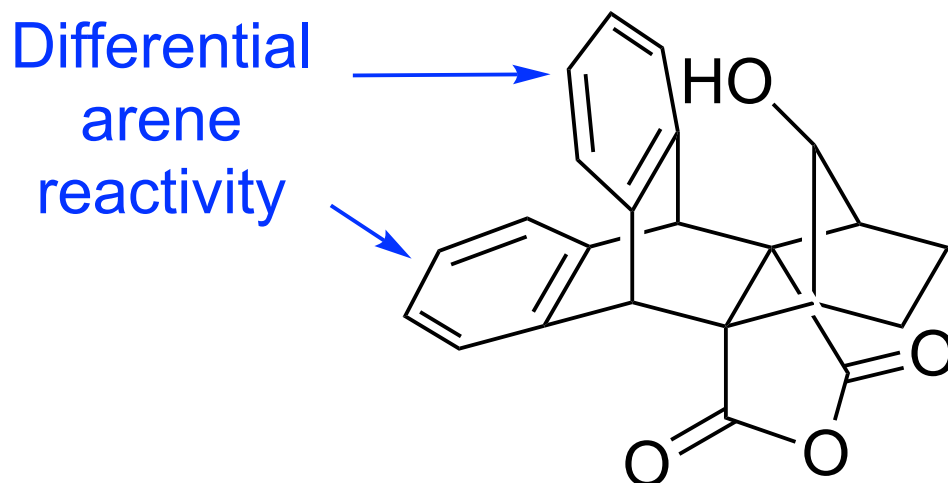
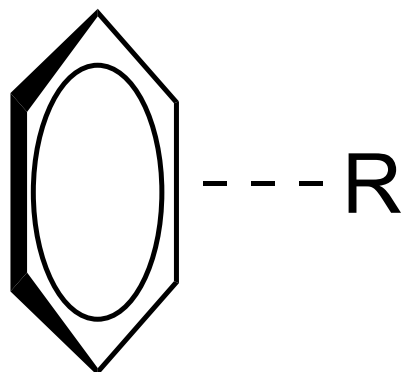


# Through-Space Activation Can Override Substituent Effects in Electrophilic Aromatic Substitution



Guan, L.; Holl, M. G. Pitts, G. C.; Struble, M. D.; Siegler, M. A. Lectka, T.  
*J. Am Chem. Soc.* DOI: 10.1021/jacs.7b09792

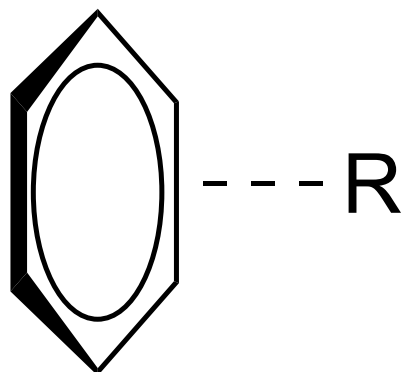
# Non-covalent arene interactions



**Many types of interactions have been characterized, including:**

- Arene-arene “edge to face”
- Arene-arene “stacking”
- CH-arene
- OH-arene
- S-arene
- Cation-arene

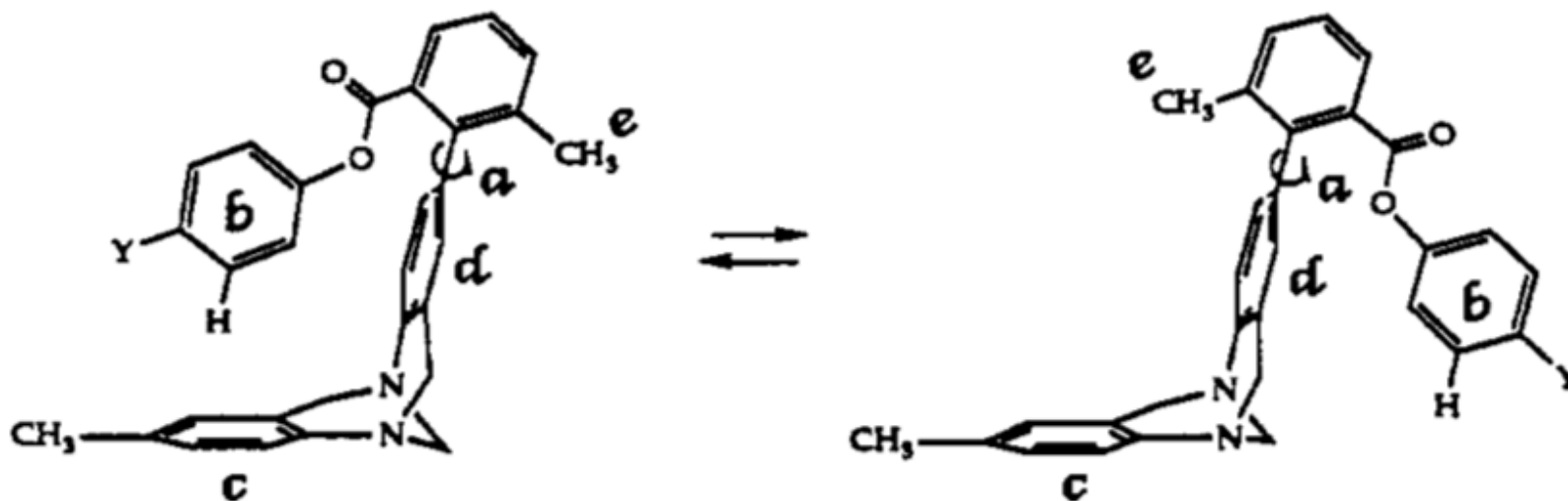
# Non-covalent arene interactions



**Many types of interactions have been characterized, including:**

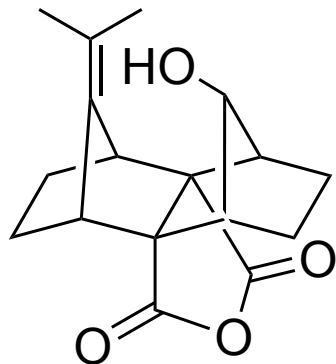
- Arene-arene “edge to face”
- Arene-arene “stacking”
- CH-arene
- OH-arene
- S-arene
- Cation-arene

# Torsion balances: tools for studying these interactions

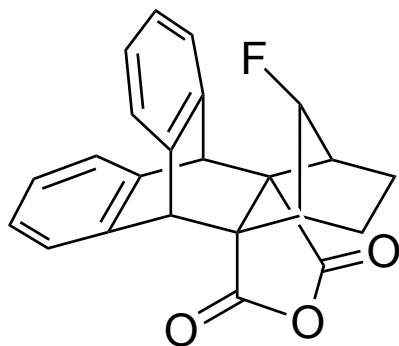


$\Delta G$  of "edge to face" interaction can be deduced through relative population of the rotomers (observable by NMR)

# Previous work by Lectka group



OH-alkene interaction

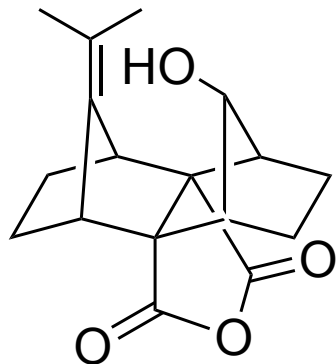


F-arene interaction

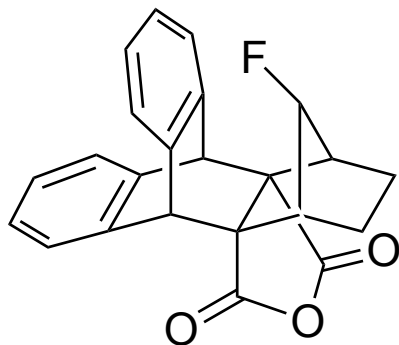
Struble, M. D.; Holl, M. G.; Coombs, G.; Siegler, M. A. Lectka, T. *J. Org. Chem.* **2015**, *80*, 4803-4807.

Holl, M. G.; Struble, M. D.; Singal, P.; Siegler, M. A. Lectka, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 8266-8269.

# Previous work by Lectka group



OH-alkene interaction



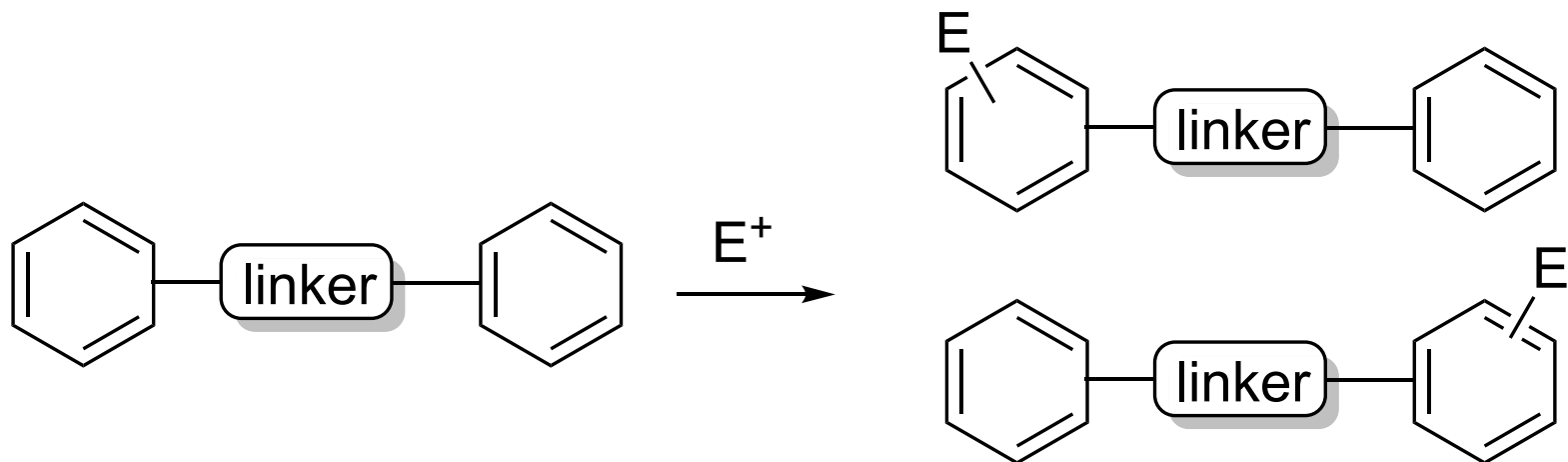
F-arene interaction

**Can an –OH-arene interaction impact reactivity?**

Struble, M. D.; Holl, M. G.; Coombs, G.; Siegler, M. A. Lectka, T. *J. Org. Chem.* **2015**, *80*, 4803-4807.

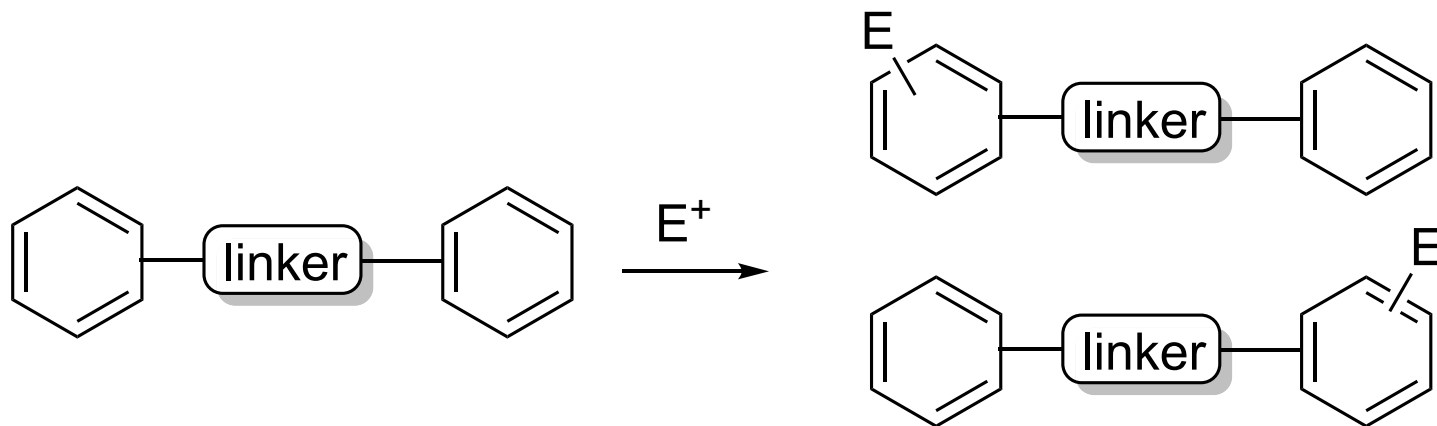
Holl, M. G.; Struble, M. D.; Singal, P.; Siegler, M. A. Lectka, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 8266-8269.

# Electrophilic Aromatic Substitution

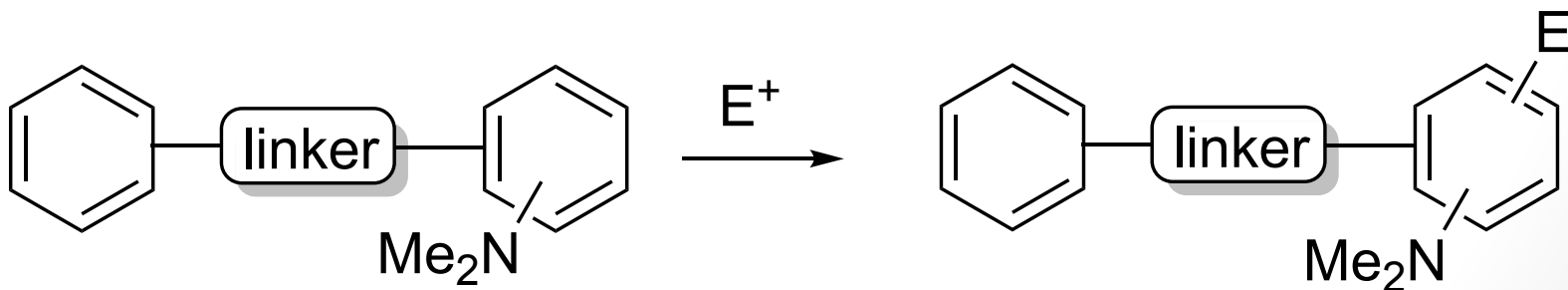


**Absent any differentiation, both rings react equally**

# Electrophilic Aromatic Substitution

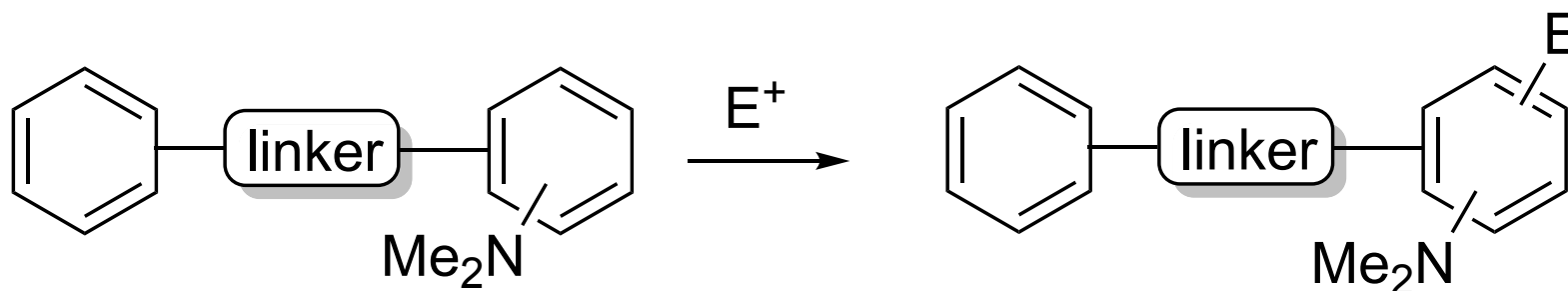


**A directing group will bias reactivity:**

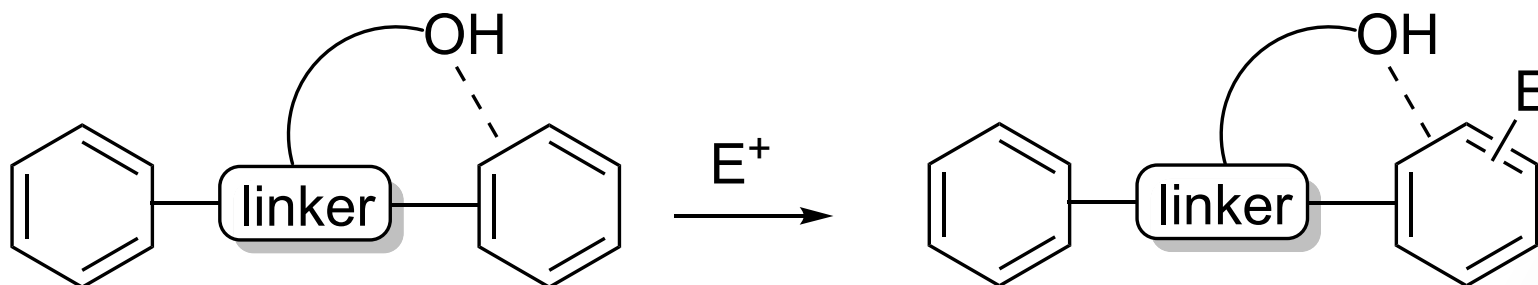




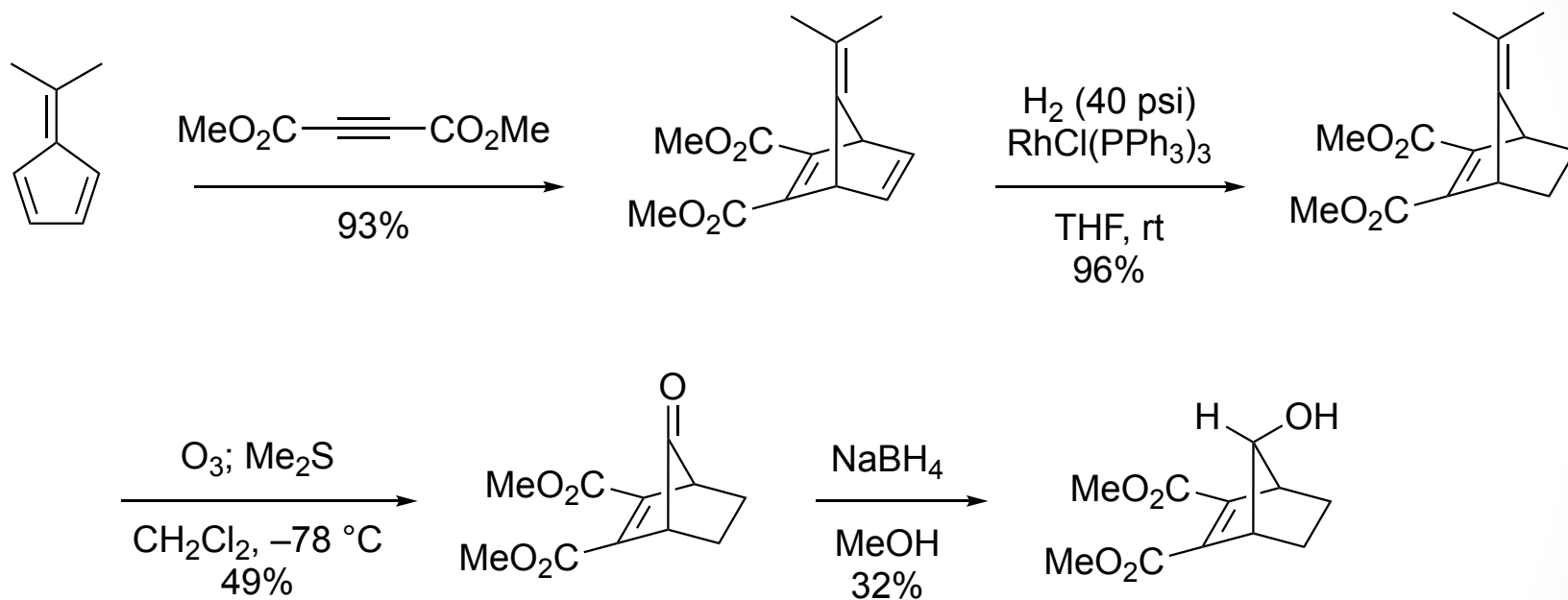
# Non-covalent influence of electrophilic aromatic substitution?



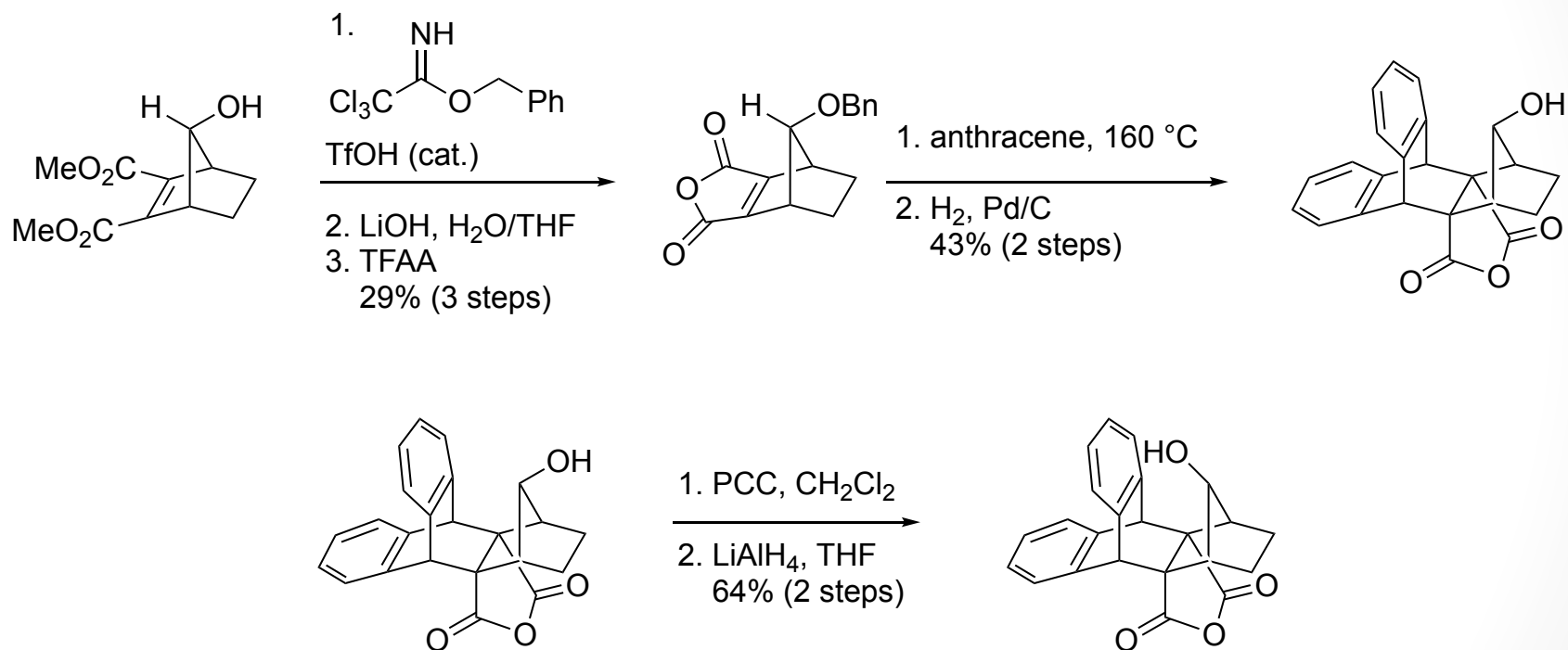
## Can reactivity be biased by a non-covalent interaction?



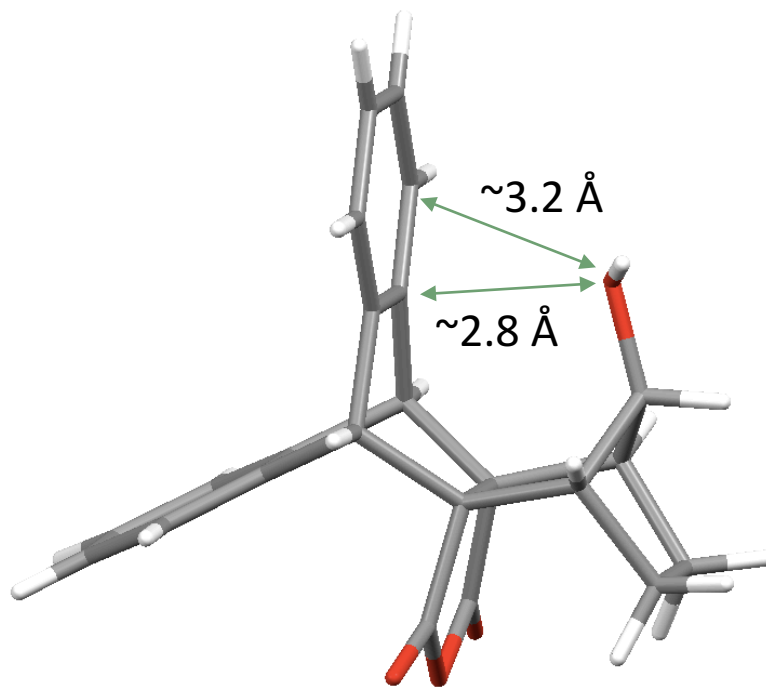
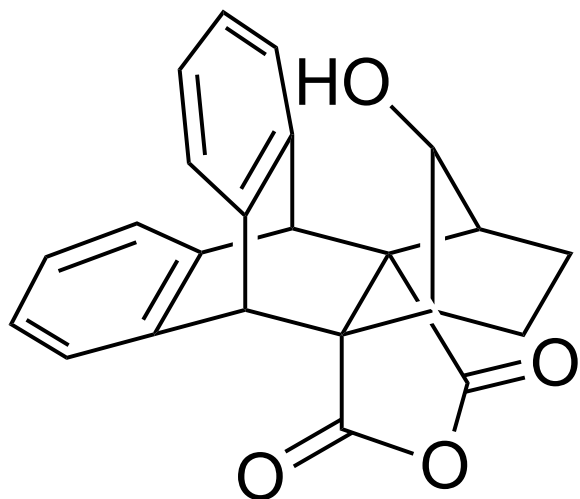
# Synthesis of test substrate



# Synthesis of substrate



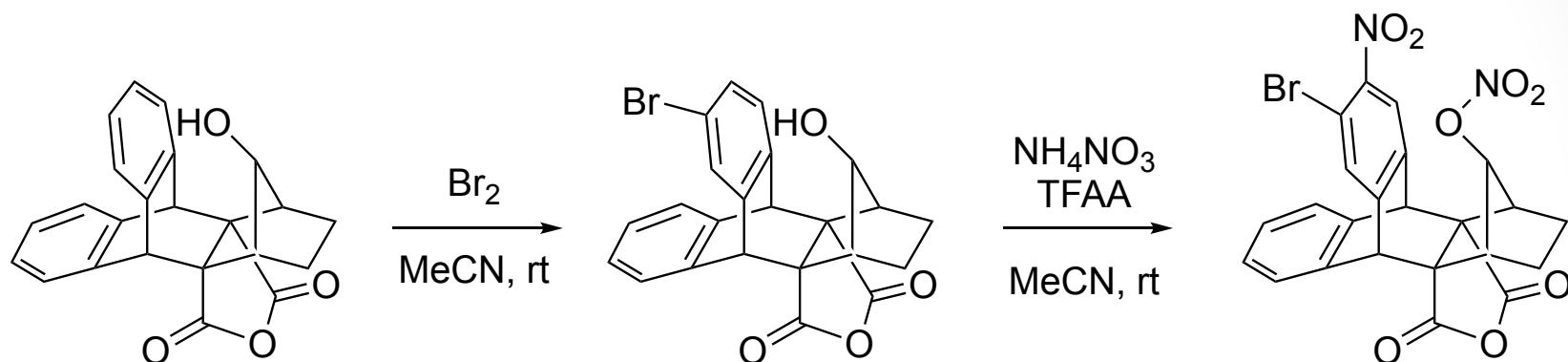
# Model compound



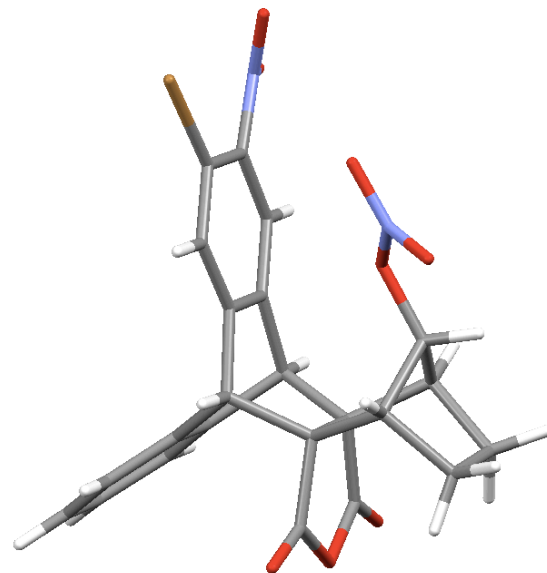
-OH IR shift red shifted  $32 \text{ cm}^{-1}$  compared to diastereomer

-OH  $^1\text{H}$  NMR:  $\delta$  -0.21 (sharp s)

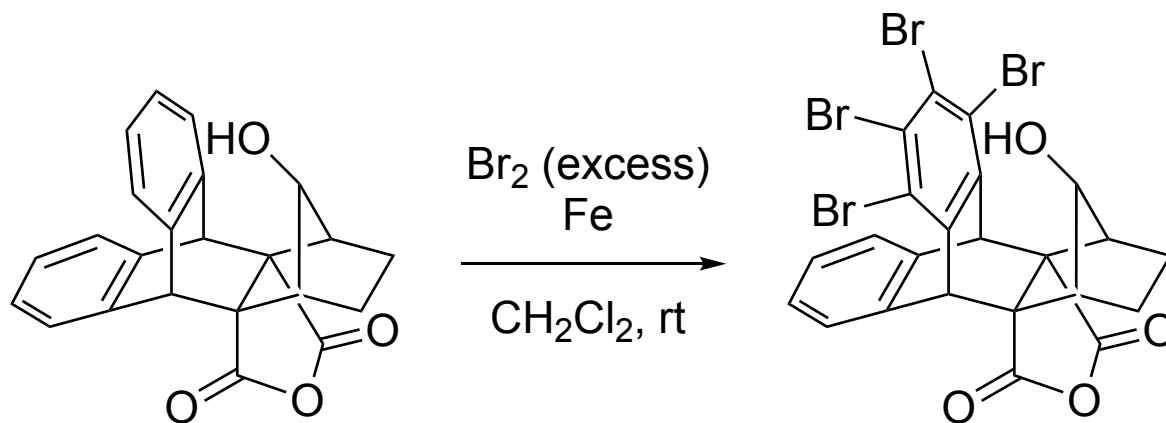
# Nitration



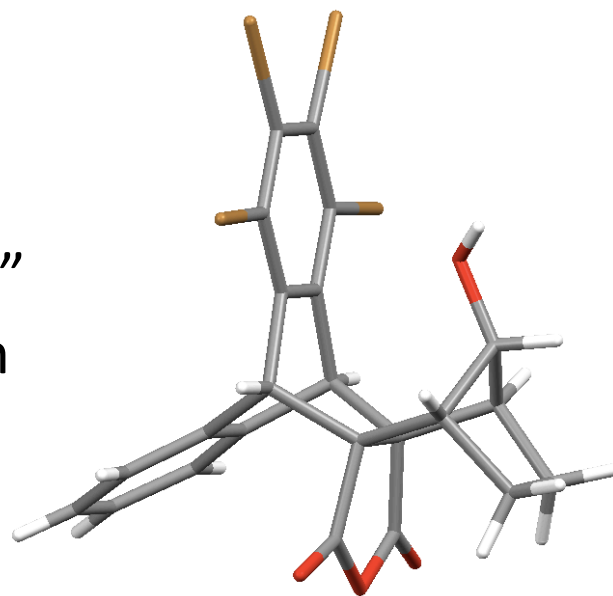
Bromination and nitration occur only at the “activated” aryl ring



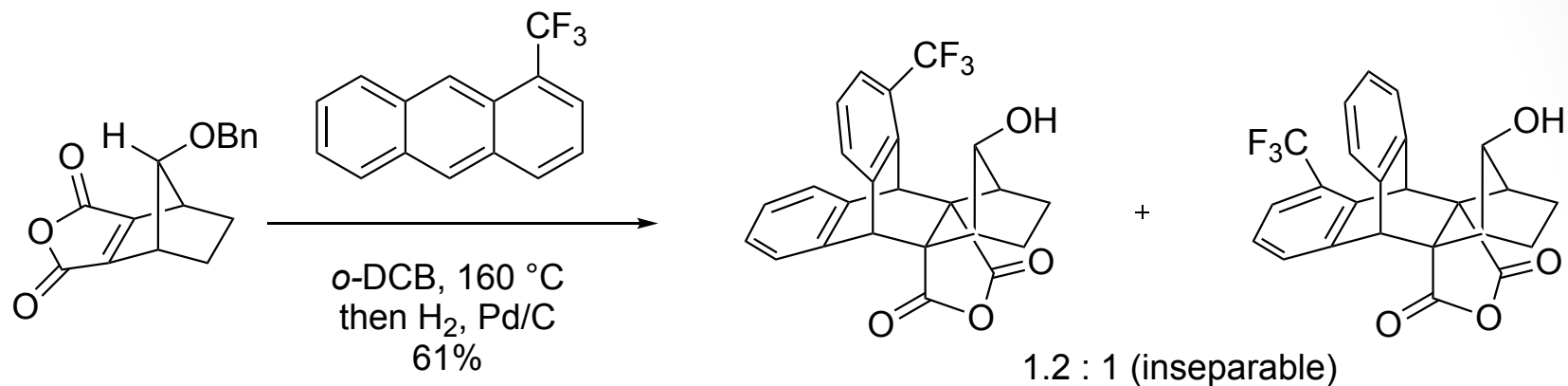
# Bromination



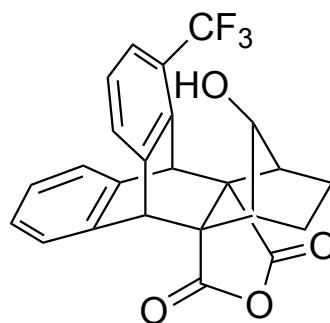
Tetrabromination of the “activated” ring occurs before any bromination of the bottom ring!



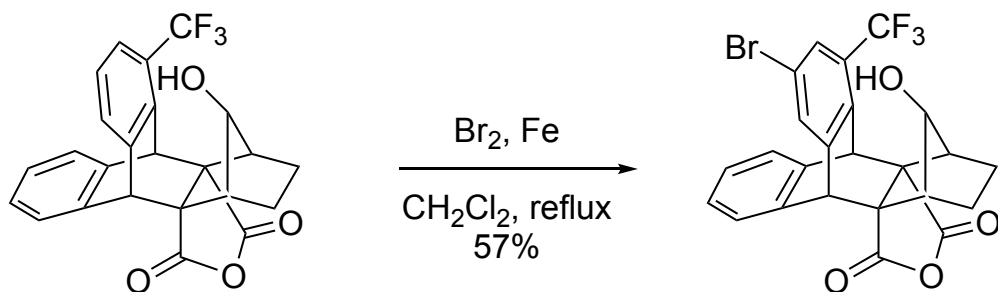
# -CF<sub>3</sub> substrate



1. PCC, CH<sub>2</sub>Cl<sub>2</sub>
2. LiAlH<sub>4</sub>, THF
3. preparative HPLC



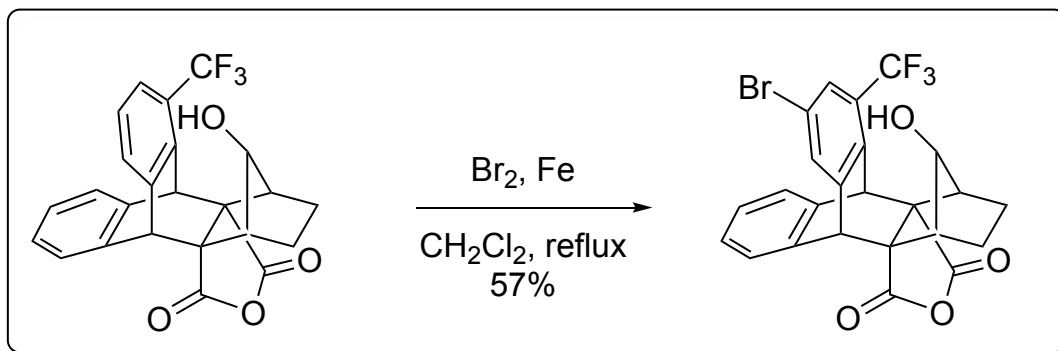
# -CF<sub>3</sub> substrate



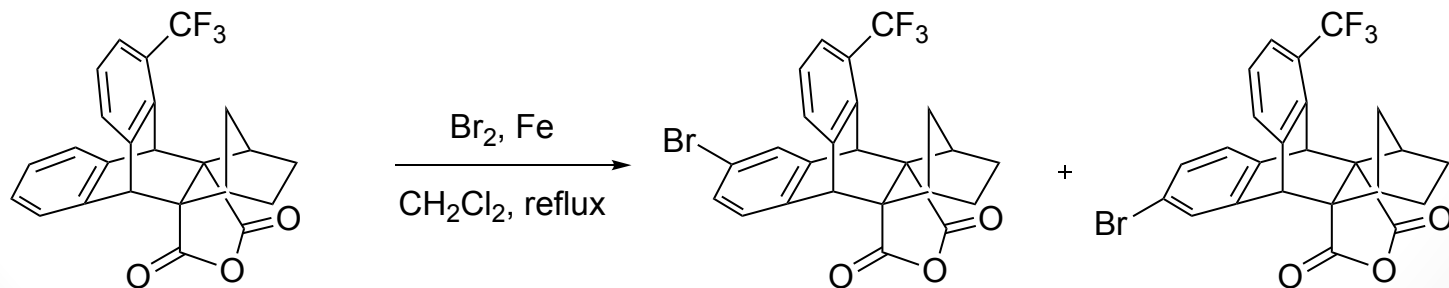
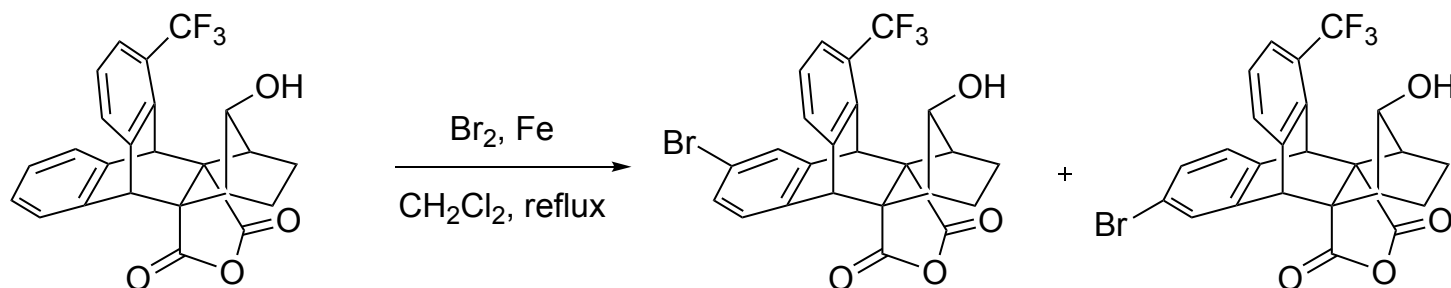
Non-covalent  
activation  
overrides -CF<sub>3</sub>  
deactivation!



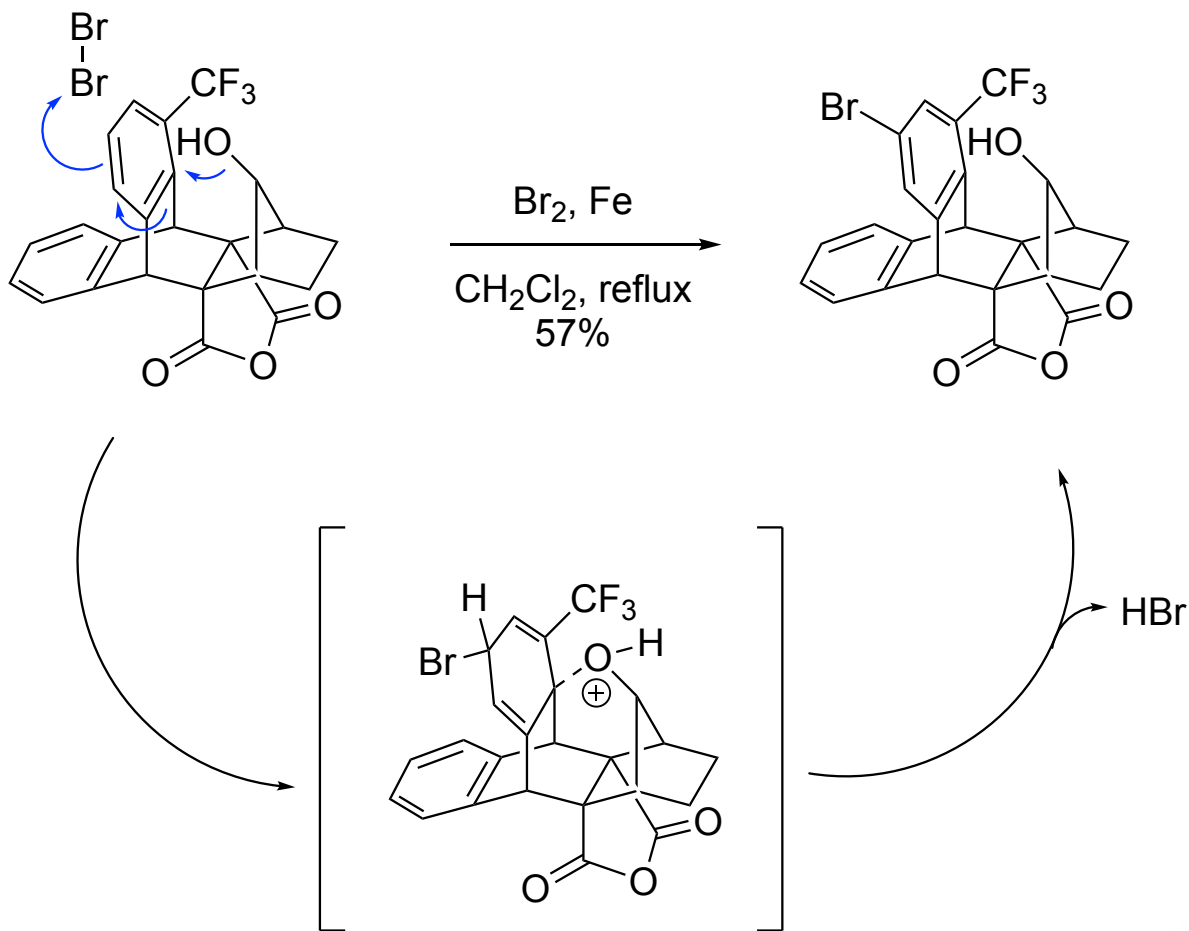
# -CF<sub>3</sub> substrate



Non-covalent  
activation  
overrides -CF<sub>3</sub>  
deactivation!



# Activation through a “Meisenheimer complex”?



# Computational model

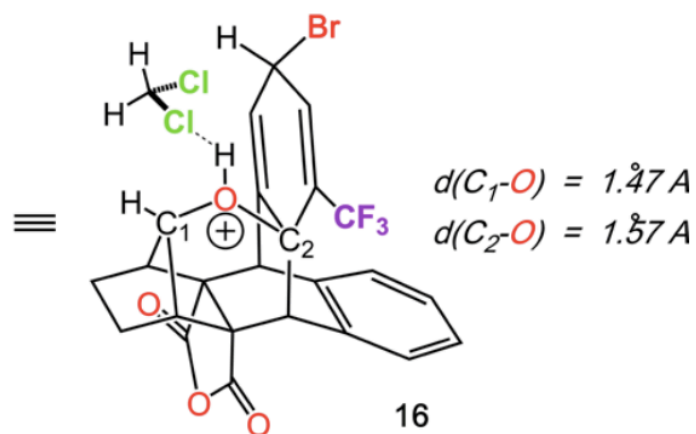
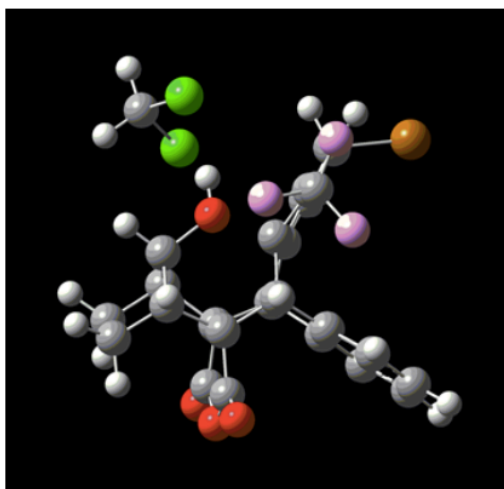
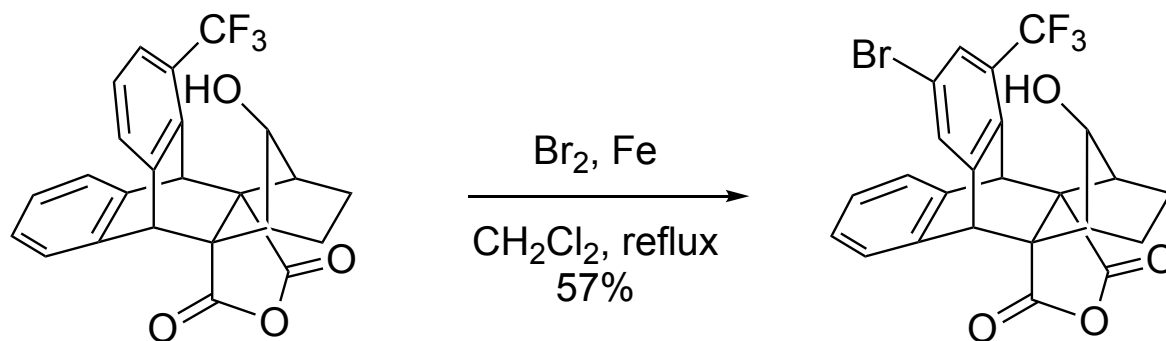
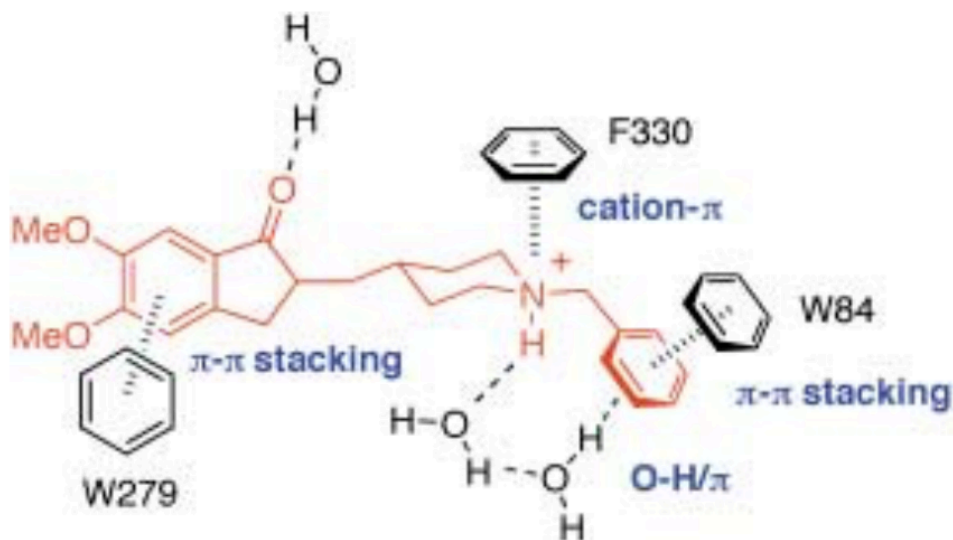
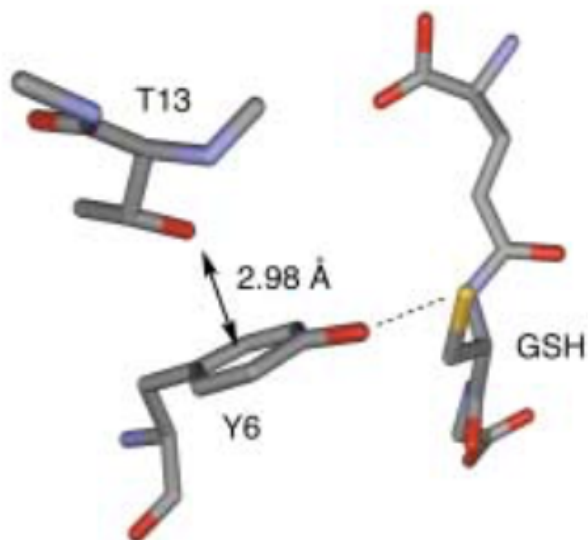


Figure 2. Optimized structure of **6A**, the  $\sigma$ -complex intermediate for endobromination of **6**, at  $\omega\text{B97XD}/6\text{-311+G}^{**}$ .

# Biological Relevance

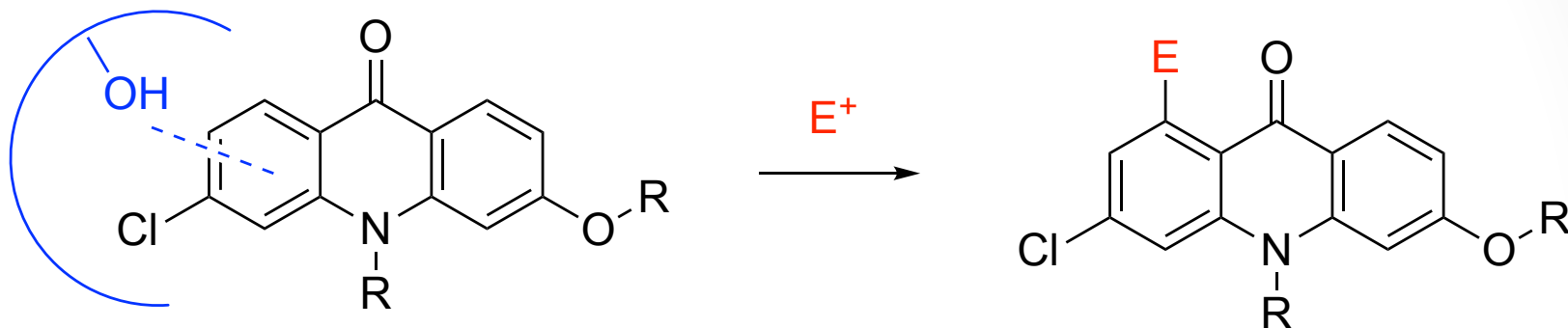


Donepezil (Alzheimer's drug) bound to acetylcholinesterase



Glutathione S-transferase active site pocket

# Possible future direction



core of acridone antimalarials

Can synthetically useful differentiation be achieved through enzymatic/supramolecular non-covalent activation?

# Ron Breslow (1931-2017)

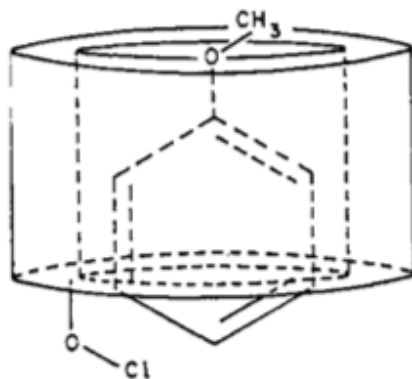
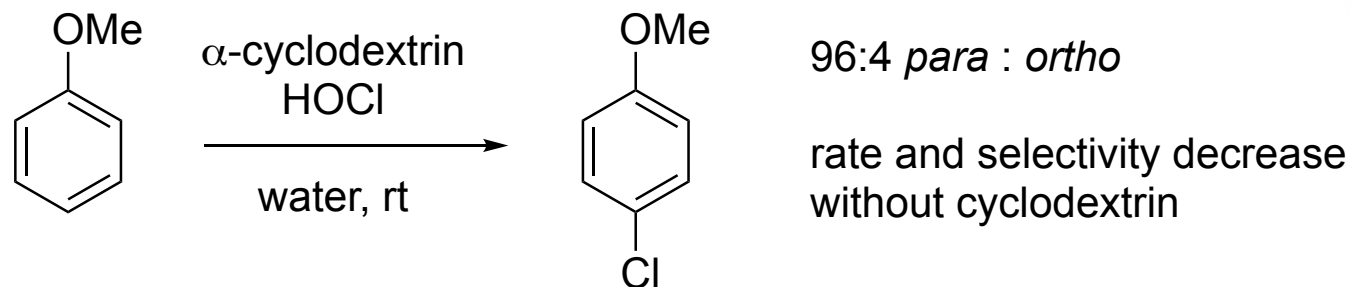


Figure 1. Schematic representation of an anisole molecule in the cavity of cyclodextrin. Eighteen hydroxyl groups (not shown) ring the mouths of the cavity, one of which is written as its hypochlorite ester to indicate a mechanism by which the increased rate of chlorination in the complex may be explained.