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Keywords **: Synthesis, Catalysis, C-H activation, Electrophilic fluorination, Nucleophilic fluorination, Transition metals, Palladium, *N*-ligands, mechanisms, DFT**




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Halogenations: crucial reactions to renew

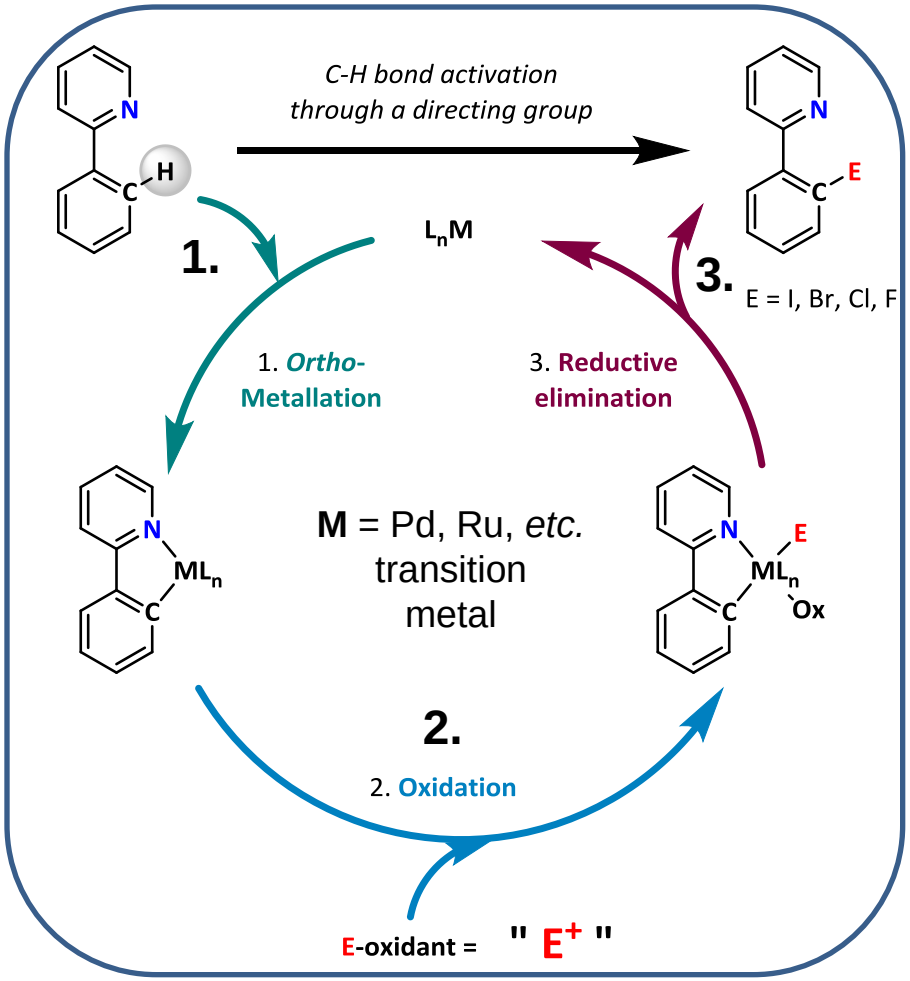
⇨ **Organohalides are…**

- **Key intermediates** in organic synthesis and total synthesis;
- Widely present in pharmaceuticals, agrochemicals, molecular materials;
- **Therapeutic agents**: [**F**] present in 20% of medical compounds ⇨ Increases lipophilicity, solubility, through-membrane transport;
- **Analytical efficient tools**: [^{19}F] magnetic resonance and radioactive elements [^{18}F]

⇨ **Halide and fluorine introduction**

- **Classically radical and organic stoichiometric reactions**
  ⇨ *harsh conditions, very limited substrates, not chemoselective/regioselective*
- **<u>Transition metals catalyzed approaches</u>** with a leaving group or C–H activation
- Halogenation reagents are distinguished as nucleophilic (F^-) or electrophilic (F^+) species

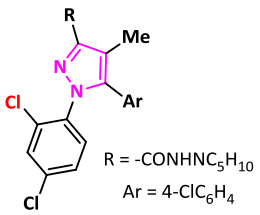
Catalytic electrophilic C–H fluorination (and halogenation) principles



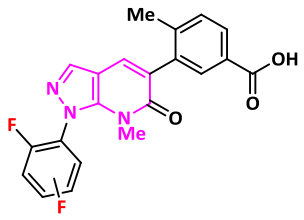
Interests

- *Atom-economic activation of unreactive C–H bond*
- *Regioselective control: ortho-direction by N-ligands*
- *Far better tolerance of additional functional groups*

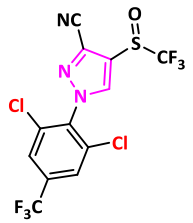
Possible directing groups



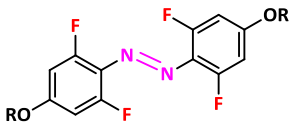
Ribomanant
anty obesity



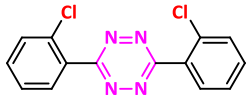
p38 MAP Kinase
Inhibitor



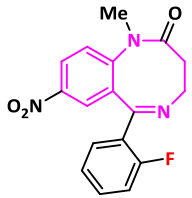
Fipronil®
Pesticide, Rhône-Poulenc



tetrafluorinated azabenzene
Liquid crystal

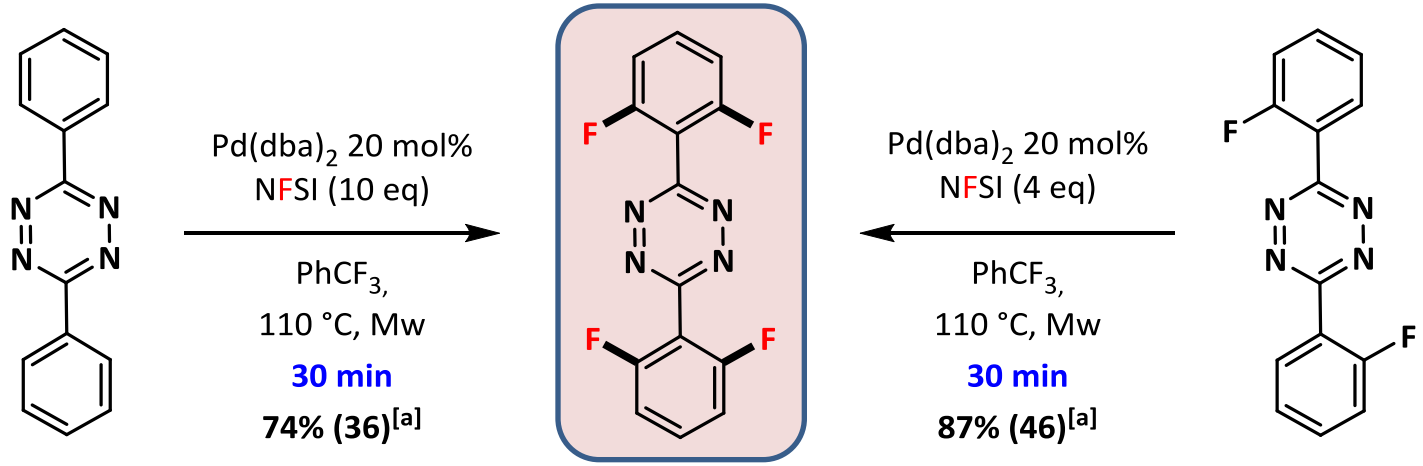


Clofentezine®
Acaricide



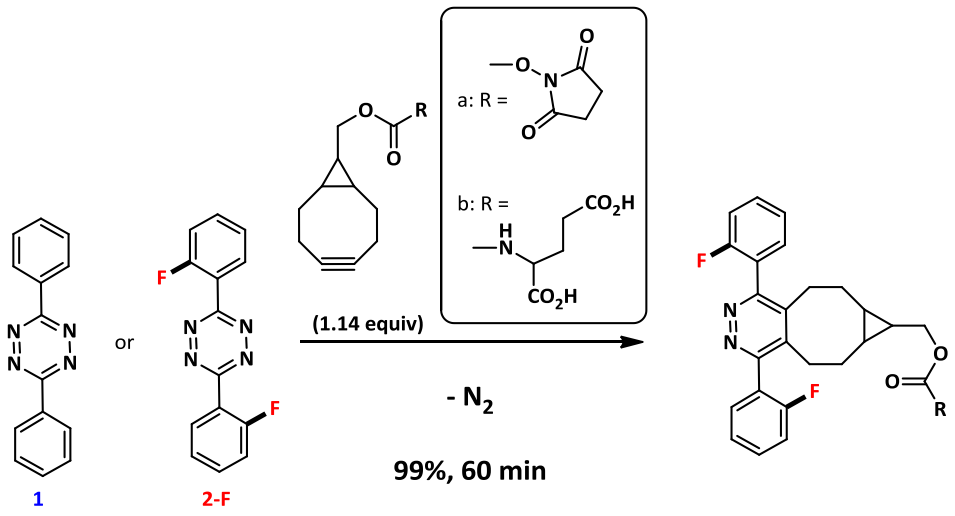
Flunitrazepam / Rohypnol®
Antipsychotic, Hoffmann-La Roche

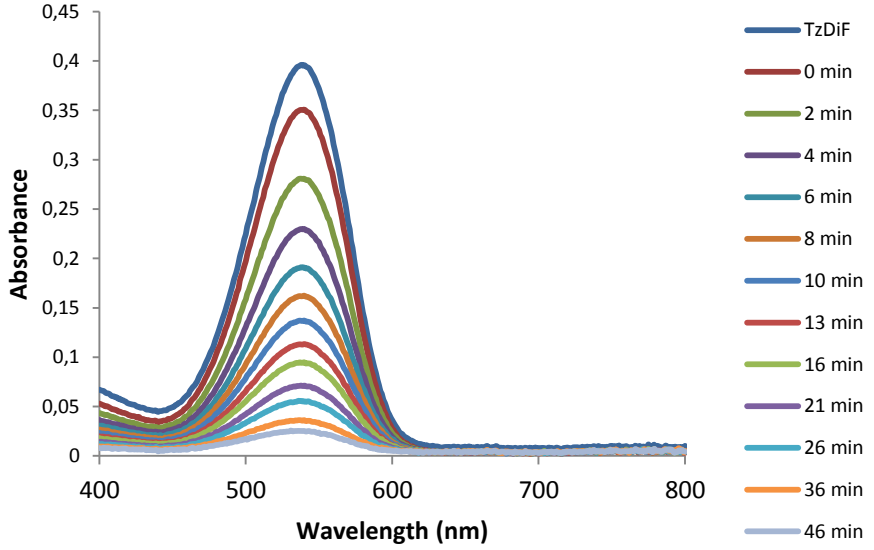
N-directed electrophilic fluorination of heterocycles



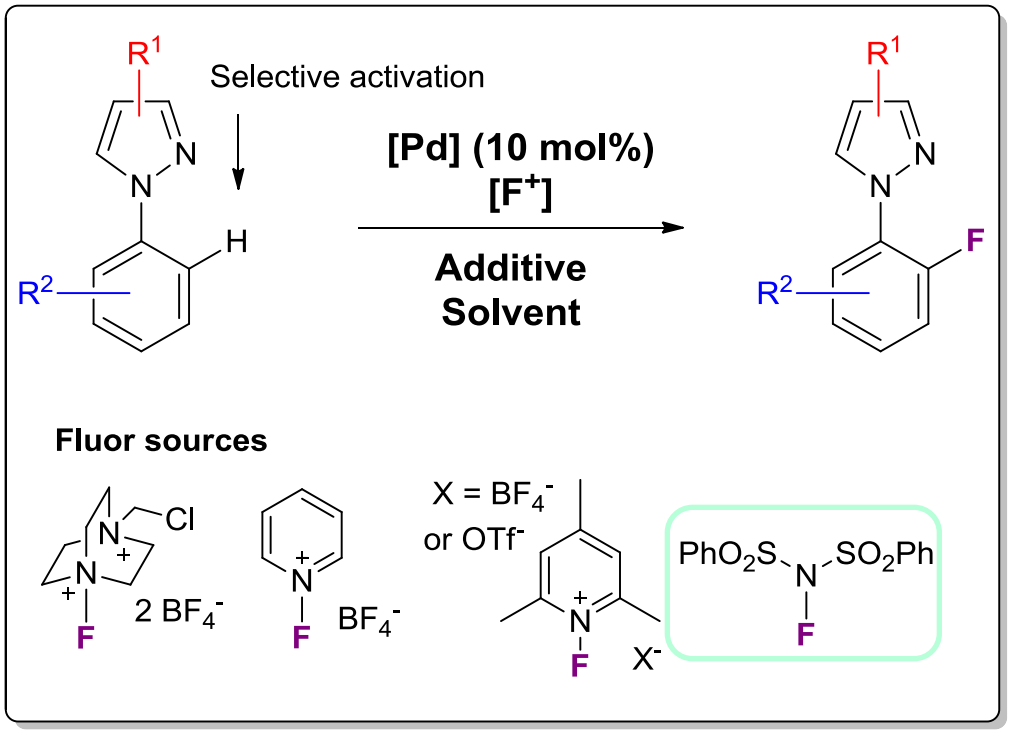
Roger, J.; Hierso, J.-C. et al. Angew. Chem. Int. Ed. ***2016****, 55, 5555.*

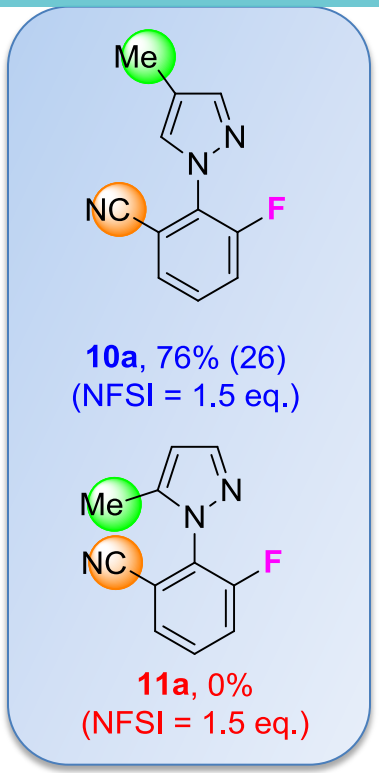
Bioconjugaison

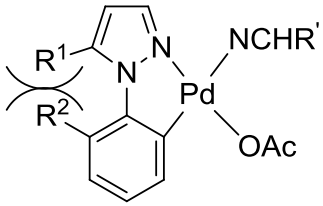


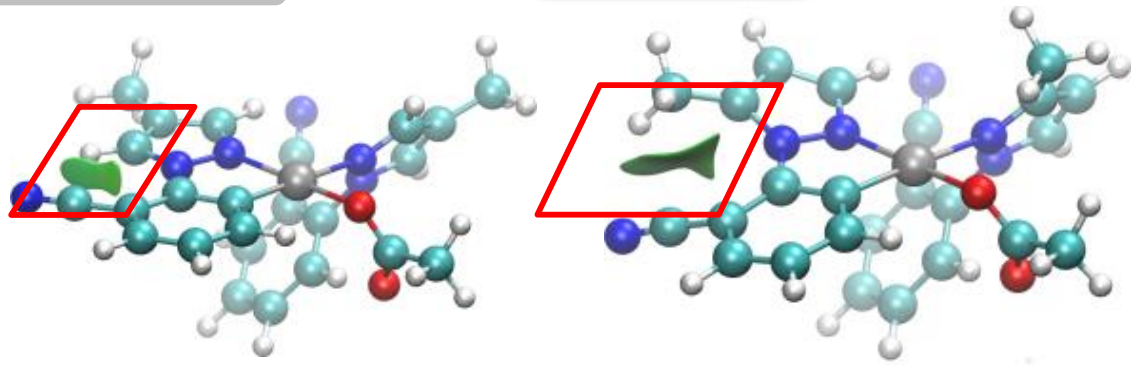


Mechanistic DFT elucidation in fluorination limitations









***Intra-ligand** sterics C3*

Roger, J.; Fleurat-Lessard, P.; J.-C. Hierso et al. 2015, Adv. Synth. Catal. 357, 2913.

VIP Very Important Publication