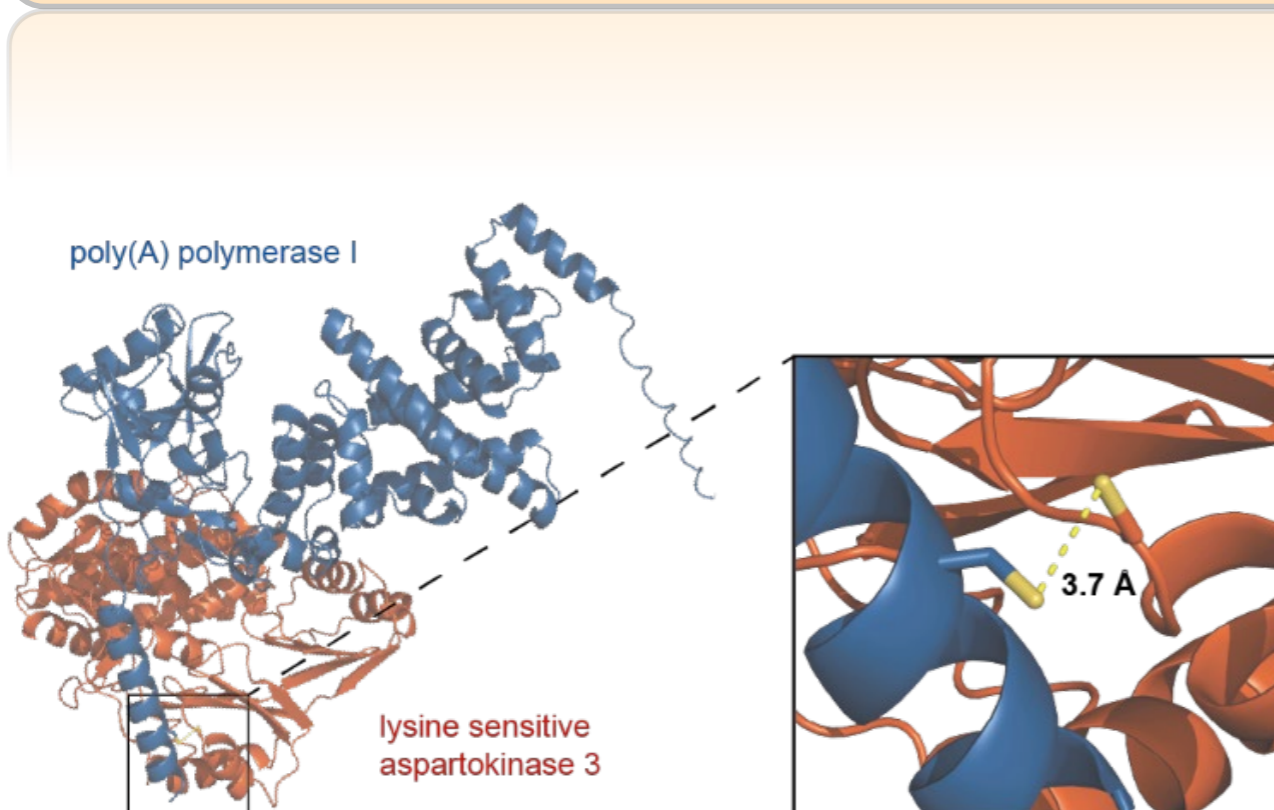
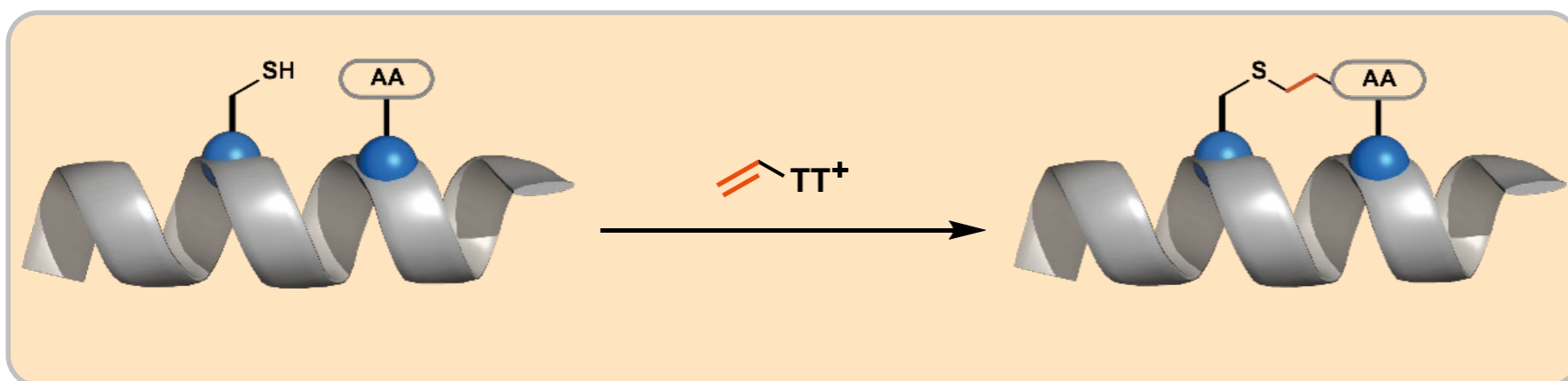
Vinyl-TT



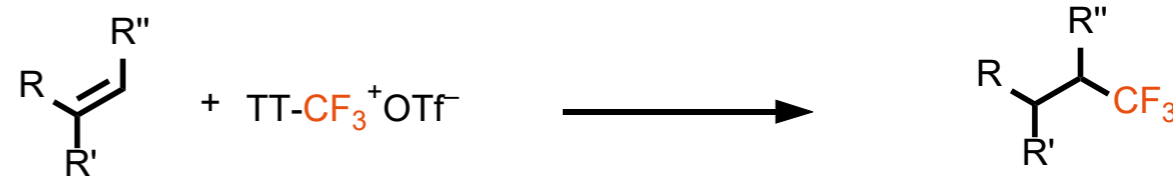
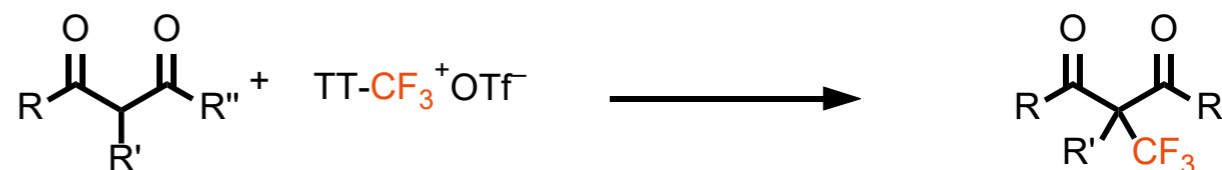
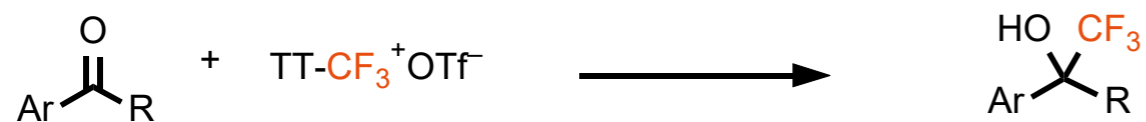
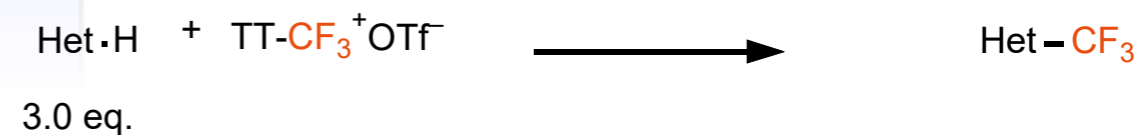
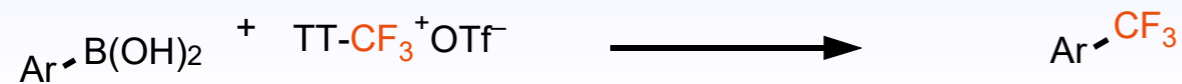
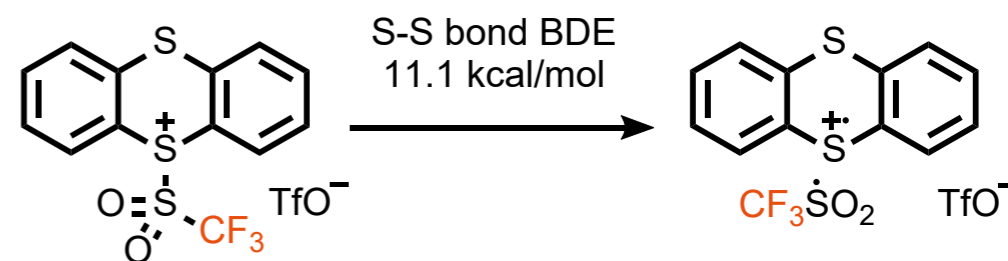
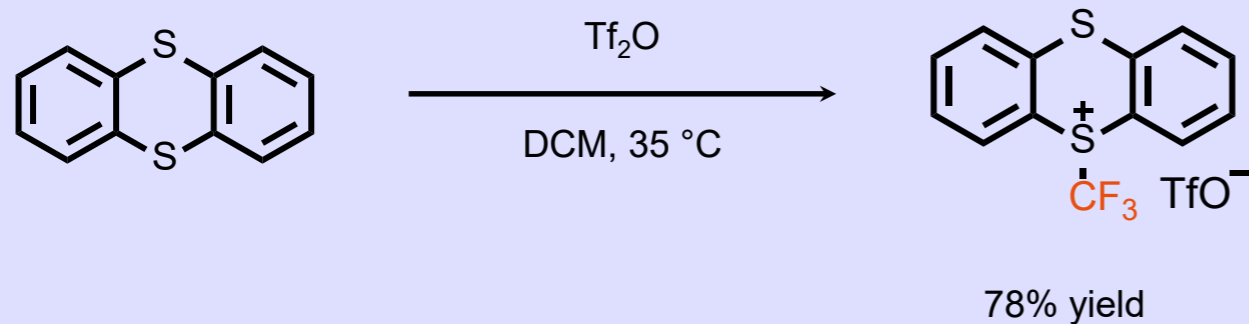
Cysteine-selective Bioconjugation



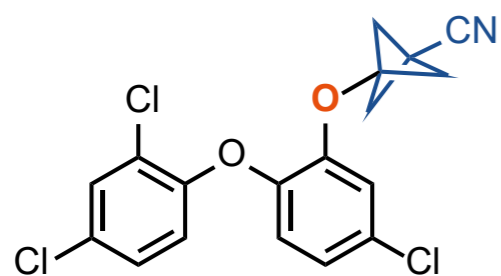
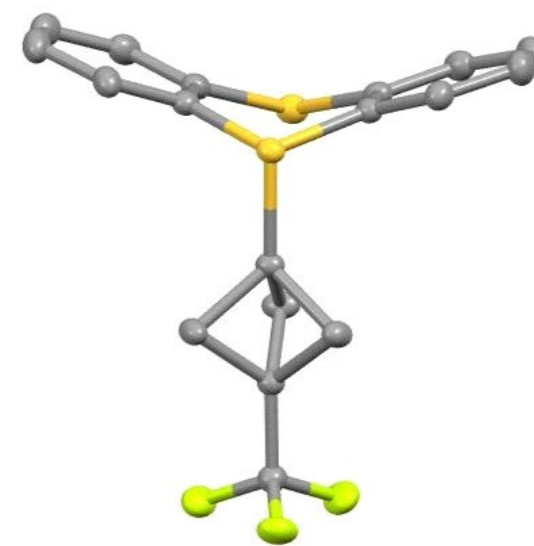
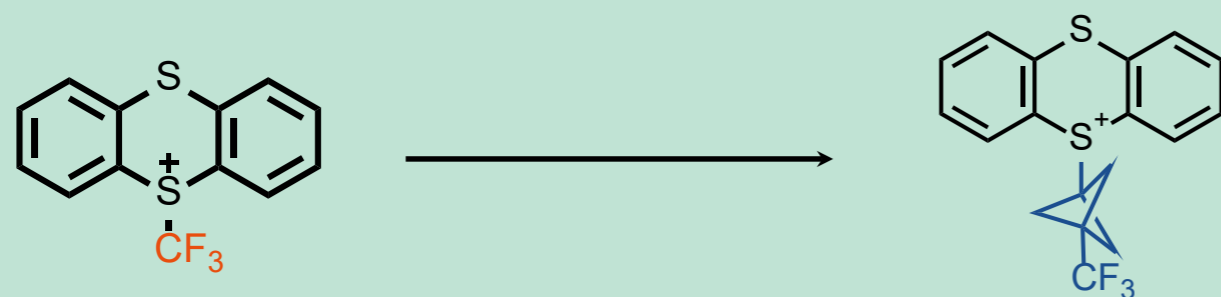
Amino acid cross-linking with ethylene linker



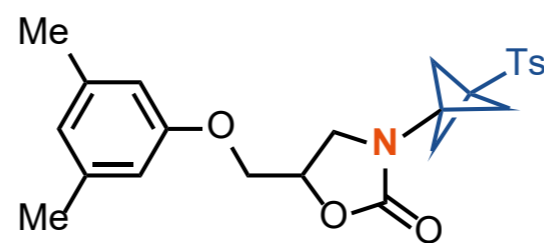
TT-based Trifluoromethylation Reagent



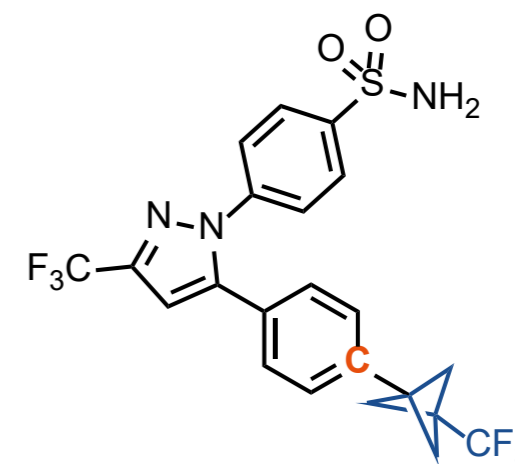
Alkyl Thianthenium Salts



83%

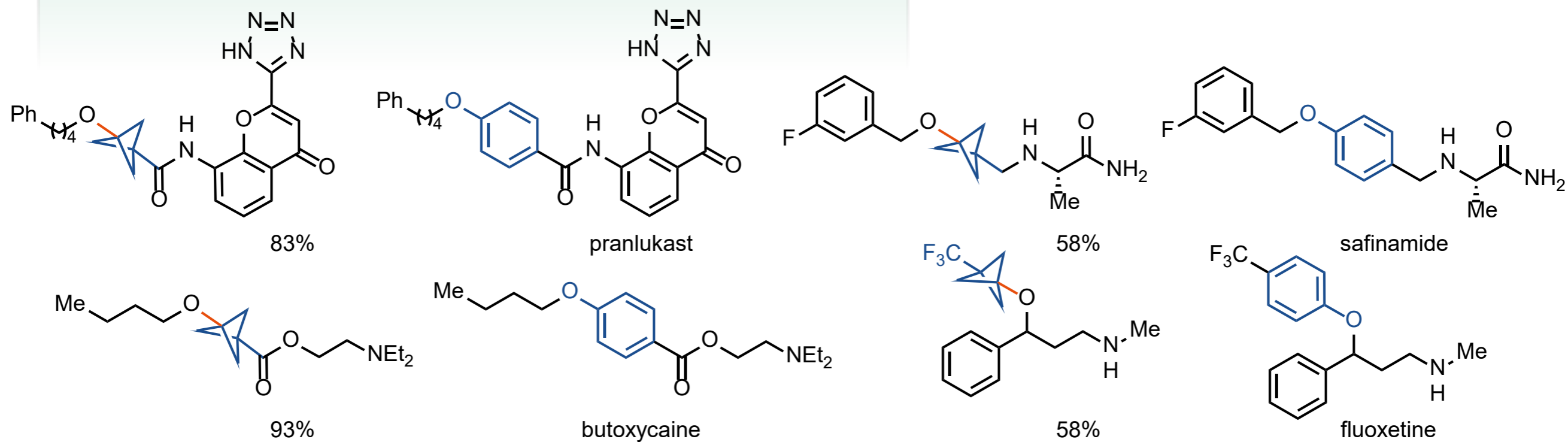
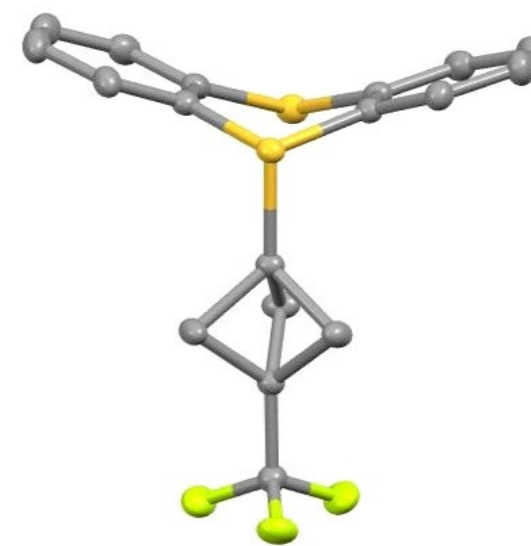
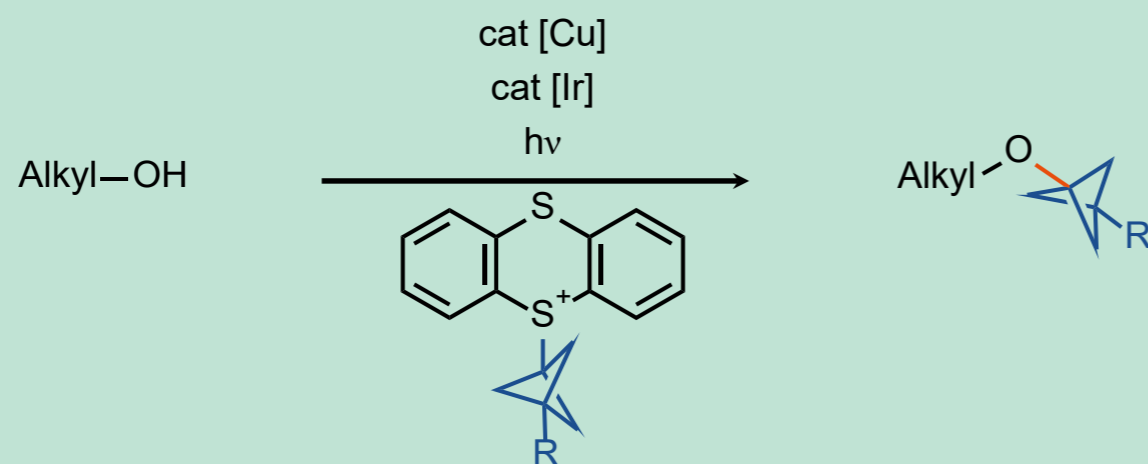


93%

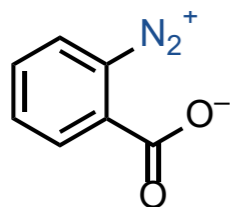


58%

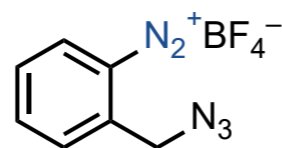
Bicyclopentenylation of Alcohols



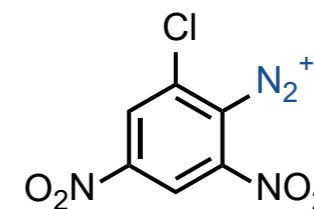
Safer Diazonium Chemistry



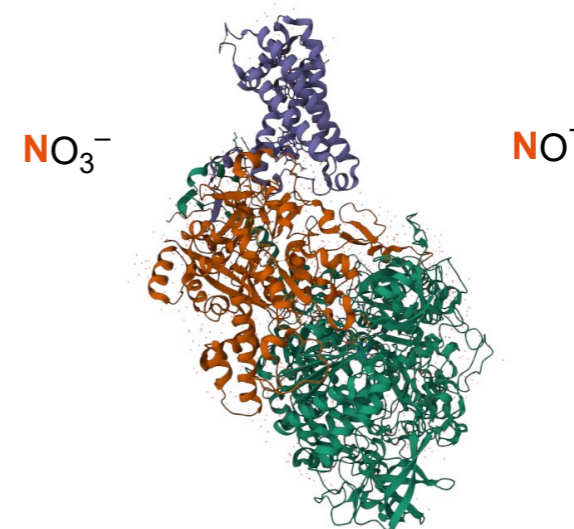
X = I, 68%



X = Cl, 48%



X = Br, 52%



Acknowledgements

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