同济大学 化学科学与工程学院
School of Chemical Science and Engineering

The Yang Research Group
Precise Synthesis Lab at Tongji University

2025.04.23

Rational Molecular Editing

汇报人：王宁

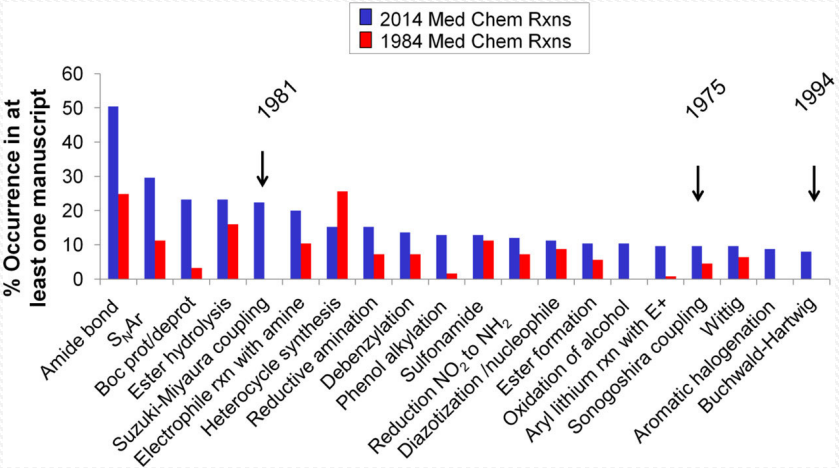
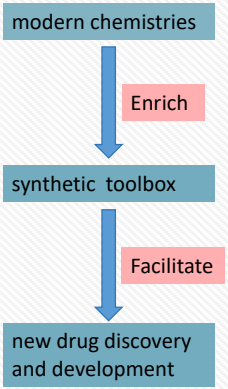
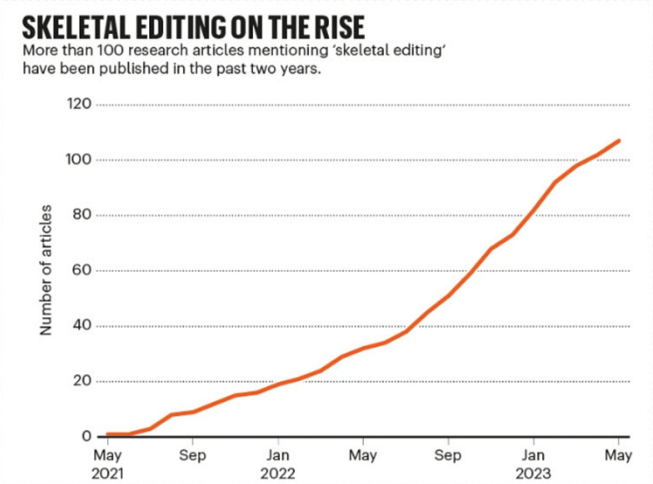


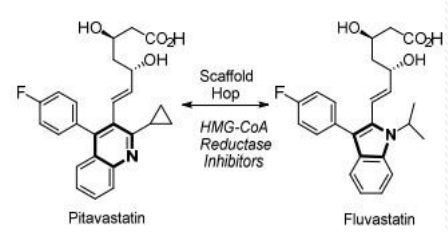
Figure 1. Occurrence of a particular reaction, plotted as the percentage of which it shows up in at least one manuscript (n = 125; representative data set taken from 2014, J. Med. Chem., blue; 1985, J. Med. Chem., red). The arrows (and years) indicated the first citation of this technology in the primary literature.



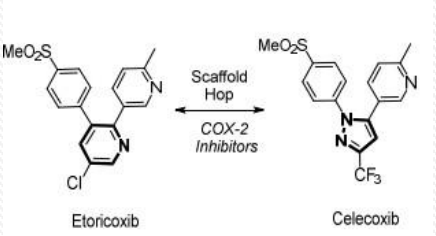
But only a limited new number of reactions was applied……

D. G. Brown, J. Boström, Journal of Medicinal Chemistry 2016, 59, 4443-4458


SKELETAL EDITING ON THE RISE
More than 100 research articles mentioning 'skeletal editing' have been published in the past two years.
Number of articles
120
100
80
60
40
20
0
May 2021
Sep
Jan 2022
May
Sep
Jan 2023
May

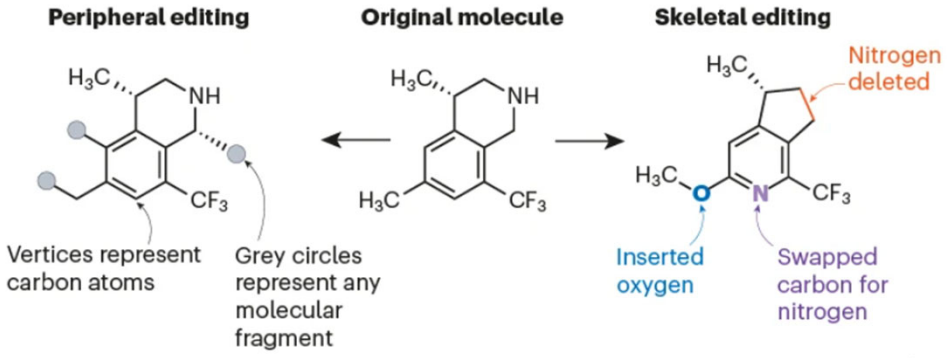

HO
CO2H
OH
F
N
Scaffold Hop
HMG-CoA Reductase Inhibitors
Pitavastatin
Fluvastatin

a.匹伐他汀与氟伐他汀


MeO2S
N
Cl
Scaffold Hop
COX-2 Inhibitors
CF3
Etoricoxib
Celecoxib

THE EMERGING CHEMISTRY OF SKELETAL EDITING

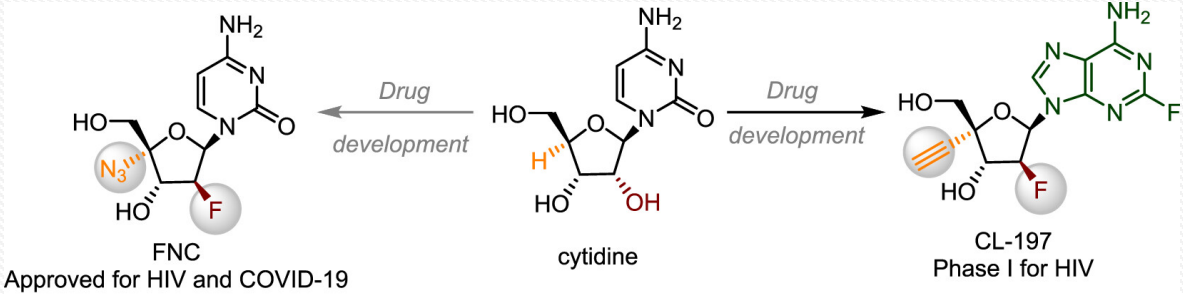
Chemists can easily add or change fragments on a molecule's periphery (left). Skeletal editing — changing the core skeleton of a molecule — is much more difficult, but chemists can now use reactions to insert, delete or swap atoms in these core areas (right).



1)*Mark Peplow.Nature*, **2023**, 618, 21-24, DOI: 10.1038/d41586-023-01735-1

2 外围编辑

Peripheral editing



Traditional method

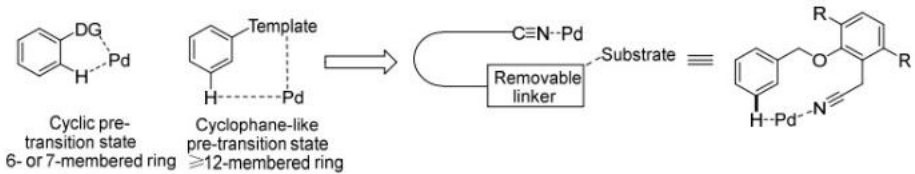
- ***De novo synthesis***
- ***Multistep***
- ***Limited access to analogs***

Future peripheral editing

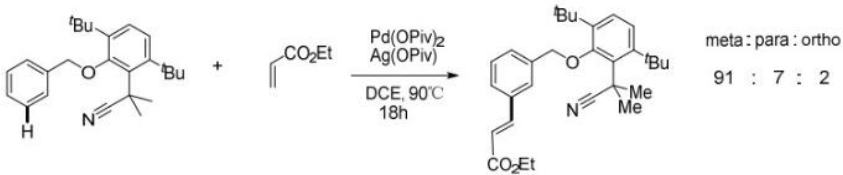
- ***Single step transformation***
- ***Chemoselective***
- ***Facile diversification***

Yu, *Journal of Medicinal Chemistry* **2024**, **67**, 11459-11466.

C–H Activation



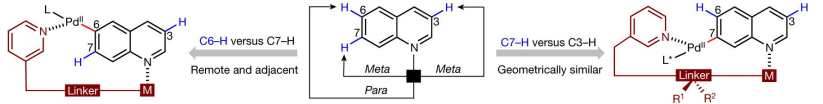
1)Remote meta-C–H activation is a challenge. Iortho-directed C–H activation. DG, directing group. II, III and IV: Remotemeta-C–H activation using an 'end-on' template. The dotted blue lines divide the arene template into four quadrants. The blue bonds in all figures highlightthe targeted C–H bonds. b, Templates for toluenes and hydrocinnamic acids

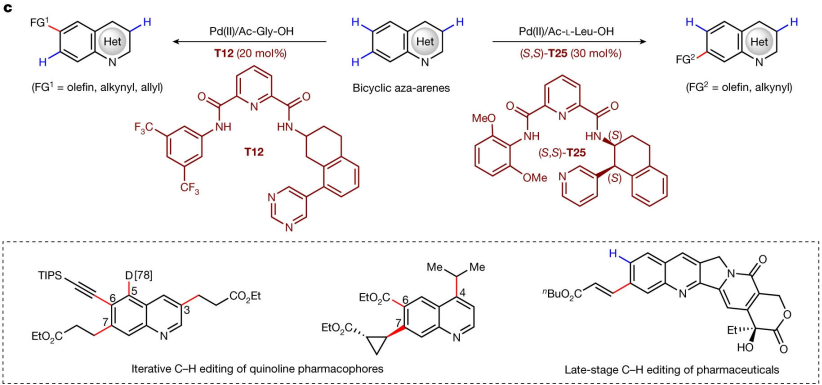


- ✓ Directing group Free
- ✓ Meta chemical selectivity

1)Jin-Quan Yu et al,*Nature* **486**, 518–522 (**2012**). https://doi.org/10.1038/nature11158

C–H Activation

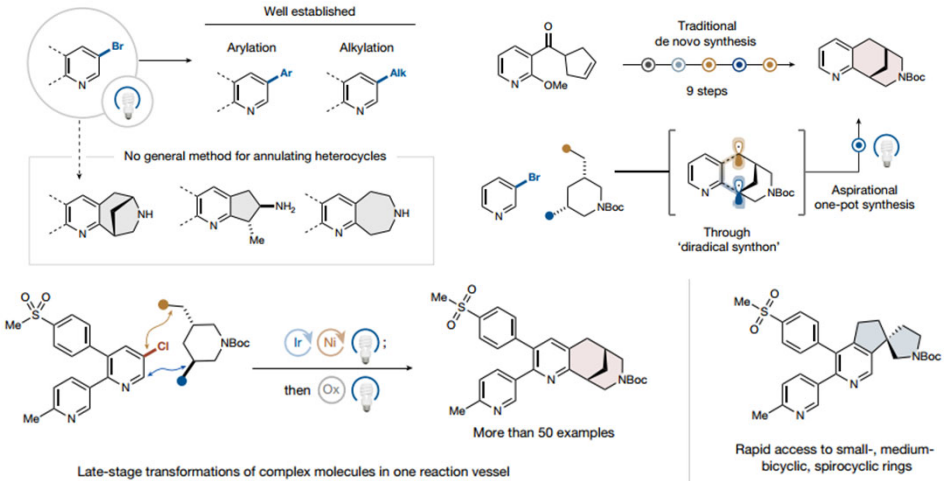




b, Challenges and solutions to C6- and C7-selective palladation. c, Catalytic C6- and C7-selective functionalizations (this work). M, metal; L, ligand; FG, functional group; TIPS, triisopropylsilyl; nBu, n-butyl.

1)Jin-Quan Yu ,*Nature* **610**, 87–93 **(2022)**.https://doi.org/10.1038/s41586-022-05175-1

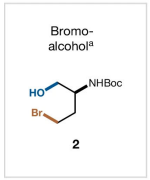
C–H Activation

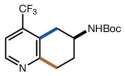


1)David W. C. MacMillan,*Nature* **628**, 326–332 (**2024**). https://doi.org/10.1038/s41586-024-07181-x

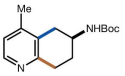
2 外围编辑

C–H Activation

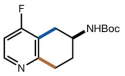




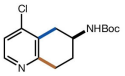
4, 60% yield (77% per step) 96% ee



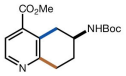
5, 41% yield (64% per step)



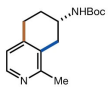
6, 45% yield (67% per step)



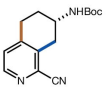
7, 45% yield (67% per step)



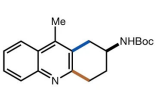
8, 41% yield (64% per step)



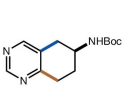
9, 75% yield (87% per step)



10, 64% yield (80% per step)

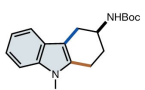


11, 56% yield (75% per step)

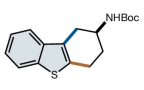


12, 46% yield (68% per step)

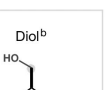
Non-traditional Minisci acceptors

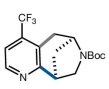


13, 44% yield (66% per step)[c]

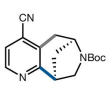


14, 55% yield (74% per step)[c]

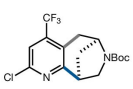




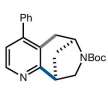
15, 50% yield (71% per step)



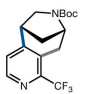
16, 48% yield (69% per step)



17, 32% yield (57% per step)

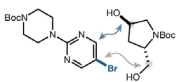


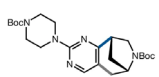
18, 41% yield (64% per step)



19, 50% yield (71% per step)

20, 51% yield (72% per step)



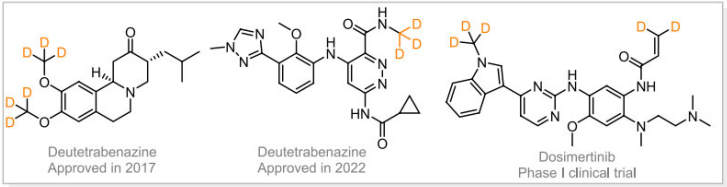


21, 34% yield (58% per step)

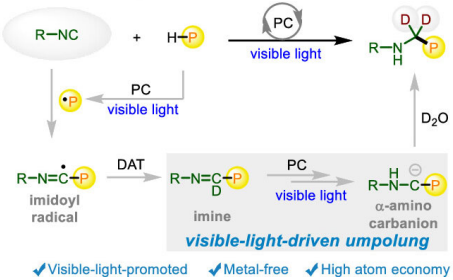
1)David W. C. MacMillan,*Nature* **628**, 326–332 (2024). https://doi.org/10.1038/s41586-024-07181-x

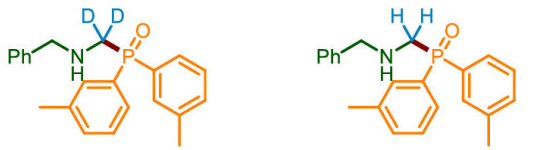
2 外围编辑

Atom/FG Exchange



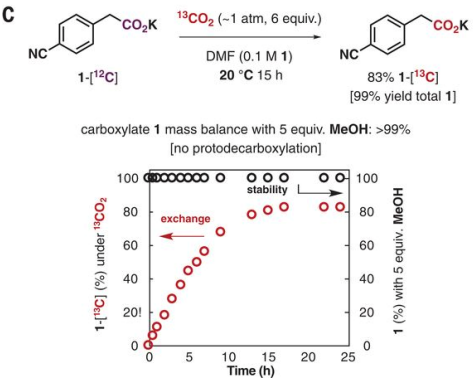
under-explored





b, Challenges and solutions to C6- and C7-selective palladation. c, Catalytic C6- and C7-selective functionalizations (this work). M, metal; L, ligand; FG, functional group; TIPS, triisopropylsilyl; nBu, n-butyl.

1)*Shu-Ting Zhang,Organic Letters* **2023**, 25, 8016-8021.



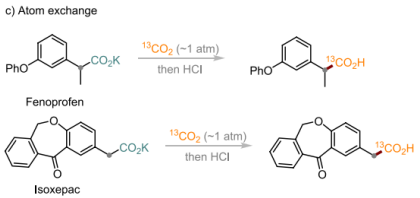
D

$^{13}CO_2$ (~1 atm), DMF 70 °C: 1-[^{12}C] → 1-[^{13}C]

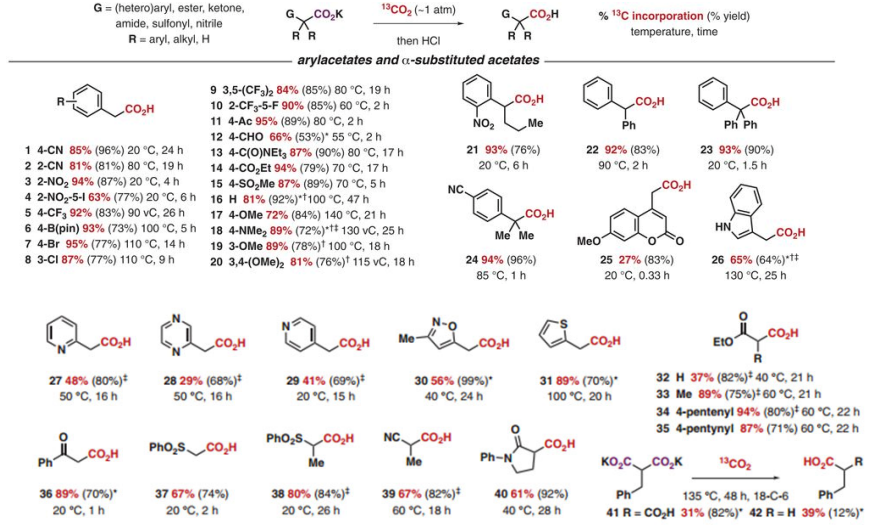
cation	^{13}C incorp. (time)
K^+	85% (1 h)
H^+	<5% (8 h)
Li^+	72% (8 h)
Na^+	77% (8 h)
Cs^+	63% (5 h, rt)
0.5 Zn^{2+}/Cu^{2+}	<5% (8 h)

$^{13}CO_2$ (~1 atm), 20 °C: 1-[^{12}C] → 1-[^{13}C]

conditions	^{13}C incorp. (time)
THF	0% (5 h)
DCE	0% (5 h)
H_2O	0% (5 h)
DMSO	47% (5 h)
DMA	45% (5 h)
DMF/18-C-6	67% (5 h)



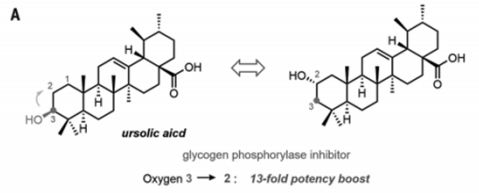
Lundgren, R. Jm,*Science***369**,557-561(**2020**).DOI:10.1126/science.abb4129

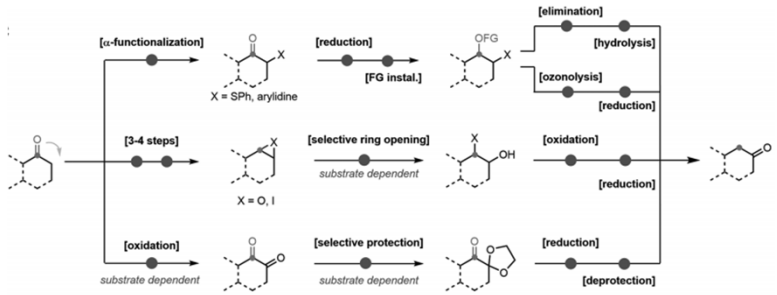


*Lundgren, R. Jm,Science***369**,557-561(**2020**).DOI:10.1126/science.abb4129

2 外围编辑

Functional Group Transposition

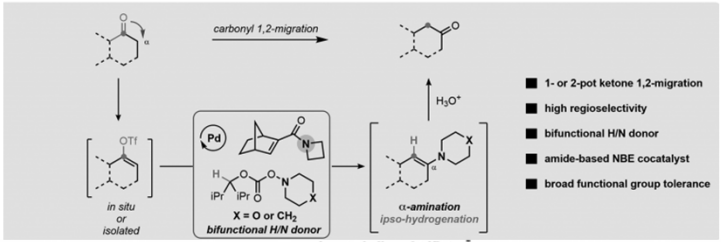


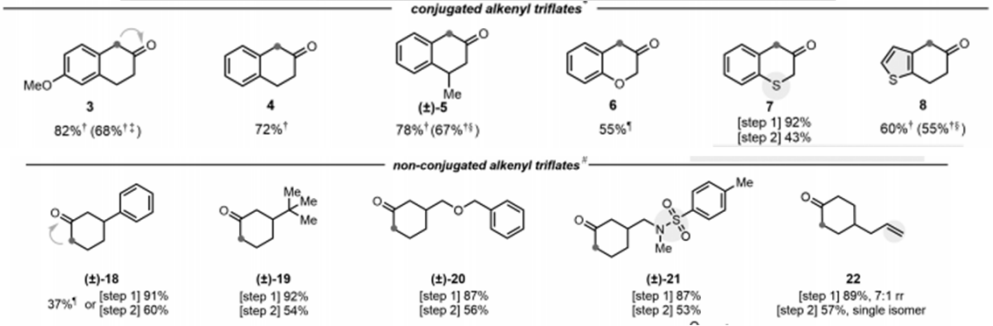


1)Dong, G.*Science***374**.734-740**(2021)**.DOI:10.1126/science.abl7854

2 外围编辑

Functional Group Transposition

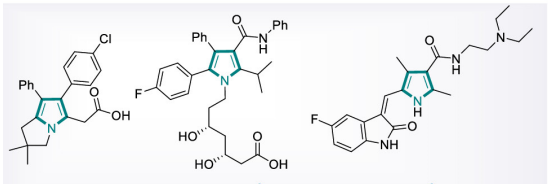




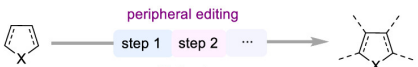
1)Dong, G.*Science***374**.734-740**(2021)**.DOI:10.1126/science.abl7854

Skeletal Recasting

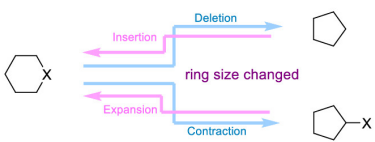
A. Biologically active fully-substituted pyrroles



Multi-step manipulation of heterocycles

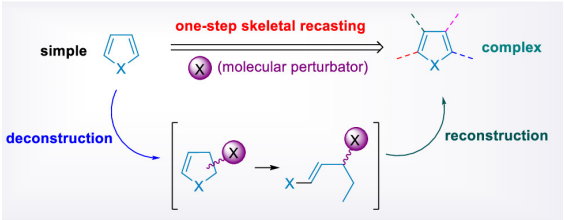


Single-atom skeletal editing of heterocycles

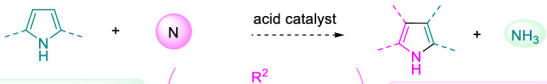


Zhou, X,ACS Central Science **2023**, 9, 1758-1767.

Our proposal: skeletal recasting strategy for heterocycle editing



Reaction design: skeletal recasting of simple pyrroles



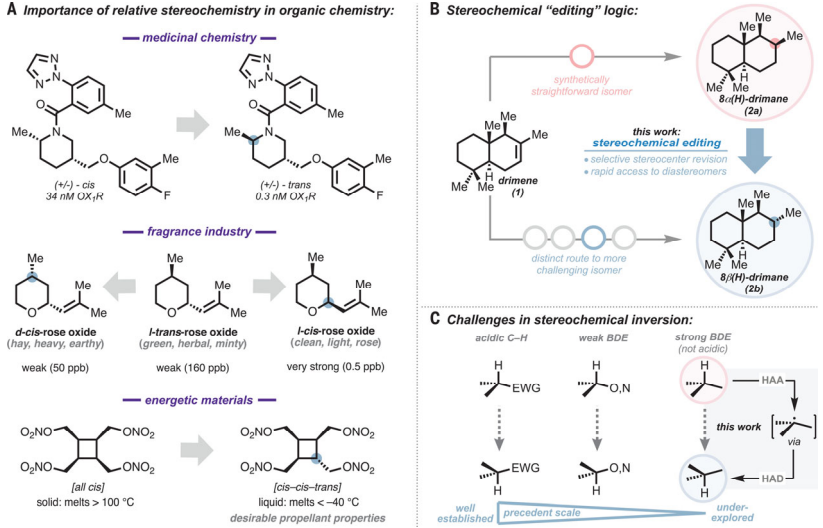
- cheap, abundant
- commercially available
- readily accessible

- biologically useful
- present in approved drugs
- synthetically challenging

deconstruction of simple pyrrole via dearomatization?
reconstruction of complex pyrrole via rearomatization??

2 外围编辑

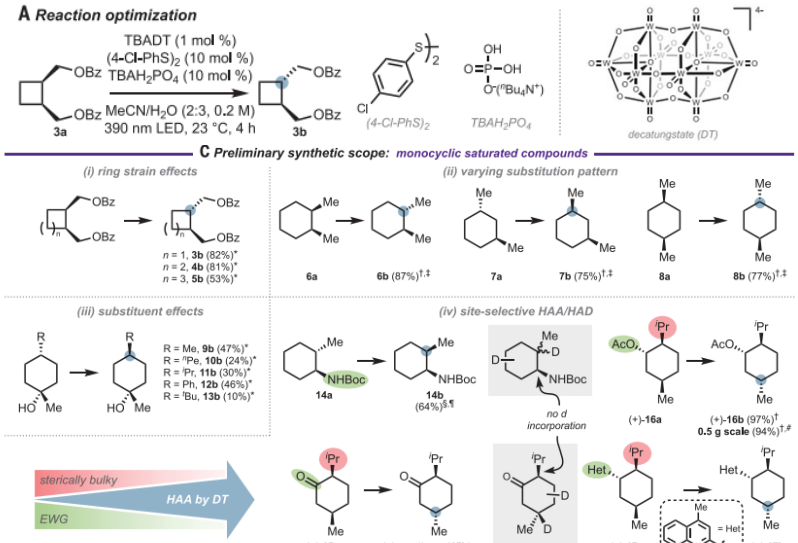
Stereochemical Editing



*Wendlandt, A. E.,Science***378**,383-390(**2022**).DOI:10.1126/science.add6852

2 外围编辑

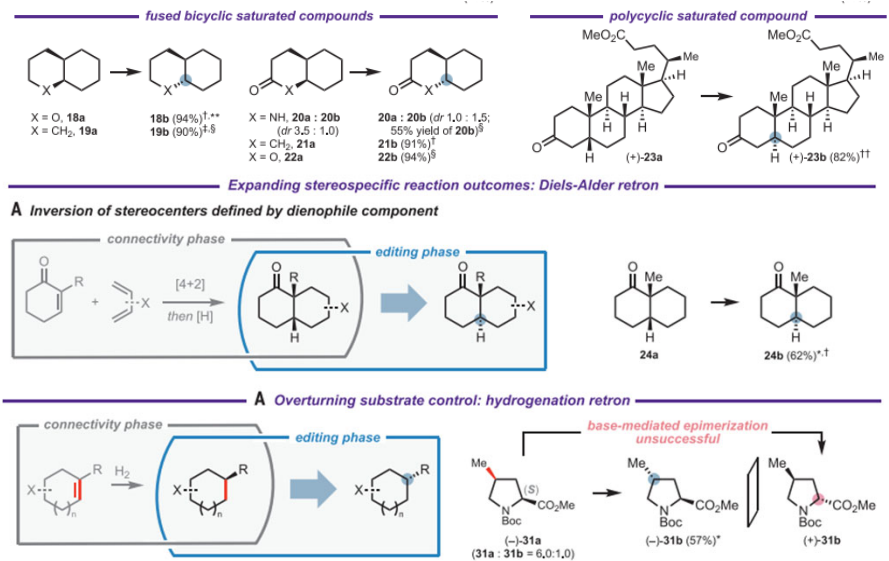
Stereochemical Editing



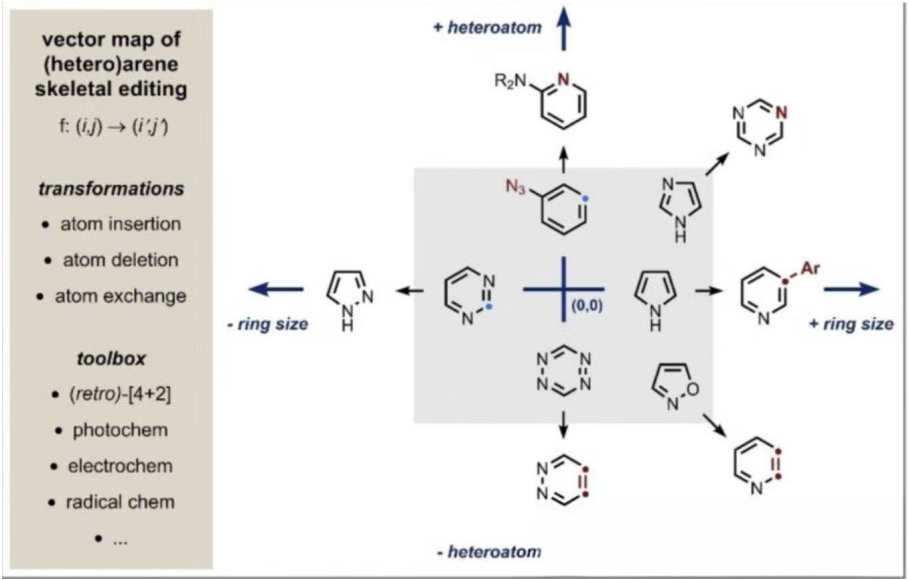
*Wendlandt, A. E.,Science***378**,383-390(**2022**).DOI:10.1126/science.add6852

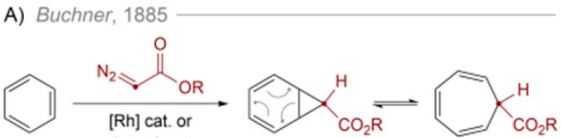
2 外围编辑

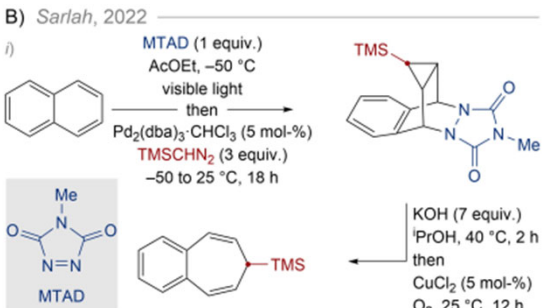
Stereochemical Editing

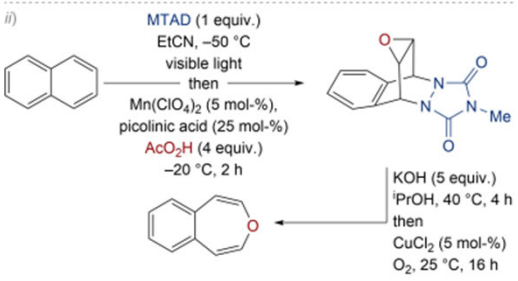


*Wendlandt, A. E.,Science***378**,383-390(**2022**).DOI:10.1126/science.add6852

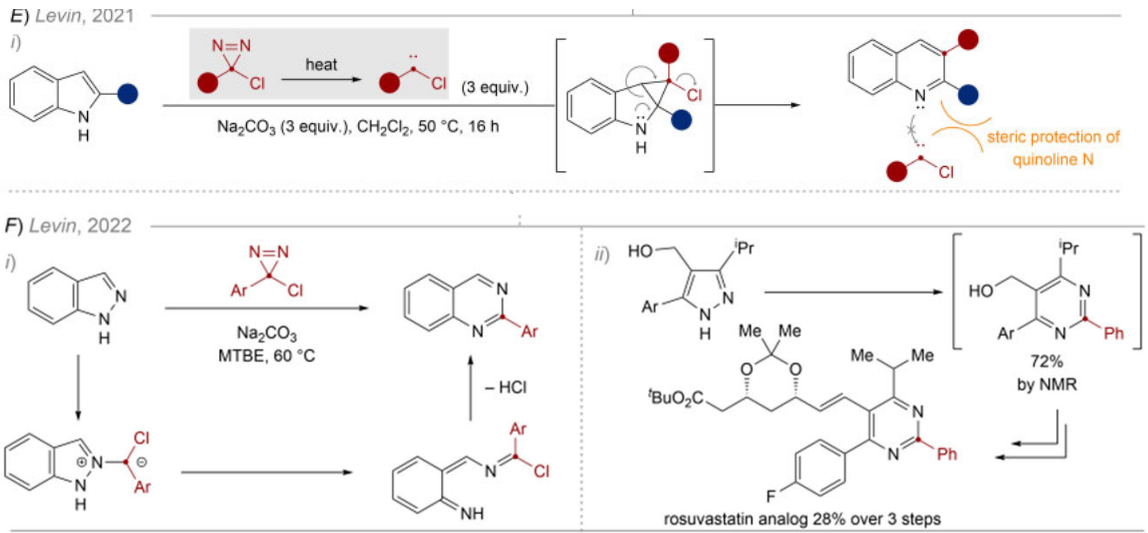

vector map of (hetero)arene skeletal editing
f: (i,j) → (i',j')
transformations
• atom insertion
• atom deletion
• atom exchange
toolbox
• (retro)-[4+2]
• photochem
• electrochem
• radical chem
• ...
+ heteroatom
- heteroatom
- ring size
+ ring size
(0,0)
R2N
N3
Ar





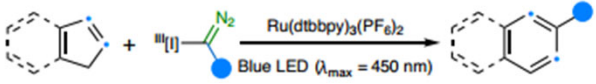


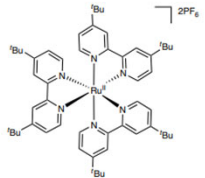
a)Ber.Dtsch. Chem. Ges. 1885, 18, 2377–2379.b)Angew. Chem. Int. Ed.2022, 61, e202208014.



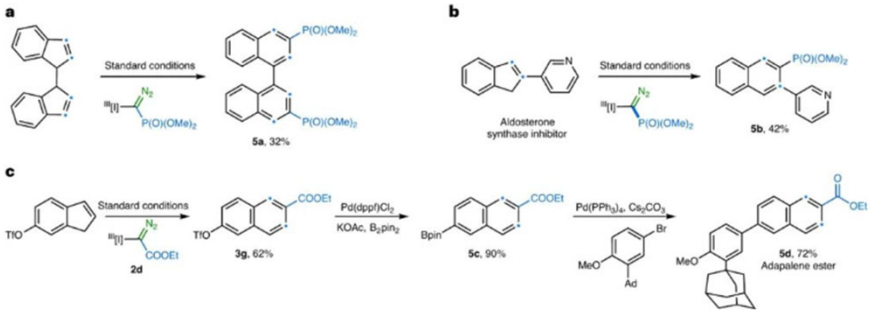
E)*M. D.Levin,J. Am. Chem. Soc.* **2021**,143, 11337–11344. F)*M. D.Levin,J.Am. Chem. Soc.* **2022**, 144, 19258–19264.

Ring Expansion（Ring Expansion with C-Atom Insertion）





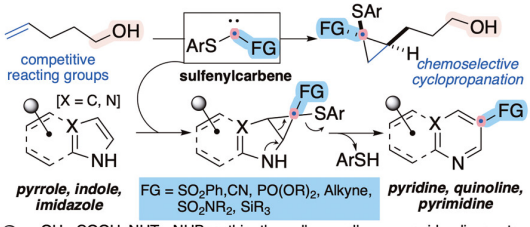
• = COOR, CF_3, CONR'R", CN, P(O)(OR)$_2$, SO_2Ph, SO_3Et, COAr, COR



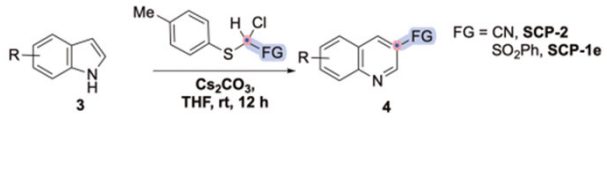
Osvaldo Gutierrez & Frank Glorius, *Nat Catal* **7**, 242–251 (**2024**). https://doi.org/10.1038/s41929-023-01089-x

3 骨架编辑

Ring Expansion（Ring Expansion with C-Atom Insertion）



- Direct carbon atom insertion bearing versatile functional group
- Easily accessible, scalable, and benchtop stable non-diazo carbene precursors
- Good functional group tolerance: -OH, -COOH, amines, amides, alkenes, alkynes, epoxide, etc.
- Late-stage skeletal modifications; 57 examples; up to 98% yield



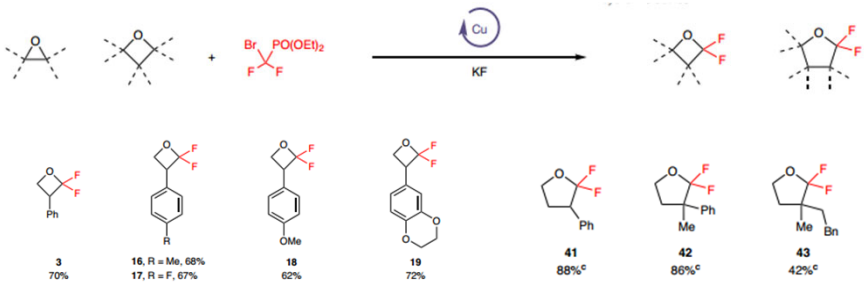
SCP-2	SCP-3	SCP-4	SCP-5	SCP-6	SCP-7
					
2ab rt, 10 h, 99%	**2ac** 0 °C - rt, 4 h, 65%	**2ad** 60 °C, 24 h, 45%	**2ae** rt, 12 h, 98%	**2ea** 0°C - rt, 6 h, 64%*	**2ca** 0°C, 12 h, 85%
				1e	**1c**

1a, Ar = *p*-tolyl, Base = Cs_2CO_3

Ar = Ph, Base = ^tBuOK

Indrajeet Sharma, *Journal of the American Chemical Society* **2025**. DOI: 10.1021/jacs.5c02012.

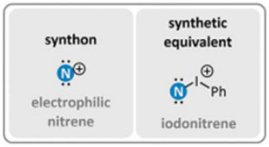
Ring Expansion（Ring Expansion with C-Atom Insertion）

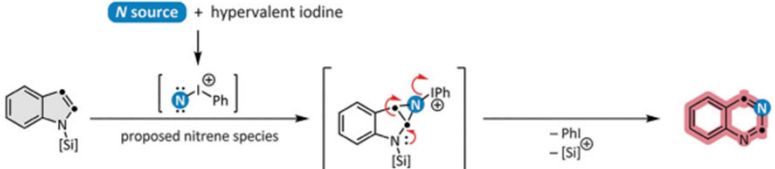


Ming Joo Koh ,*Nat. Chem.* **2025**, DOI: 10.1038/s41557-024-01730-7

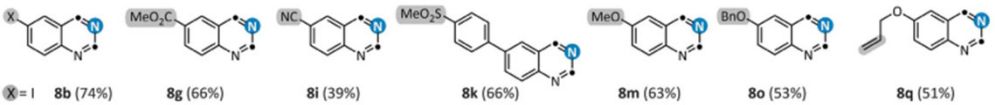
3 骨架编辑

Ring Expansion（Ring Expansion with N-Atom Insertion）

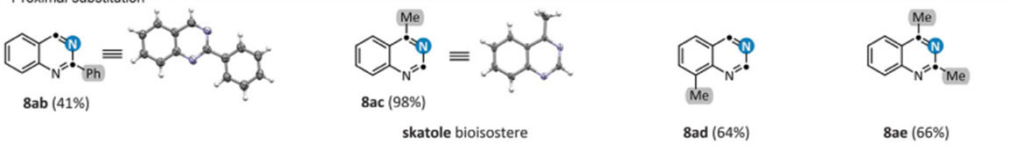




A Functional group tolerance

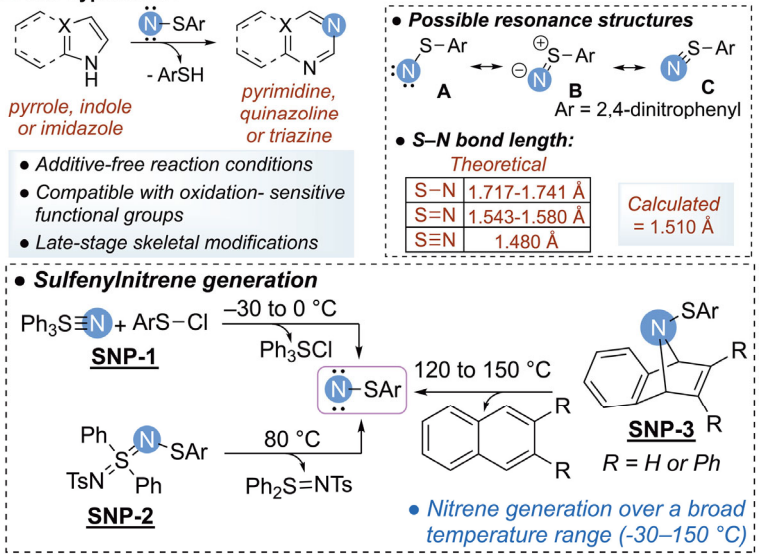


B Proximal substitution



Bill Morandi, *Science* **377**, 1104-1109 (**2022**). DOI: 10.1126/science.add1383

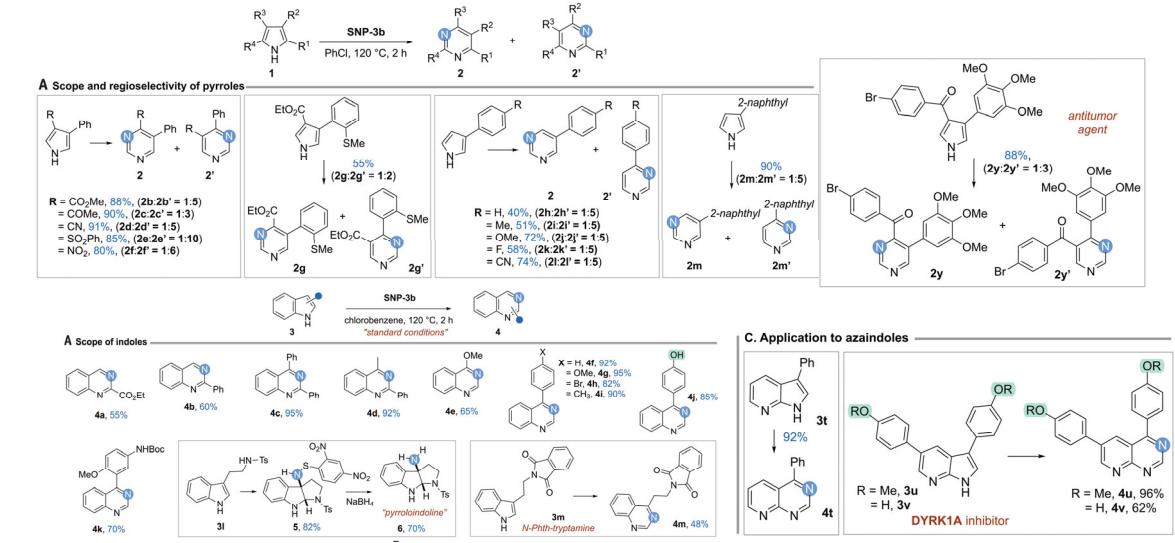
Ring Expansion (Ring Expansion with N-Atom Insertion)



Indrajeet Sharma.*Science***387**,102107(**2025**).DOI:10.1126/science.adp0974

3 骨架编辑

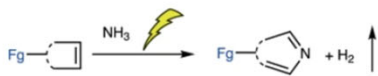
Ring Expansion（Ring Expansion with N-Atom Insertion）



Indrajeet Sharma.*Science***387**,102107(**2025**).DOI:10.1126/science.adp0974

Ring Expansion（Ring Expansion with N-Atom Insertion）

b this work

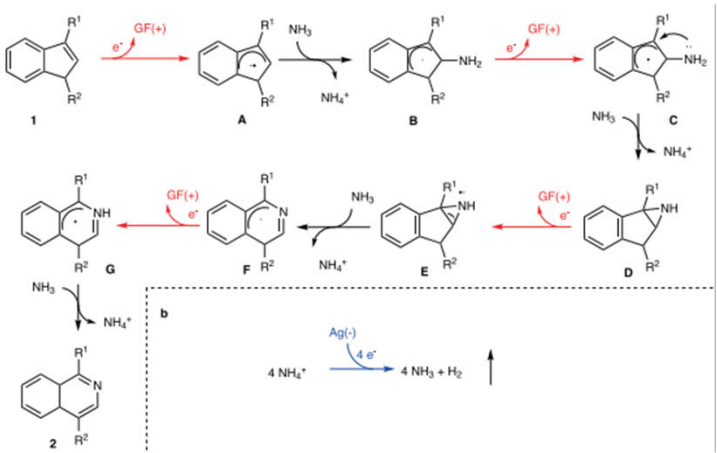


Fg dehydrogen

i) single step ii) only H_2 by-product

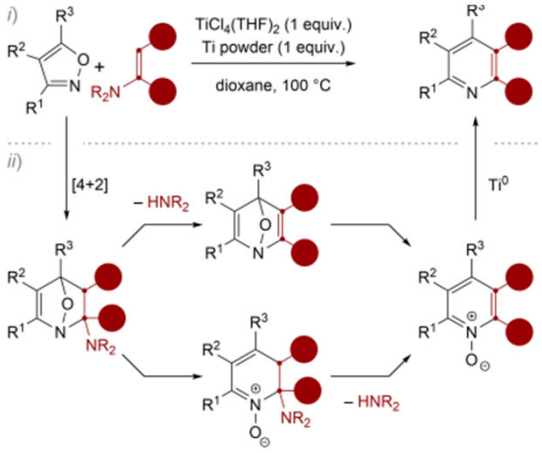
iii) unexplored diverse functional groups

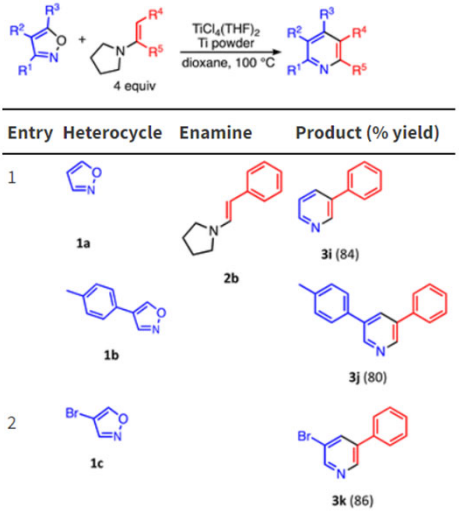
iv) theoretical atom economy up to 99.2%



*Xu Cheng,Nat Commun **13***, 425 (**2022**). https://doi.org/10.1038/s41467-022-28099-w

Ring Expansion with Atom Exchange





Aaron L. Odom,*Org. Biomol. Chem.*, **2022**,20, 6630-6636

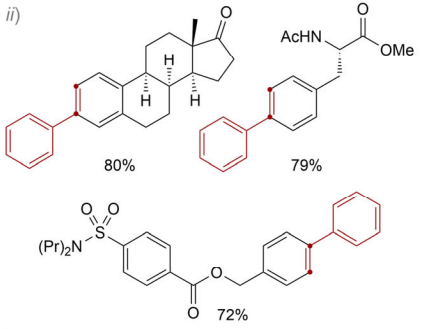
3 骨架编辑

Ring Expansion with Atom Exchange

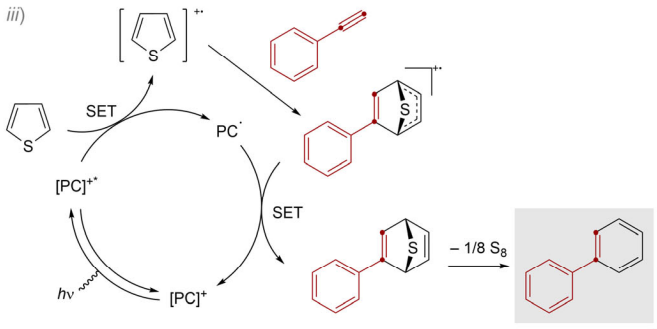
Lei & Chiang, 2019

i)

ii)



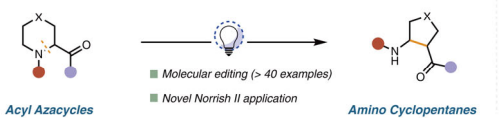
iii)



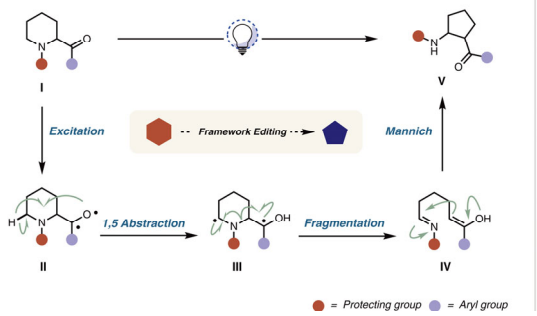
Prof. Aiwen Lei,Angew. Chem. Int. Ed. **2019**, 58, 12206

Ring Contraction

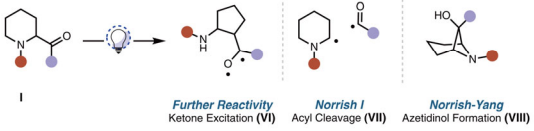
E *This Work*



A *Proposed Mechanism*



B *Potential Challenges*

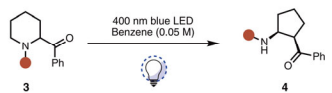


Richmond Sarpong,*Science***373**,1004-1012(**2021**).DOI:10.1126/science.abi7183

3 骨架编辑

Ring Contraction

A



Cyclic Amine	Product
3a: R = H	**4a**: 84% (20:1 d.r.)
3b: R = *p*–Me	**4b**: 79% (12:1 d.r.) (*78%*)††
3c: R = *p*–OMe	**4c**: 68% (8:1 d.r.)
3d: R = *o*–Me	**4d**: 48% (19:1 d.r.)
3e: R = *p*–Br	**4e**: 74% (12:1 d.r.)
3f: R = *p*–F	**4f**: 63% (19:1 d.r.)
3g: R = *p*–Cl	**4g**: 59% (3.3:1 d.r.)
3h: R = *p*–Ac	**4h**: 22% (5:2 d.r.)
3i: R = *p*–CO_2Me	**4i**: 24% (19:1 d.r.)
3j: R = *p*–NO_2	**4j**: 0%

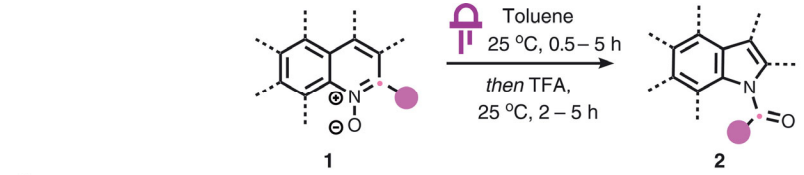
Cyclic Amine	Product
3m: R = Piv	**4m**: 54% (14:1 d.r.)* 44% (19:1 d.r.)† (*40%*)††
3n: R = COBn	**4n**: 39% (20:1 d.r.)*
3o: R = Bz	**4o**: 44% (14:1 d.r.)* 30% (6:1 d.r.)†
3p:	**4p**: 27% (2.6:1 d.r.)*
3q:	**4q**: 22% (20:1 d.r.)* 23% (20:1 d.r.)† (*21%*)††

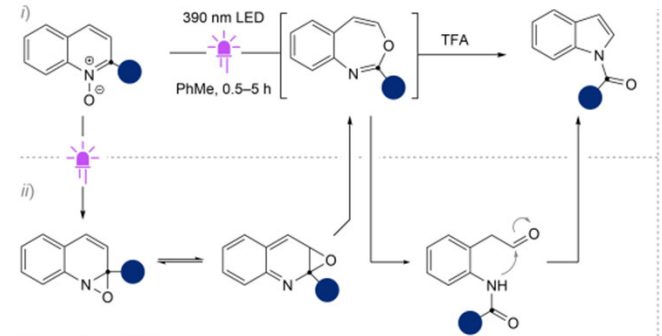
Heterocycle	Product
7c	**8c**: 66% (3:1 d.r.)
7d	**8d**: 83% (20:1 d.r.)
7e	**8e**: 75% (20:1 d.r.)

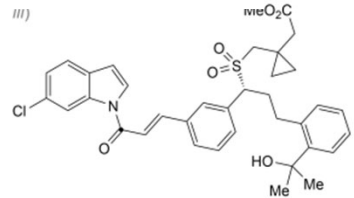
Heterocycle	Product
7f	**8f**: 37% (20:1 d.r.)
7g	**8g**: 80% (20:1 d.r.)#
7h	**8h**: 85% (20:1 d.r.) **

*Science***373**,1004-1012(**2021**).DOI:10.1126/science.abi7183

Ring Contraction





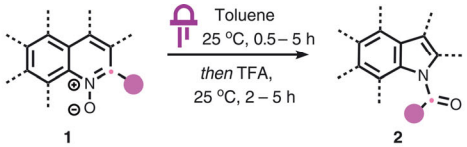


44%
from montelukast
(leukotriene receptor antagonist)

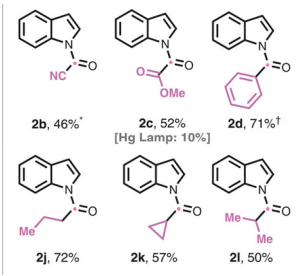
Mark D. Levin,*Science*, **2022**, 376, 527-532, DOI: 10.1126/science.abo4282

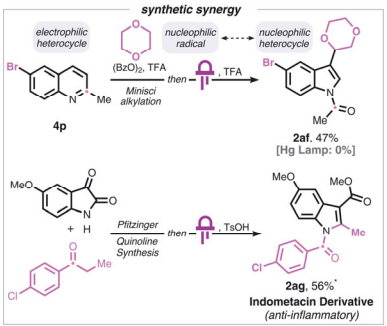
3 骨架编辑

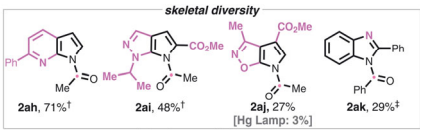
Ring Contraction

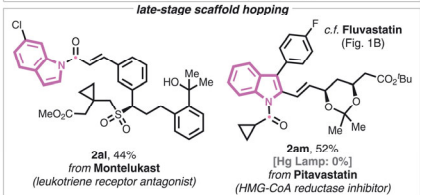


Selected example





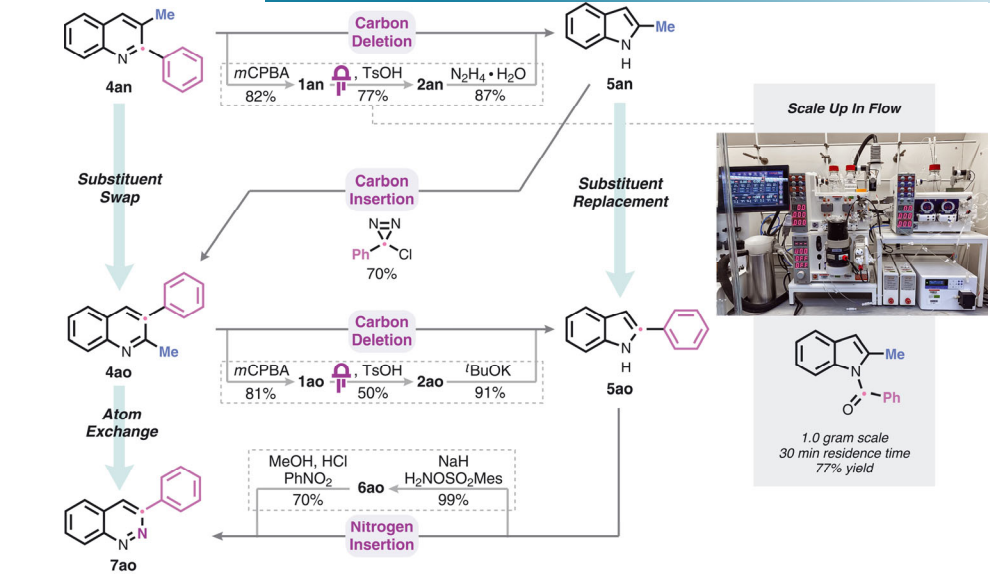




Mark D. Levin,*Science*, **2022**, 376, 527-532, DOI: 10.1126/science.abo4282

3 骨架编辑

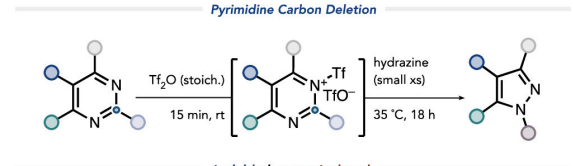
Ring Contraction



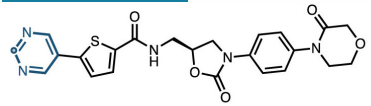
Mark D. Levin,*Science*, **2022**, 376, 527-532, DOI: 10.1126/science.abo4282

3 骨架编辑

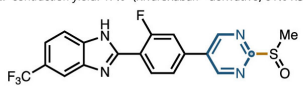
Ring Contraction



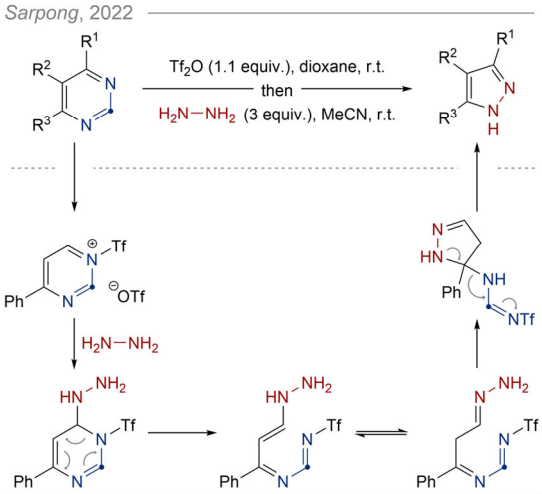
Selected example



42: *contraction yield:* 17%[d] (Rivaroxaban® derivative; 81% RSM)



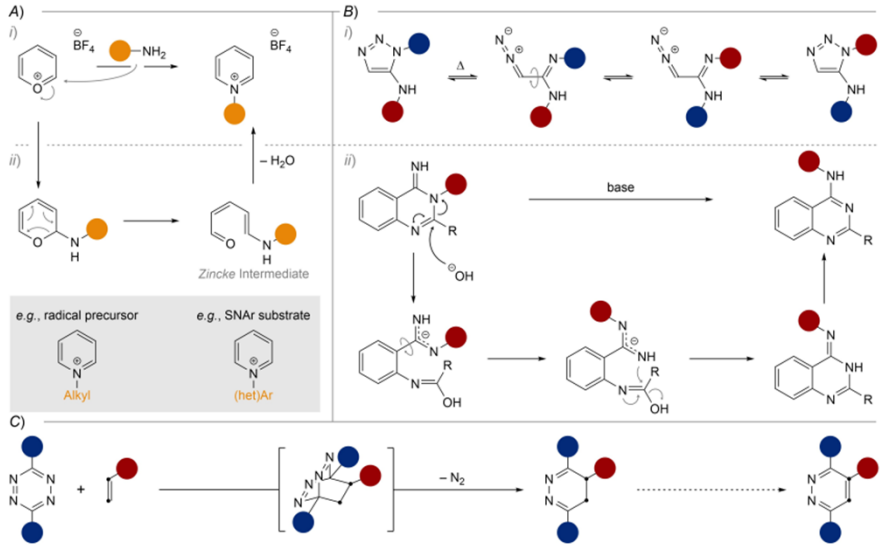
43: *contraction yield:* 65% (31% RSM)



Richmond Sarpong,*J. Am. Chem. Soc.* **2022**, 144, 48, 22309–22315

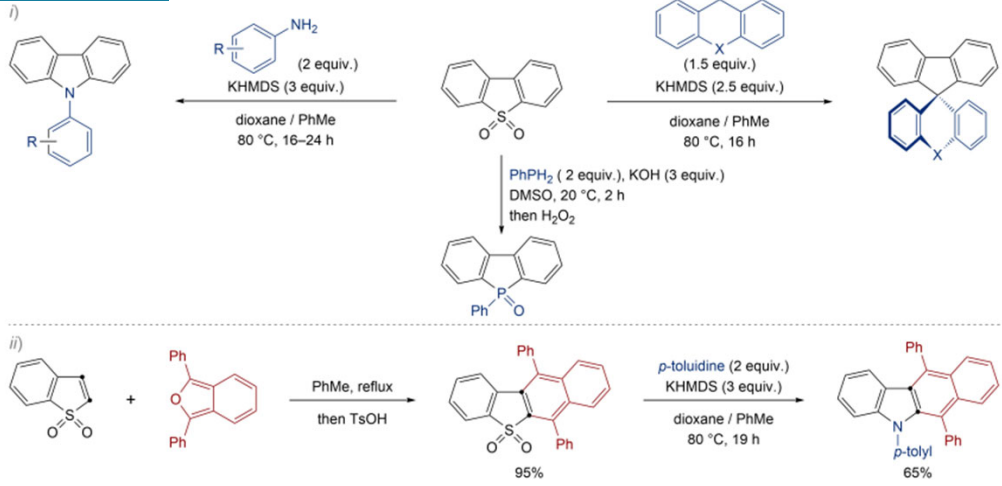
3 骨架编辑

Atom Exchange



1)*J. Chem. Soc. Perkin Trans*. 11979, 430–432.2)*J. Org. Chem*. **2021**, 86, 8286–8294

Yorimitsu (2016)



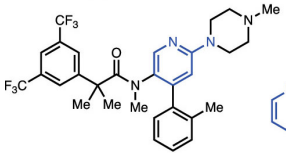
1)*Yorimitsu,Synlett* **2016**, 27, 1765–1774. 2)*Yorimitsu,Chem. Commun*. **2017**, 53, 4055–4065.

C. This Work: Aryl Azide to Aminopyridine

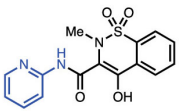
Specific advance:

N insertion + C deletion

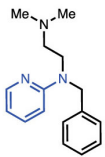
D. Aminopyridine Pharmaceuticals



netupitant (component of Akynzeo): antiemetic

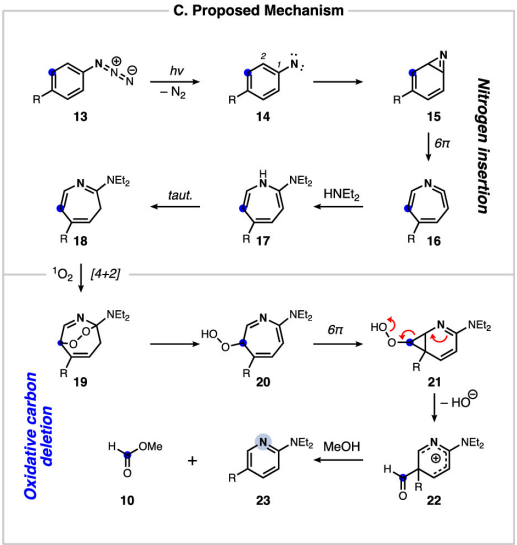


piroxicam (Feldene): NSAID



tripelennamine (Pyribenzamine): antihistamine

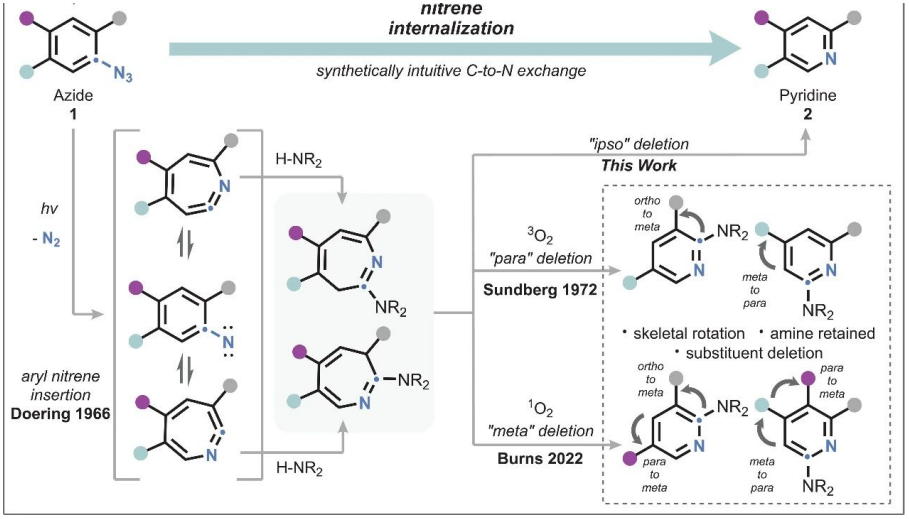
C. Proposed Mechanism



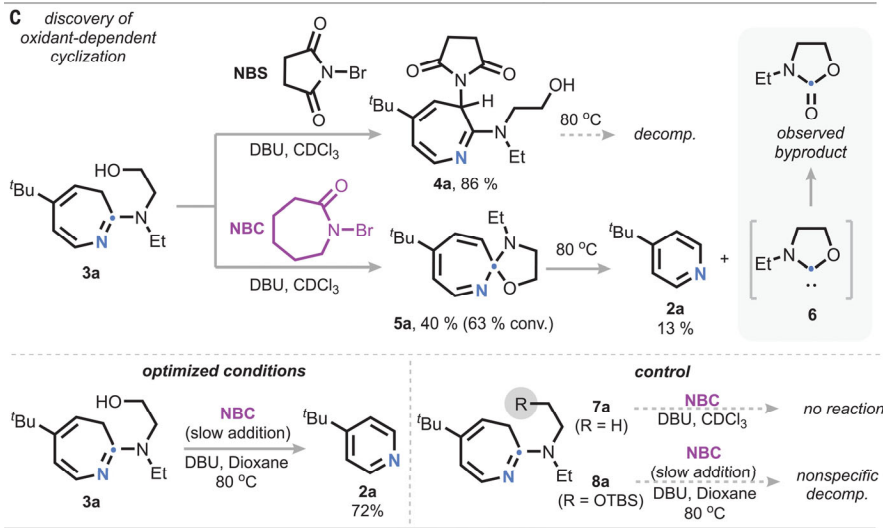
N. Z. Burns.*J. Am. Chem. Soc.* **2022**, 144, 39, 17797–17802

3 骨架编辑

Atom Exchange



Mark D. Levin ,*Science*, **2023**, **381**, 1474-1479. DOI: 10.1126/science.adj5331



Mark D. Levin ,*Science*, **2023**, **381**, 1474-1479. DOI: 10.1126/science.adj5331

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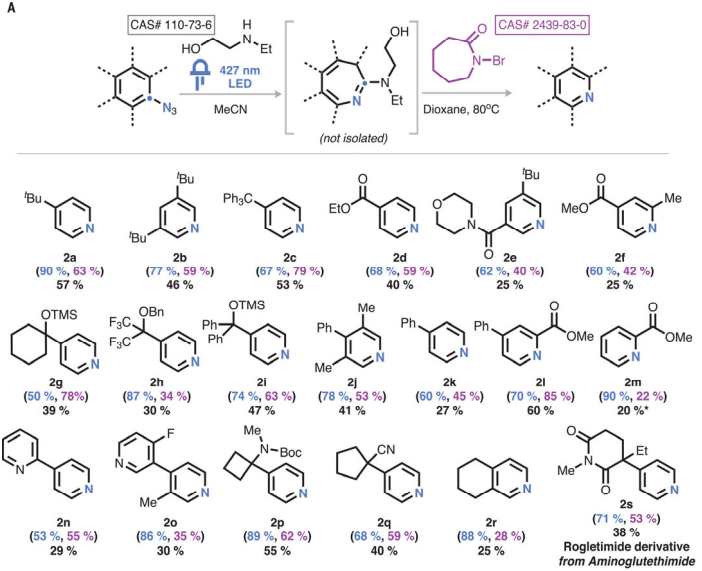

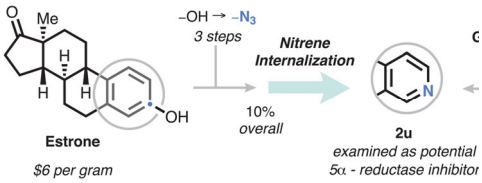

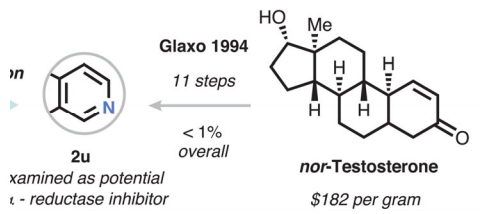

Mark D. Levin ,*Science*, **2023**, **381**, 1474-1479. DOI: 10.1126/science.adj5331

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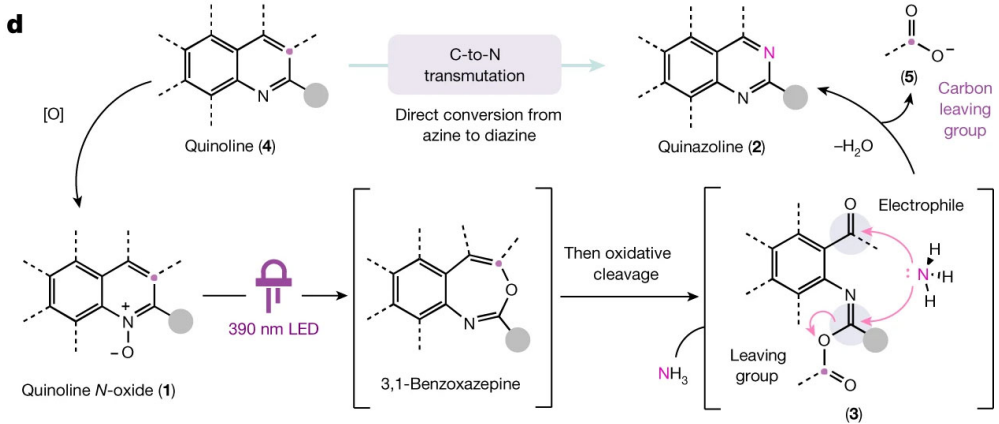

Mark D. Levin,*Nature*, **2023**, **623**, 77-82. DOI: 10.1038/s41586-023-06613-4

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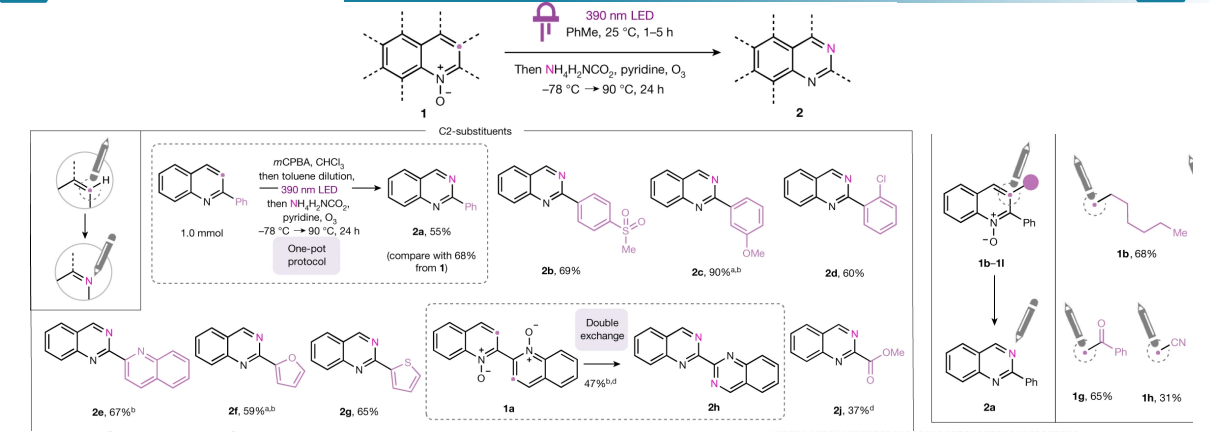
Atom Exchange



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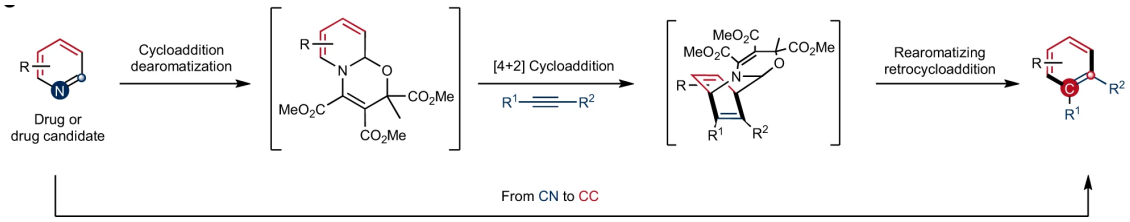
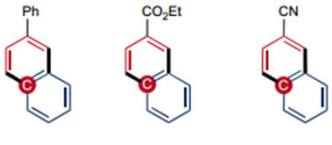
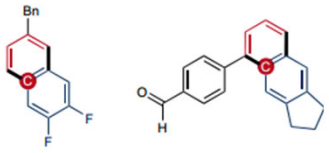


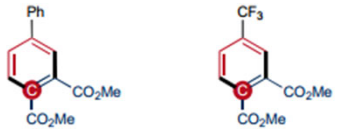
Scope of different oxazinopyridines with benzyne:



Scope of different oxazinopyridines with different arynes:



Scope of different oxazinopyridines with different alkynes:



Armido Studer,*Nat. Chem*. **16**, 741–748 (**2024**).https://doi.org/10.1038/s41557-023-01428-2

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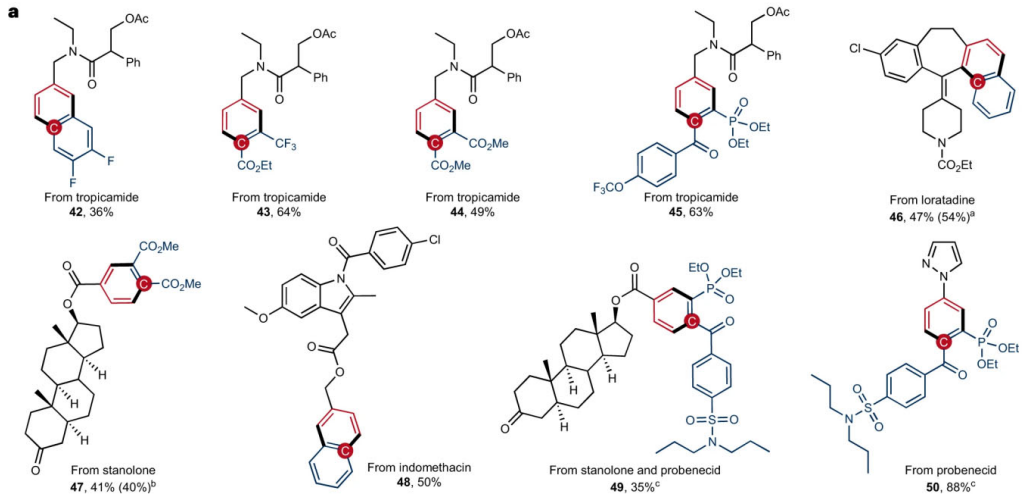
Atom Exchange



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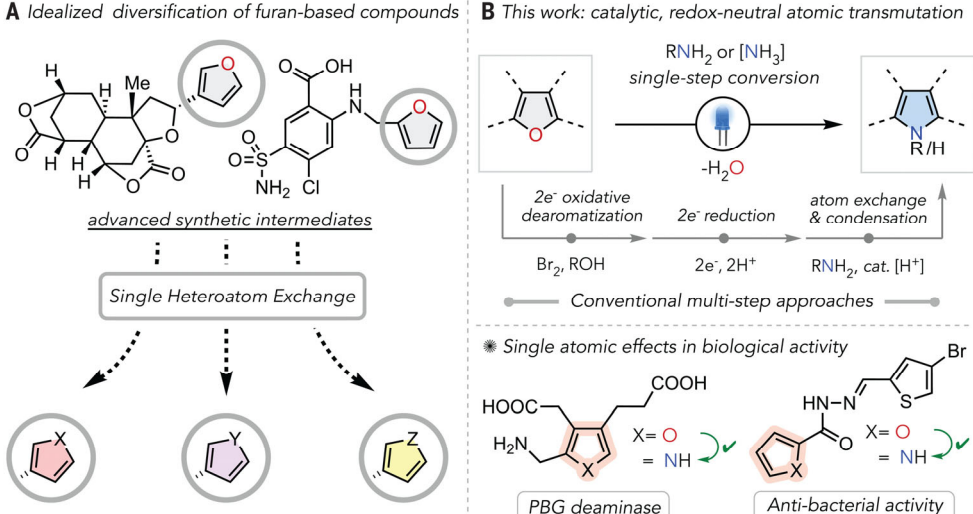

Yoonsu Park,*science***386**,99-105(**2024**).DOI:10.1126/science.adq6245

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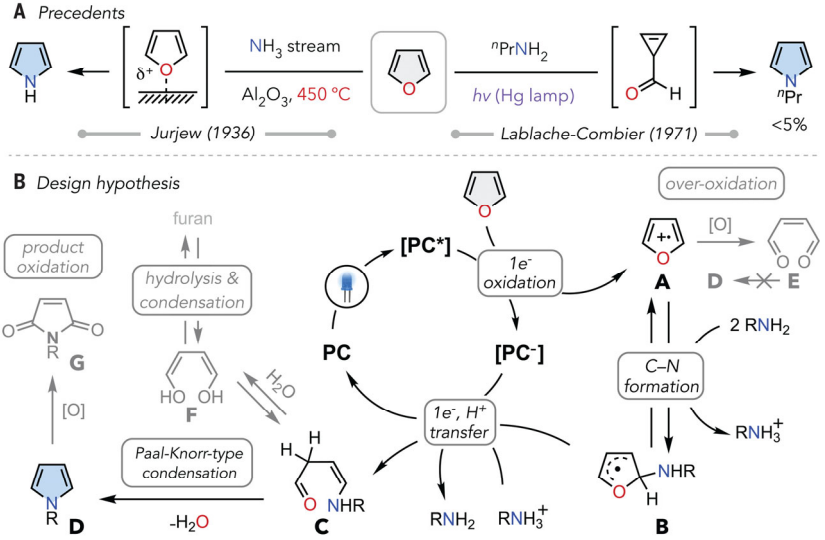
Atom Exchange



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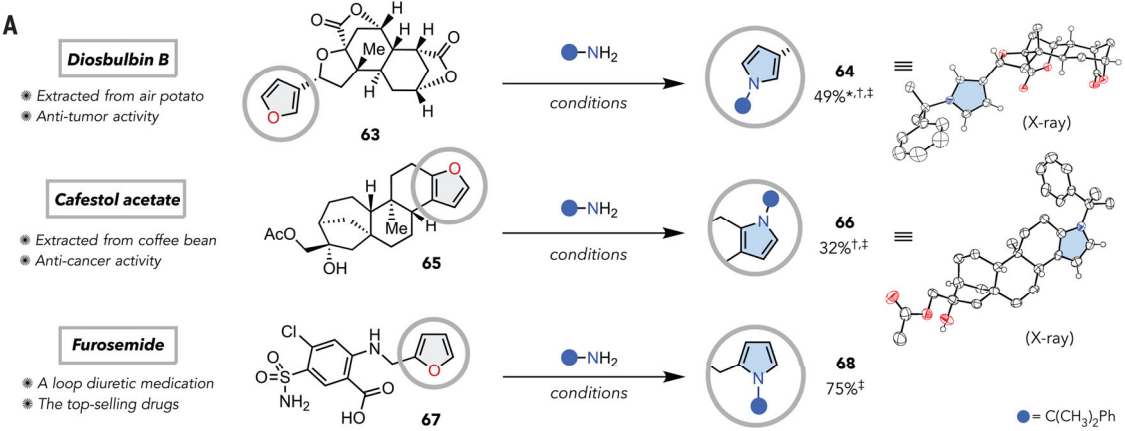

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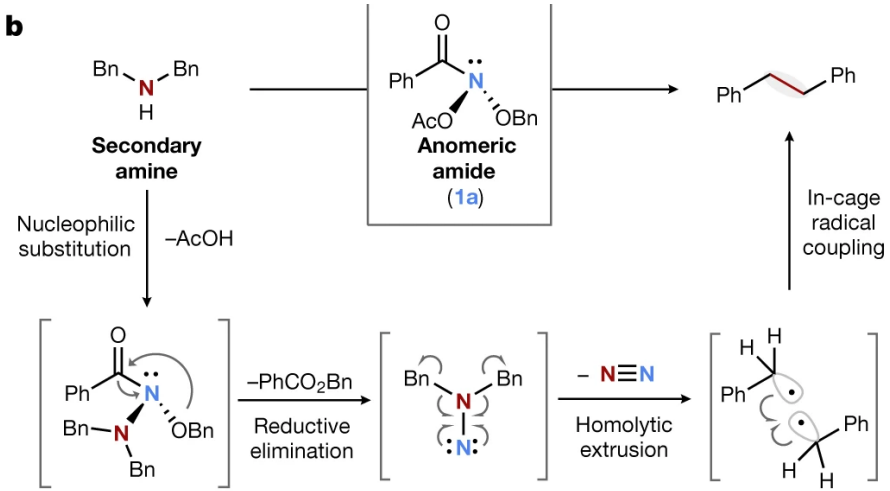
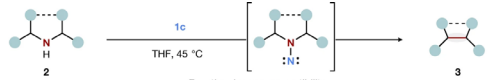
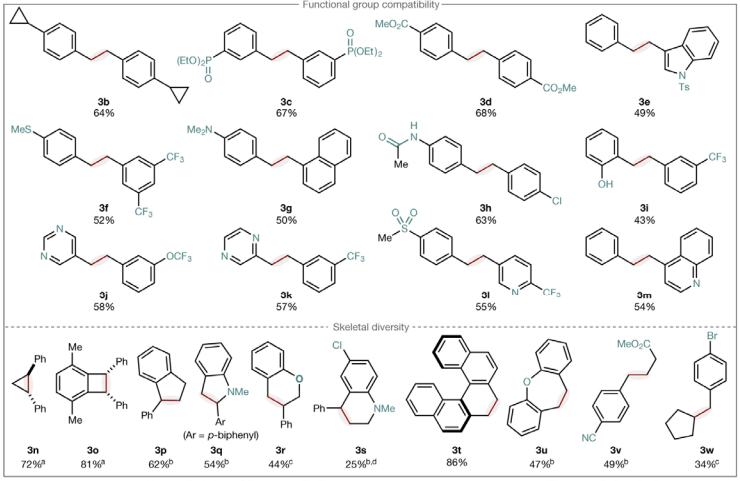
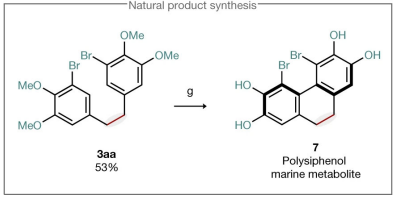


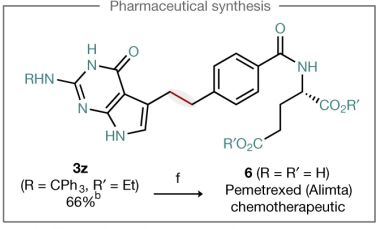
Mark D. Levin,*Nature* **593**, 223–227 (**2021**). https://doi.org/10.1038/s41586-021-03448-9

Others









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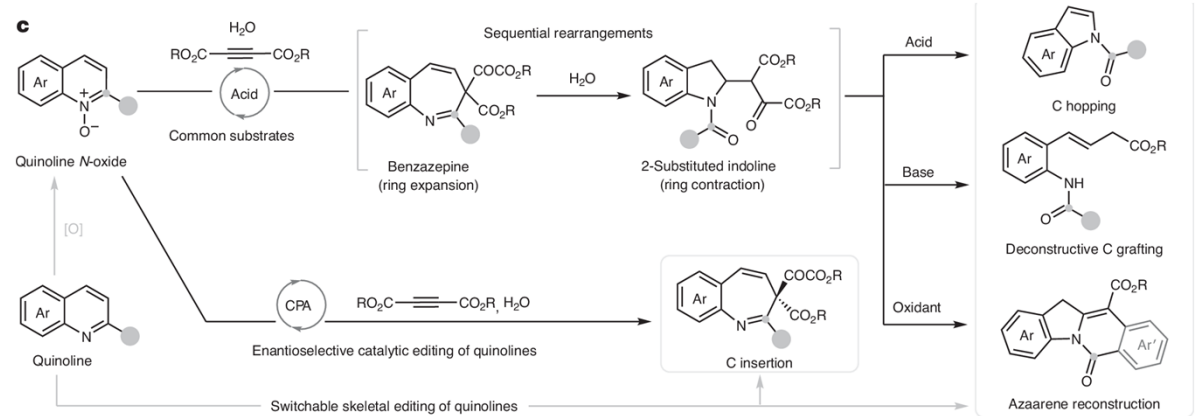

Hua Wu,*Nat. Chem*. (**2025**). https://doi.org/10.1038/s41557-025-01793-0

3 骨架编辑

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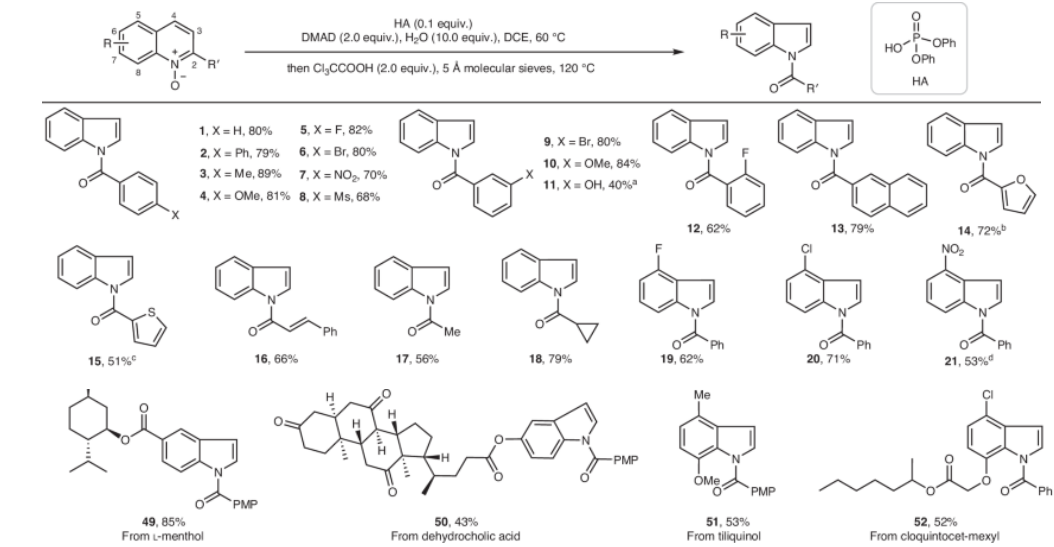

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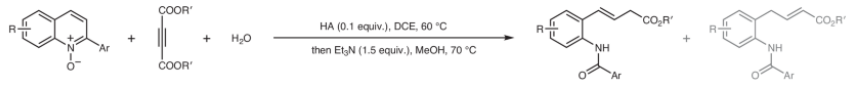

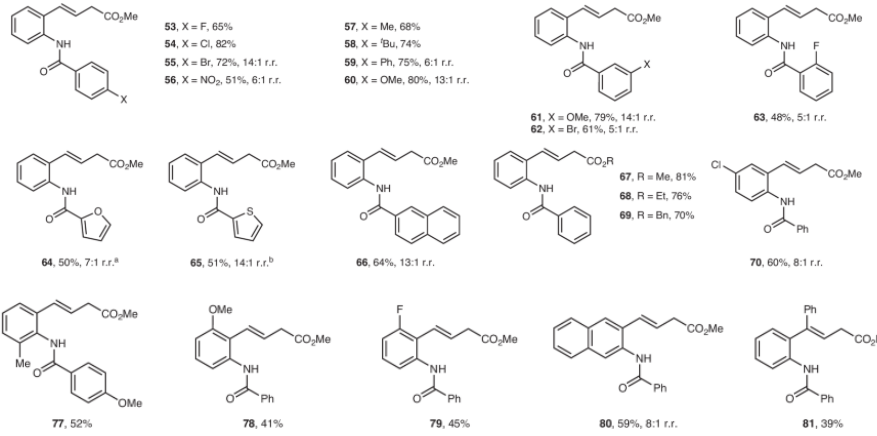

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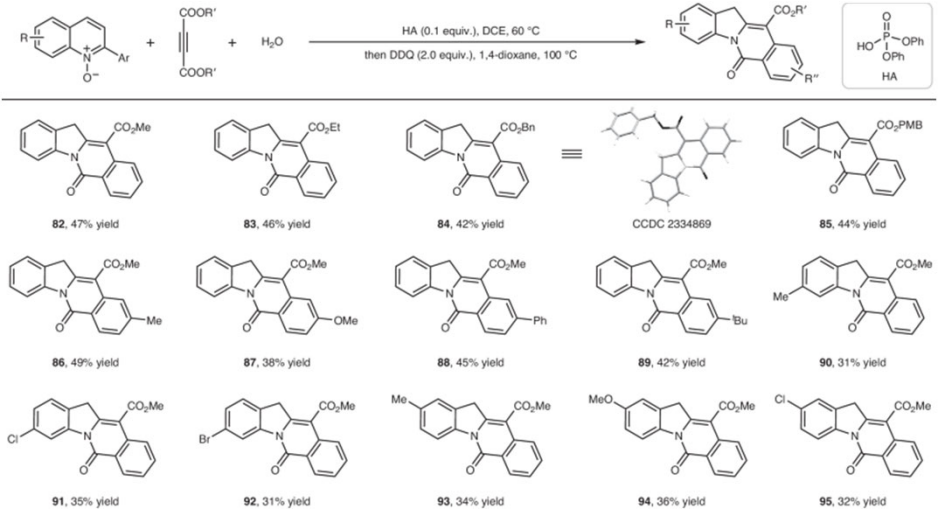

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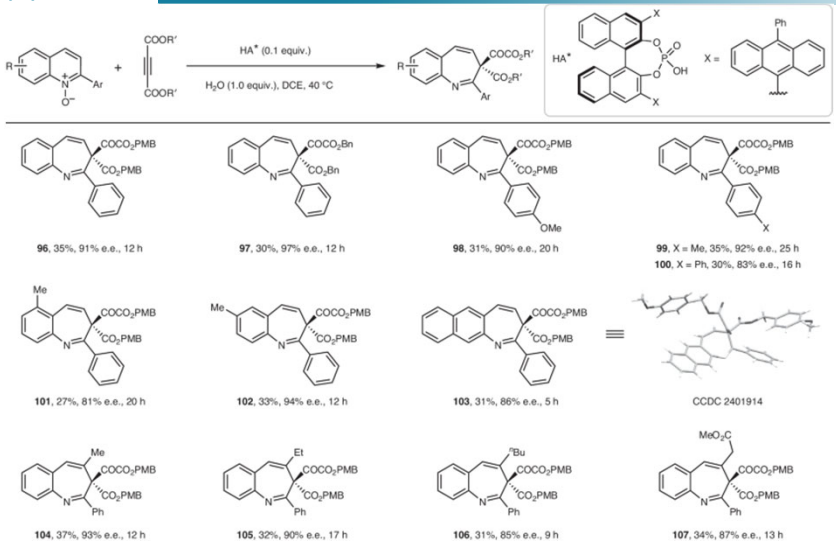

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Thanks for listening

汇报人：王宁