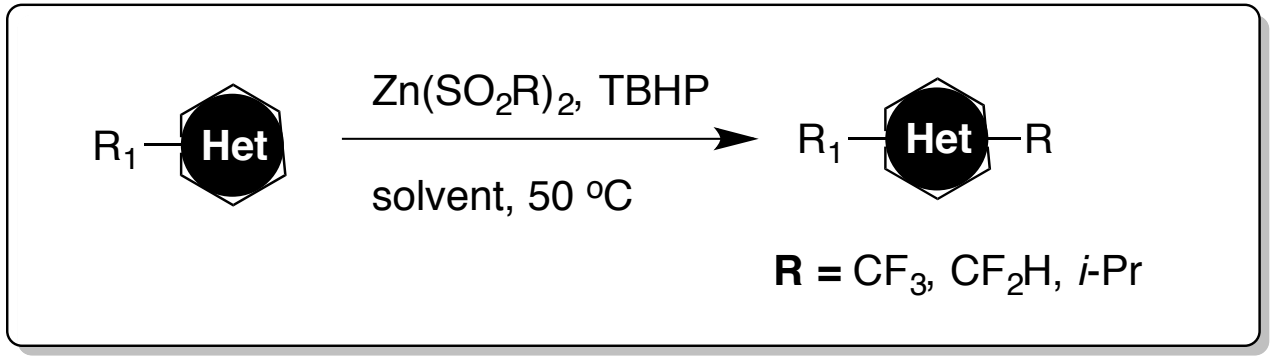
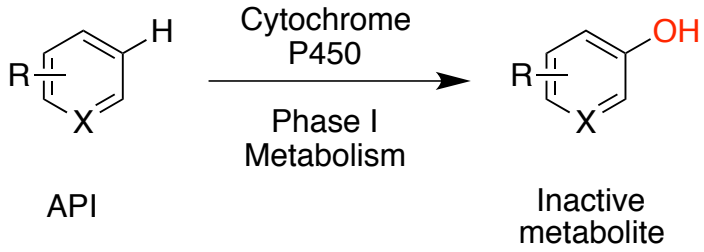
Radical-Based Regioselective C-H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability

O'Hara, F.; Blackmond, D.G.; Baran, P.S. *J. Am. Chem. Soc.* **2013**, 135, 12122.



Evan Carder
Wipf Group Current Literature
24 August 2013

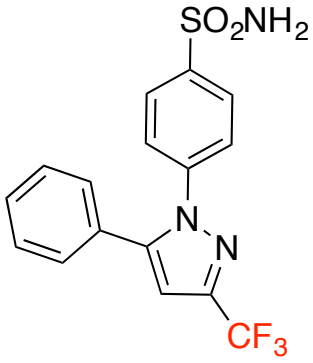
Trifluoromethylation and Pharmaceuticals



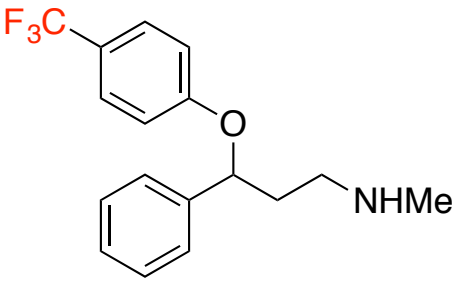
- Medicinal chemists face major challenges converting drug candidates into viable pharmaceutics[1].
- Pharmacologically active compounds can have poor structural characteristics that adversely influences its metabolism and excretion[2].
- Trifluoromethylation is commonly employed to rationally protect labile positions against cytochrome P450 oxidation[3].

[1] S. Purser et al. *Chem. Soc. Rev.* **2008**, 37, 320.
[2] W.K. Hagmann et al. *J. Med. Chem.* **2008**, 51, 4359.
[3] K. Muller et al. *Science,* **2007**, 317,1881.

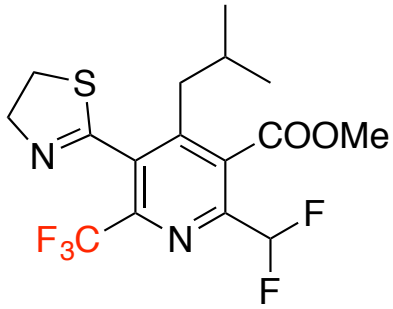
Examples Currently Available in the Market



Celebrex
Arthritis, Pfizer

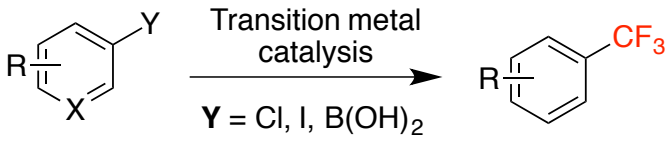


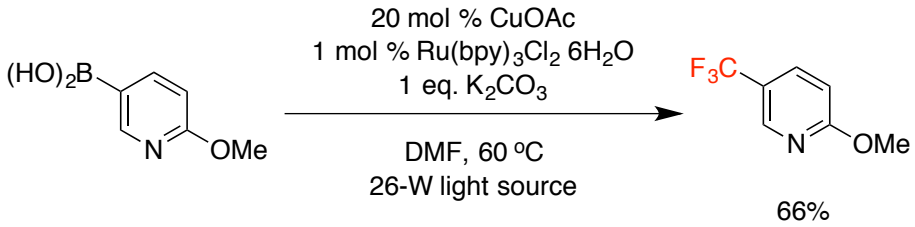
Prozac
Depression, Eli Lilly



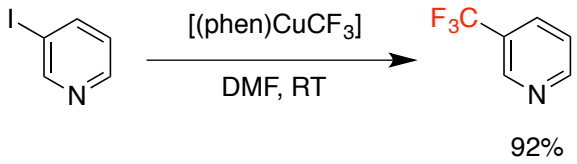
Monsanto
Herbicide

Programmed Trifluoromethylation



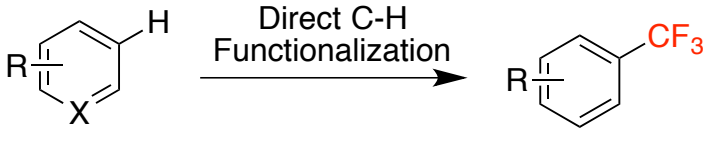


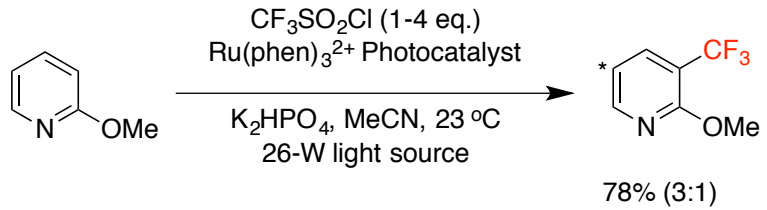
Ye, Y.; Sanford, M.S. *J. Am. Chem. Soc.* **2012**, 134, 9034.



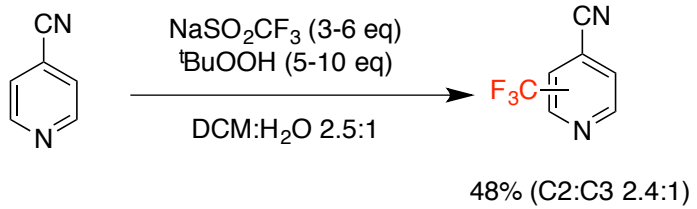
H. Morimoto et al. *Angew. Chem. Int. Ed.* **2011**, 50, 3793.

Innate Trifluoromethylation





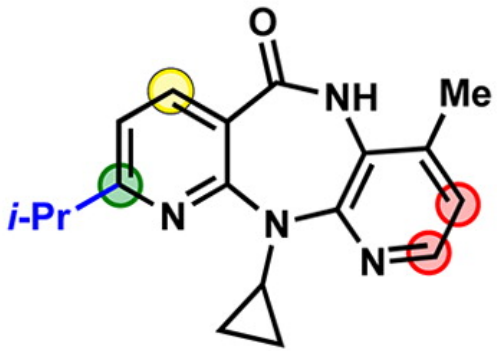
Nagib, D.A.; MacMillian, D. *Nature* **2011**, 480, 224.



Ji et al. *PNAS*, **2011**, 108, 14411.

Value in Exploiting Innate Reactivity

- Incorporates electrophilic radicals at potentially metabolically labile positions.
- Reduces the need for pre-functionalization and allows late-stage trifluoromethylation of diverse arenes and heteroarenes.
- Potentially predictable regioselectivity and tunable regiocontrol, which offers divergent synthetic strategies.
- Allows substitution on various π-deficient heteroarenes – pyridines, pyrimidines, pyradazines, and pyrazines.

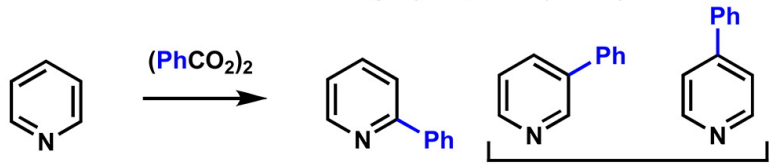


28%
nevirapine **45**
anti-retroviral drug

Objective

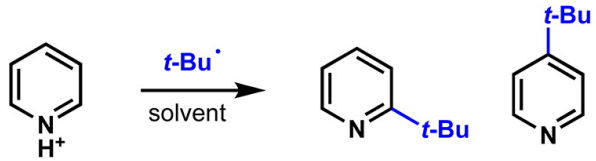
- Establish trends that allow for practical predictions in regioselectivity of radical functionalization of heteroarenes

A. Influence of acid additives: e.g. Lynch, 1964 (ref. 10)



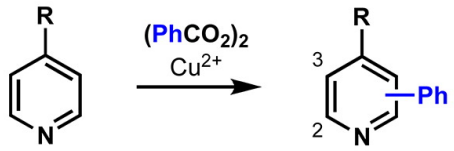
no additive:	62	:	38
AcOH:	80	:	20

B. Influence of solvent: e.g. Minisci, 1974 (ref. 11)



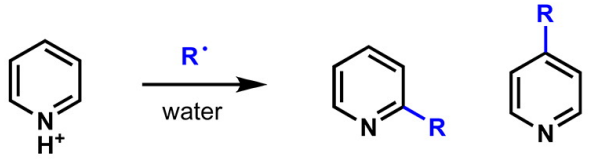
benzene:	71	:	29
water:	23	:	77

C. Influence of functional groups: e.g. Minisci,1986 (ref. 13)



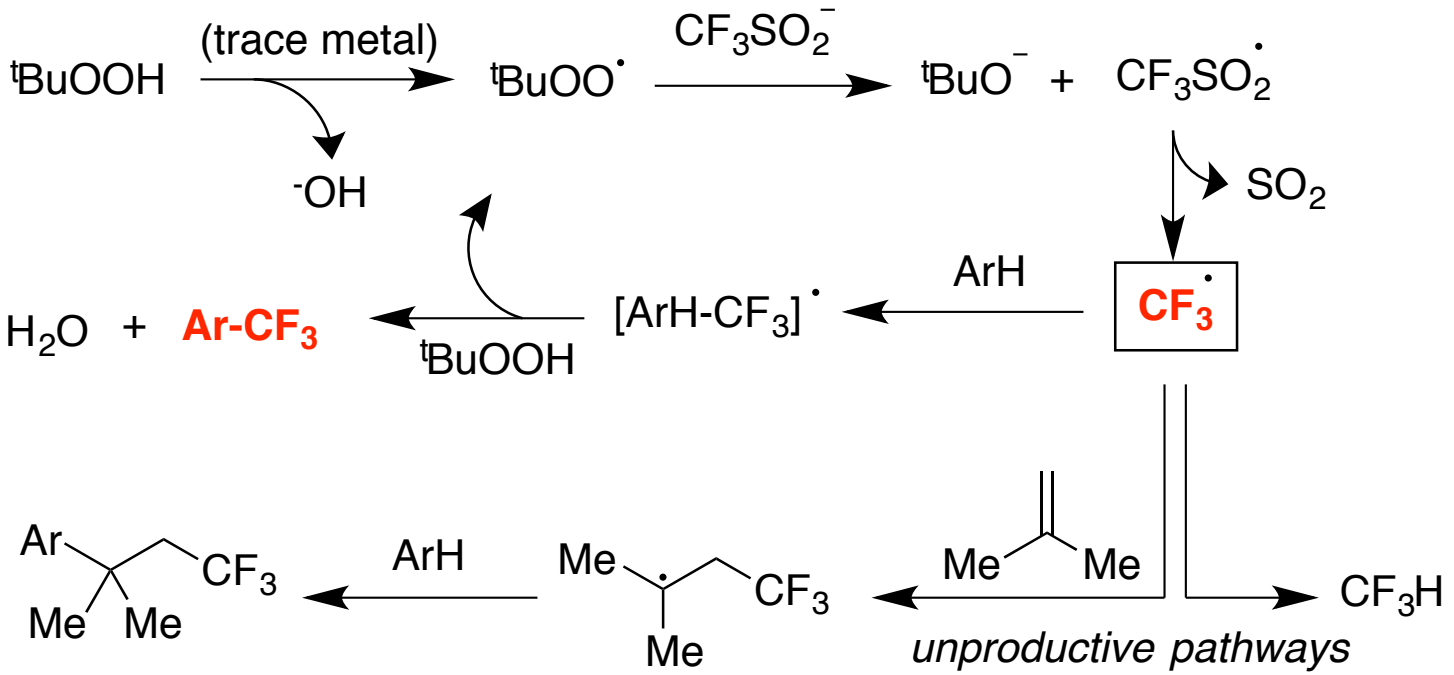
R	$k_3 : k_2$
CN	2.8 : 1
OMe	1.7 : 1
Cl	1.5 : 1
Me	1.1 : 1
H	0.6 : 1

D. Influence of nature of radical: e.g. Minisci, 1974 (ref. 11)



R = Me	62	:	38
R = *n*-Pr	58	:	42
R = *t*-Bu	23	:	77

Mechanism of Heteroarene Functionalization using Alkylsulfinate-Derived Radicals



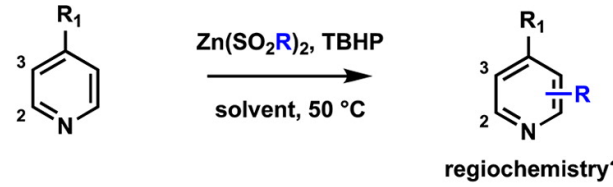
Ji et al. *PNAS*, **2011**, 108, 14411.

Regioselectivity is influenced by three major factors:

i. Innate reactivity of the parent heterocycle

ii. Conjugate activity of π-conjugating electron withdrawing groups

iii. Electron properties of the radical



regiochemistry?

(A) solvent/pH effect: (R = *i*-Pr, R_1 = CN)

solvent	C-3 : C-2
DMSO	4.3 : 1
DMF	2.7 : 1
MeCN	1 : 2.3
$CHCl_3/H_2O$	1 : 3.0
DMSO/1 eq. H_2SO_4	1 : 3.9
$CHCl_3/H_2O$/excess TFA	1 : 5.0
DMSO/excess H_2SO_4	1 : 6.6

addition of acid reduces influence of conjugate reactivity

(B) nature of substituent R_1: (R = *i*-Pr, solvent = DMSO)

R_1	σ	C-3 : C-2
π-conjugating EWG		
CN	0.66	4.3 : 1
Ac	0.50	1.4 : 1
CO_2Me	0.45	1.3 : 1
Bz	0.43	1.3 : 1
$CONH_2$	0.36	1 : 4.3
non π-conjugating EWG and other groups		
CF_3	0.54	C2 only
$CON(i\text{-}Pr)_2$	-	C2 only
H	0.0	C2 only
Ph	-0.01	C2 only
t-Bu	-0.20	C2 only
OMe	-0.27	C2 only

influence of conjugate reactivity decreases with decreasing electrophilicity of **π–conjugating** EWG

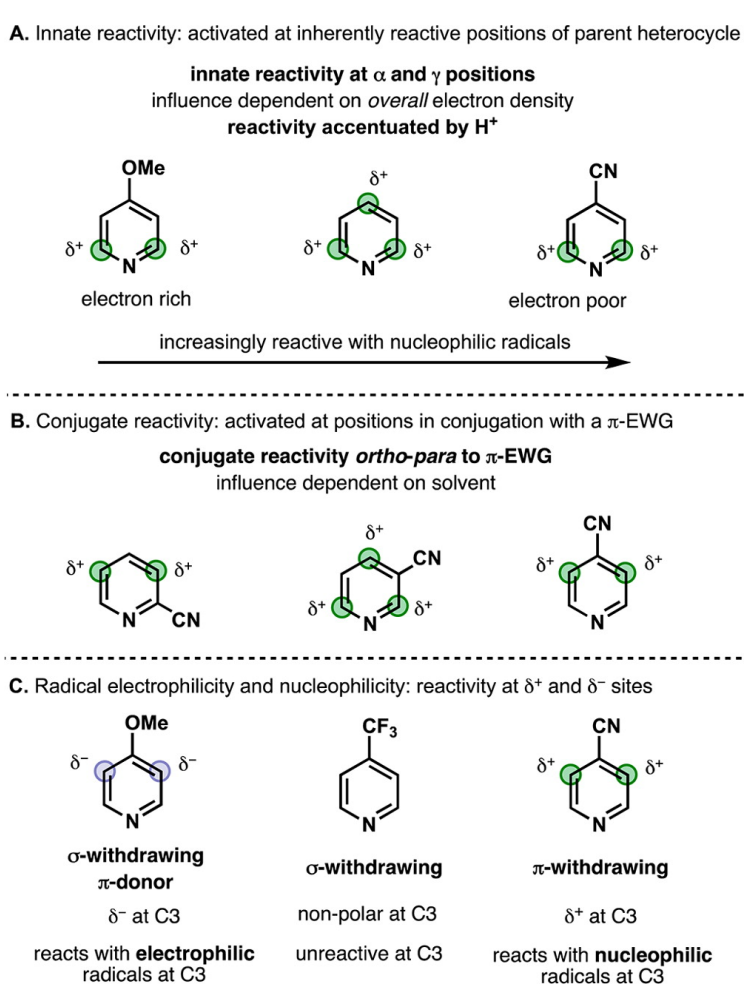
no C3 products observed in the absence of a **π–conjugating** EWG

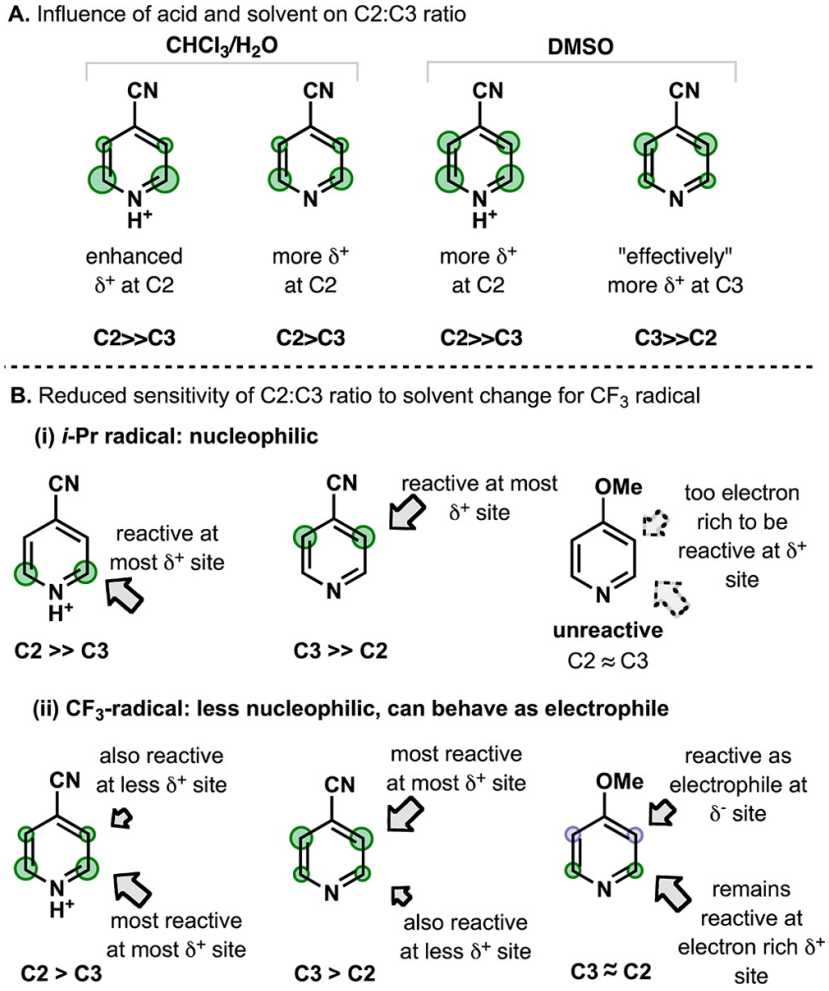
(C) nature of radical R: (R_1 = CN, solvent = DMSO)

R	C-3 : C-2
i-Pr	4.3 : 1
CF_2H	3.2 : 1
CF_3	2.5 : 1
CF_3 (+ 1 eq. H_2SO_4)	2.4 : 1
CF_2H (+ 1 eq. H_2SO_4)	1 : 1.8
i-Pr (+ 1 eq. H_2SO_4)	1 : 3.9

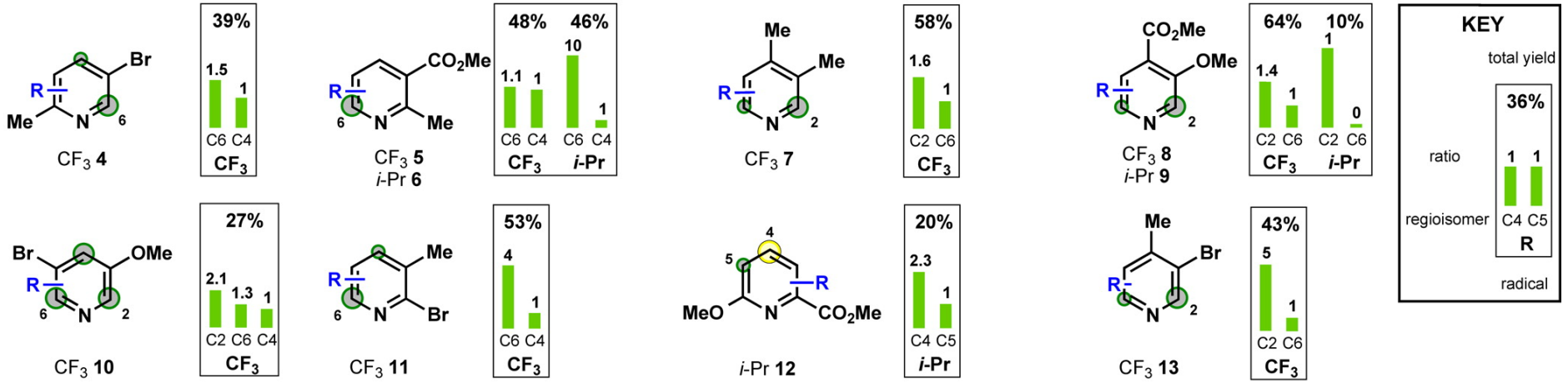
effect of protonation increases with radical nucleophilicity

Innate Reactivity and Tunability

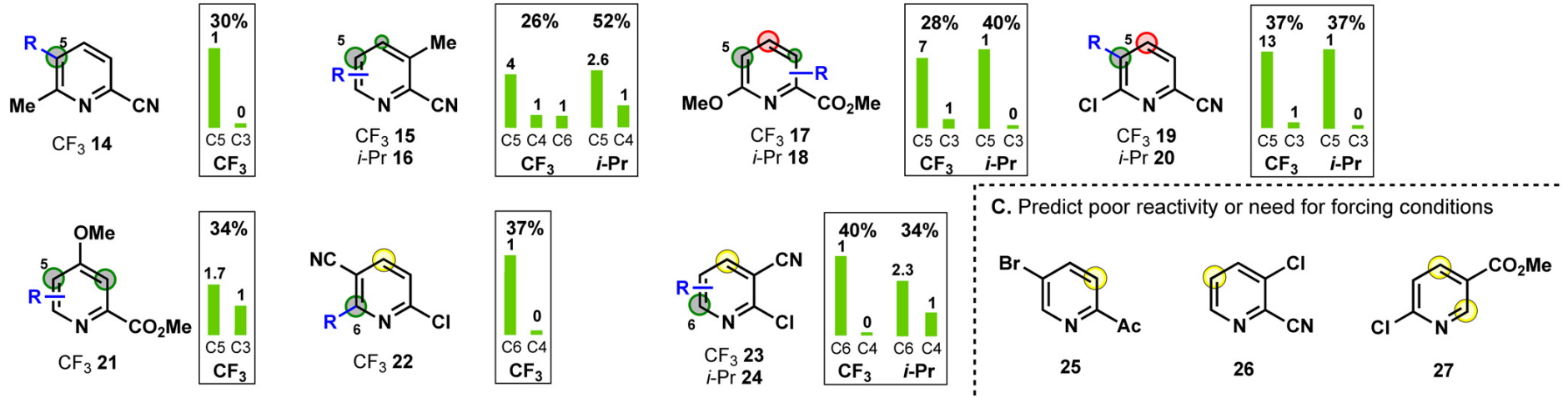




A. Predictable selectivity in $CHCl_3/H_2O$ or $CHCl_3/H_2O$/TFA: innate reactivity dominates



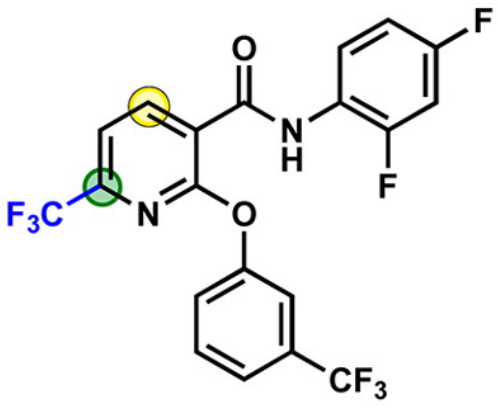
B. Predictable selectivity in DMSO: conjugate reactivity dominates



C. Predict poor reactivity or need for forcing conditions

25 26 27

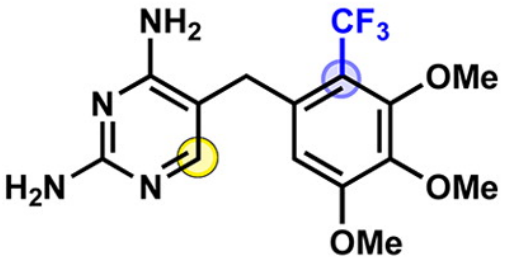
Application in Biologically Available Compounds



11%
diflufenican **49**[a]
herbicide

heterocycle electrophilic
arenes poorly nucleophilic

CF_3 behaves as nucleophile



35%
trimethoprim **50**[b]
antibiotic

heterocycle poorly electrophilic
arene nucleophilic

CF_3 behaves as electrophile

Conclusion

- This paper provides an empirical model to predict regioselectivity of radical functionalization in diverse heterocycles.
- Proposes solvent mediated regiochemical control
- Guidelines were shown to have application in biologically relevant compounds, which may influence future efforts on radical-mediated functionalization of pharmaceuticals.