

Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction

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Date: 2013.11.25

About Author



John F. Hartwig

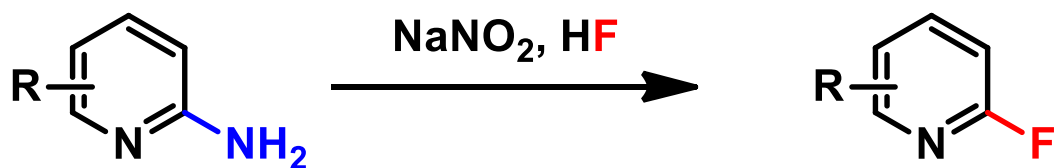
- Catalytic Formation of Amines, Ethers and Sulfides.
- Catalytic Alpha Arylation of Carbonyl Compounds
- Regioselective Functionalization of Alkyl and Aryl C-H Bonds
- Olefin Hydroamination
- Enantioselective Allylic Amination and Etherification
- Catalysis for renewable chemicals and fuels
- Organometallic Chemistry and Enzymes
- Combinatorial Catalyst Discovery

Out Line of this talk

Conventional method

-----Conventional reaction classes require **prefunctionalized** substrates.

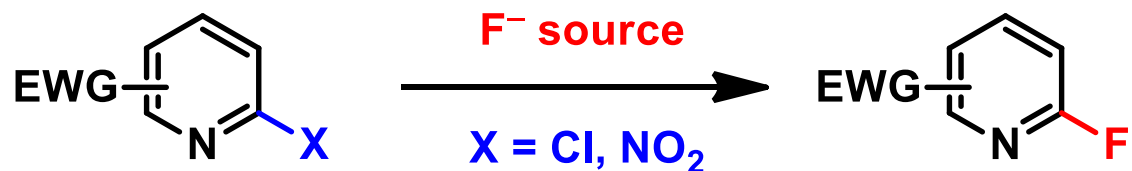
Balz-Schiemann reaction



- Involving strongly acidic and oxidizing conditions
- Using anhydrous HF or an isolated tetrafluoroborate salt as F source

T. Fukuhara, N. Yoneda, A. Suzuki, *J. Fluor. Chem.* **38**, 435–438

Nucleophilic Aromatic substitution



- High yield only with strongly electron-deficient heteroarenes

D. J. Adams, J. H. Clark, *Chem. Soc. Rev.* **28**, 225–231

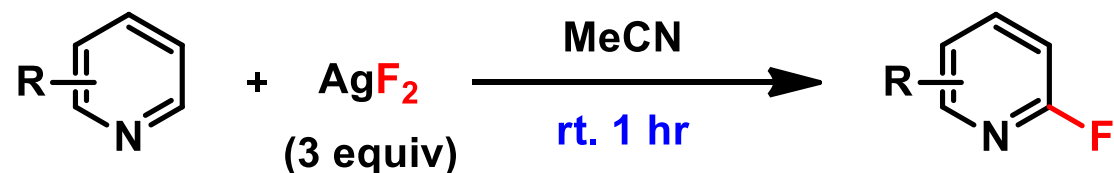
H. Sun, S. G. DiMagno, *Angew. Chem. Int. Ed.* **45**, 2720–2725

11. S. D. Kuduk, R. M. DiPardo, M. G. Bock, *Org. Lett.* **7**, 577–579

Out Line of this talk

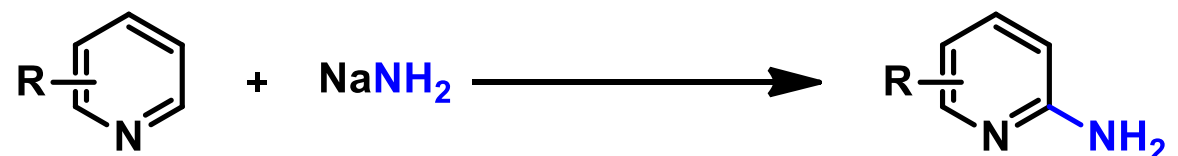
New method of Fluorination

Hartwig's reaction



- Mild conditions and fast reaction times
- Exclusive selectivity for fluorination adjacent to nitrogen
- A broad range of substrates
- High tolerance for auxiliary functionality
- A single, commercially available reagent----- AgF_2

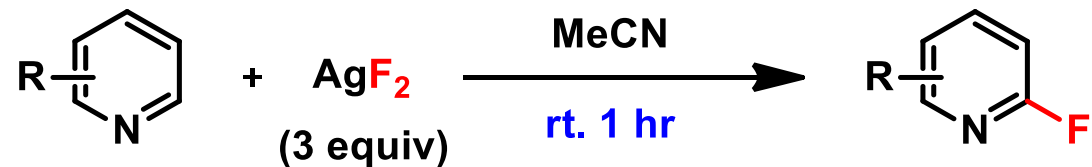
Chichibabin reaction



Inspired

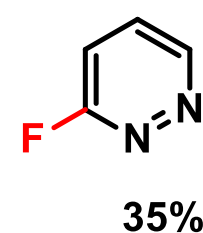
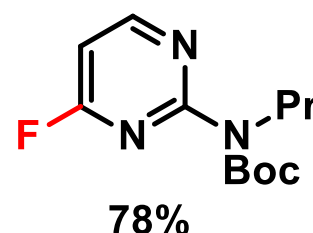
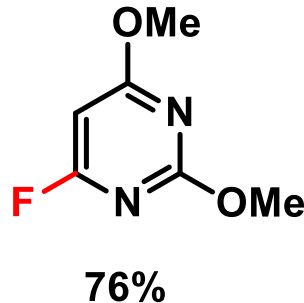
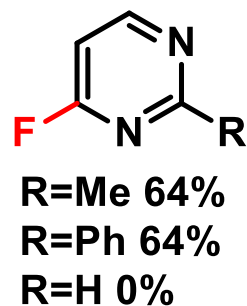
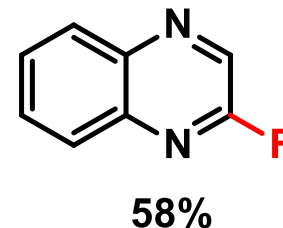
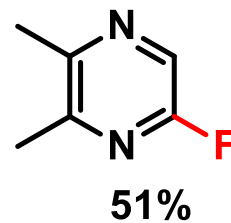
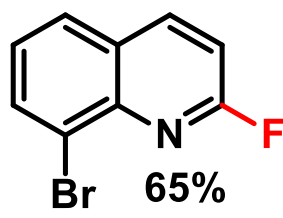
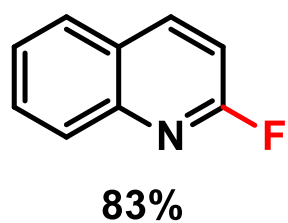
Scope of Fluorination with AgF_2

Optimal Conditions of Fluorination



- R = **electron-donating** and **electron-withdrawing** groups **at each position** of pyridines.
- Notably, **Br^- and Cl^- substituents** in the 2-position of the pyridine **remained intact during the reaction**.
- The reactions with pyridines containing functional groups in the 3-positions formed **the 2-fluoro-3-functionalized pyridine products preferentially**.

Other Types of Six-membered Nitrogen Heterocycles



Mechanism of the reactions between pyridines and AgF_2



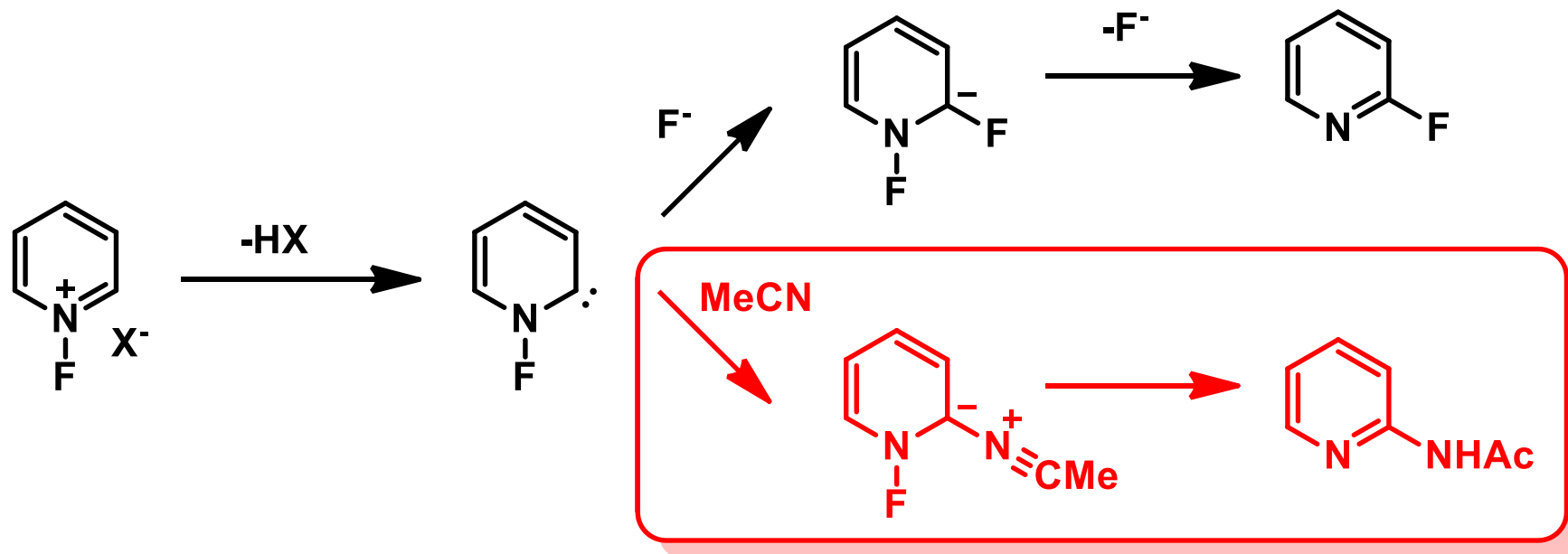
- The base-induced rearrangements of isolated N-fluoropyridinium salts occur through electrophilic carbene intermediates .

- Addition of a fluorine radical from AgF_2 to the pyridine to form a delocalized radical and AgF .

- The fluorination occurs by a mechanism similar to that of the Chichibabin reaction.

Mechanism of the reactions between pyridines and AgF_2

- The base-induced rearrangements of isolated N-fluoropyridinium salts occur through electrophilic carbene intermediates.



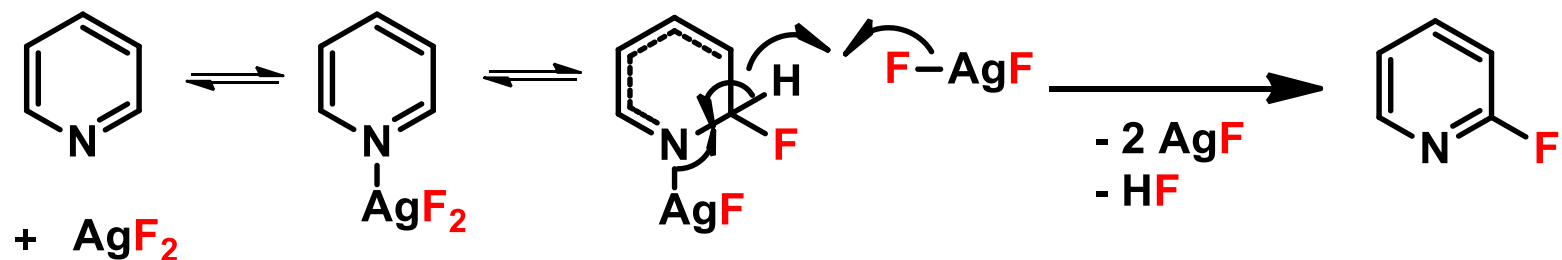
It is unlikely that a similar mechanism occurs for the reactions with AgF_2 .

Mechanism of the reactions between pyridines and AgF_2

Reaction results are inconsistent with such a pathway.

- Addition of a fluorine radical from AgF_2 to the pyridine to form a delocalized radical and AgF .
The exclusive selectivity for fluorination at the 2-position of pyridines.
2,6-dimethylpyridine does not undergo fluorination, and so on.

Mechanism of the reactions between pyridines and AgF_2



■ The same trend in regioselectivity is observed in the Chichibabin reaction.

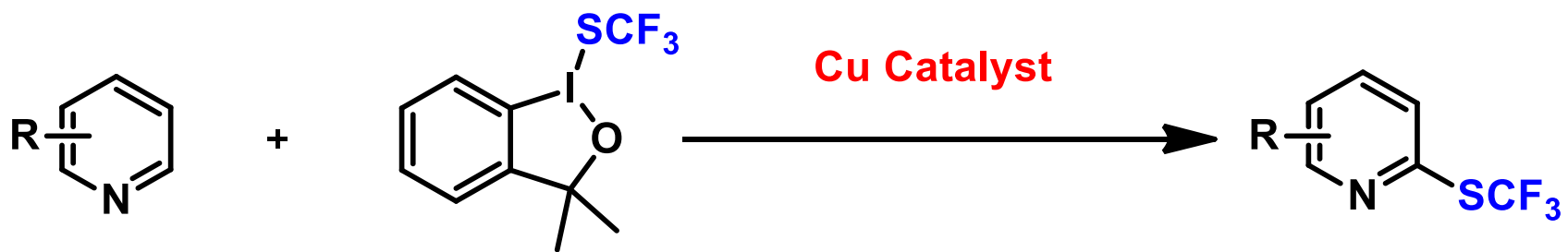
■ The fluorination occurs by a mechanism similar to that of the Chichibabin reaction.

Summary

The reaction have some advantages:

- One step (*Conventional reaction classes* require *prefunctionalized* substrates)
- High yield
- the mild conditions (rt. No base or acid), fast reaction times (1 hr)
- broad scope (R = *electron-donating* and *electron-withdrawing* groups *at each position* of pyridines)
- High tolerance for auxiliary functionality (*Br* and *Cl* substituents)
- commercial availability of the reagent (AgF_2)

My Idea



Thank you