饱和碳(杂)环的骨架结构编辑

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导师：左智伟 研究员

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The ways we make molecules…

bond formation, step by step

addition, substitution

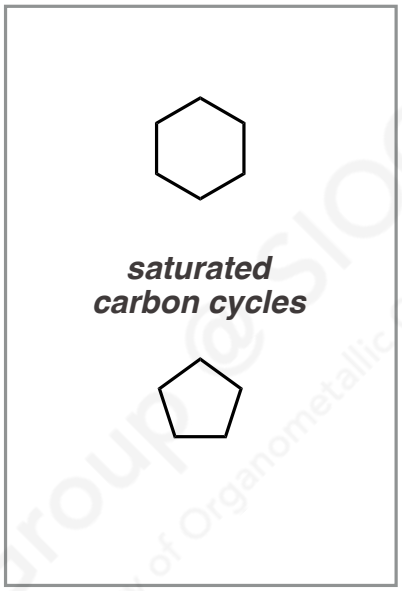
elimination, cyclization, etc.

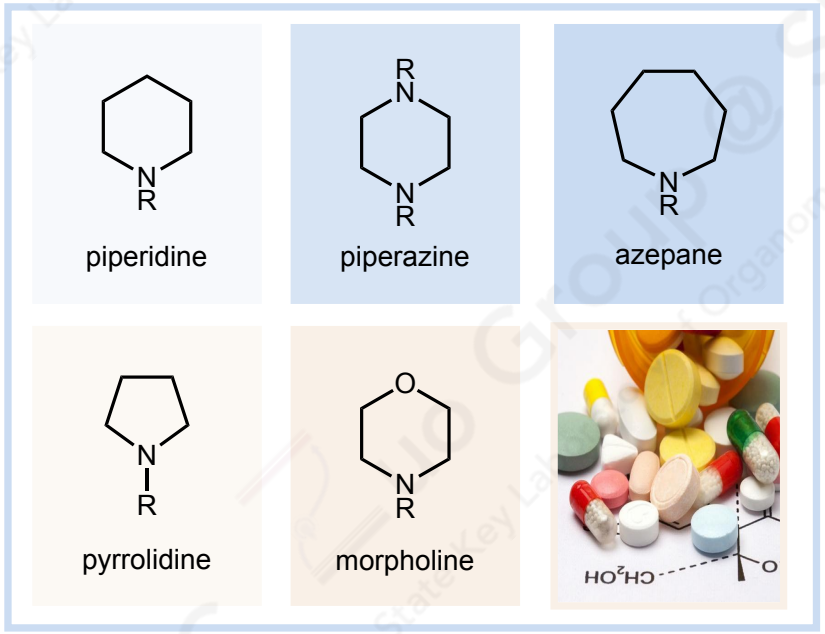
structural reconstruction

C–H functionalizations (late-stage)

ring expansion/contraction

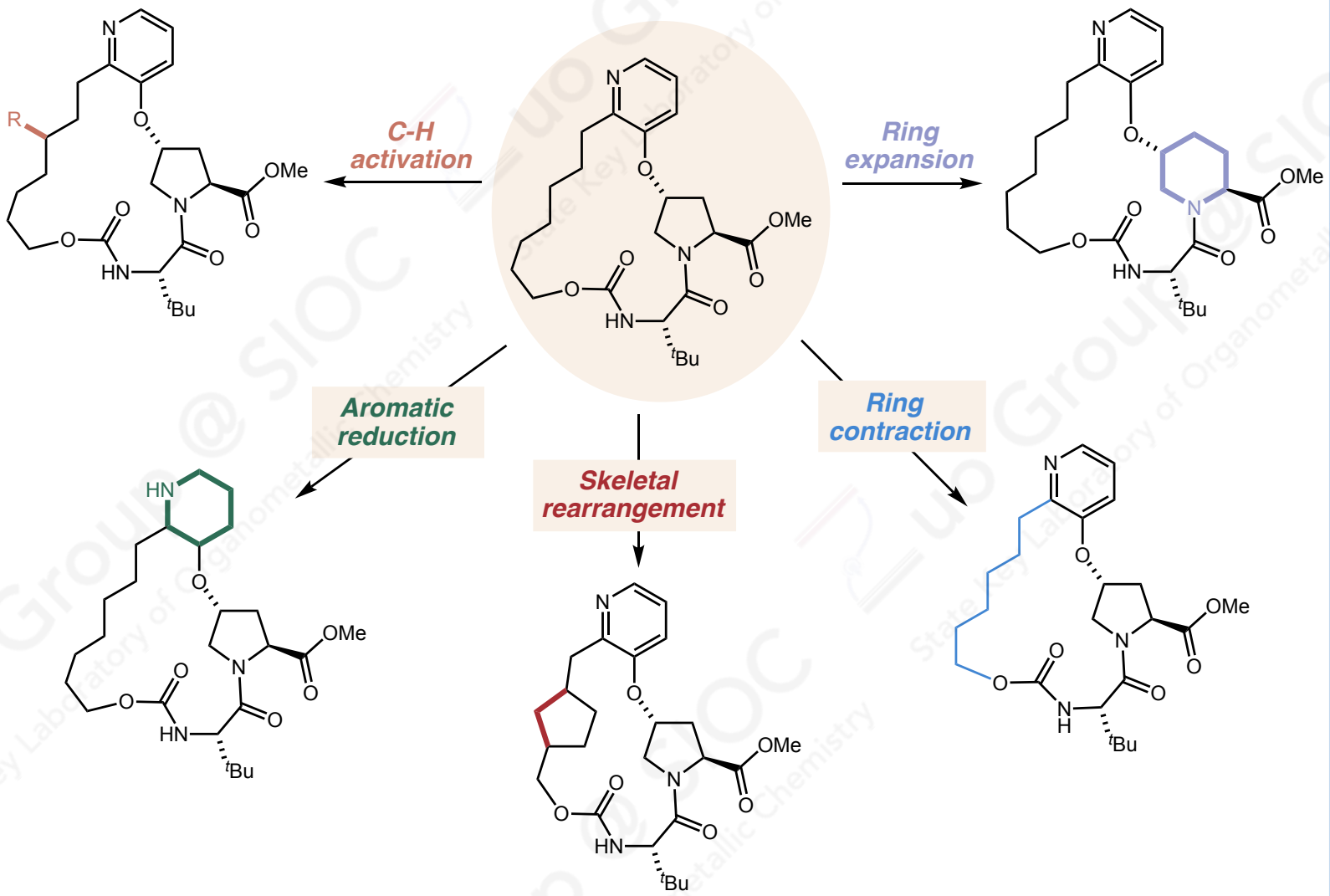
Can we edit ring structures directly ?





Structural reconstruction for molecular editing

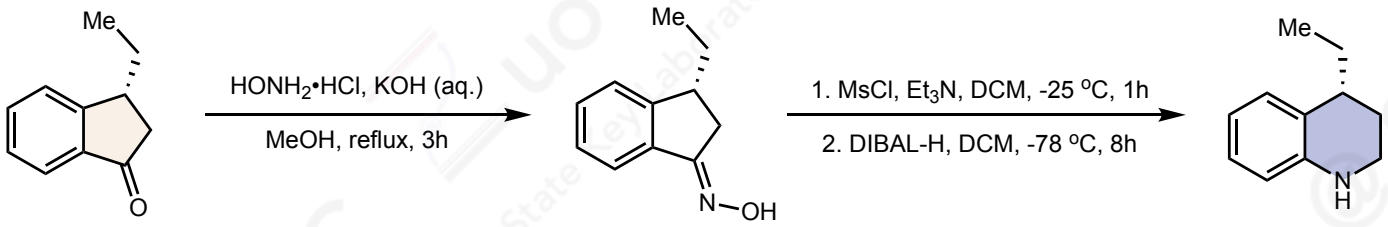
Proposed late-stage modification



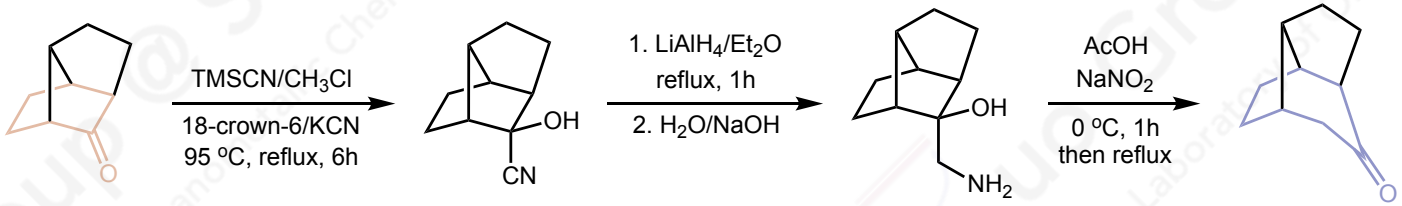
经典的扩环缩环反应

Classical name reaction

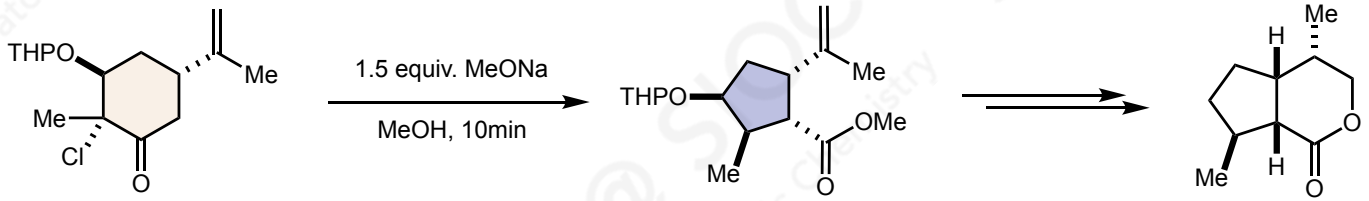
■ *Beckmann rearrangement*



■ *Demjanov rearrangement*

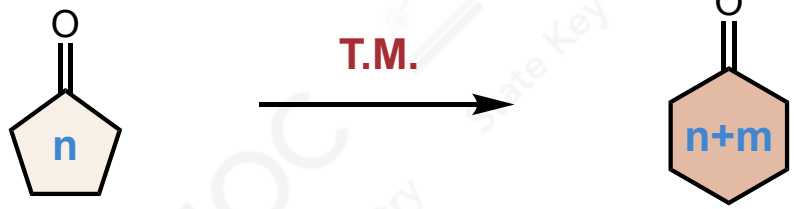


■ *Favorskii rearrangement*



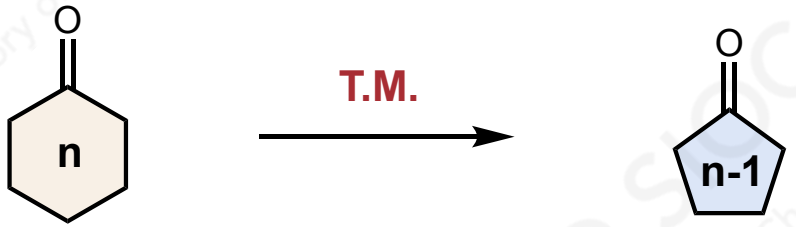
局限：特殊官能团 当量的反应试剂 多步转化

一. 非张力饱和碳(杂)环的扩环反应



- 过渡金属催化活化
- 自由基介导转化
- 饱和杂环

二. 非张力饱和碳(杂)环的缩环反应



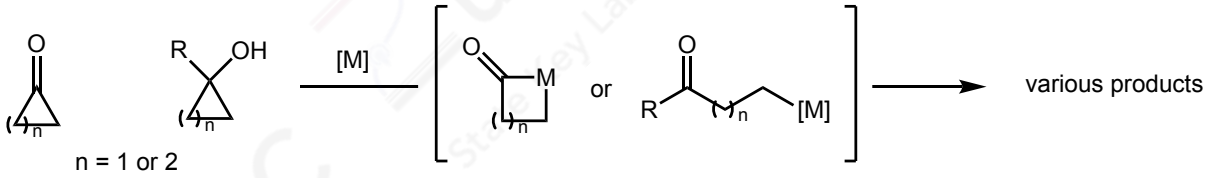
- 脱羰
- 环酮缩环
- 饱和杂环
- N deletion

1. 1 过渡金属催化的碳碳键活化扩环反应

General strategies in C-C bond activation

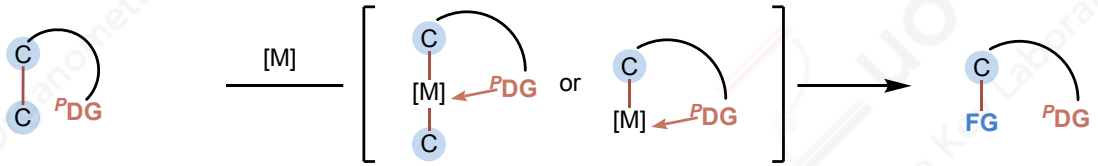
Strategies 1: Relief of ring string

- *C-C bond activation in strained rings.*

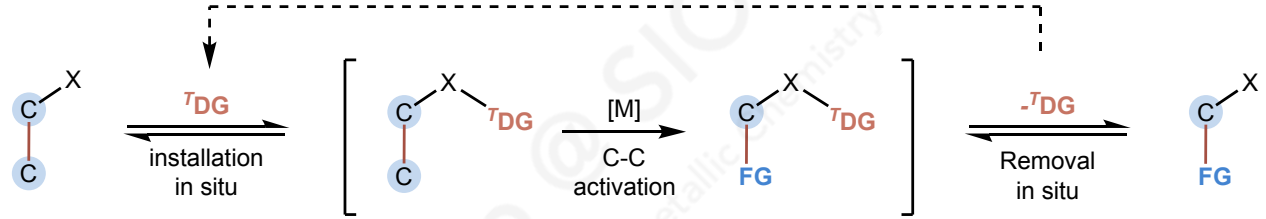


Strategies 2: Proximity effect of DG

- *Unstrained C-C bond activation assisted by permanent DGs.*



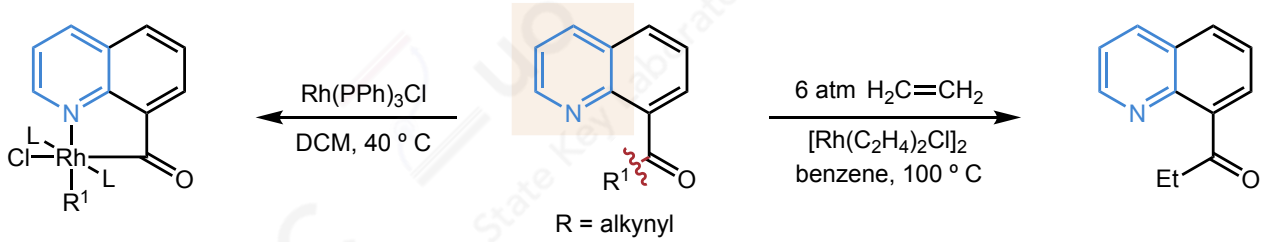
- *Unstrained C-C bond activation enabled by temporary DGs.*



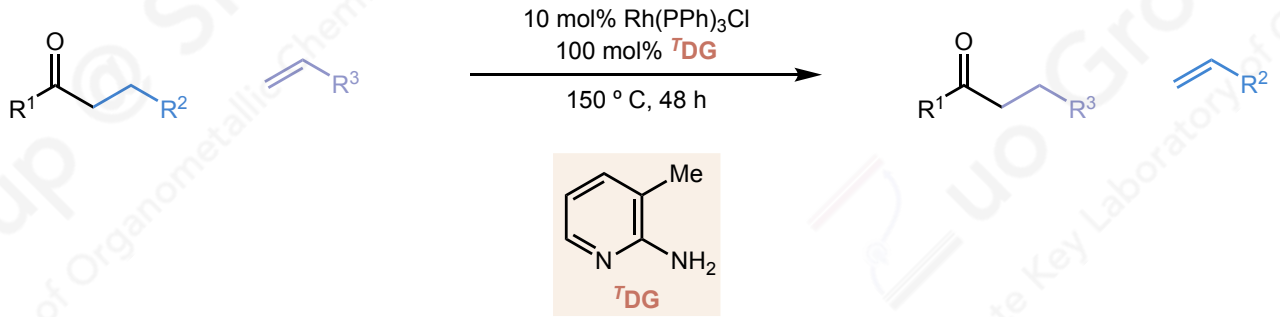
1. 1 过渡金属催化的碳碳键活化扩环反应

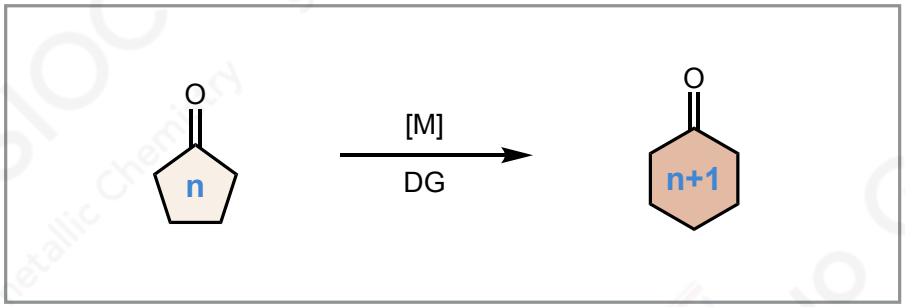
Diercting groups in C-C bond activation

■ ***First example of permanent DGs (1981 Suggs)***



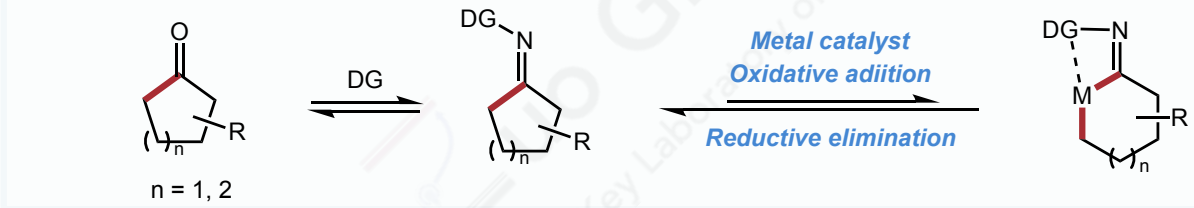
■ ***First example of temporary DGs (1999 Jun)***



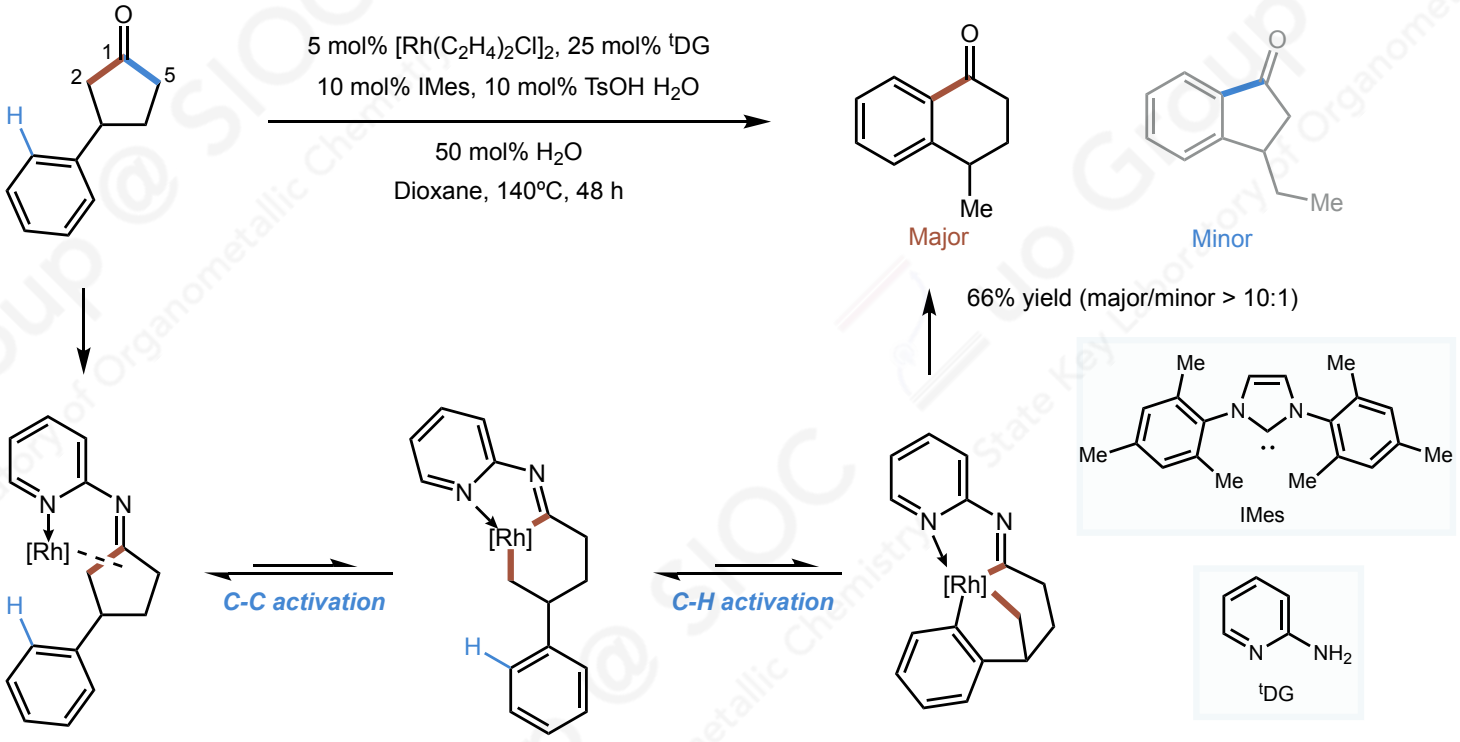

O
n
[M]
DG
O
n+1

1. 1 过渡金属催化的碳碳键活化扩环反应

C-C C-H cascade strategy



■ *Dong's strategy: merging unfavourable C-C activation with C-H functionalization*

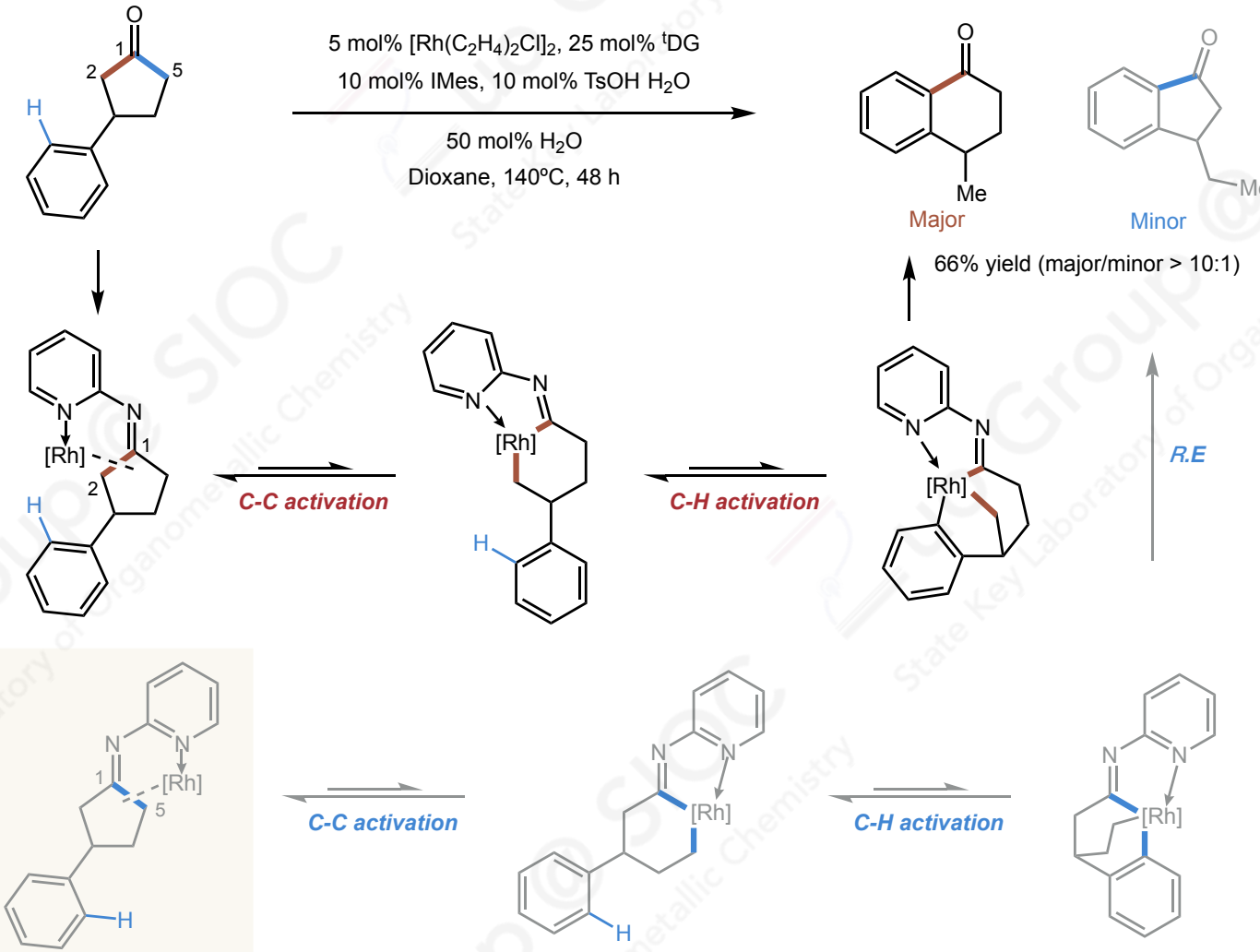


Dong. G. *et al*., *Nature* **2016,** *539*, 546–550.

1. 1 过渡金属催化的碳碳键活化扩环反应

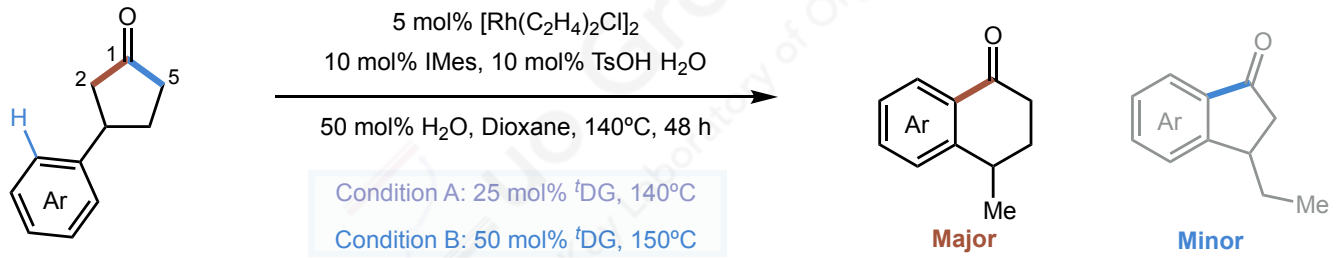
Regioselectivity

■ ***Dong's strategy: merging unfavourable C-C activation with C-H functionalization***

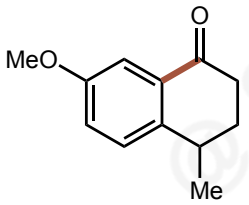


1. 1 过渡金属催化的碳碳键活化扩环反应

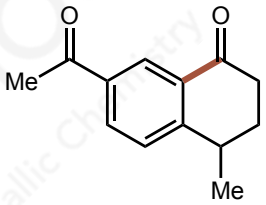
Scope of substrate



Para-substituted

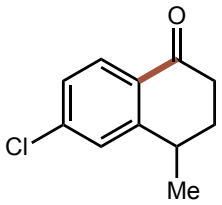


A: 75% (>10:1)



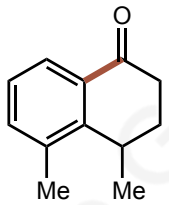
A: 54% (>10:1)
B: 71% (>10:1)

Meta-substituted

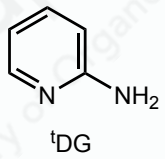


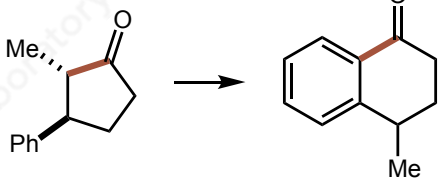
B: 63% (>10:1)

Ortho-substituted

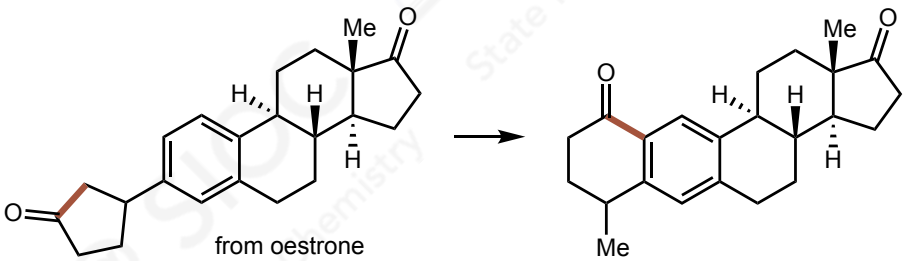


A: 70% (3.5:1)





B: 30% (6.0:1)



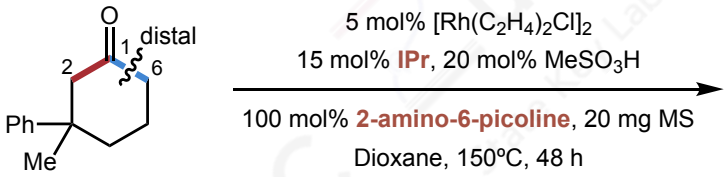
B: 47% (3.8:1)

Dong. G. *et al*., *Nature* **2016,** *539*, 546–550.

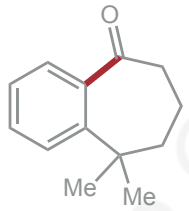
1.1 过渡金属催化的碳碳键活化扩环反应

Opposite regioselectivity

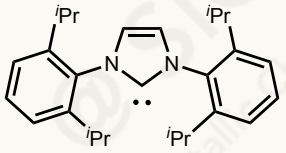
■ *Cyclohexone: more chanlleging than cyclopentanones*



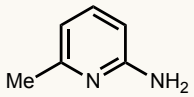
34% yield



not observed



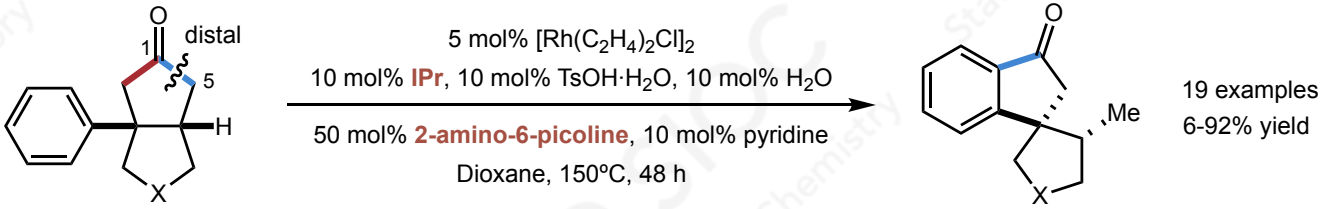
IPr



2-amino-6-picoline

Dong. G. *et al*., *Nature* **2016,** *539*, 546–550.

■ *C-C activation of cyclopentanones at distal position*

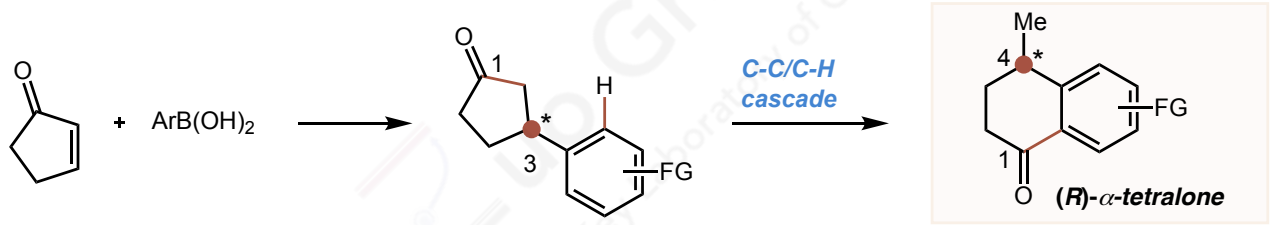


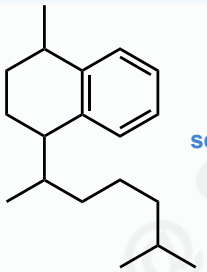
19 examples
6-92% yield

Dong. G. *et al*., *Angew. Chem. Int. Ed*. **2017,** *56*, 2376–22380.

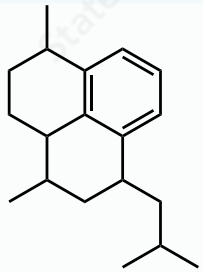
1. 1 过渡金属催化的碳碳键活化扩环反应

Synthesis application



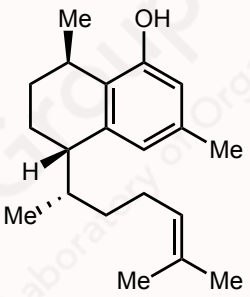


serrulatane skeleton

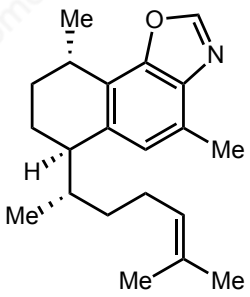


amphilectane skeleton

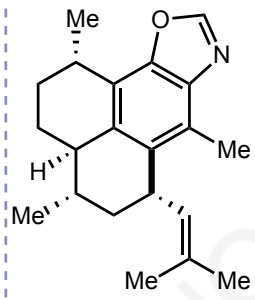
- ***Promising biological activitity***
  antimalarial, anti-inflammatory, analgesic, etc.
- ***Synthetic chanllenges***
  1. Nonpolar stereogenic centers
  2. 5 or 6 substituted benzene



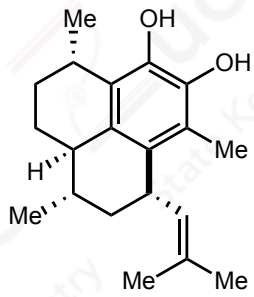
(**1**) leubethanol
previous:11-13 steps
Perkins & Luo



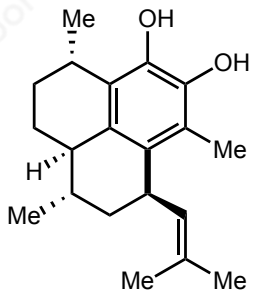
(**2**) *seco*-pseudopteroxazole
previous:14 steps
Li



(**3**) pseudopteroxazole
previous:15-22 steps
Corey, Harmata,
Luo, Li, & Hu



(4) pseudopterosin
G-J aglycone
previous:10-21 steps
Corey, Sherburn, Luo *et.al*

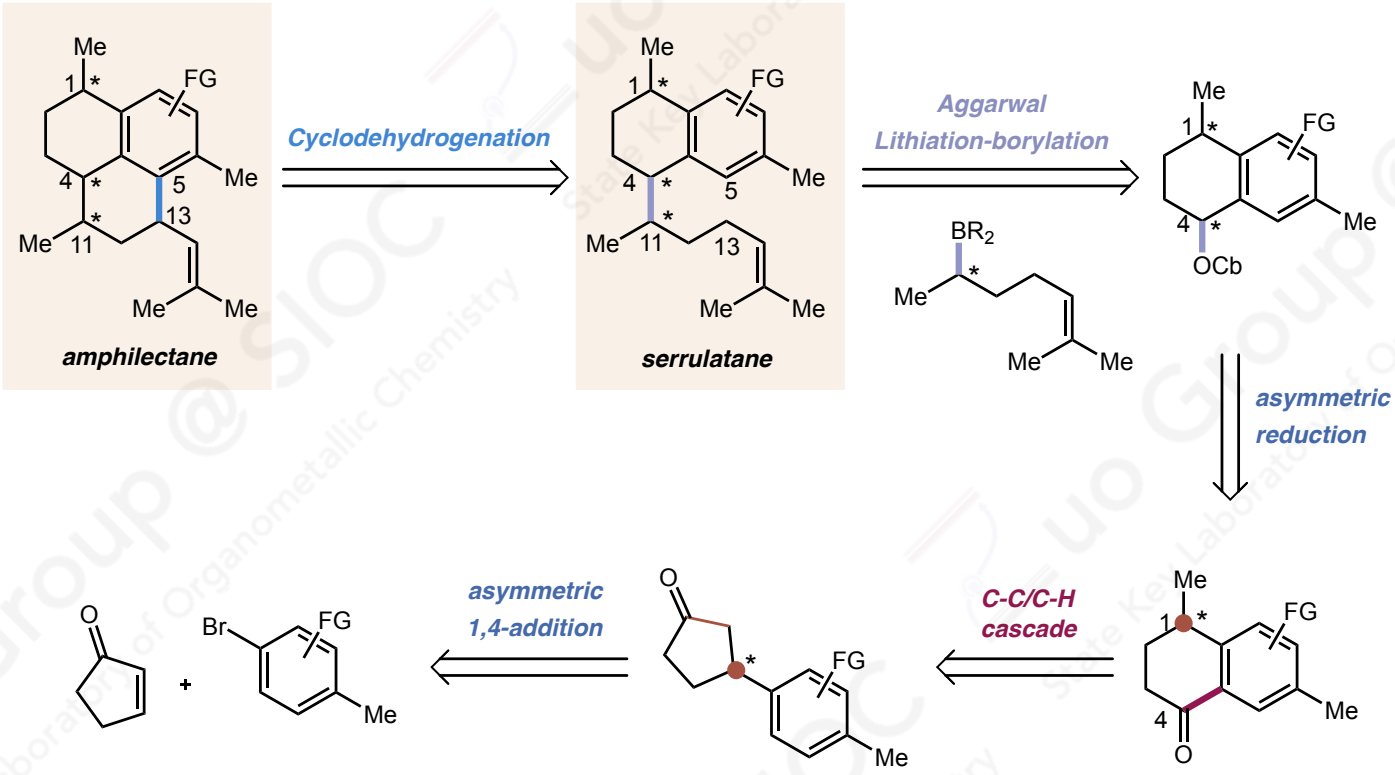


(5) pseudopterosin
A-F aglycone
previous:16-30 steps
Broka, Corey, Mccombie *et.al*

Dong. G. *et al*., *Angew. Chem. Int. Ed*. **2020,** *59*, 7848–7856.

1.1 过渡金属催化的碳碳键活化扩环反应

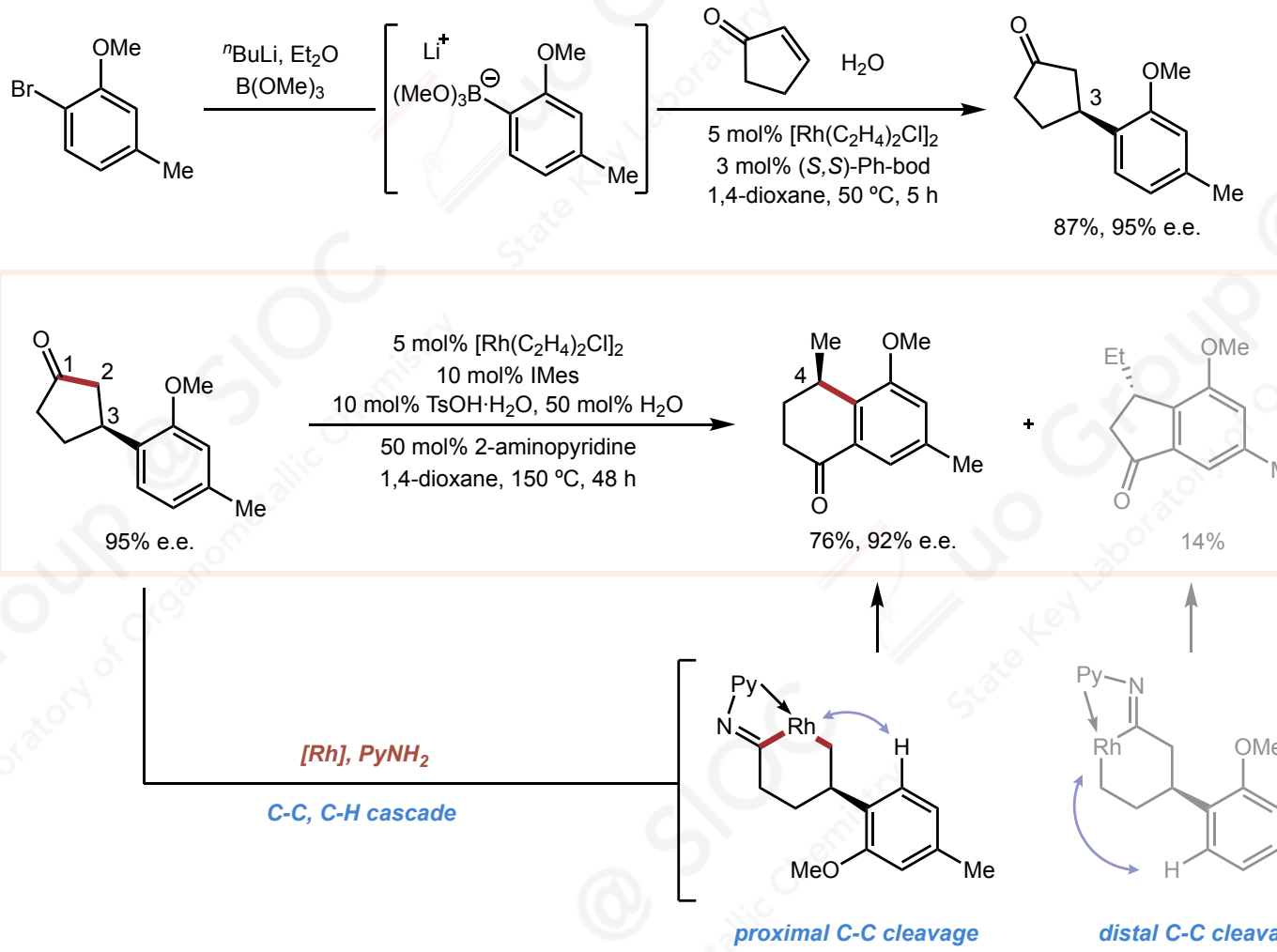
Retro-synthetic analysis



Dong. G. *et al*., *Angew. Chem. Int. Ed.* **2020,** *59*, 7848–7856.

1.1 过渡金属催化的碳碳键活化扩环反应

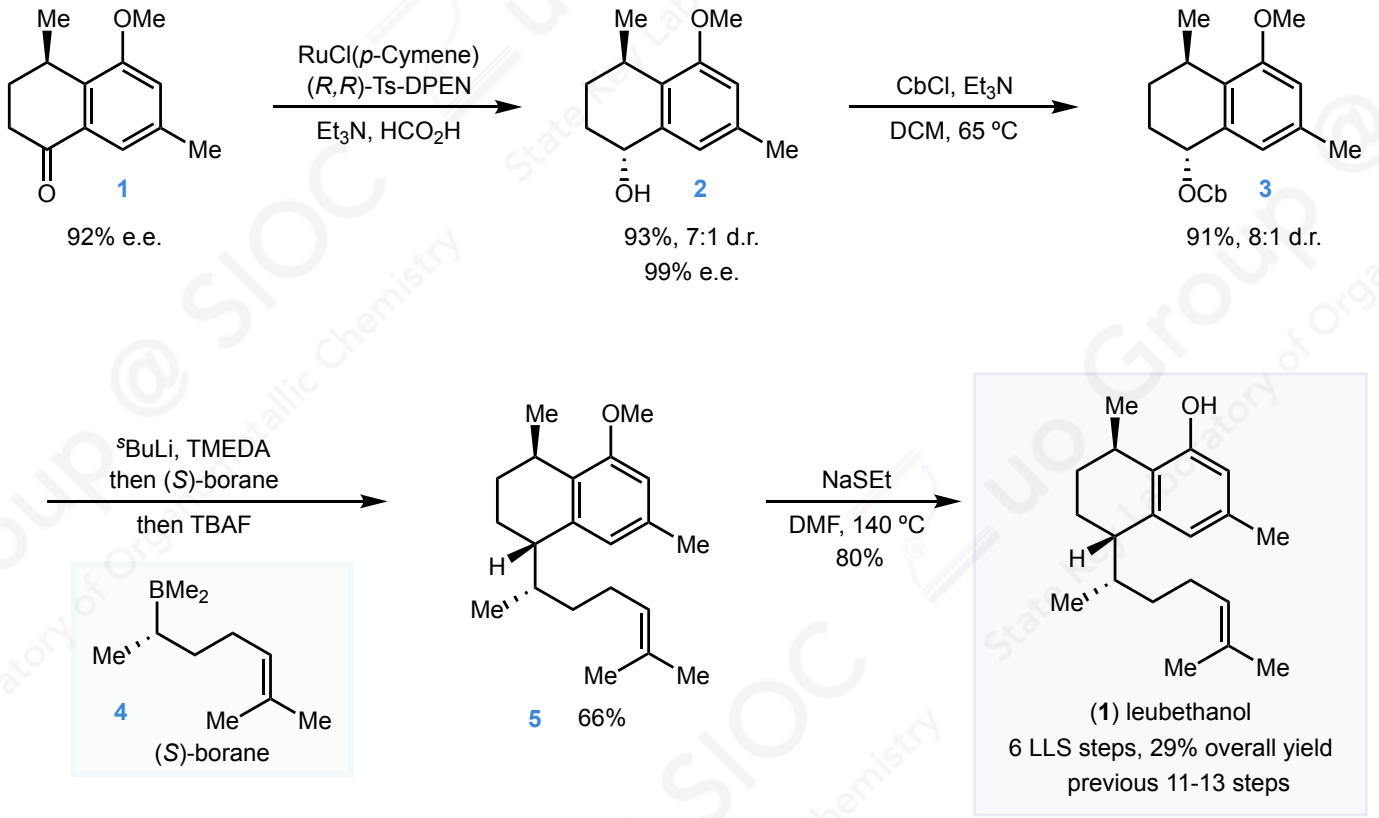
Total synthesis of leubethanol



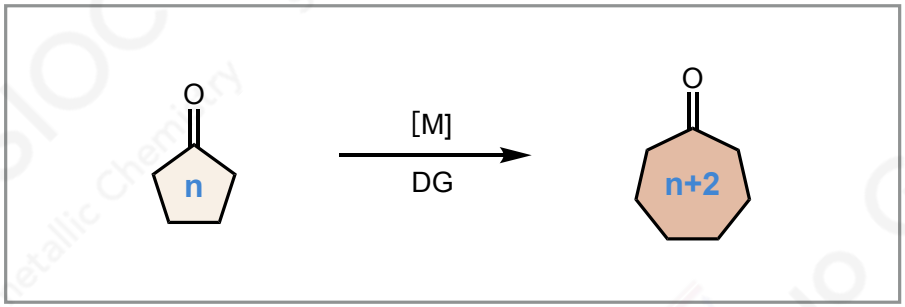
Dong. G. *et al*., *Angew. Chem. Int. Ed.* **2020,** *59*, 7848–7856.

1.1 过渡金属催化的碳碳键活化扩环反应

Total synthesis of leubethanol

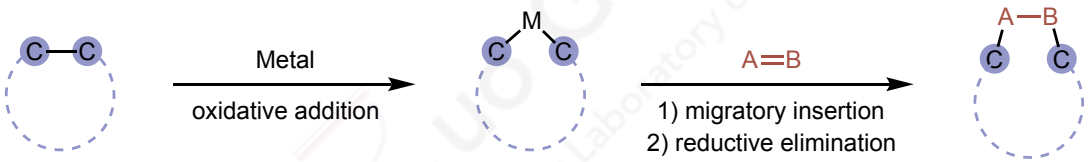


Dong. G. *et al*., *Angew. Chem. Int. Ed.* **2020,** *59*, 7848–7856.

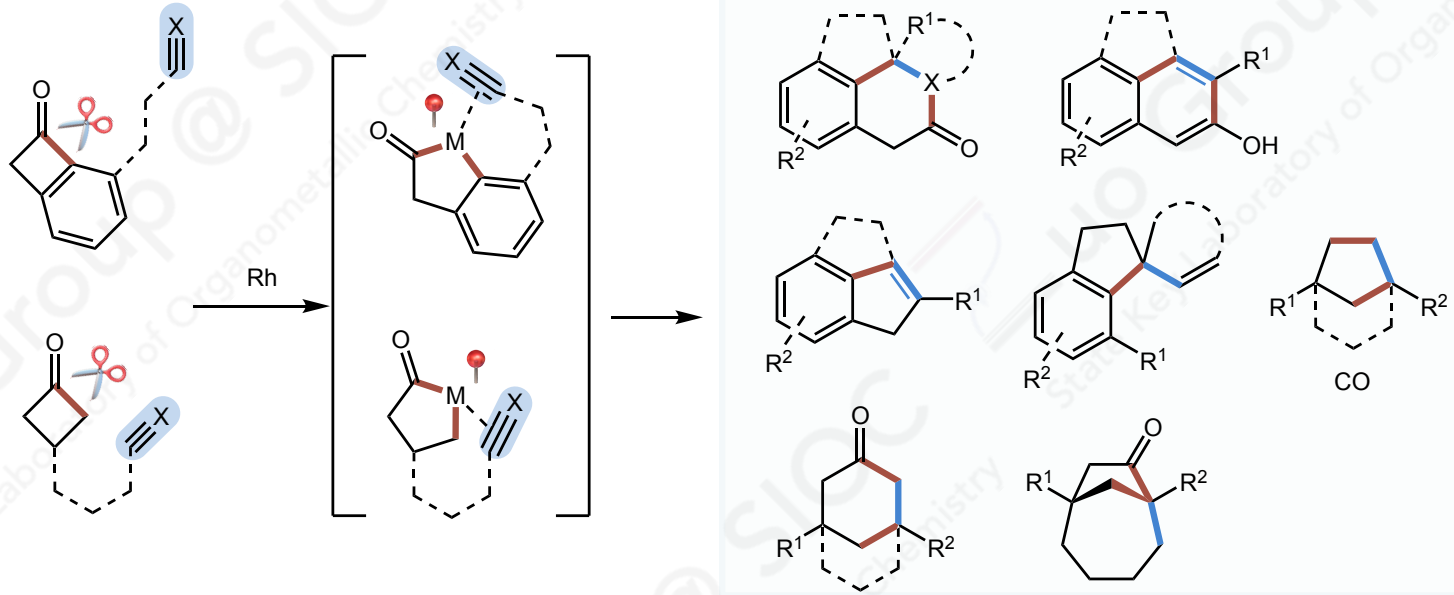

O
n
[M]
DG
O
n+2

1. 1 过渡金属催化的碳碳键活化 扩环反应

Cut and sew method



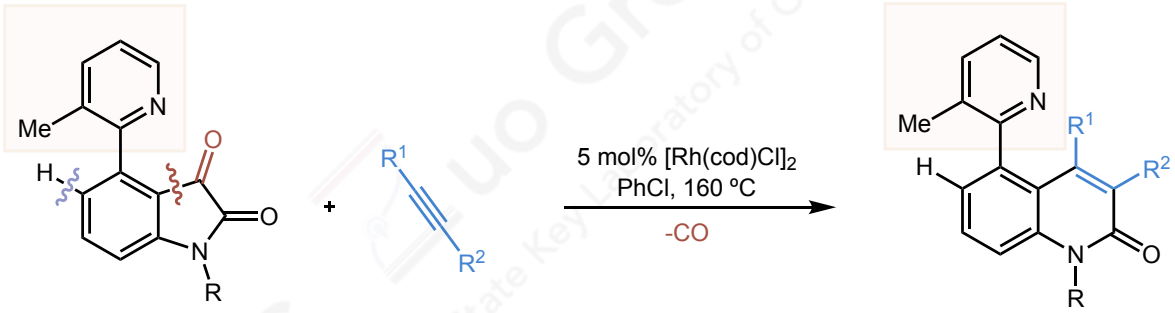
■ ***Application in the synthesis of fused or bridged cyclic molecules.***



Dong. G. *et al*., *Acs Catal*. **2017,** *7*, 1340–1360.

1.1 过渡金属催化的碳碳键活化 扩环反应

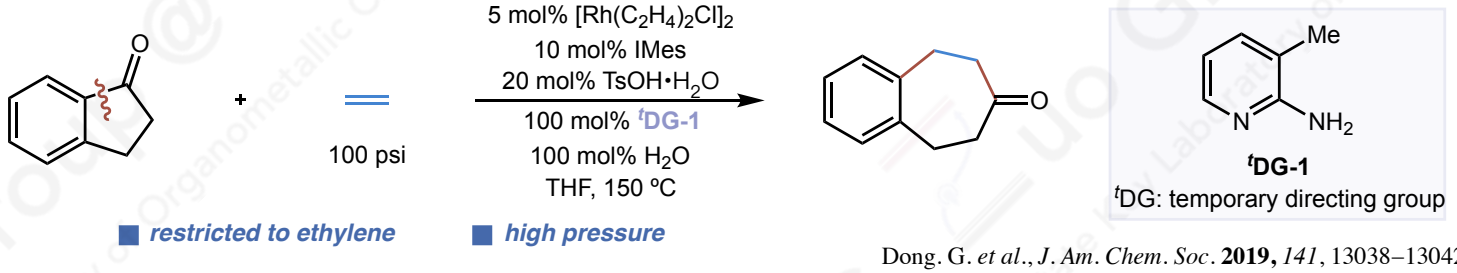
C-C activation of Isatins: [5+2-1]-type transformation



■ *Selective C-C vs C-H functinalization*

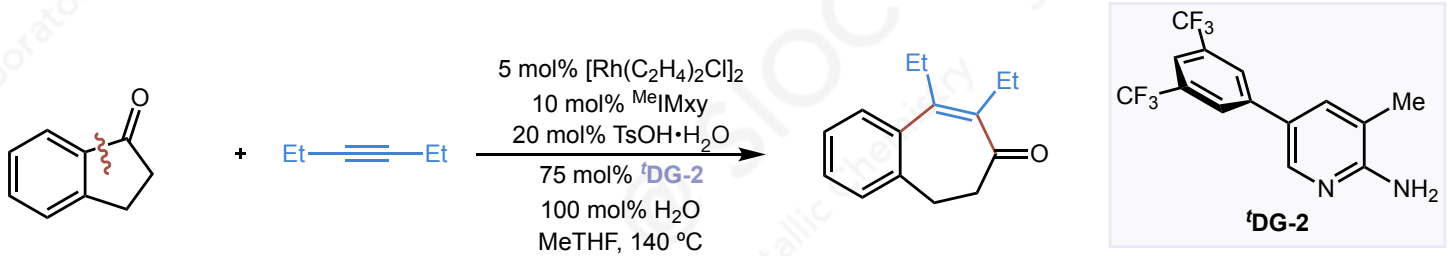
Dong. G. *et al*., *J. Am. Chem. Soc*. **2015,** *137*, 1408–1411.

Two-carbon ring expansion of 1-indanones

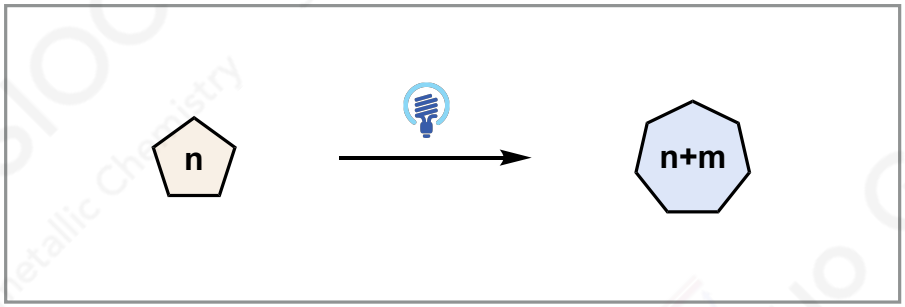


■ *restricted to ethylene*　　■ *high pressure*

Dong. G. *et al*., *J. Am. Chem. Soc*. **2019,** *141*, 13038–13042.

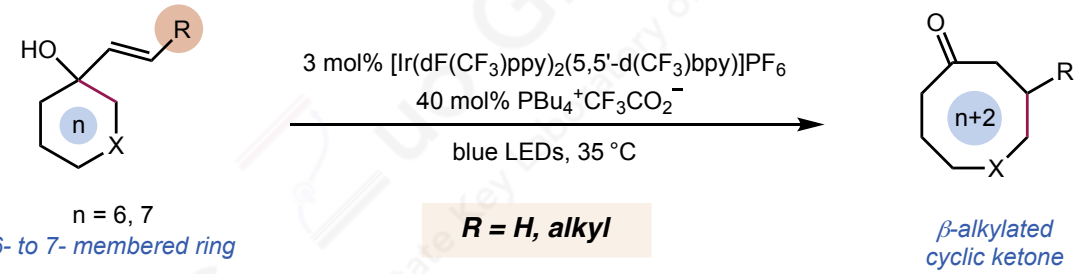


Dong. G. *et al*., *Angew. Chem. Int. Ed*. **2021,** *60*, 20476–20482.

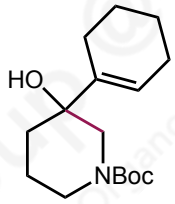
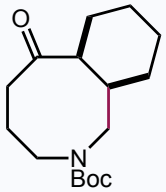
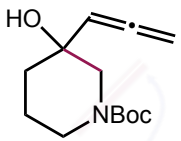
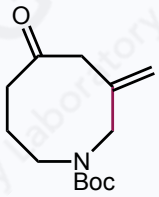
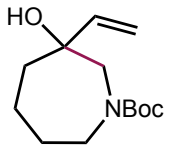
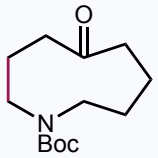
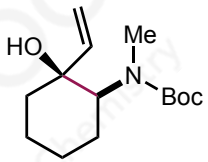
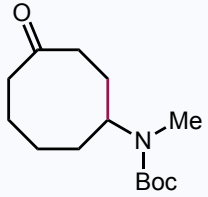

n
n+m

1. 2 自由基介导的碳碳键活化扩环反应

Catalytic ring expansions of cyclic alcohols enabled by PCET



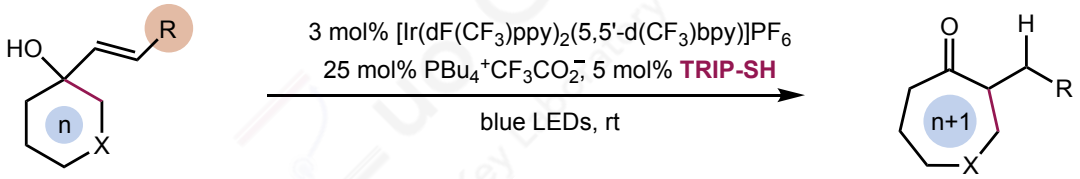
selected scope

Starting material	Product	Starting material	Product
	 92% yield >20:1 dr		 70% yield
	 48% yield		 45% yield

Knowles, R. *et al.*, *J. Am. Chem. Soc.* **2019,** *141*, 8752-8757.

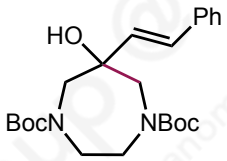
1. 2 自由基介导的碳碳键活化扩环反应

Catalytic ring expansions of cyclic alcohols enabled by PCET

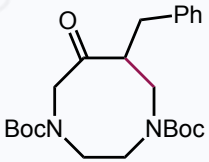


selected scope

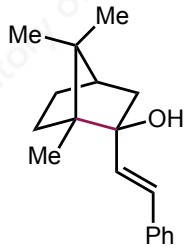
Starting material

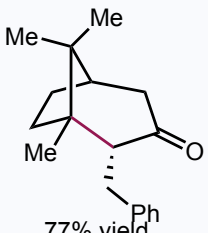


Product



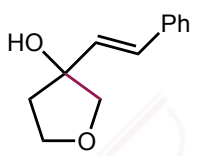
82% yield

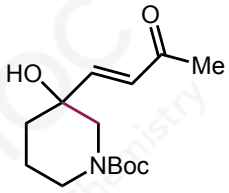




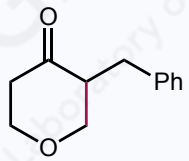
77% yield
>20:1 dr

Starting material

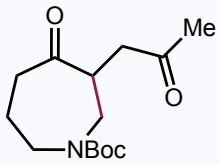




Product



74% yield



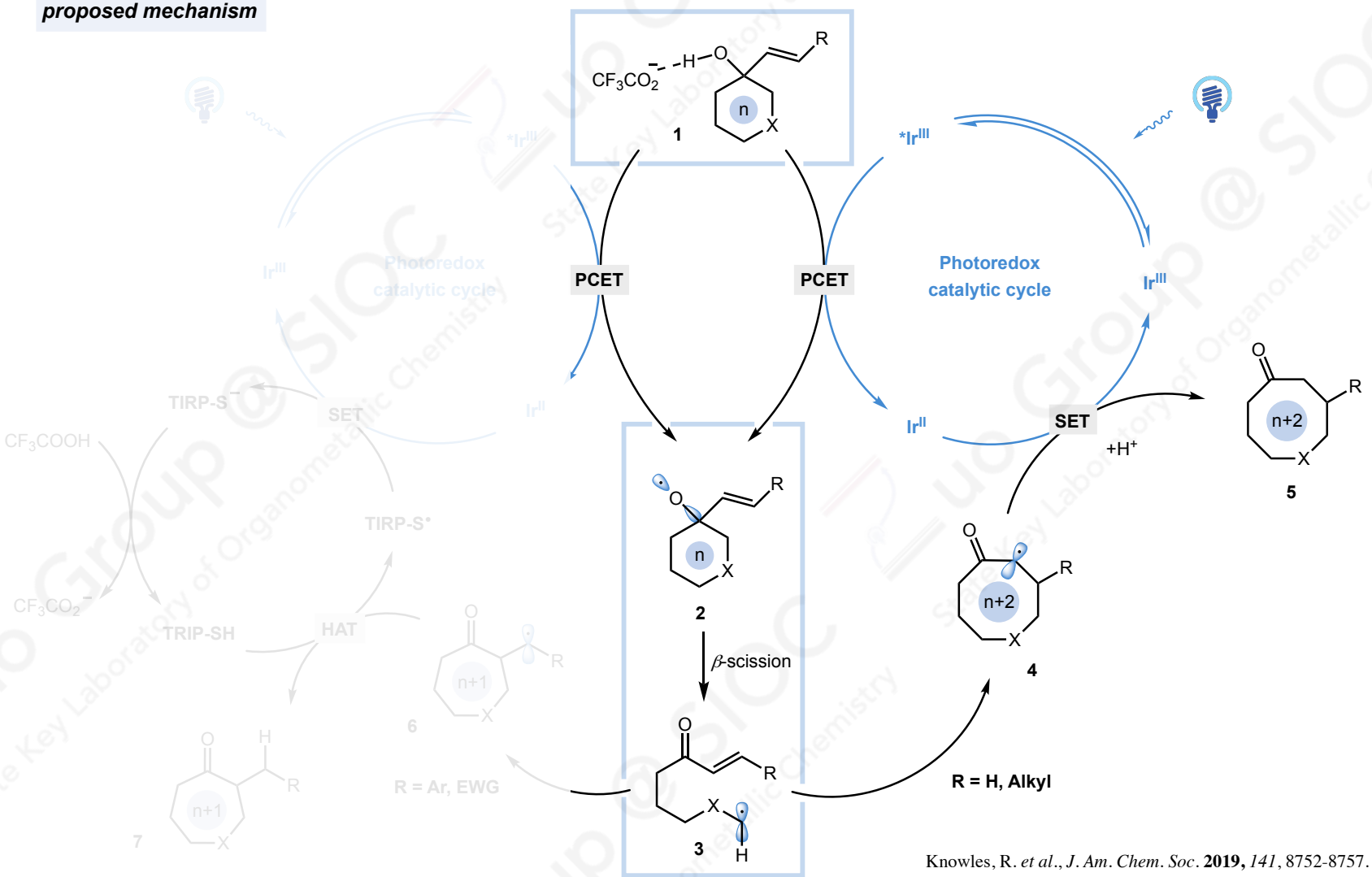
66% yield

Knowles, R. *et al*., *J. Am. Chem. Soc*. **2019,** *141*, 8752-8757.

1.2 自由基介导的碳碳键活化扩环反应

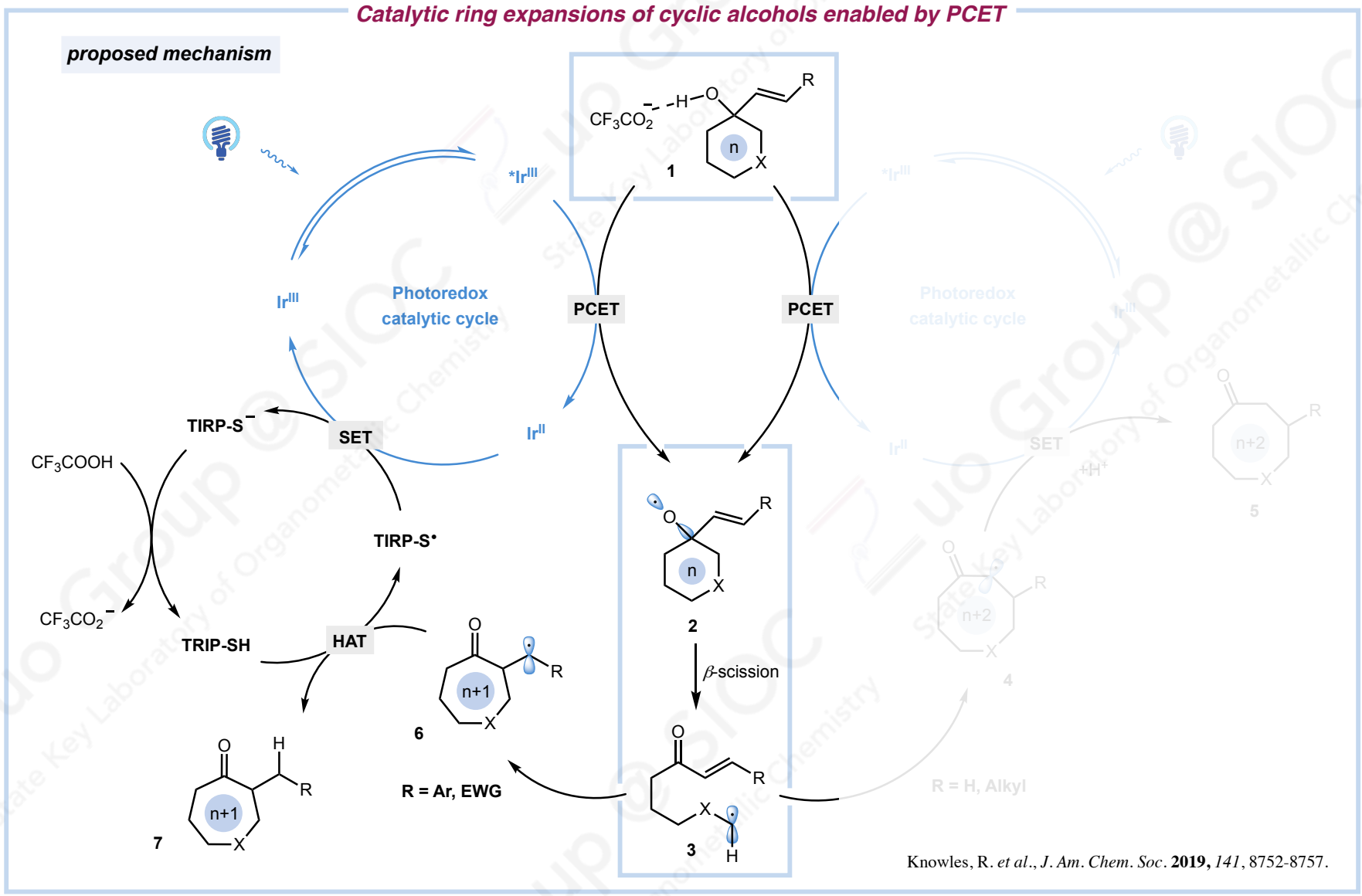
Catalytic ring expansions of cyclic alcohols enabled by PCET

proposed mechanism



Knowles, R. *et al*., *J. Am. Chem. Soc*. **2019,** *141*, 8752-8757.

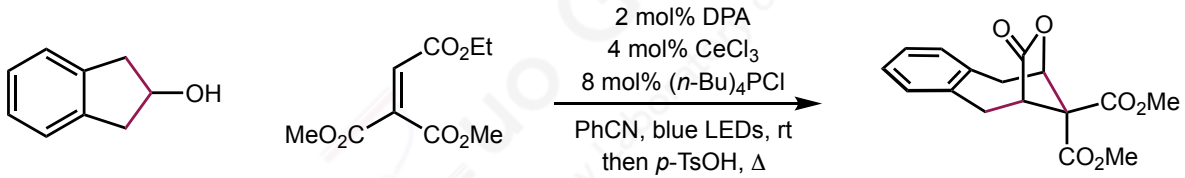
1.2 自由基介导的碳碳键活化扩环反应



Knowles, R. *et al*., *J. Am. Chem. Soc*. **2019,** *141*, 8752-8757.

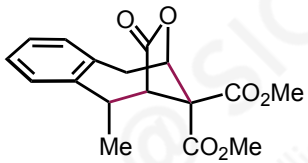
1. 2 自由基介导的碳碳键活化扩环反应

Ce-catalyzed formal cycloaddtion of cycloalkanol with alkenes



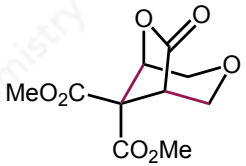
selected scope

[4,2,1]

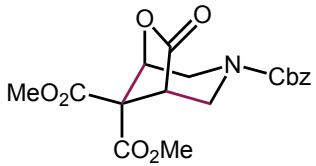


69% yield, 1.4:1 dr

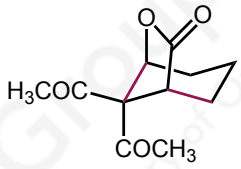
[3,2,1]



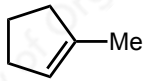
61% yield

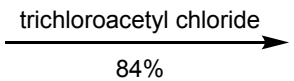


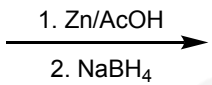
75% yield

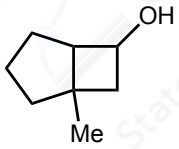


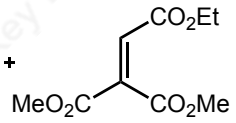
86% yield

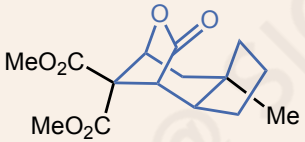


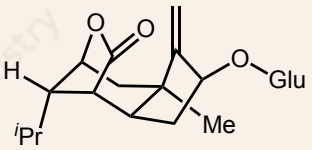








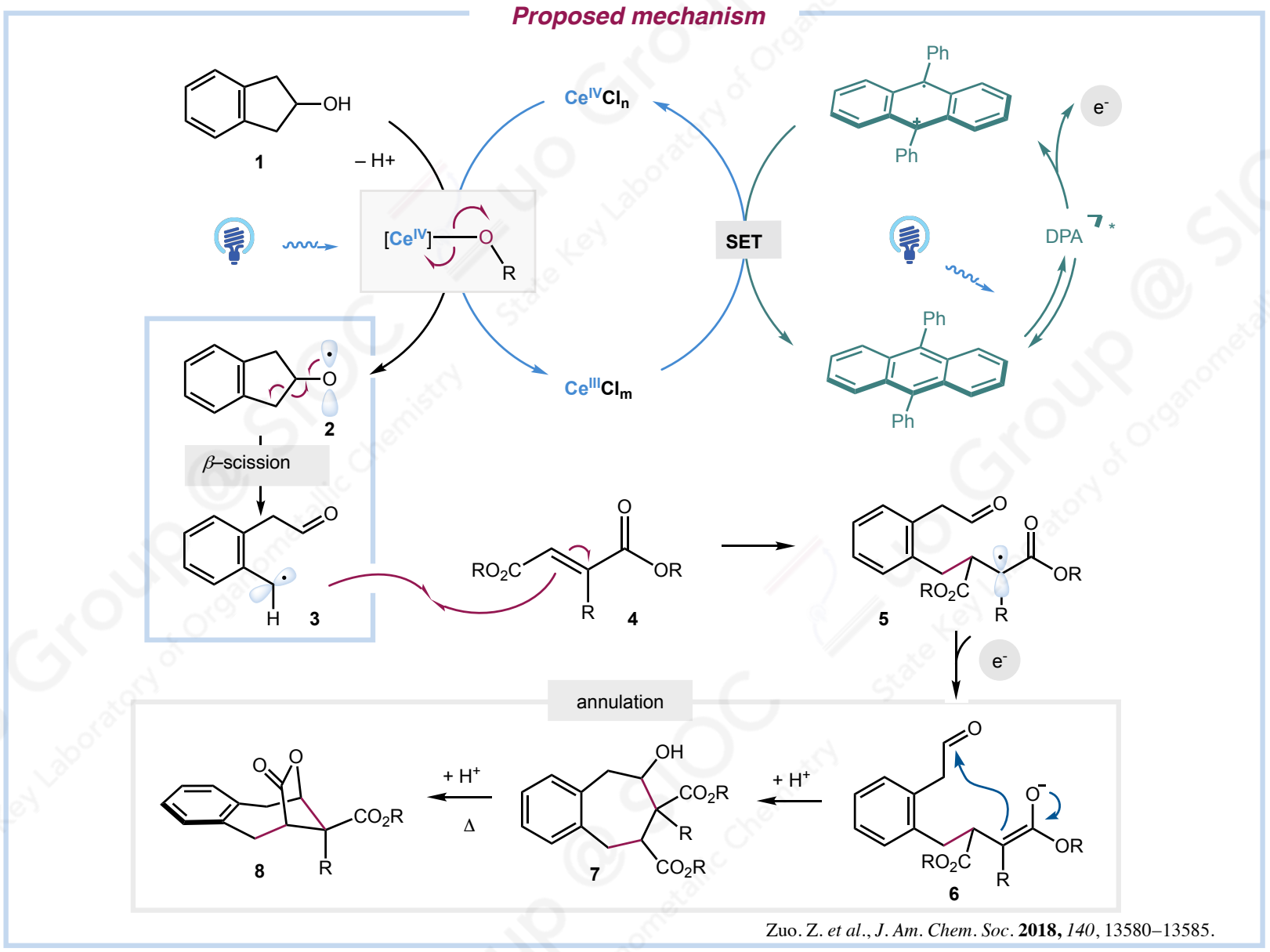




Nepalactone A

Zuo. Z. *et al*., *J. Am. Chem. Soc*. **2018,** *140*, 13580−13585.

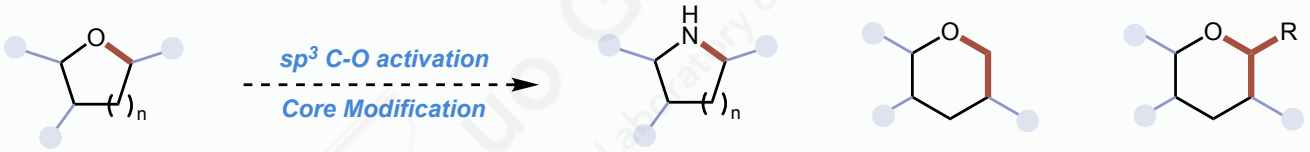
1.2 自由基介导的碳碳键活化扩环反应



Zuo. Z. *et al*., *J. Am. Chem. Soc*. **2018,** *140*, 13580–13585.

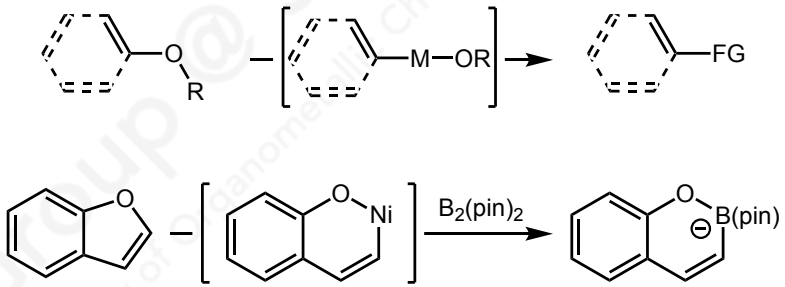
1. 3 饱和杂环的扩环反应

Cyclic Ether Diversification



- High stability
- Stuctural linkers & PG
- Surrogates for sensitive chemical groups

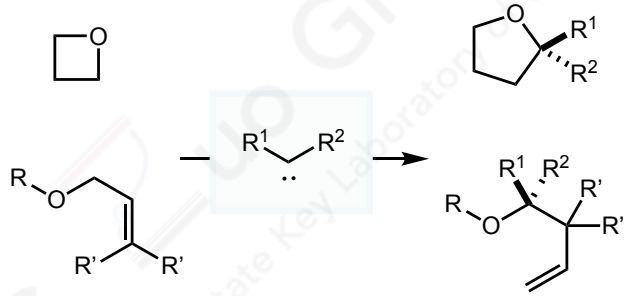
Metal oxidative addition



sp², allylic or benzylic C-O bonds

Yorimitsu, N. et al., *J. Am. Chem. Soc.* **2016,** *138*, 15315-15318

Carbene insertion



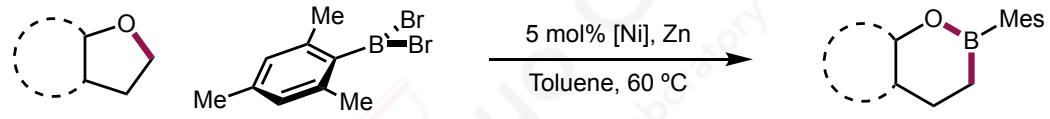
Strained cyclic ethers or allyl ethers

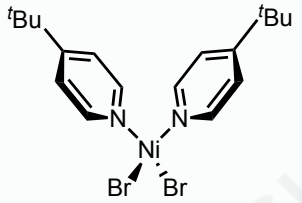
- Alkyl ether: Harsh & Strongly acidic condition

Develop mild method to edit alkyl ether !

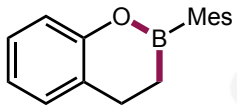
1. 3 饱和杂环的扩环反应

Boron insertion into alkyl ether

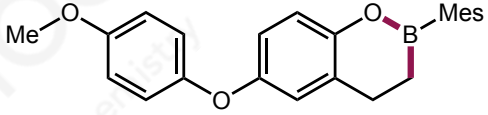




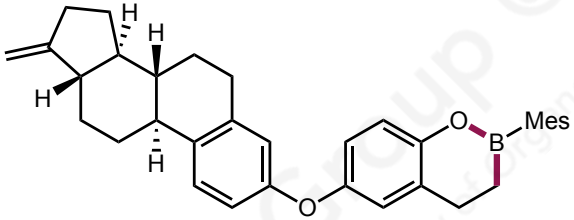
Cat: Ni(4-^{t}Bu-Py)$_2$Br$_2$



80%



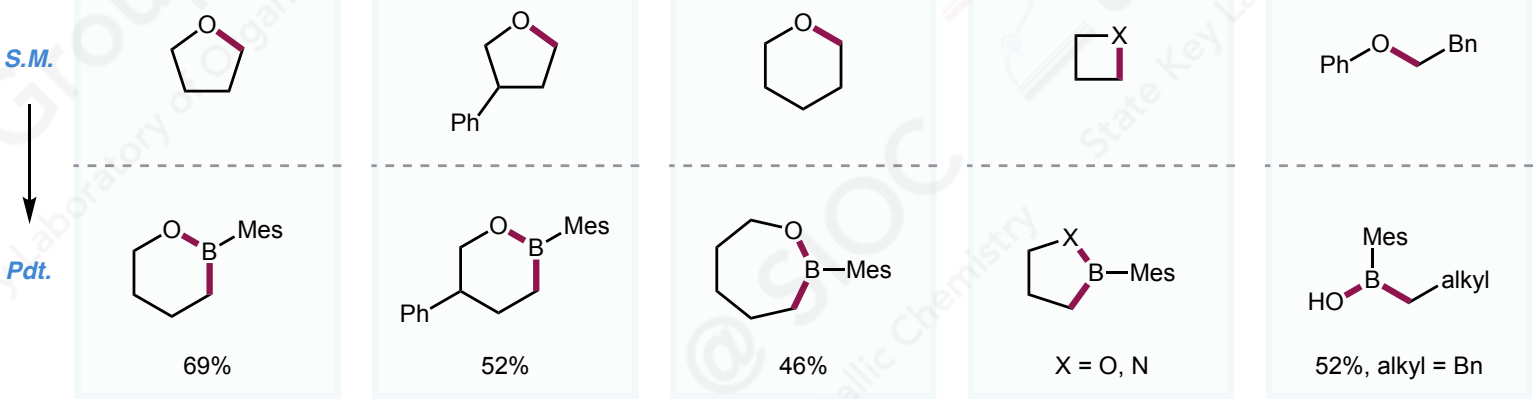
80%



80%

S.M.

Pdt.

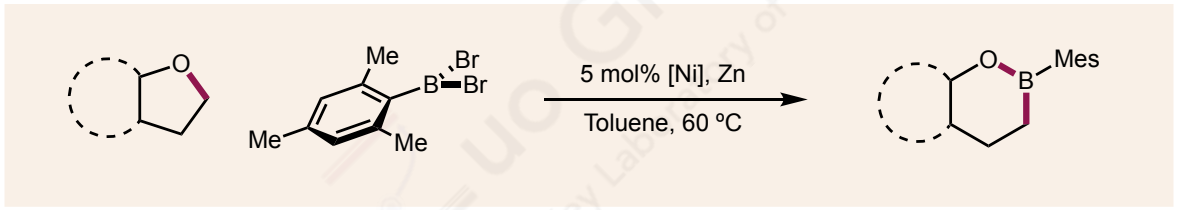


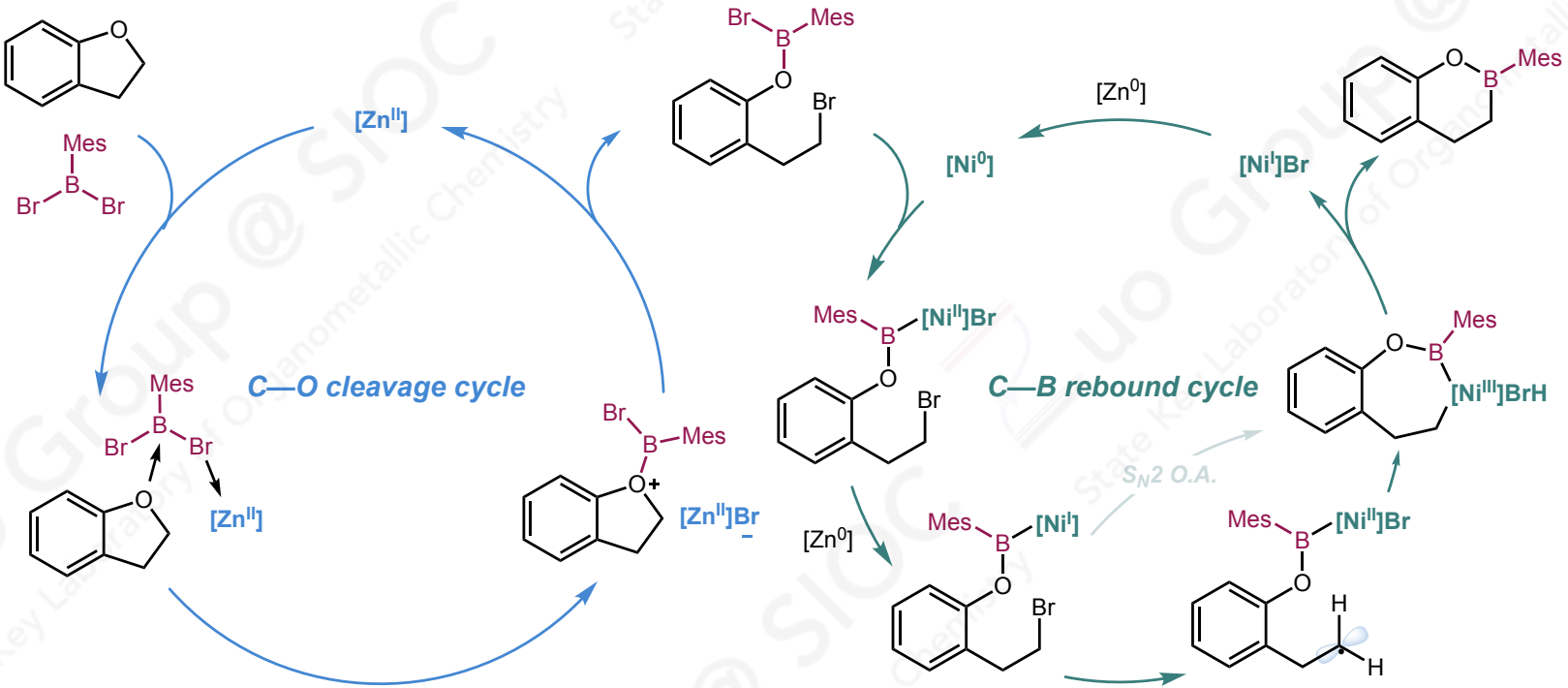
69% | 52% | 46% | X = O, N | 52%, alkyl = Bn

Dong, G. *et al*., *J. Am. Chem. Soc*. **2021,** *372*, 175-182.

1. 3 饱和杂环的扩环反应

Boron insertion into alkyl ether

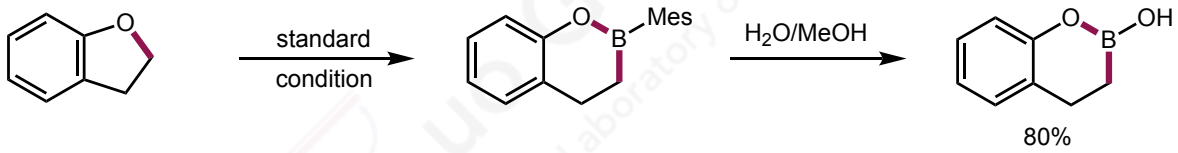




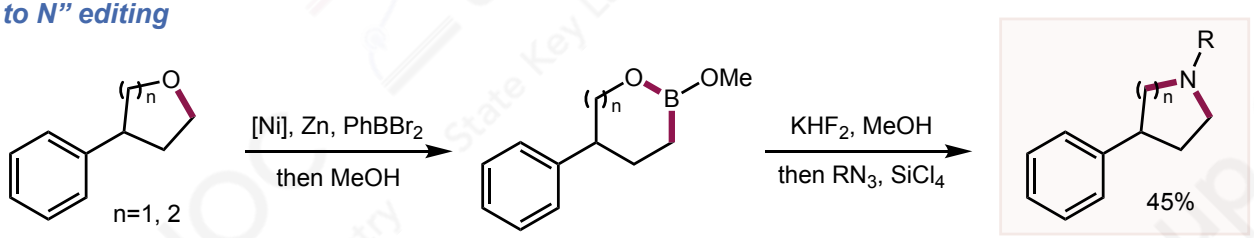
1. 3 饱和杂环的扩环反应

Boron insertion into alkyl ether

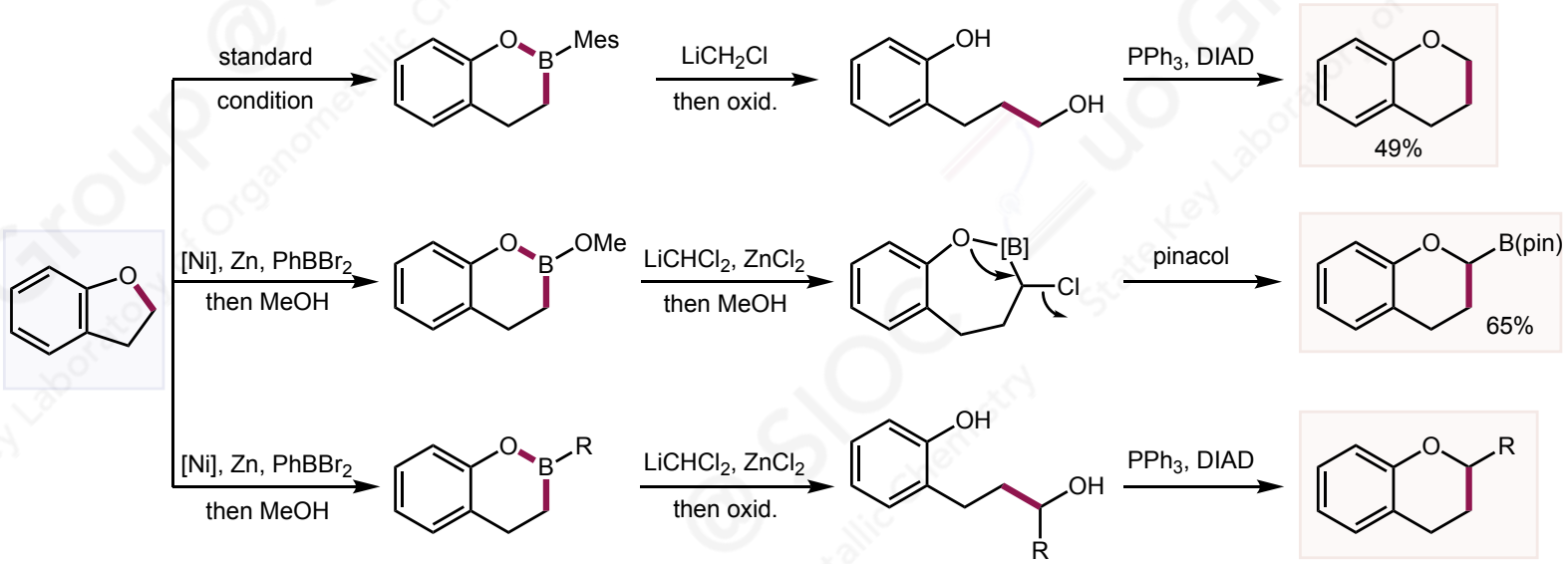
■ ***Rapid access to cyclic boronates***



■ ***"O to N" editing***

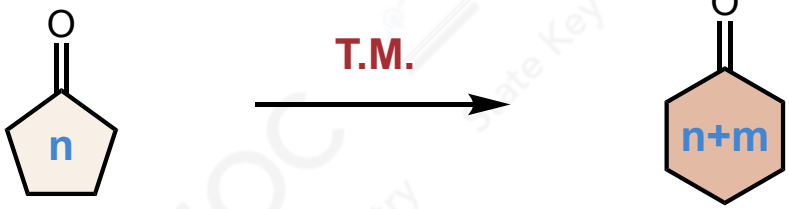


■ ***One-carbon ring expansion***



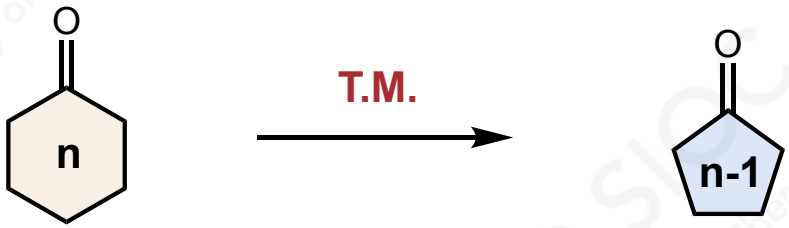
Dong, G. *et al*., *J. Am. Chem. Soc*. **2021,** *372*, 175-182.

一. 非张力饱和碳(杂)环的扩环反应

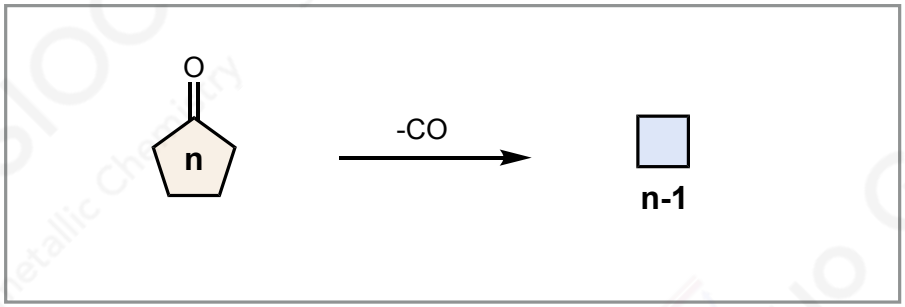


- 过渡金属催化活化
- 自由基介导转化
- 饱和杂环扩环

二. 非张力饱和碳(杂)环的缩环反应



- 脱羰
- 环酮缩环
- 饱和杂环
- N deletion


O
n
-CO
n-1

2.1 脱羰反应

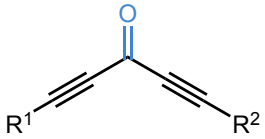
Stoichiometric decarbonylation of diynones

■ *Driving force*

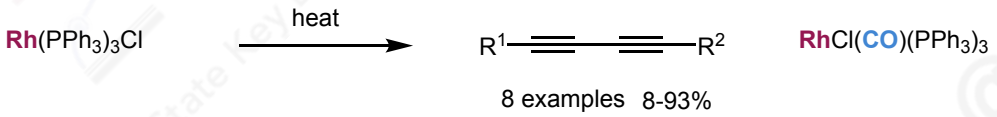
△S : CO extrusion △H : strong M-CO bond

■ *Still chanllenging*

activated substrates, stoichiometric metals

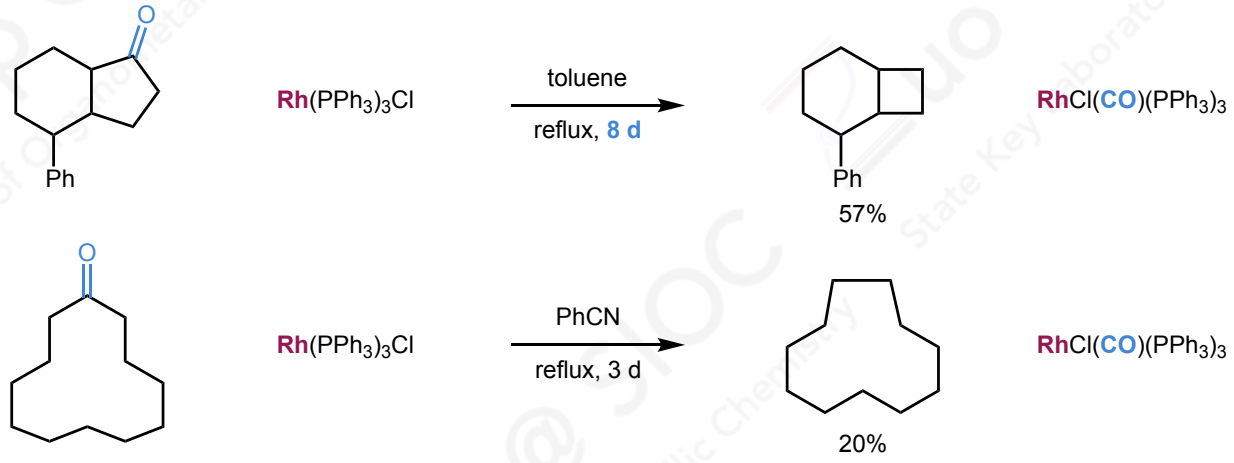


first examples

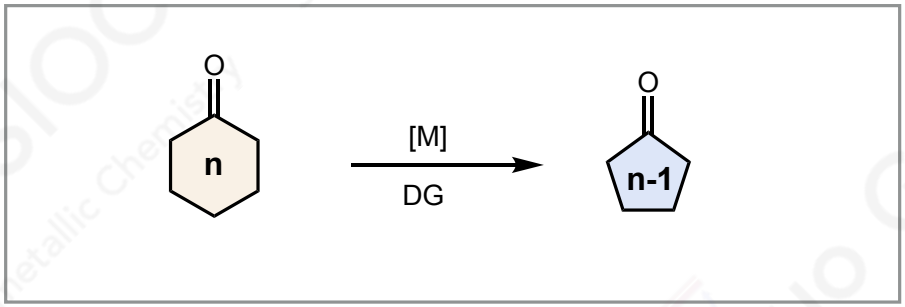


Muller, E. *et al*., *Tetrahedton Lett*. **1969,** *10*, 1129–1132.

Stoichiometric decarbonylation of cyclic ketones



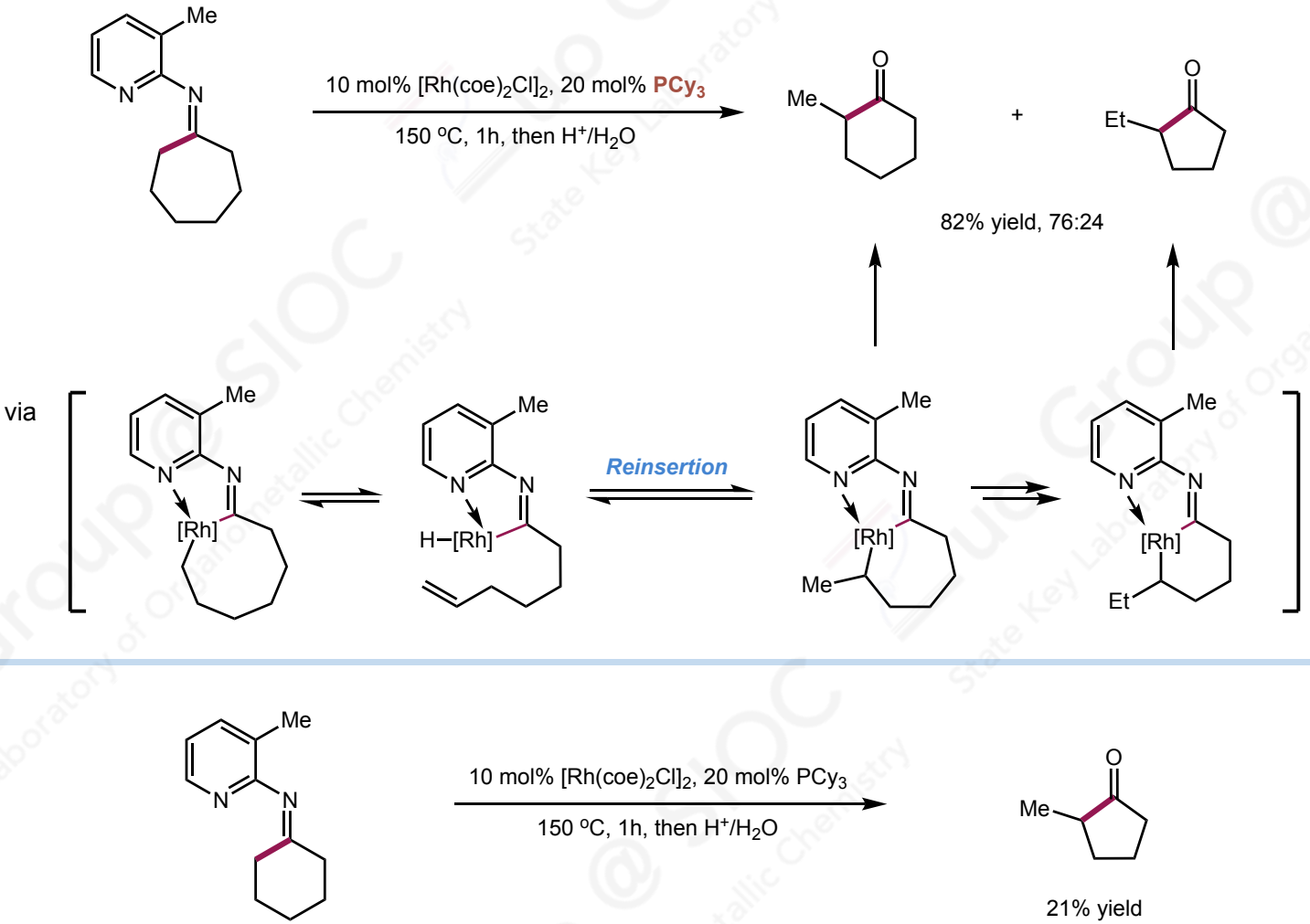
Murakami, M. *et al*., *Nature* **1994,** *370*, 540–541.


O
n
[M]
DG
O
n-1

2.1 金属催化的缩环反应

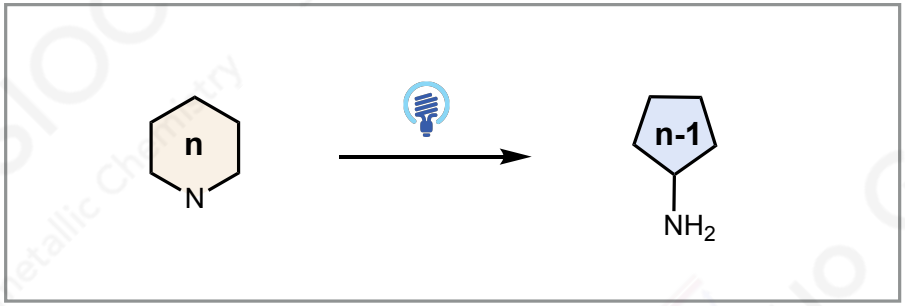
Rh-catalyzed ring contraction

■ ***Driving force: more stable product.***



21% yield

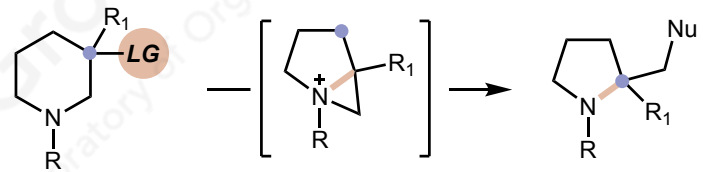
Jun, H. *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 751-752.


n
N
n-1
NH2

2.3 光催化饱和杂环的缩环反应

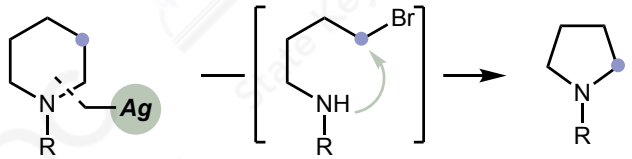
Piperidine Diversification

General strategy



Quaternary ammonium

Deconstruction of cyclic amine

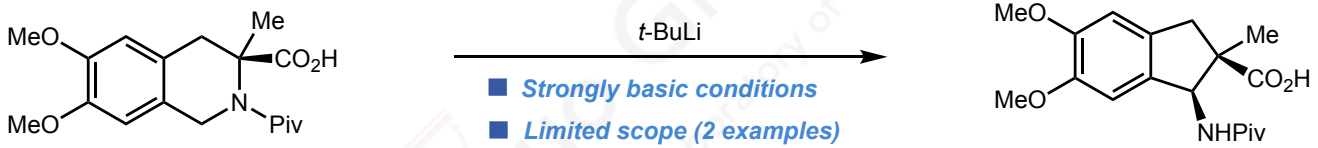


Deconstructive halogenation

Sarpong. R. et al., *Nature* **2018,** *564*, 244–248.

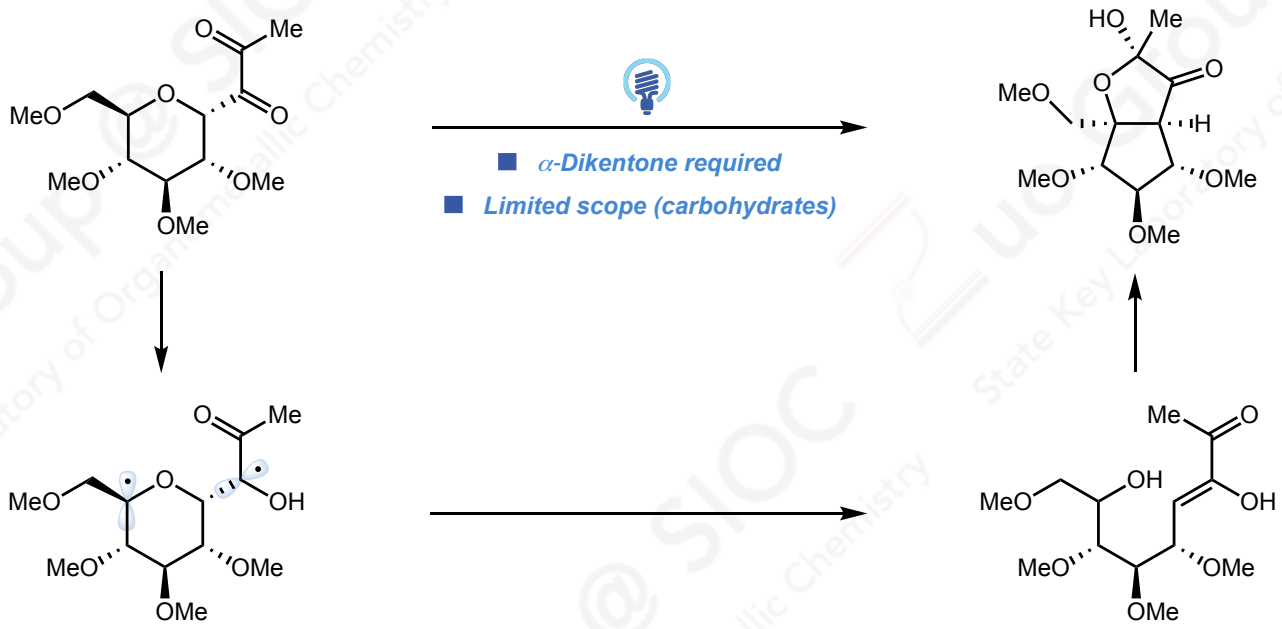
2.3 光催化饱和杂环的缩环反应

Rearrangement to peperidine ring contraction



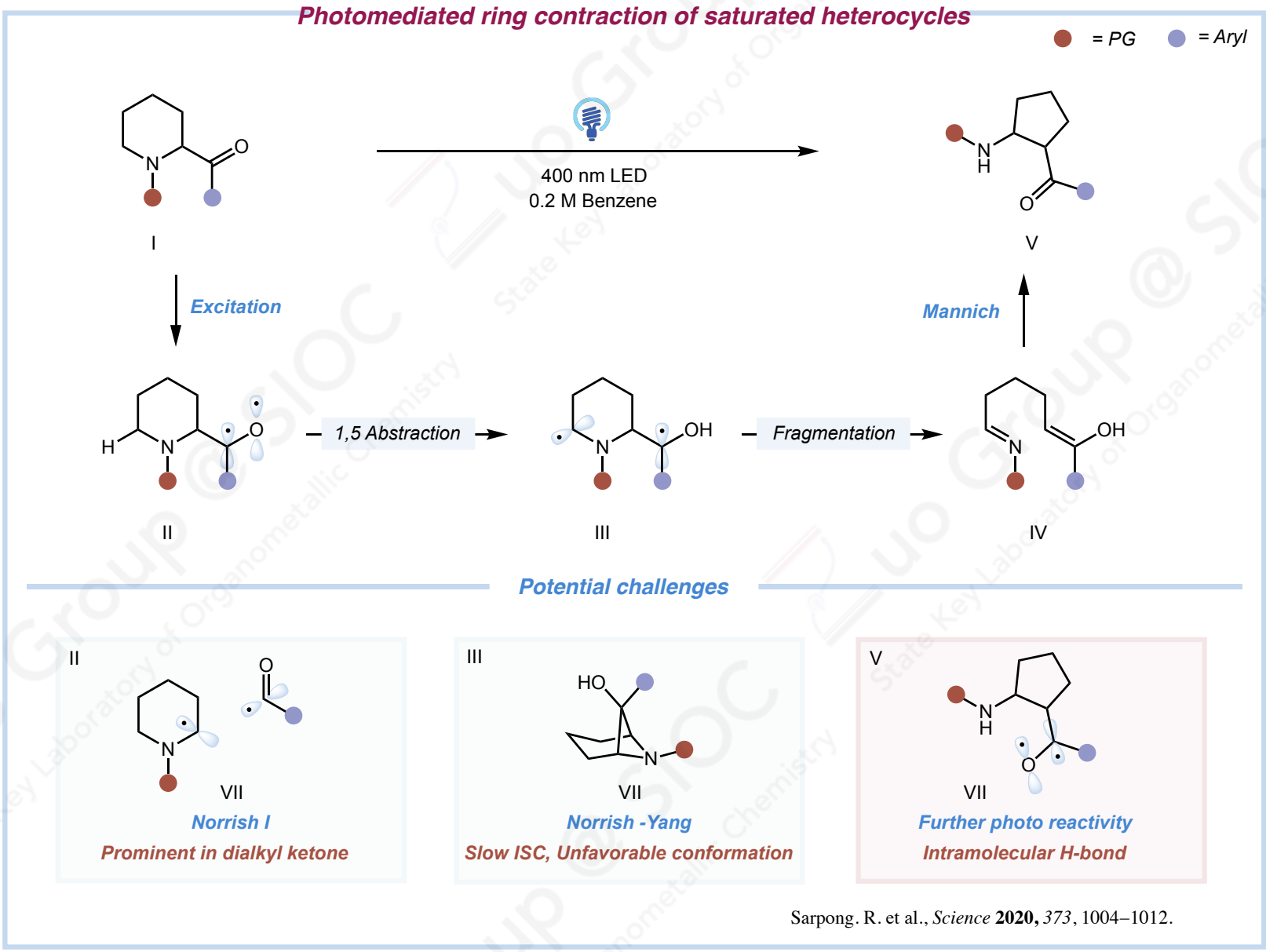
Seebach, D. *et al*., *Helv. Chim. Acta*. **1993,** *76*, 2640-2653.

Norrish type II photoelimination & Aldol cyclization



Suarez, E. *et al*., *Angew. chem*. **2008,** *120*, 9049-9051

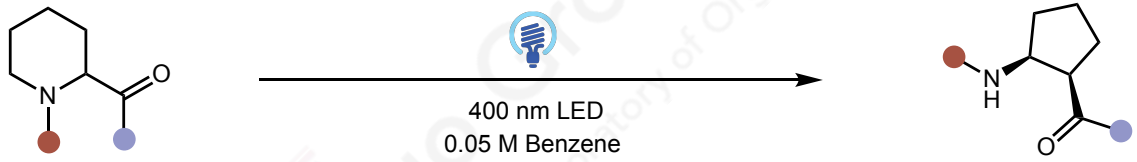
2.3 光催化饱和杂环的缩环反应



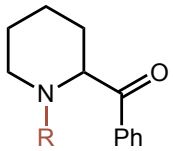
Sarpong. R. et al., *Science* **2020,** *373*, 1004–1012.

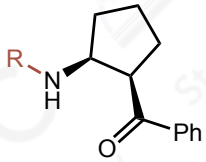
2.3 光催化饱和杂环的缩环反应

Substrate scope



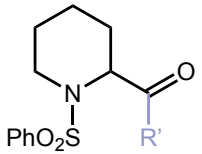
N-protecting group

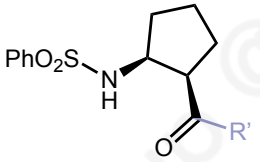




R = SO_2Ph	84% (20:1 d.r.)
R = Ts	79% (12:1 d.r.)
R = Boc	23% (20:1 d.r.)

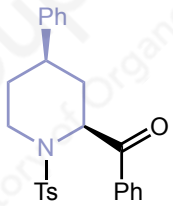
Aryl ketone



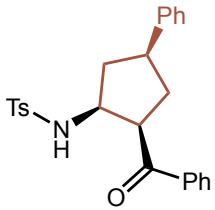


R' = β-Naphth	75% (1.3:1 d.r.)
R' = Thiophenyl	56% (10:1 d.r.)
R' = Me	25% (2.2:1 d.r.)

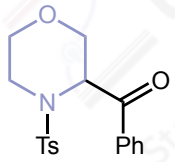
Scope of heterocyclic core



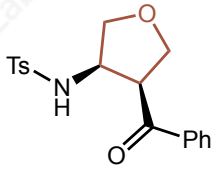
Substituted piperidine



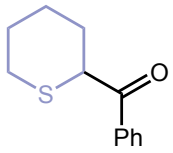
33% (10:1 d.r.)



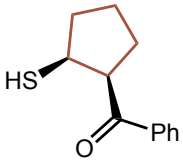
Morpholine



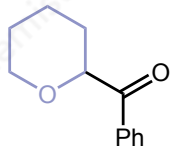
66% (3:1 d.r.)



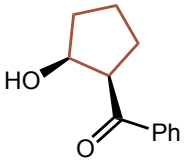
Thiane



83% (20:1 d.r.)



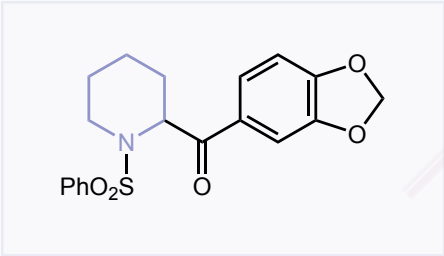
Tetrahydropyran

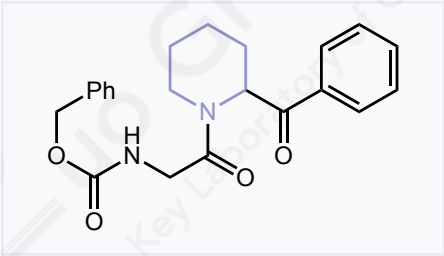


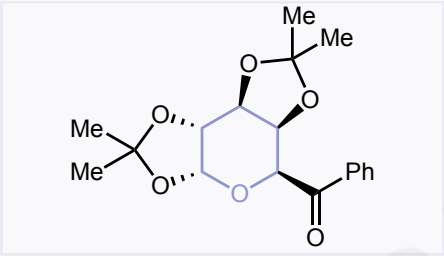
75% (20:1 d.r.)

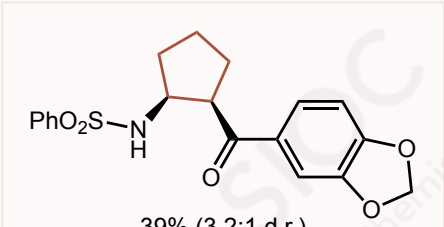
2.3 光催化饱和杂环的缩环反应

Applications



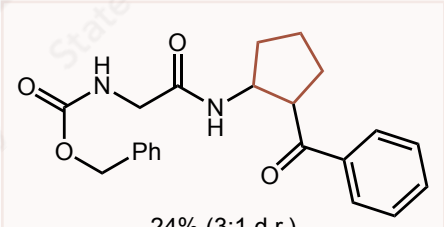






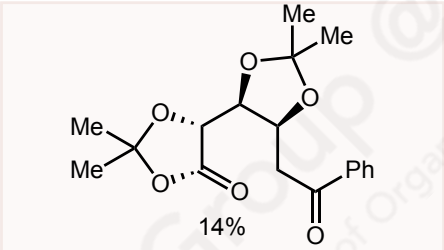
39% (3.2:1 d.r.)

Drug molecule derivatization



24% (3:1 d.r.)

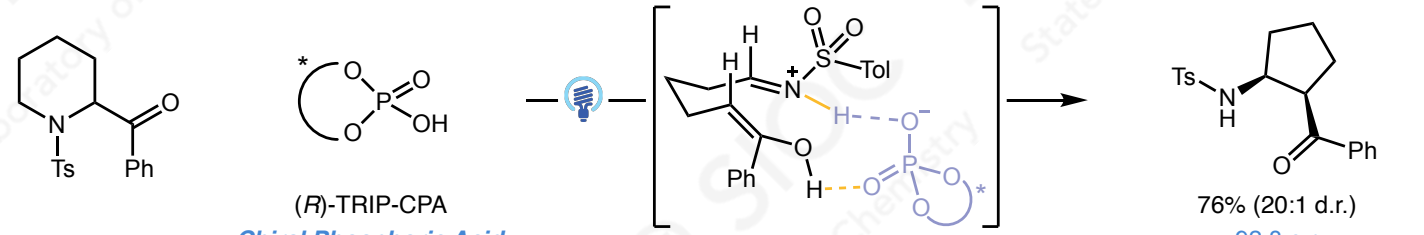
Peptide editing



14%

Sugar Editing

Asymmetric contraction variant



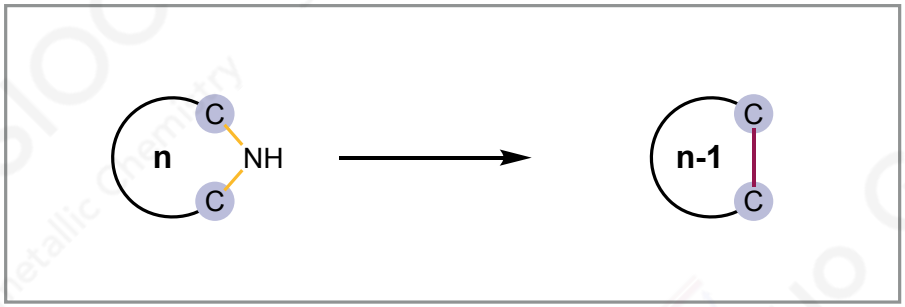
(*R*)-TRIP-CPA

Chiral Phosphoric Acid

76% (20:1 d.r.)

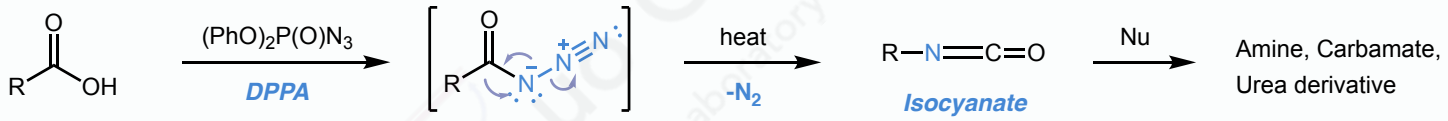
92:8 e.r.

Sarpong. R. et al., *Science* **2020,** *373*, 1004–1012.

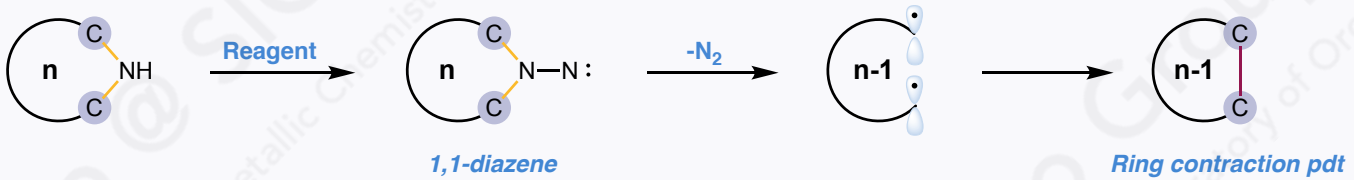

C
n
NH
C
n-1
C
C

2.4 氮原子消除反应

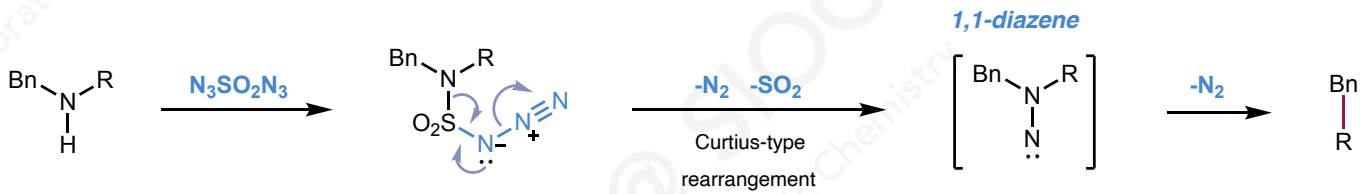
Curtius rearrangement



General N-atom deletion strategy



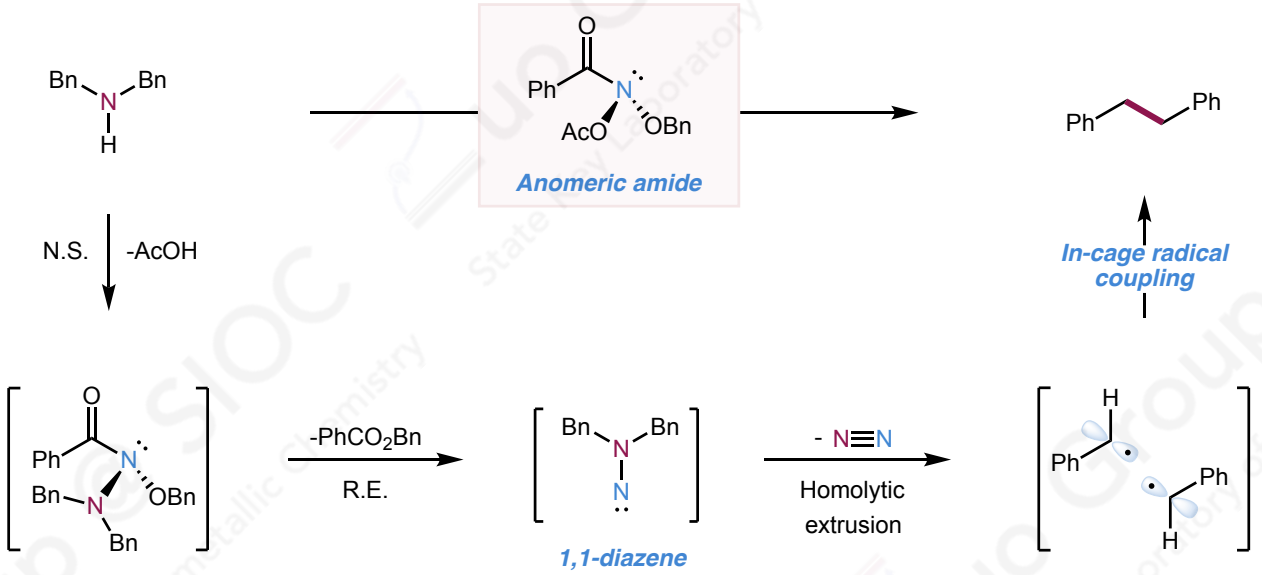
Rearrangement of sylfamoyl azides



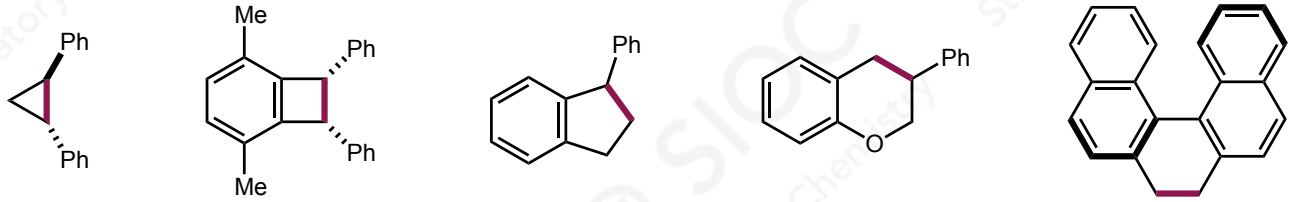
Lu, H. et al., *J. Org. Chem.* **2017,** *82*, 4677–4688.

2.4 氮原子消除反应

Nitrogen deletion of secondary amine



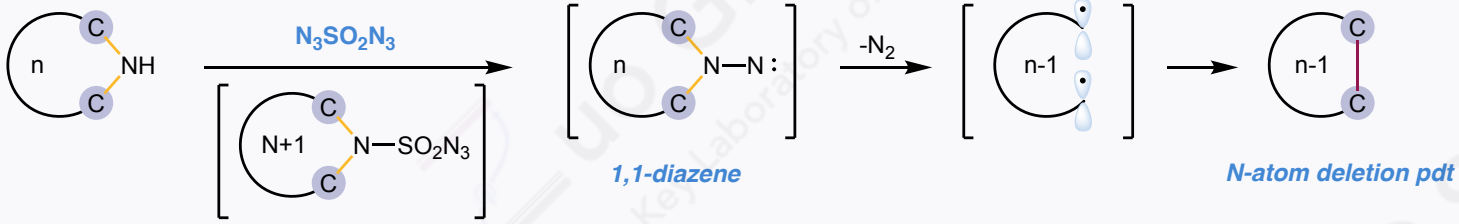
■ *Two benzylic stablilizing element was necessary*



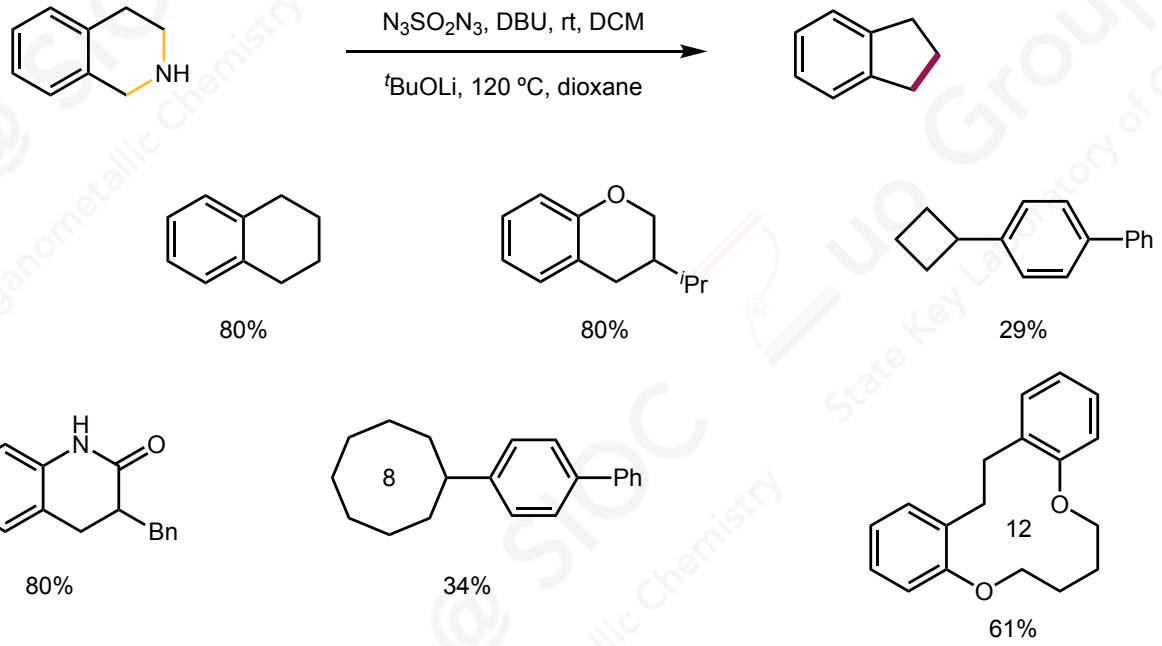
Levin, M. et al., *Nature* **2021,** *593*, 223–227.

2.4 氮原子消除反应

N-atom deletion in heterocycles



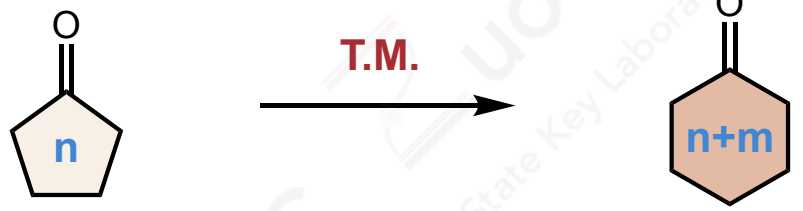
Scope of sustrate



■ *One benzylic stablilizing element was still necessary.*

Lu, H. et al., *Angew. Chem.* **2021,** *133*, 20846-20851.

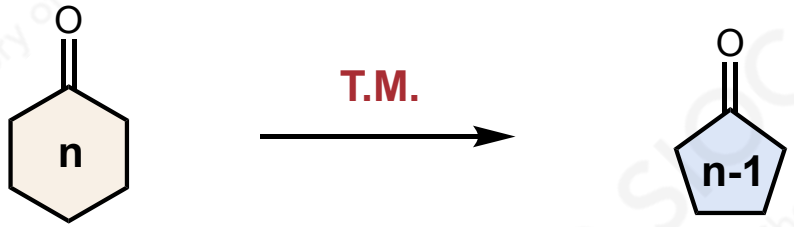
一. 非张力饱和碳(杂)环的扩环反应



- 过渡金属催化活化
- 自由基介导转化
- 饱和杂环

Rh *DG* 底物局限 自由基活性控制

二. 非张力饱和碳(杂)环的缩环反应



- 脱羰
- 环酮缩环
- 饱和杂环
- N deletion