2026

seminar

Recent advances in anomeric amide reagents

Speaker：Shiwen Fan

Supervisor：Prof. Shengming Ma

Prof. Hui Qian

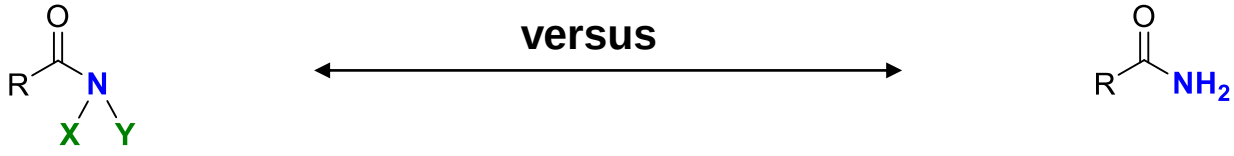
Content

/01

Background

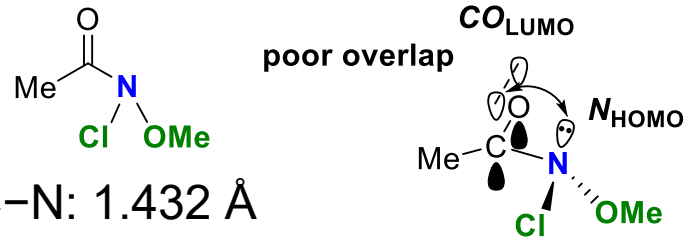
1.1 Background

Anomeric amides: *N*,*N*-bis-heteroatom-substituted amides



X,Y: halogen, OR^1, NR^2R^3

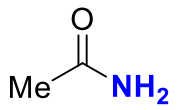
anomeric amides



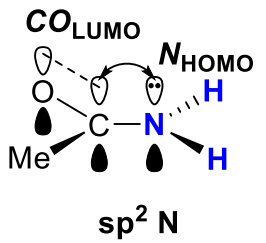
poor overlap

sp^3 N

normal amides



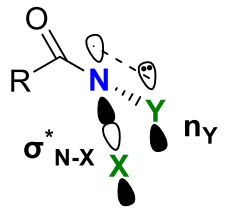
C−N: 1.370 Å

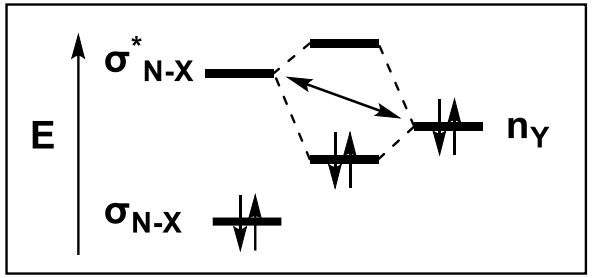


sp^2 N

average C−N: 1.480 Å, C=N: 1.350 Å.

Anomeric interaction: lone pair stabilization

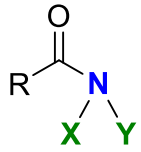




Glover, S. A. *Tetrahedron* **1998**, *54*, 7229−7271.
Glover, S. A. *J. Org. Chem*. **2012**, *77*, 5492−5502.
Glover, S. A. *Molecules* **2018**, *23*, 2834.

1.1 Background

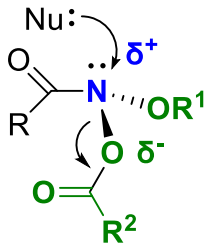
aminonitrene precursors



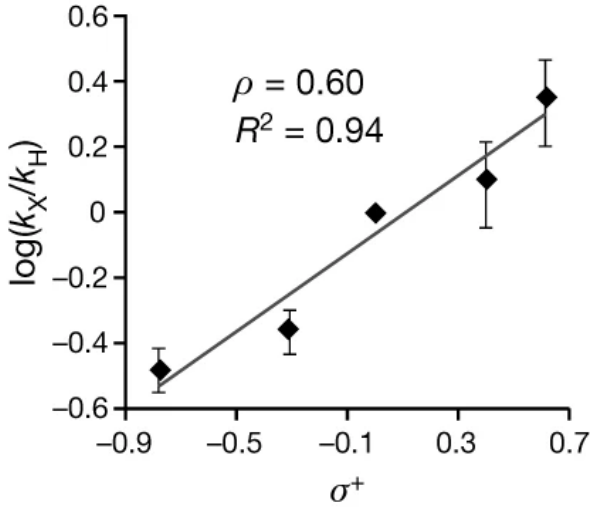
X,Y: halogen, OR^1, NR^2R^3

electrophilic reagents

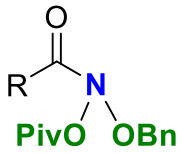
$[N]^+$ synthon

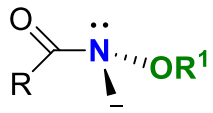


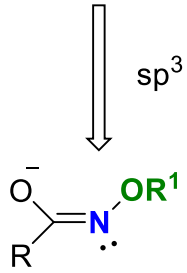
Nitrenium ion precursor



R = Ar
Hammett plot

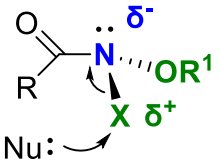




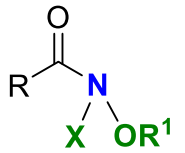


Driving force

$[N]^-$ leaving group



X^+ precursor



X = Cl, Br, NO_2

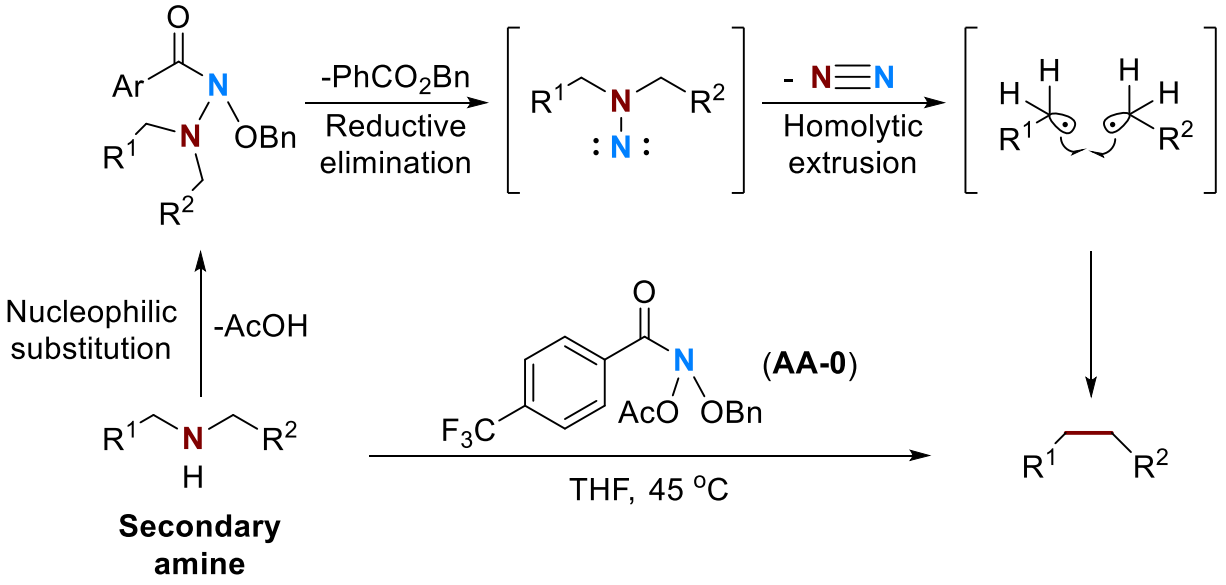
Baran, P. S. *Nat. Chem*. **2024**, *16*, 1539−1545.
Besset, T. *Angew. Chem. Int. Ed*. **2026**, *65*, e25799.

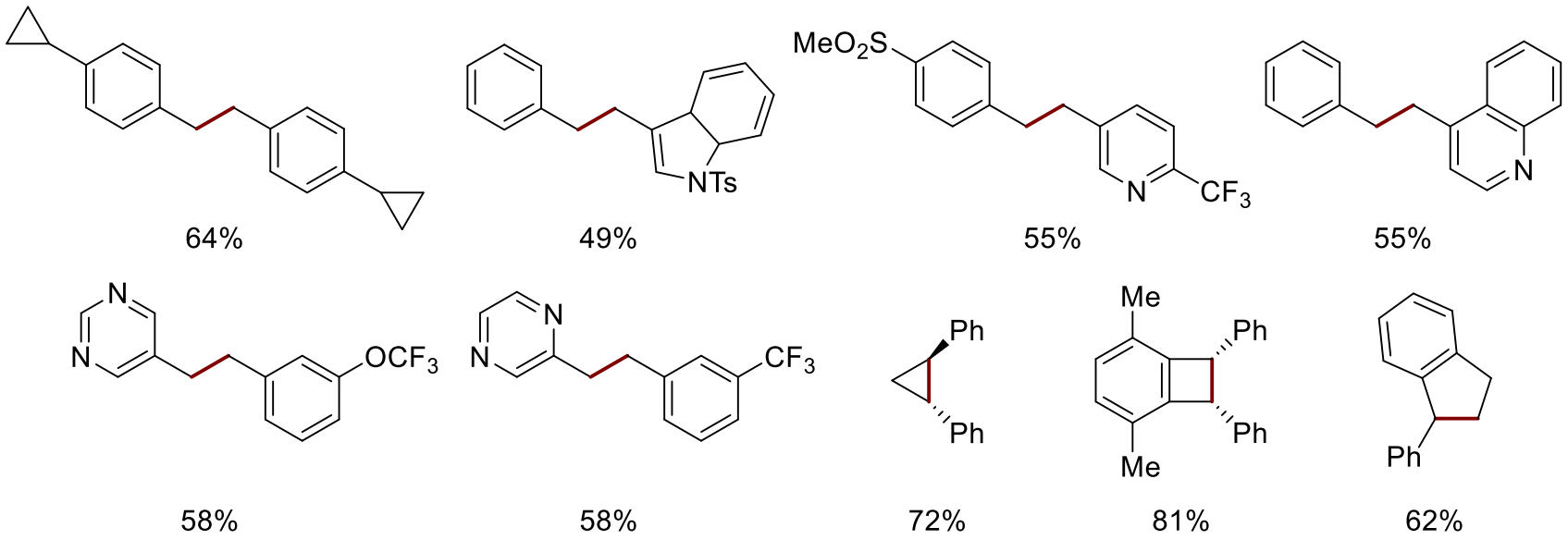
/02

Anomeric amides as aminonitrene precursors

2.1 Anomeric amides as aminonitrene precursors

2021 Levin, M. D.

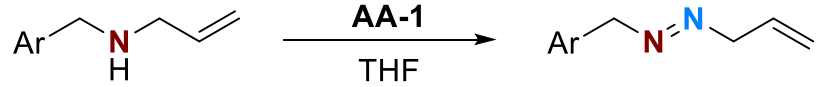




Levin, M. D. *Nature* **2021**, *593*, 223−227.

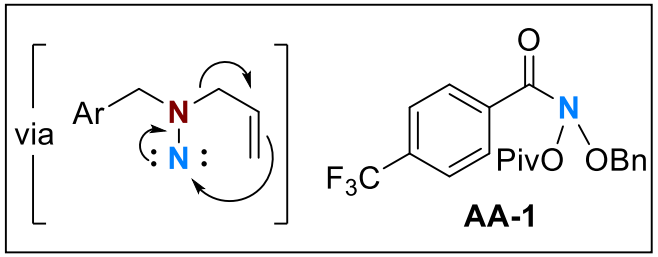
2.1 Anomeric amides as aminonitrene precursors

Evidence for the aminonitrene intermediate

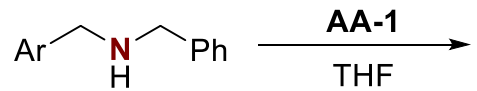


Ar = 2,6-dimethoxyphenyl

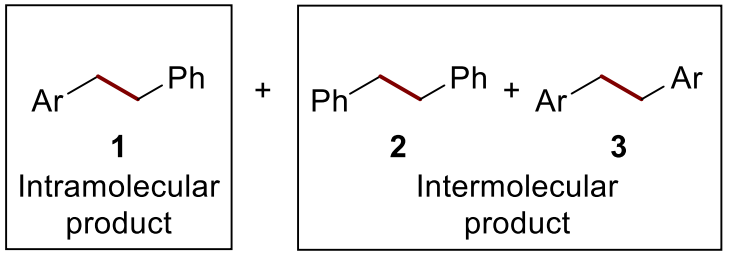
61%



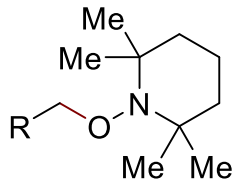
Radical trapping experiment



Ar = *p*-chlorophenyl

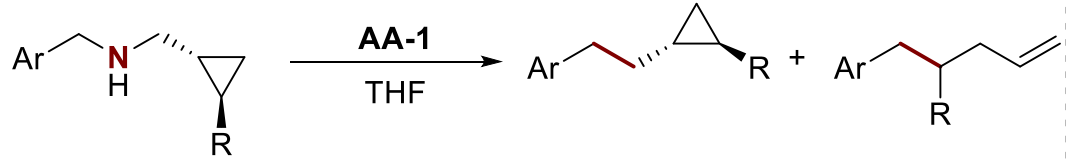


No additive = 93:4:3 (**1**/**2**/**3**)
+ 1 equiv. TEMPO = 100:0:0 (**1**/**2**/**3**)

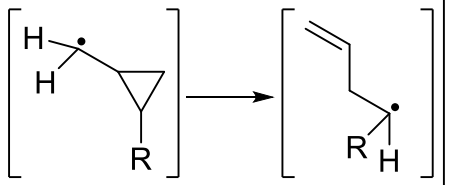


R = Ph, Ar
TEMPO adducts observed

Radical clock experiment



R = H	30%	Not observed
R = Ph	20%	19%

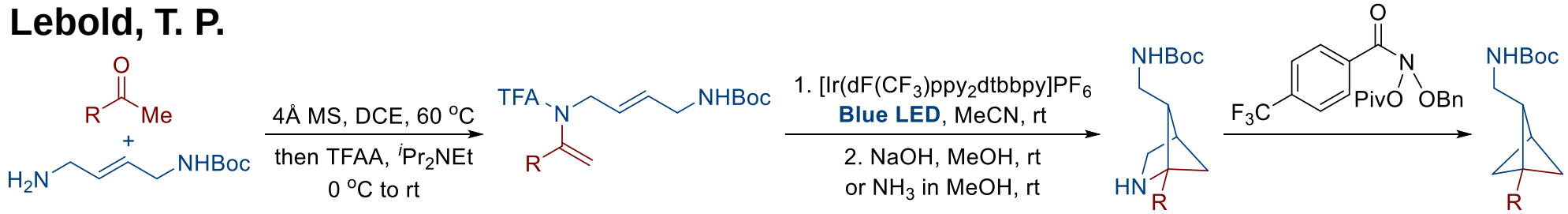


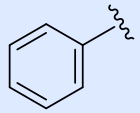
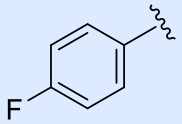
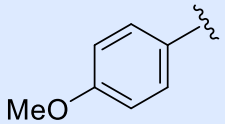
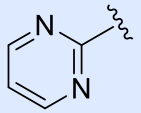
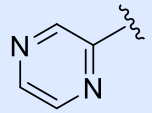
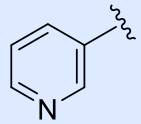
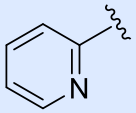
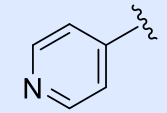
R = H	$k_r = 10^8\ s^{-1}$
R = Ph	$k_r = 10^{10}\ s^{-1}$

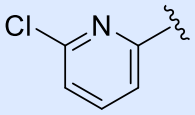
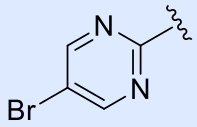
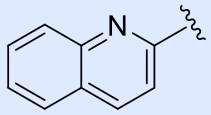
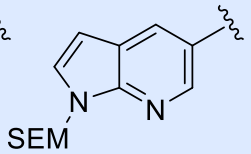
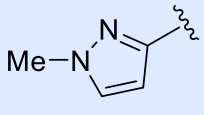
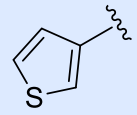
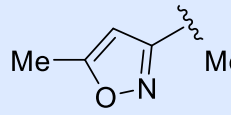
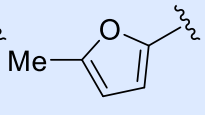
Levin, M. D. *Nature* **2021**, *593*, 223−227.

2.1 Anomeric amides as aminonitrene precursors

2023 Lebold, T. P.



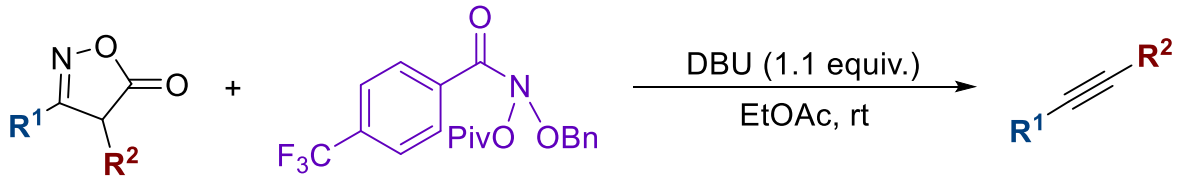
	Phenyl			***6-Membered Heterocycles***				
								
A. Ennamide yield (%)	48	45	63	71	66	55	83	44
B. [2+2] yield (%, d.r.)	49 (6:1)	75 (5:1)	87 (5:1)	52 (6:1)	80 (7:1)	76 (6:1)	68 (7:1)	65 (10:1)
C. Deprotection yield (%)	79	91	86	82	97	76	96	70
D. BCP yield (%)	32	28	26	47	52	28	44	30

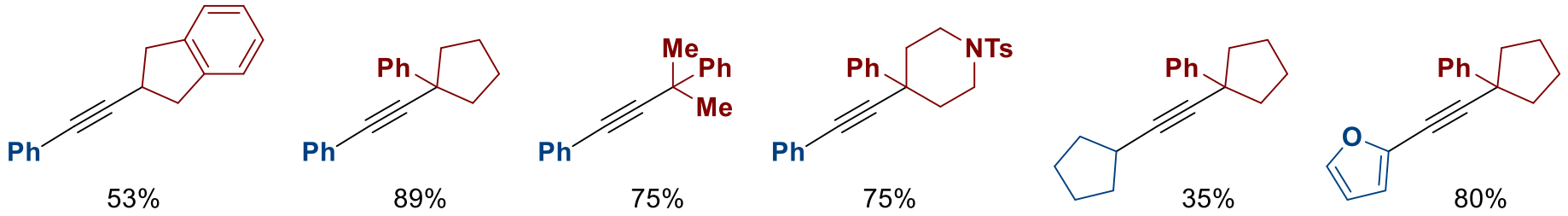
	Halogenated Heterocycles		***Fused Heterocycles***		***5-Membered Heterocycles***			
								
A. Ennamide yield (%)	37	72	47	40	56	57	50	22
B. [2+2] yield (%, d.r.)	79 (5:1)	35 (10:1)	57 (10:1)	80 (10:1)	77 (5:1)	72 (7:1)	53 (7:1)	51[a]
C. Deprotection yield (%)	86	60	82	52	98	99	93	95
D. BCP yield (%)	61	35	60	29	41	39	(35)	26

Lebold, T. P. *J. Am. Chem. Soc*. **2023**, *145*, 10960−10966.

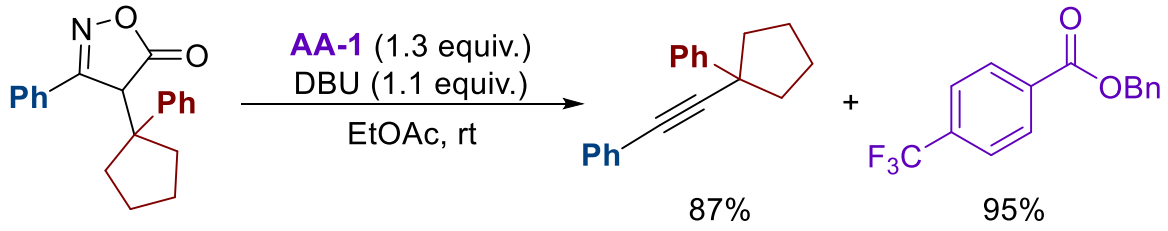
2.1 Anomeric amides as aminonitrene precursors

2025 Ociepa, M.

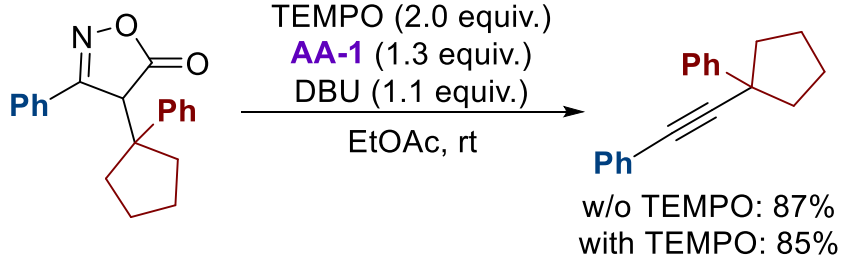




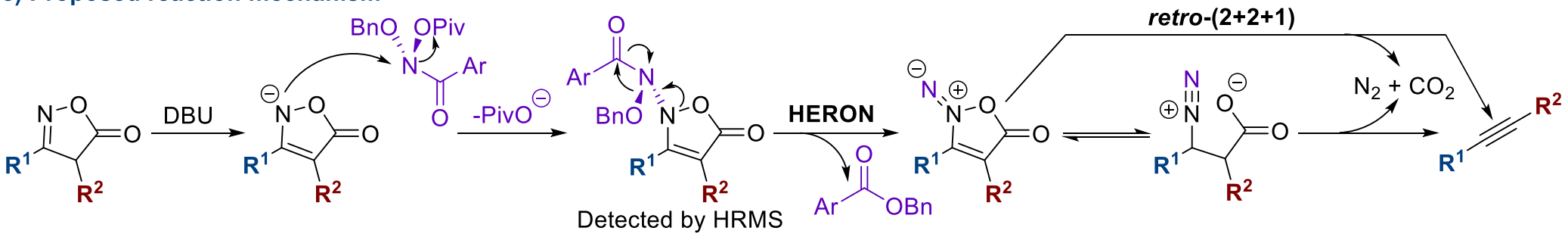
a) Isolation of HERON byproduct



b Reaction with radical scavenger



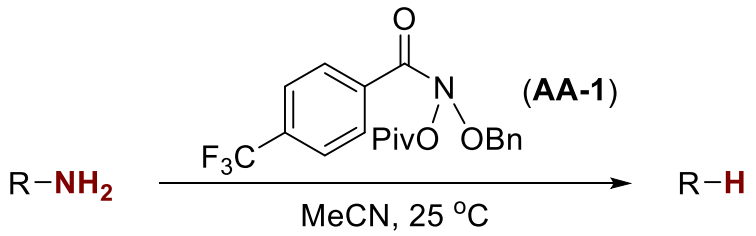
c) Proposed reaction mechanism

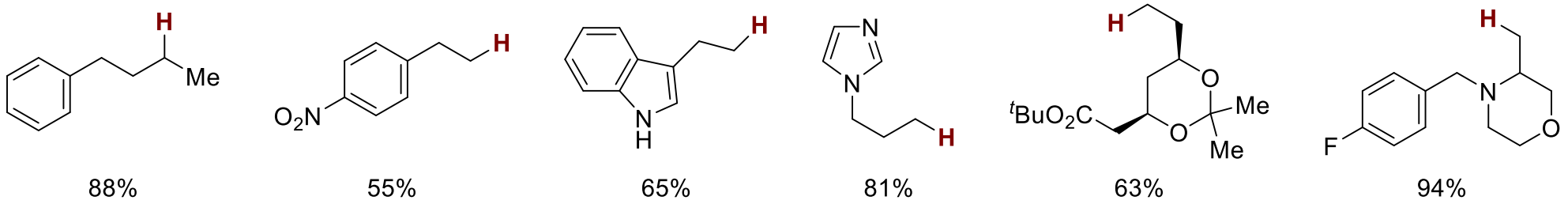


Ociepa, M. *Angew. Chem. Int. Ed*. **2026**, *65*, e18256.

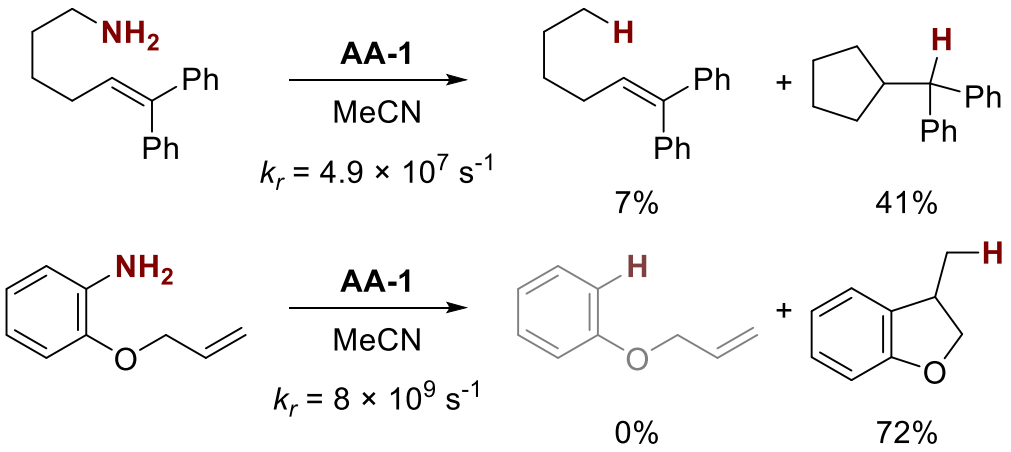
2.1 Anomeric amides as aminonitrene precursors

2021 Levin, M. D.

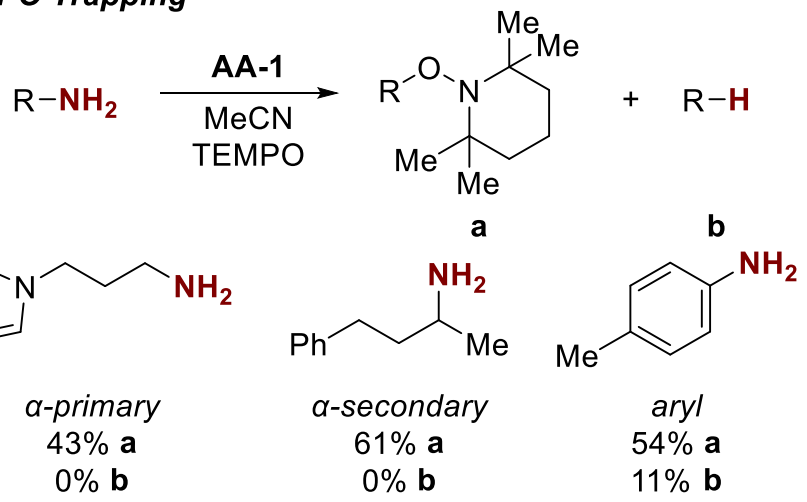




Radical Clock Experiments

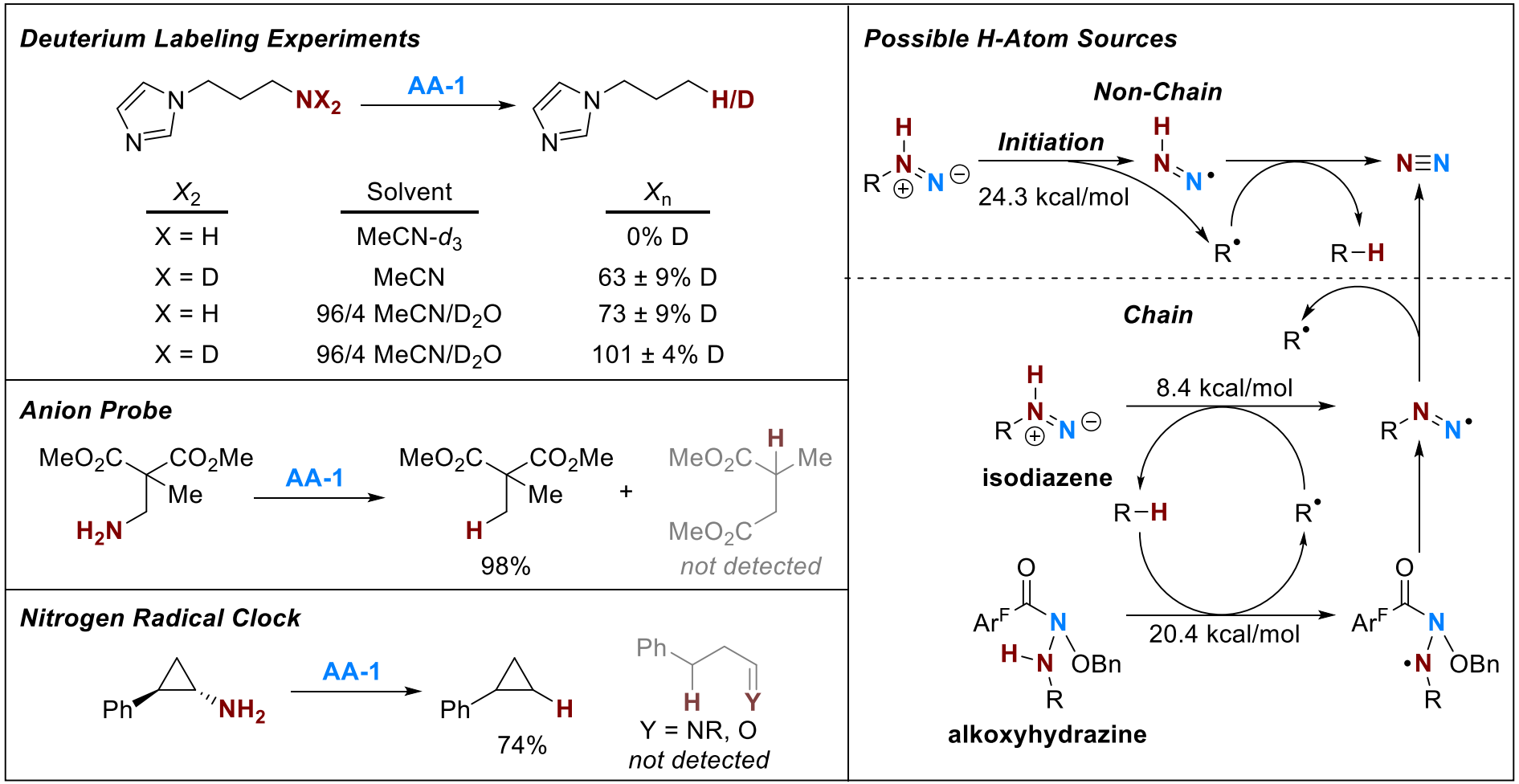


TEMPO Trapping



Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 17366−17373.

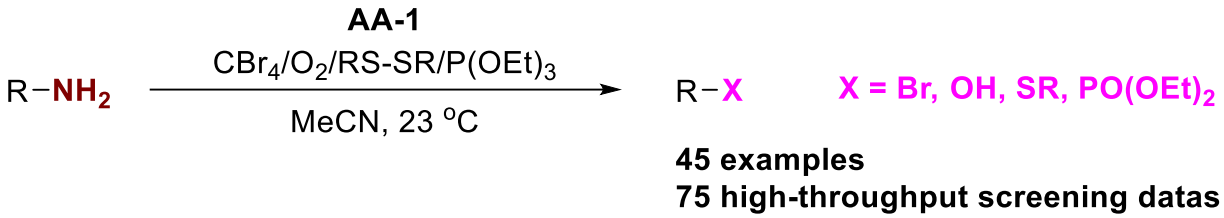
2.1 Anomeric amides as aminonitrene precursors

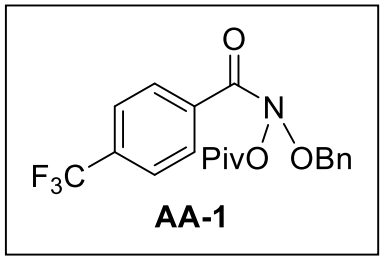


Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 17366−17373.

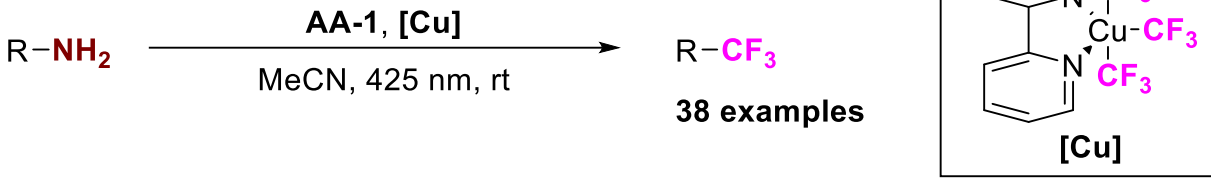
2.1 Anomeric amides as aminonitrene precursors

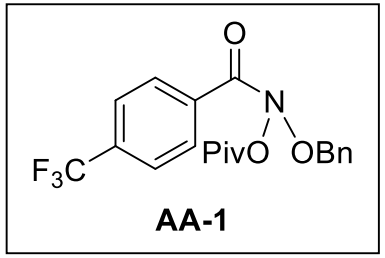
2023 Levin, M. D.



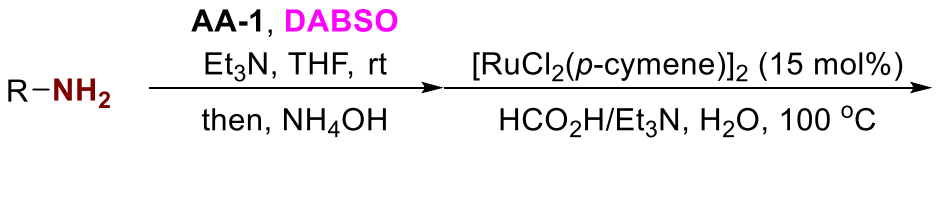


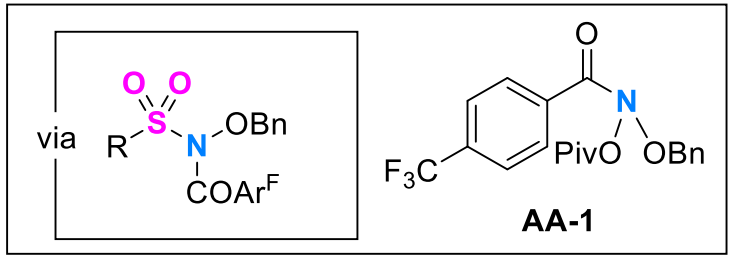
2024 Wang, H.





2025 Levin, M. D.

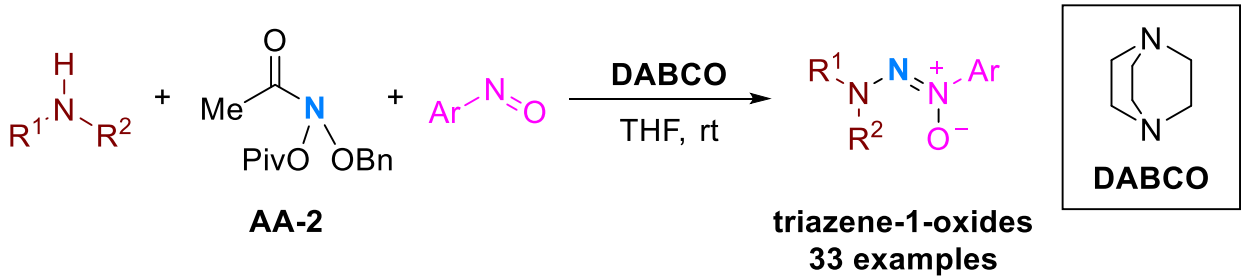




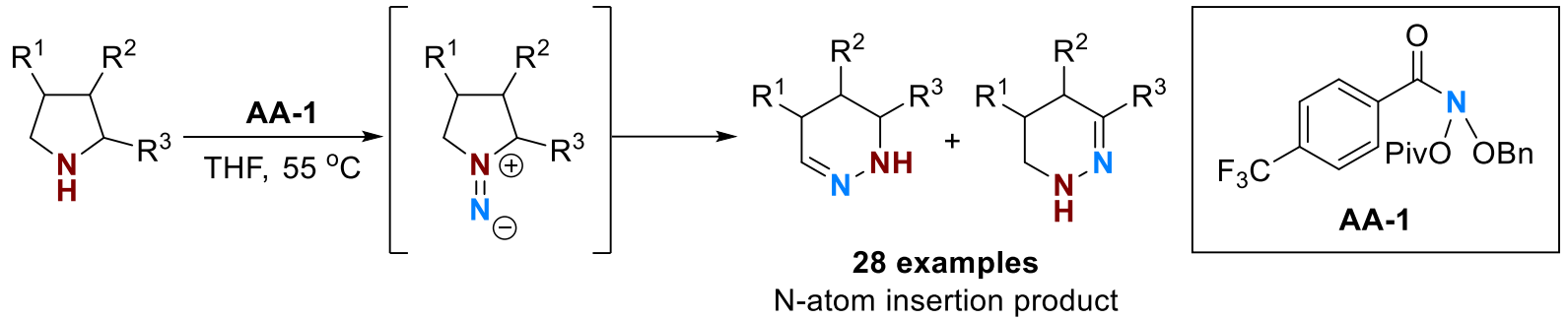
Levin, M. D. *J. Am. Chem. Soc*. **2023**, *145*, 17−24.
Wang, H. *Angew. Chem. Int. Ed*. **2024**, *63*, e202319030.
Levin, M. D. *Nat. Chem*. **2025**, *17*, 1247−1255.

2.1 Anomeric amides as aminonitrene precursors

2025 Wang, H.



2025 Levin, M. D.



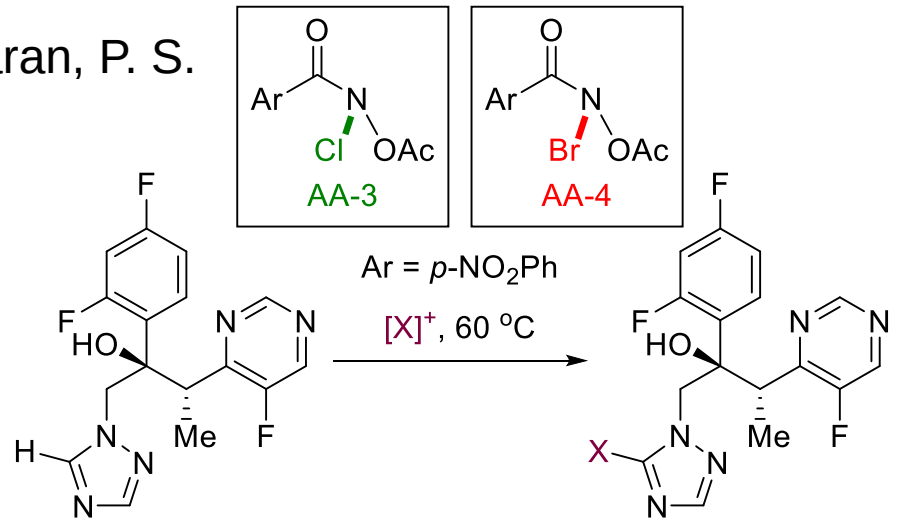
Wang, H. *Chem. Sci*. **2025**, *16*, 6458−6467.
Levin, M. D. *J. Am. Chem. Soc*. **2025**, *147*, 28179−28188.

/03

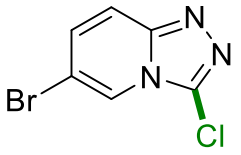
Anomeric amides as electrophilic reagents

3.1 Anomeric amides as electrophilic reagents

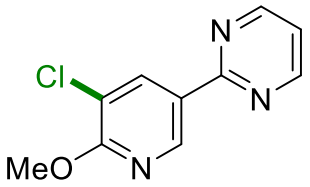
2024 Baran, P. S.



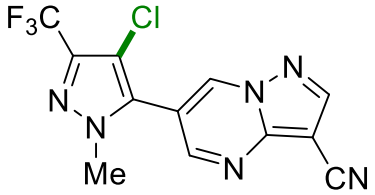
X = Cl	X = Br
^{t}BuOCl: 21%	AcOBr: 11%
NCS, AcOH: 7%	Br_2, AcOH: 30%
Palau'chlor: 16%	NBS, H_2SO_4: 0%
DCDMH, AcOH: 5%	NBS, AcOH: 36%
TCCA, TfOH, HFIP: 27%	DBDMH, *m*-NBSA, HFIP: 7%
AA-3, MeCN: 52%	**AA-4, MeCN: 79%**



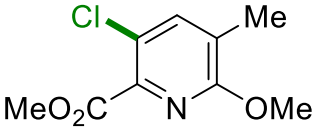
72% (1.34 g, 77%)
Palau'chlor: 28%
NCS: 60%



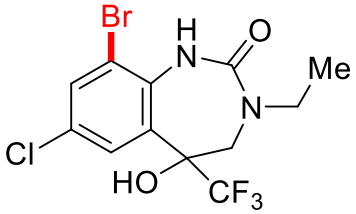
92% (1.07 g, 90%)
Palau'chlor: 6%



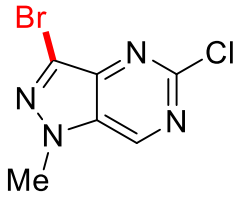
89% (X-ray) (1.12 g, 87%)
Palau'chlor: 4%



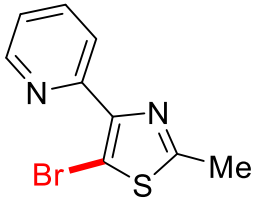
86% (8:1)
Palau'chlor: 17% (8.2:1)



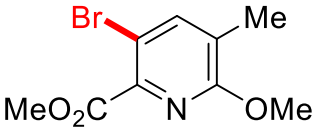
88%
NBS: 55%



82% (X-ray)
NBS: 25%



67%
NBS: 54%

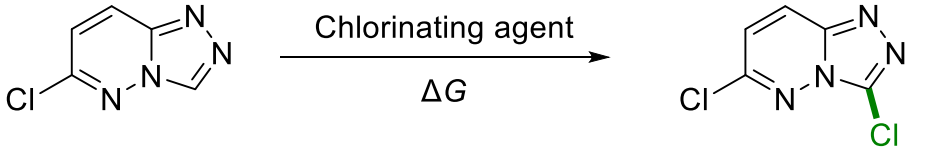


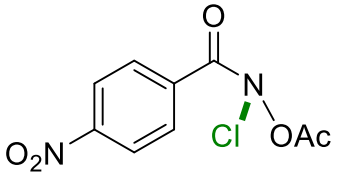
91% (>50:1)
NBS: 81% (4:1)

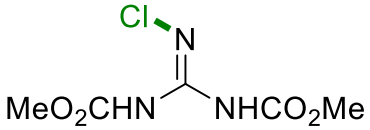
Baran, P. S. *Nat. Chem*. **2024**, *16*, 1539−1545.

3.1 Anomeric amides as electrophilic reagents

Mechanistic Experiments





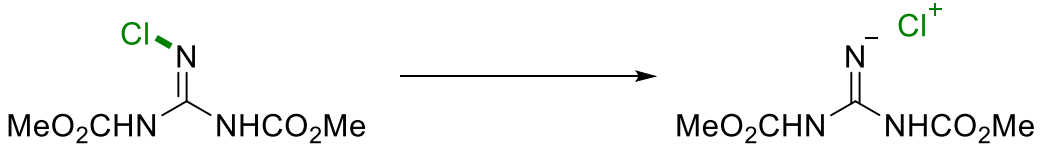


ΔG = -29.0 kcal/mol

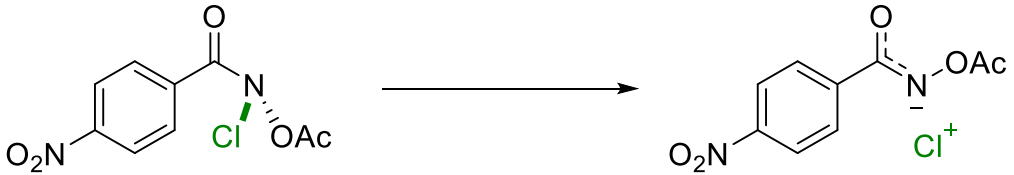
ΔG = -25.6 kcal/mol

ΔΔG = 3.4 kcal/mol more downhill for chlorination with reagent **AA-3**

Calculated N–Cl dissociation energy



ΔΔG = 22.0 kcal/mol less uphill
for **AA-3** over Palau'chlor

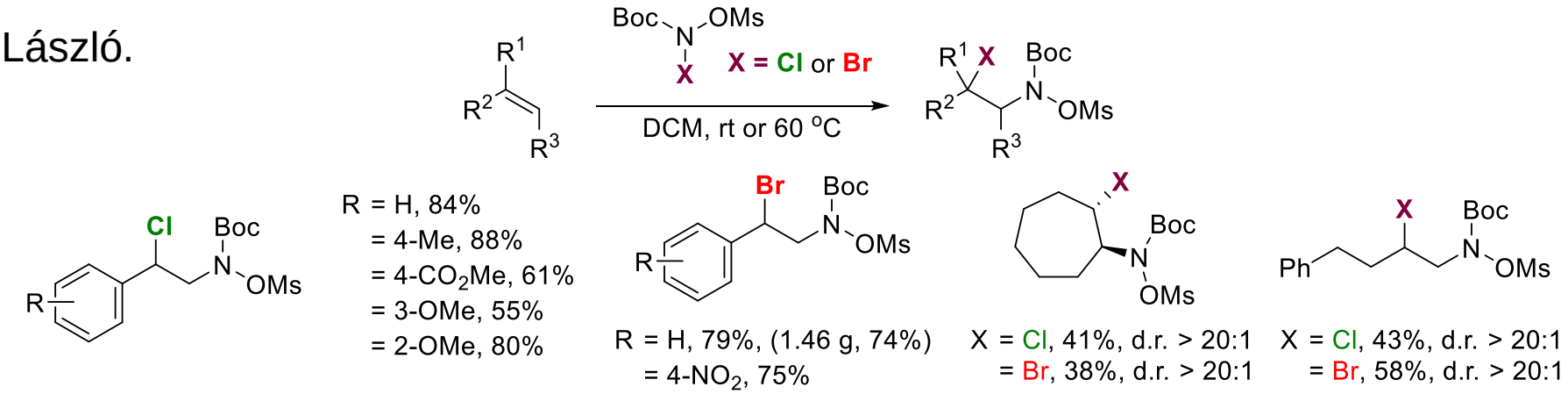


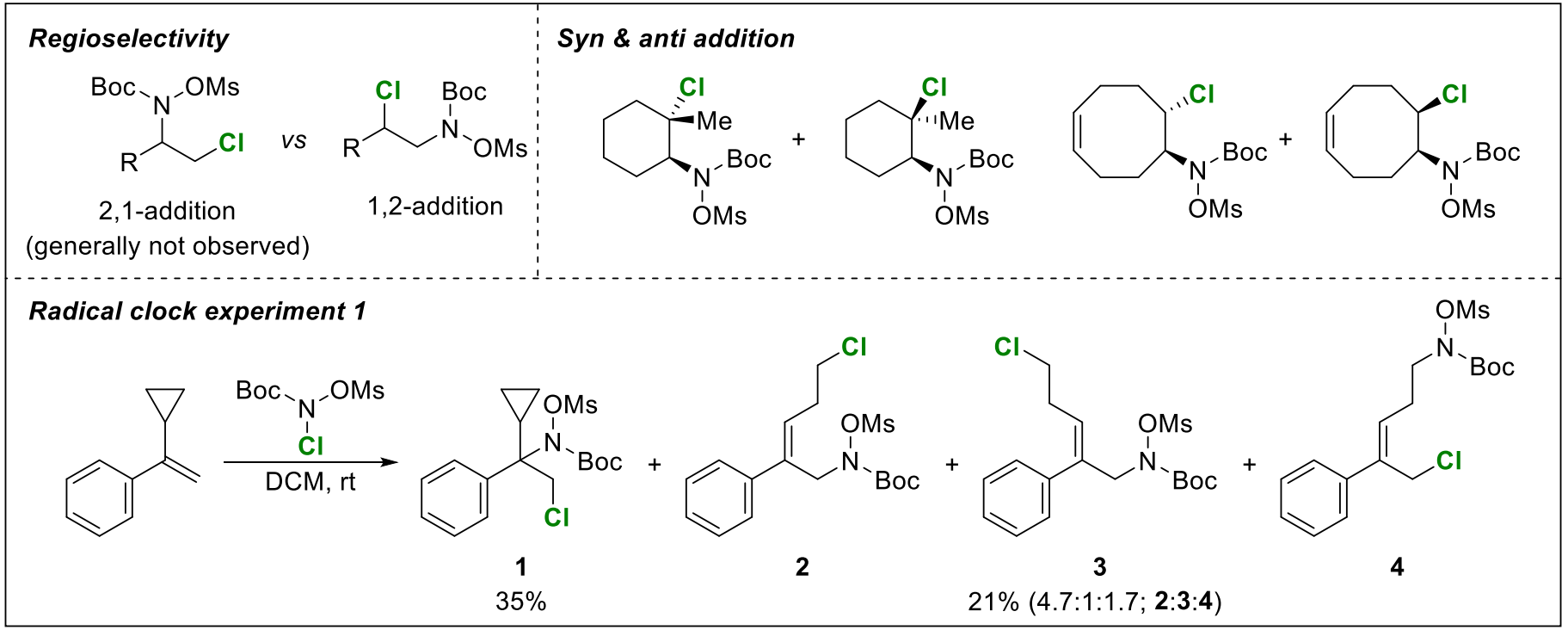
C-N bond shortening indicates the formation of C-N multiple bond
Energy gain by anion delocalization to the carbonyl group

Baran, P. S. *Nat. Chem*. **2024**, *16*, 1539−1545.

3.1 Anomeric amides as electrophilic reagents

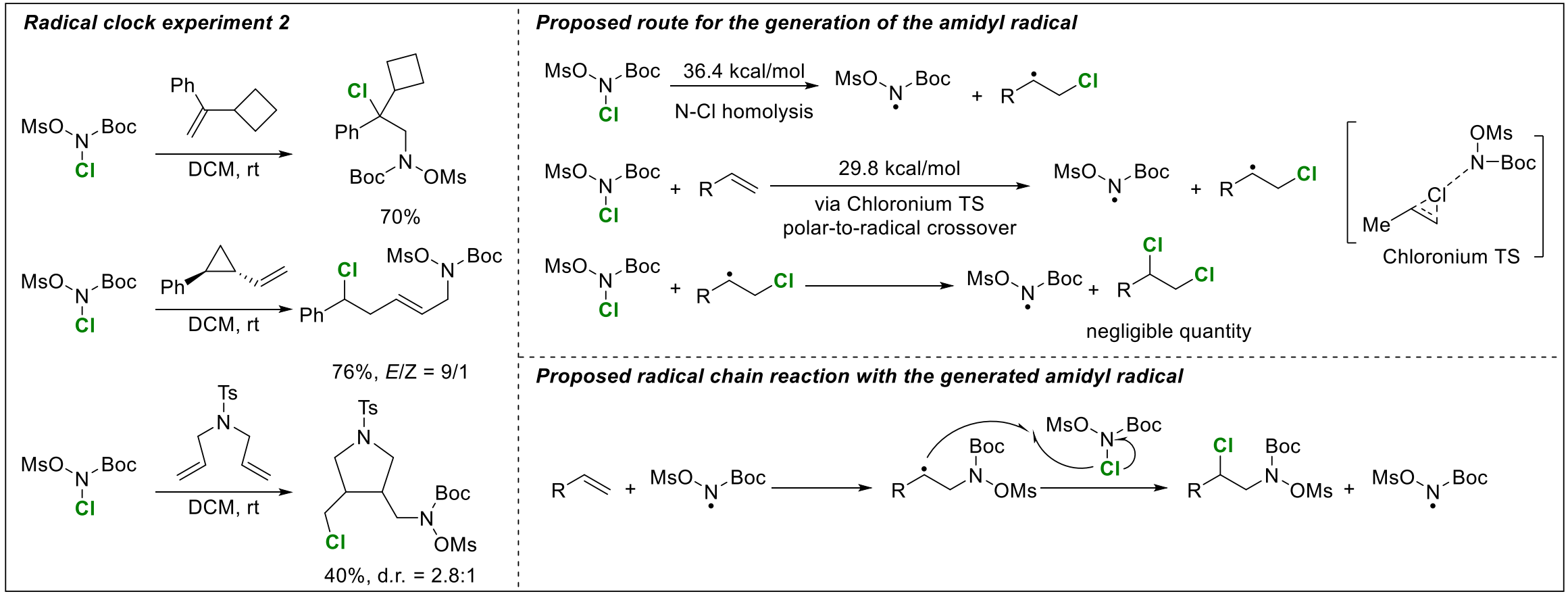
2024 Kürti, László.





Kürti, László. *JACS Au* **2026**, *6*, 521−533.

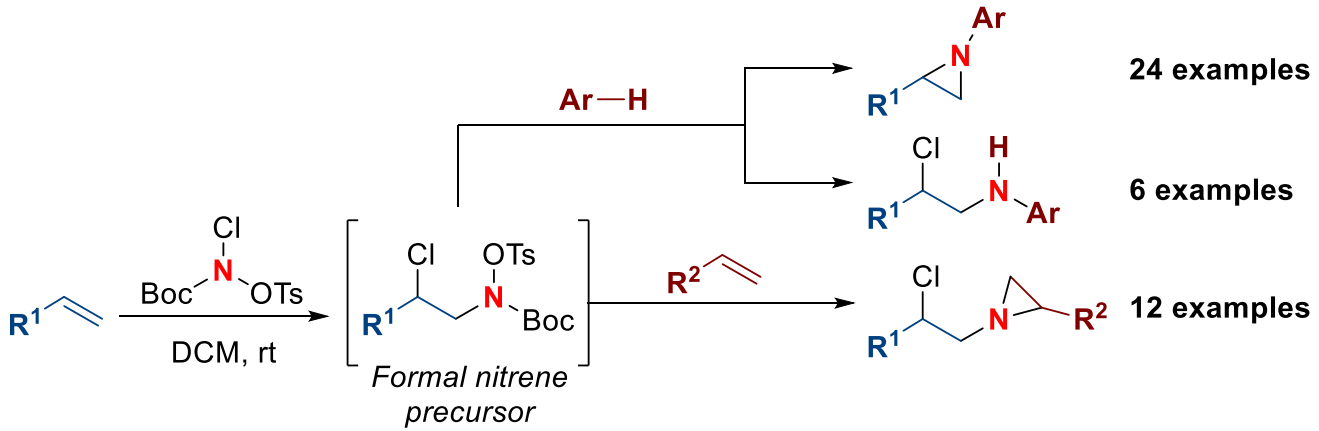
3.1 Anomeric amides as electrophilic reagents



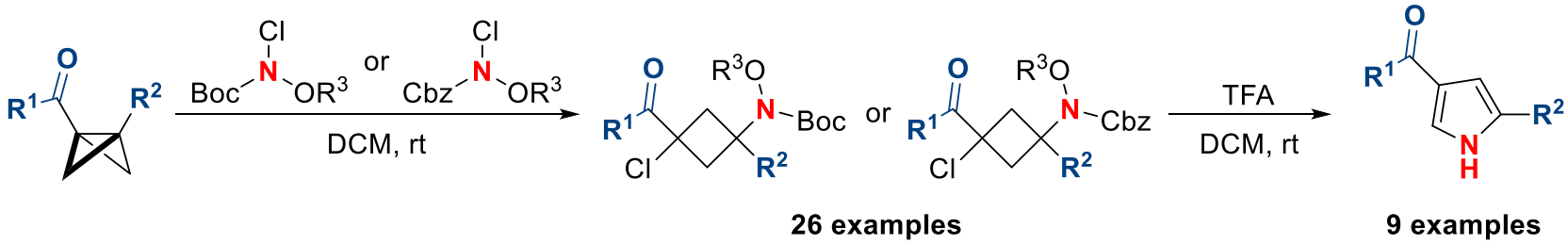
Kürti, László. *JACS Au* **2026**, *6*, 521−533.

3.1 Anomeric amides as electrophilic reagents

2025 Glorius, F.



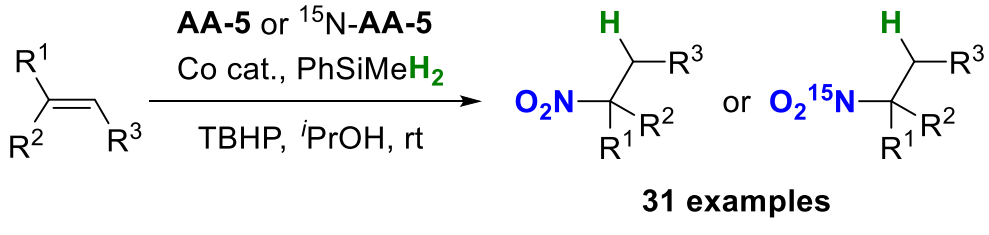
2025 He, L.

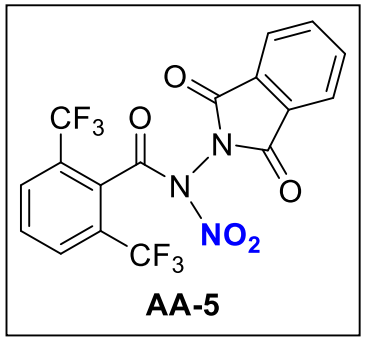


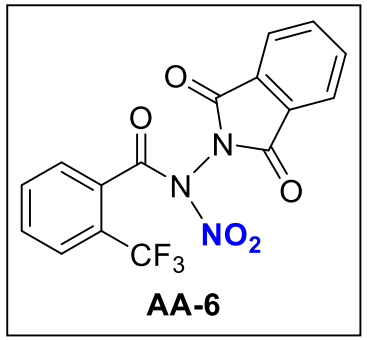
Glorius, F. *Angew. Chem. Int. Ed*. **2025**, *64*, e202418141.
He, L. *Org. Lett.* **2025**, *27,* 14156−14161.

3.1 Anomeric amides as electrophilic reagents

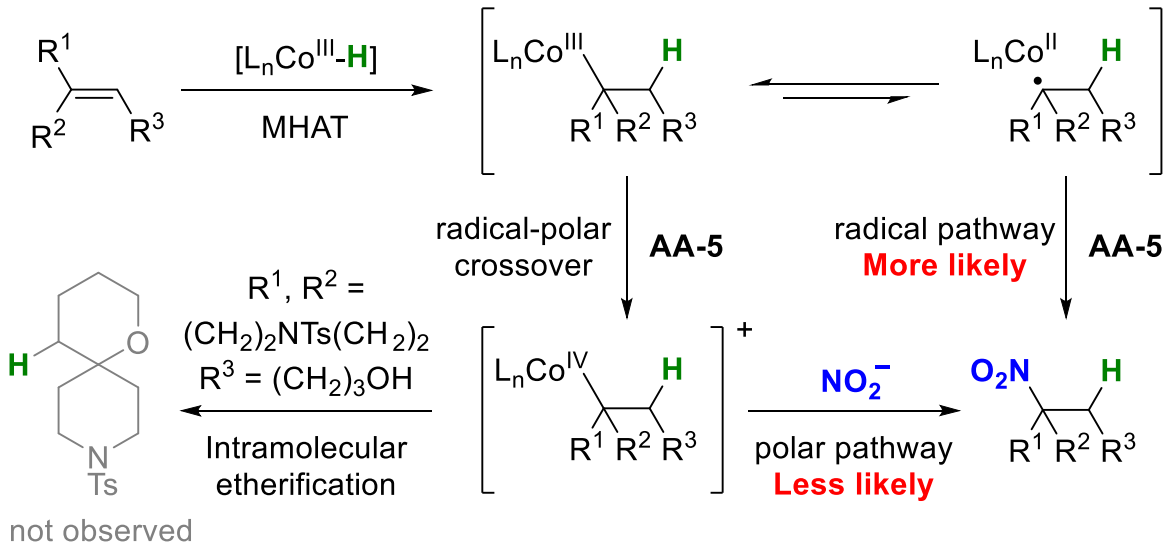
2025 Baran, P. S.

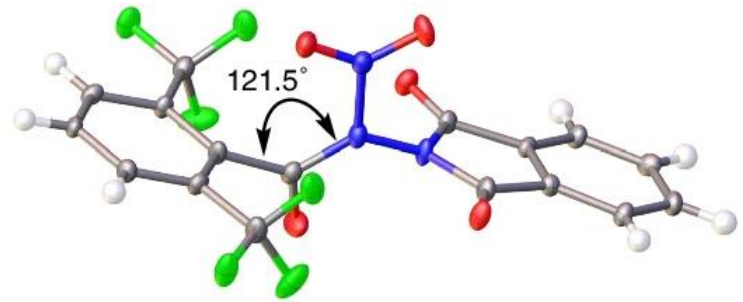




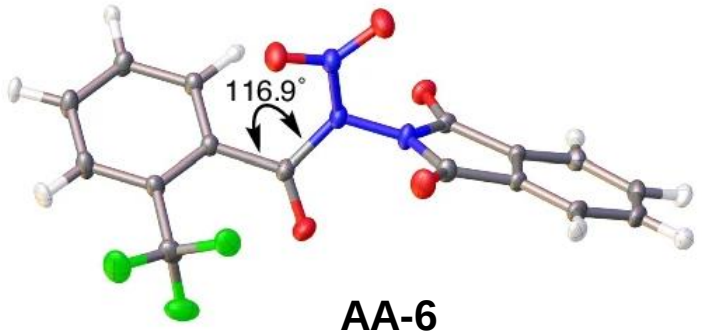


Mechanistic Experiments





AA-5



AA-6

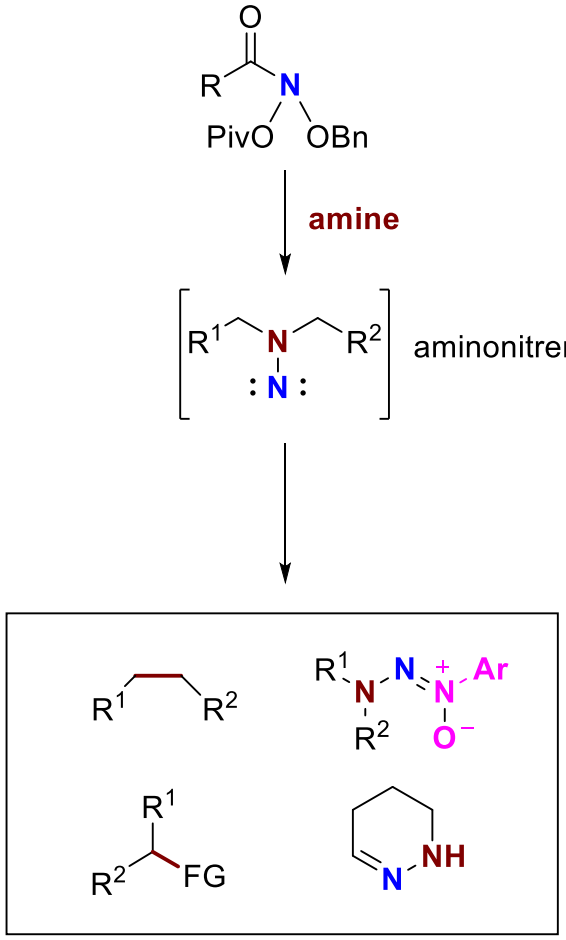
Baran, P. S. *Nat. Catal*. **2025**, *8*, 457−464.

/04

Summary and Outlook

4.1 Summary and Outlook

N-Acyloxy-N-alkoxyamides



As deaminating or aminating reagents

tolerate various substrates

without light and metal

mild reaction conditions

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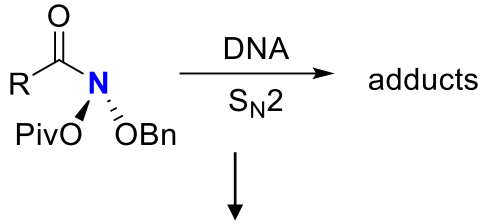
reactivity control

radical coupling or dimerization products

deaminating or aminating products

mutagenic toxicity

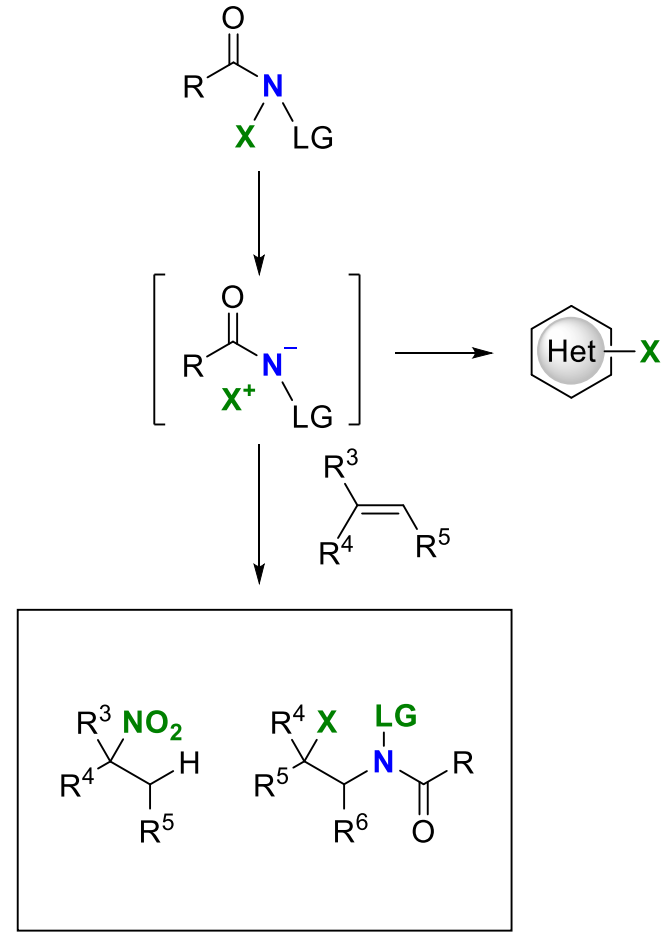


Optimize the structure

Glover, S. A. *Aust. J. Chem*. **2023**, *76*, 1−24.

4.1 Summary and Outlook

N–X anomeric amides



As electrophiles reagents

bench-stable solids

high reactivity and regio- and chemoselectivity

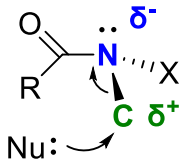
safe for gram-scale batch reactions

---

more types of electrophiles
almost all of them are Cl and Br

↓

-F, -CF_3, -SR



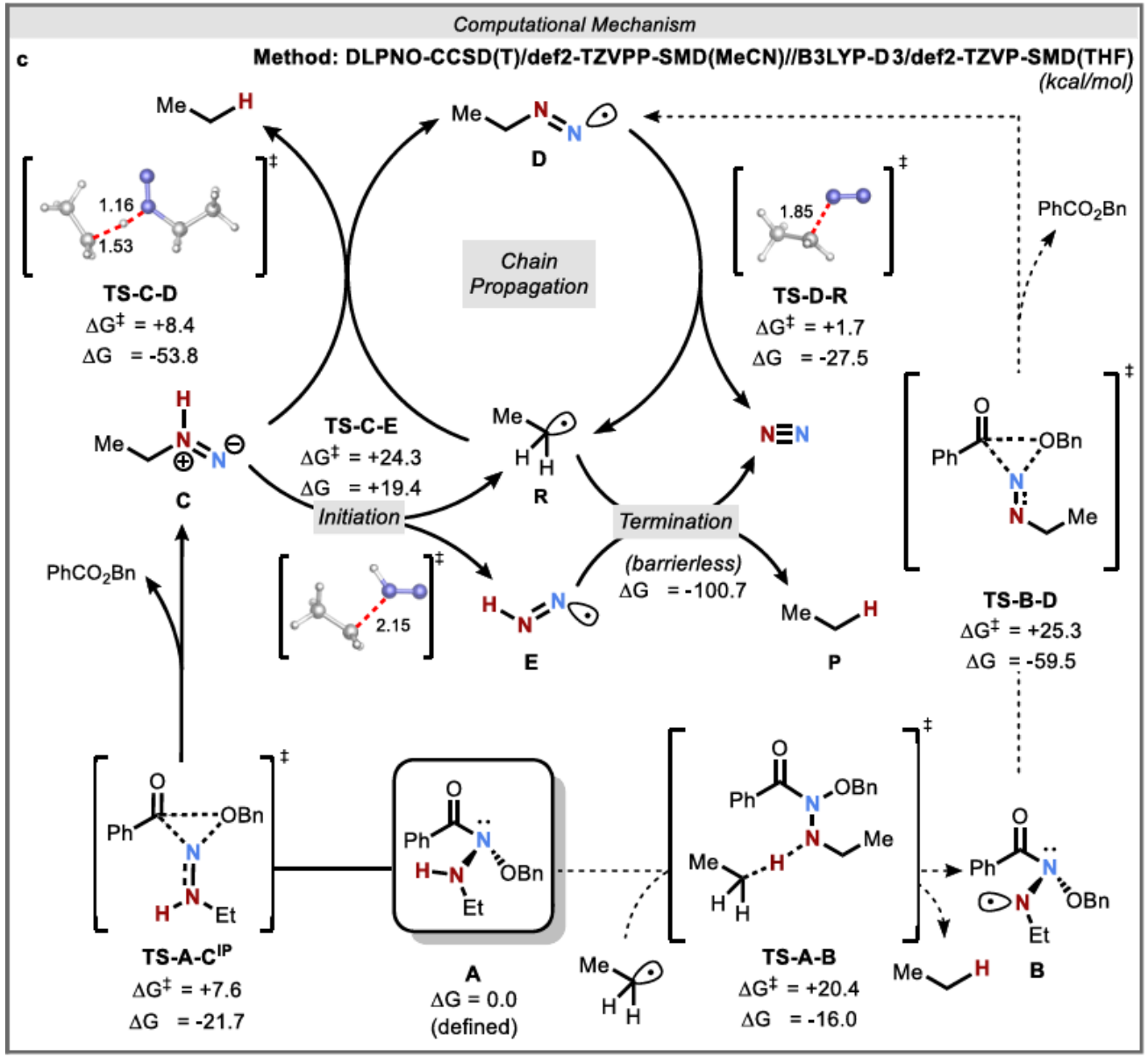
C^+ Source

Thank you for your attention.

Shiwen Fan

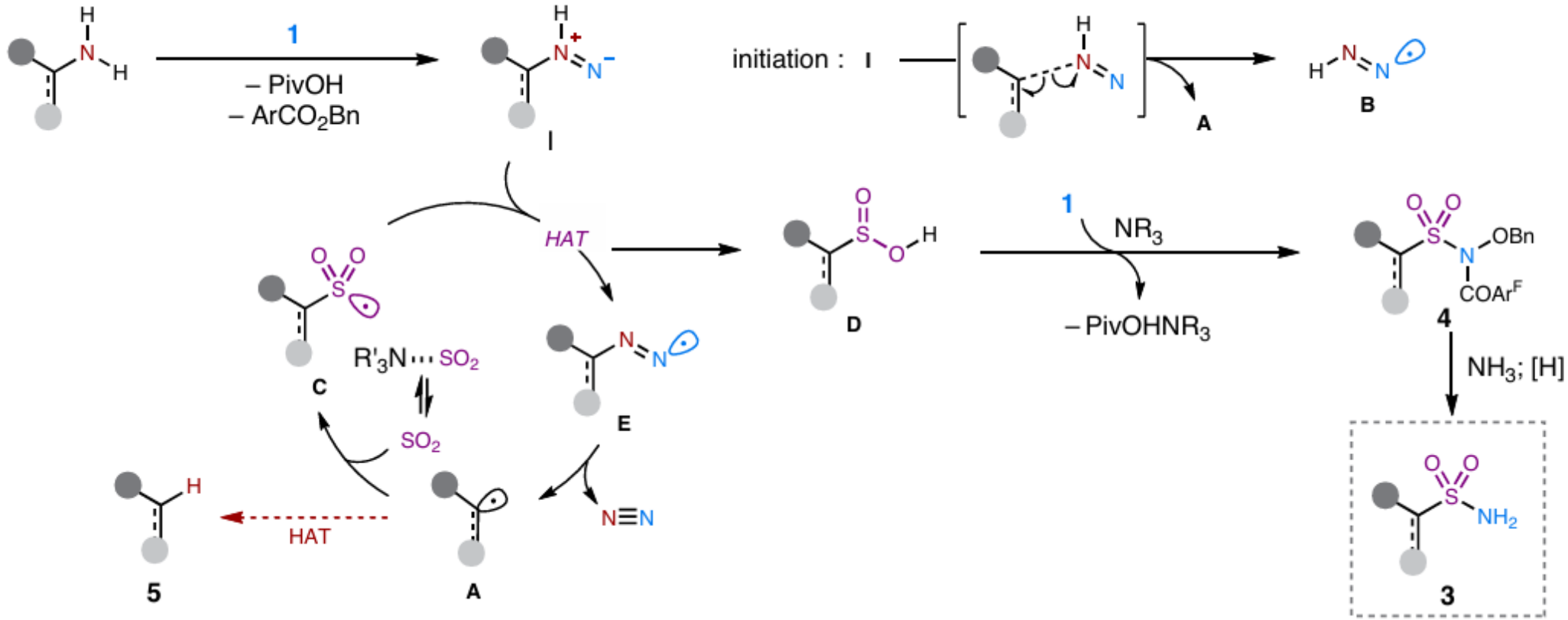
2026.04.24

Appendix



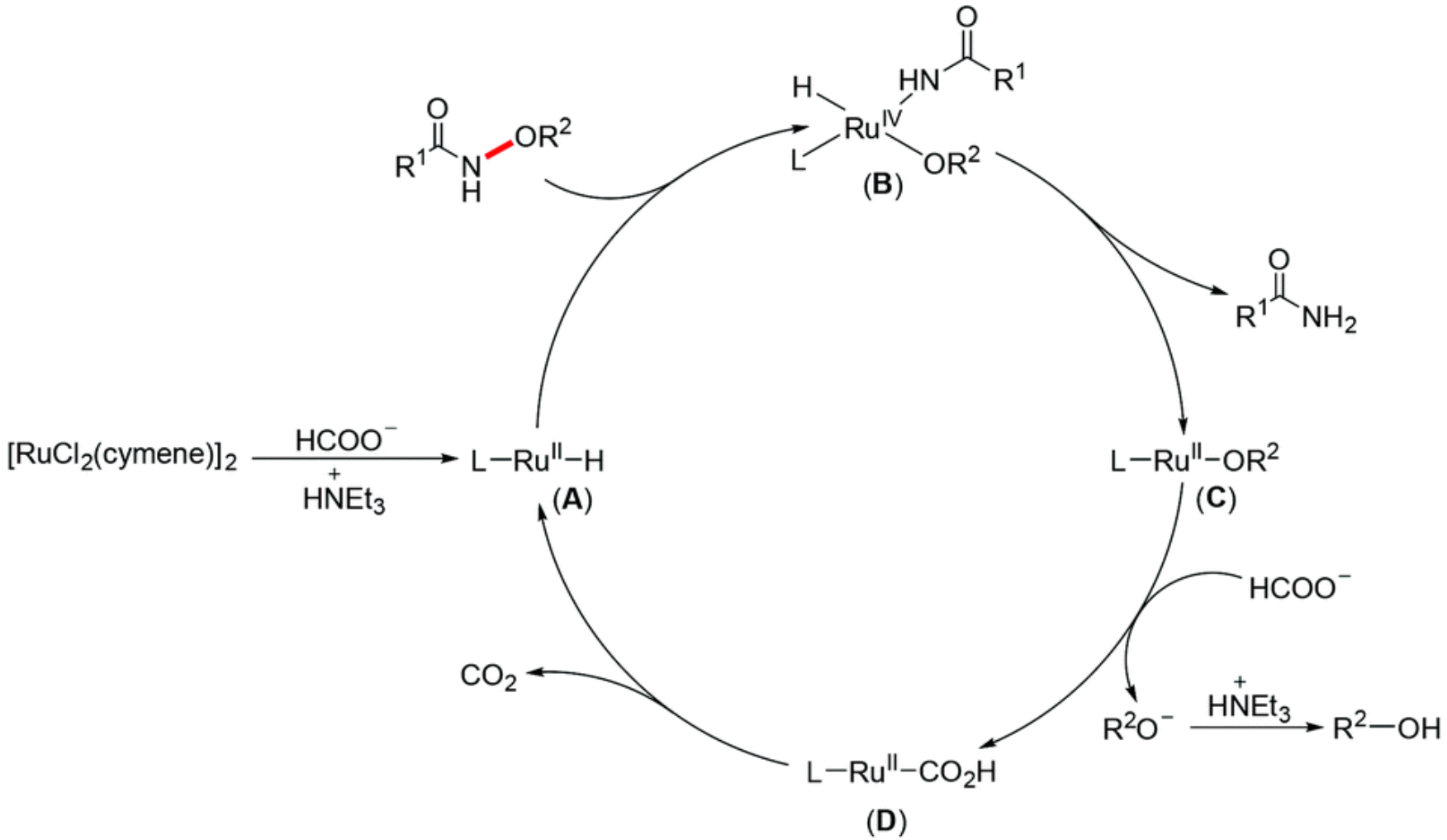
Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 17366−17373.

Appendix



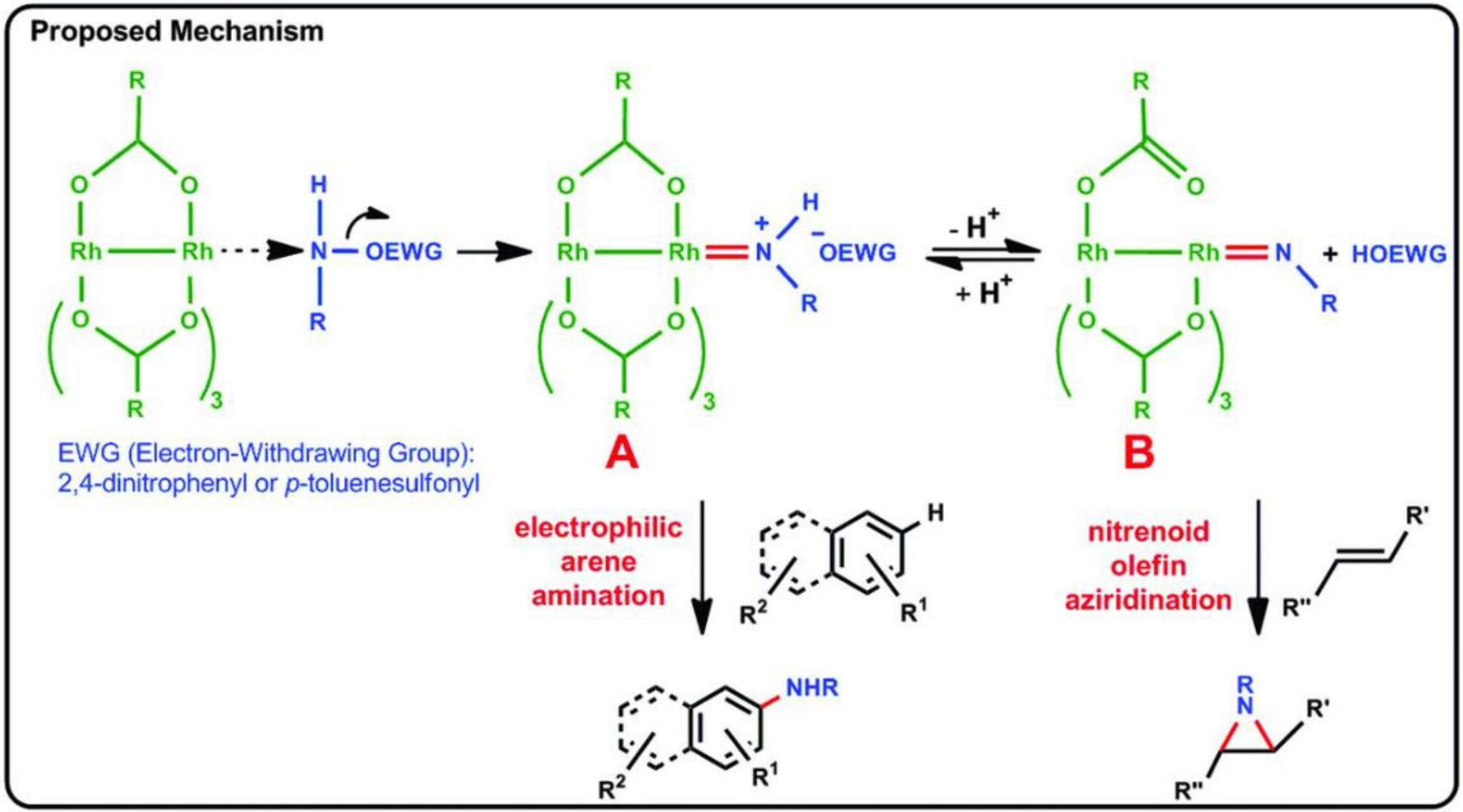
Levin, M. D. *Nat. Chem*. **2025**, *17*, 1247–1255.

Appendix



Xia, Y. *Org. Chem. Front*. **2021**, *8*, 112-119.

Appendix



Falck, J. R. *Science* **2016**, *353*, 1144.