杂环骨架上氮原子的编辑

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指导老师: 麻生明 教授

汇报时间: 2022-12-16

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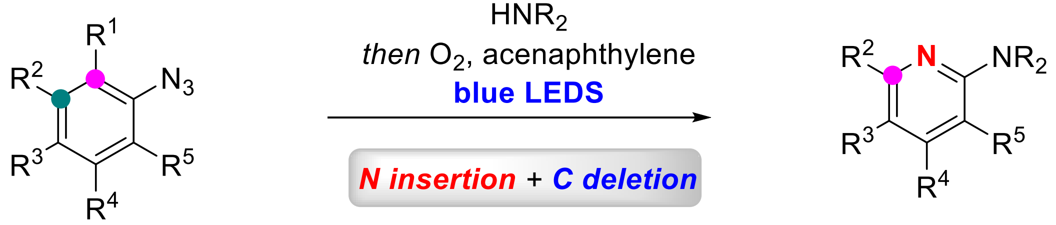
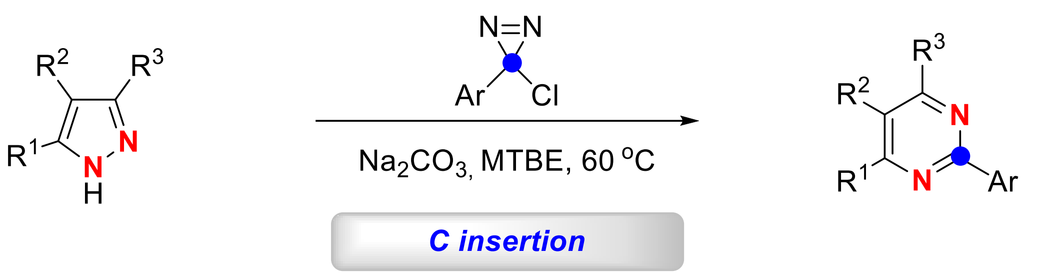
1 背景介绍

Skeletal editing ?

(1)

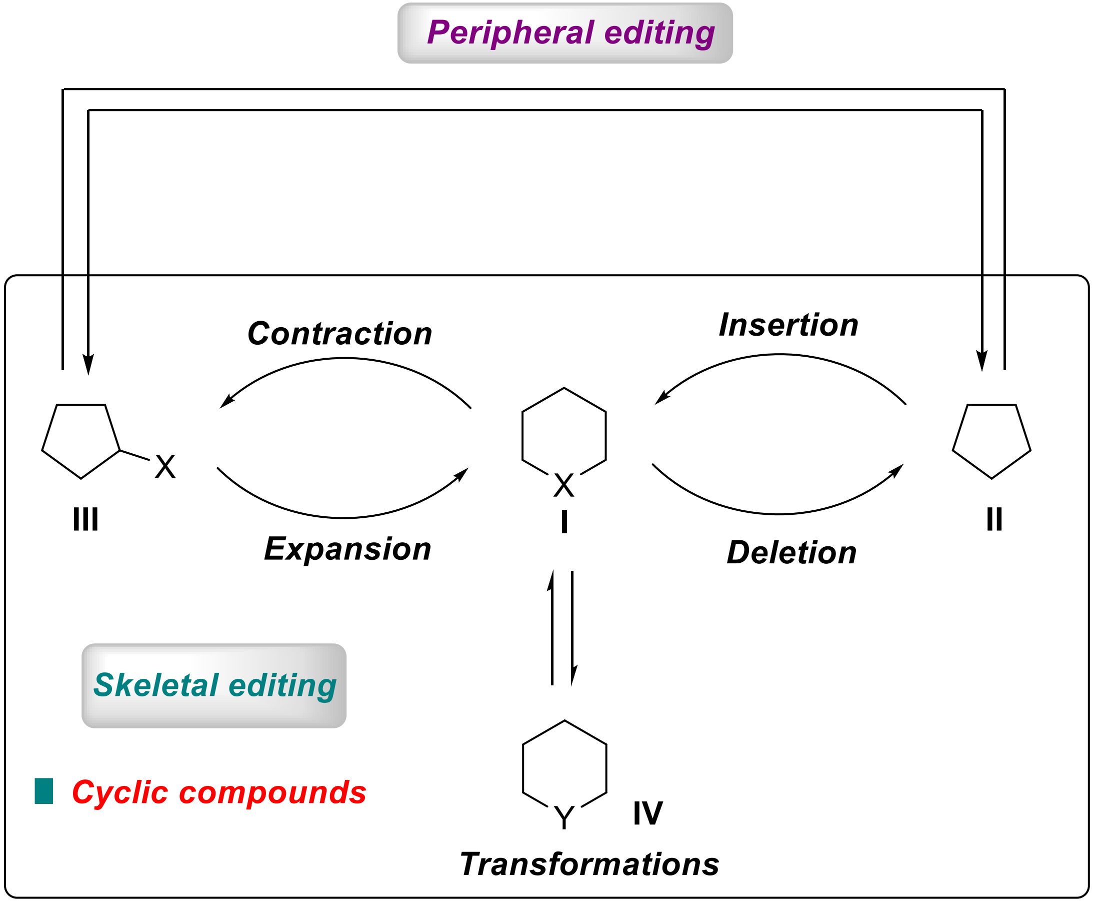


(2)



N. Z. Burns et al. *J. Am. Chem. Soc*. **2022**, *144*, 17797−7802.
M. D. Levin et al. *J. Am. Chem. Soc*. **2022**, *144*, 19258−9264.

1 背景介绍

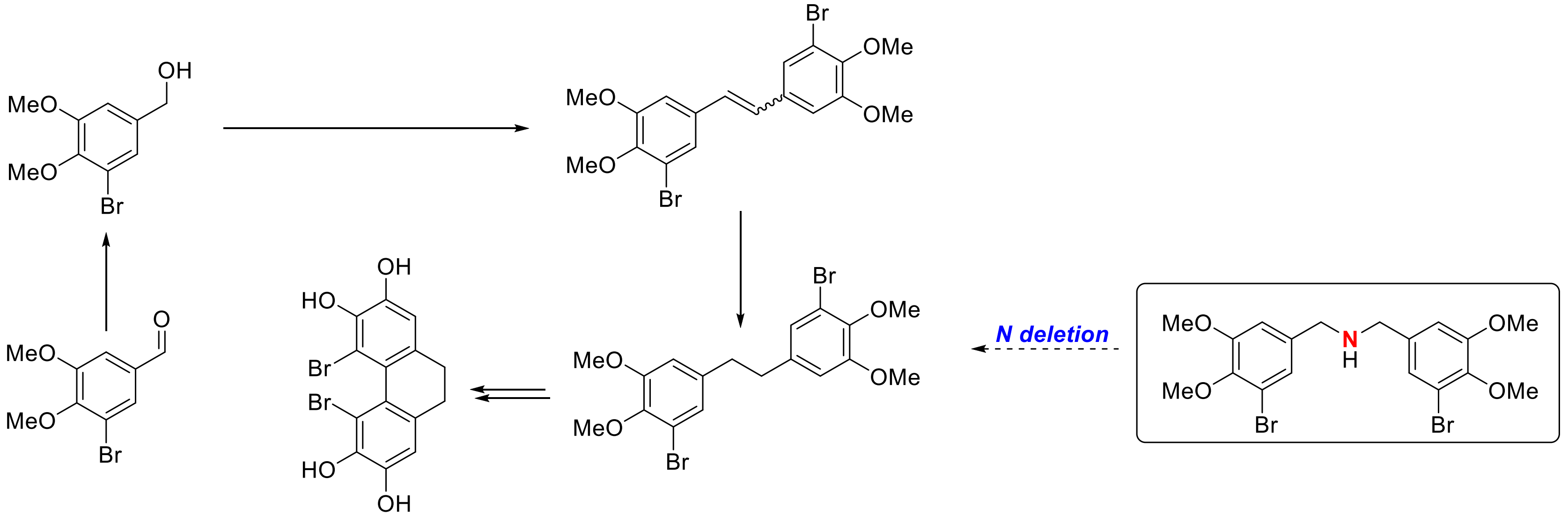


M. D. Levin et al. *Nature* **2021**, *593*, 223−227.
M. D. Levin et al. *Nat. Synth*. **2022**, *1*, 352–364.

1 背景介绍

Skeletal editing

Synthesis of Polysiphenol



(±)-Polysiphenol

Conventional transformation of ethers

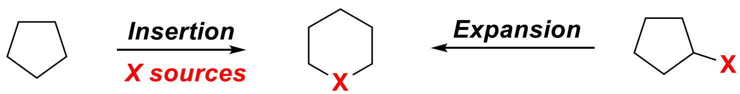
Skeletal editing of ethers

Andrew J. P. White et al. *J. Nat. Prod*. **2011**, *74*, 1980–1984.
M. D. Levin et al. *Nature* **2021**, *593*, 223−227.
Z. J. Shi et al. *J. Am. Chem. Soc.* **2017**, *139*, 6546−6549.

1 背景介绍

Skeletal editing

n + 1

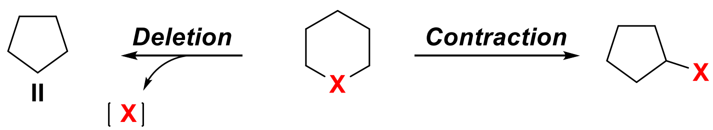


Classic name reaction:Beckmann Rearrangement, Schmidt Rearrangement, Favorskii rearrangement, etc.

Common methods: I Transition-metal (Cu, Rh, Co), $h\nu$, Metallic Reagents.

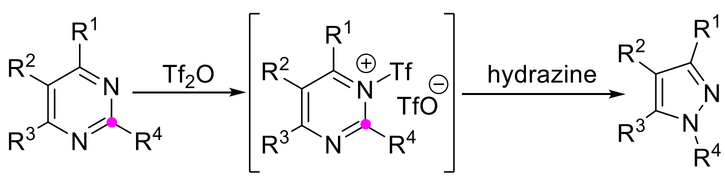
II Active intermediates. Carbene Nitrene

n - 1

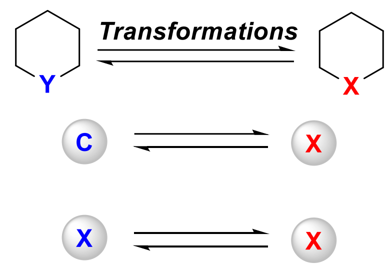


Classic Name reaction: Norrish II reaction.

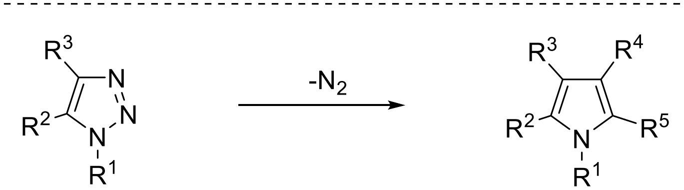
Common methods: $h\nu$, Electrophilic reagents.



n



Common methods: Metal, $h\nu$.



R. Sarpong et al. *J. Am. Chem. Soc*. **2022**, *48*, 22309–22315.

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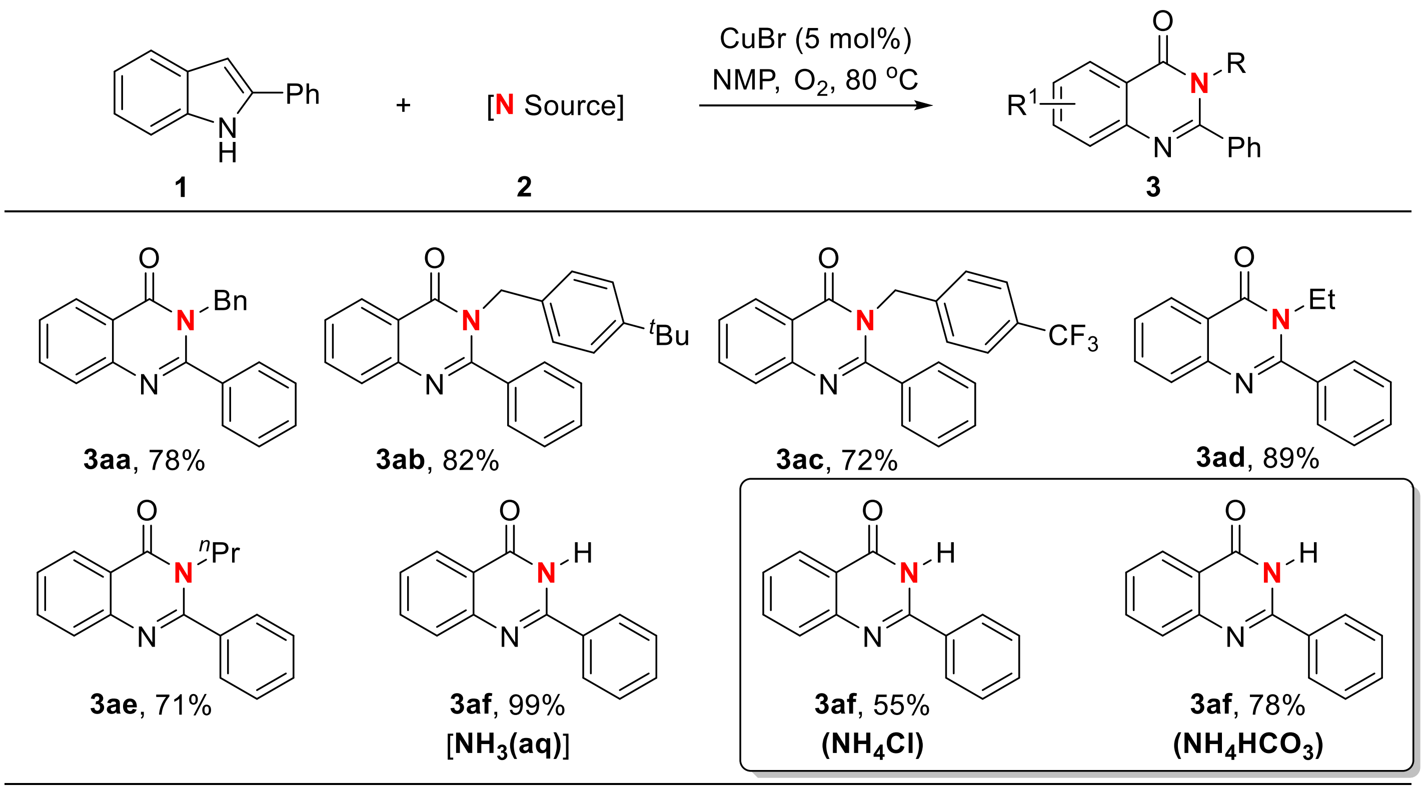
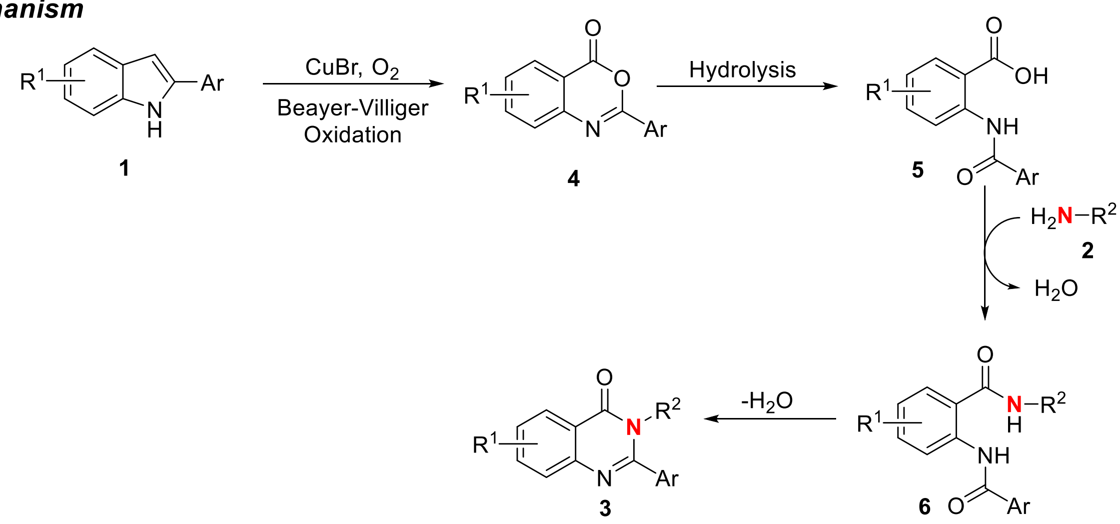
2 杂环骨架上氮原子的插入



A. Iida et al. *Tetrahedron Lett.* **2014**, *55*, 2991–2993.
X. L. Cui et al. *J. Org. Chem*. **2015**, *80*, 7099−7107.

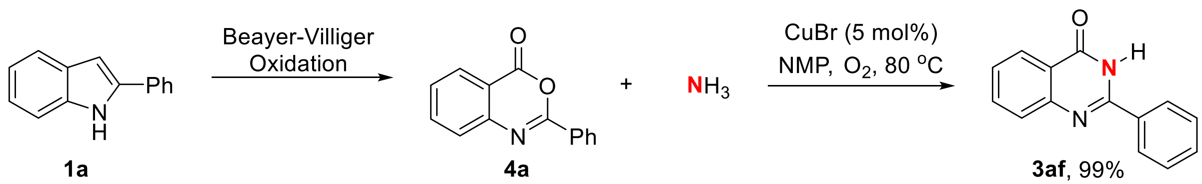
2 杂环骨架上氮原子的插入

Proposed mechanism

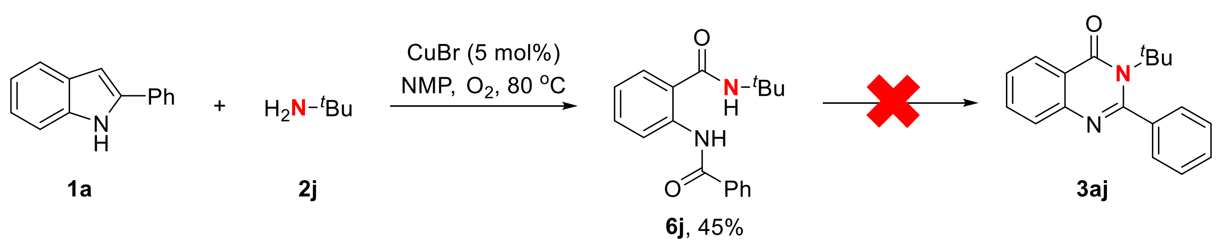


Mechanistic experiments

A



B



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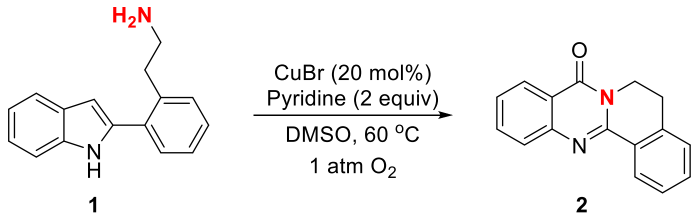
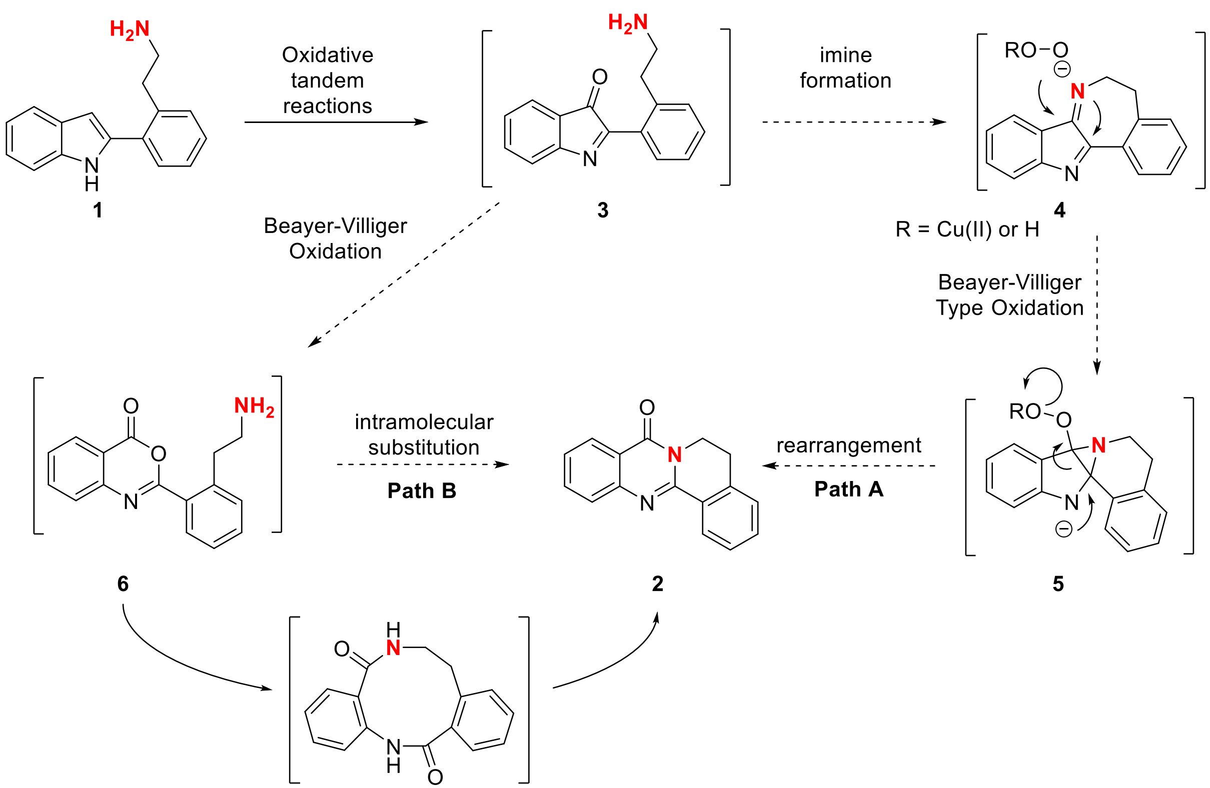


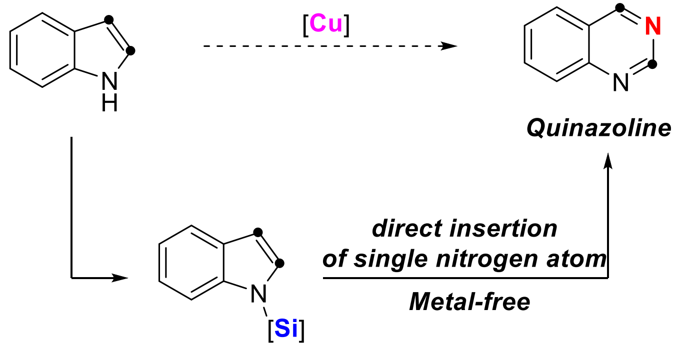
Proposed mechanism



A. Iida et al. *Tetrahedron Lett*. **2016**, *72*, 4123−4131.

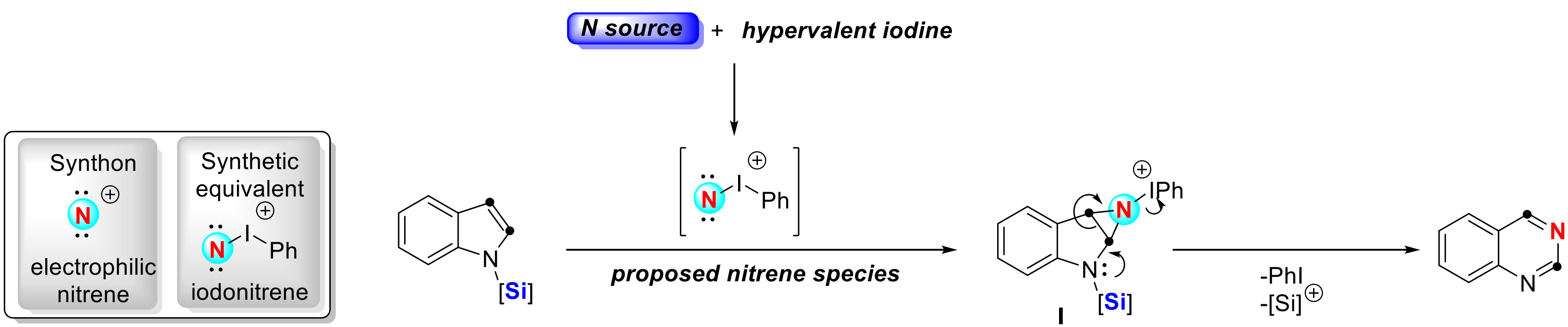
2 杂环骨架上氮原子的插入

Outline



- ***Less naturally abundant***
- ***Common motif in approved drugs***

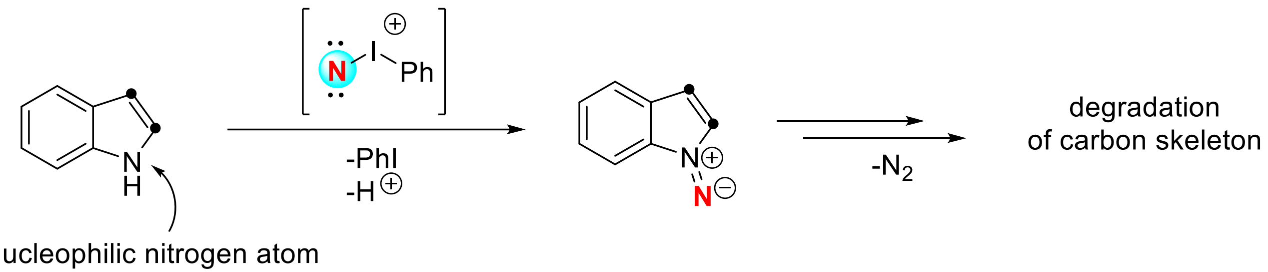
Mechanistic design



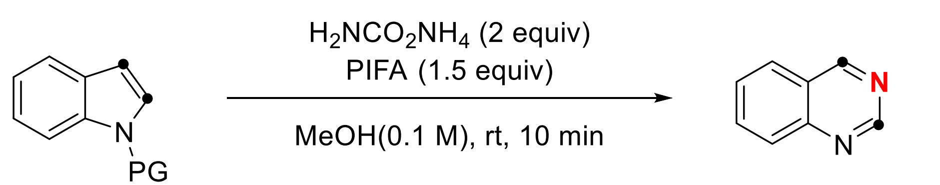
B. Morandi et al. *Science* **2022**, *377*, 1104–1109.

2 杂环骨架上氮原子的插入

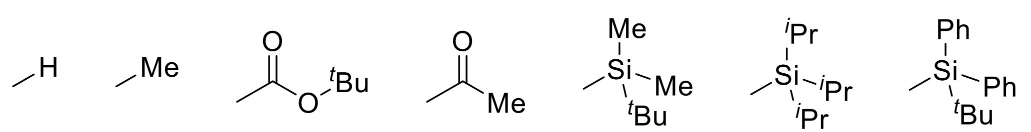
Inherent challenge



Protecting group effect

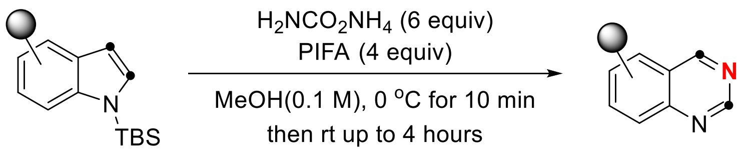


PG =

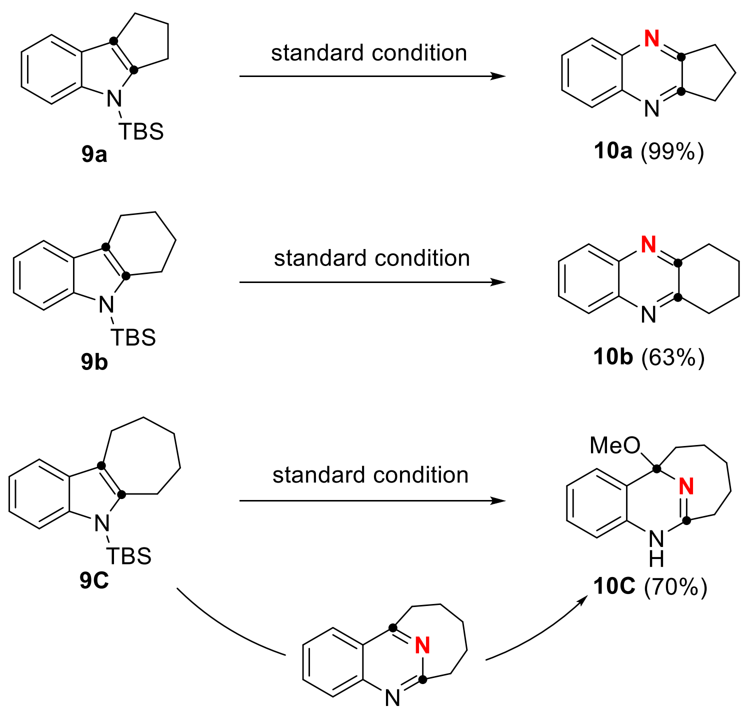


	1a	2a	3a	4a	5a	6a	7a
GC yield	1%	-	4%	2%	47%	27%	9%

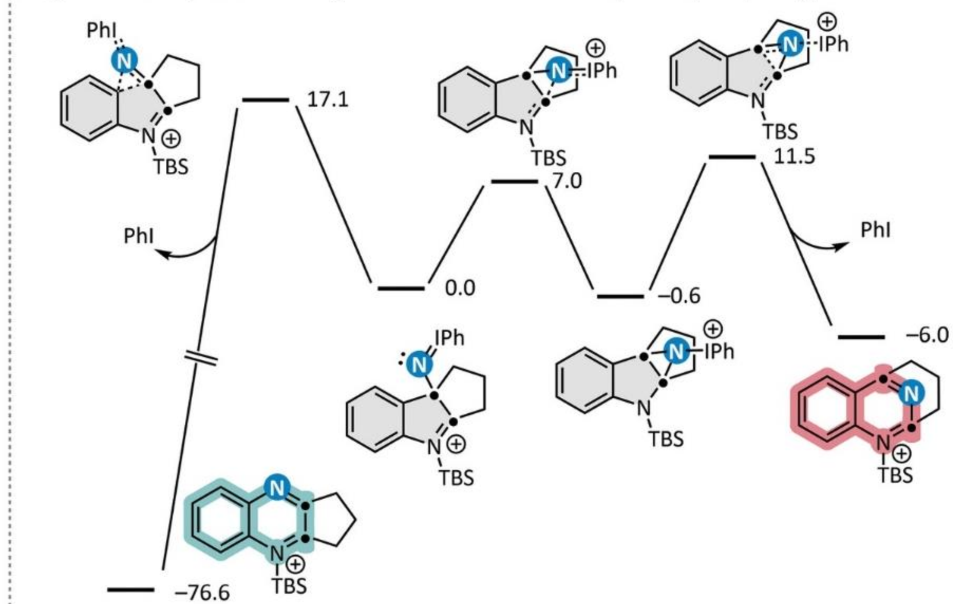
2 杂环骨架上氮原子的插入



A Quinazoline vs. Quinoxaline



Regioselectivity for sterically constrained substrates ($\Delta G^{0°C}$ [kcal/mol])



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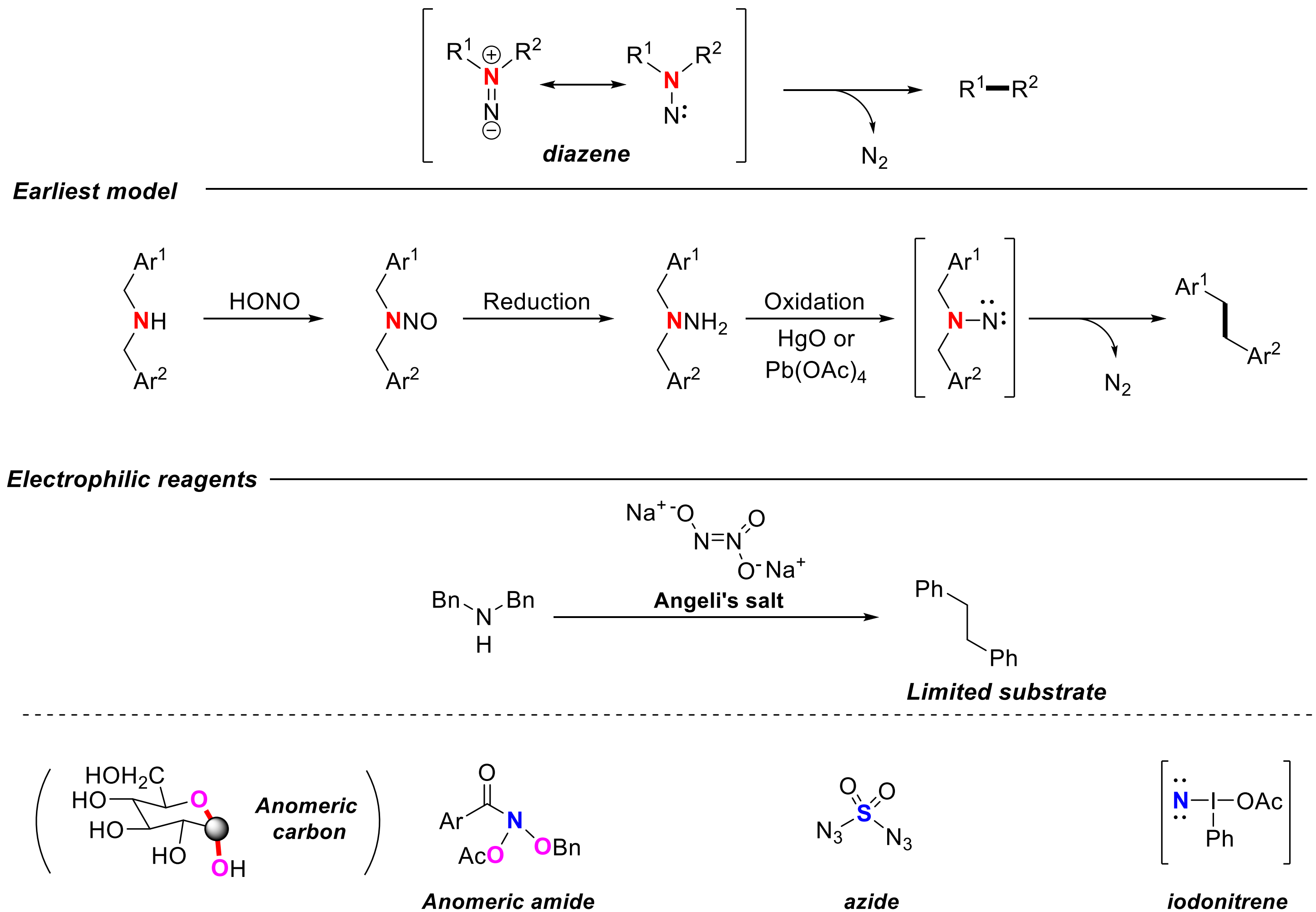
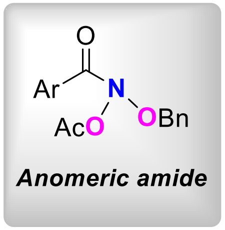
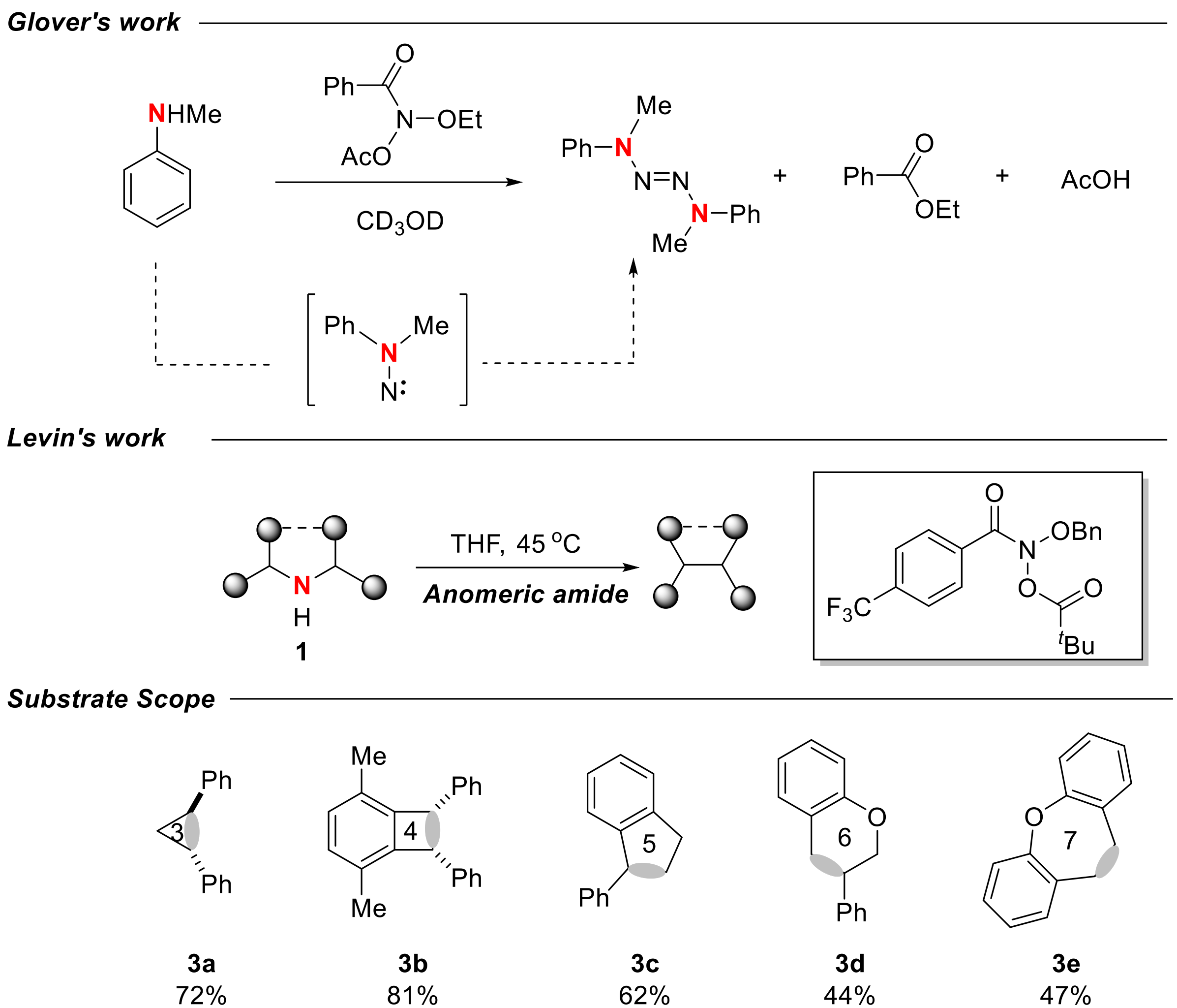
3 杂环骨架上氮原子的删除



W. R. McBride et al. *J. Am. Chem. Soc.* **1957**, *79*, 6568–6569.
K. L. Hamm et al. *J. Am. Chem. Soc.* **1959**, *81*, 3294–3297.
R. G. Hiskey et al. *J. Am. Chem. Soc.* **1961**, *83*, 1374–1378.
T. W. Rave et al. *J. Am. Chem. Soc.* **1965**, *87*, 393–394.
P . B. Dervan et al. *J. Am. Chem. Soc.* **1978**, *100*, 1608–1610.

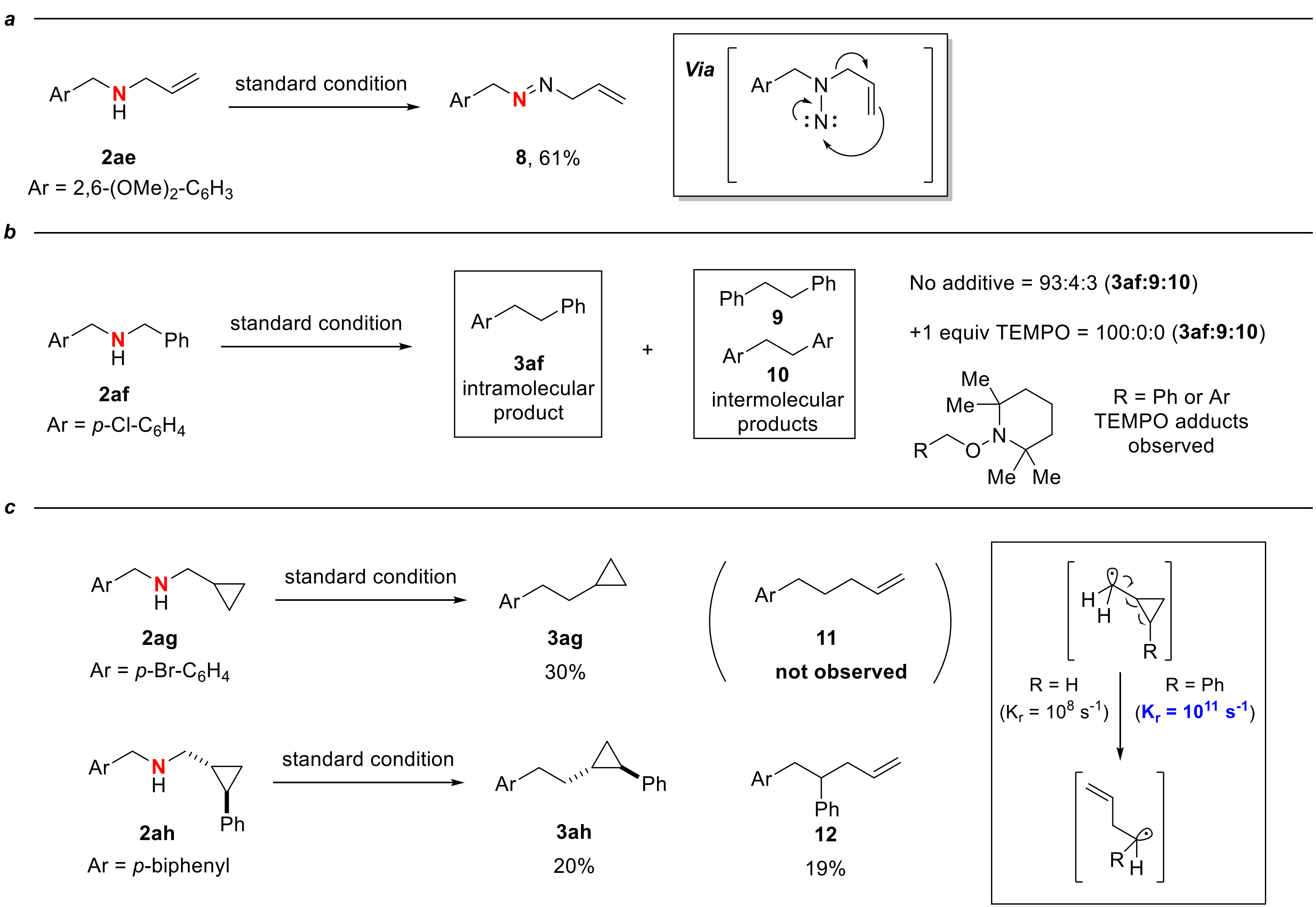
3 杂环骨架上氮原子的删除





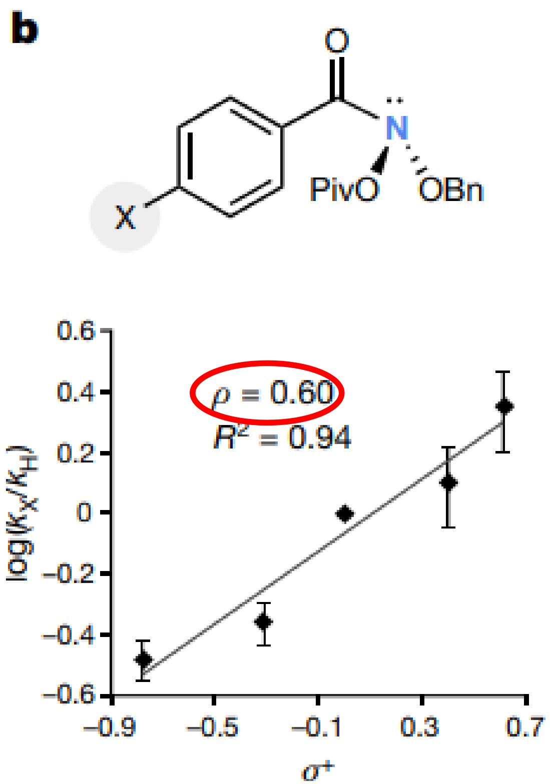
S. A. Glover et al. *J. Chem. Soc. Perkin Trans. 2*, **1992**, *1661−663*.
Mark D. Levin et al. *Nature* **2021**, *593*, 223−227.

3 杂环骨架上氮原子的删除



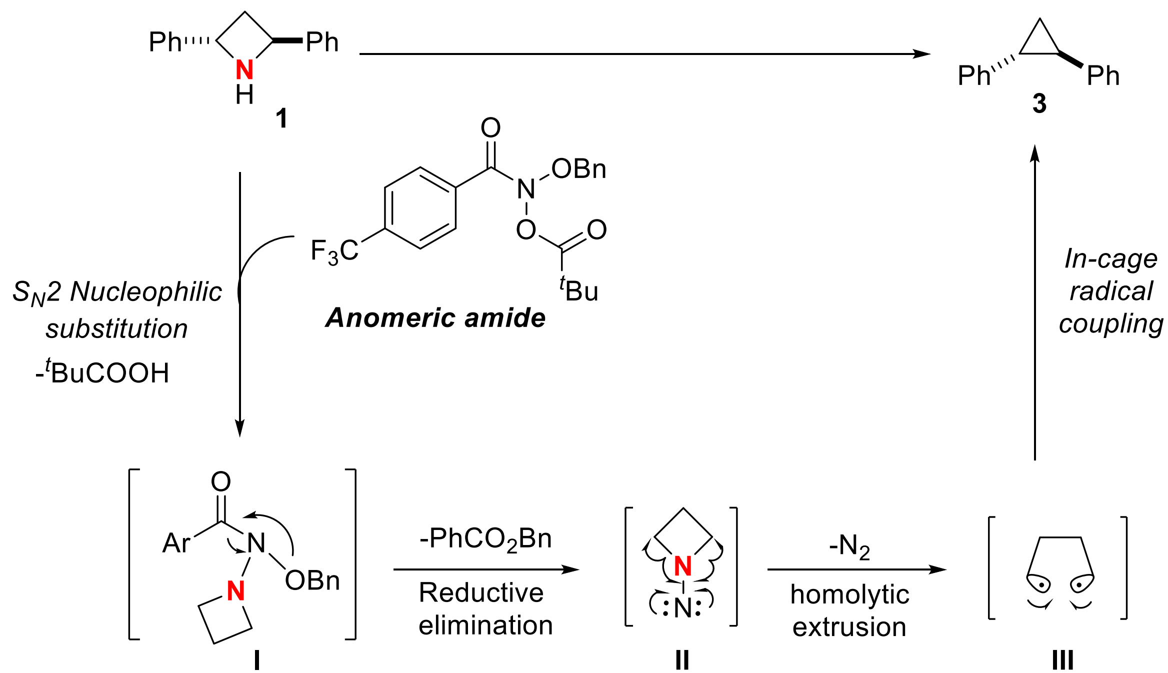
3 杂环骨架上氮原子的删除

Hammett plot

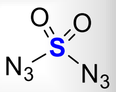


$0 < \rho = 0.60 < 1$

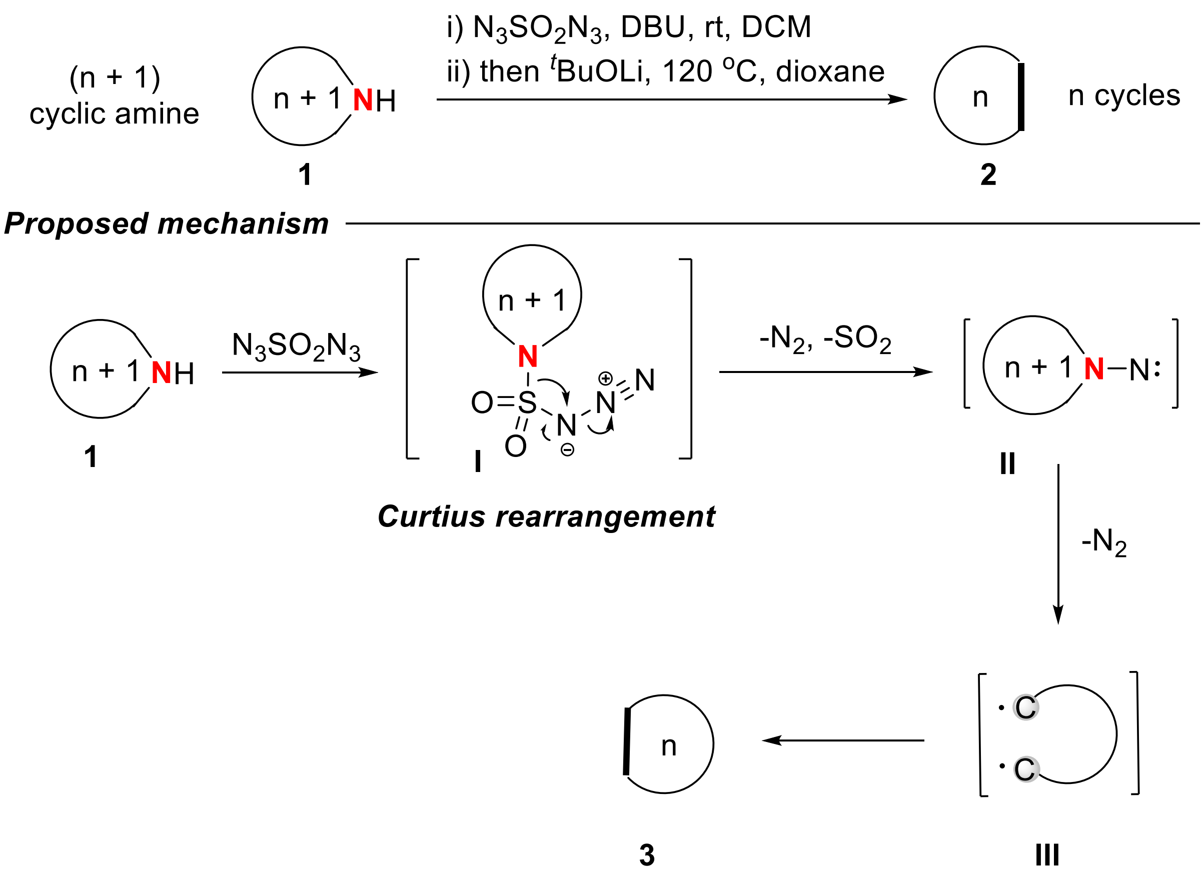
Proposed mechanism



3 杂环骨架上氮原子的删除



azide

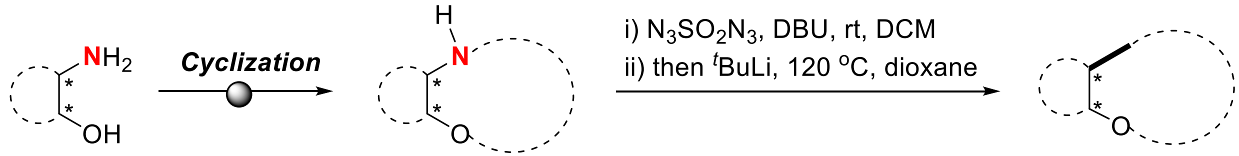


H. J. Lu et al. *Angew. Chem. Int. Ed*. **2021**, *60*, 20678–20683.

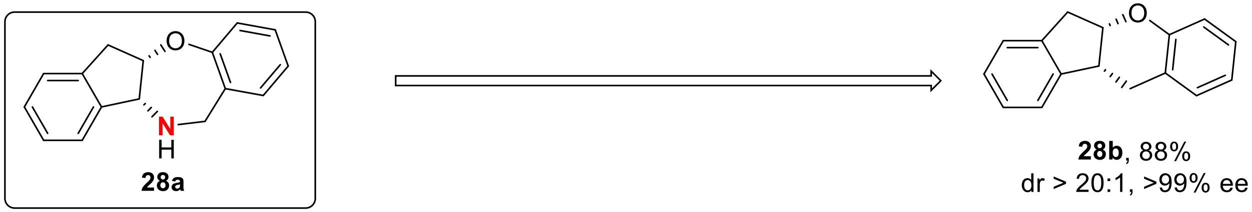
3 杂环骨架上氮原子的删除

Synthesis of chiral cycles

available chiral hydroxylamines

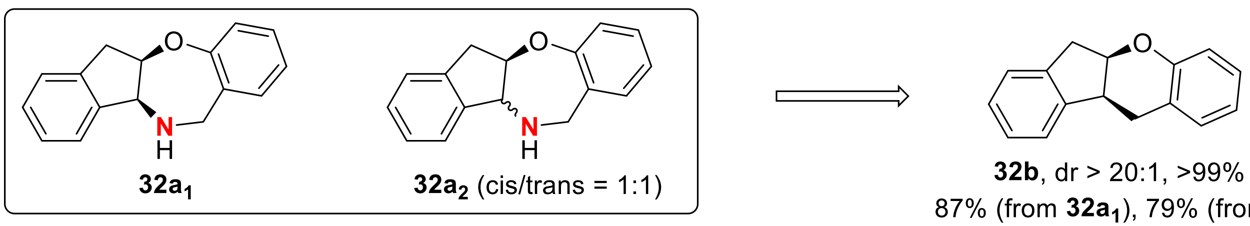


28a', 32a$_1$', 32a$_2$' **28a, 32a$_1$, 32a$_2$** **28b, 32b**



28a

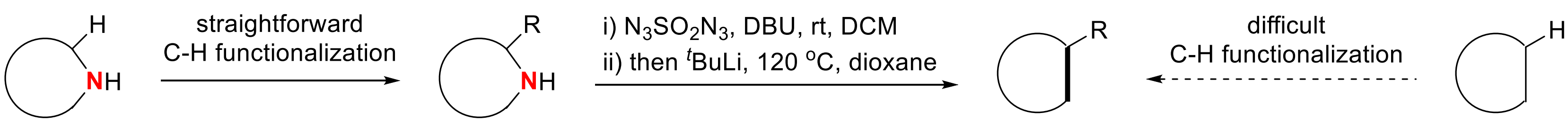
28b, 88%
dr > 20:1, >99% ee



32a$_1$ **32a$_2$** (cis/trans = 1:1)

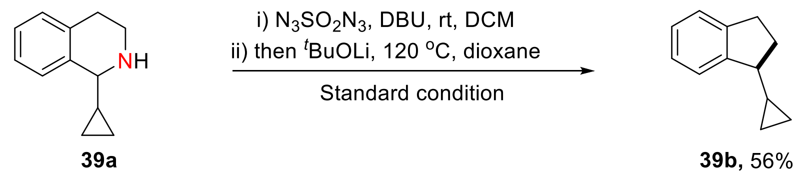
32b, dr > 20:1, >99% ee
87% (from **32a$_1$**), 79% (from **32a$_2$**)

C-H functionalization

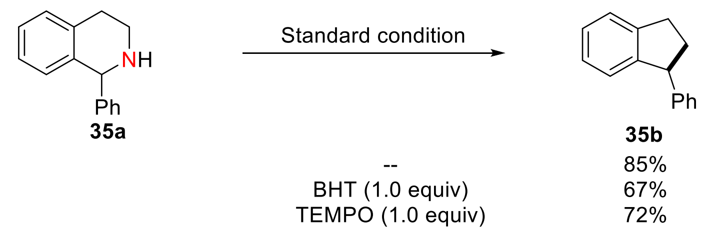


3 杂环骨架上氮原子的删除

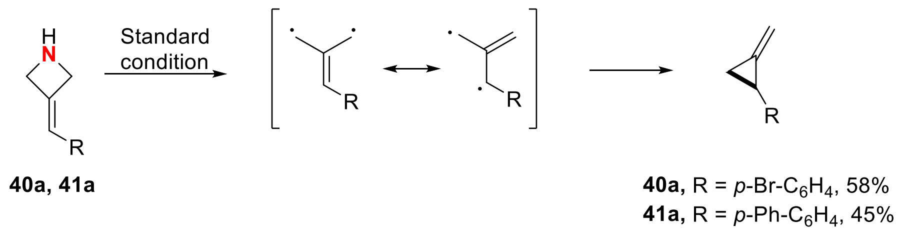
A radical clock experiment



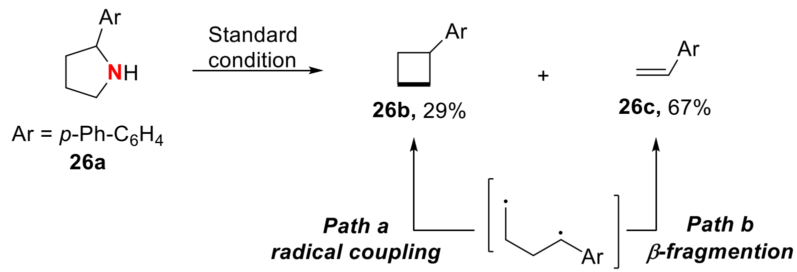
B radical trapping experiment



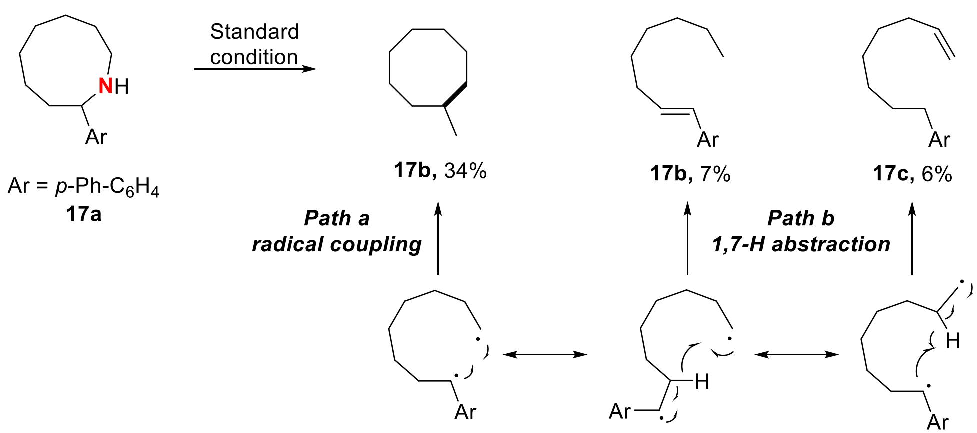
C 1,3-radical shift experiment



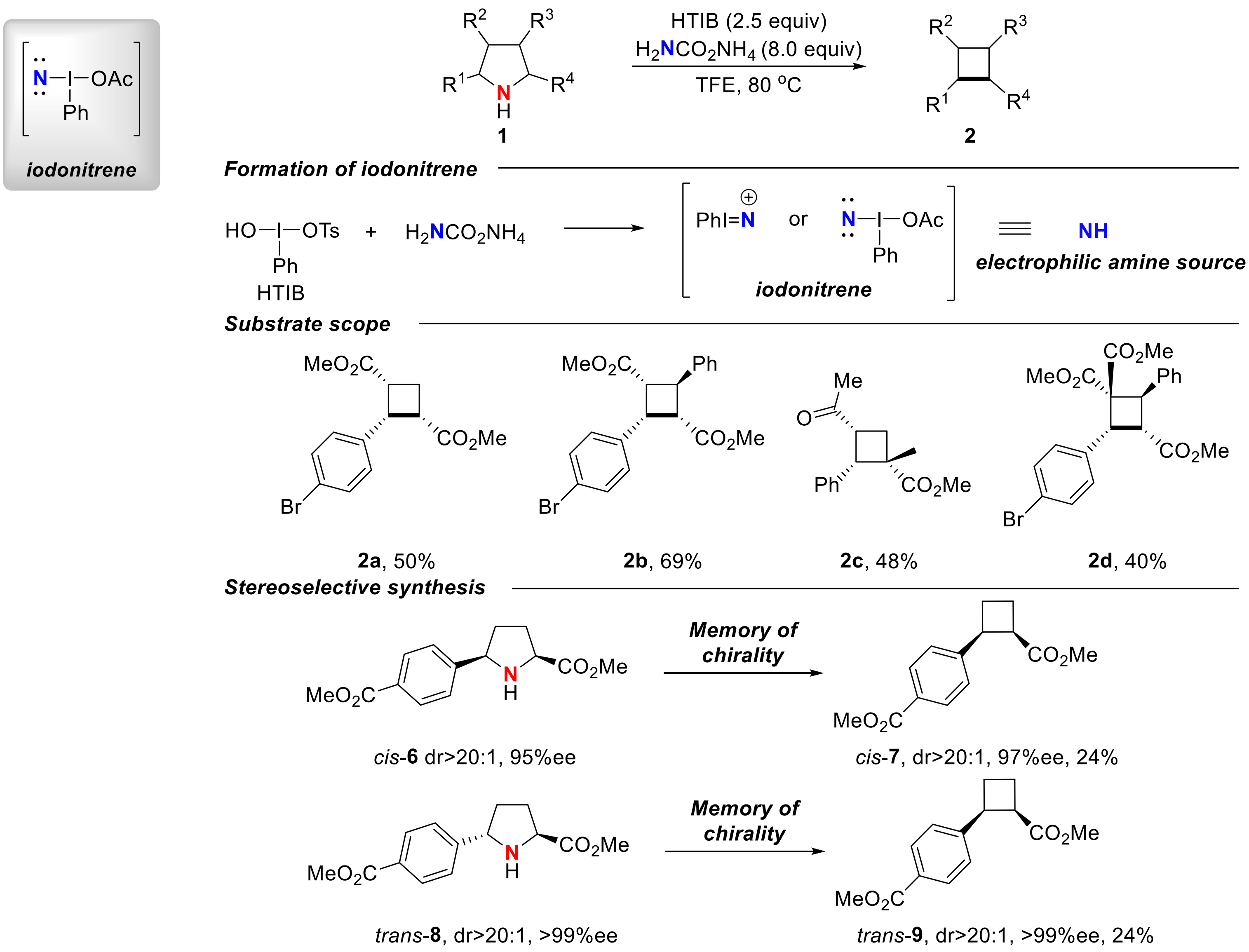
D β-fragmention



E 1,7-H abstraction



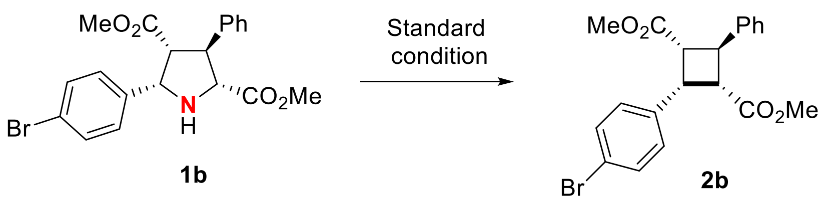
3 杂环骨架上氮原子的删除



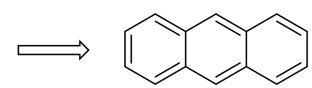
A. P. Antonchick et al. *J. Am. Chem. Soc*. **2021**, *143*, 18864−18870.

3 杂环骨架上氮原子的删除

Mechanistic experiments

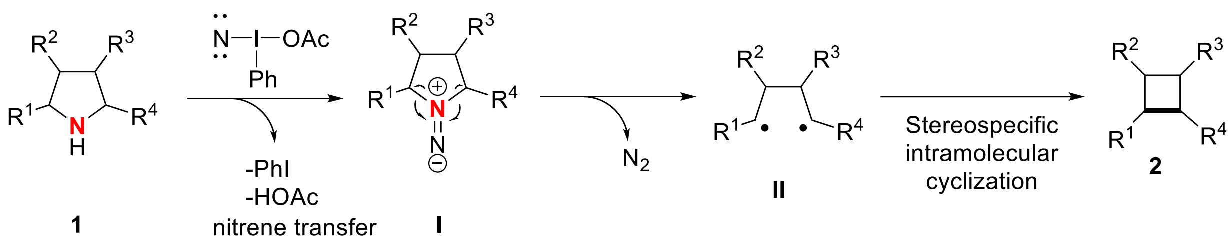


no additive	69%
TEMPO	nd
1,1-diphenylethylene	21%
9,10-dihydroanthracene	48%



observed

Proposed mechanism



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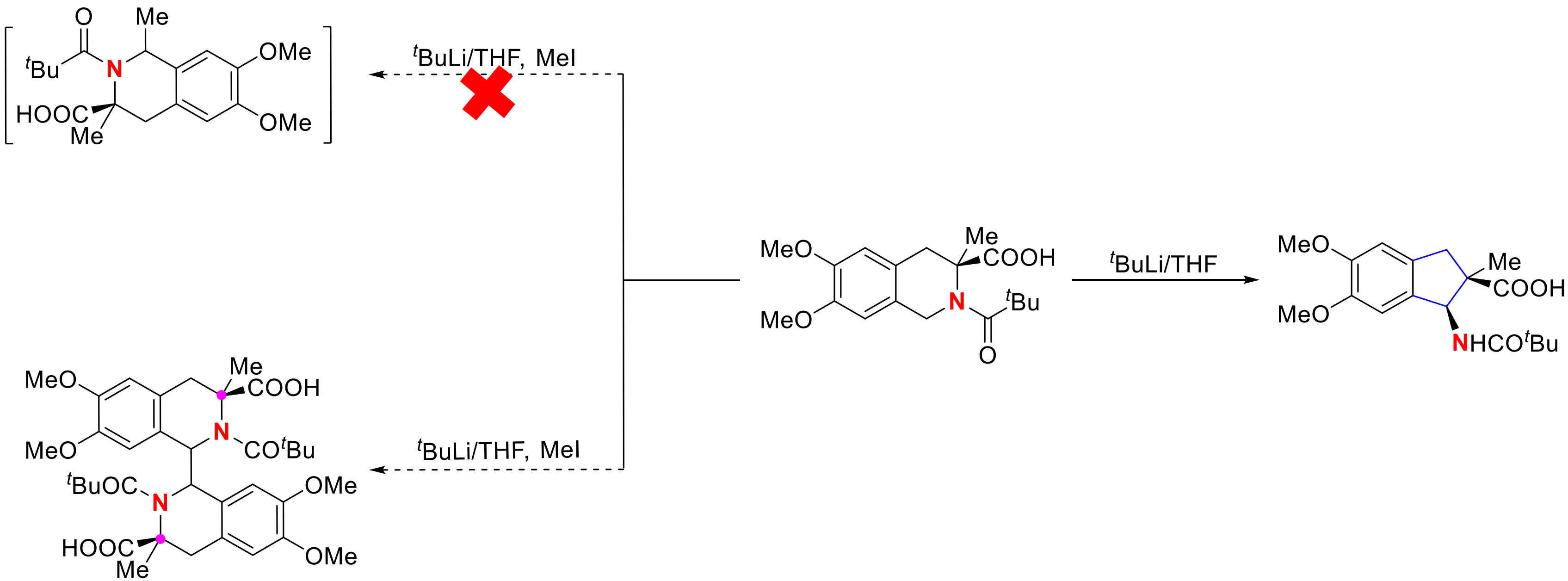
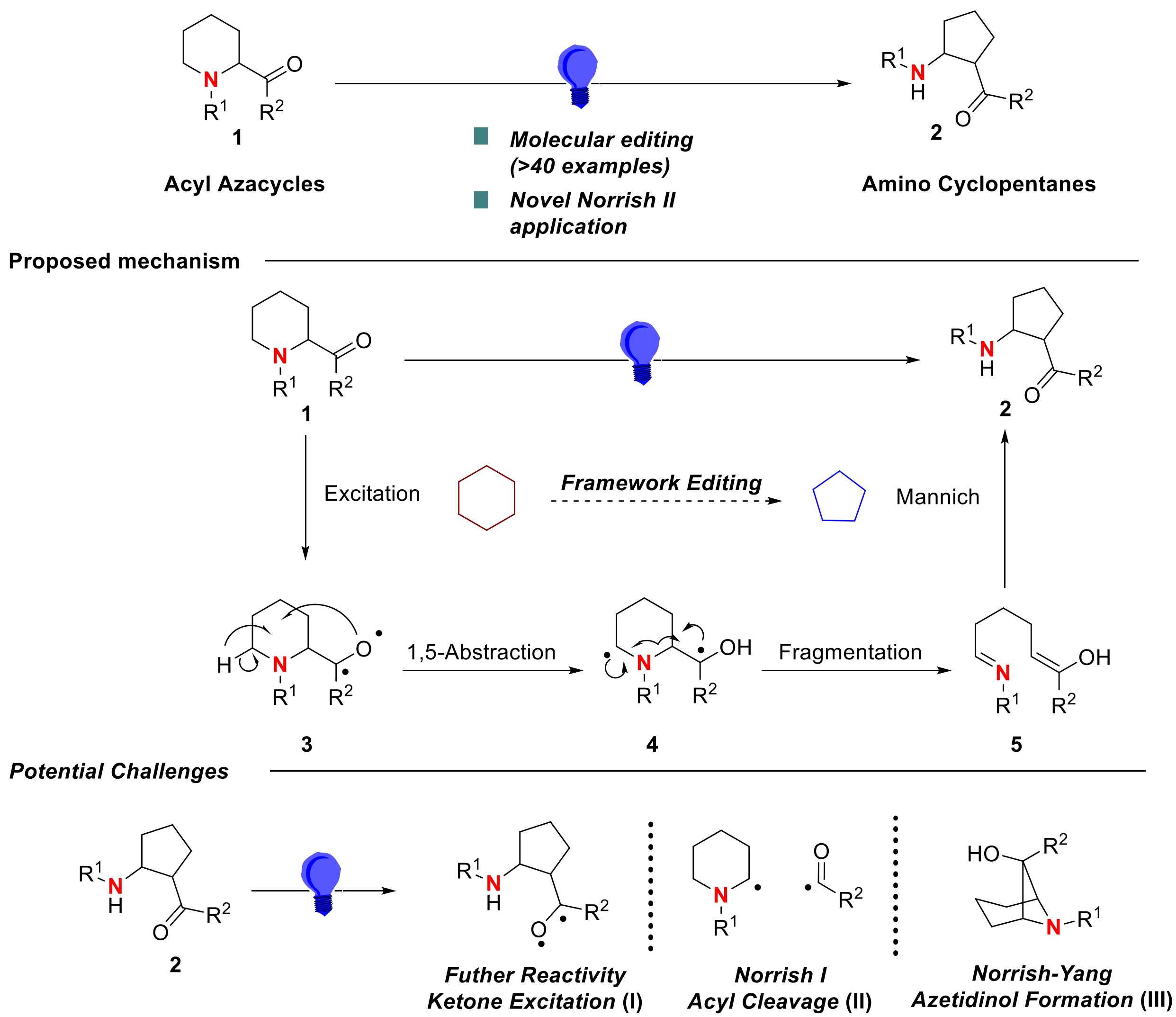
4 杂环骨架上氮原子的缩减

Seebach's group (1993)



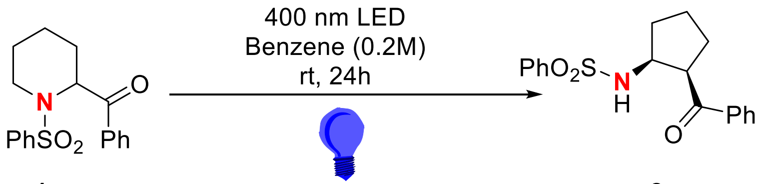
D. Seebach et al. *Helv. Chim. Acta*. **1993**, *76*, 2640–2653.

4 杂环骨架上氮原子的缩减

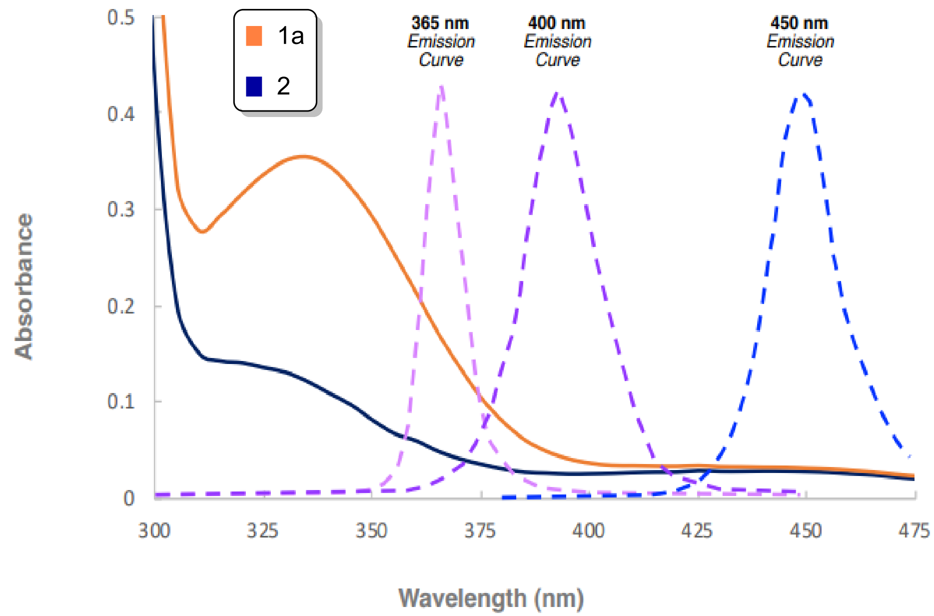


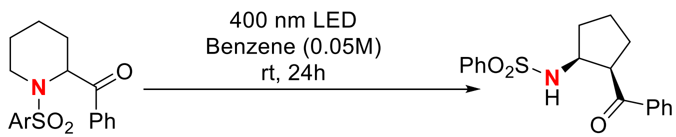
R. Sarpong et al. *Science* **2021**, *373*, 1004–1012.

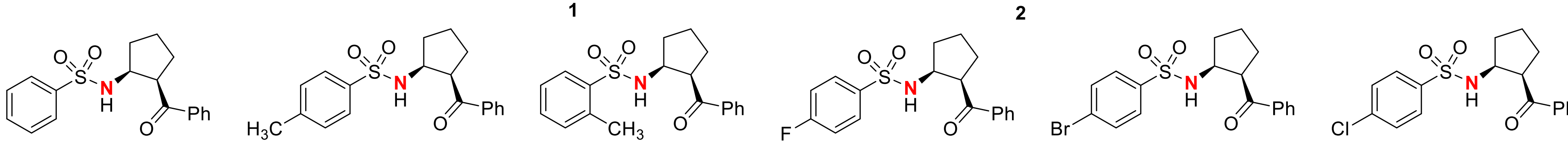
4 杂环骨架上氮原子的缩减



Entry	λ (blue LED)	NMR Yield	dr
1	365 nm	17%	20:1
2	400 nm	73%	20:1
3	450 nm	0	-





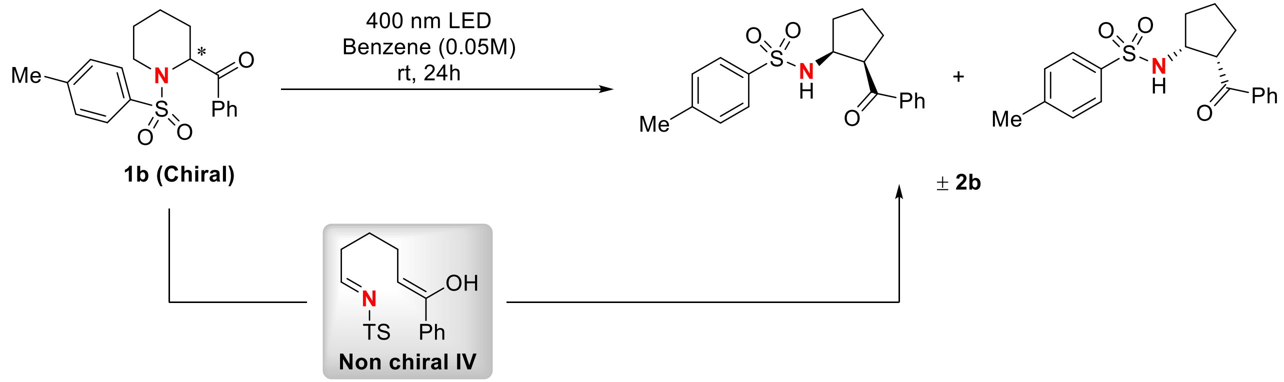


2a, 84% (20:1 dr) **2b,** 79% (12:1 dr) **2c,** 48% (19:1 dr) **2d,** 63% (19:1 dr) **2e,** 74% (12:1 dr) **2f,** 59% (3.3:1 dr)

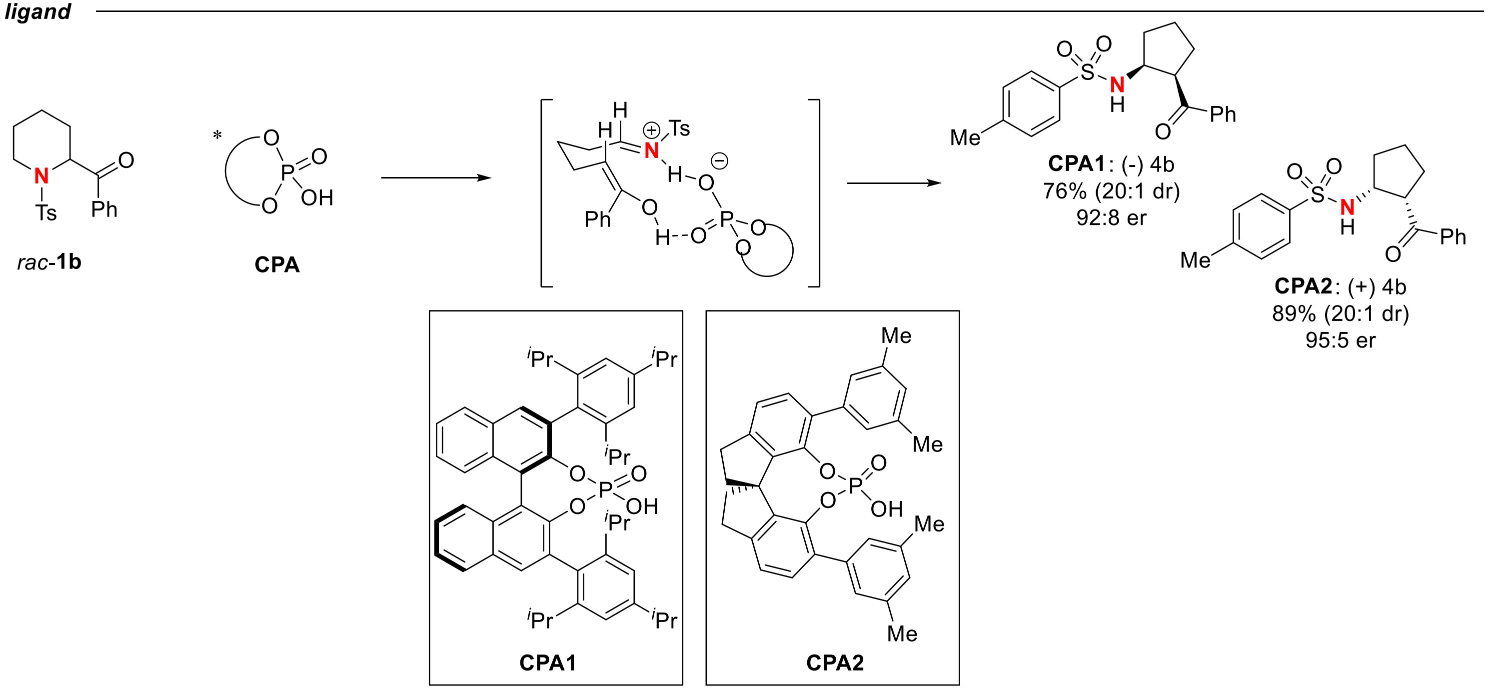
4 杂环骨架上氮原子的缩减

Asymmetric contraction variant

Enantiopure substrate



Chiral ligand



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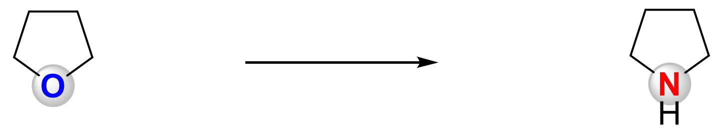
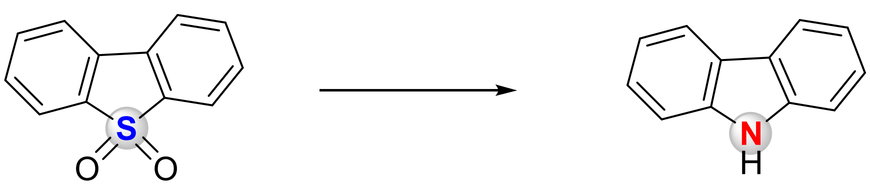
5 杂环骨架上氮原子的转换

Transformations

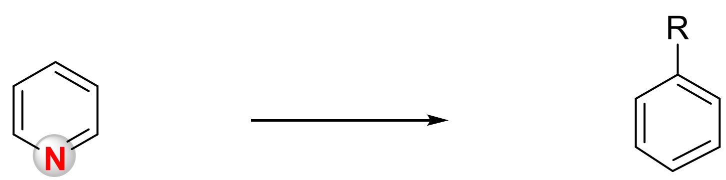
O to N



S to N



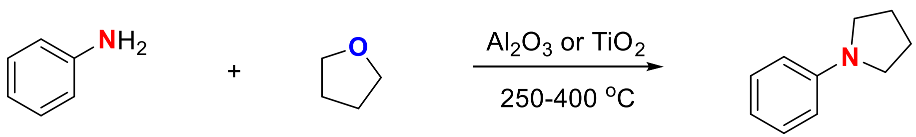
N to C



5 杂环骨架上氮原子的转换

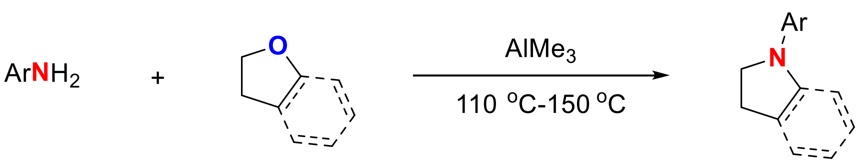
(O → N)

Classic work



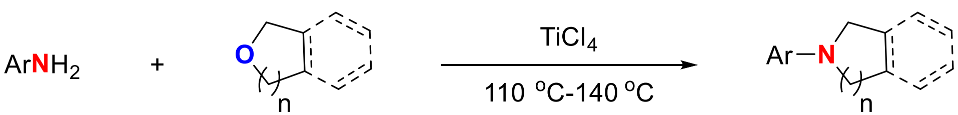
metallic Lewis acid-based N-hetero-cyclization of arylamine

Lee's group (2014)



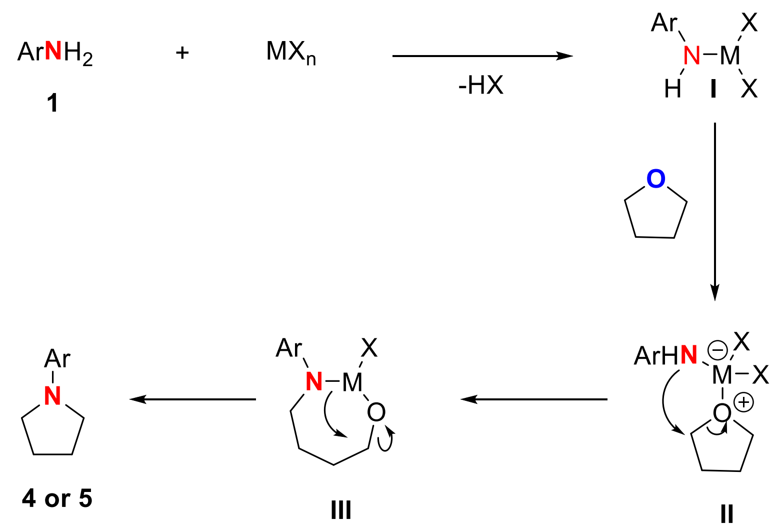
1 **2** **4**

Wang's group (2017)



1 **3** **5**

Proposed mechanism



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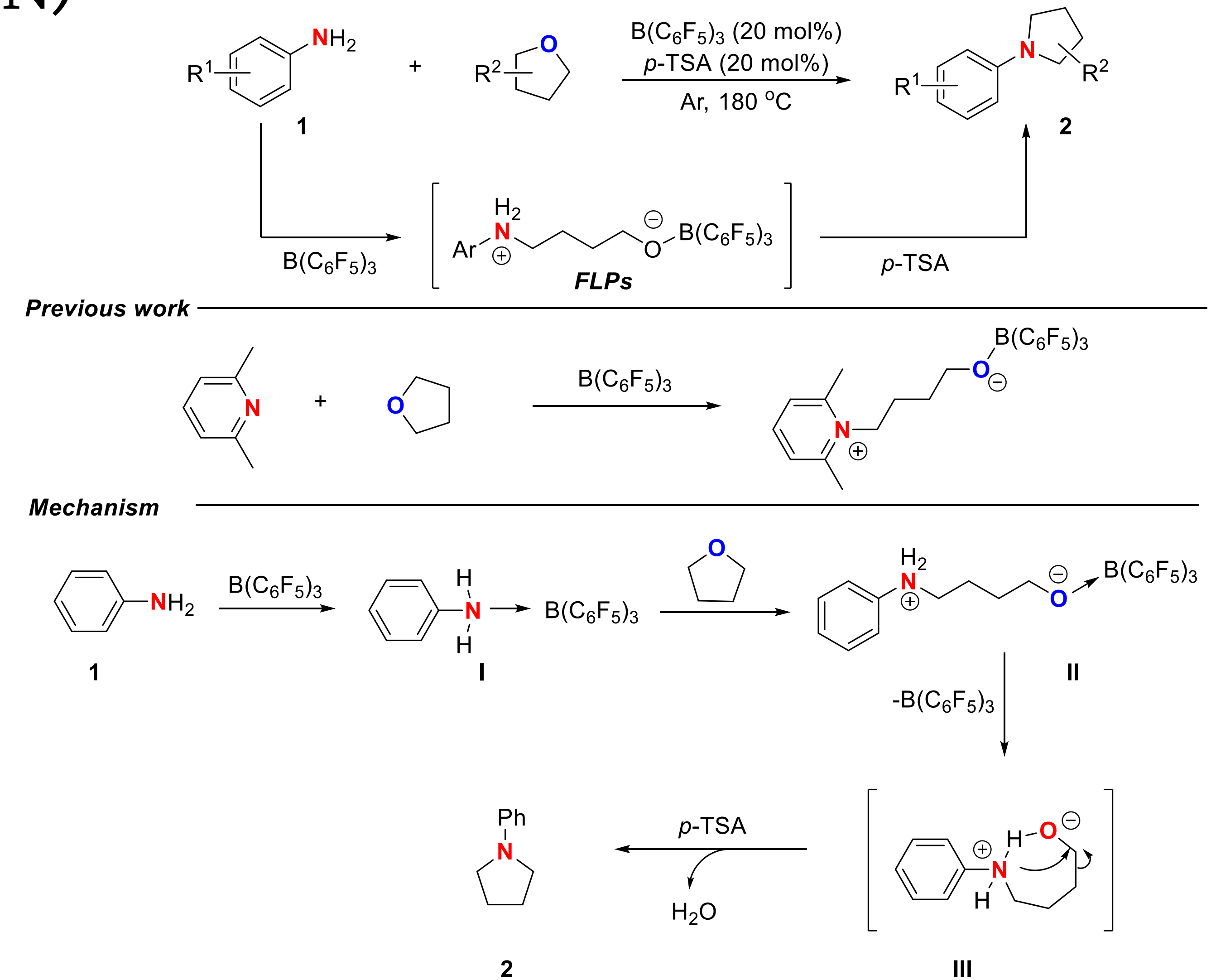
5 杂环骨架上氮原子的转换

（O ⟶ N）



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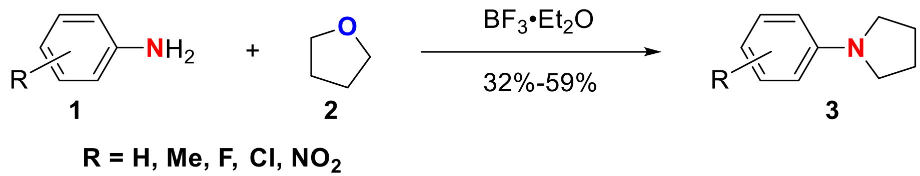
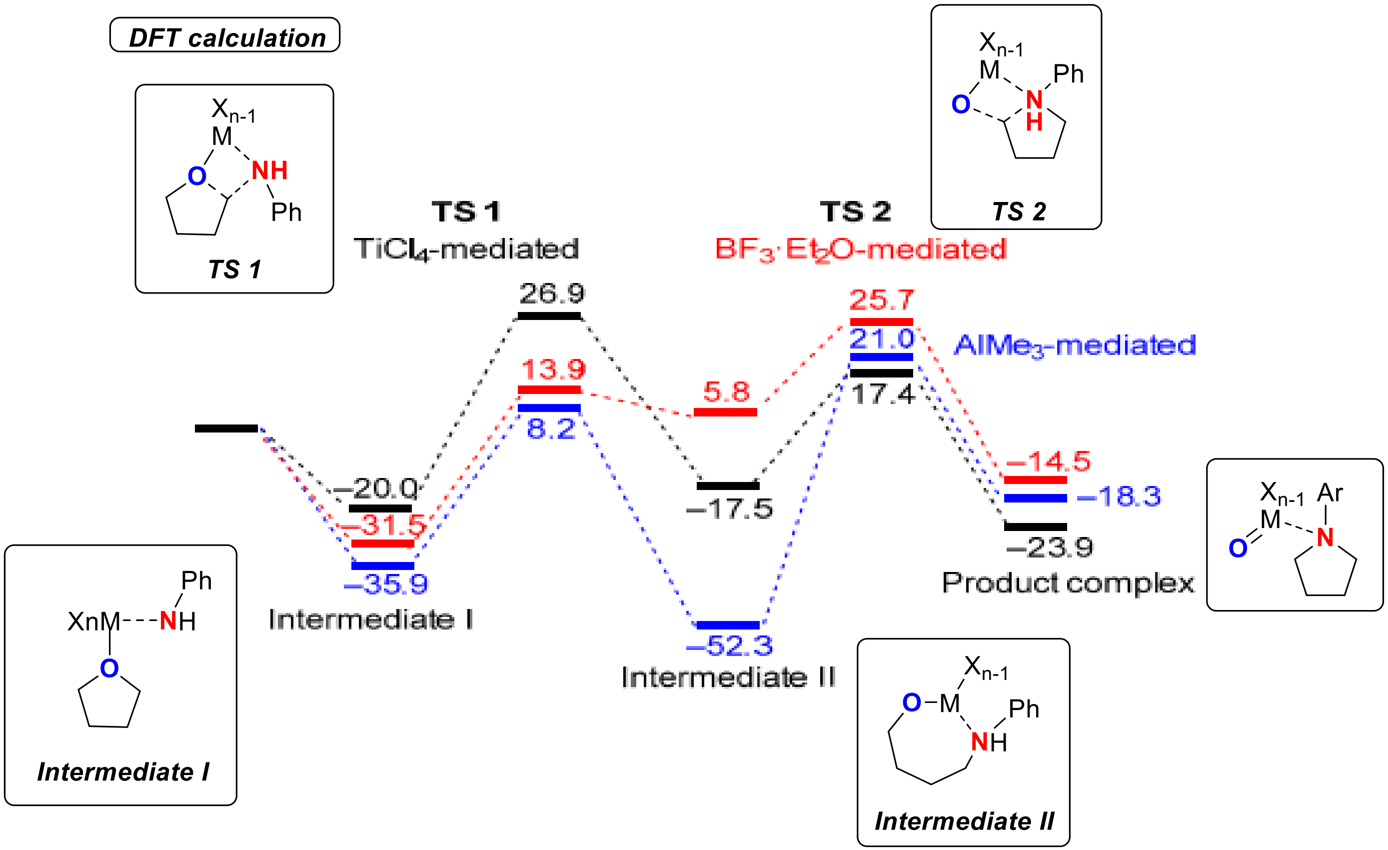
5 杂环骨架上氮原子的转换

（O → N）





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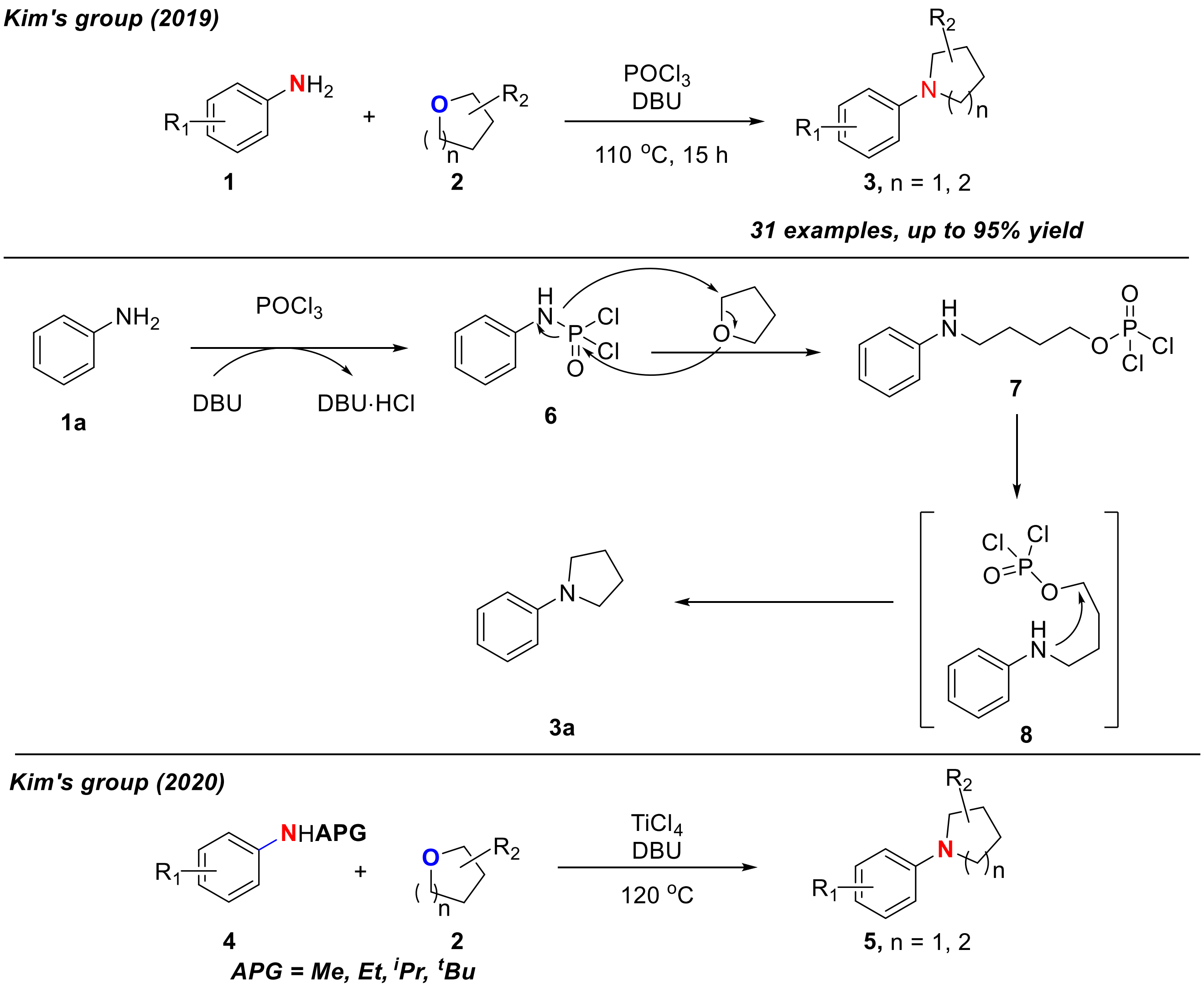
5 杂环骨架上氮原子的转换

（O → N）



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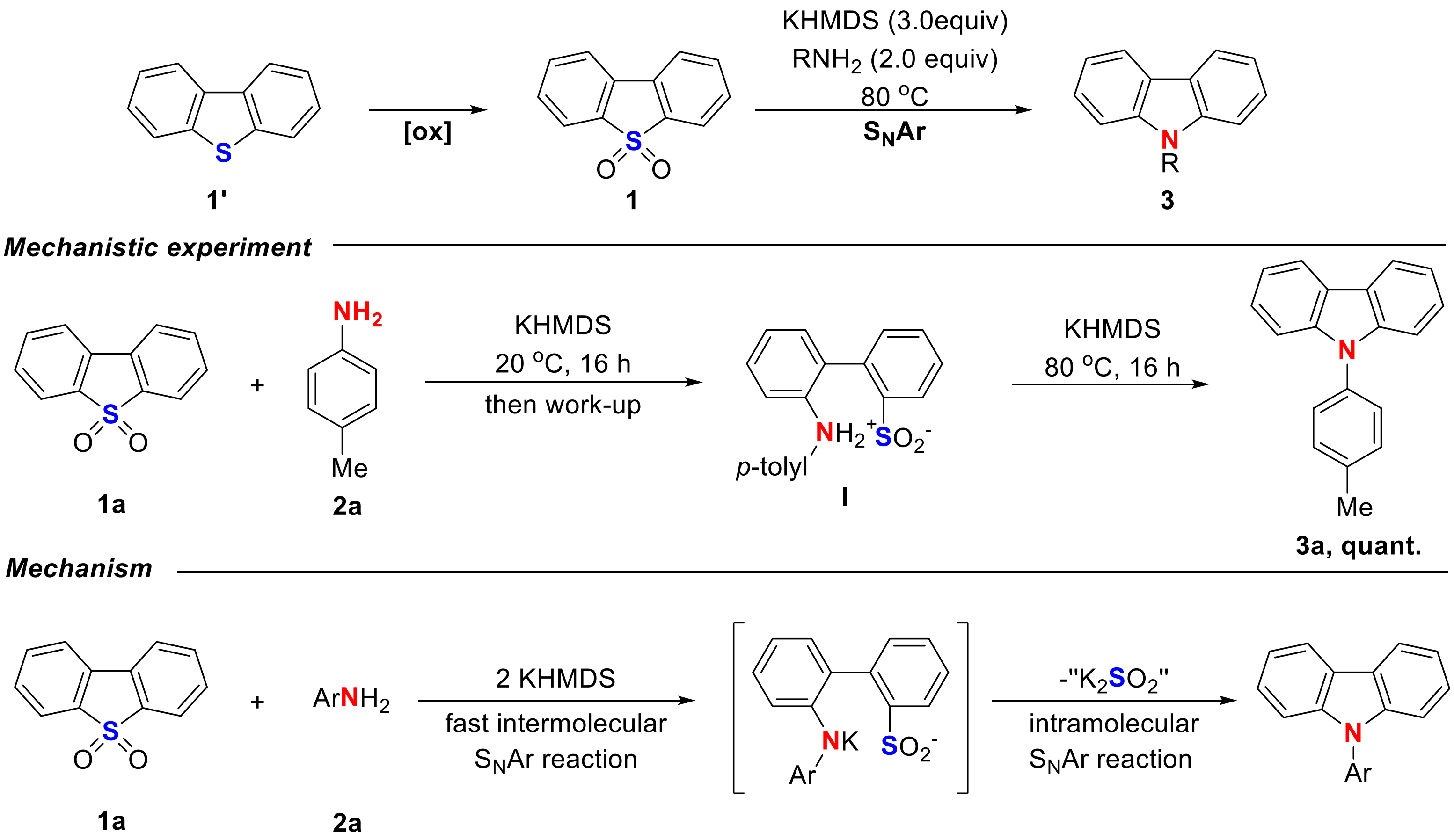
5 杂环骨架上氮原子的转换

(S → N)



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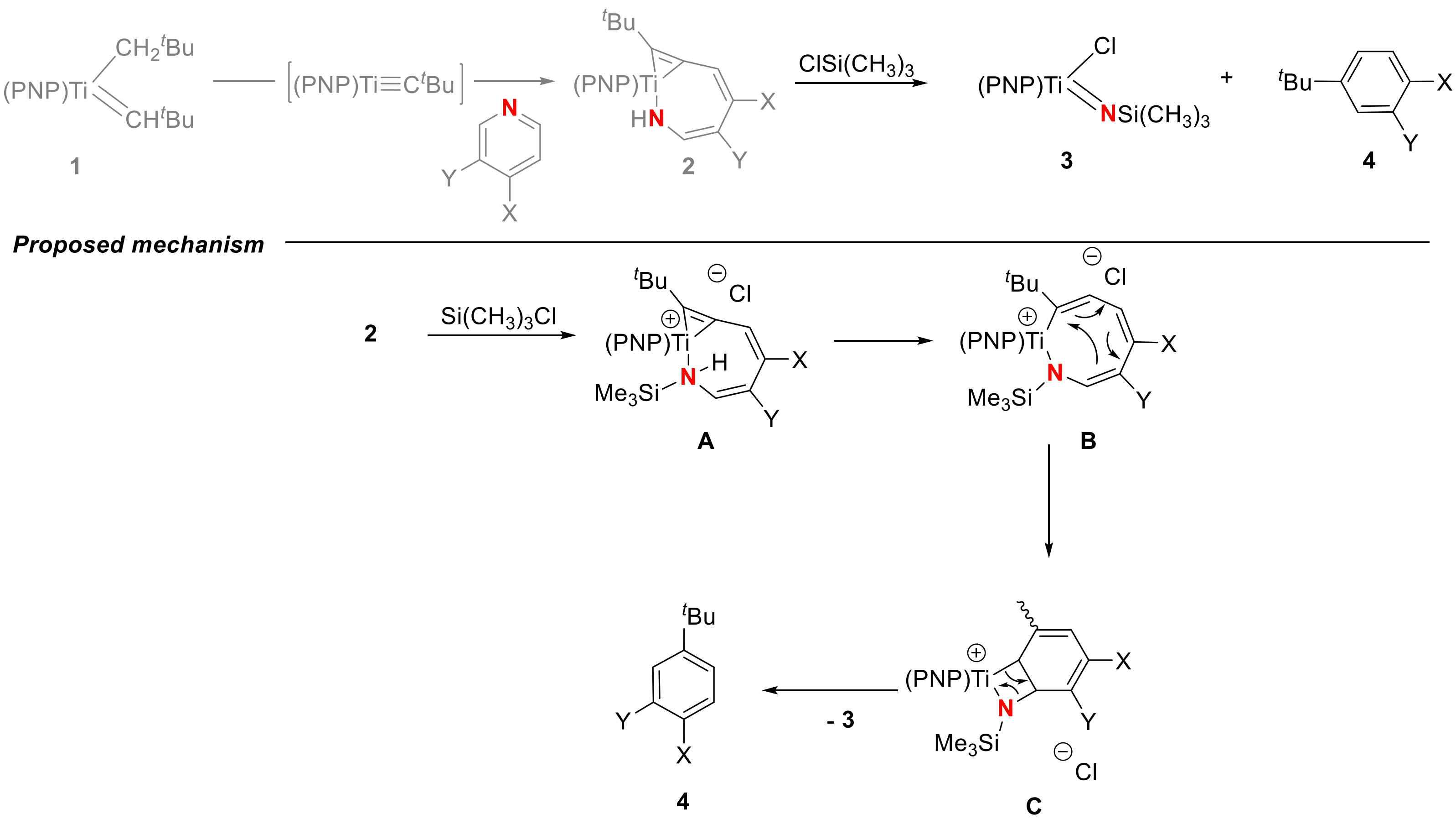
5 杂环骨架上氮原子的转换

（N ➡ C）



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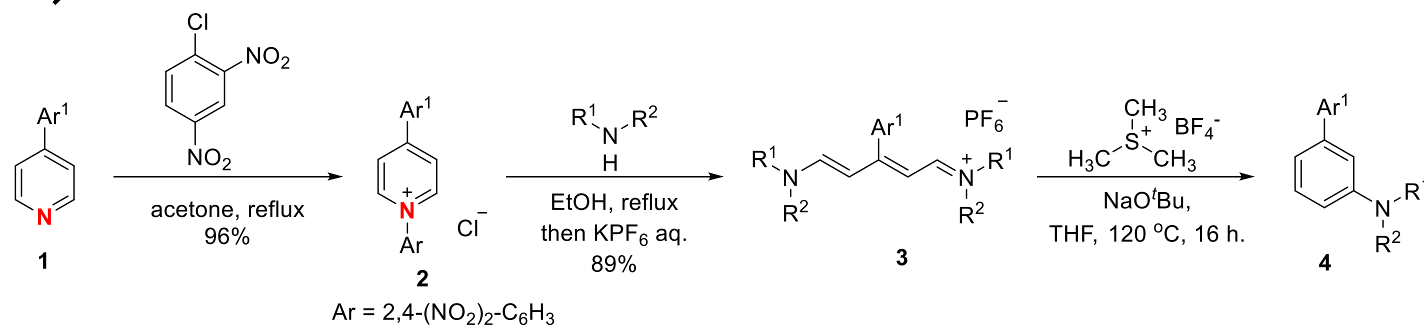
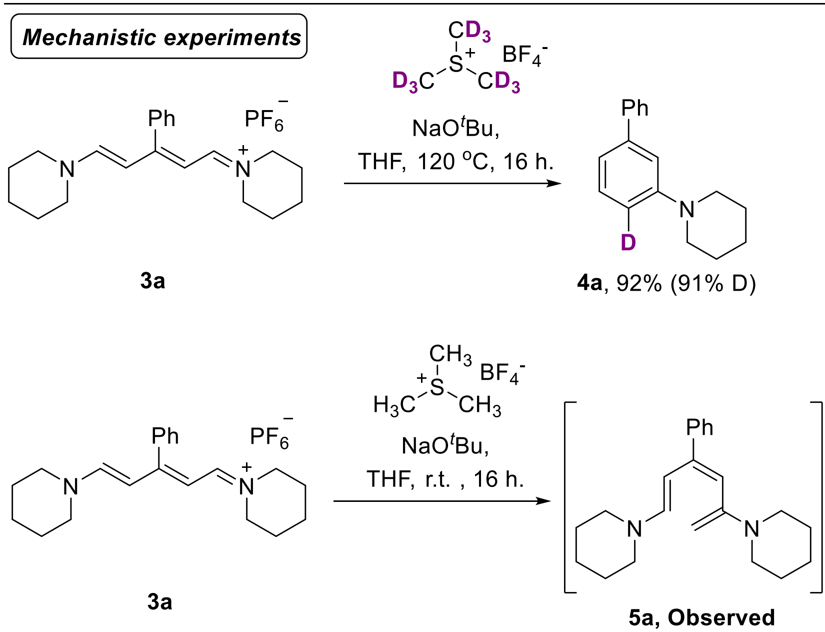
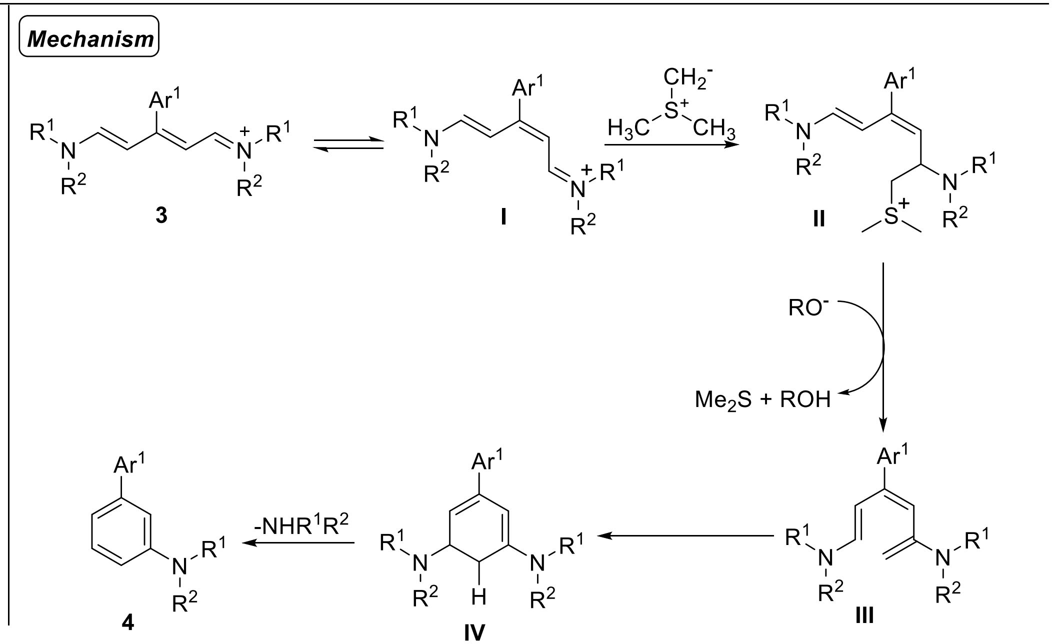
5 杂环骨架上氮原子的转换

（N → C）







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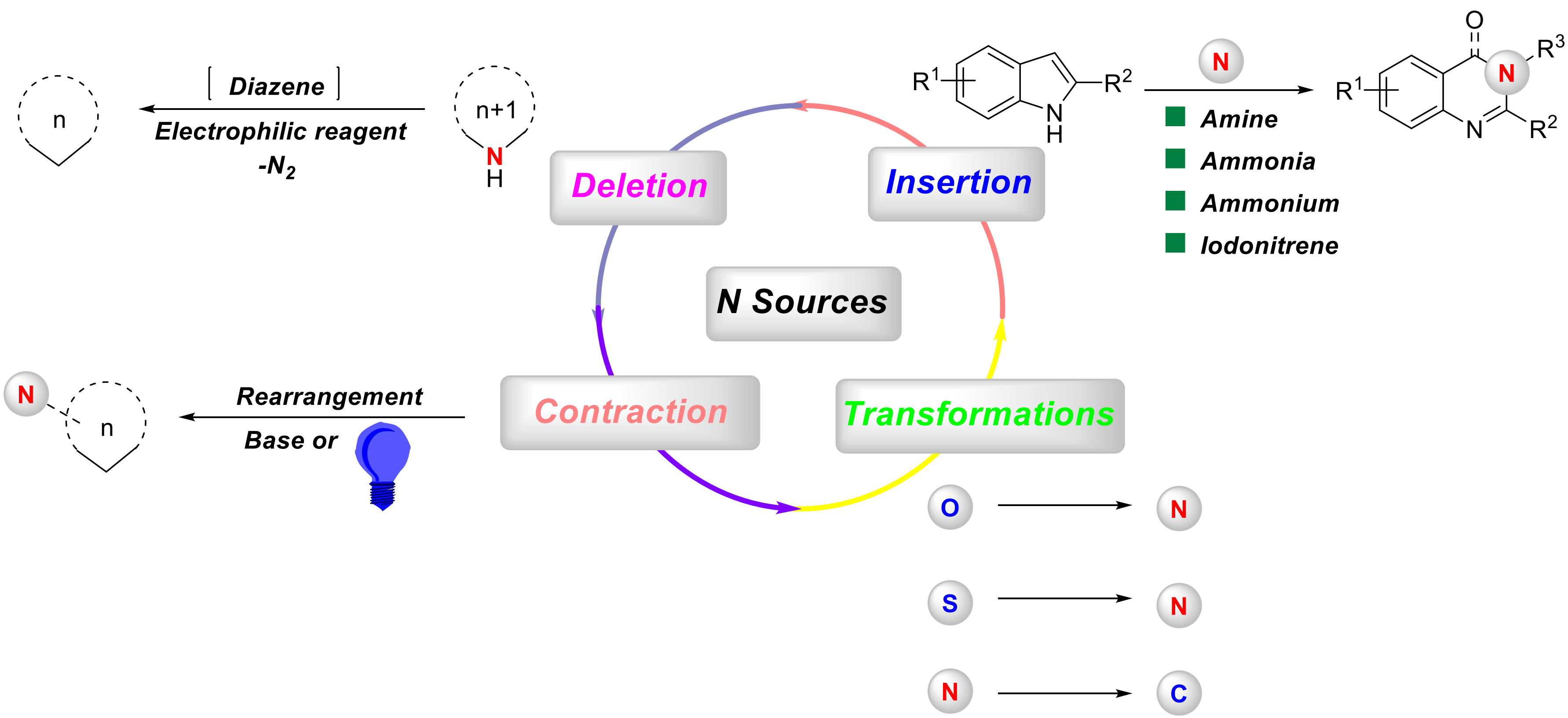
CONTENTS

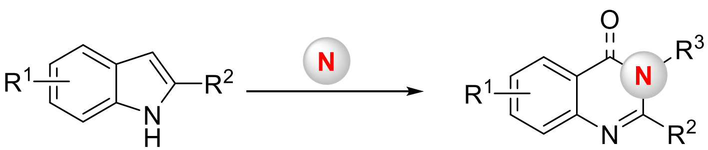
6 总结与展望



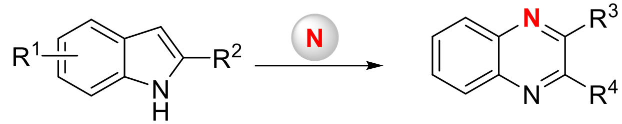
Diazene
Electrophilic reagent
-N2
n
n+1
N
H
R1
R2
N
H
O
R3
N
R1
N
R2
Amine
Ammonia
Ammonium
Iodonitrene
Deletion
Insertion
N Sources
Contraction
Transformations
Rearrangement
Base or
N
n
O
N
S
N
N
C

6 总结与展望

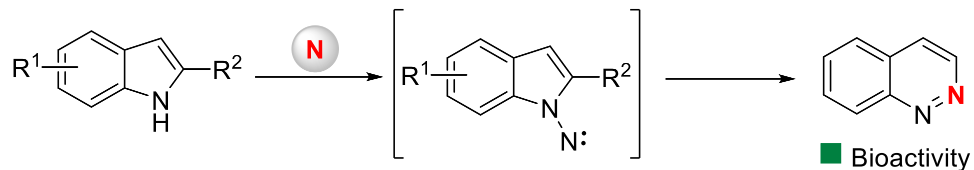
Insertion



Limited to indole

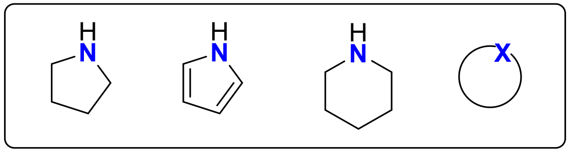


intermediate



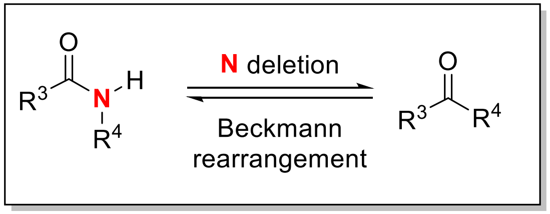
Bioactivity

Ligand



Deletion

Electron-rich



Chiral Ligands

Enzymes

THANKS

恳请各位老师、同学批评指正