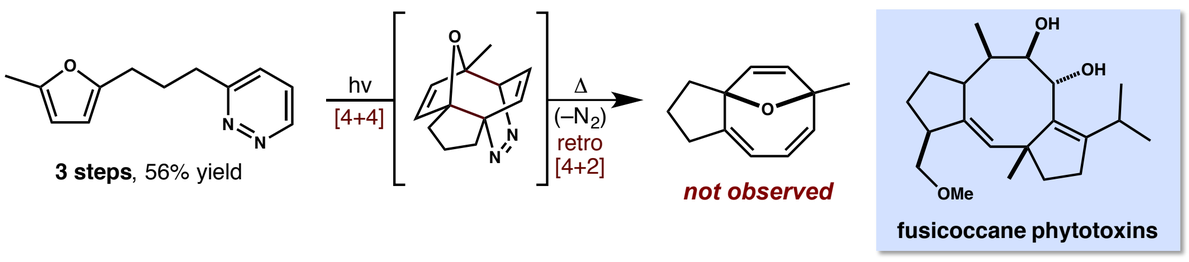
Complexity Building Cascade Reactions Initiated by [4+4]-Photocycloadditions

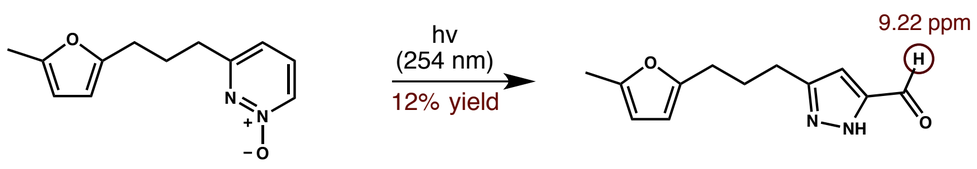
Maribel Portillo, Michael Maxwell, and James H. Frederich*
Department of Chemistry and Biochemistry, Florida State University

A Serendipitous Discovery During Early Investigations

FYAP Aim: Practical access to functionalized cyclooctenes

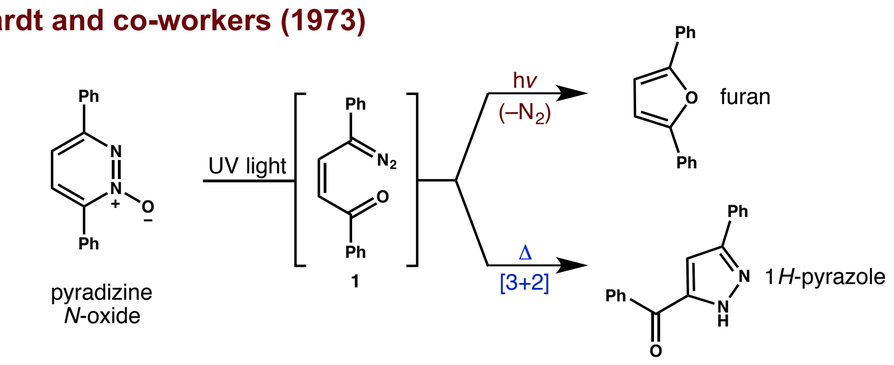


An Unanticipated Observation



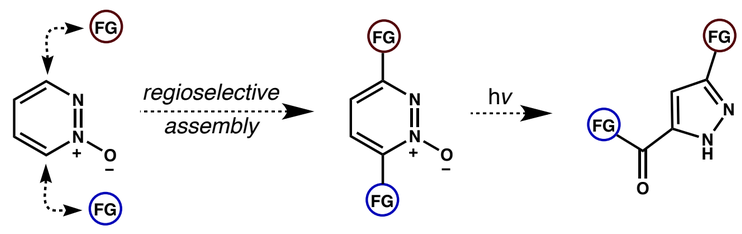
Fundamental Photochemistry of Pyridazine N-Oxides

Buchardt and co-workers (1973)

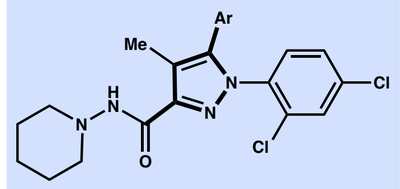


Creed, D. et. al. **Photochemical behavior of aromatic 1,2-diazine *N*-oxides**. *J. Am. Chem. Soc.* **1973**, *95*, 7402.

Our Strategy: Modular Approach to Pyrazoles

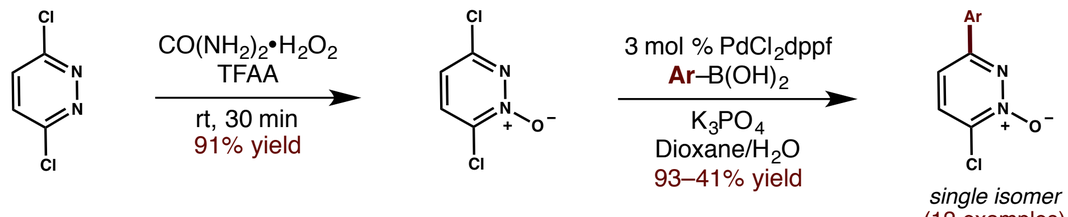


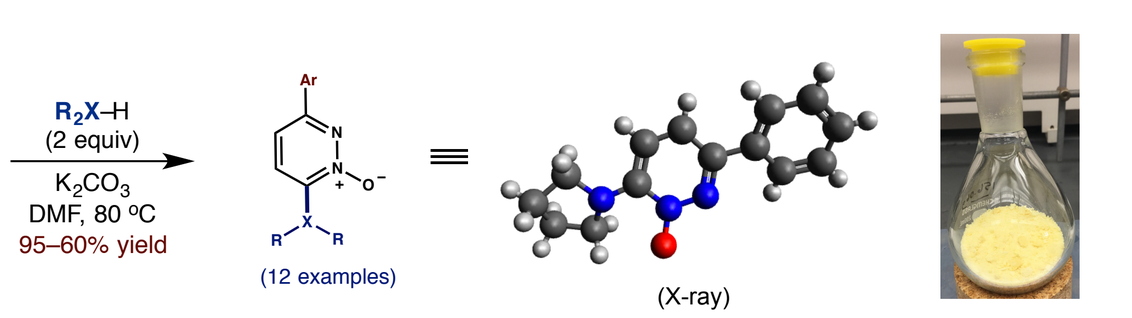
entry to neurological drugs



Rimonabant (Ar = *p*-Cl-C_6H_4)
CB1 receptor inverse angonist

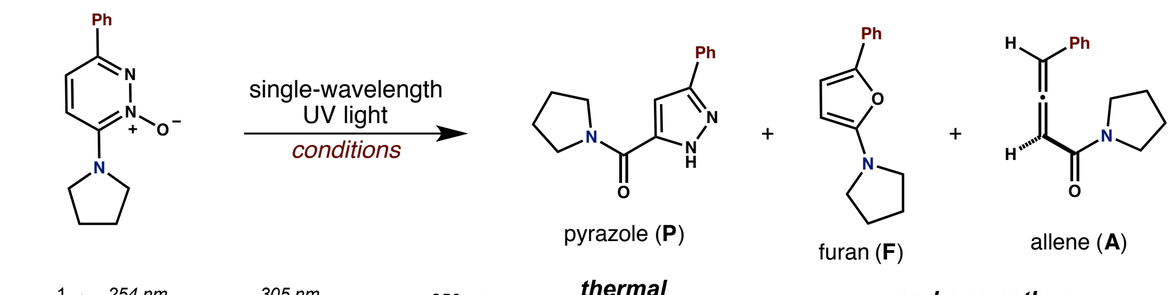
Modular Synthetic Entry to Pyridazine N-oxides

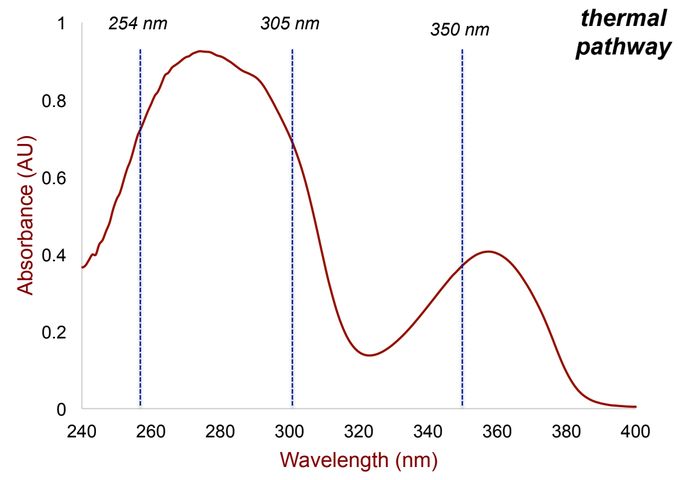




multi-gram quantities available

Controlling Reaction Pathways *via* Reaction Conditions





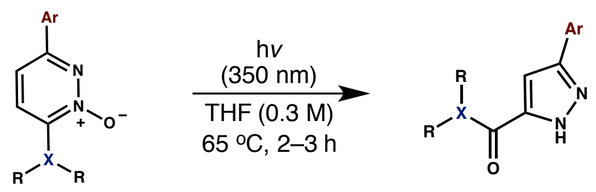
thermal pathway

carbene pathway

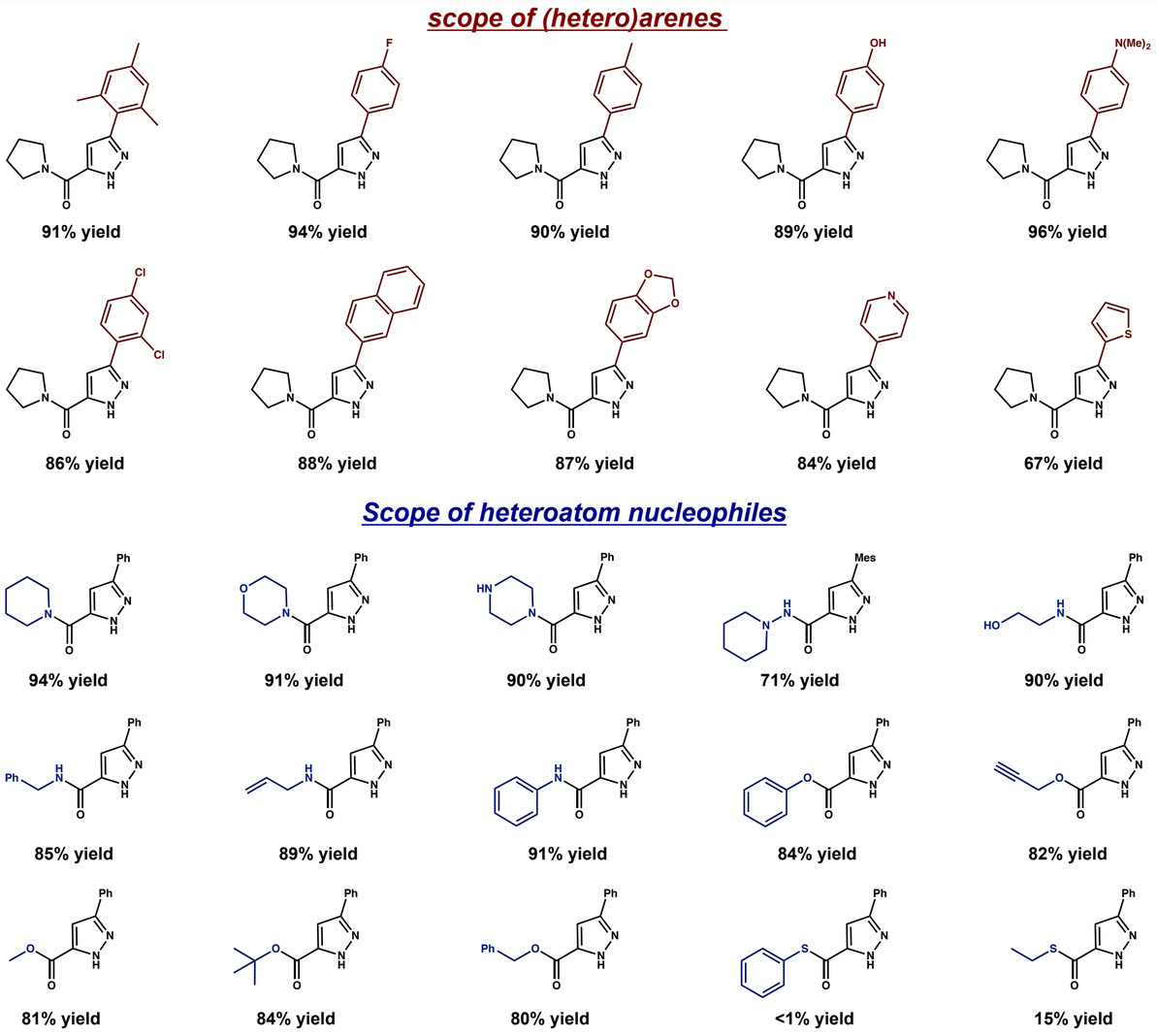
solvent	hv (nm)	temp (°C)	**P**:**F**:**A**
CH_2Cl_2	254	35	2:1:1
PhH	254	35	6:2:1
CH_3CN	254	35	10:3:1
THF	254	35	8:4:1
THF	305	35	20:1:3
THF[a]	**350**	**65**	**98:0:2**

[a] 0.3 M (THF), 65 °C, 2h, 94% isolated yield of **P**

Reaction Scope and Limitations

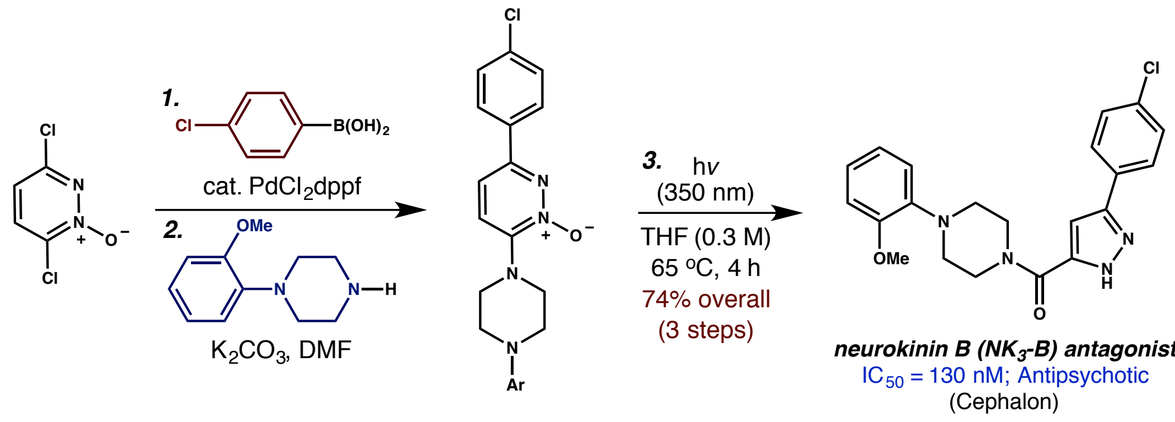


scope of (hetero)arenes



Scope of heteroatom nucleophiles

Application: Three-step Synthesis of Drug Candidate



neurokinin B (NK_3-B) antagonist
IC_{50} = 130 nM; Antipsychotic
(Cephalon)

Hoveyda, H, R. et. al. **discoveryof 3-aryl-5-acylpiperazinyl-pyrazoles as antagonists to the NK_3 receptor**. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1991–1996.

Acknowledgements and Contact Information

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Crystallography

Dr. Ron Clark
Chem & Biochem

Prof. Jim Frederich
frederich@chem.fsu.edu

Maribel Portillo
mp14s@my.fsu.edu

Michael Maxwell
mam15y@my.fsu.edu