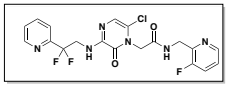
Lecture 3: General Reactivity 3

Synthesis of thrombin inhibitor:



Merck, *Org. Proc. Res. Dev.* **2004**, *8*, 192

A **B** **C**

Synthesis of **A** (Med Chem route):

Synthesis of **A** (Process route):



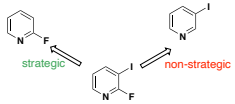
Ring Substitution:

Functional Group Retrosynthetic Priority (in general):

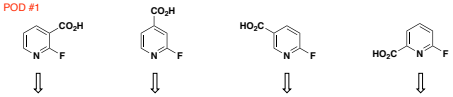
Early Group → Late Group

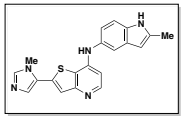
Ar, Alkyl Si I, Br OMe COR Cl F

For example:



POD #1

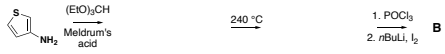




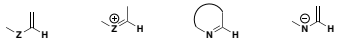
Pfizer, *OPRD*, **2003**, *7*, 676

A **B** **C**

Synthesis of **B**



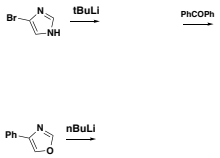
Lithiation:



favorable pyrrole-like | *extremely favorable* | *5-memb (fast) 6-memb (slower)* | *impossible*

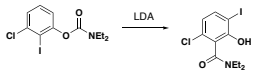
Synthesis of **A**:



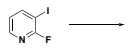


Org. Proc. Res. Dev. **2003**, *7*, 676

POD #2



Time… to… DANCE!

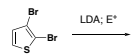


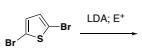
Iodinate each position



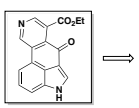
Carboxylate each position

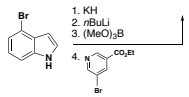






POD #3

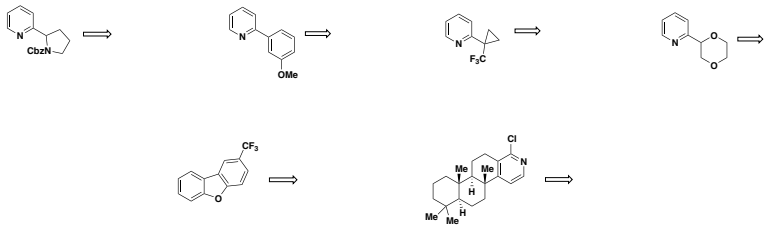




Doll, *J. Org. Chem.* **1999**, *64*, 1372

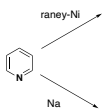
Minisci reaction review:
Synthesis **1973**, 1-24; *MedChemComm* **2011**, *2*, 1135-1161
Applications in modern medicinal and process chemistry:
Org. Lett., **2003**, 5, 4497
Radical additions with zinc sulfinates:
J. Med. Chem. **2019**, *62*, 2266-2264

Minisci + related reactions can be very useful "C-H functionalization"

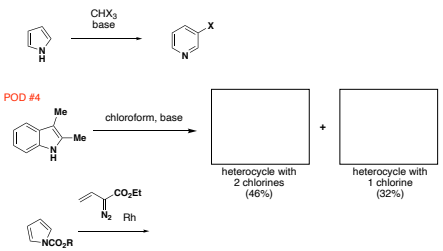


Consulting Corner: Predicting sites of radical reactivity

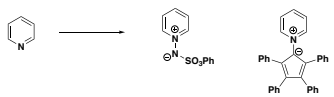
Addition of e⁻ to e-deficient rings

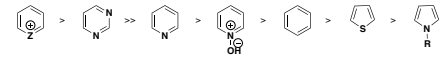


Addition of carbenes to e-rich rings



Addition of carbenes to e-deficient rings





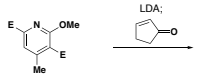
EASIER (e- deficient) *HARDER (e- rich)*



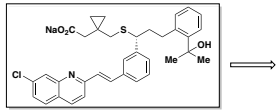
- nucleophilic displacement (of nitro, chloro, etc.)
- proton loss
- decarboxylation tendency
- Michael additions (susceptibility)

Refer to PCC book: Compare Pyridine Section 2.2, "Pyridine Substitution Methods Report Card" (p.44) to Pyrrole Section 2.2, "Pyrrole Substitution Methods Report Card" (p.231) under the column "scope/generality" in order to compare typical reactivities of electron-deficient vs electron-rich heteroarenes.

Boger Fredericamycin



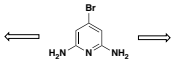
Synthesis of singulair:



singulair (montelukast sodium)

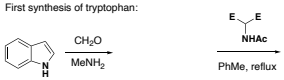
Merck, *BMCL* **1992**, 1141 and **1995**, 283

POD #5



e-donation effects on substituent reactivity
-ex: woodward chlorophyl & consulting problem #1

First synthesis of tryptophan:



NaOH
then H+
heat

