RWTH AACHEN UNIVERSITY



Novel Synthetic Methods Using Photochemistry and Photocatalysis

Daniele Leonori

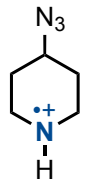
Institute of Organic Chemistry, RWTH Aachen University

www.leonorigroup.com • @LeonoriLab

RWTH AACHEN UNIVERSITY

Current Research Areas

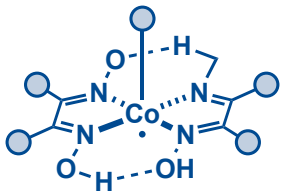
nitrogen radicals



radical strategies for C–N bond assembly

Nat. Chem. **2019**; *ACIE* **2021**; *ACIE* **2020**; *ACIE* **2019**; *ACIE* **2018**; *JACS* **2016**; *ACIE* **2015**

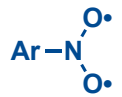
desaturative catalysis



desaturative approaches to aromatic synthesis

Nature **2020**; *Nat. Catal.* **2024** *ACIE* **2023**; *ACIE* **2022**; *JACS* **2022**

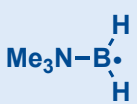
photoexcited nitroarenes



novel reagents and novel heterocycles

Science **2025**; *Nature* **2022** *Nat. Chem.* **2024**; *Chem* **2024**, *JACS* **2023**

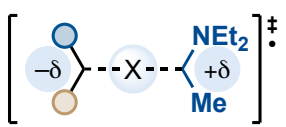
boryl radicals



radical blueprints for for C–H borylation

Nature **2021**; *Nat. Synth* **2024**; *JACS* **2024**; *Chem* **2025**

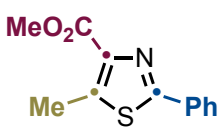
halogen-atom transfer



novel strategies for carbon radical generation

Science **2020**; *Science* **2022** *Nat. Catal.* **2022**; *JACS* **2022**; *JACS* **2024**

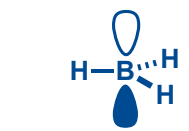
chemical permutation



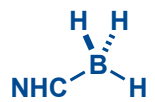
a novel approach to heteroaromatic synthesis

Nature **2025**; *Nat. Synth.* **2025** *ACIE* **2025**; *Nat. Commun.* **2025**

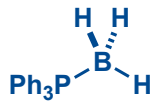
Type of Ligated-Boryl Radicals



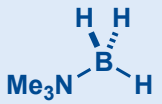
B–H ≃ 112 kcal/mol
JACS **2008**, 10082



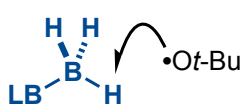
B–H ≃ 80 kcal/mol
JACS **2008**, 10082



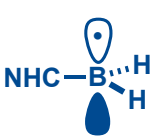
B–H ≃ 91 kcal/mol
JACS **1997**, 8350



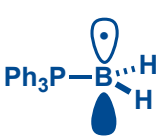
B–H ≃ 101 kcal/mol
JPOC **2009**, 986



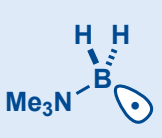
HAT
polarity matched



π-radicals
CSR **2021**, 8995



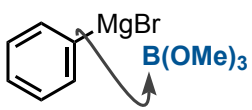
π-radicals
CSR **1999**, 25



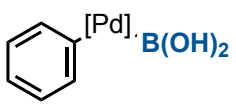
σ-radicals
CSR **1999**, 25

nucleophilicity

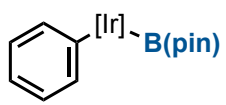
Aromatic Borylation



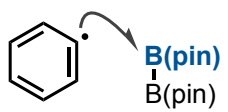
aryl nucleophiles
OM **1983**, 1316



Miyaura borylation
OPRD **2017**, 65



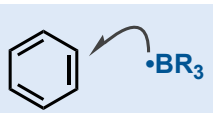
C–H borylation
Chem. Rev. **2010**, 890



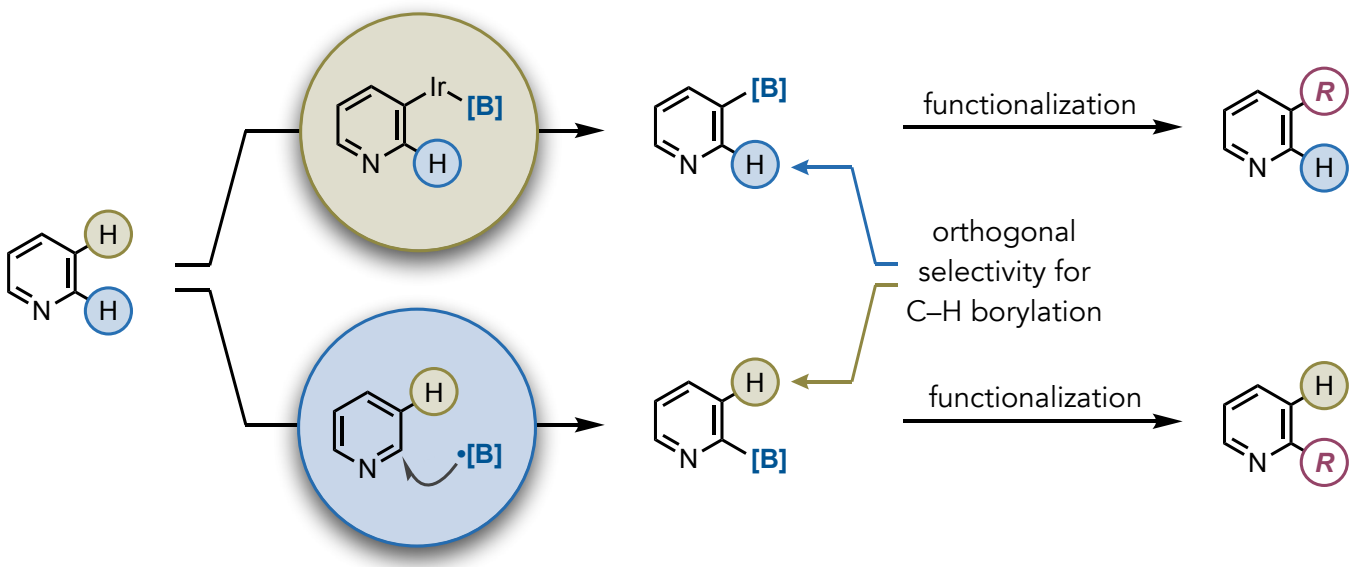
aryl radicals
JACS **2016**, 607



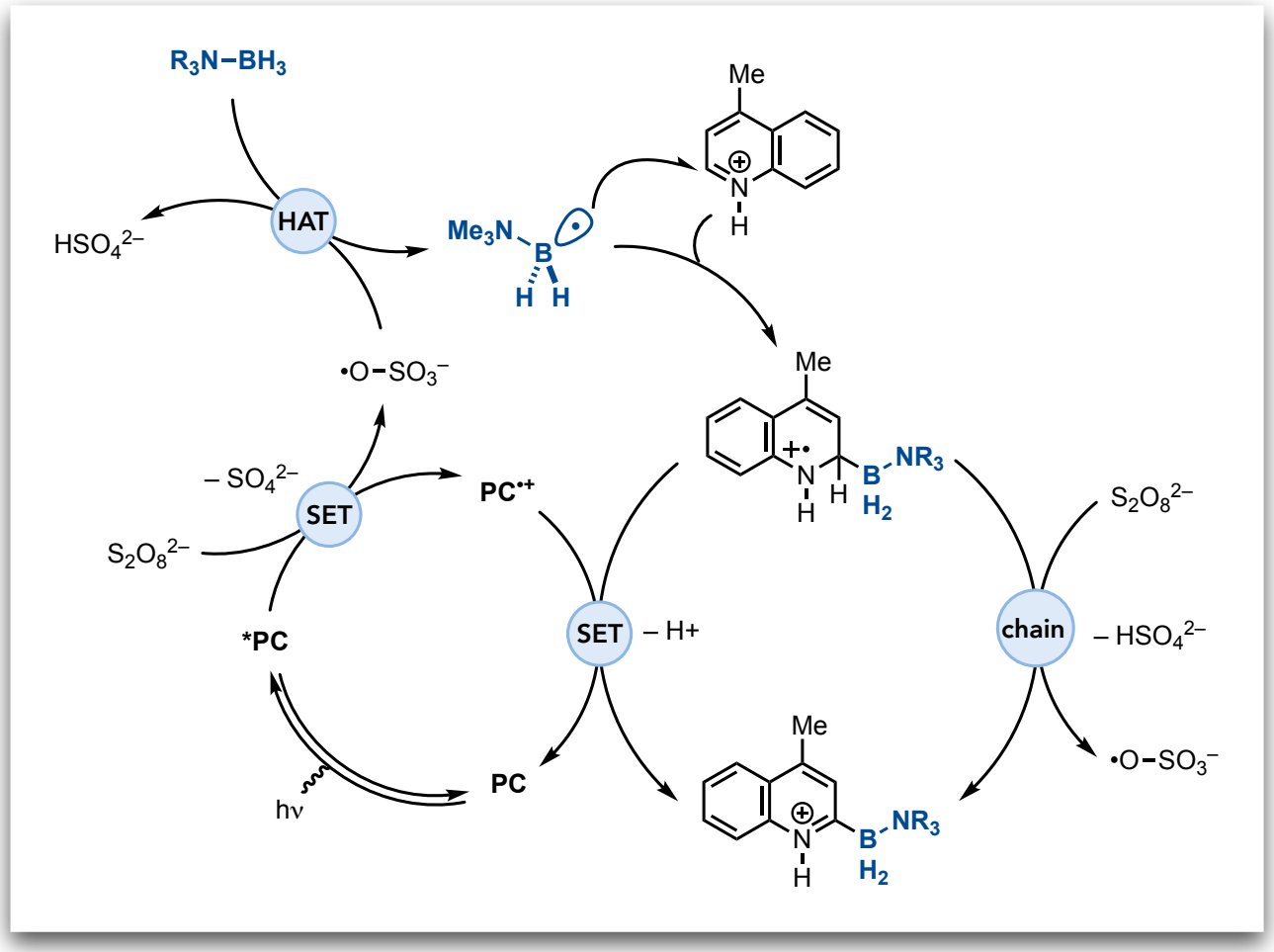
borocations
JACS **2013**, 474



boryl radicals?
unprecedented



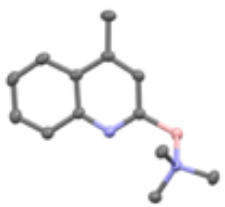
Minisci-Style Borylation – Mechanism

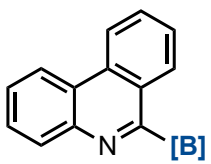


Nature **2021**, *595*, 577

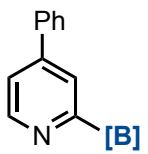
Minisci-Style Borylation – Scope



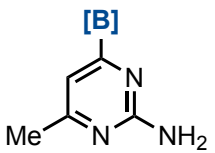




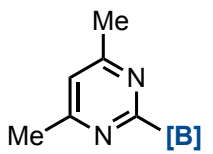
81%



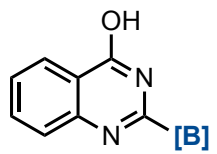
55%



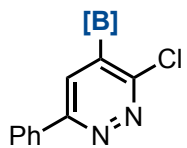
77%



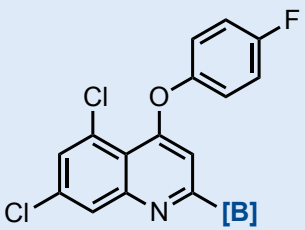
35%



quant.

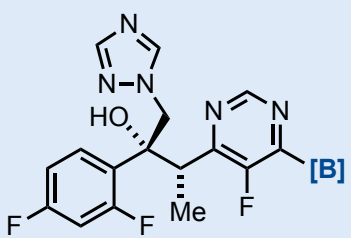


47%



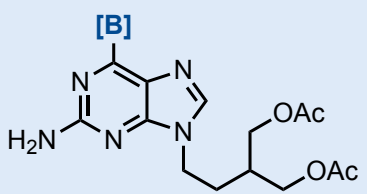
quinoxyfen – *fungicide*

44%



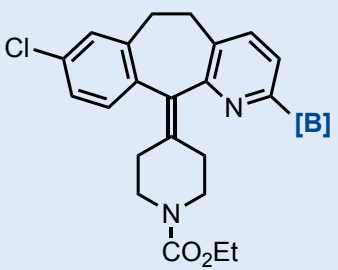
voriconazole – *fungicide*

45%



famciclovir – *antiherpetic*

42%



loratadine – *antiallergic*

21%

Nature **2021**, *595*, 577

Minisci-Style Borylation – Scope



GDCh **Reviews** Angewandte International Edition Chemie

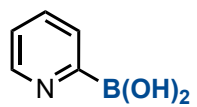
Check for updates

How to cite:
International Edition: doi.org/10.1002/anie.202010631
German Edition: doi.org/10.1002/ange.202010631

Cross-Coupling Reactions

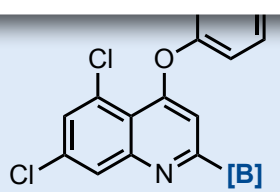
The 2-Pyridyl Problem: Challenging Nucleophiles in Cross-Coupling Arylations

*Xinlan A. F. Cook⁺, Antoine de Gombert⁺, Janette McKnight⁺, Loïc R. E. Pantaine⁺, and Michael C. Willis**



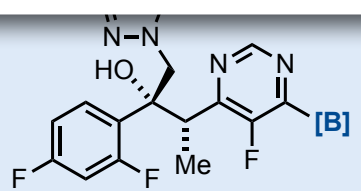
τ = 26 s

Lloyd-Jones *JACS* **2017**, *139*, 13156



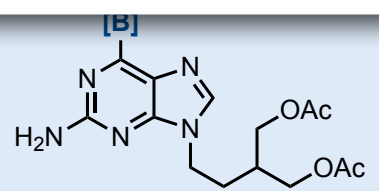
quinoxyfen – *fungicide*

44%



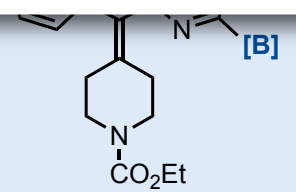
voriconazole – *fungicide*

45%



famciclovir – *antiherpetic*

42%



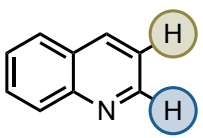
loratadine – *antiallergic*

21%

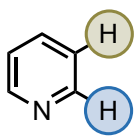
C–H activation vs Minisci Borylation

position functionalized by C–H activation

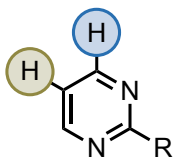
position functionalized by this strategy



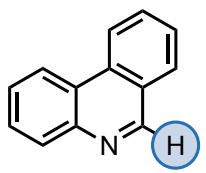
quinoline



pyridine

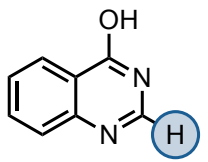


pyrimidine



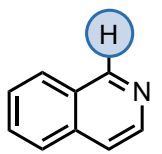
phenanthridine

C–H borylation was unprecedented



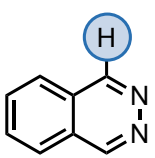
quinazolin-4-ol

C–H borylation was unprecedented



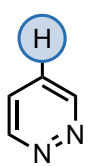
isoquinoline

C–H borylation was unprecedented



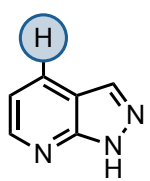
phthalazine

C–H borylation was unprecedented



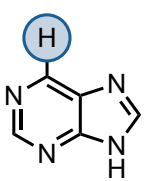
pyridazine

C–H borylation was unprecedented



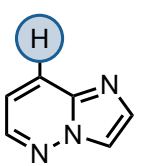
1H-pyrazolo[3,4-b]pyridine

C–H borylation was unprecedented



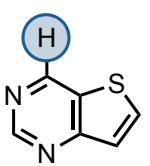
purine

C–H borylation was unprecedented



imidazo[1,2-b]pyridazine

C–H borylation was unprecedented

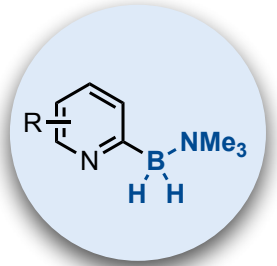


thieno[3,2-d]pyrimidine

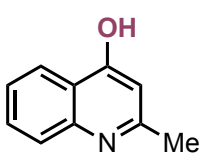
C–H borylation was unprecedented

Nature **2021**, *595*, 577

Amine-Boranes as Functionality Handles

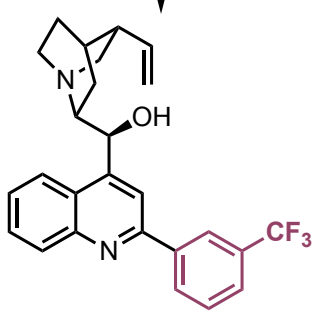


oxone (8.0 eq.)
$THF–H_2SO_4$
40 °C, air
85%



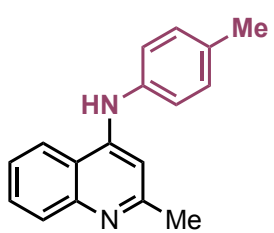
oxidation

Ar–I (2.0 eq.)
Na_2CO_3 (5.0 eq.)
$Pd_2(dppf)Cl_2$ (10%)
MeOH, 40 °C
30%



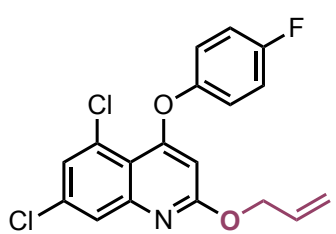
sp^2–sp^2 Suzuki-Miyaura

Et_3N (10.0 eq.)
Ar-NH_2 (4.0 eq.)
Cu(OAc) (1.0 eq.)
4Å MS, O_2 (balloon)
CH_2Cl_2, 50 °C
24%



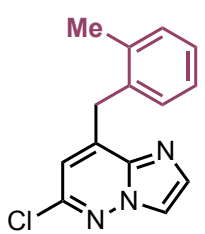
Chan-Lam

R–OH (solv.)
Cu(OAc) (1.0 eq.)
4Å MS, O_2 (balloon)
55 °C
92%



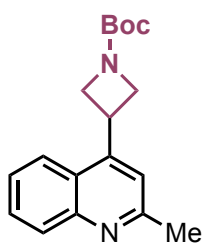
Chan-Lam

Bn–Cl (2.0 eq.)
$Pd(dba)_2$ (10%)
$P(PMP)_3$ (20%)
K_3PO_4 (3 eq.)
tol/H_2O, 80 °C
63%



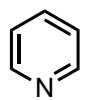
sp^2–sp^3 Suzuki-Miyaura

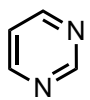
alkyl–I (2.0 eq.)
$NiBr_2$•glyme (20%)
dtbbpy (22 mol%)
K_2CO_3 (2 eq)
DME, 80 °C
41%

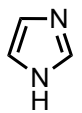


sp^2–sp^3 Suzuki-Miyaura

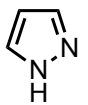
Heteroaromatics in Clinical Trials and Drugs

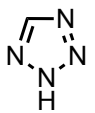
1st  pyridine

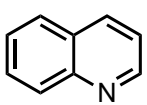
2nd  pyrimidine

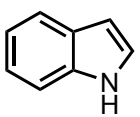
3rd  imidazole

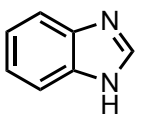
4th  thiazole

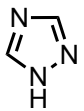
5th  pyrazole

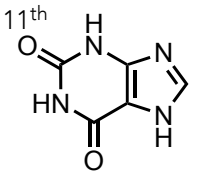
6th  tetrazole

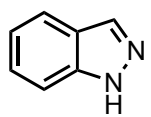
7th  quinoline

8th  indole

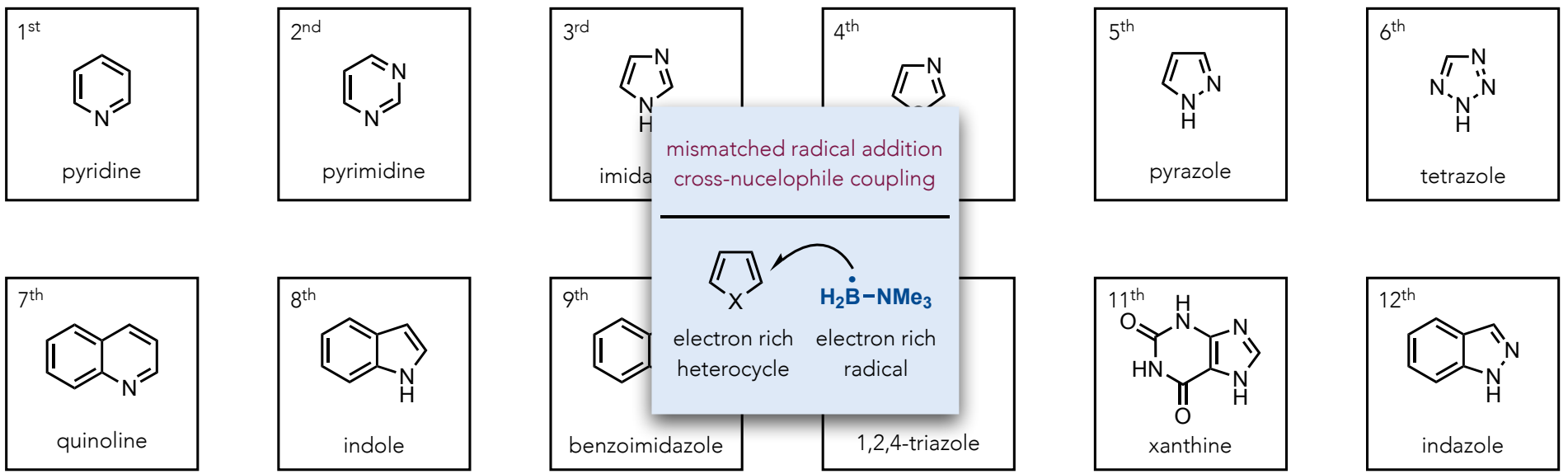
9th  benzoimidazole

10th  1,2,4-triazole

11th  xanthine

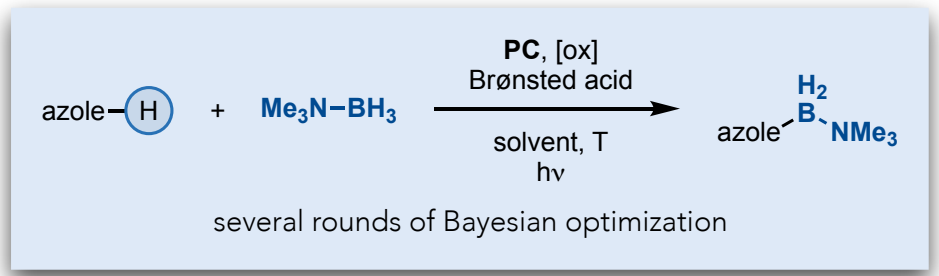
12th  indazole

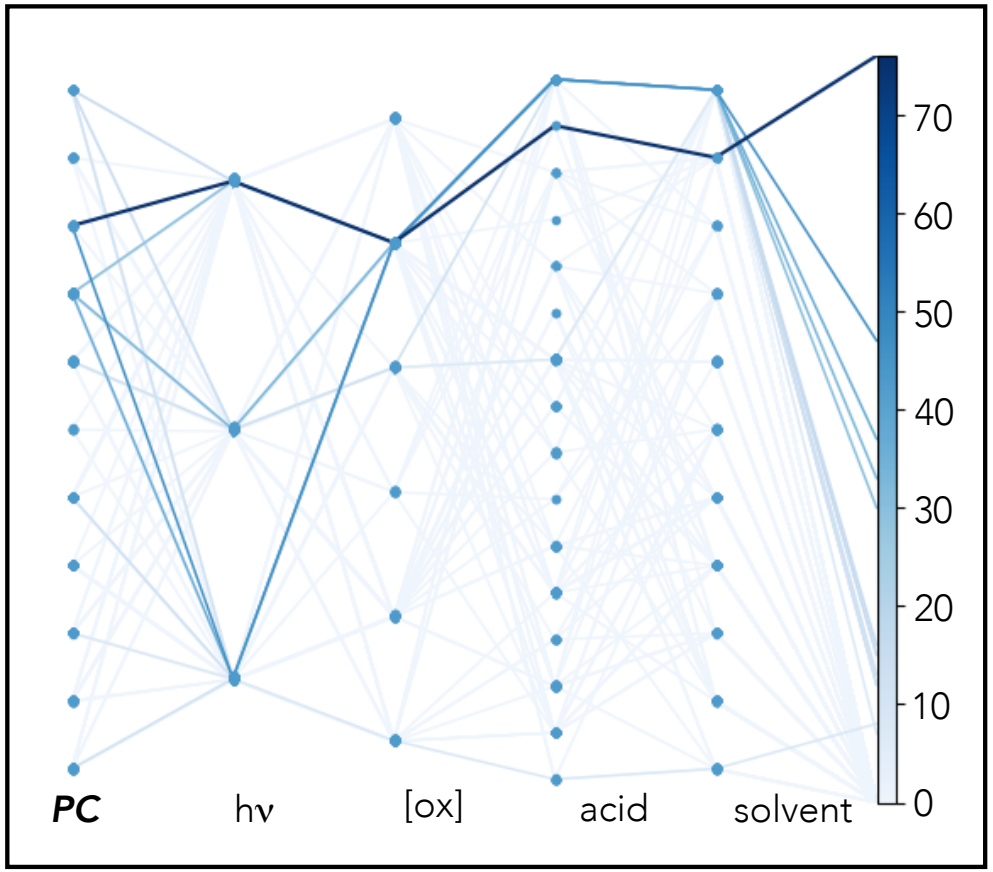
Heteroaromatics in Clinical Trials and Drugs



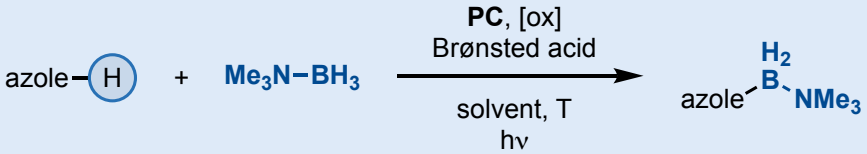
R. D. Taylor (UCB) *J. Med. Chem.* **2022**, *65*, 8699

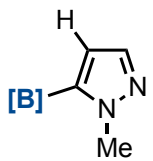
Azole Borylation



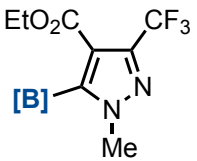


New Heteroaromatic Borylations

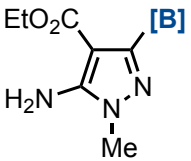




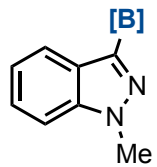
56% (gram-scale)
pyrazoles
orthogonal



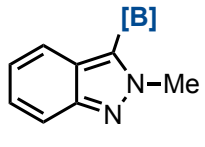
45%



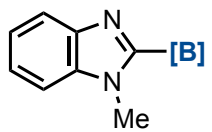
57%
C3 borylation



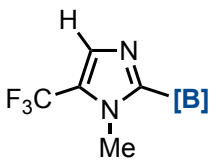
68% (gram-scale)
1H-indazoles
same selectivity



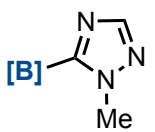
77%
2H-indazoles
same selectivity



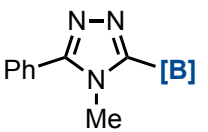
66%
benzimidazole
no C–H borylation



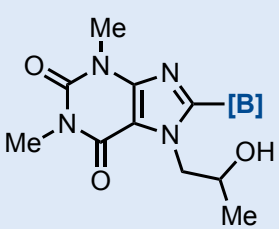
43% (gram-scale)
imidazoles
orthogonal



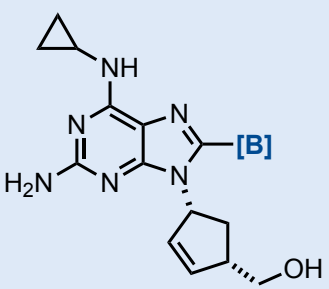
63%
1,2,4-triazoles
no C–H borylation



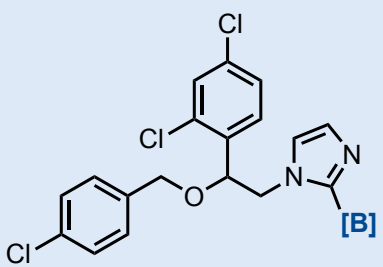
56%
1,3,4-triazoles
no C–H borylation



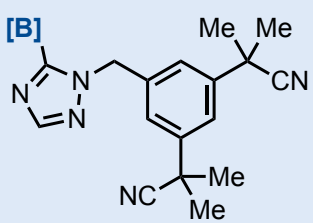
proxyphylline: **47%**



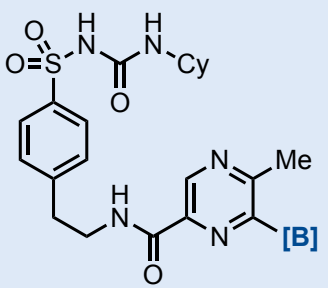
abacavir: **41%**



econazole: **55%**

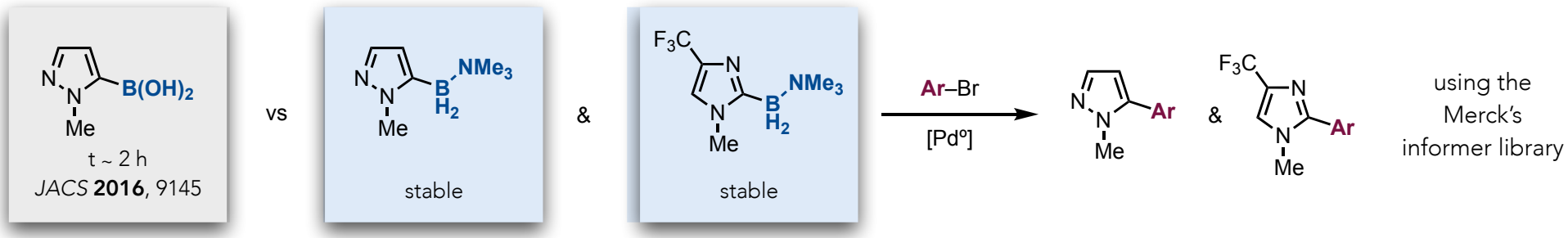


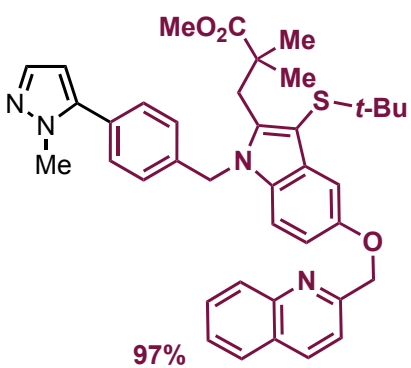
anastrozole: **47%**

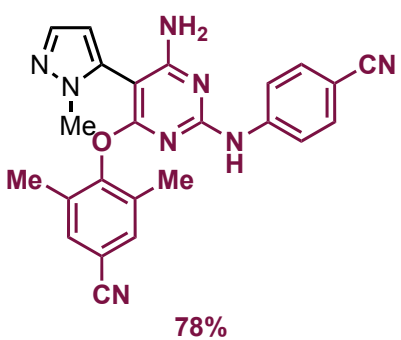


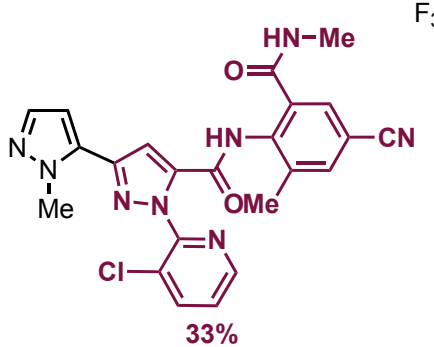
glipicide: **35%**

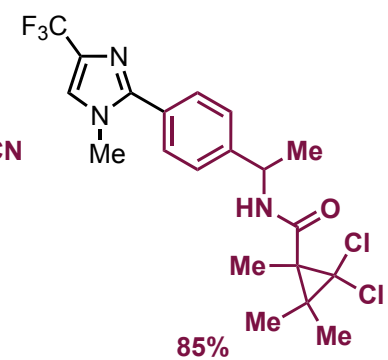
Suzuki-Miyaura Cross-Couplings

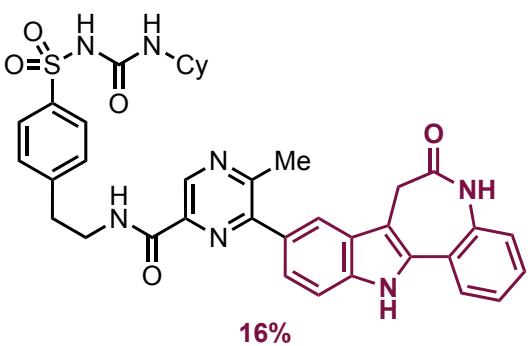












Aromatics in Clinical Trials and Drugs

1st

pyridine

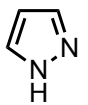
2nd

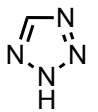
pyrimidine

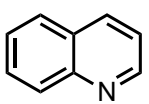
3rd

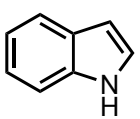
4th

benzene

5th

pyrazole

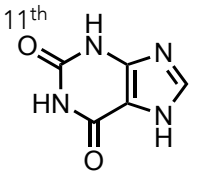
6th

tetrazole

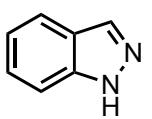
7th

quinoline

8th

indole

9th
benzoimidazole

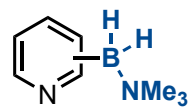
1,2,4-triazole

11th

xanthine

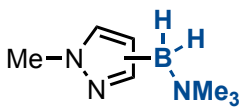
12th

indazole

R. D. Taylor (UCB) *J. Med. Chem.* **2022**, *65*, 8699

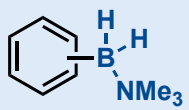
Aromatic Borylation



azines



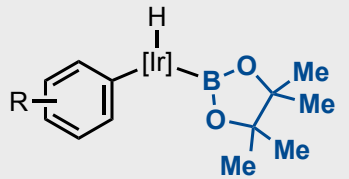
azoles



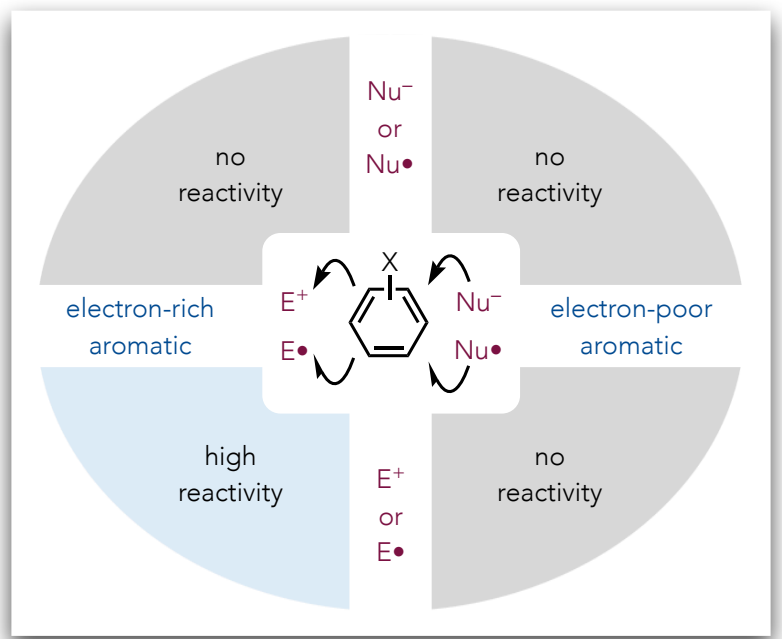
benzenes ???

current approach

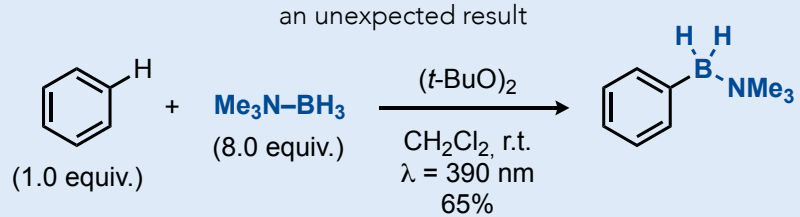
C–H activation via transition-metal catalysis



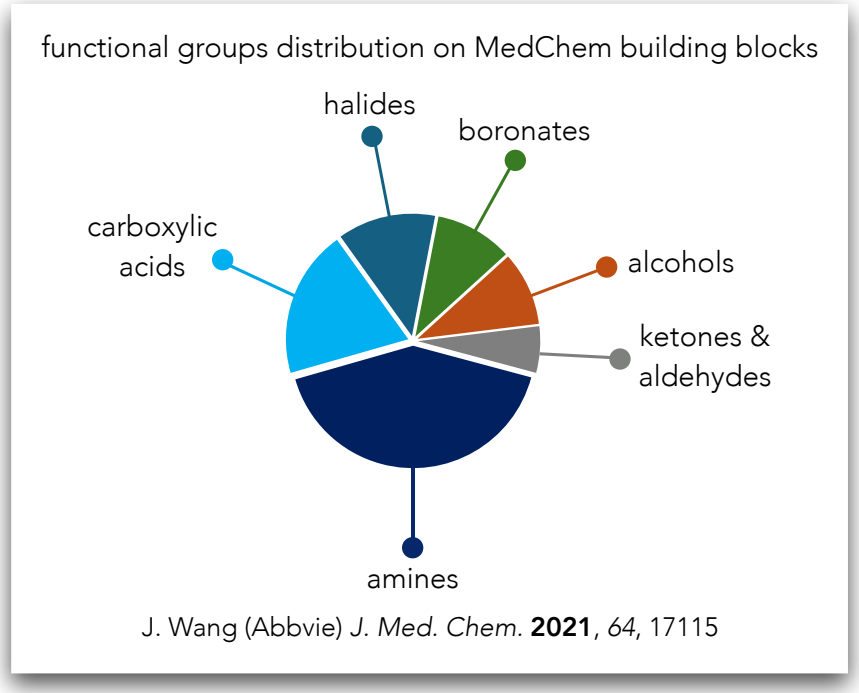
- steric effects = *meta*
- directing effects = *ortho*

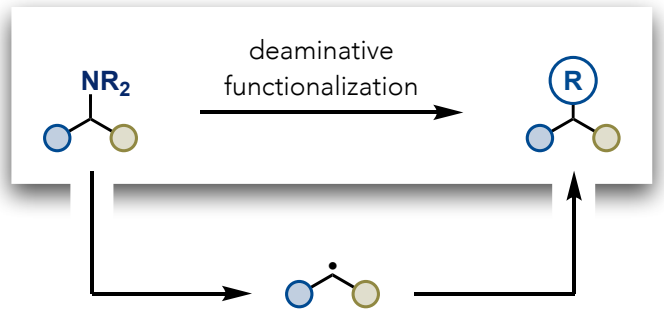


an unexpected result

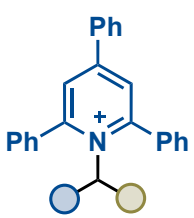


Deaminative Radical Functionalizations

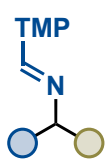




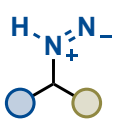
challenges
poor nucleofugacity
high C-N BDE
high basicity



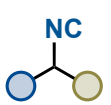
Katritzky's salts
Watson & Glorius **2017**



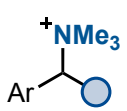
imines
Rovis **2020**



isodiazene intermediates
Levin **2023**



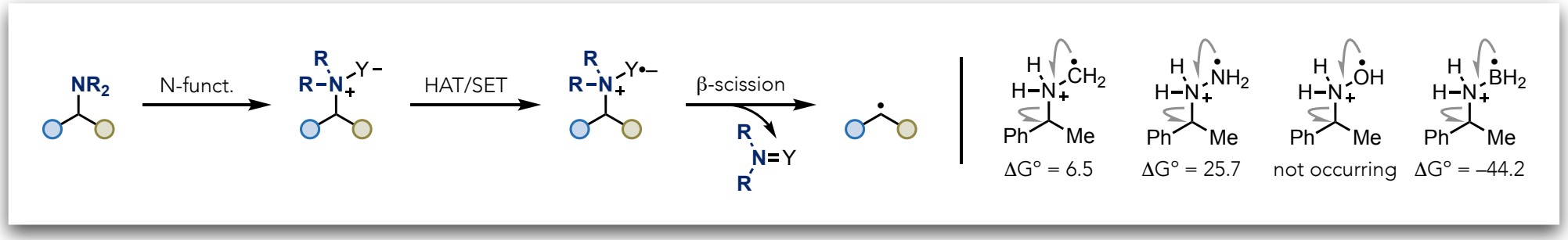
isocyanides
Tortosa **2024**



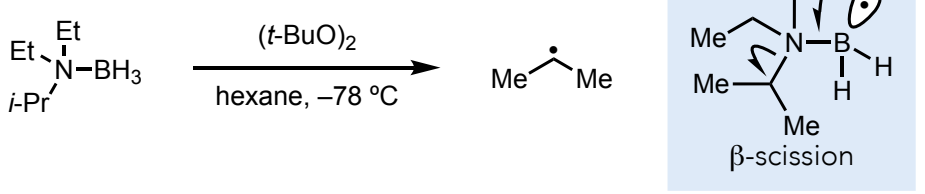
benzyl ammonium salts
Yu **2018**

review on current deamination methods: Lee *Chem. Commun.* **2025**, *61*, 6997

Deaminative Radical Functionalizations

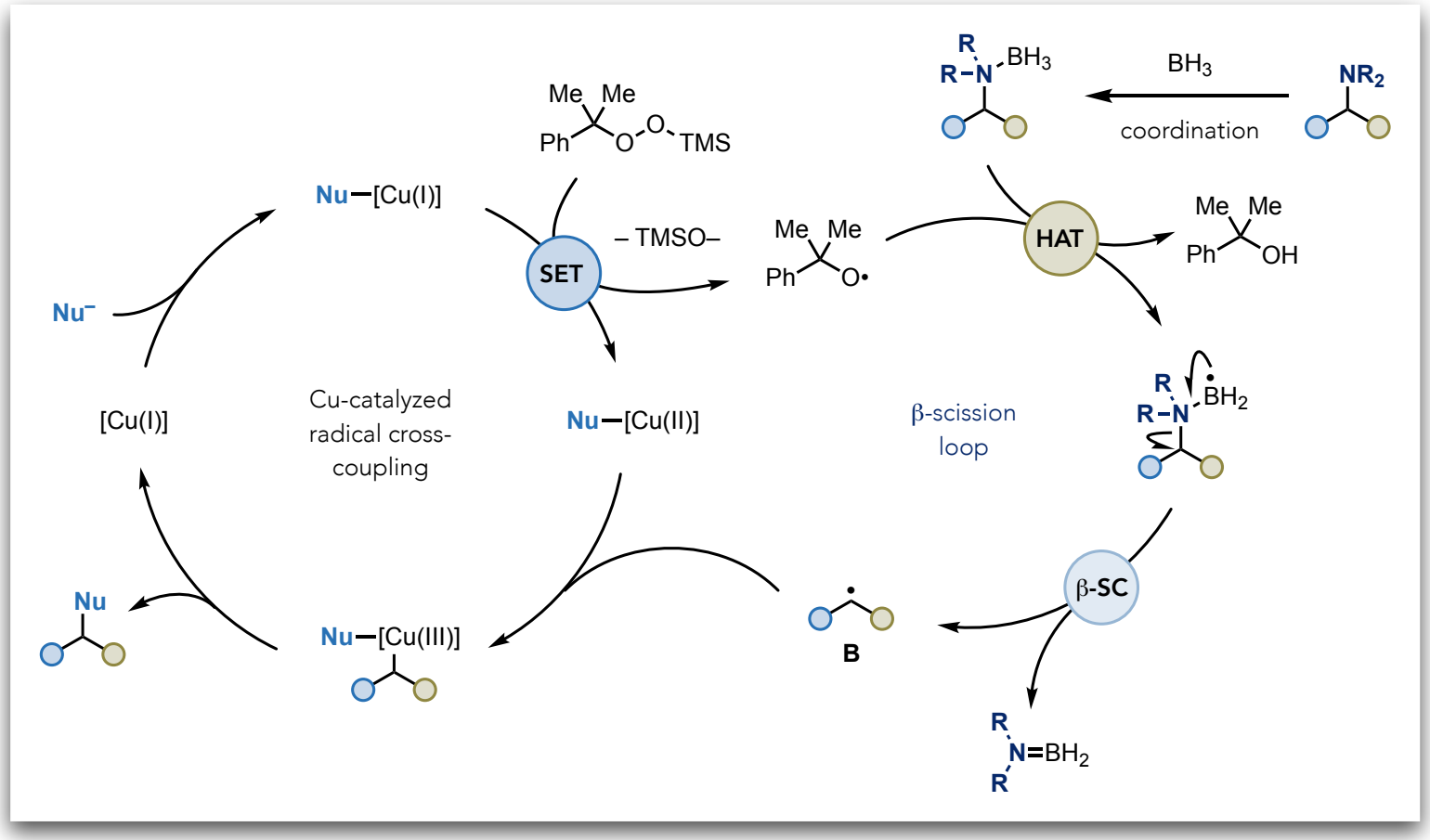


an EPR experiment from Roberts

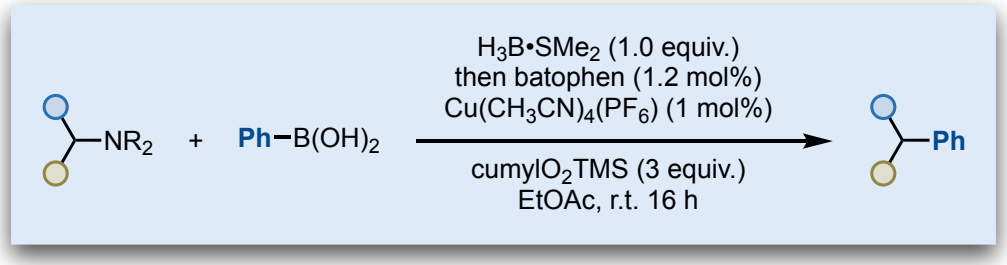


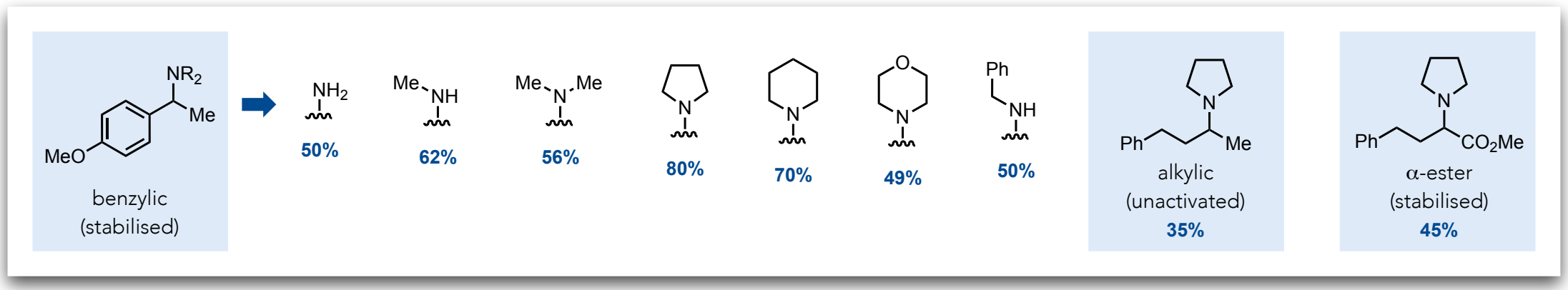
B. Roberts *J. Chem. Soc. Perkin Trans. 2* **1983**, 743

Radical Deamination–Functionalization

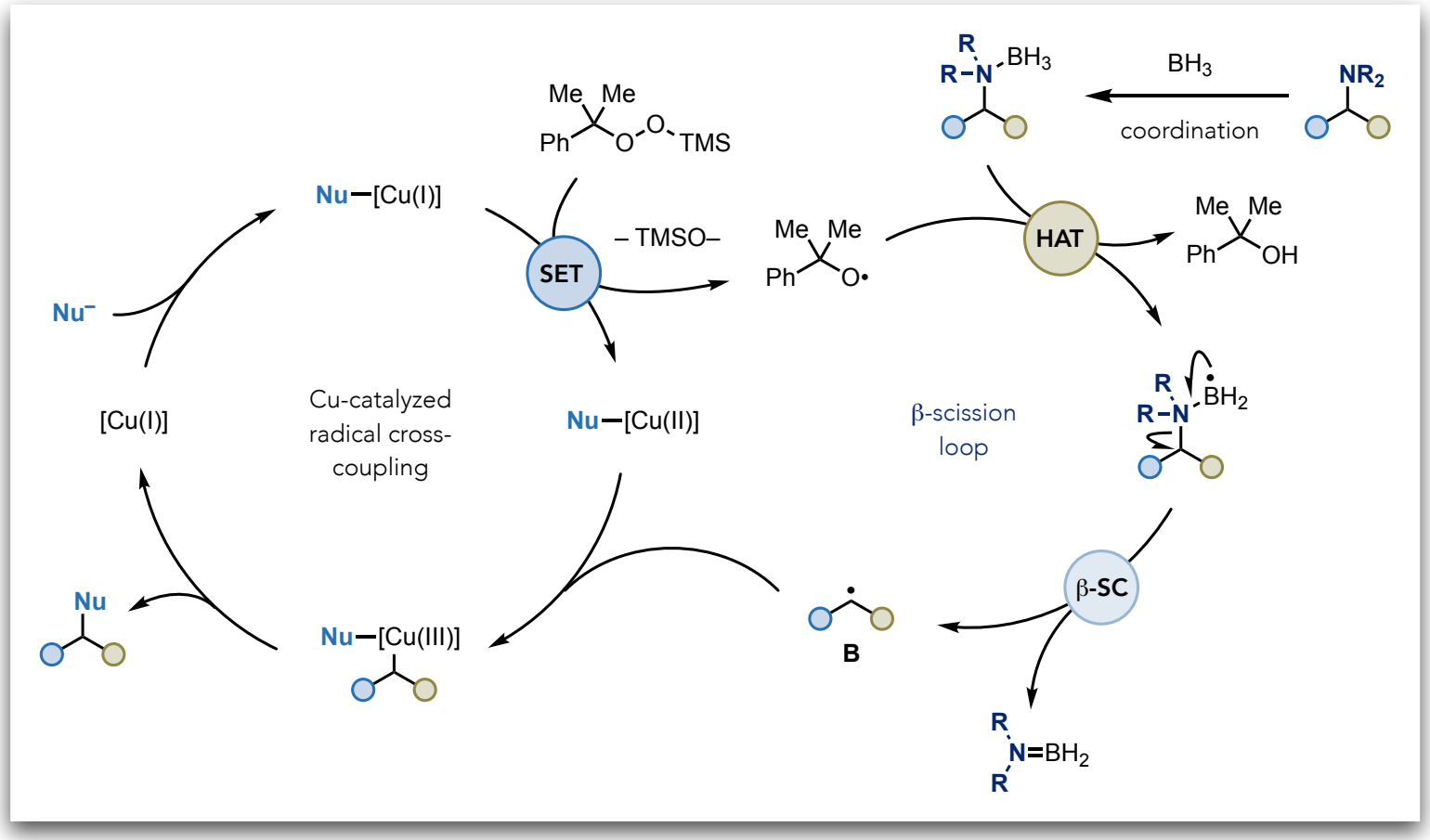


Deaminative Arylations

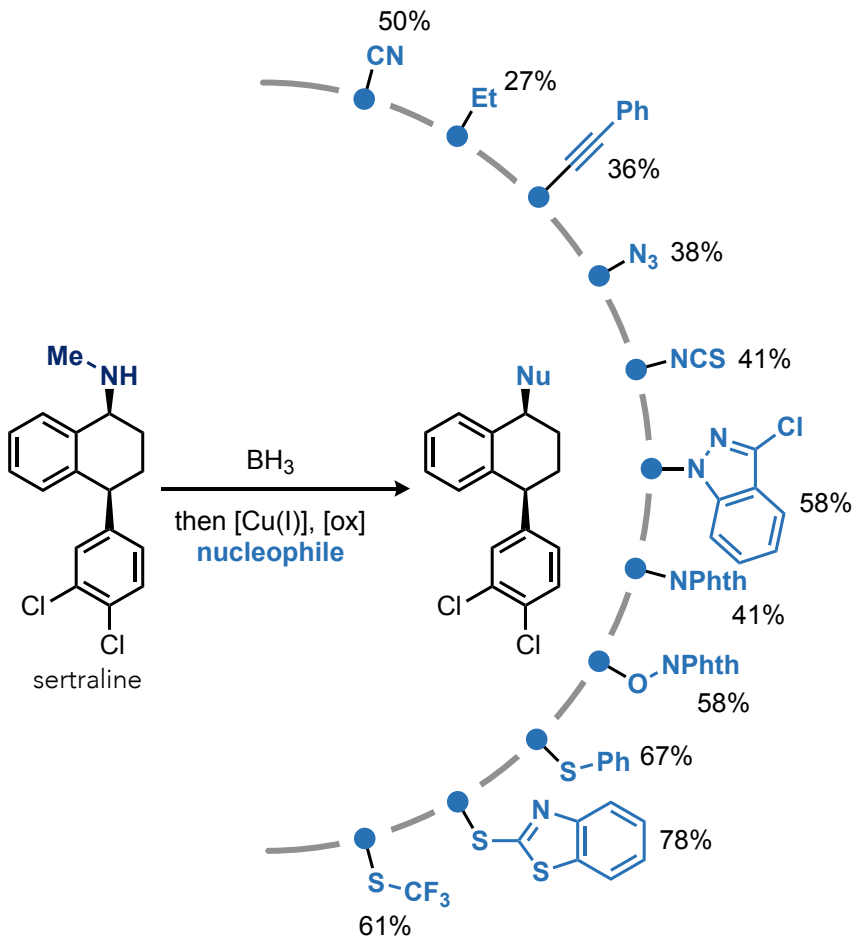


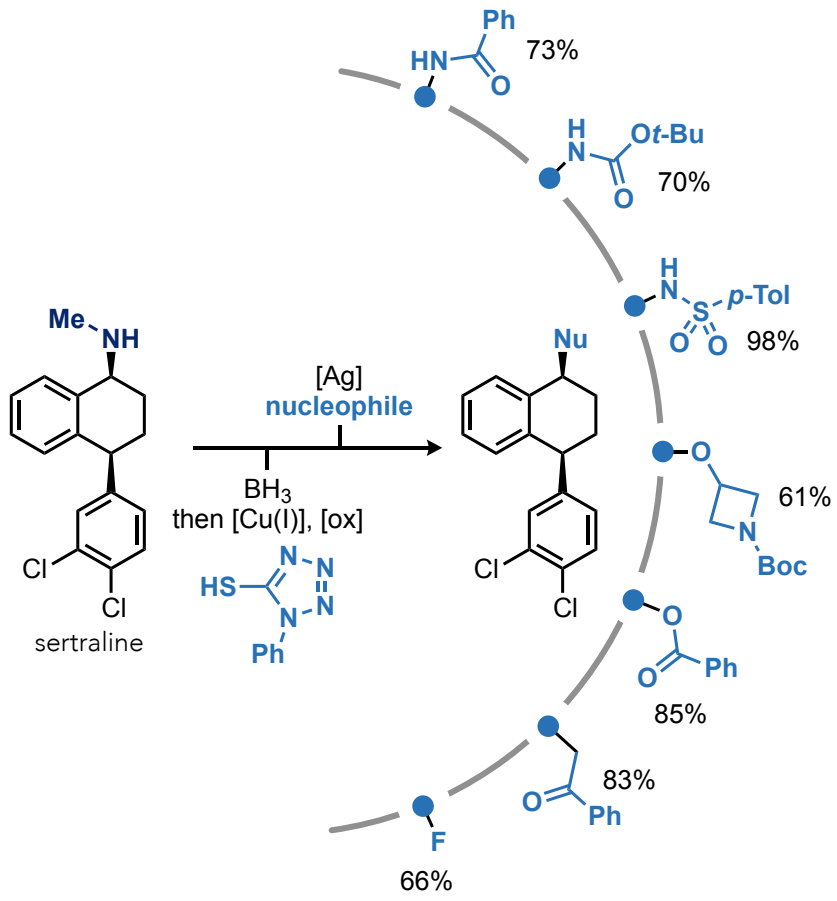


Divergent Deaminative Functionalizations



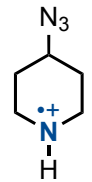
Late-Stage Functionalizations





Current Research Areas

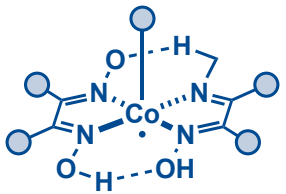
nitrogen radicals



radical strategies for C–N bond assembly

Nat. Chem. **2019**; *ACIE* **2021**; *ACIE* **2020**; *ACIE* **2019**; *ACIE* **2018**; *JACS* **2016**; *ACIE* **2015**

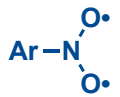
desaturative catalysis



desaturative approaches to aromatic synthesis

Nature **2020**; *Nat. Catal.* **2024** *ACIE* **2023**; *ACIE* **2022**; *JACS* **2022**

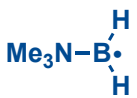
photoexcited nitroarenes



novel reagents and novel heterocycles

Science **2025**; *Nature* **2022** *Nat. Chem.* **2024**; *Chem* **2024**, *JACS* **2023**

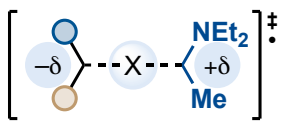
boryl radicals



radical blueprints for for C–H borylation

Nature **2021**; *Nat. Synth* **2024**; *JACS* **2024**; *Chem* **2025**

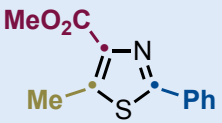
halogen-atom transfer



novel strategies for carbon radical generation

Science **2020**; *Science* **2022** *Nat. Catal.* **2022**; *JACS* **2022**; *JACS* **2024**

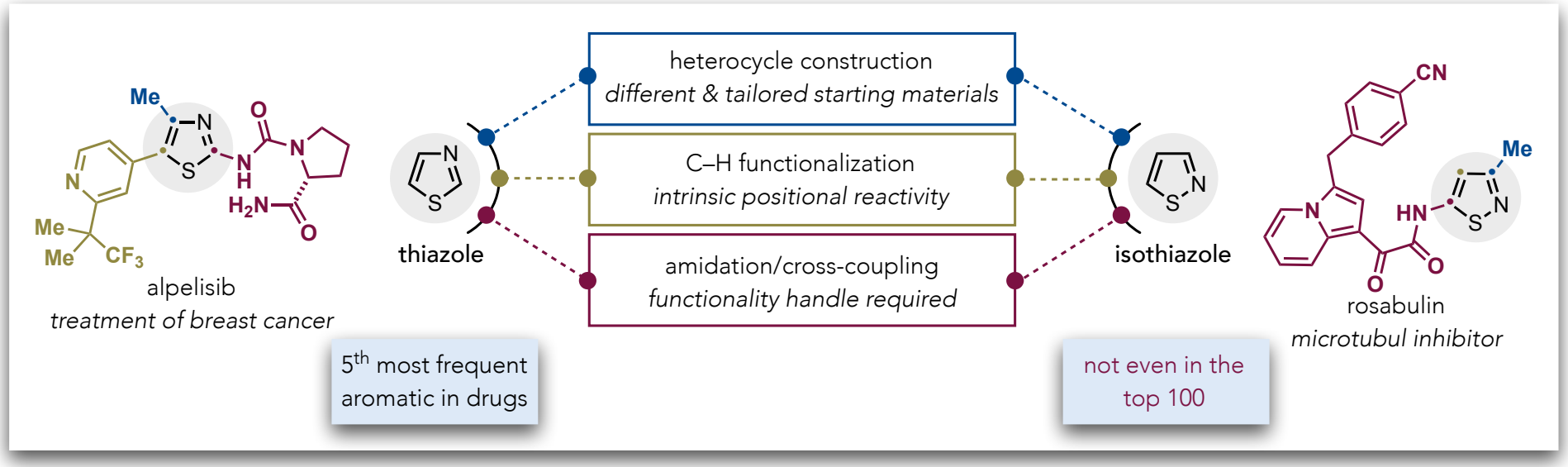
chemical permutation

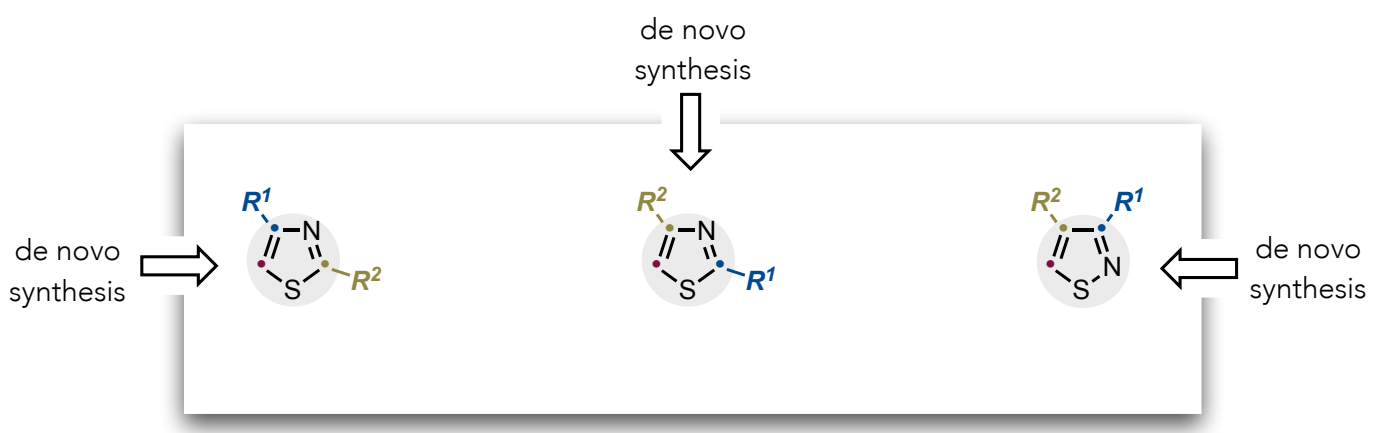


a novel approach to heteroaromatic synthesis

Nature **2025**; *Nat. Synth.* **2025** *ACIE* **2025**; *Nat. Commun.* **2025**

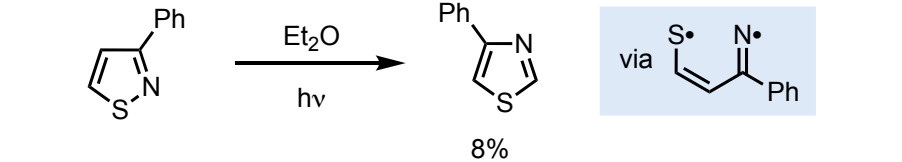
Thiazoles & Isothiazoles



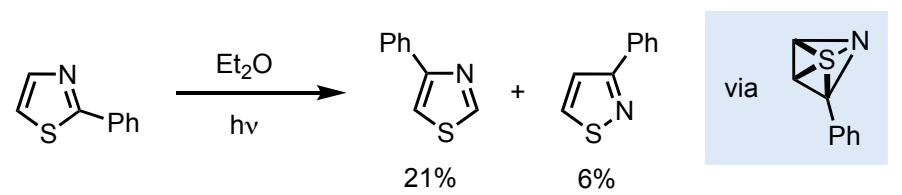


relevance of thiazole & isothiazoles in MedChem: J. Med. Chem. **2022**, *65*, 8699

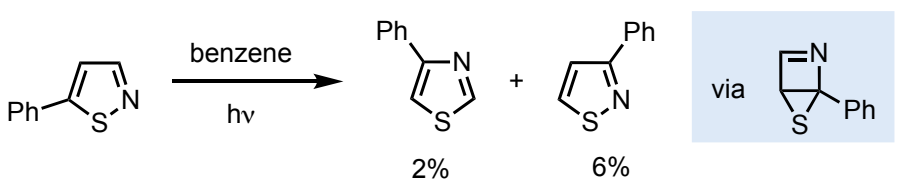
Chemical Permutations – How To Give Directionality?



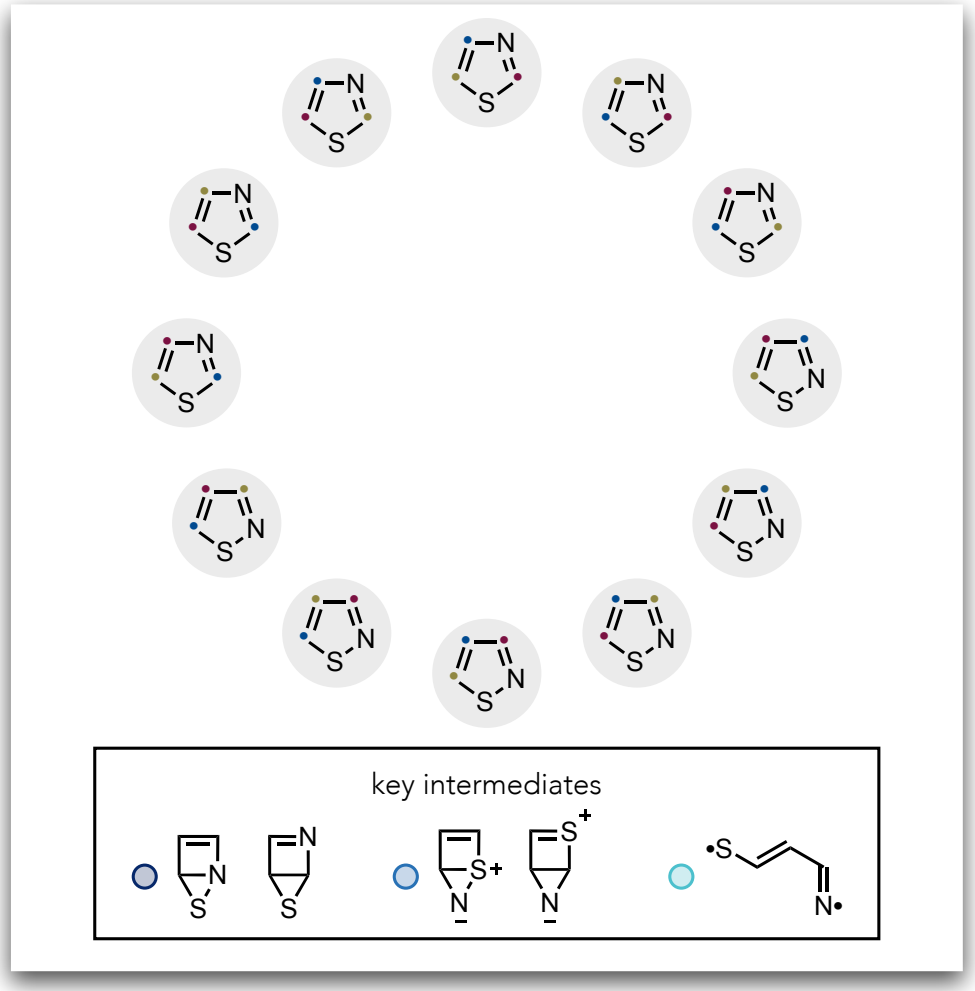
Lablanche-Combier *J. Chem. Soc. Chem. Commun.* **1969**, 1018
Maeda *Chem. Commun.* **1970**, 1148



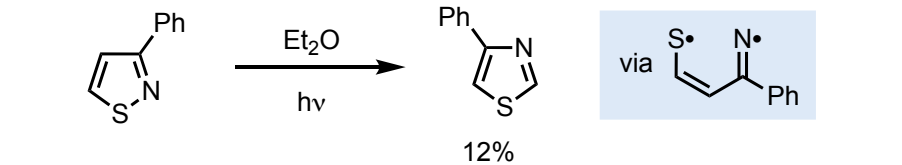
Kojima *Tetrahedron Lett.* **1973**, 3523
Kojima *J. Chem. Soc. Perkin Trans. 1* **1978**, 685



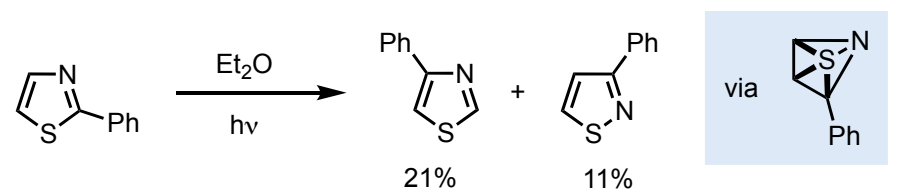
Pavlik *J. Am. Chem. Soc.* **1994**, *116*, 2292
Pavlik *J. Org. Chem.* **1998**, *63*, 5592



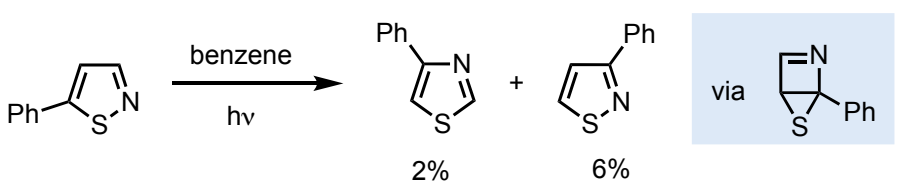
Chemical Permutations – How To Give Directionality?



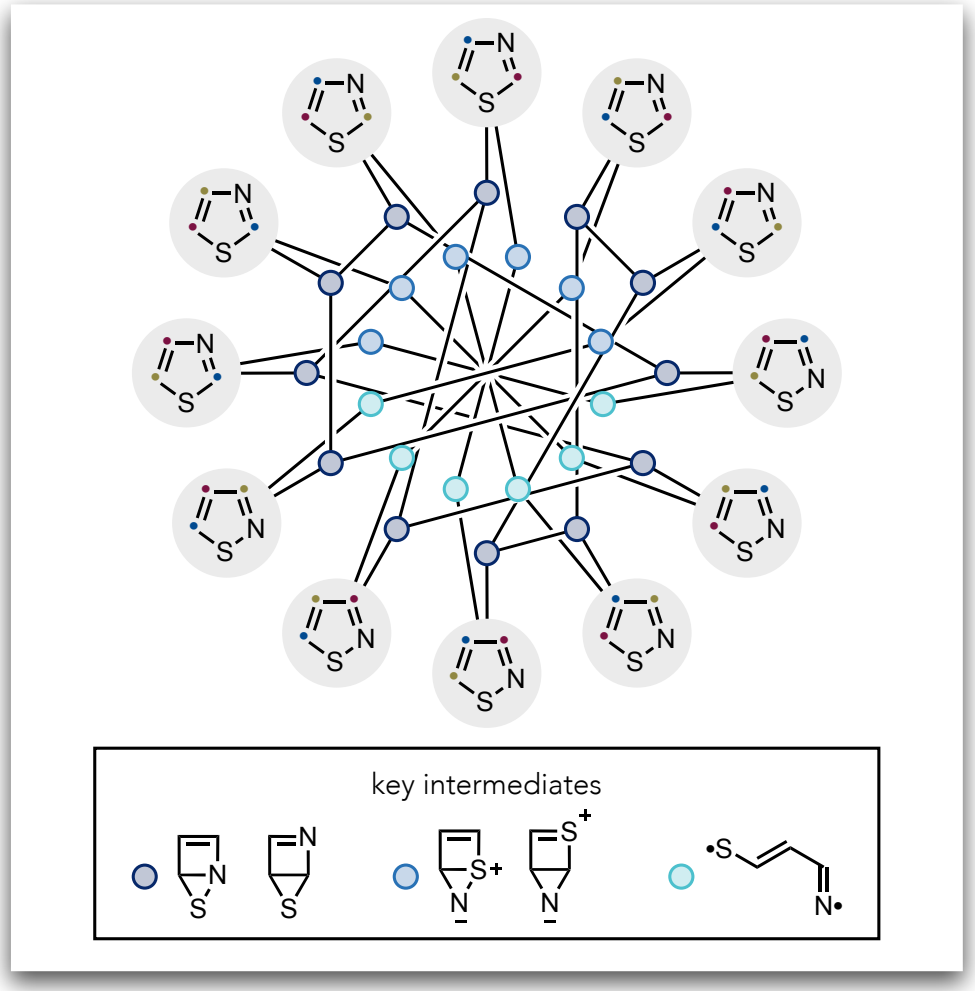
Lablanche-Combier *J. Chem. Soc. Chem. Commun.* **1969**, 1018
Maeda *Chem. Commun.* **1970**, 1148



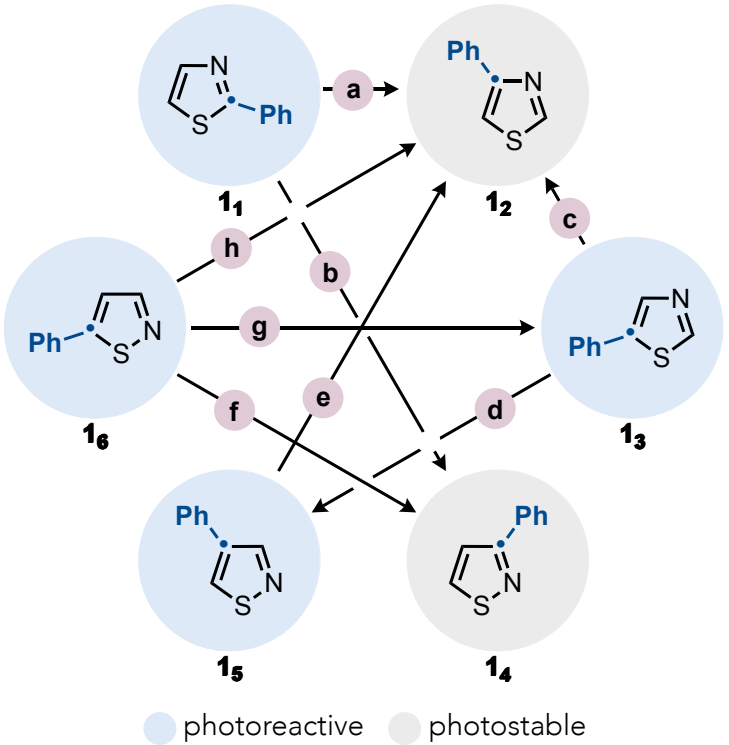
Kojima *Tetrahedron Lett.* **1973**, 3523
Kojima *J. Chem. Soc. Perkin Trans. 1* **1978**, 685



Pavlik *J. Am. Chem. Soc.* **1994**, *116*, 2292
Pavlik *J. Org. Chem.* **1998**, *63*, 5592



Permutation Development

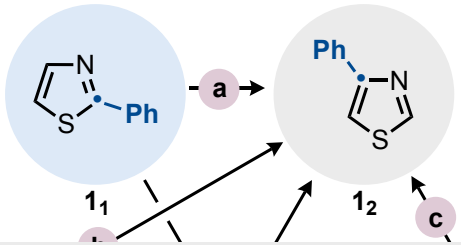


substrate		photochemical conditions (λ = 310 nm, r.t., 14-24 h)	yield (%)
1_1	a	DCE (0.025 M)	1_2: 65%
	b	Et_3N (1.0 equiv.), MeOH (0.1 M)	1_4: 66%
1_3	c	Et_3N (1.0 equiv.), MeOH (0.05 M)	1_2: 67%
	d	MeOH (0.05 M)	1_5: 35%
1_5	e	Et_3N (1.0 equiv.), CH_3CN (0.05 M)	1_2: 85%
1_6	f	DCE (0.05 M)	1_4: 28% + 1_2: 15%
	g	Et_3N (1.0 equiv.), HFIP (0.05 M)	1_3: 53%
	h	EtOAc (0.05 M)	1_2: 22% + 1_4: 19%

permutation framework

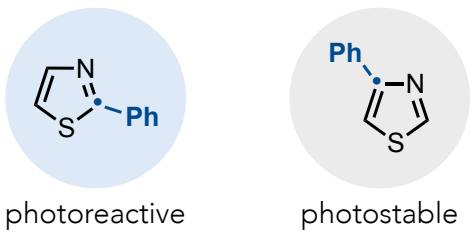


Permutation Development

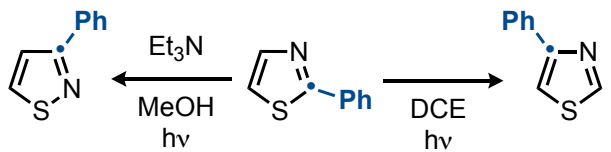


substrate	photochemical conditions (λ = 310 nm, r.t., 14-24 h)	yield (%)
	a DCE (0.025 M)	1_2: 65%

question 1
photoreactivity vs photostability



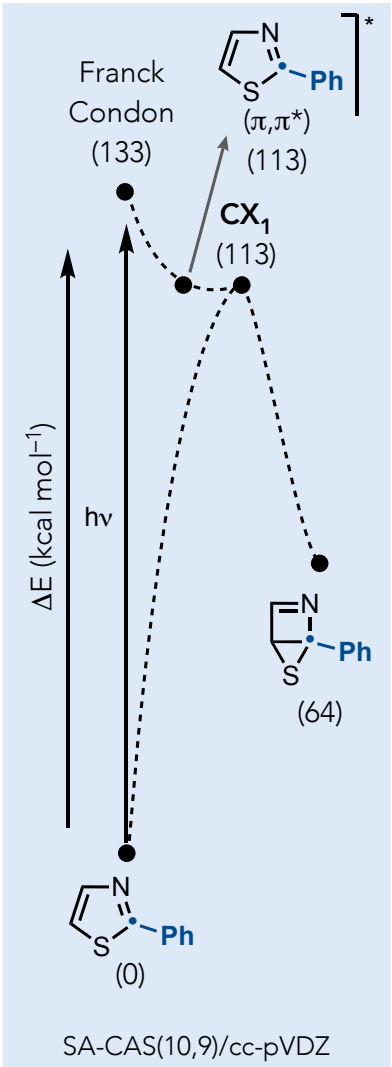
question 2
reaction directionality

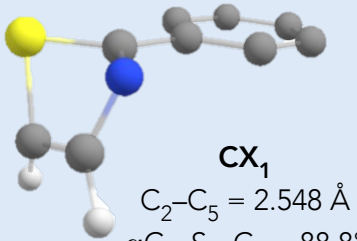


permutation framework

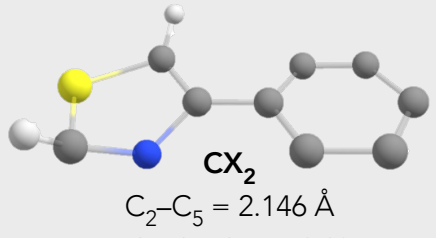


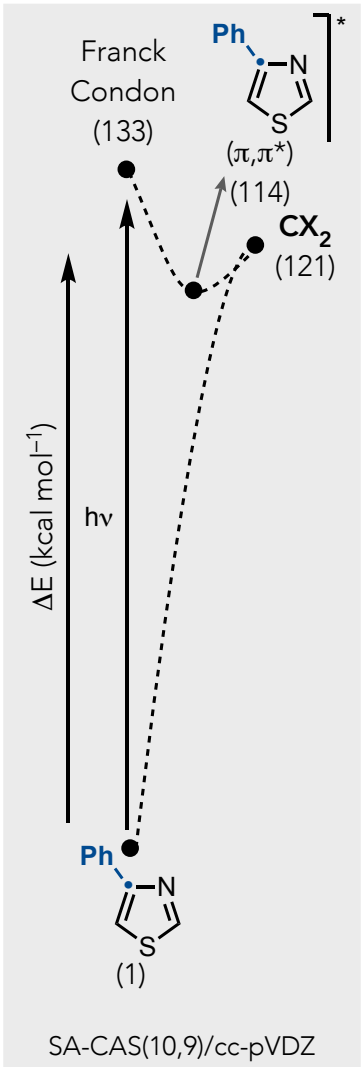
A Preliminary & Partial Understanding



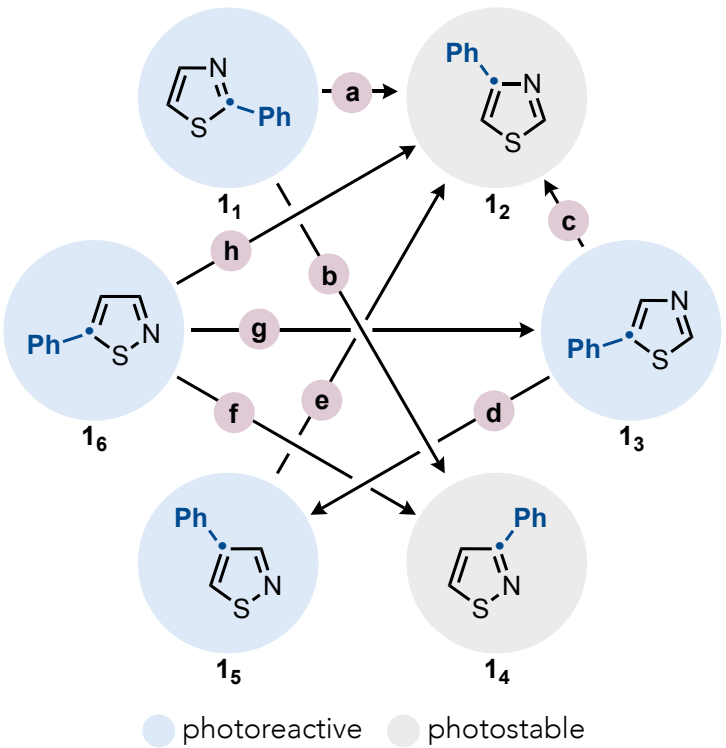


vs

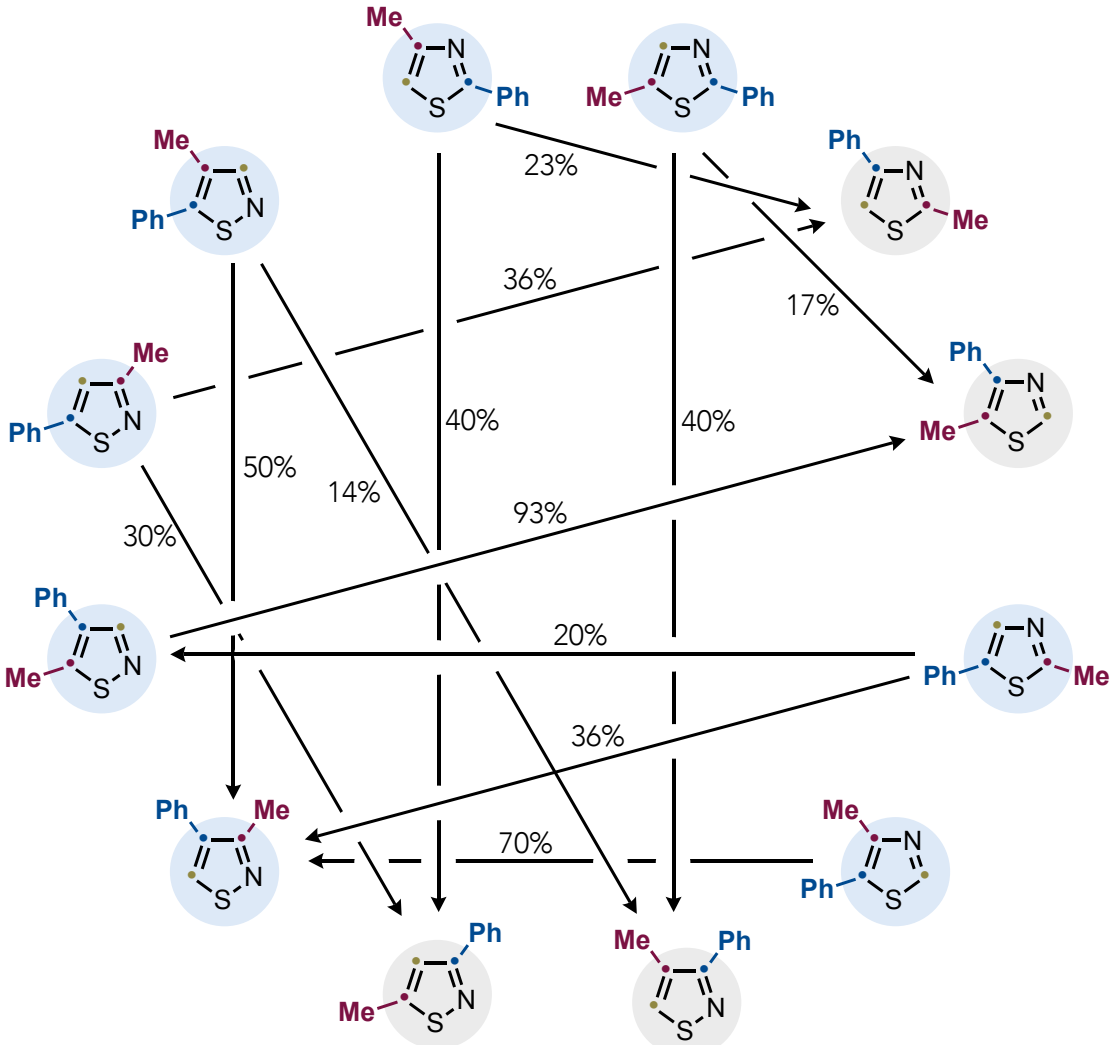




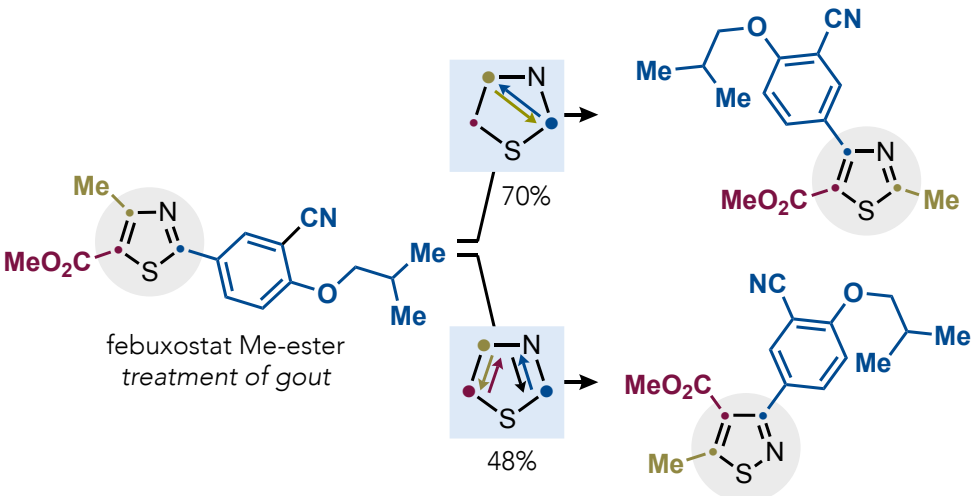
Permutation Development



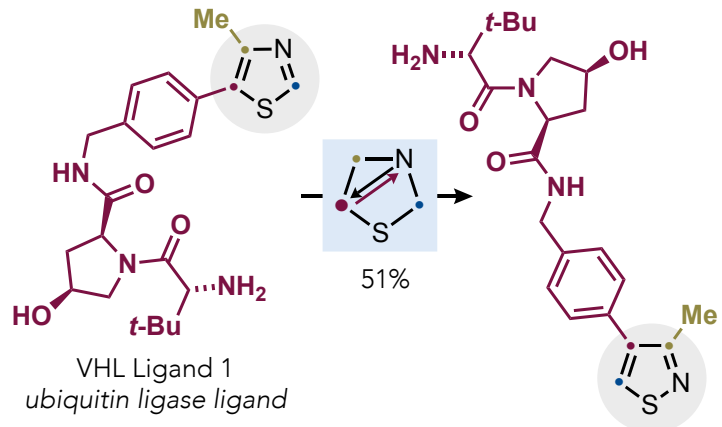
Permutation on a full duodecimal library



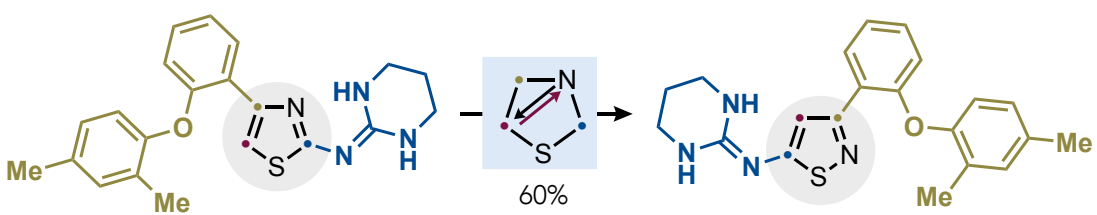
Permutating Drugs



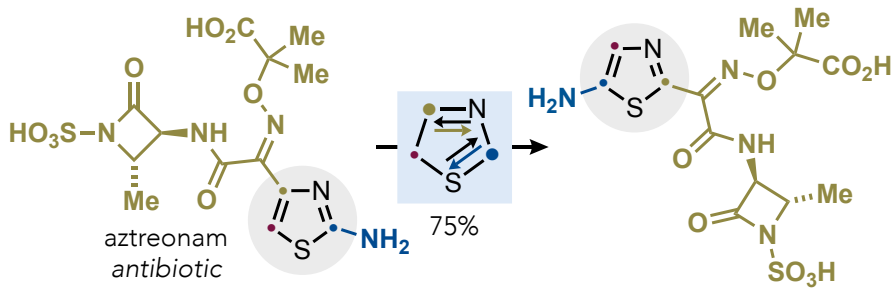
febuxostat Me-ester
treatment of gout



VHL Ligand 1
ubiquitin ligase ligand



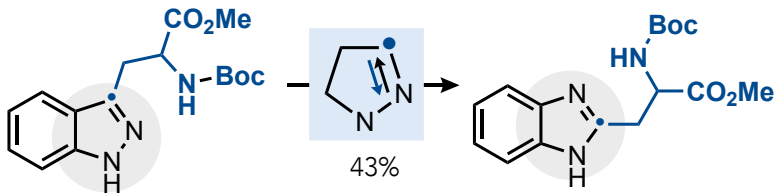
abafungin
antifungal



aztreonam
antibiotic

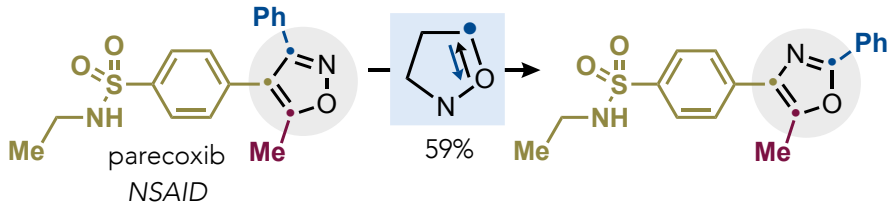
Other Permutations We Are Currently Developing

indazole → benzimidazole



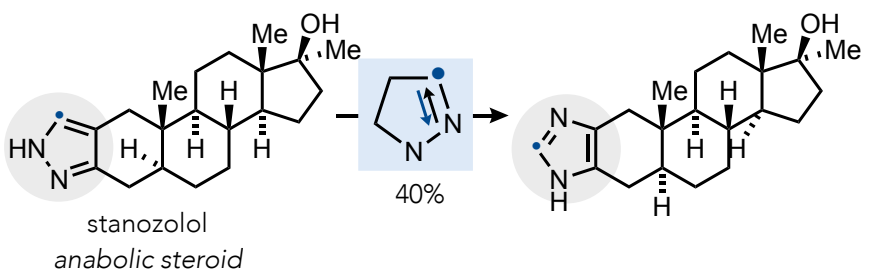
ACIE **2025**, *64*, e202423804

isoxazole → oxazole



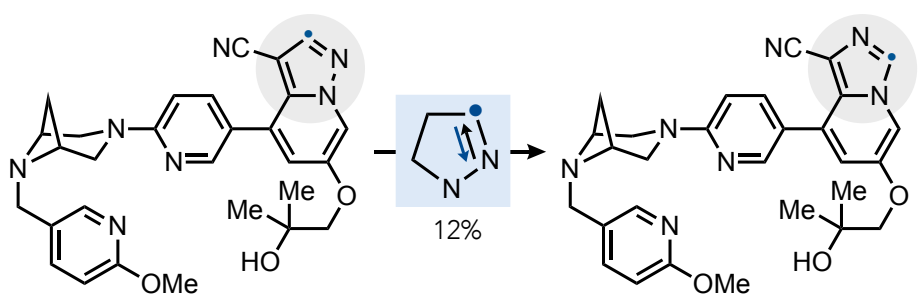
Nat. Commun. **2026**, asap

pyrazole → imidazole



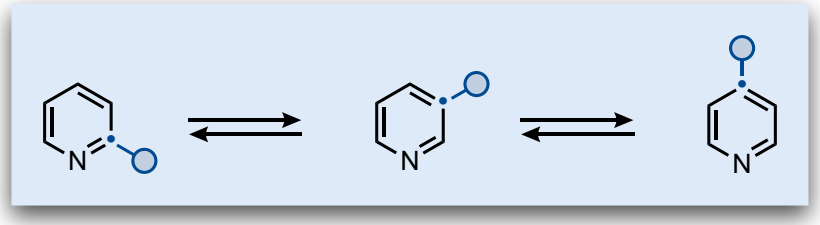
Chem. Sci. **2026**, asap

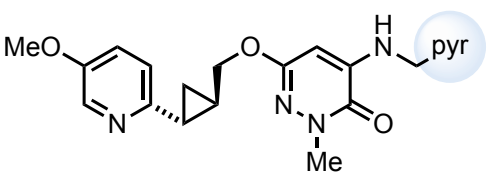
pyrazolo[1,5a]azine → imidazolo[1,5a]azine



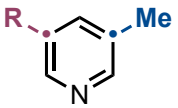
Chem. Sci. **2026**, asap

Pyridine Permutation

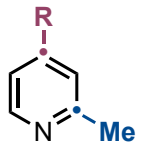




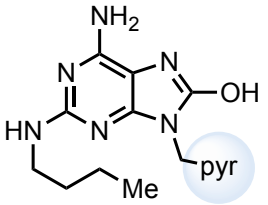
PDE10 inhibitors (MSD)



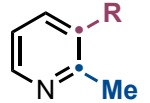
K_i = 0.12 nm



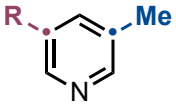
K_i = 0.049 nm



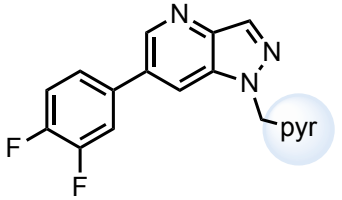
interferon inducers (Sunitomo)



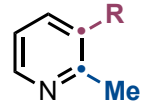
IFN-IA = 12.8



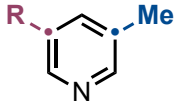
IFN-IA = 2.4



glun2b modulators (Janssen)

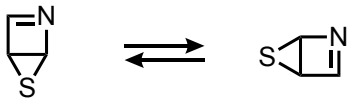


IC_{50} = 3.62 nm



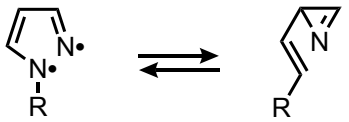
IC_{50} = 0.07 nm

thiazoles, isothiazoles



4π electrocyclization
then "S-shift"

pyrazoles, isoxazoles



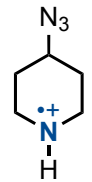
N–N bond homolysis
then azirine formation

pyridines

?

Current Research Areas

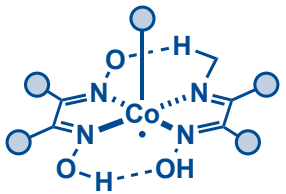
nitrogen radicals



radical strategies for C–N bond assembly

Nat. Chem. **2019**; *ACIE* **2021**; *ACIE* **2020**; *ACIE* **2019**; *ACIE* **2018**; *JACS* **2016**; *ACIE* **2015**

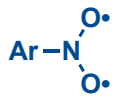
desaturative catalysis



desaturative approaches to aromatic synthesis

Nature **2020**; *Nat. Catal.* **2024** *ACIE* **2023**; *ACIE* **2022**; *JACS* **2022**

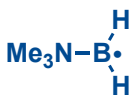
photoexcited nitroarenes



novel reagents and novel heterocycles

Science **2025**; *Nature* **2022** *Nat. Chem.* **2024**; *Chem* **2024**, *JACS* **2023**

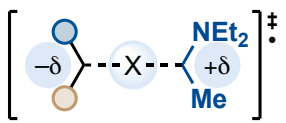
boryl radicals



radical blueprints for for C–H borylation

Nature **2021**; *Nat. Synth* **2024**; *JACS* **2024**; *Chem* **2025**

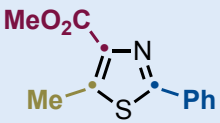
halogen-atom transfer



novel strategies for carbon radical generation

Science **2020**; *Science* **2022** *Nat. Catal.* **2022**; *JACS* **2022**; *JACS* **2024**

chemical permutation



a novel approach to heteroaromatic synthesis

Nature **2025**; *Nat. Synth.* **2025** *ACIE* **2025**; *Nat. Commun.* **2025**

Acknowledgements



Borylations
Dr J. Y. Kim (now @ ETH)
Dr T. Constantin (now @ Novartis)
Dr M. Tilby (now @ Uni Bristol)
Dr C. Buettner
Chiara Stavagna
Martin Ritarsic
M. Fimm
R. Güdük
X. Yzeiri
G. Lonardi

Deaminations
Dr. Z. Zhang (now @ Uni Sicuan)
Dr G. Lonardi
Dr T. Sephton
Y. C. Stavagna
Y. Wei
G. Lenardon
M. Weisgerber