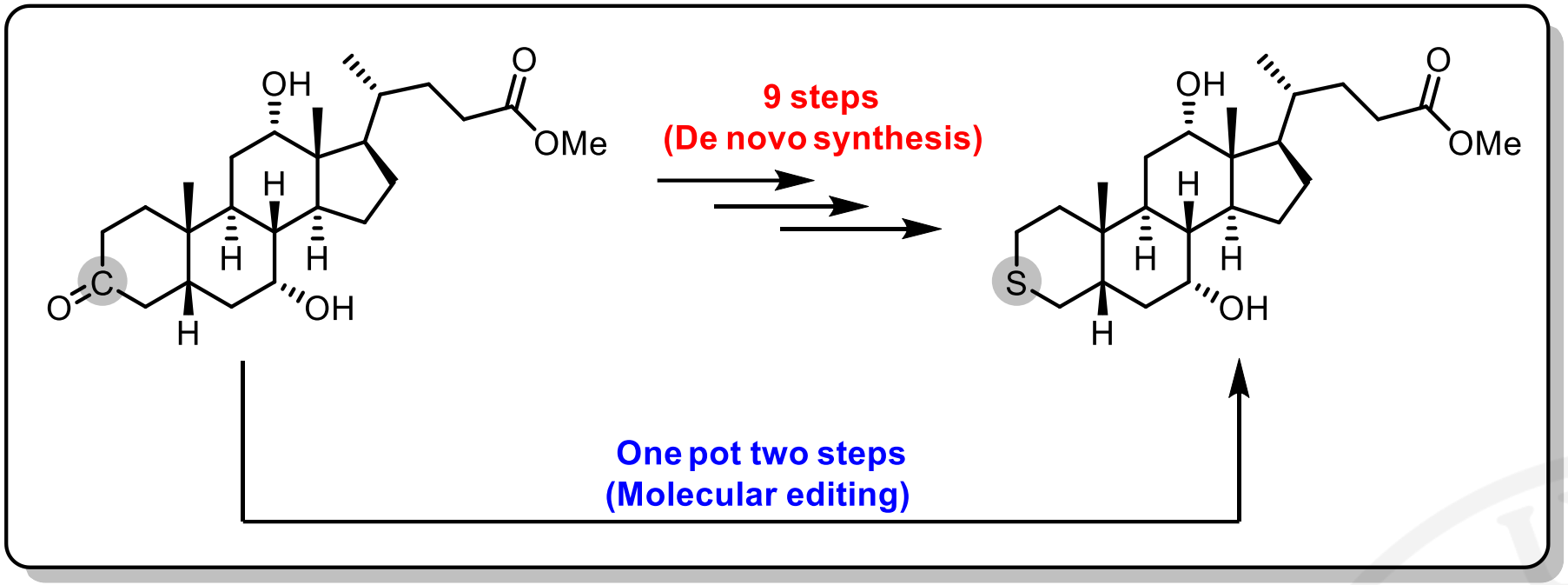
Recent Advances in Skeletal Editing Invoving Nitrogen Atoms

Reporter: Zheng Zhang

Shi Group
Faculty of Chemistry, Fudan University

CONTENTS

Background



De novo synthesis vs. Molecular editing

De novo synthesis

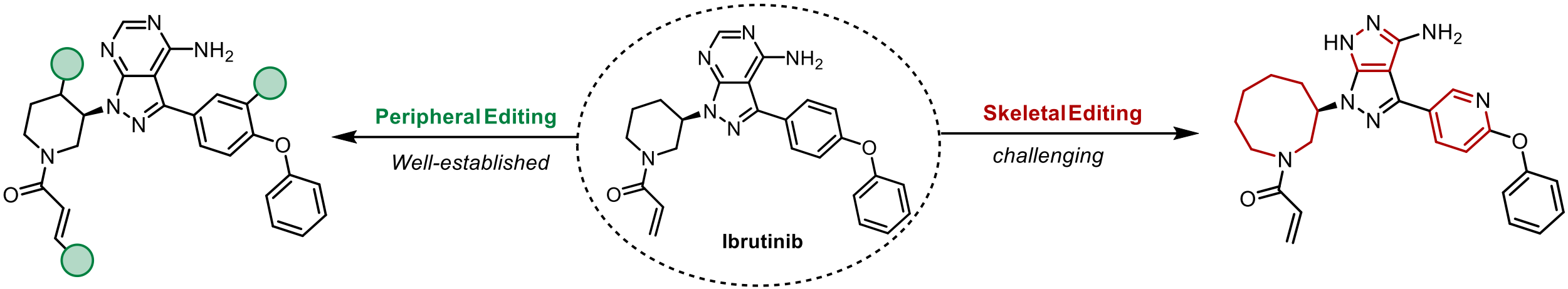
- Long history
- Low efficiency
- Long synthetic procedures

Molecular editing

- New method
- High efficiency
- Short synthetic procedures

G. Dong et al. *Science* **2025**, *388*, 1436-1440

Background

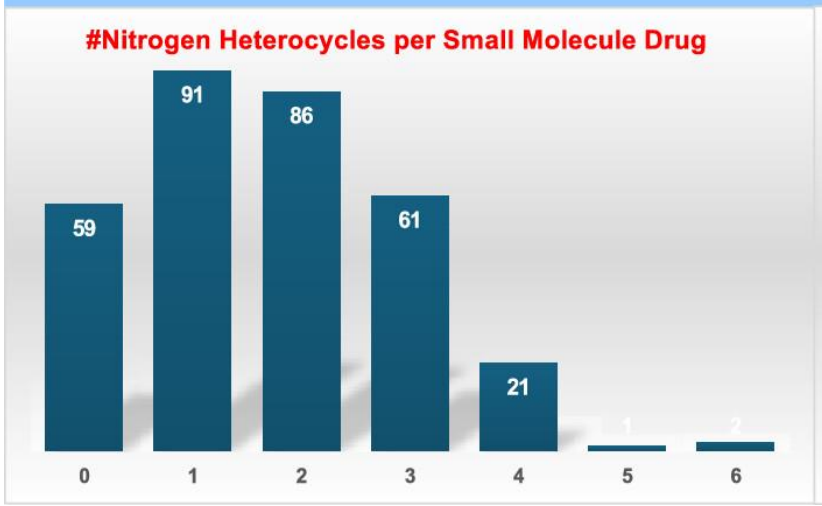


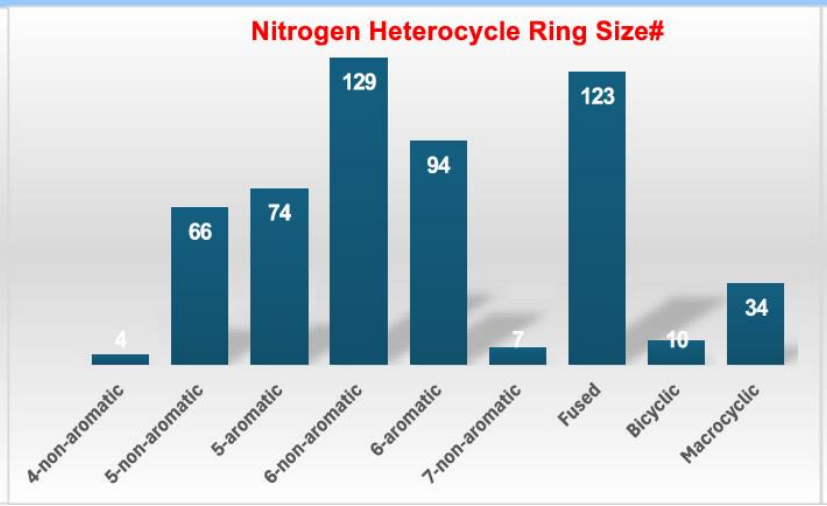
January 2013 - December 2023
U.S. FDA approved

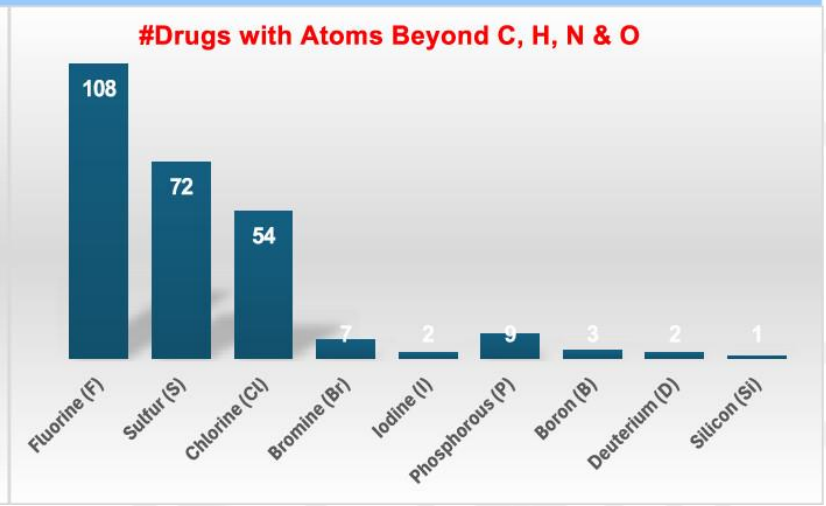
320 Unique New Small Molecule Drugs
(36 are part of combination drugs = 11%)

82% contain a Nitrogen Heterocycle
53% contain multiple Nitrogen heterocycles

34% contain a fluorine (F) substituent
23% contain a sulfur (S) subsituent
17% contain a chlorine (Cl) atom

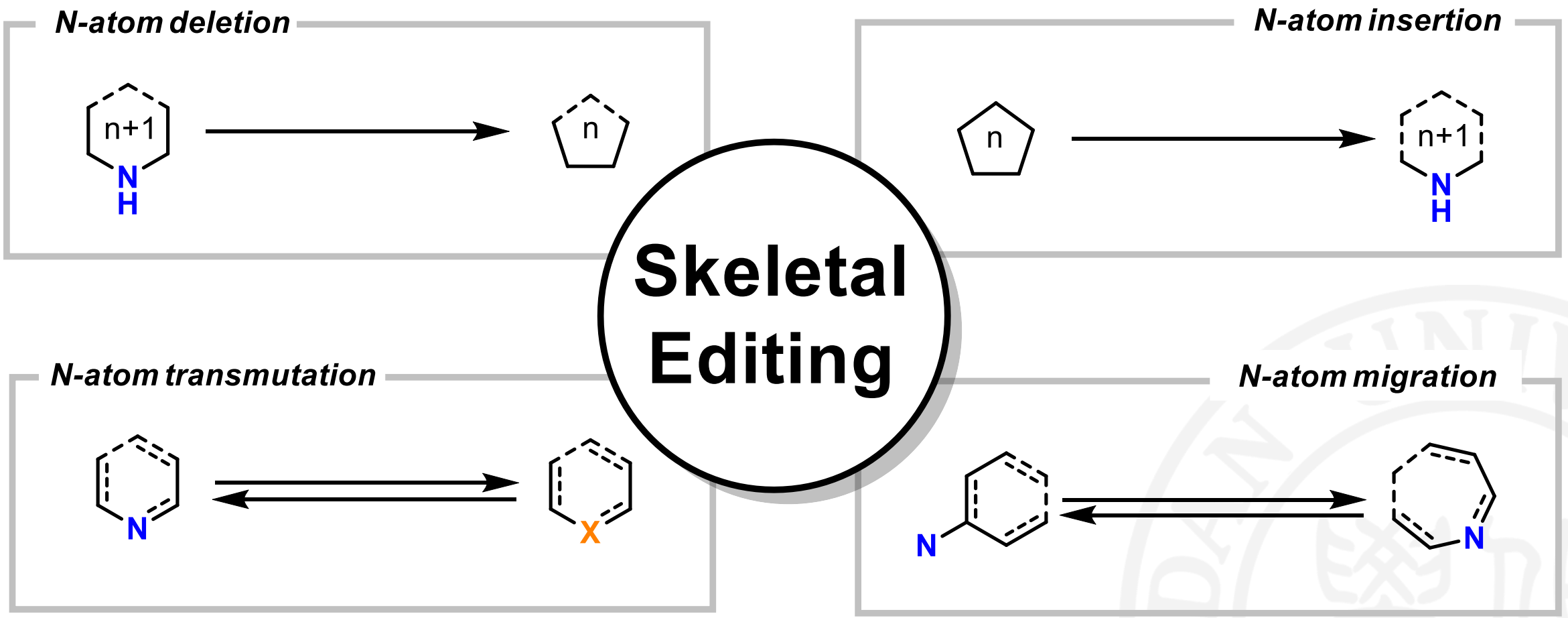


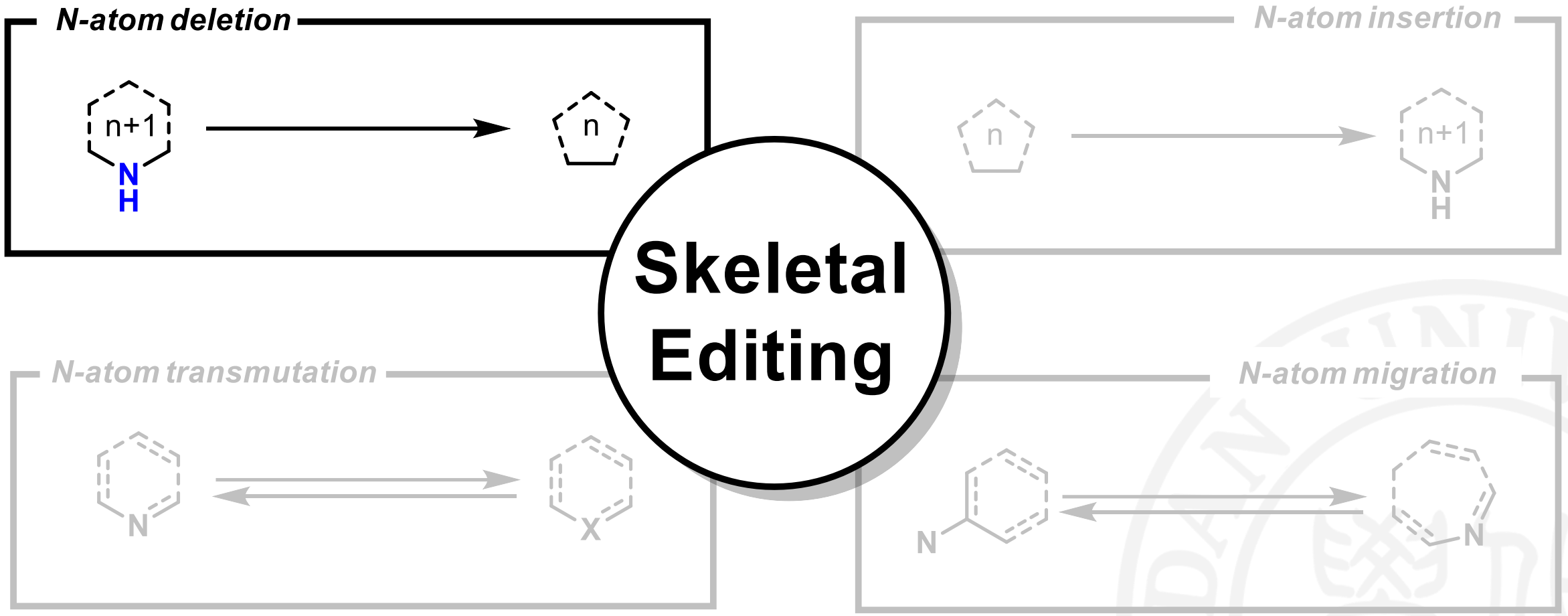




A. M. Rabie, *Mini. Rev. Med. Chem.*, **2025**, *25*, 190 –195

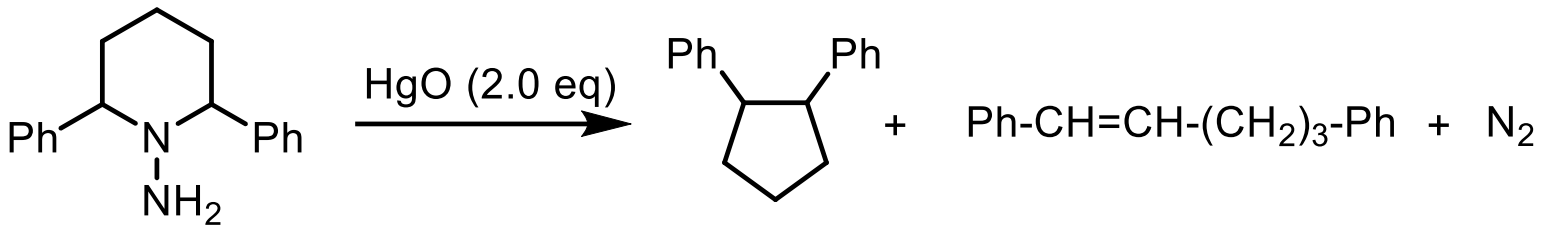
Categrories of skeletal editing involving N atom



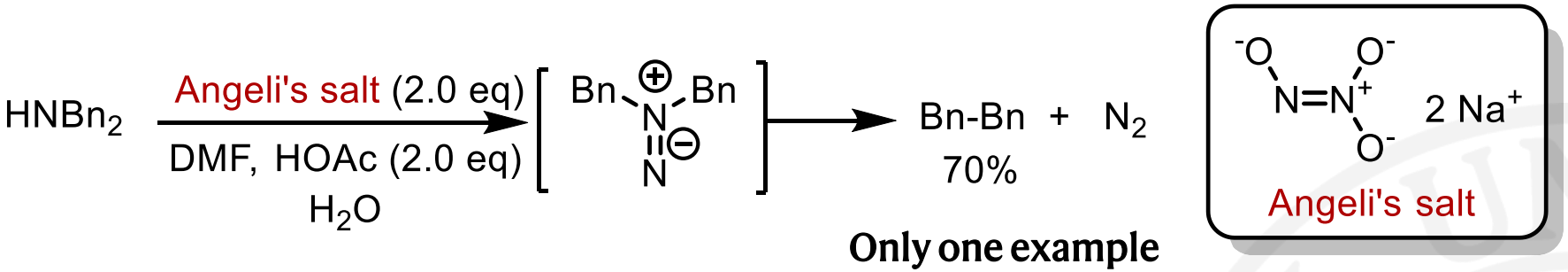

N-atom deletion
n+1
N
H
n
N-atom insertion
n
n+1
N
H
Skeletal Editing
N-atom transmutation
N
X
N-atom migration
N
N

N-atom deletion

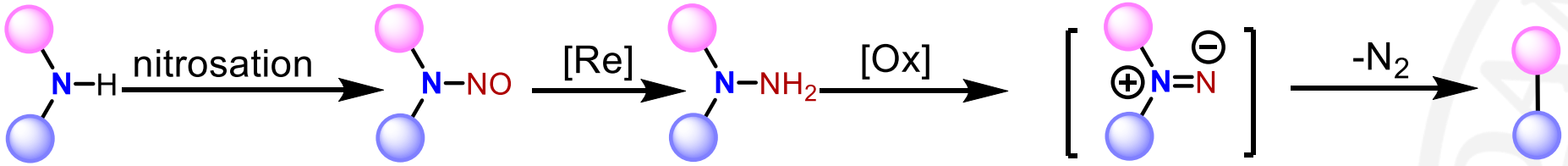
1957 Overberger



1961 Lemal



Only one example



isodiazene
or 1,1-diazene

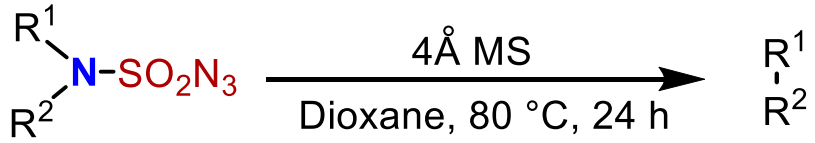
- Limited scale
- Poisonous reagent
- Harsh conditions

G. Overberger et al. *J. Am. Chem. Soc.*, **1957**, *79*, 6430 –6435

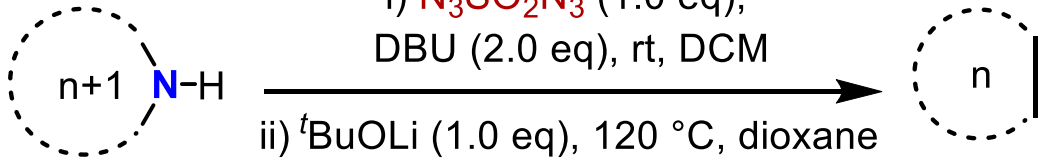
M. Lemal et al. *J. Am. Chem. Soc.*, **1961**, *87*, 393 –394

N-atom deletion

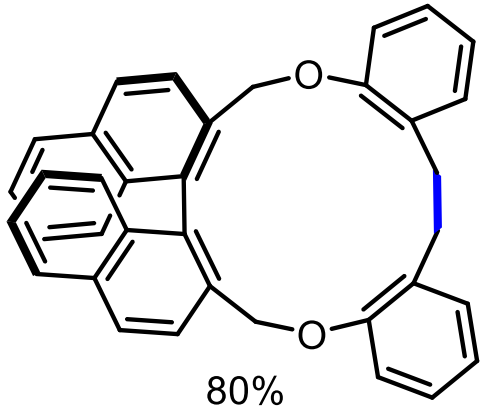
2017 Lu



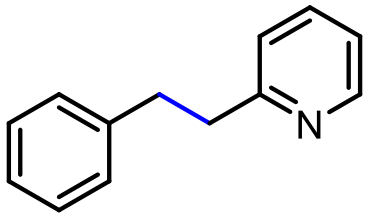
2021 Lu



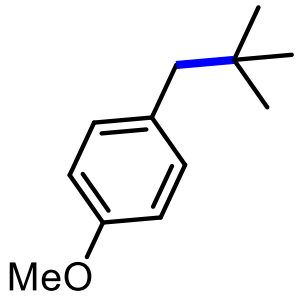
Selectedexamples



80%

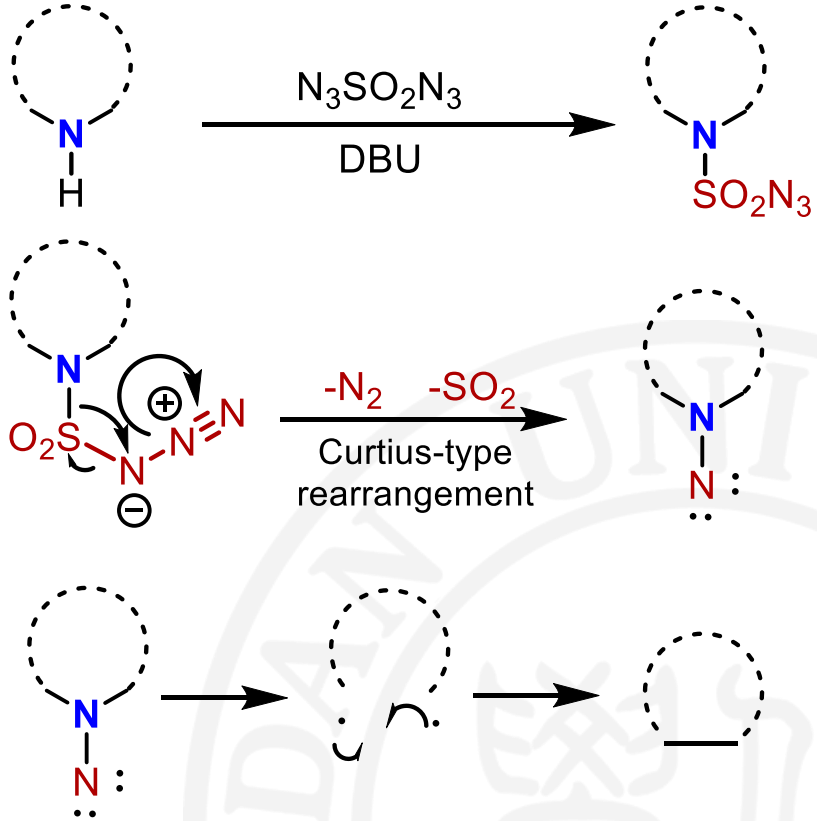


76%



55%

Mechanism

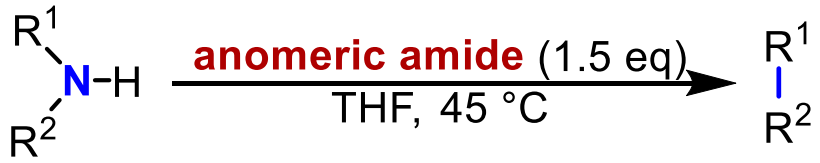


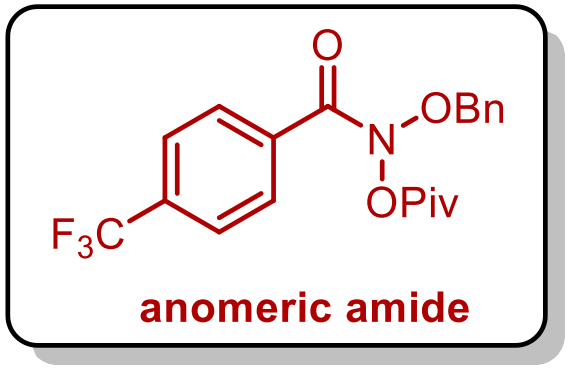
H. Lu et al. *J. Org. Chem.*, **2017**, *82*, 4677 −4688

H. Lu et al. *Angew. Chem. Int. Ed.*, **2021**, *60*, 20678 −20683

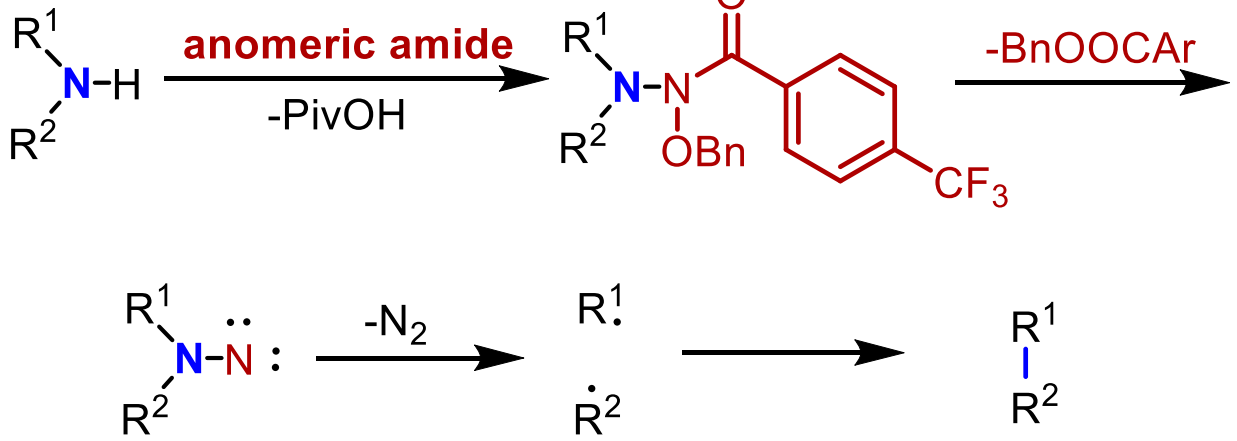
N-atom deletion

2021 Levin

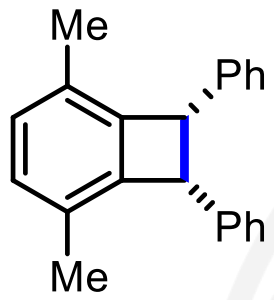




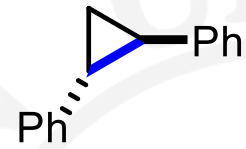
Mechanism



Selectedexamples



81%

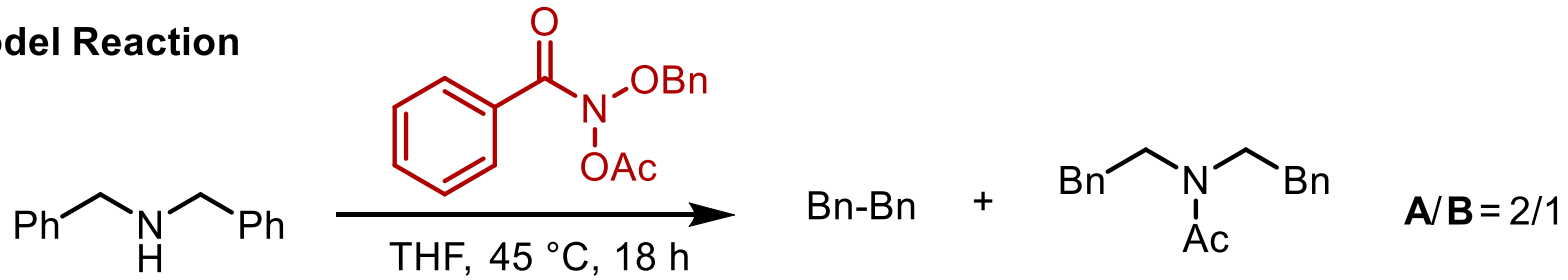


72%

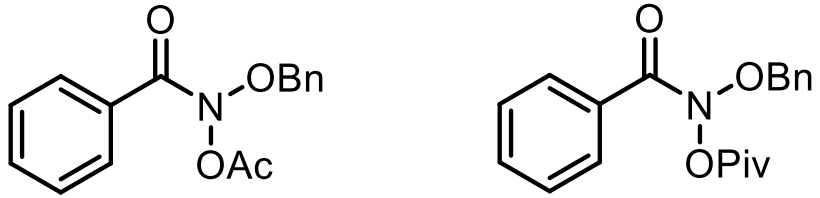
M. Levin et al. *Nature,* **2021**, *593* , 223 −227

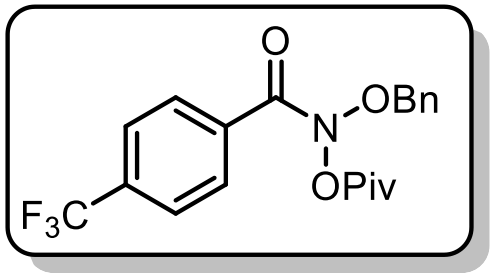
N-atom deletion

Model Reaction

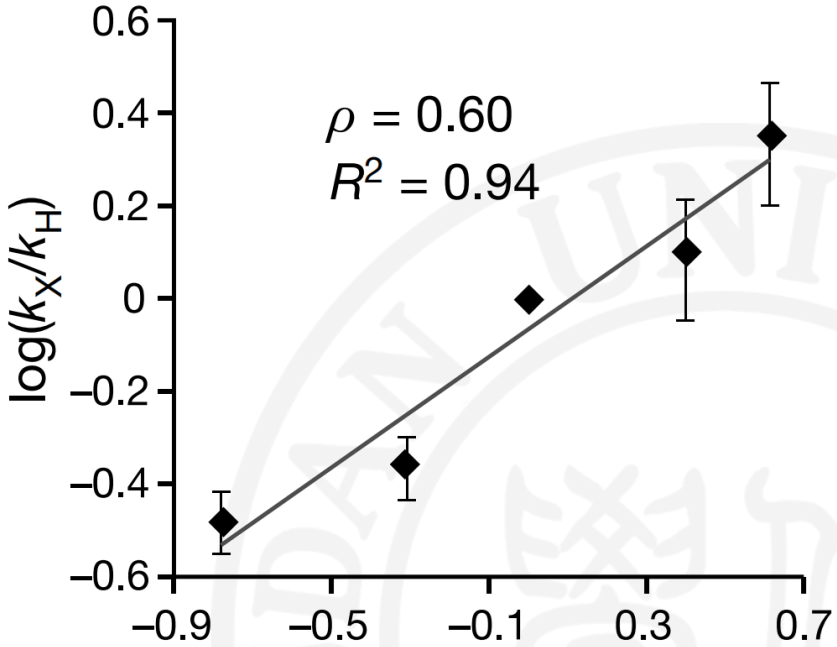


Optimizations





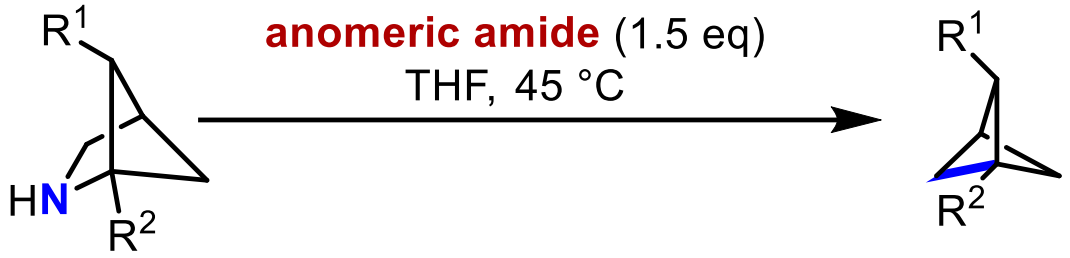
Best selectivity (**A**/**B** analogue > 20/1)
Highest yield (74%)
Shortest time (5 h)

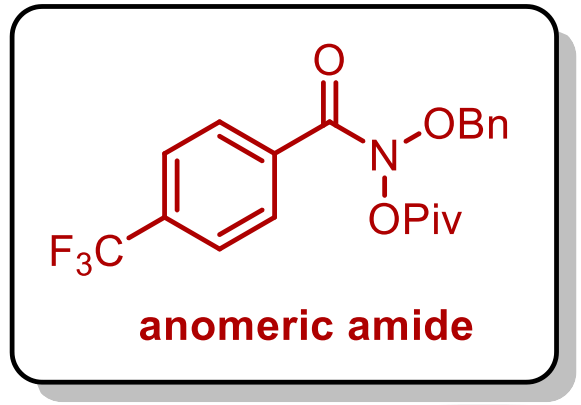


M. Levin et al. *Nature,* **2021**, *593* , 223 −227

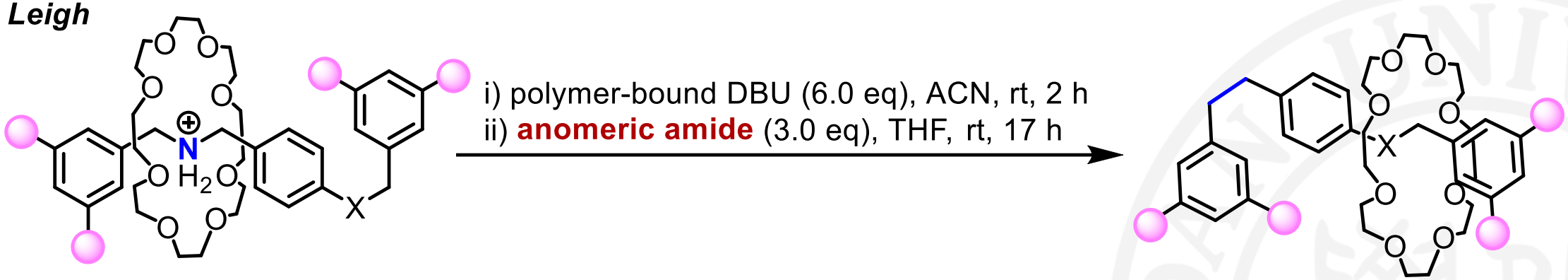
N-atom deletion

2023 Sarpong





2024 Leigh

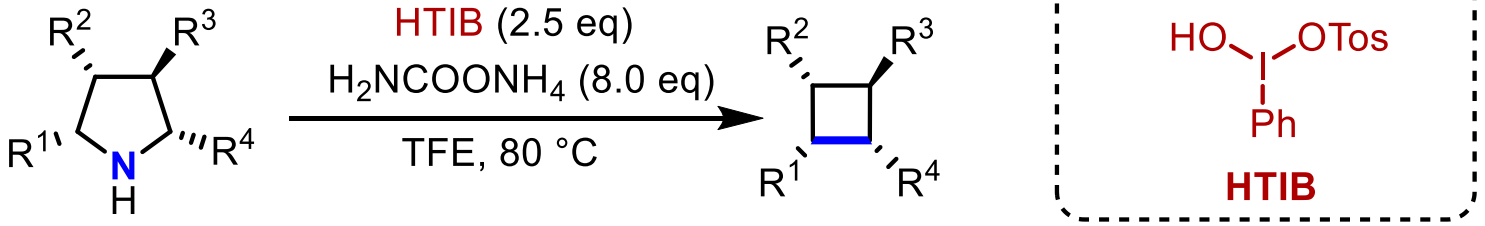


R. Sarpong et al. *J. Am. Chem. Soc.*, **2023**, *145* , 10960 −10966

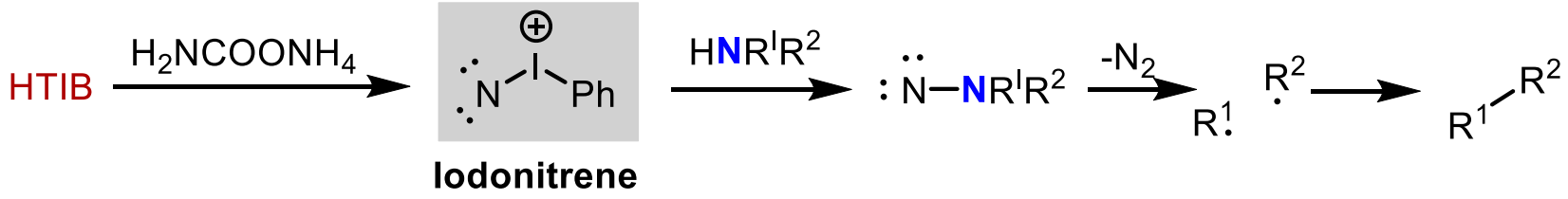
D. Leigh et al. *J. Am. Chem. Soc.*, **2024**, *146* , 29496 −29502

N-atom deletion

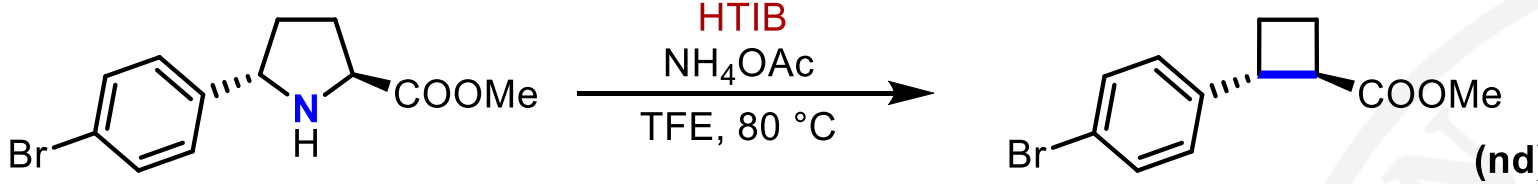
2021 Antonchick



Mechanism

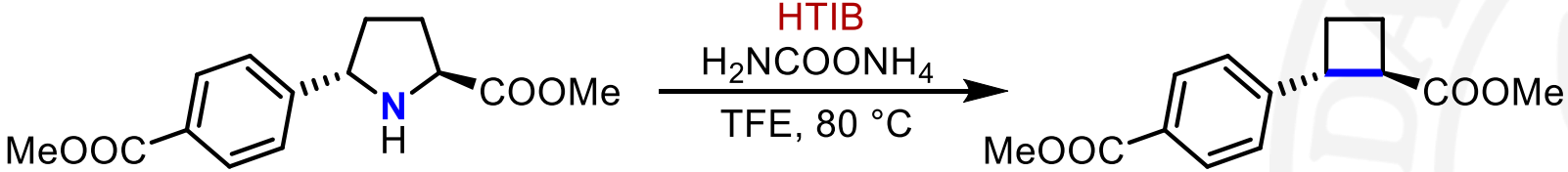


Iodonitrene



(nd)

Selectedexample



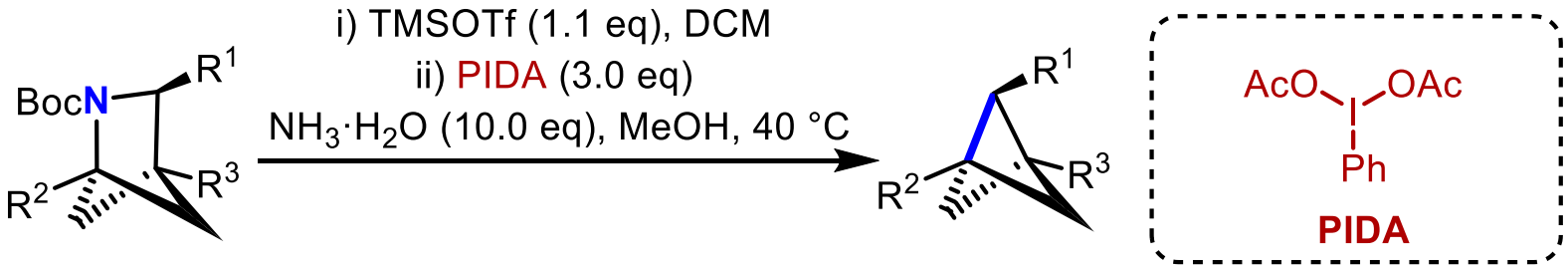
>99% ee, >20:1 *dr*

24% yield, >99% ee, >20:1 *dr*

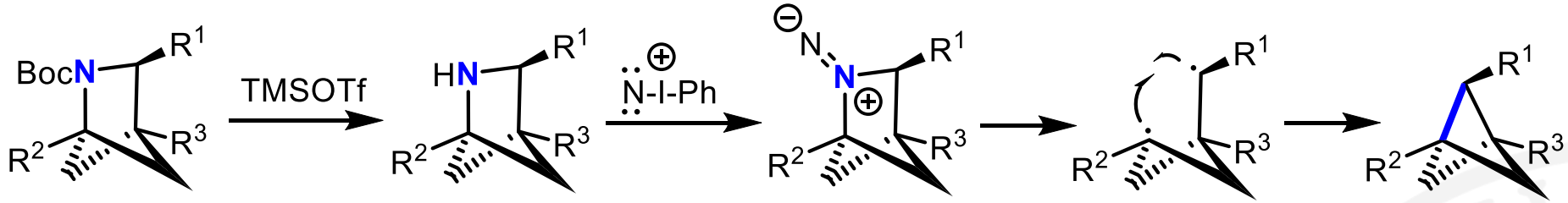
A. Antonchick et al. *J. Am. Chem. Soc.*, **2021**, *143*, 18864 –18870

N-atom deletion

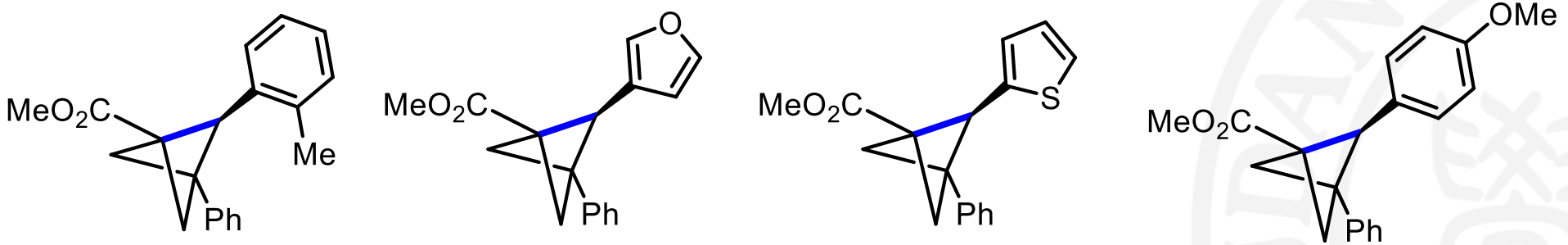
2025 Tan



Mechanism



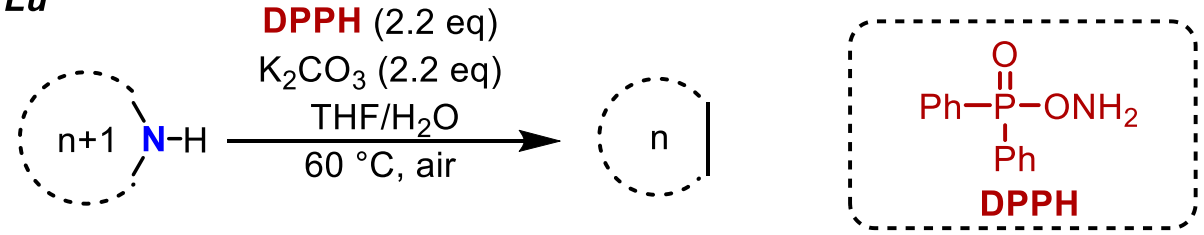
Selectedexamples



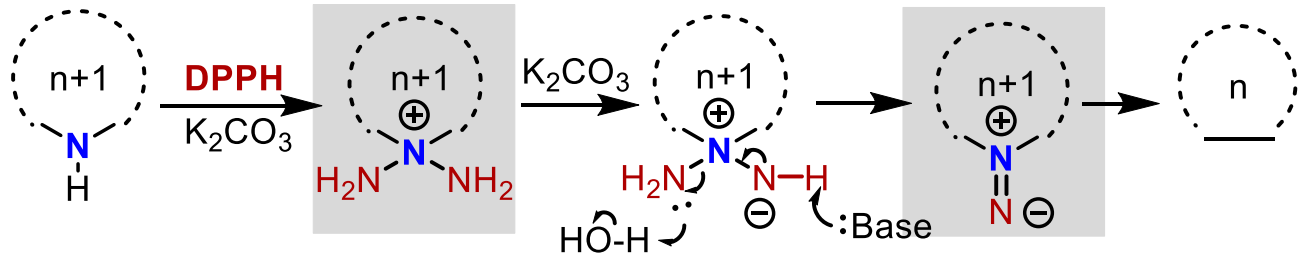
B. Tan et al. *Nat. Chem.*, **2025**, *17*, 393 –402

N-atom deletion

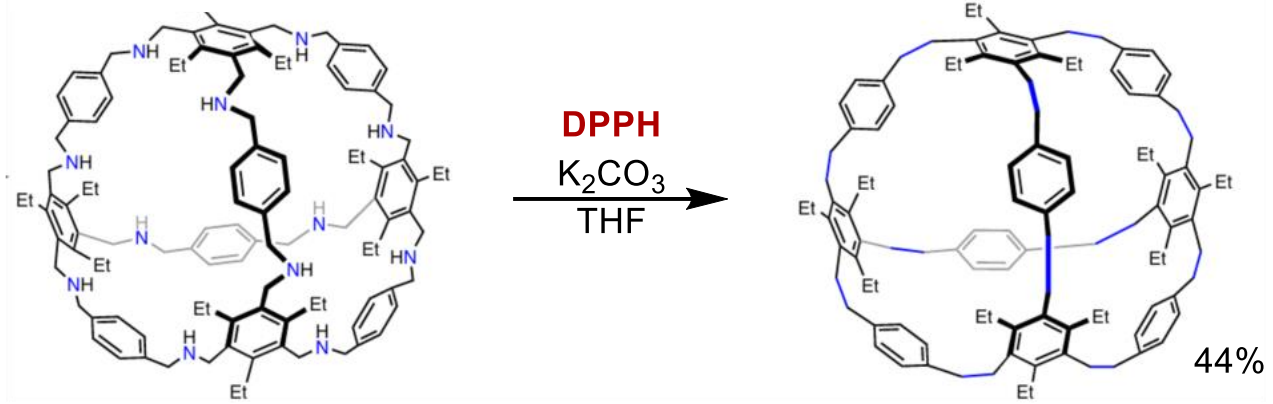
2024 Lu



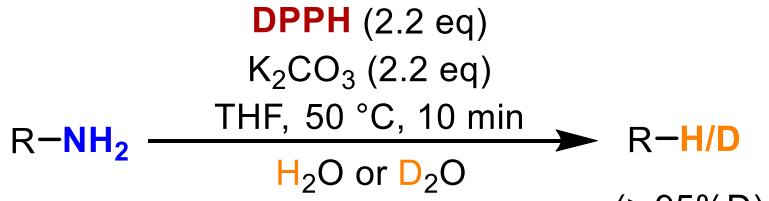
Mechanism



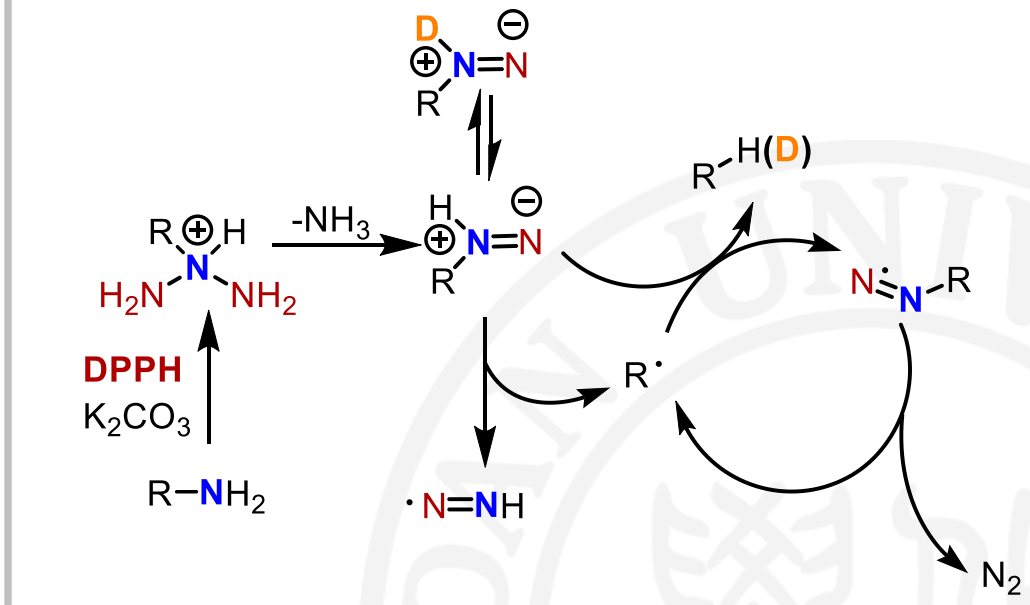
Selectedexamples



2024 Lu



Mechanism

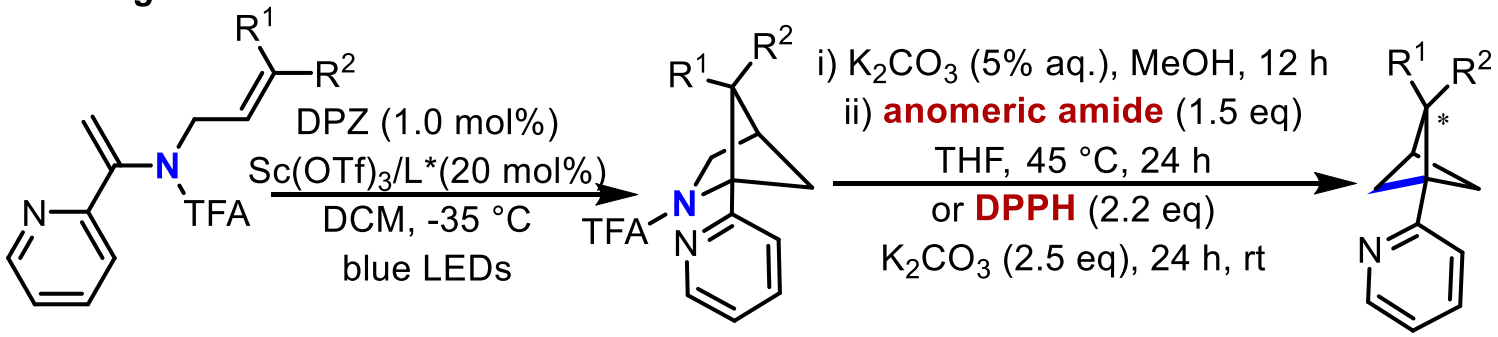


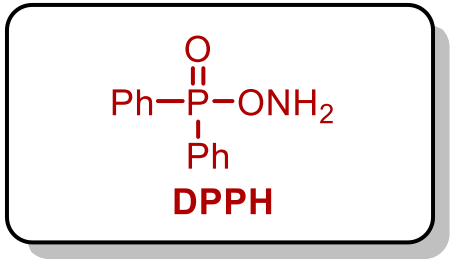
H. Lu et al. *Nat. Synth.*, **2024**, *3*, 913 –921

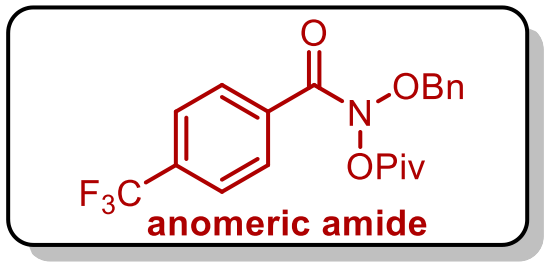
H. Lu et al. *Nat. Commun.* **2024**, *15*, 10190

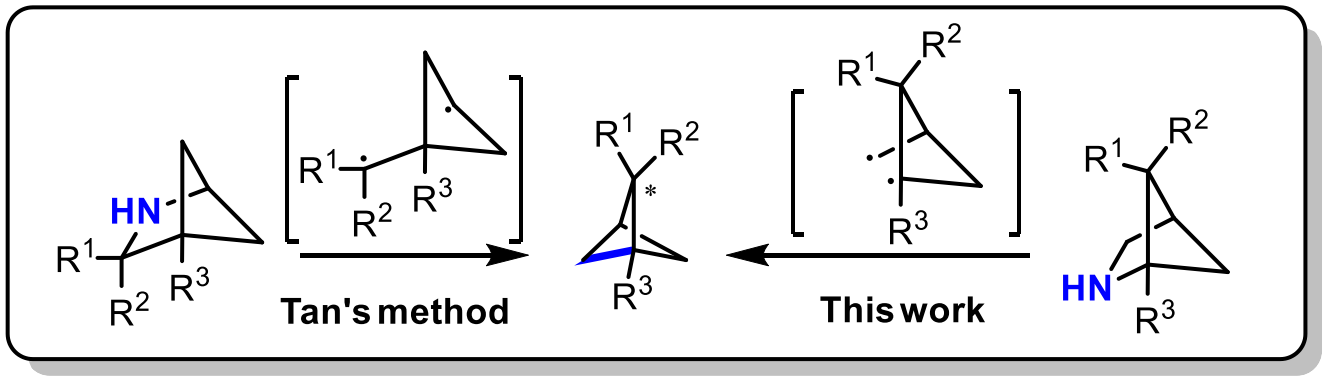
N-atom deletion

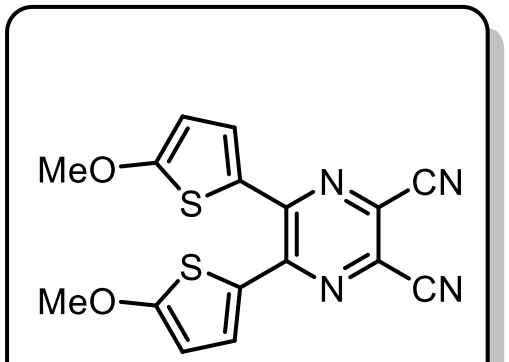
2025 Jiang

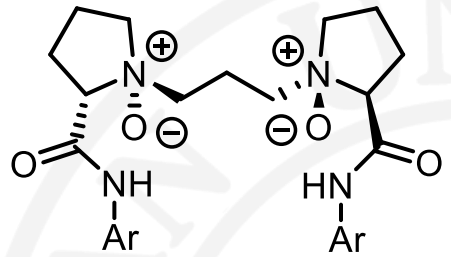








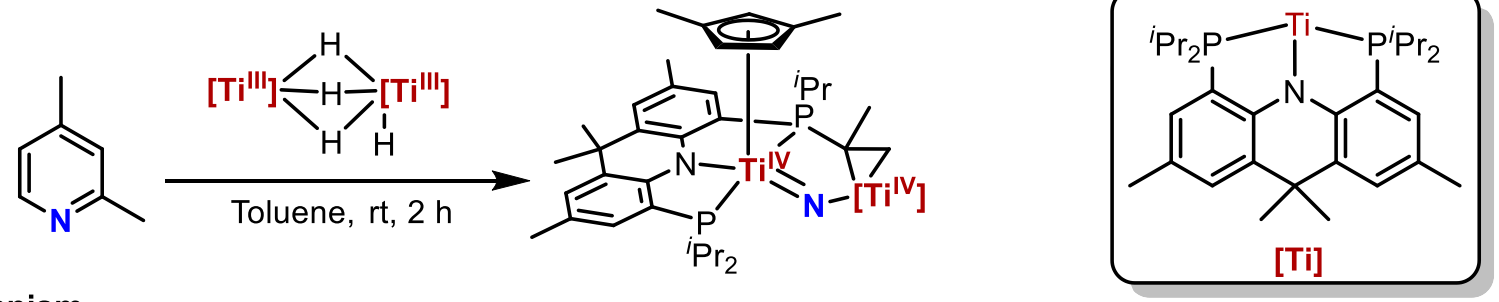




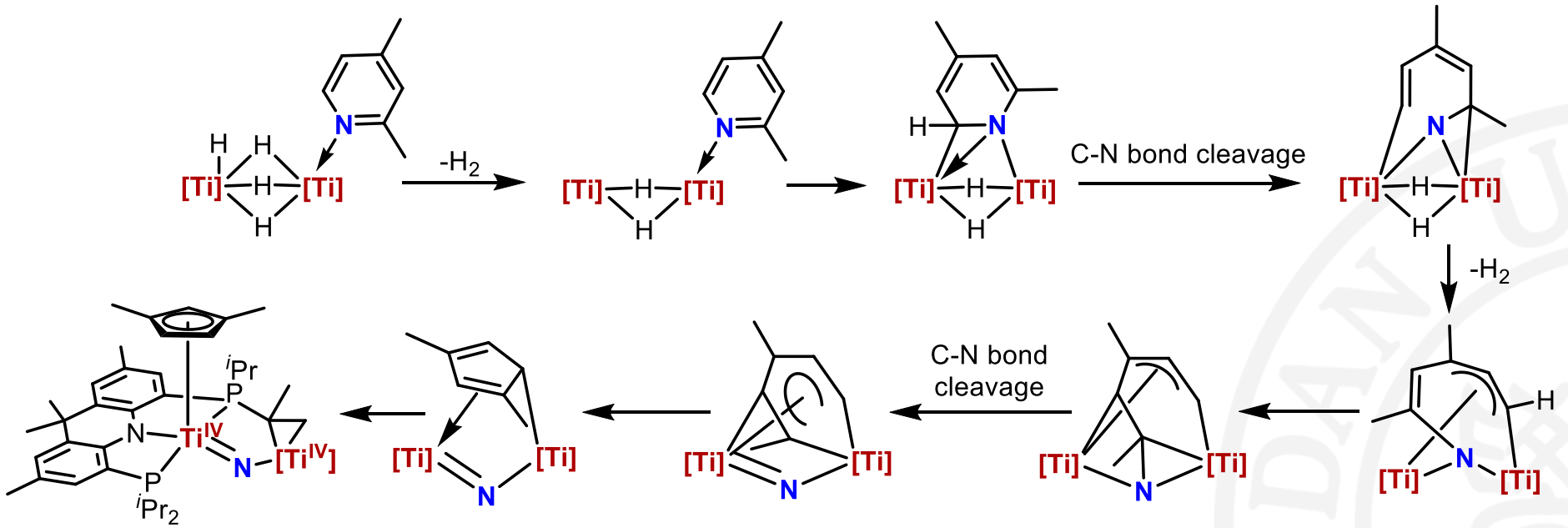
Z. Jiang et al. *J. Am. Chem. Soc.*, **2025**, *15*, 12410 −12417

N-atom deletion

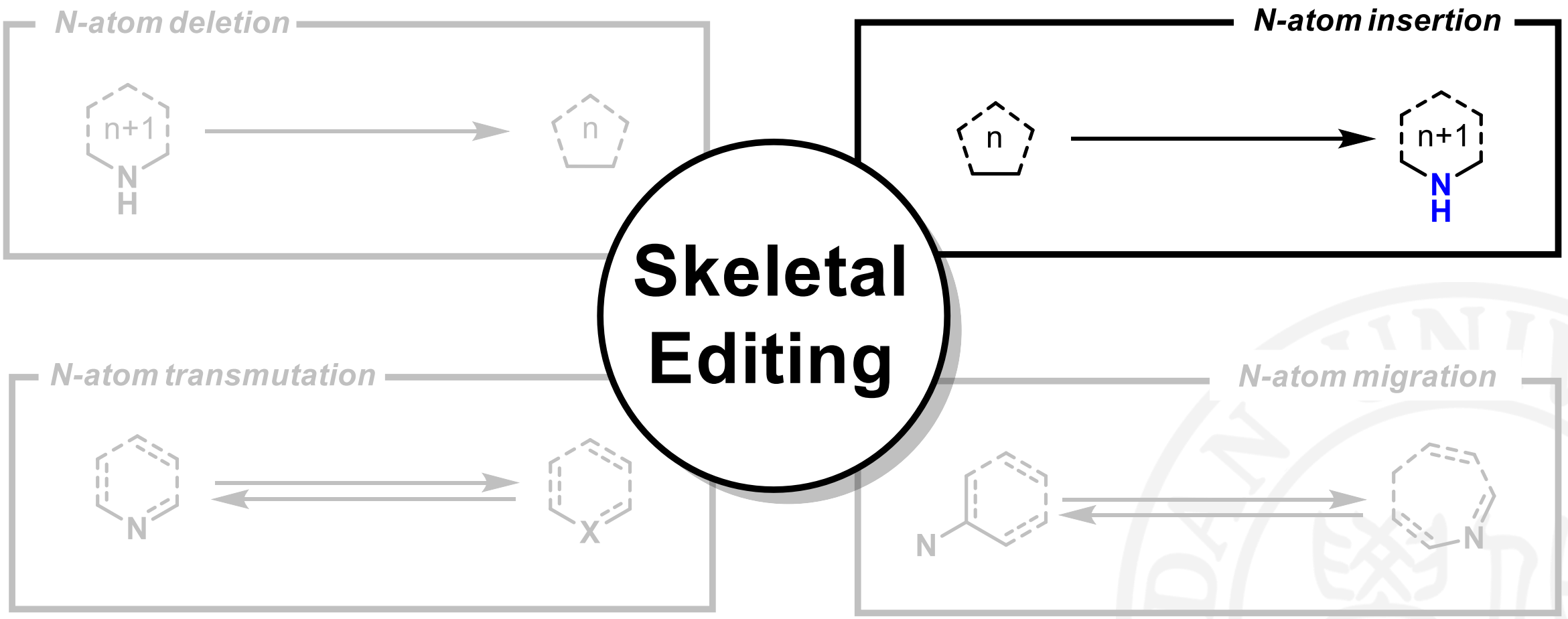
2024 Hou



Mechanism

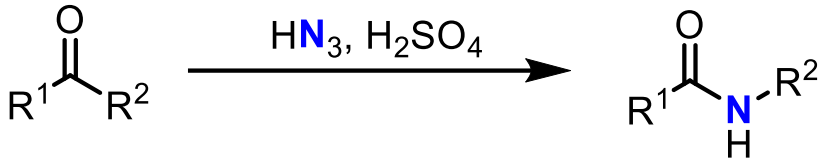


Z. Hou et al. *J. Am. Chem. Soc.*, **2024**, *146* , 31348 −31355


N-atom deletion
n+1
N
H
n
N-atom insertion
n
n+1
N
H
Skeletal Editing
N-atom transmutation
N
X
N-atom migration
N
N

N-atom insertion

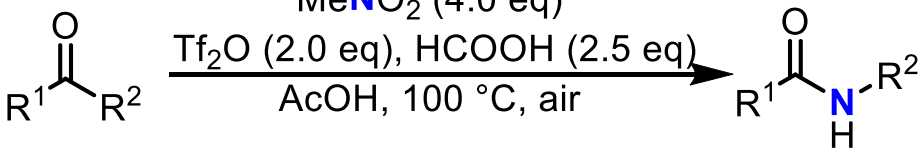
1923 Schmidt Known as "***Schmidtrearrangement***"



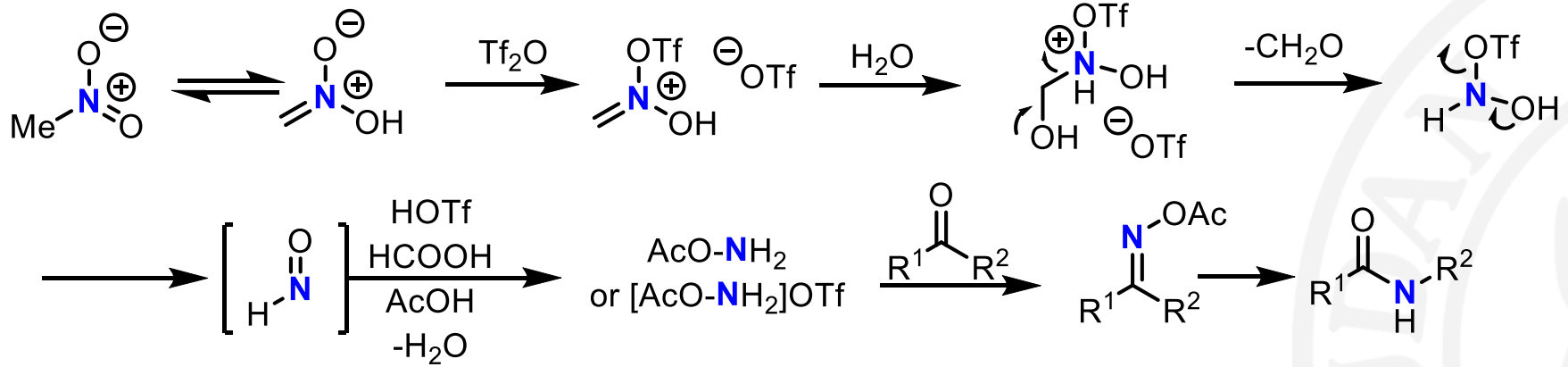
Drawbacks

- **Toxic nitrogen source**
- **Hard to reserve**

2020 Jiao



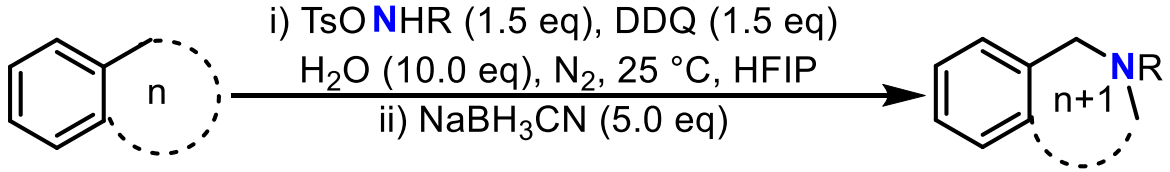
Mechanism



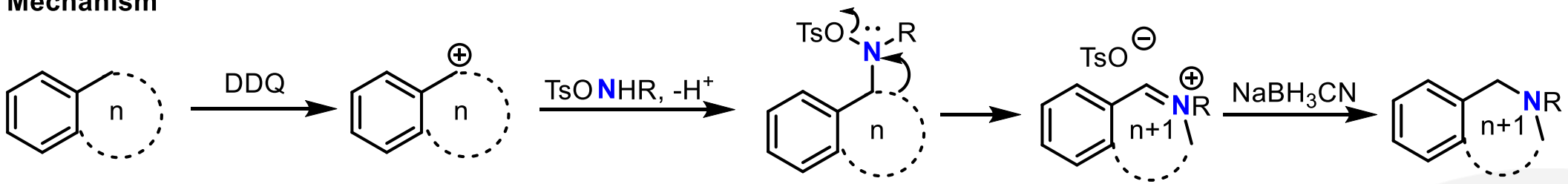
N. Jiao et al. *Science*, **2020**, *367*, 281 –285

N-atom insertion

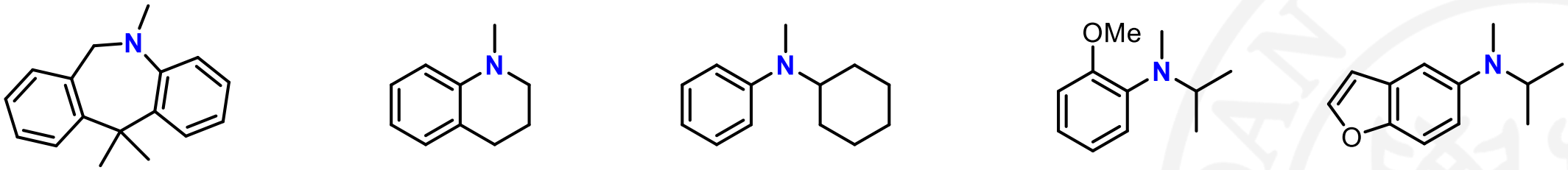
2024 Jiao



Mechanism



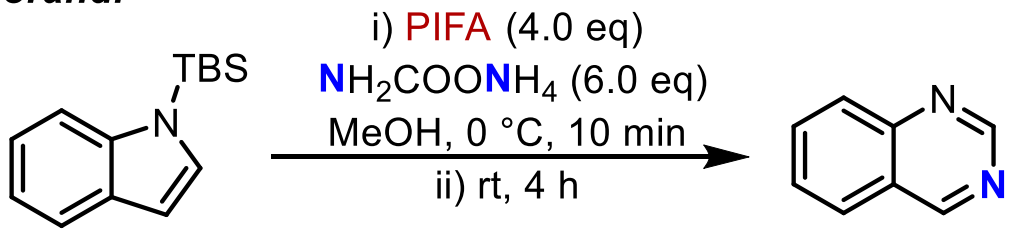
Selectedexample

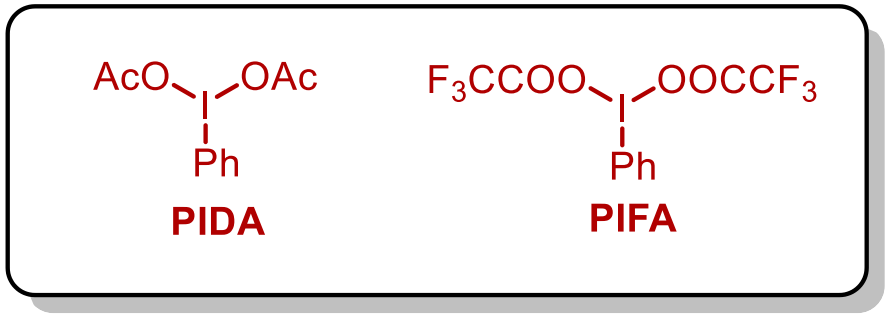


N. Jiao et al. *Nat. Commun.*, **2024**, *15* , 6016

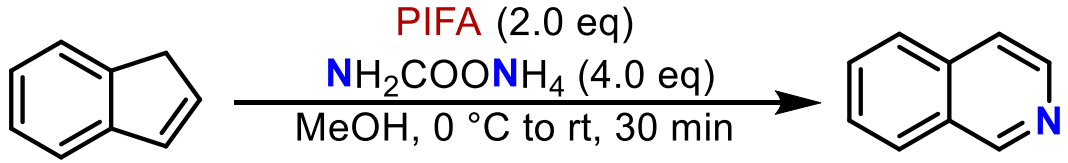
N-atom insertion

2022 Morandi

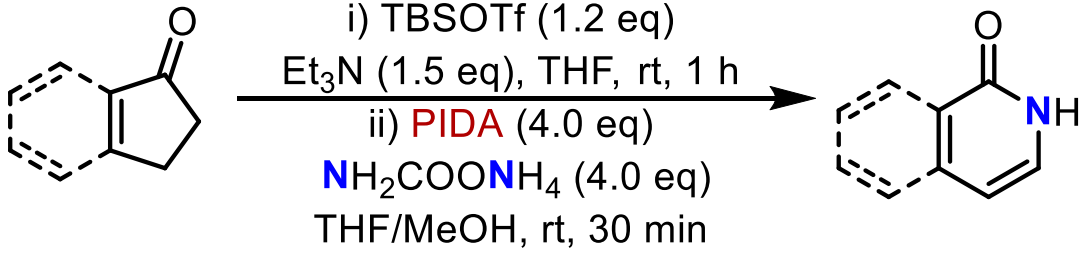


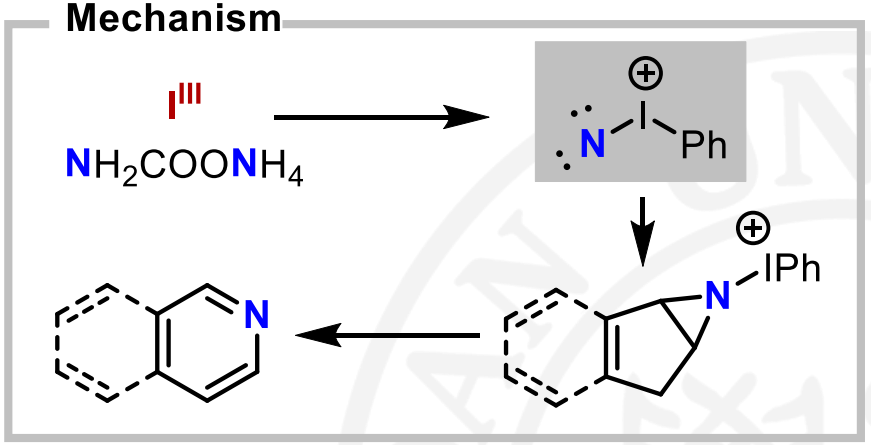


2023 Morandi



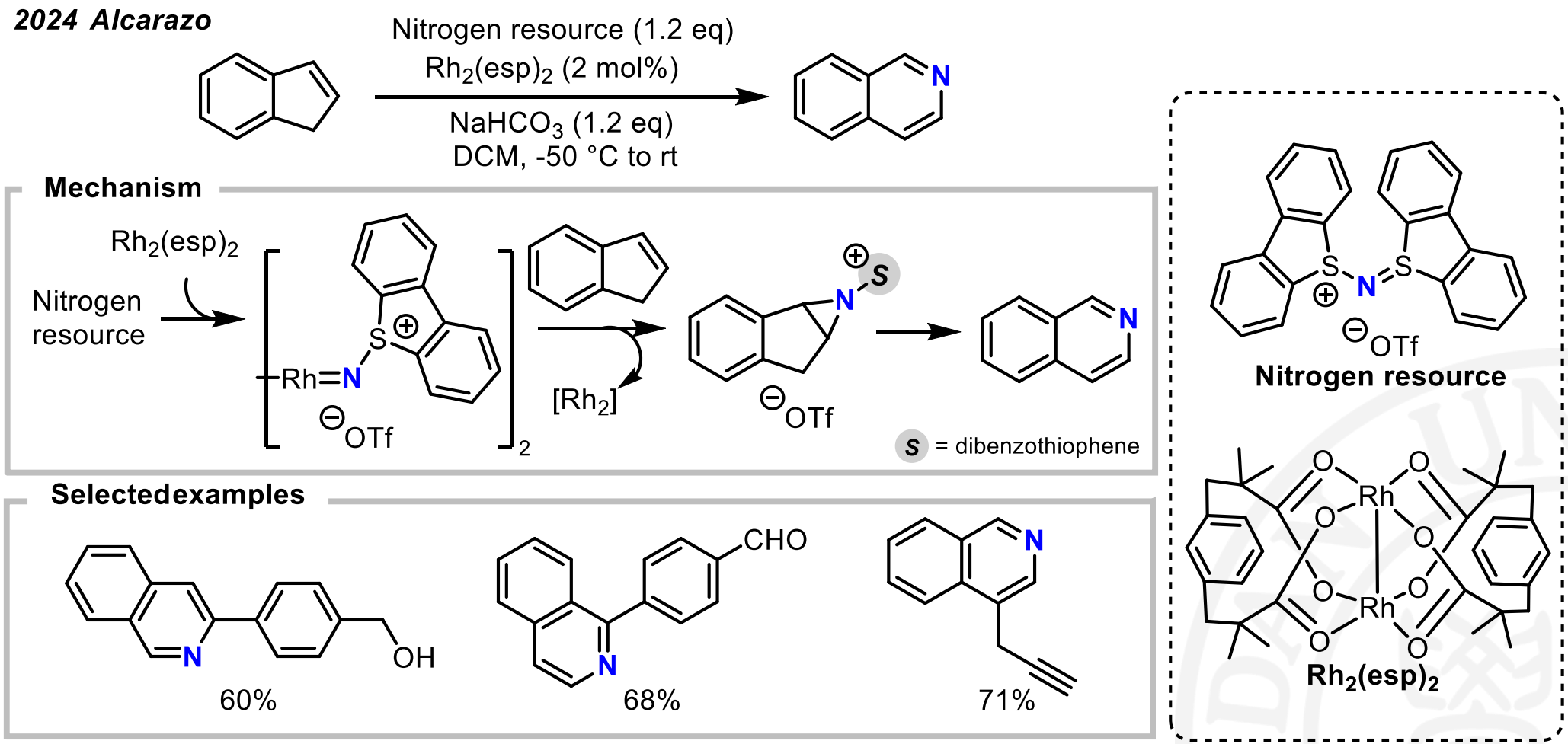
2024 Morandi





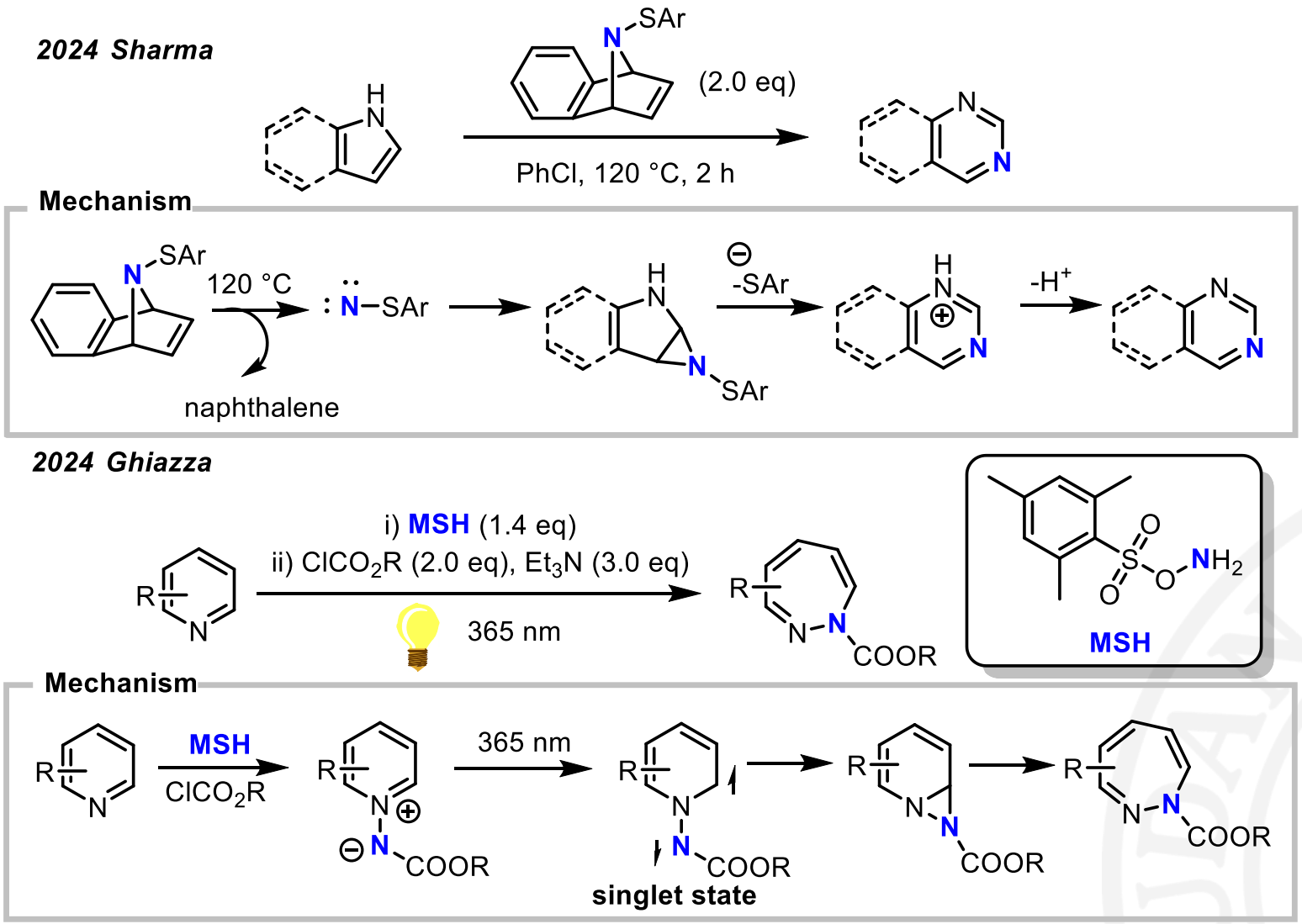
B. Morandi et al. *Science*, **2022**, *377*, 1104 –1109
B. Morandi et al. *Chem. Sci.*, **2023**, *14*, 2954 –2959
B. Morandi et al. *Angew. Chem. Int. Ed.*, **2024**, *63* , e202408230

N-atom insertion



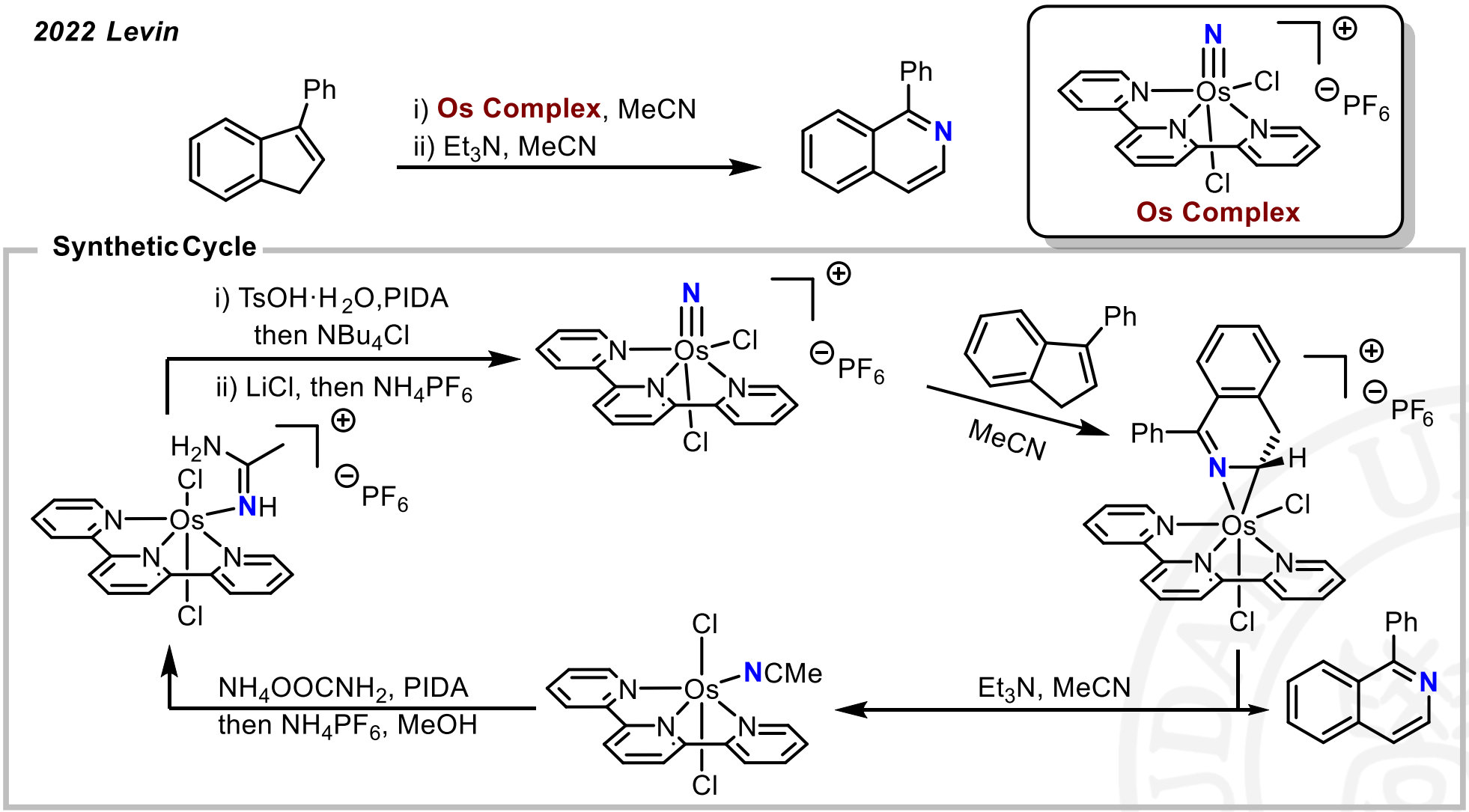
M. Alcarazo et al. *Angew. Chem. Int. Ed.*, **2024**, *63*, e202403826

N-atom insertion



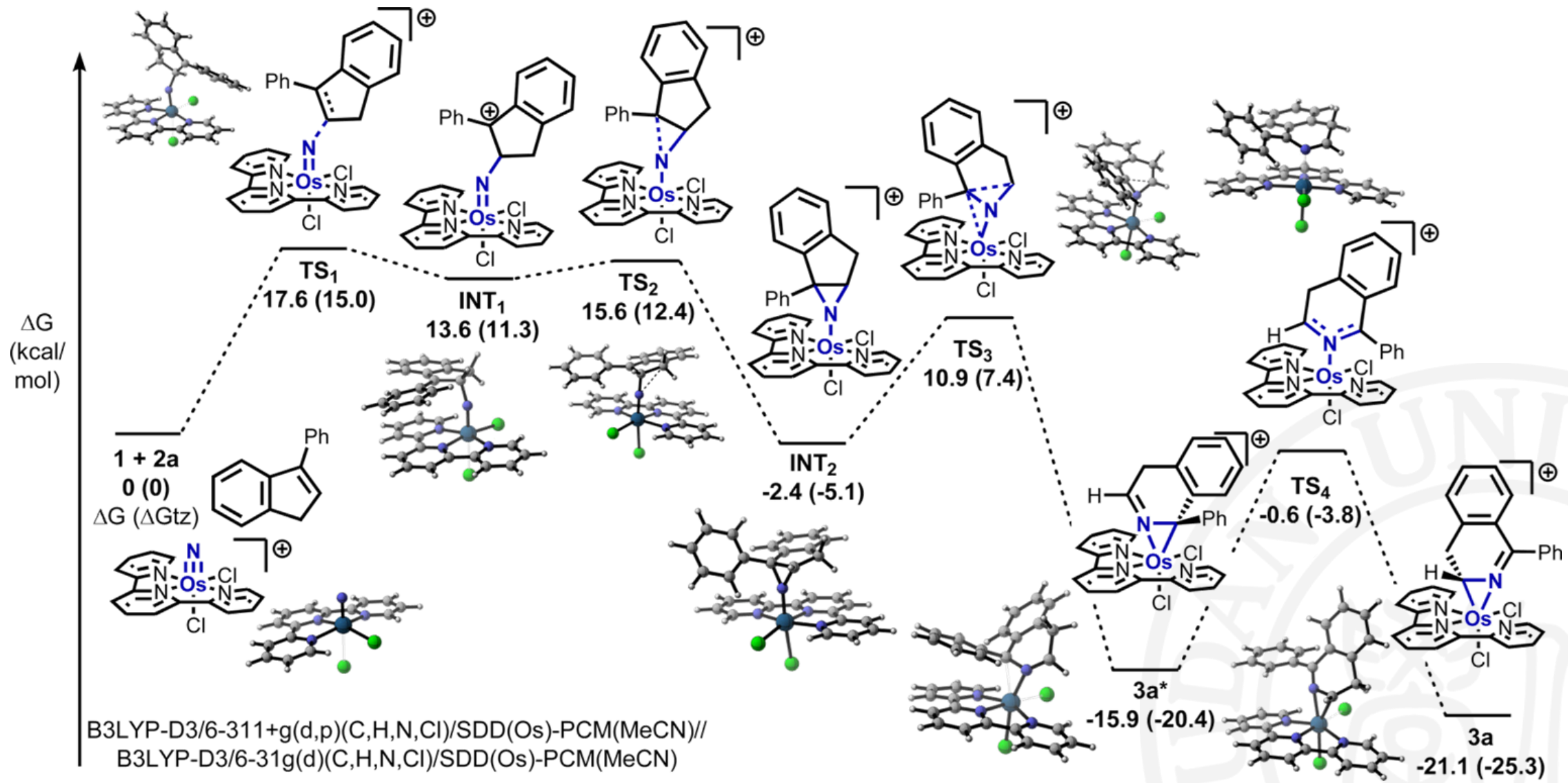
I. Sharma et al. *Science*, **2025**, *387*, 102 –107
C. Ghiazza et al. *J. Am. Chem. Soc.*, **2024**, *146*, 2845 –2854

N-atom insertion



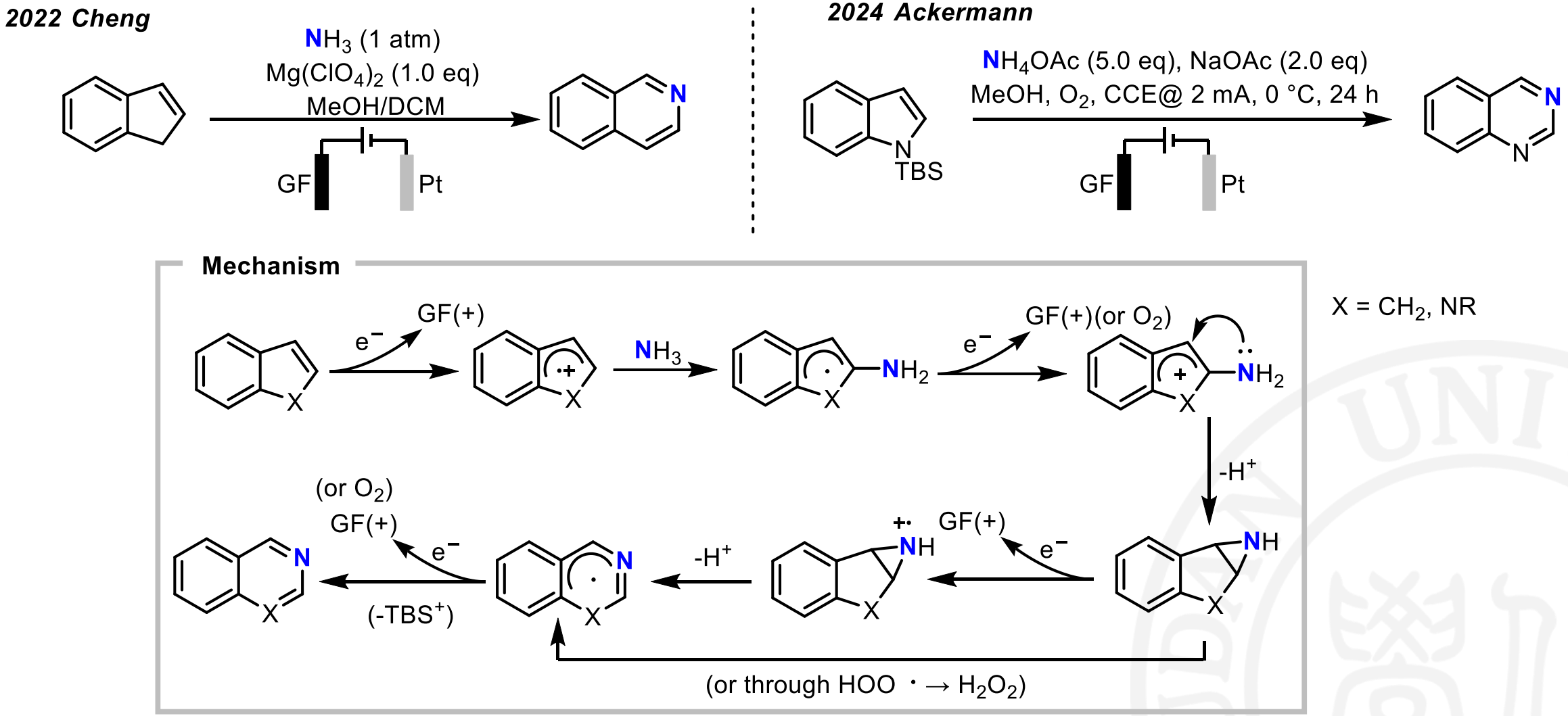
M. Levin et al. *Angew. Chem. Int. Ed.*, **2022**, *61* , e202213041

N-atom insertion

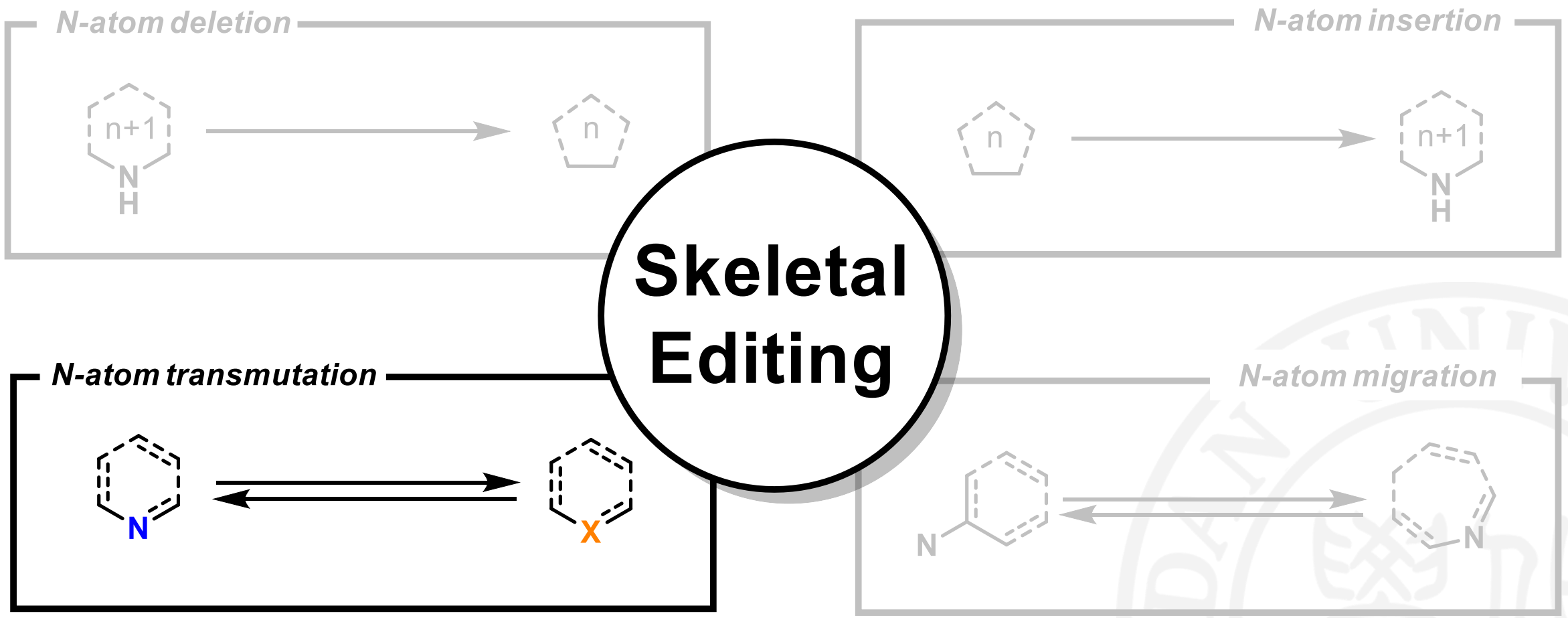


M. Levin et al. *Angew. Chem. Int. Ed.*, **2022**, *61* , e202213041

N-atom insertion



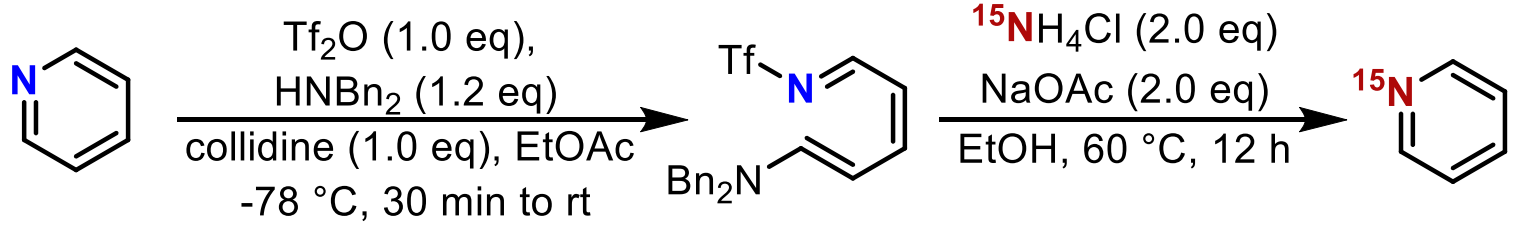
X. Cheng et al. *Nat. Commun.*, **2022**, *13* , 425
L. Ackermann et al. *Angew. Chem. Int. Ed.*, **2024**, e202407384


N-atom deletion
n+1
N
H
n
N-atom insertion
n
n+1
N
H
Skeletal Editing
N-atom transmutation
N
X
N-atom migration
N
N

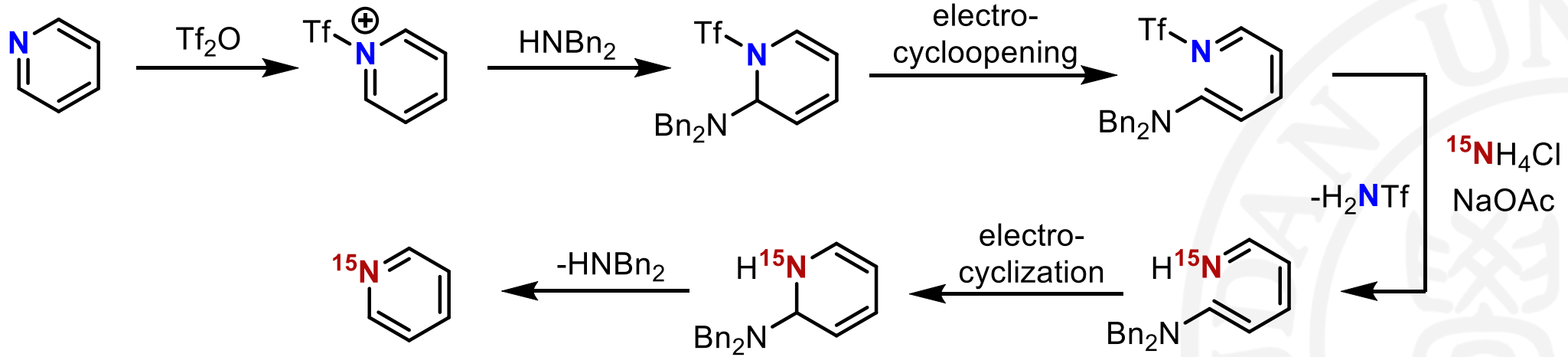
N-atom transmutation

➢ Transmutation Reactions Between Isotropic Nitrogen Atoms

2024 McNally



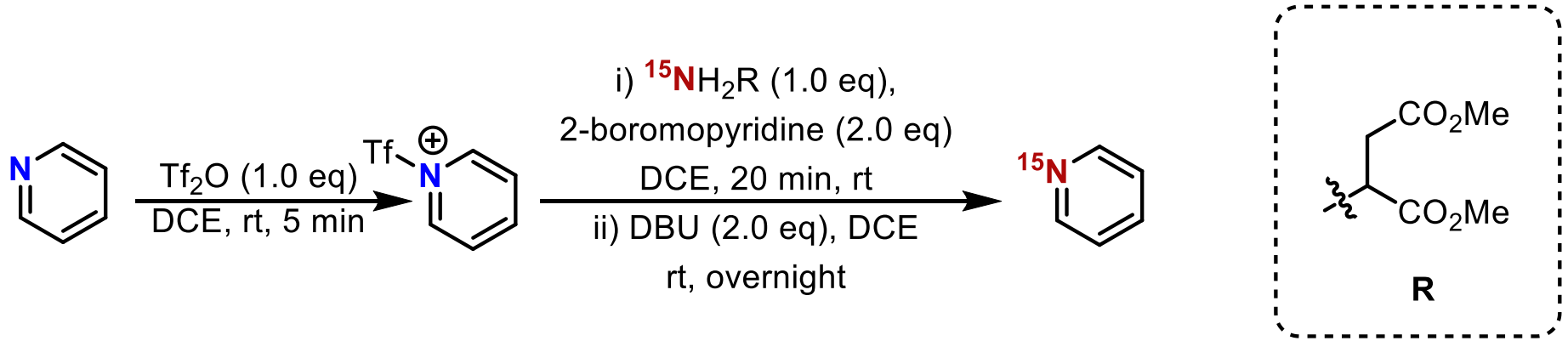
Mechanism



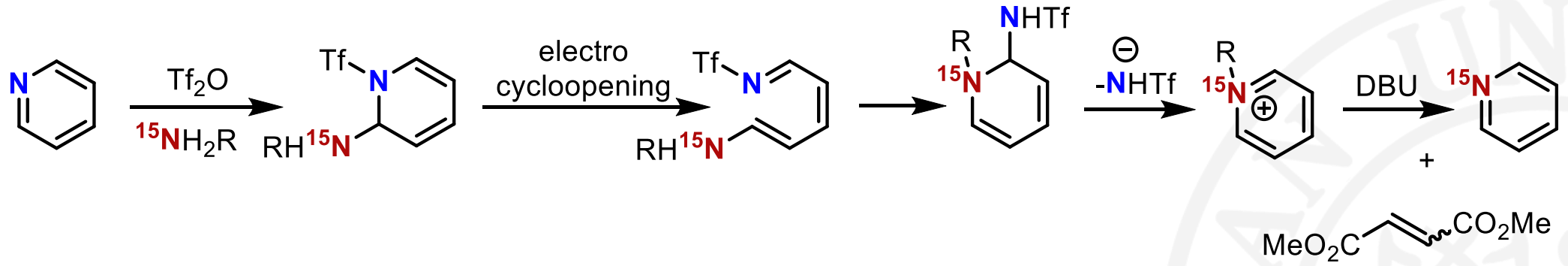
A. McNally et al. *J. Am. Chem. Soc.*, **2024**, *146* , 2944 −2949

N-atom transmutation

2024 Sarpong



Mechanism

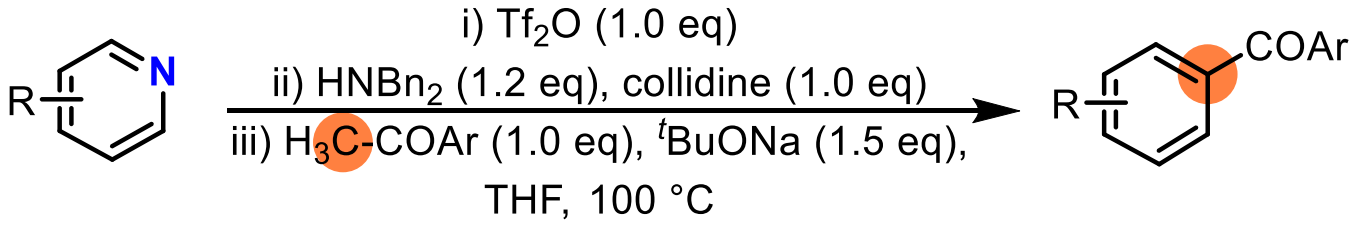


R. Sarpong et al. *J. Am. Chem. Soc.*, **2024**, *146* , 2950 −2958

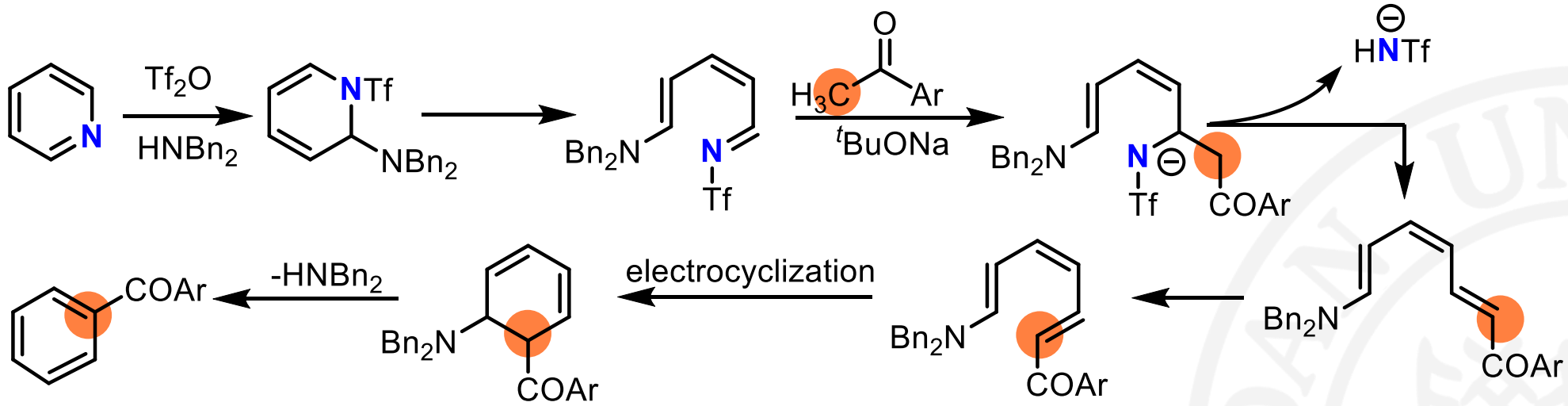
N-atom transmutation

➢ Transmutation Reactions From Nitrogen To Carbon Atoms

2024 Audisio



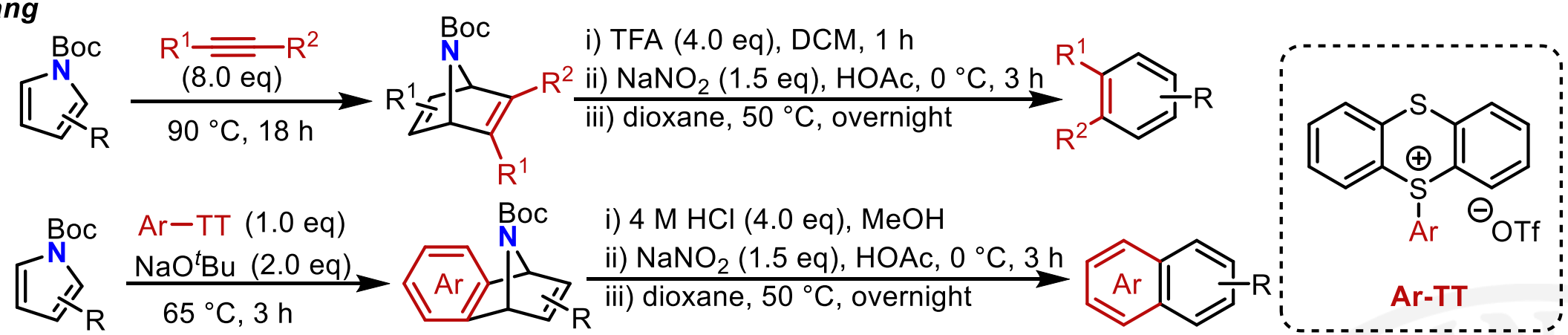
Mechanism



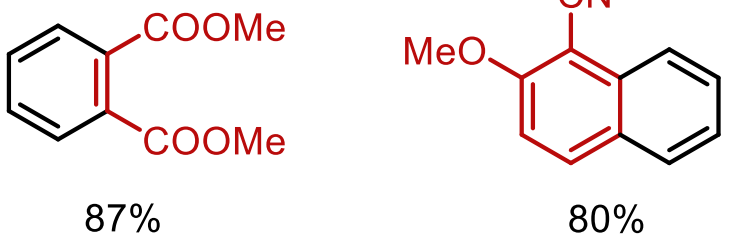
D. Audisio et al. *Nat. Commun.*, **2024**, *15* , 6063

N-atom transmutation

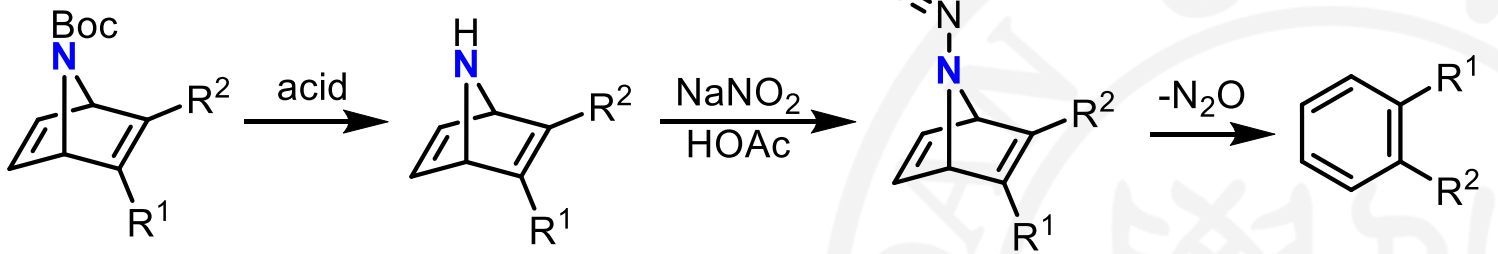
2024 Zhang



Selectedexamples



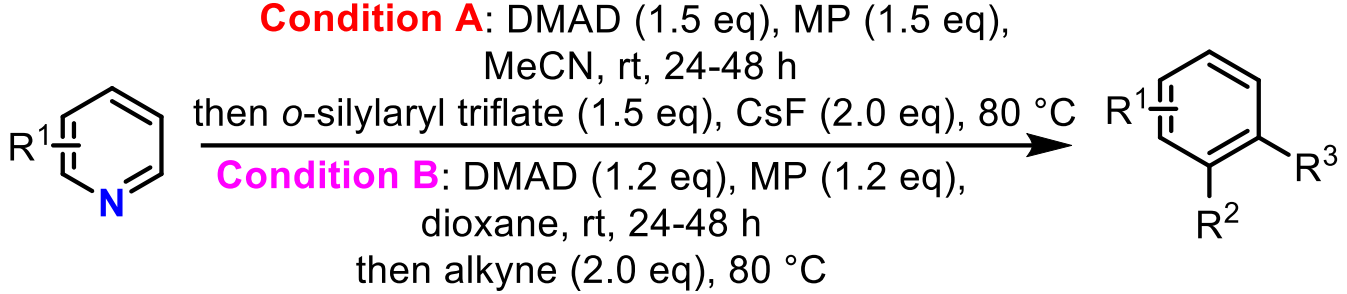
Mechanism

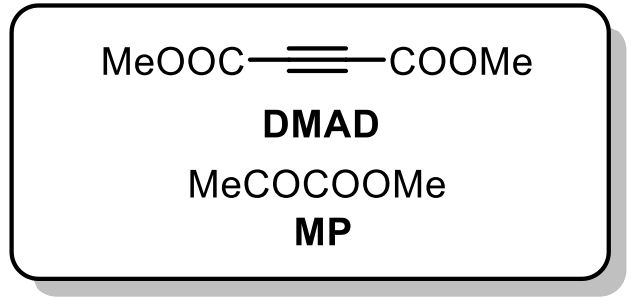


X.-J. Zhang et al. *Angew. Chem., Int. Ed.*, **2024**, *63* , e202411166

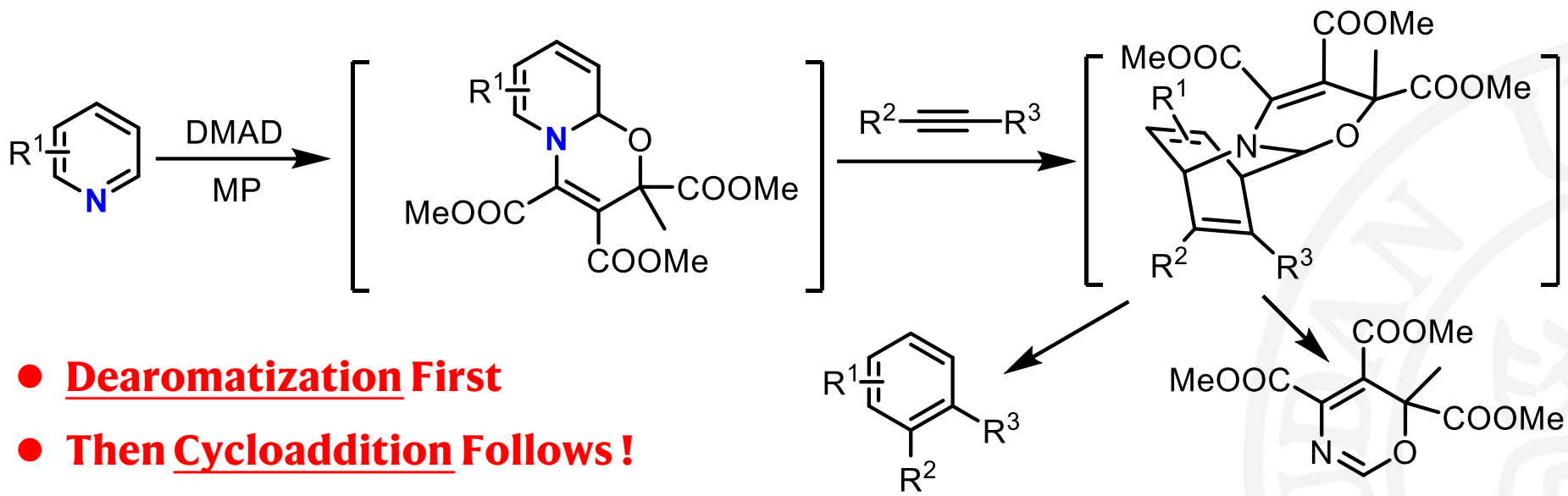
N-atom transmutation

2024 Studer





Mechanism

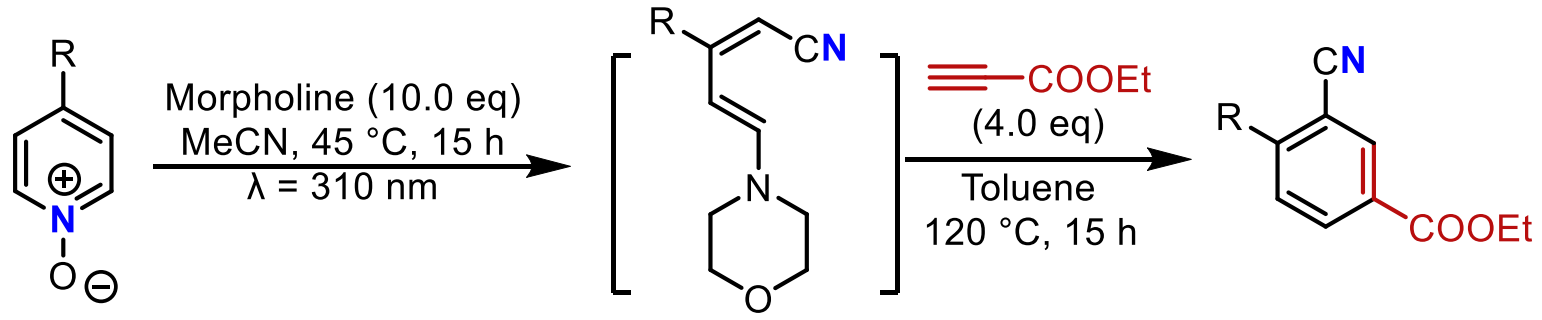


- **Dearomatization First**
- **Then Cycloaddition Follows !**

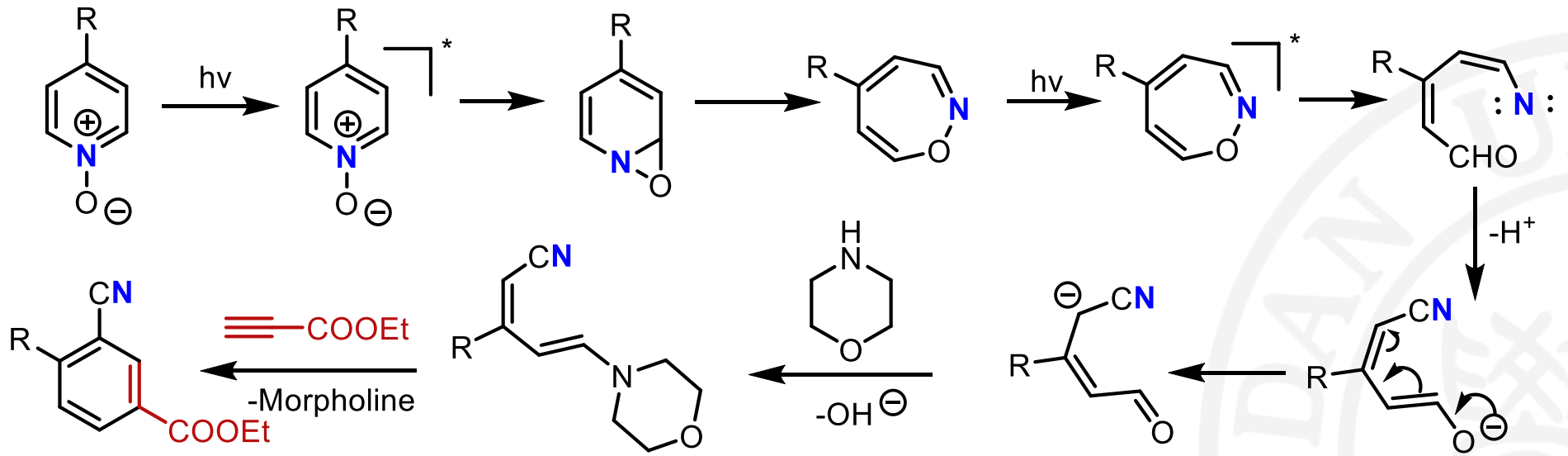
A. Studer et al. *Nat. Chem.* **2024**, *16* , 741 –748

N-atom transmutation

2025 Leonori



Mechanism

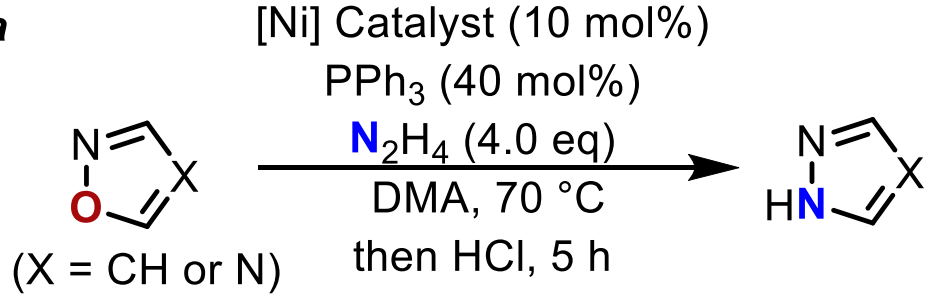


D. Leonori et al. *Nat. Synth.*, **2025**, *4*, 848 –858

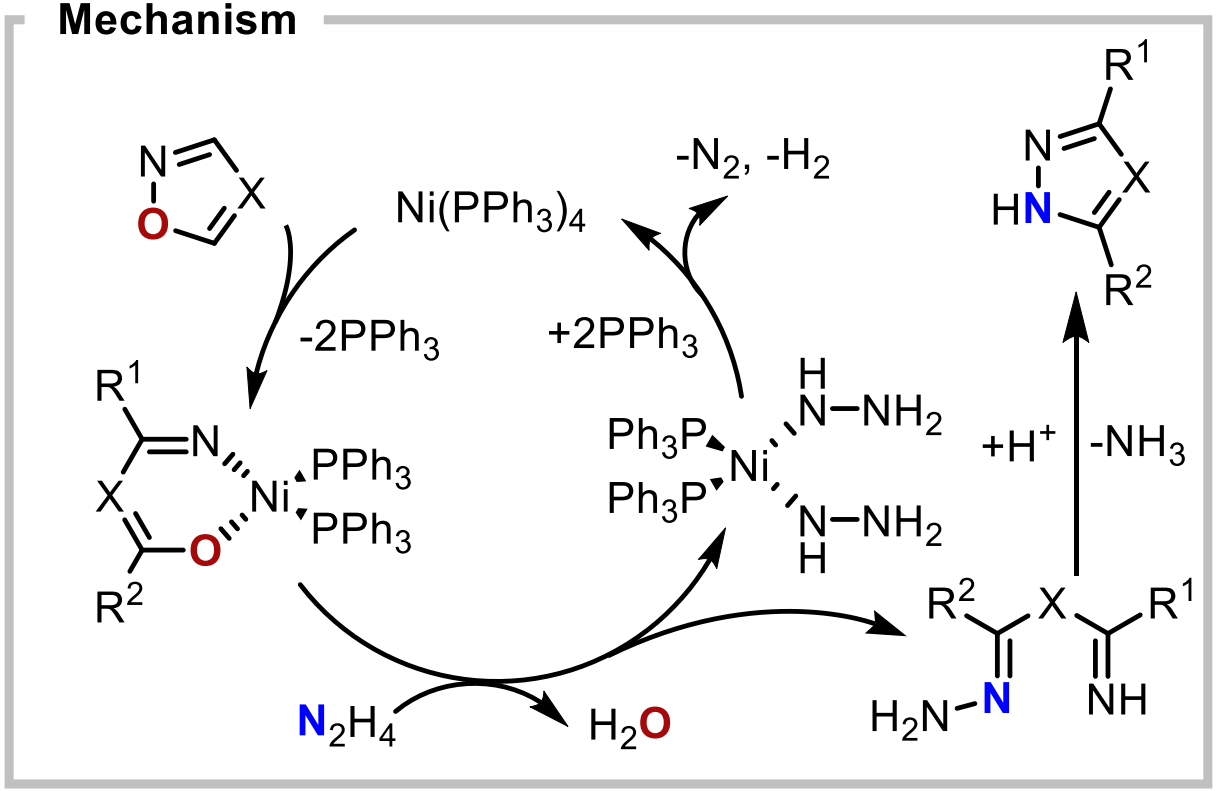
N-atom transmutation

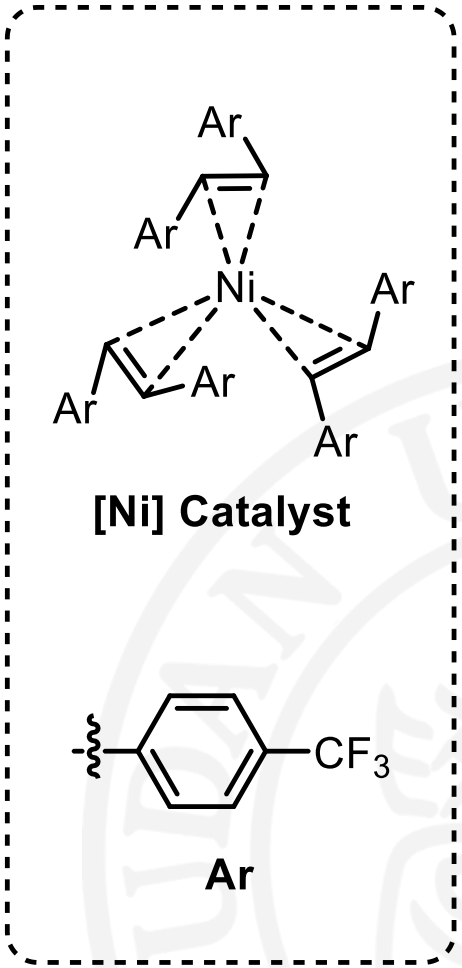
➢ Transmutation Reactions From Oxygen To Nitrogen Atoms

2024 Cornella



Mechanism

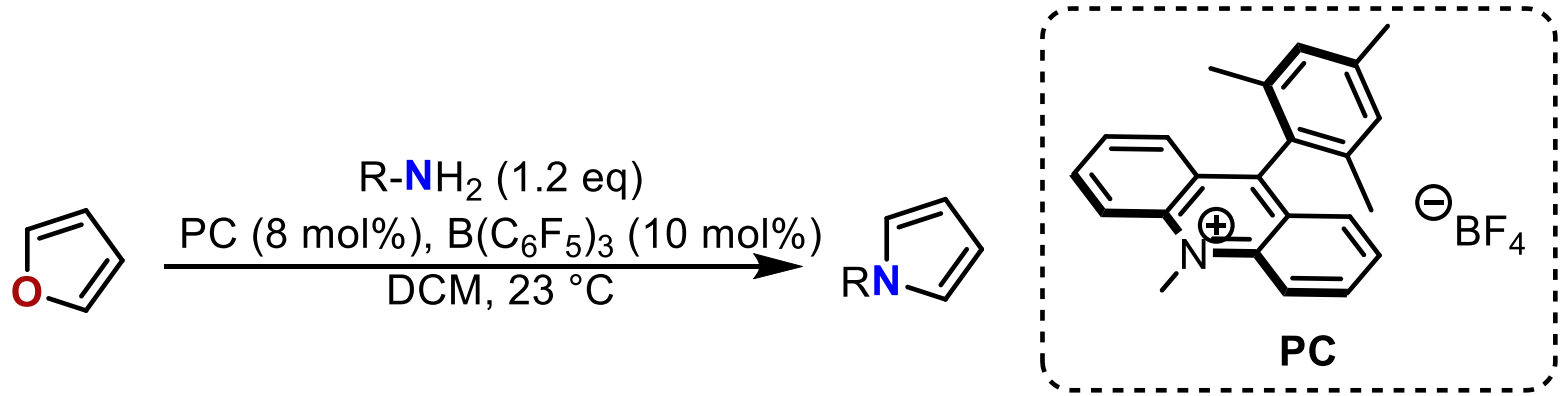




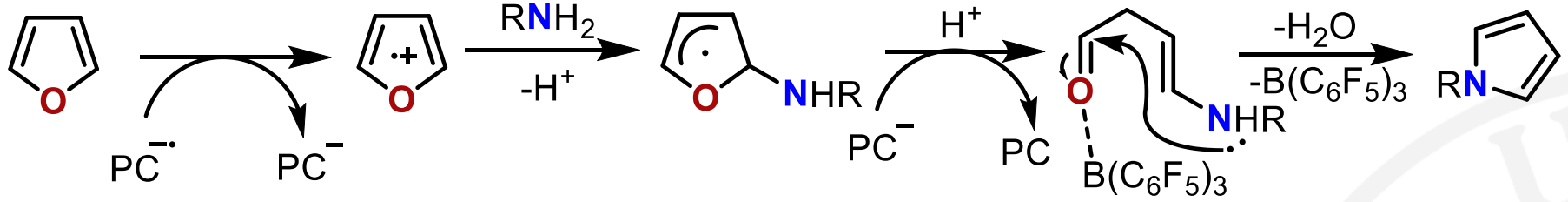
J. Cornella et al. *Synlett,* **2024**, *35* , 1015 –1018

N-atom transmutation

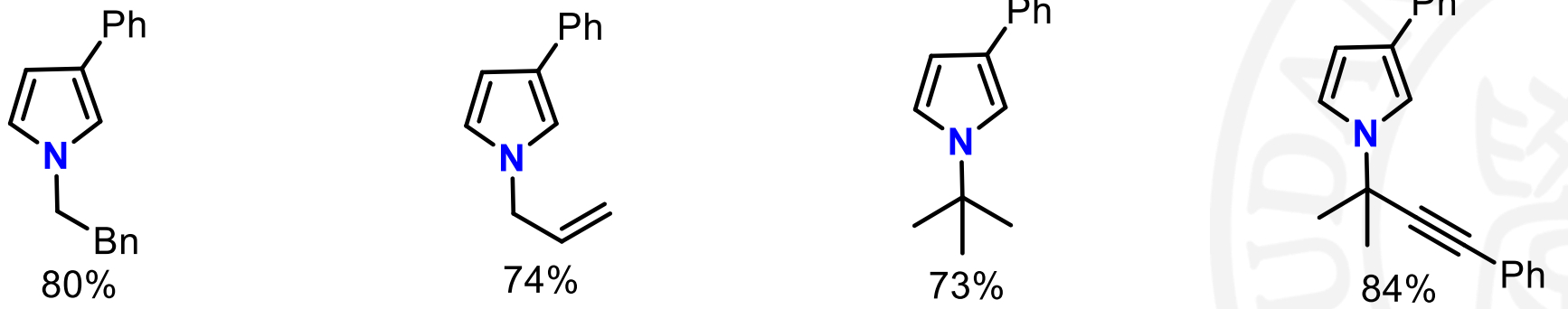
2024 Park



Mechanism



Selectedexamples

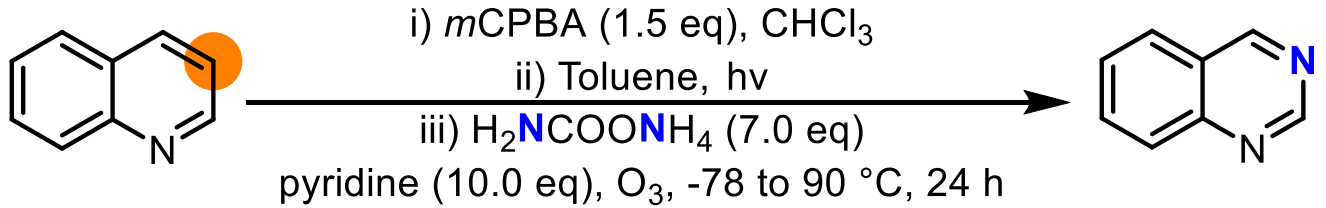


Y. Park et al. *Science,* **2024**, *386* , 99 –105

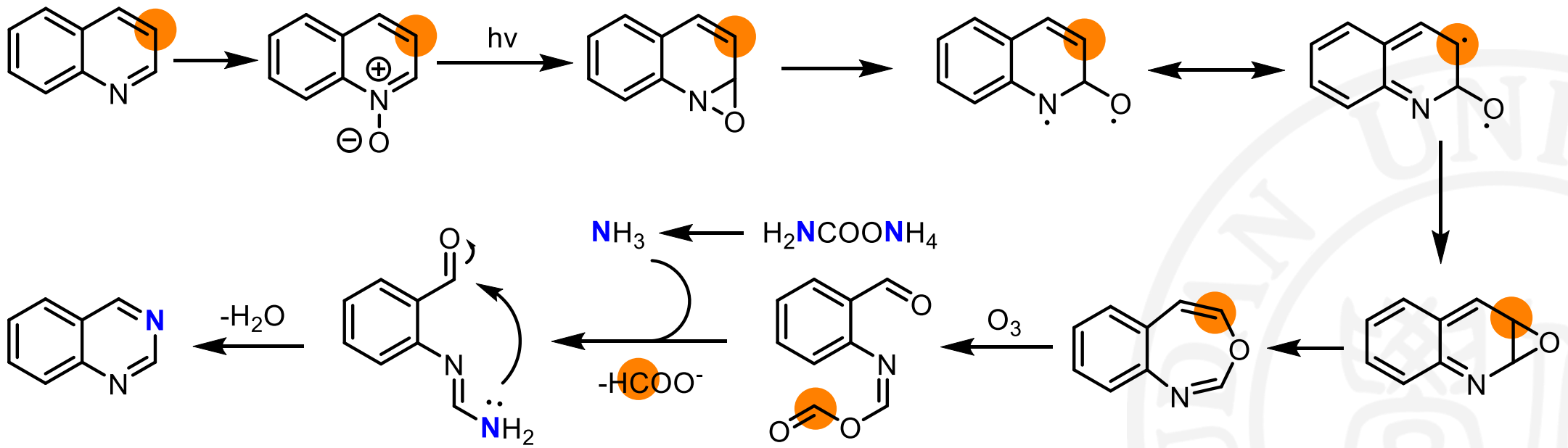
N-atom transmutation

➢ Transmutation Reactions From Carbon To Nitrogen Atoms

2023 Levin



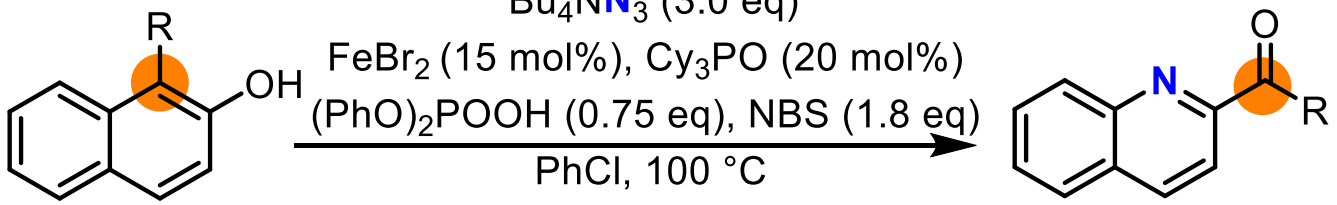
Mechanism



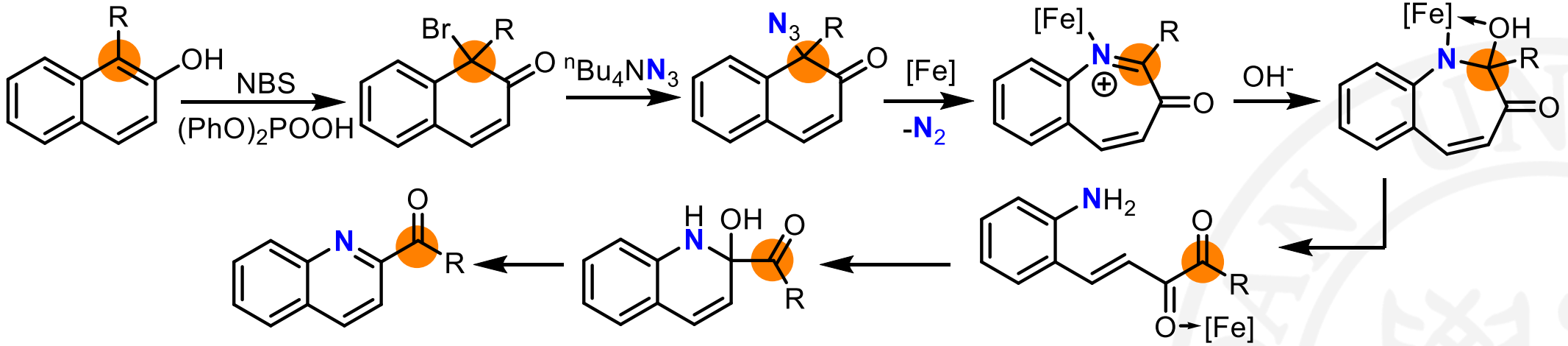
M. Levin et al. *Nature,* **2023,** *623* , 77 −82

N-atom transmutation

2024 Wei



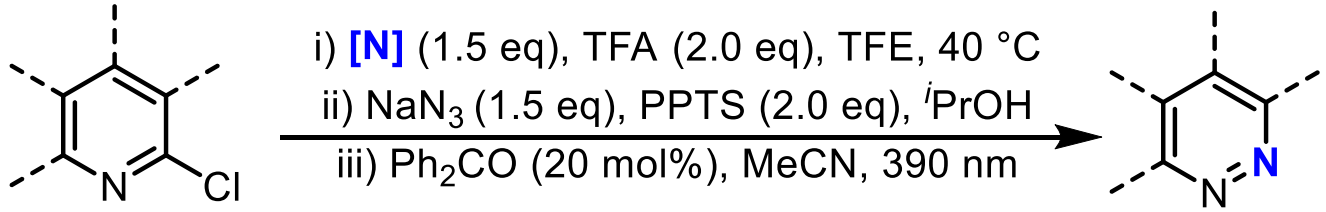
Mechanism



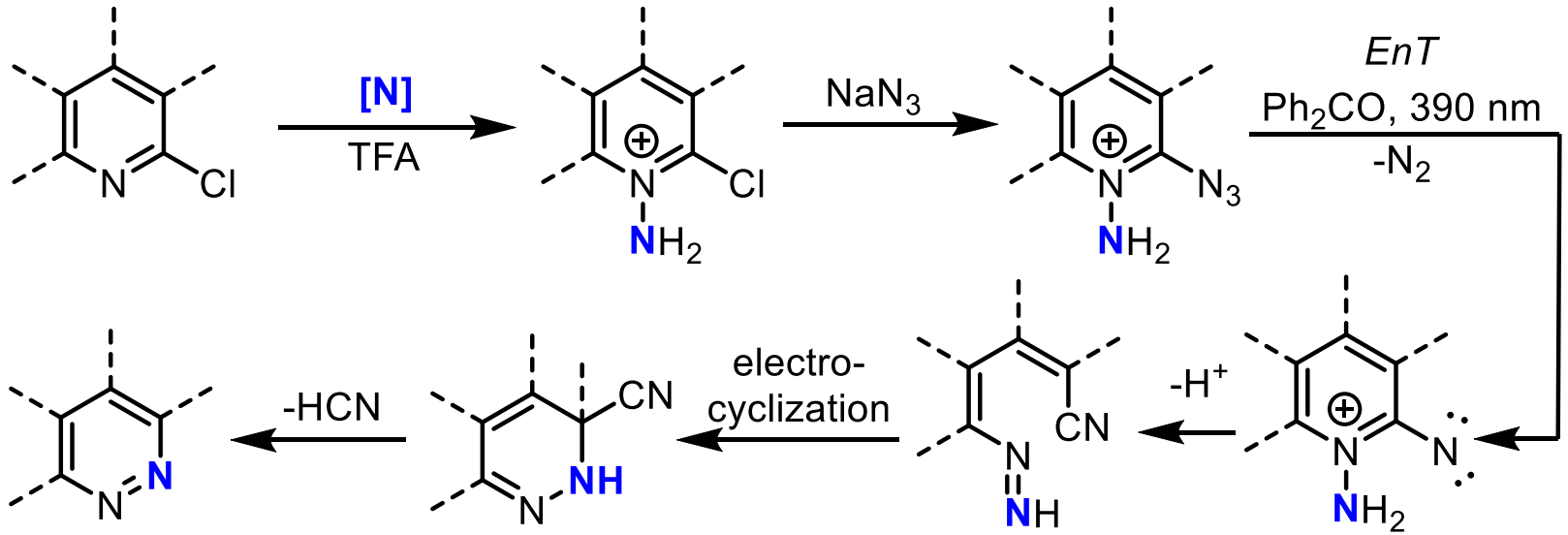
H. Wei et al. *Nat. Commun.*, **2024**, *15* , 3772

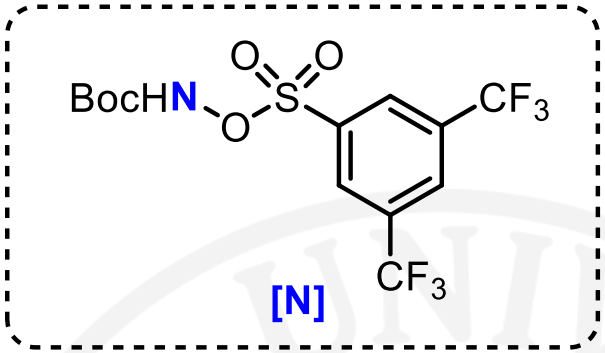
N-atom transmutation

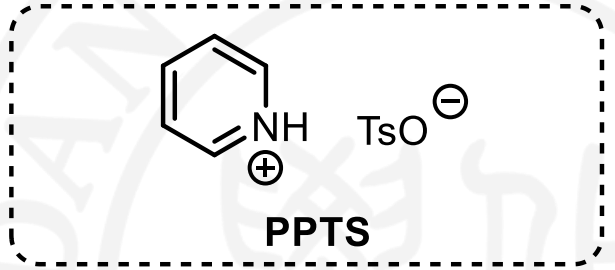
2025 Levin



Mechanism



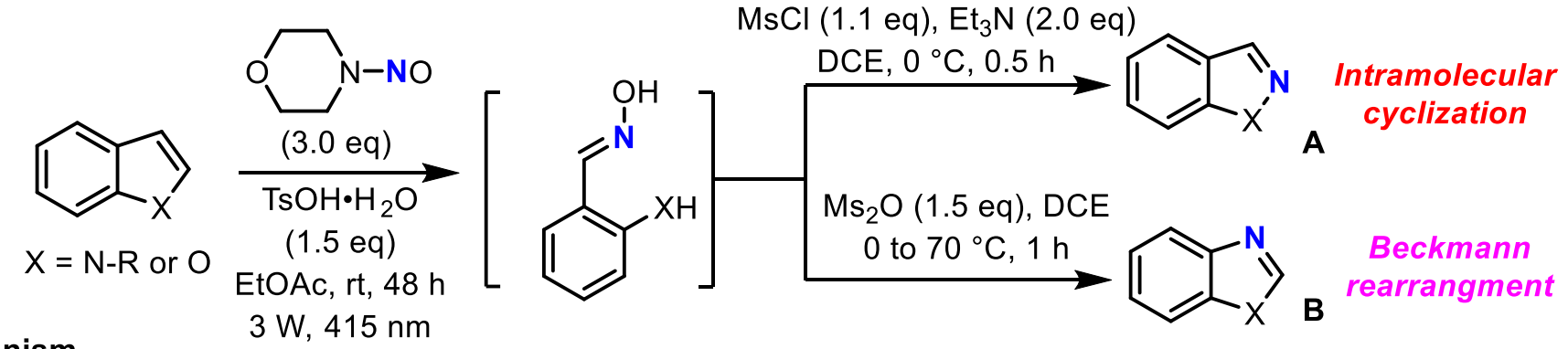




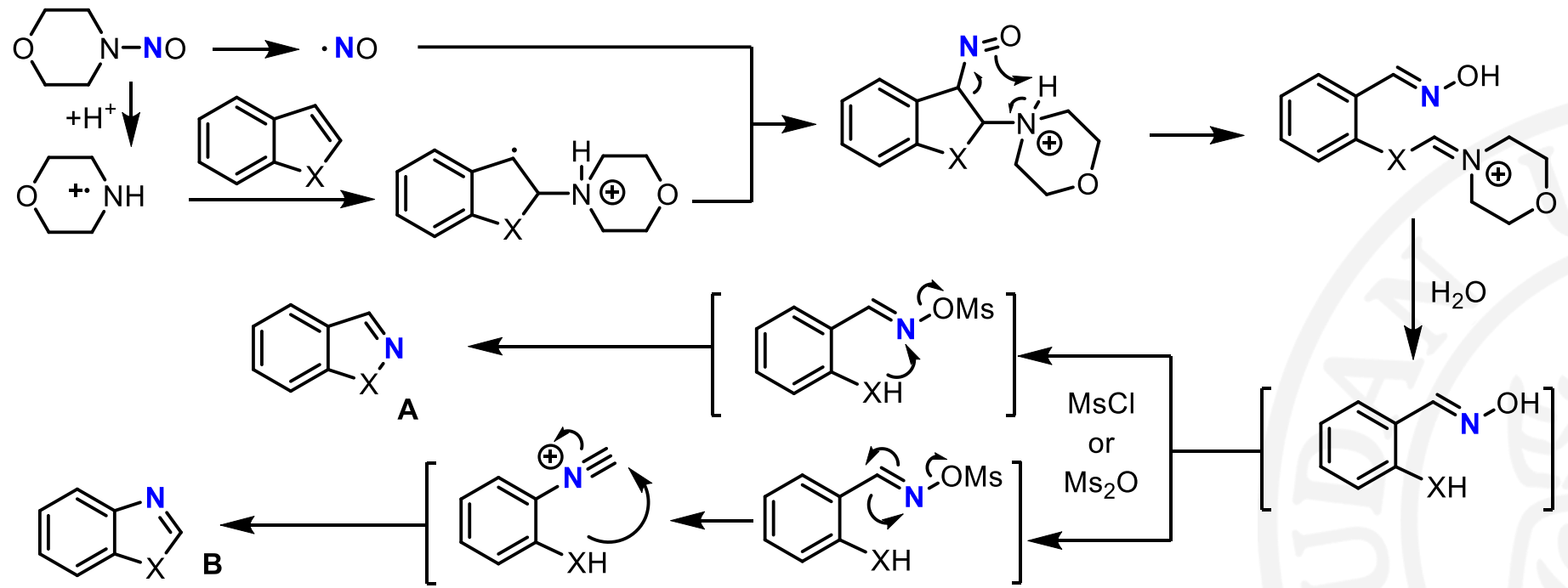
Mark. Levin et al. *Science,* **2025**, *389*, 295-298

N-atom transmutation

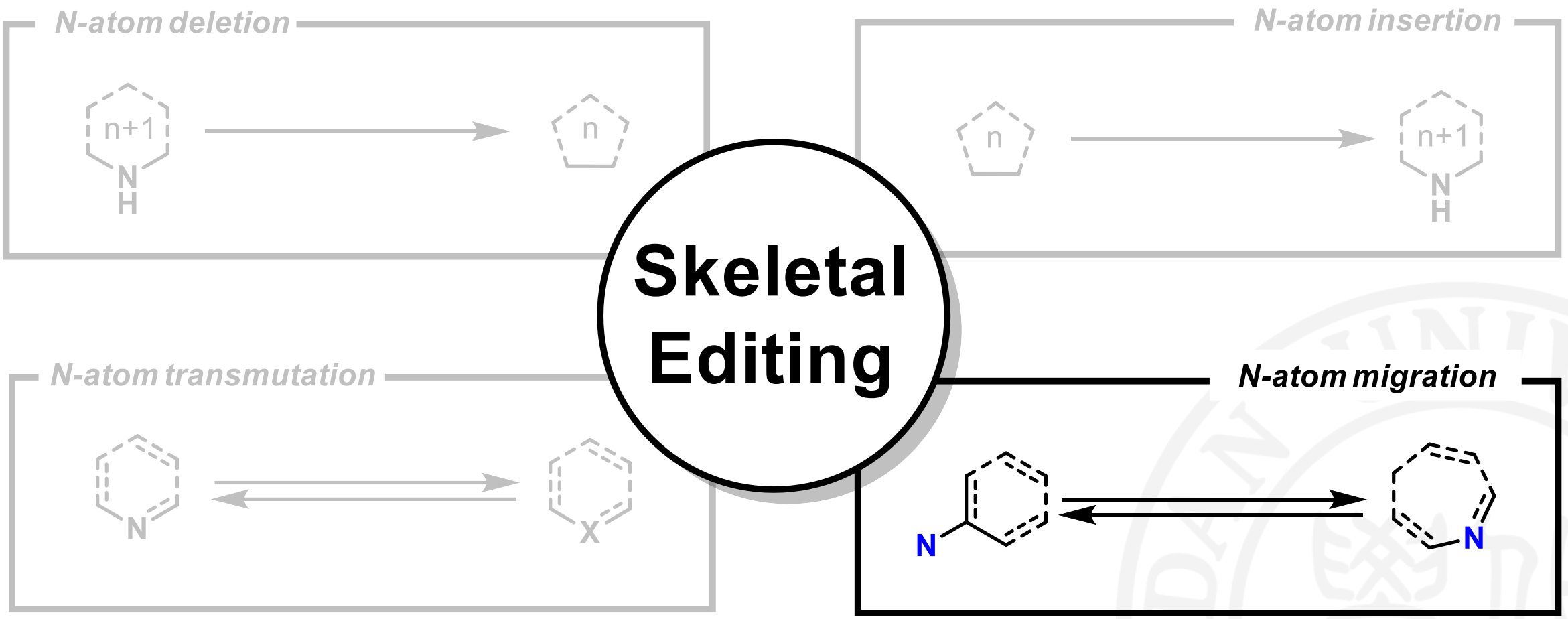
2025 Studer



Mechanism

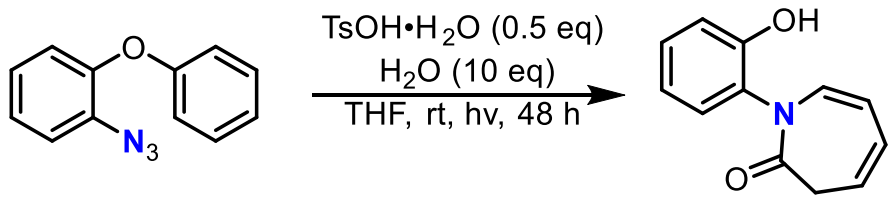


A. Studer et al. *Nature*, **2025**, *642* , 92 −98

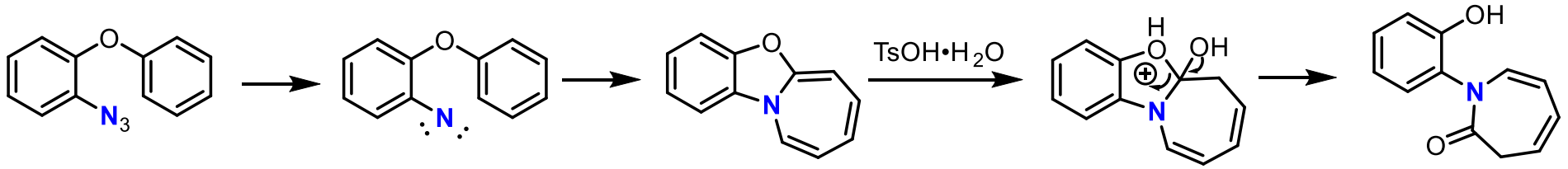

N-atom deletion
n+1
N
H
n
N-atom insertion
n
n+1
N
H
Skeletal Editing
N-atom transmutation
N
X
N-atom migration
N
N

N-atom migration

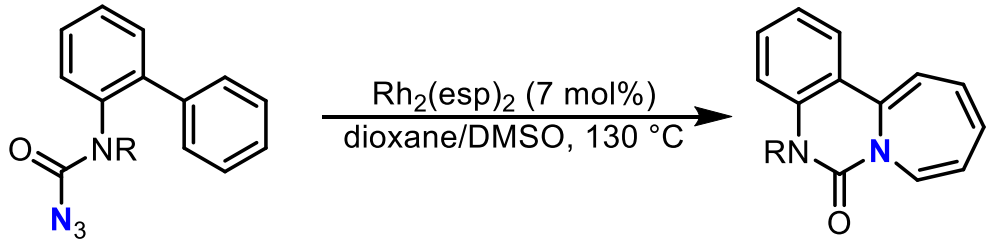
2023 Hashmi



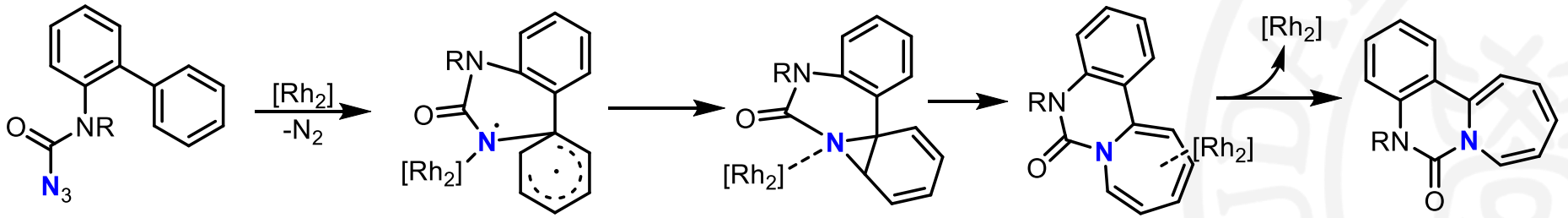
Mechanism



2023 Wei



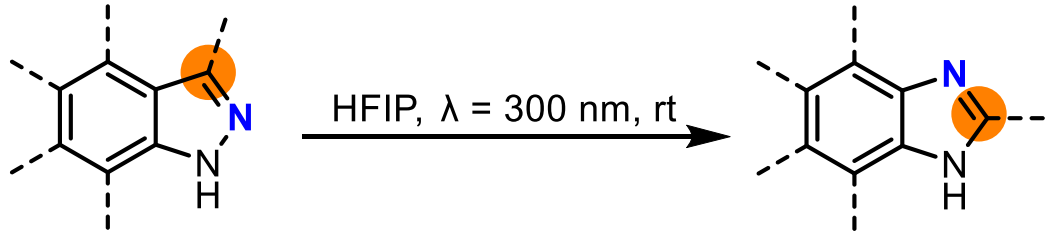
Mechanism



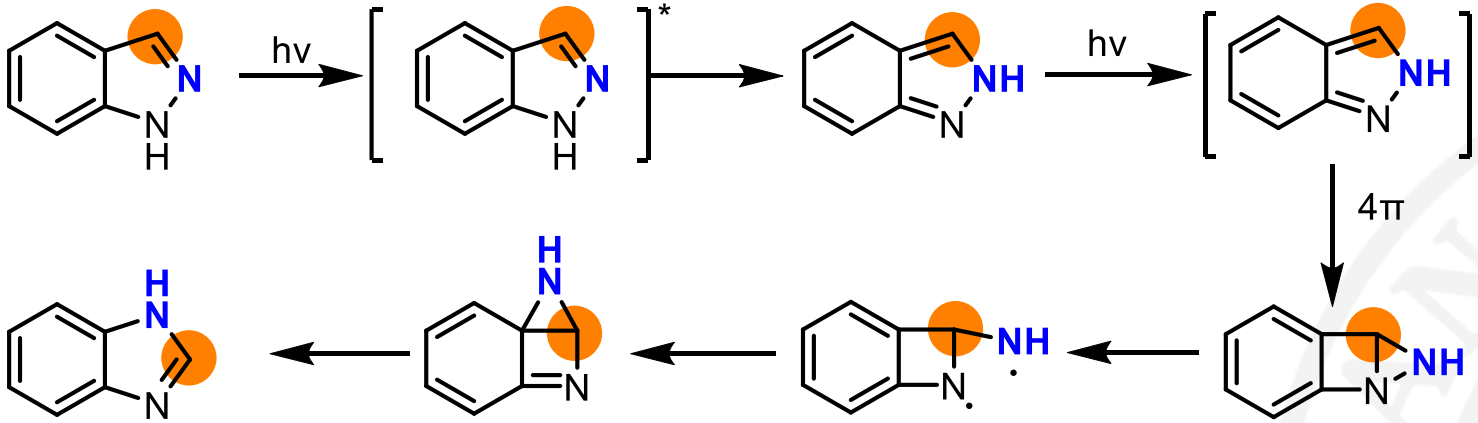
A. Hashmi et al. *Nat. Commun.*, **2023**, *14* , 831
H. Wei et al. *J. Am. Chem. Soc.*, **2023**, *145* , 17570 −17576

N-atom migration

2025 Leonori



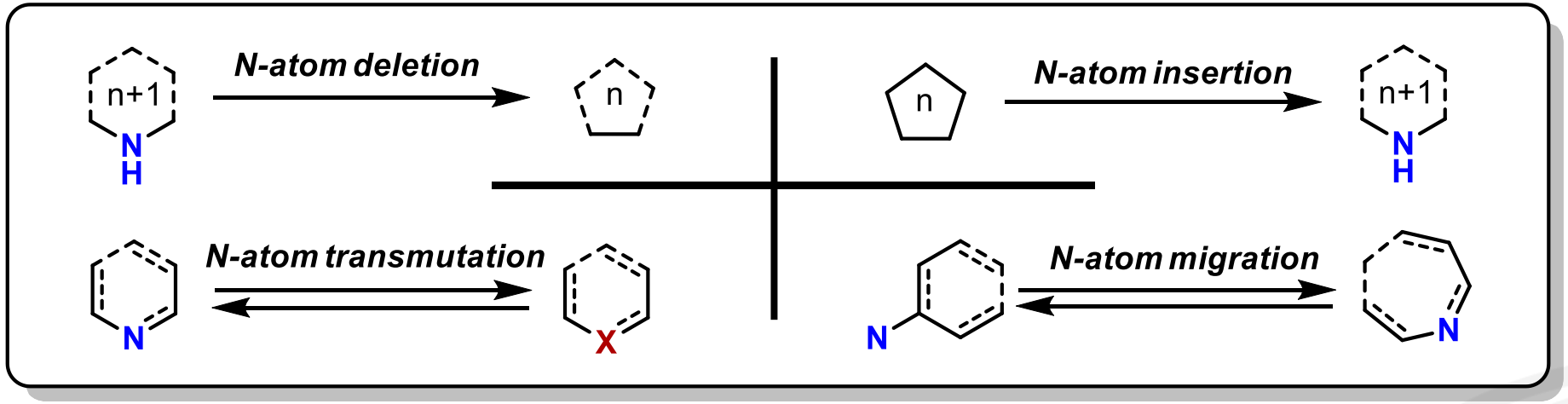
Mechanism



A. Ruffoni et al. *Angew. Chem. Int. Ed.*, **2025**, e202423804

Summary

Skeletal editing of nitrogen atom in organic compounds



Breakthroughs:

- Powerful tool for late-stage functionalization
- Access to valuable isotropically labeled compounds
- Green chemistry

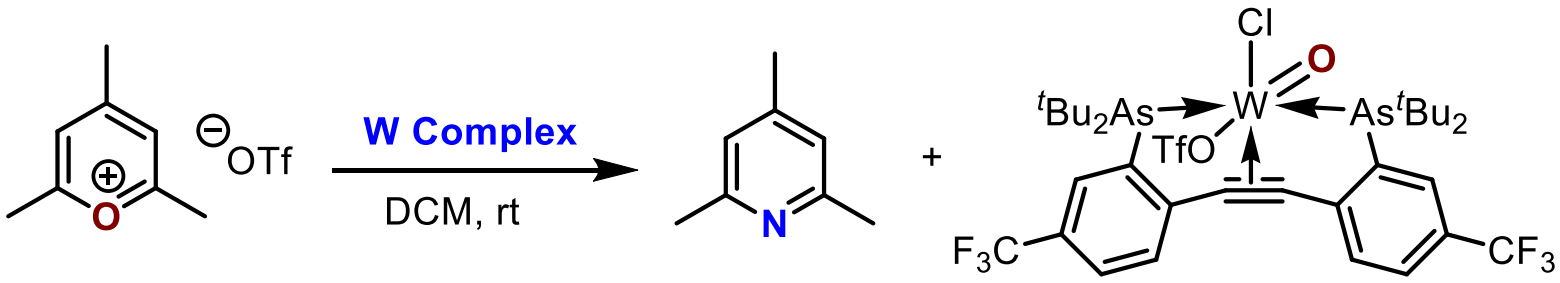
Limitations:

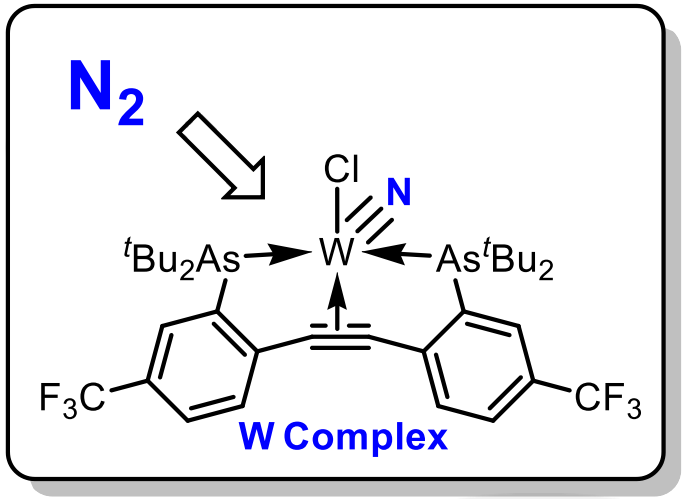
- Highly substrate-specific
- Narrow applicability to complex molecular frameworks
- Insufficient mechanistic understanding for predictive design

Perspectives

Nitrogen Atom transmutation through metal nitride complex

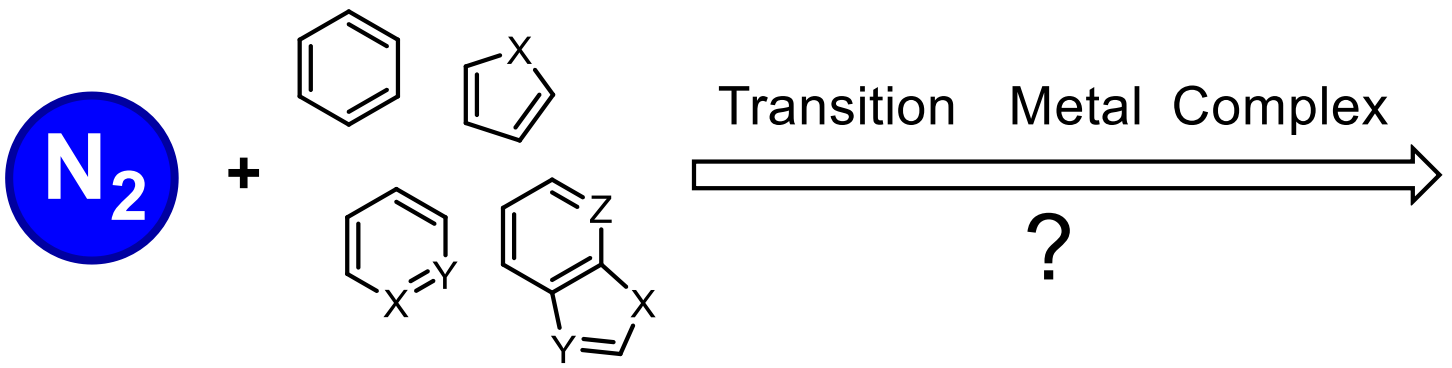
2024 Ballmann

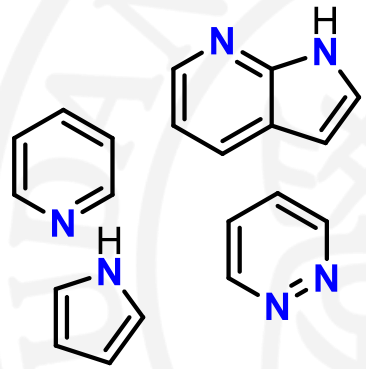




J. Ballmann et al. *J. Am. Chem. Soc.* **2024**, *146*, 7979–7984

Direct synthesis of N containing molecules from nitrogen gas





THANKS