过渡金属催化的β-氨基酸的不对称合成

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张俊良 教授

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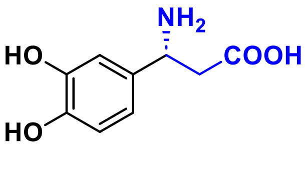
目　录

目　录

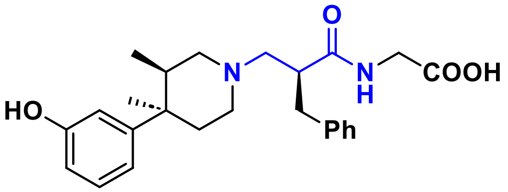
1 研究背景简介

β-氨基酸及衍生物在药物和生物学中的应用

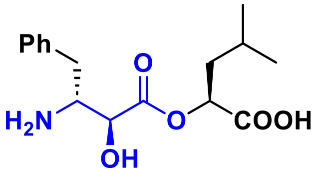
➢ 含β-氨基酸结构的药物分子



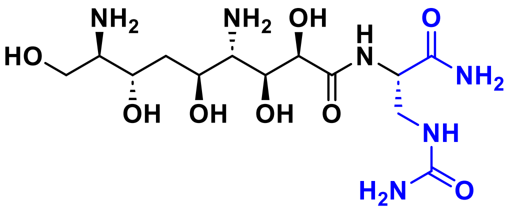
(*R*)-β-Dopa



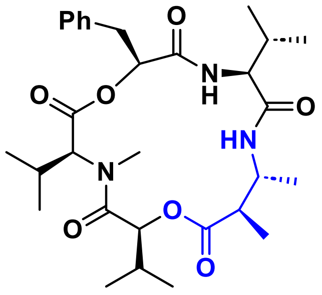
Alvimopan



Bestatin

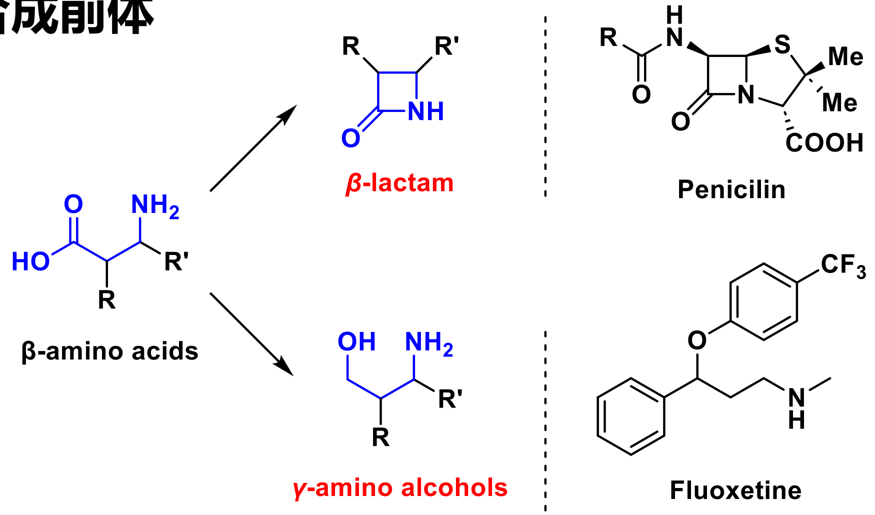


Zwittermicin A

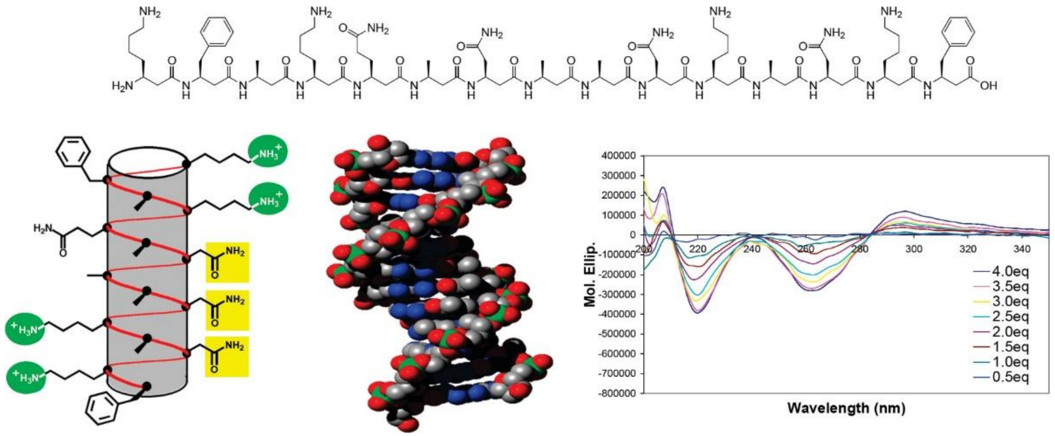


Dolastain D

➢ 作为合成前体



➢ β-氨基酸多肽二级结构研究

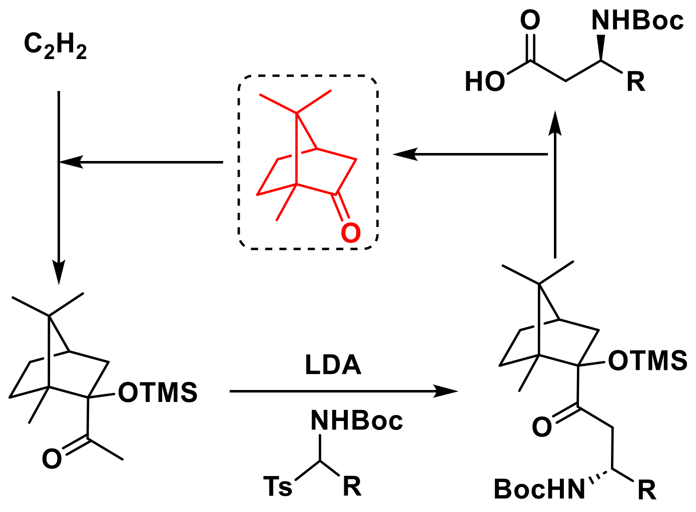


(1) Lima, M. L.; et al. *Eur. J. Med. Chem.* **2020**, *205* (8), 21941-21971. (2) Seebach, D., Gardiner, J.; *Acc. Chem. Res.* **2008**, *41* (10), 1366-1375.

复旦大学 FUDAN UNIVERSITY 1905

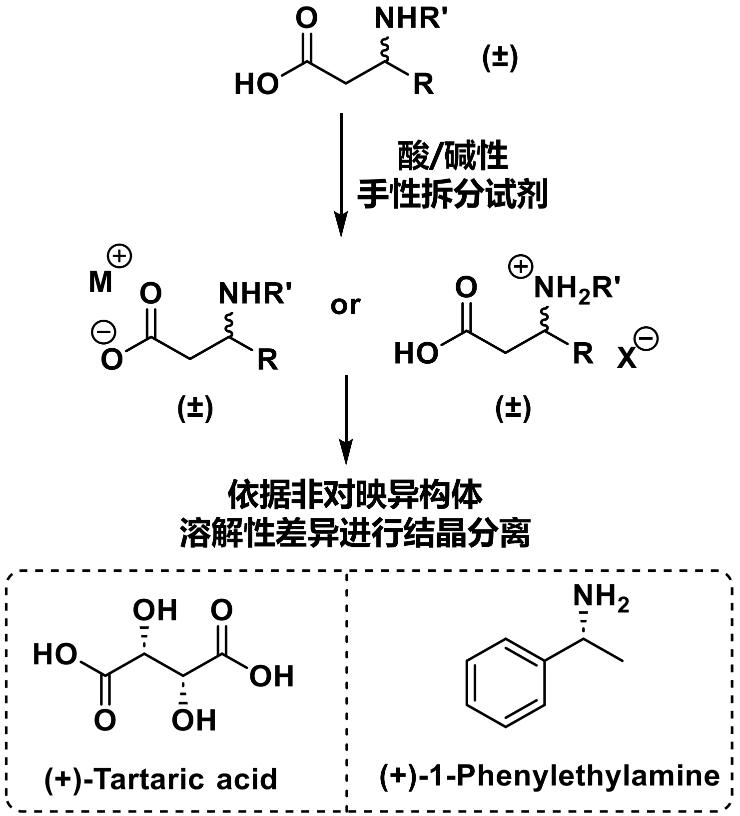
➢ 添加化学计量的手性辅基

Palomo (2000)



手性辅基无法体系内循环

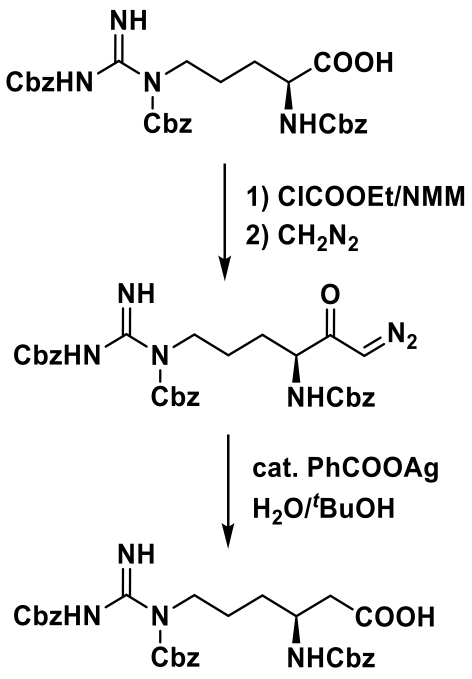
➢ 化学拆分法



产率低，操作繁琐

➢ α-氨基酸的同系增碳

Williams (1997)



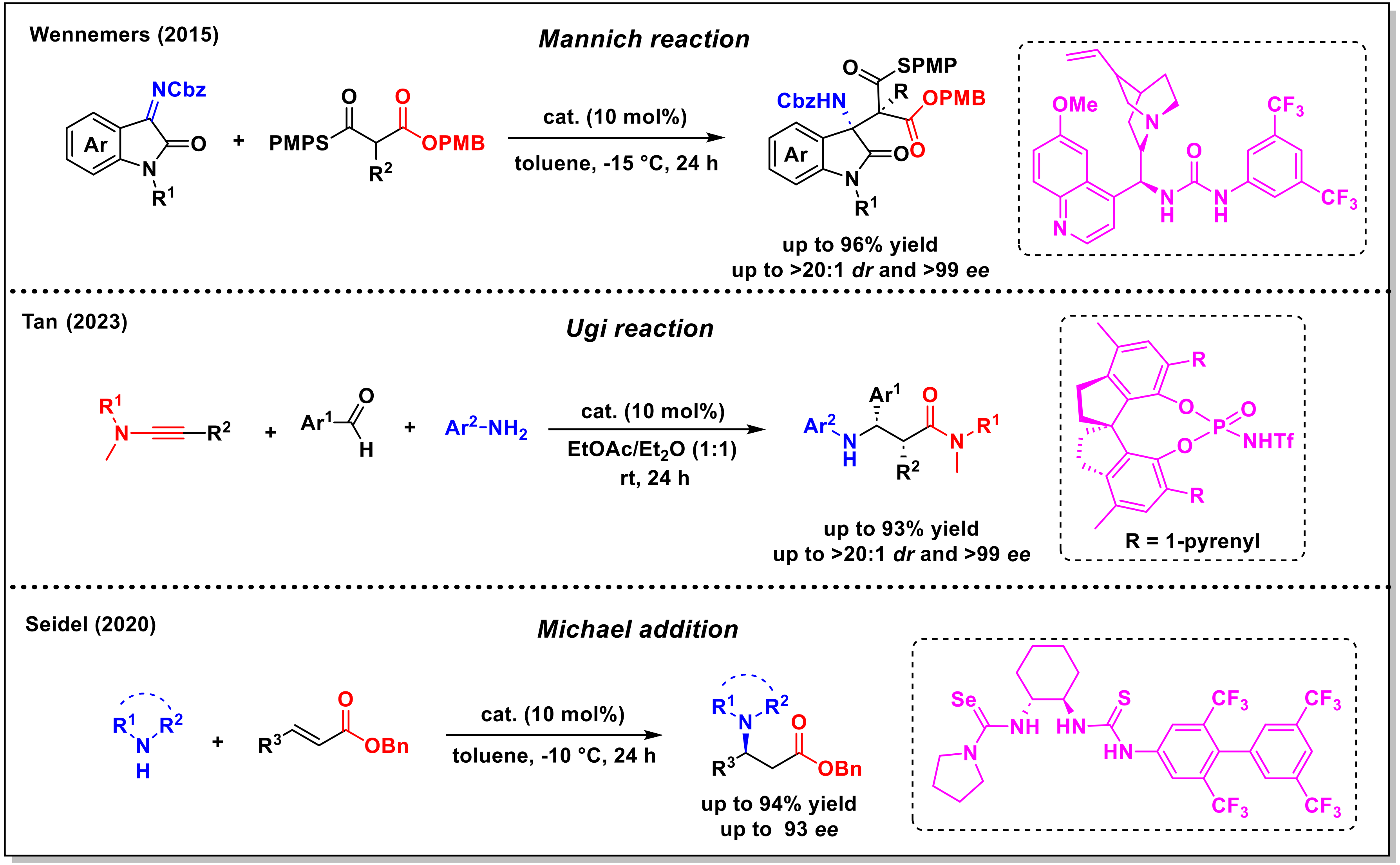
Arndt–Eistert reaction

底物结构受限，试剂毒性大

发展催化反应

(1) Palomo, C.; et al. *Angew. Chem. Int. Ed.* **2000**, *39* (6), 1063-1065. (2) Williams, M. A.; et al. *J. Am. Chem. Soc.* **1997**, *57* (4), 681-690.

1 研究背景简介——有机催化



优势:

- 水氧不敏感，后处理简单
- 催化剂丰富易得

劣势:

- 催化剂用量较大
- 反应类型较少

过渡金属催化

(1) Wennemers, H.; et al. *Angew. Chem. Int. Ed.* **2015,** *54* (28), 8193-8197. (2) Tan, B.; et al. *Nat. Chem.* **2023,** *15*, 647–657.
(3) Seidel, D.; et al. *J. Am. Chem. Soc.* **2020,** *142* (12), 5627-5635.

1 研究背景简介——过渡金属催化

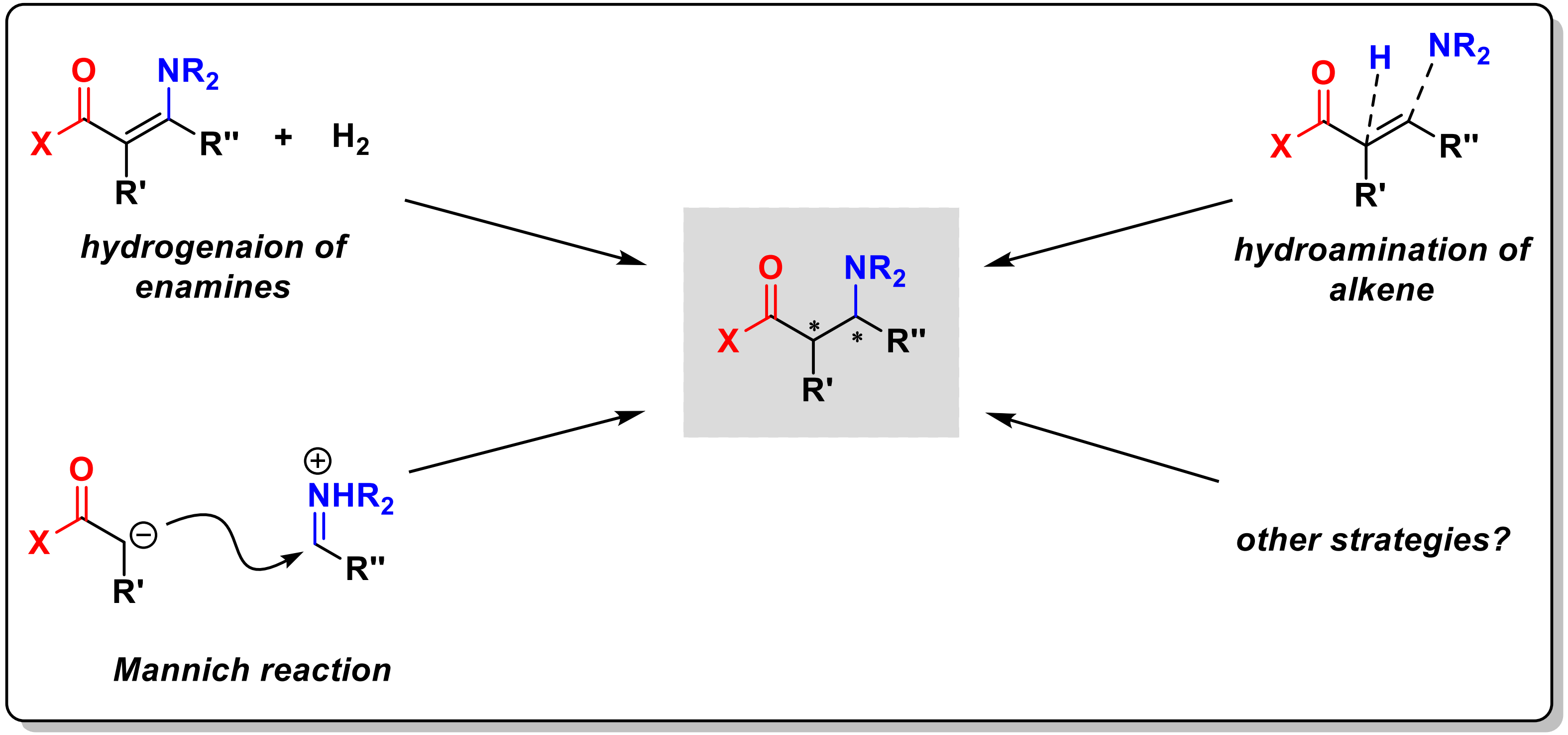
过渡金属催化优势：

- 强大的键构建能力
- 对惰性键的活化能力
- 更高的催化效率

➢ 更丰富的反应类型

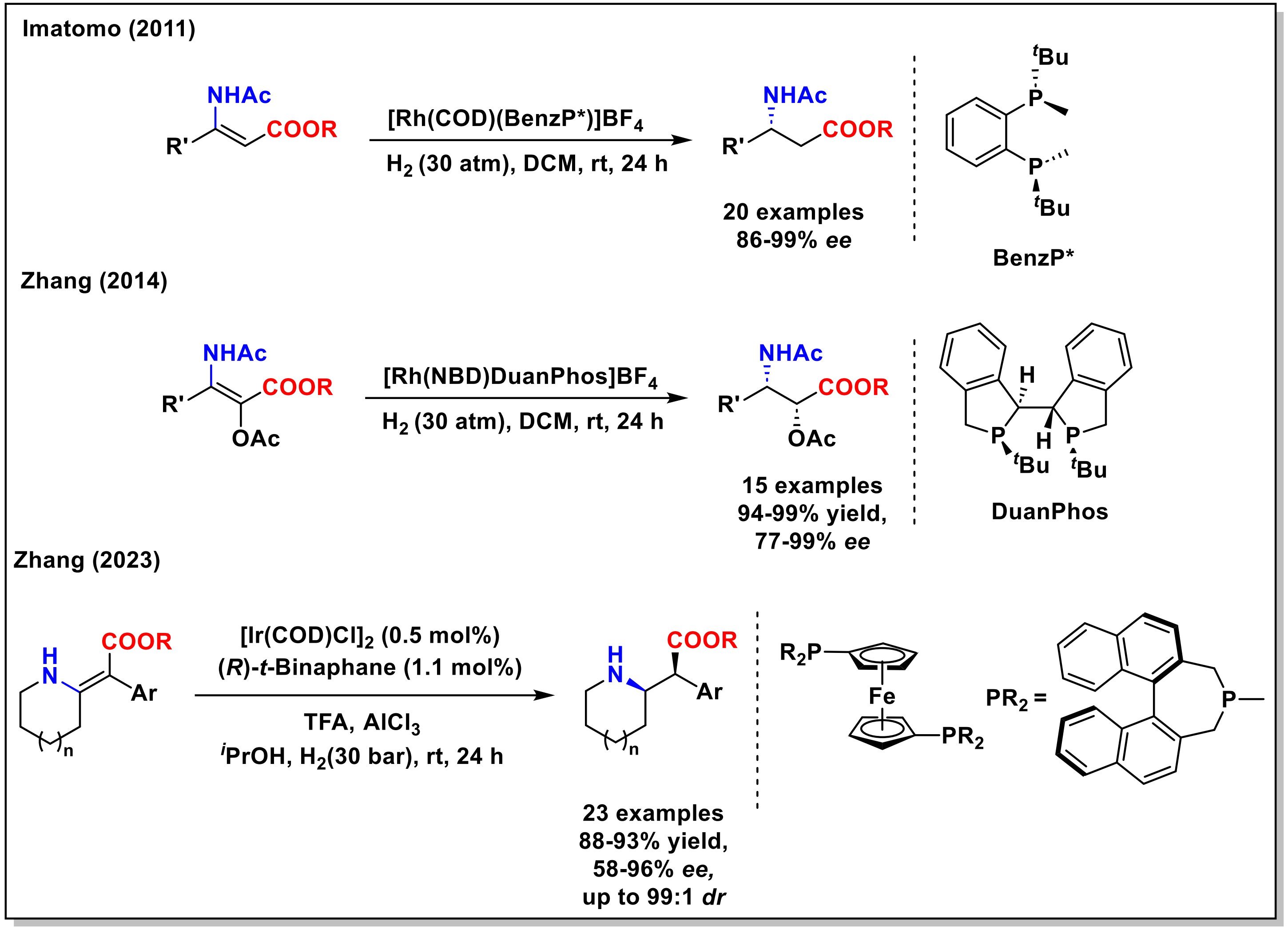
➢ 更少的催化剂用量

过渡金属催化策略



Xu, M.-H.; et al. *Synthesis*. **2024**, *57* (5), 891-916.

1 研究背景简介——过渡金属催化的不对称氢化



- 高转化率
- 高对映选择性

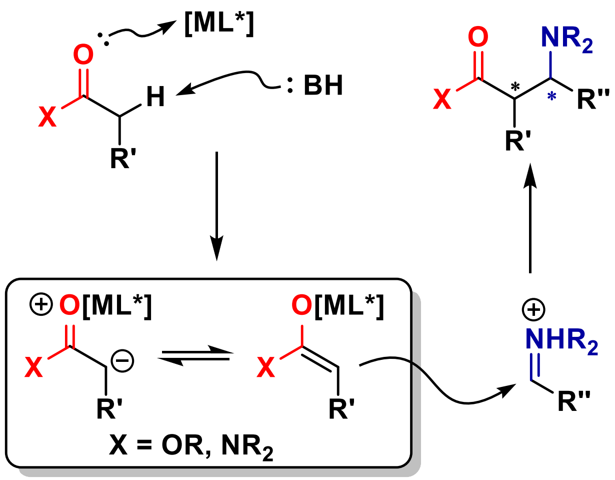
- 贵金属催化剂
- 高压反应条件

(1) Imamoto, T.; et al. *J. Am. Chem. Soc.* **2012,** *134* (3), 1754-1769. (2) Zhang, X.; et al. *J. Am. Chem. Soc.* **2024,** *136*, (46), 16120-16123.
(3) Zhang, X.; et al. *CCS Chem.* **2023,** *5* (12), 2808–2817.

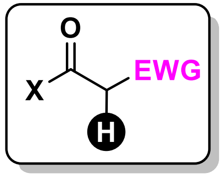
目　录

2.1 传统Mannich反应

Mannich reaction

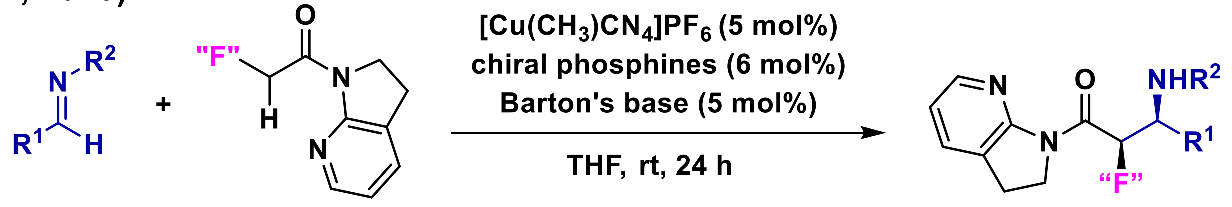


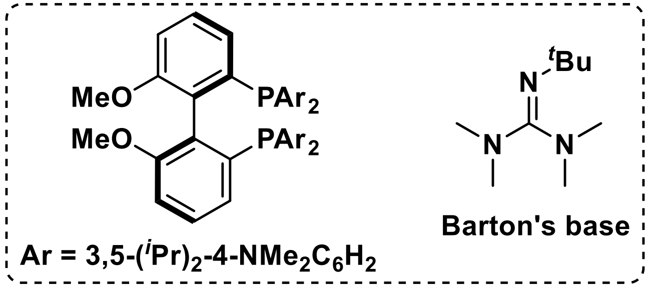
烯醇亲核试剂活性低



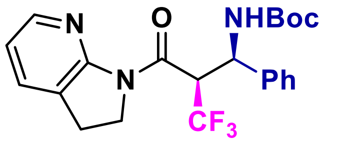
提高羰基α-H酸性

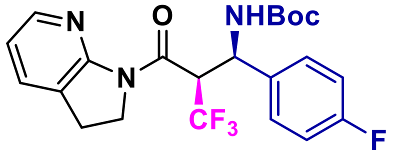
Shibasaki (2014, 2015)

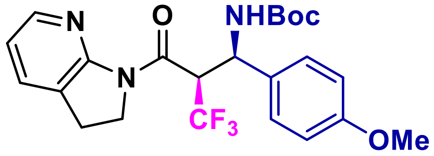


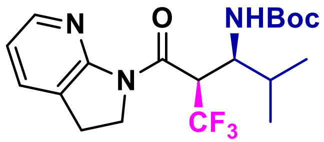


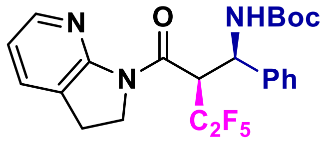
Selected examples

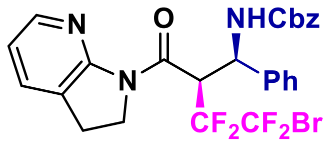

94% yield, >20:1 *dr*, 98% *ee*

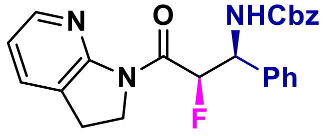

92% yield, >20:1 *dr*, 99% *ee*

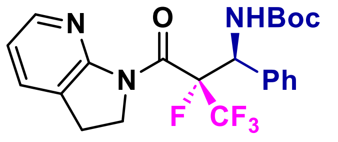

94% yield, >20:1 *dr*,98% *ee*


84% yield, >20:1 *dr*,94% *ee*


87% yield, >20:1 *dr*, 97% *ee*


91% yield, >20:1 *dr*, 98% *ee*

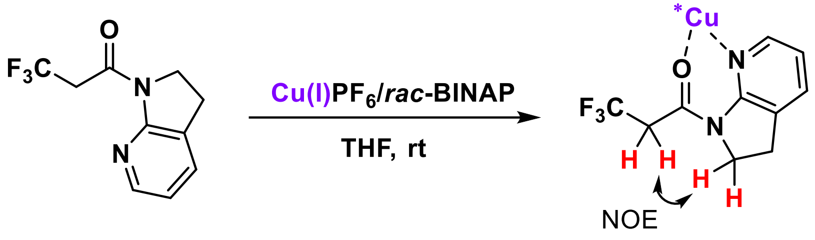

79% yield, 8.9:1 *dr*, 91% *ee*


93% yield, >20:1 *dr*, 95% *ee*

(1) Sibasaki, M.; et al. *J. Am. Chem. Soc.* **2014**, *136* (8), 17958-17961. (2) Sibasaki, M.; et al. *J. Am. Chem. Soc.* **2015**, *137* (50), 15929-15939

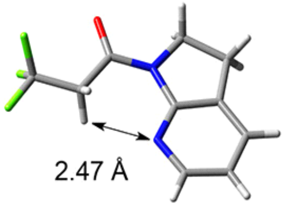
2.1 传统Mannich反应

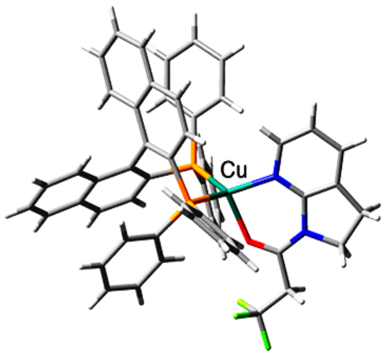
➢ 底物单晶X射线晶体分析



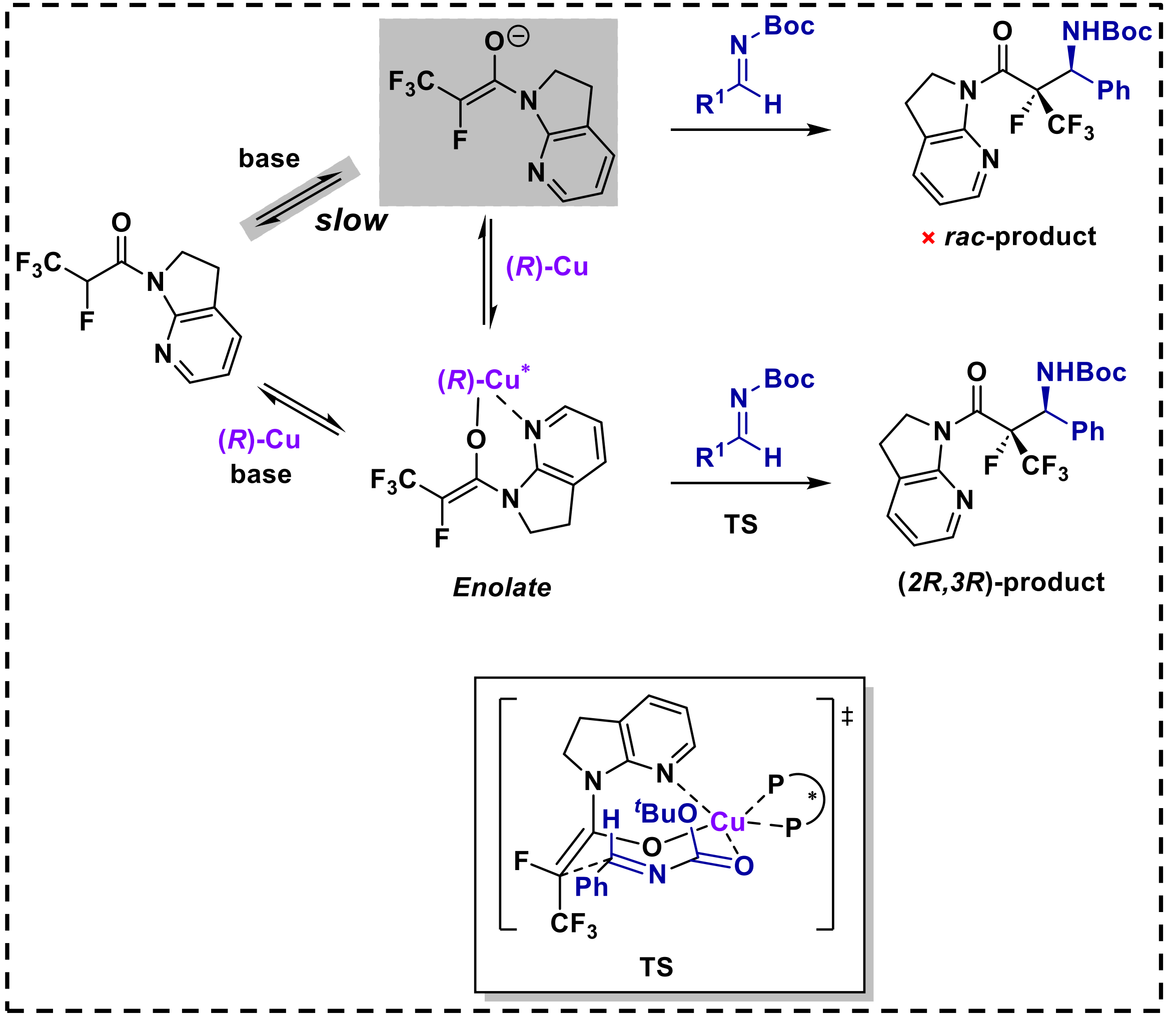
1a | 1a/Cu(I)PF$_6$/*rac*-L

E-conformer | *Z*-conformer





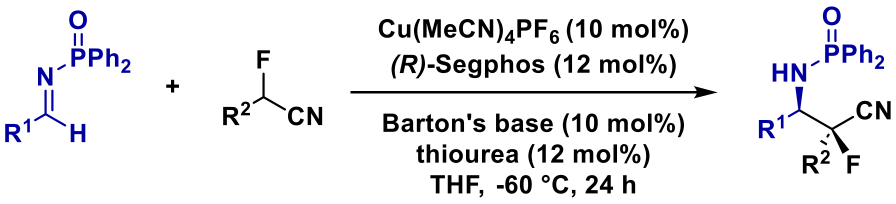
➢ 可能的反应历程

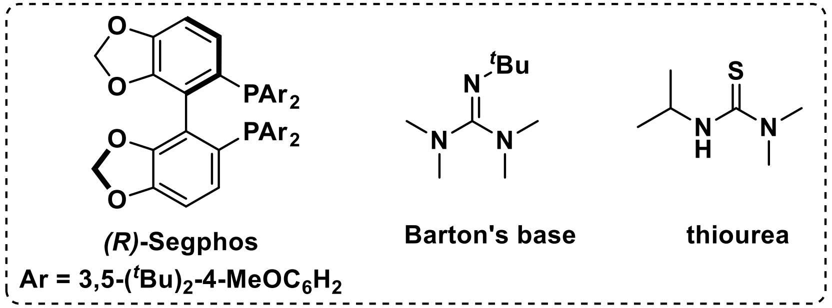


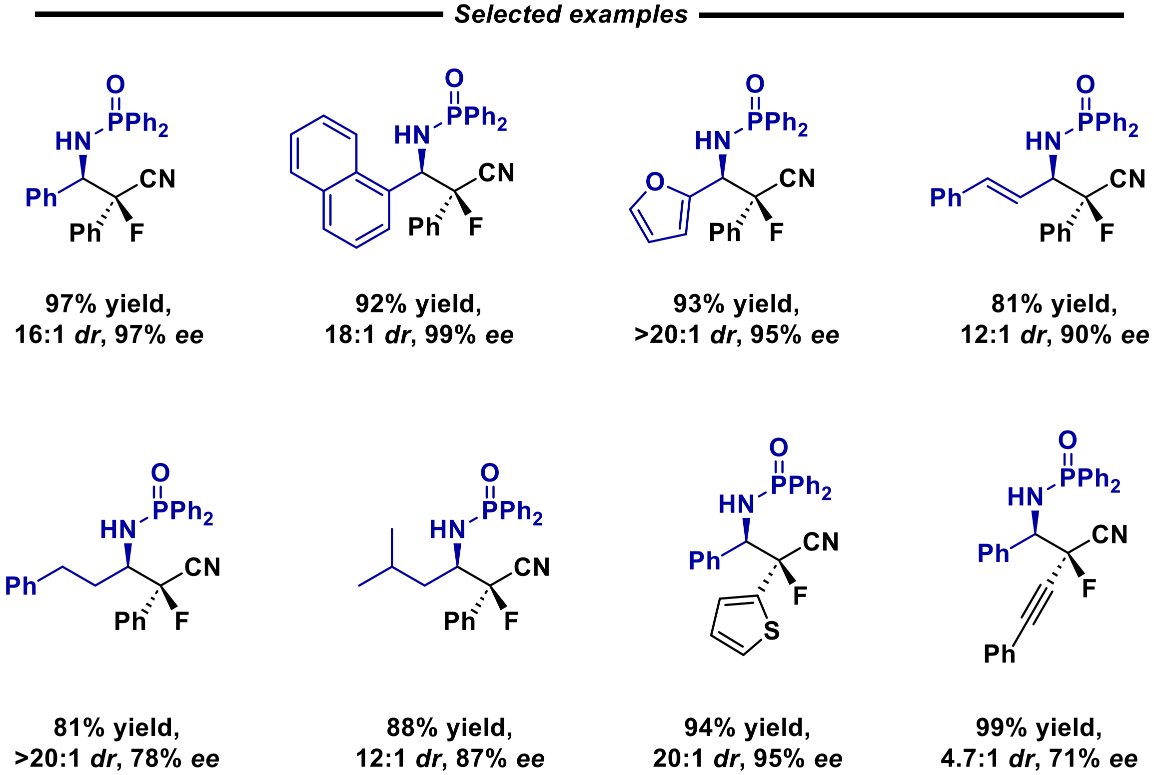
(1) Sibasaki, M.; et al. *J. Am. Chem. Soc.* **2014**, *136* (8), 17958-17961. (2) Sibasaki, M.; et al. *J. Am. Chem. Soc.* **2015**, *137* (50), 15929-15939

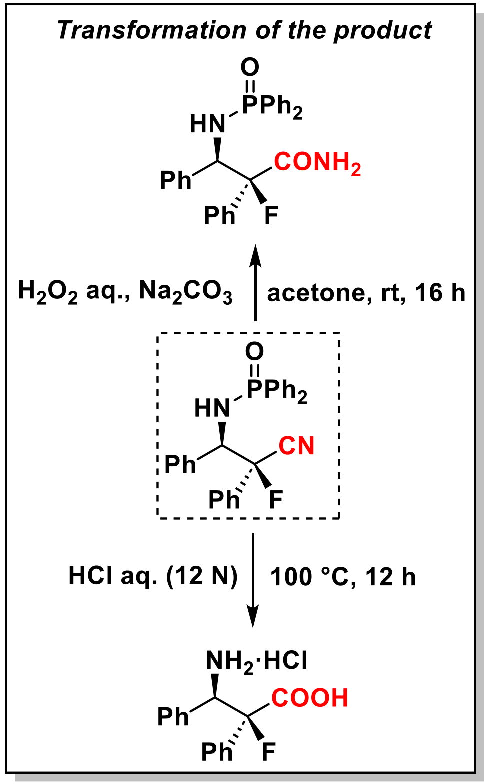
2.1 传统Mannich反应

Shibasaki (2018)









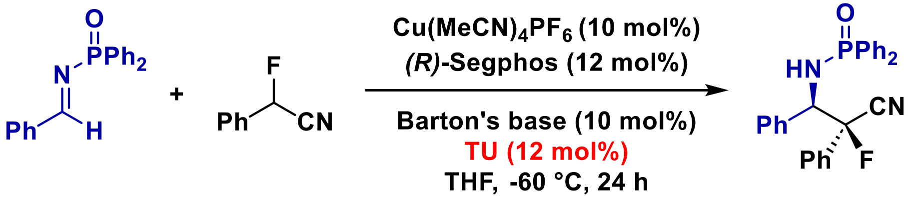
减小取代基吸电子需求

构建α–含氟季碳手性中心

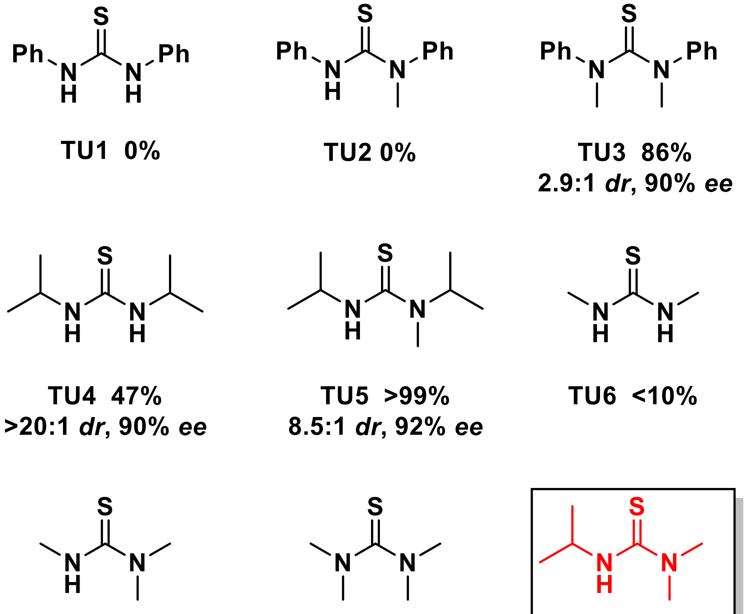
Sibasaki, M.; et al. *Angew. Chem. Int. Ed.* **2019**, *58* (9), 2644-2648

2.1 传统Mannich反应

➢ 硫脲配体(TU)筛选



(Without TU : 88% yield, 2.4:1 dr, 82% ee)



TU1 0%

TU2 0%

TU3 86%
2.9:1 *dr*, 90% *ee*

TU4 47%
>20:1 *dr*, 90% *ee*

TU5 >99%
8.5:1 *dr*, 92% *ee*

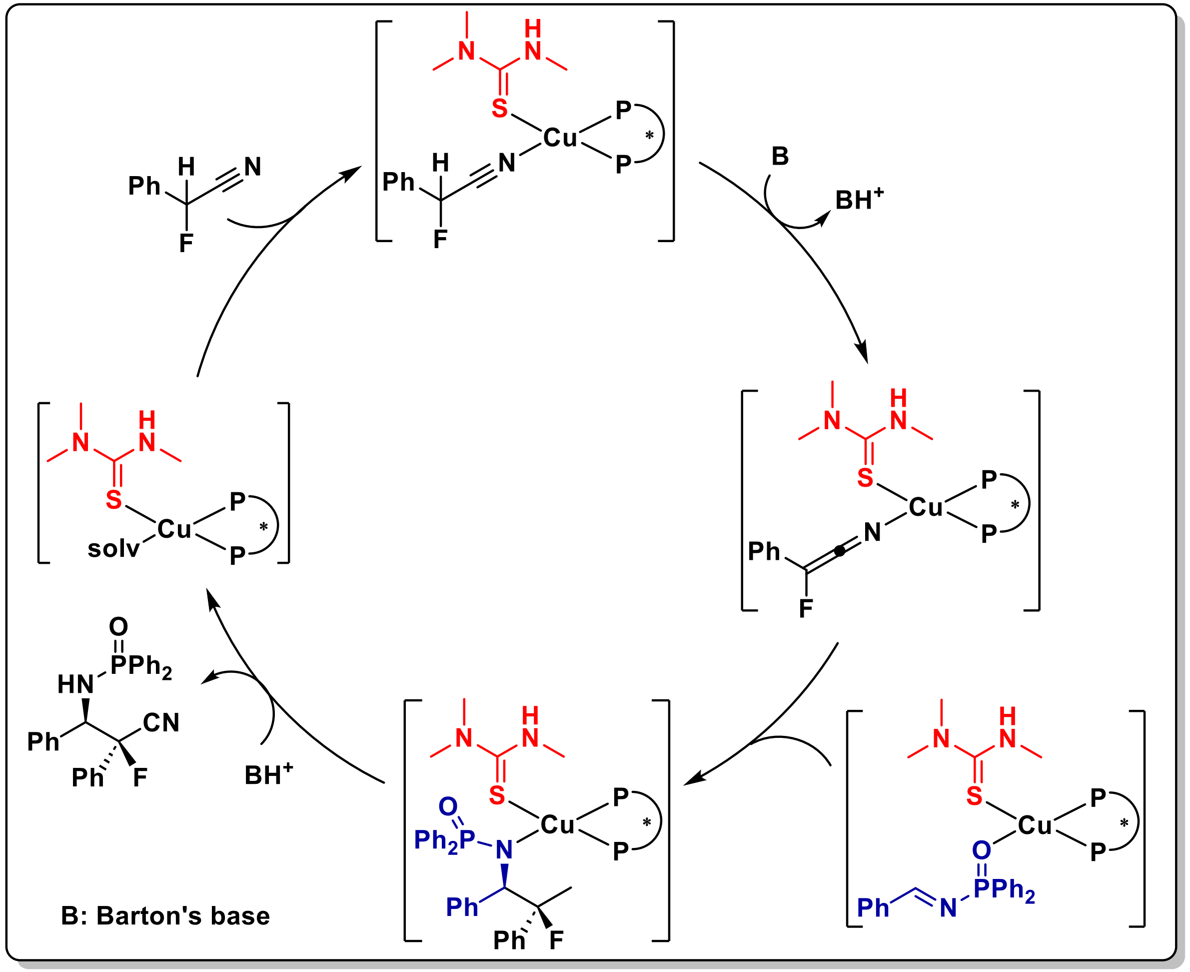
TU6 <10%

TU7 70%
16:1 *dr*, 91% *ee*

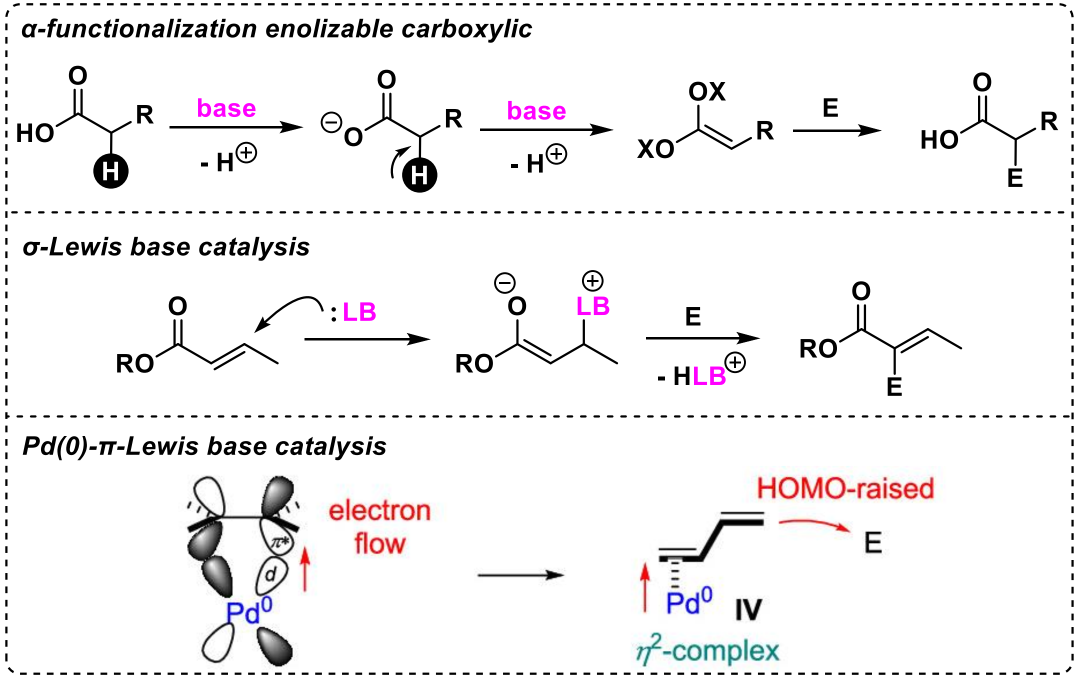
TU8 88%
5.1:1 *dr*, 89% *ee*

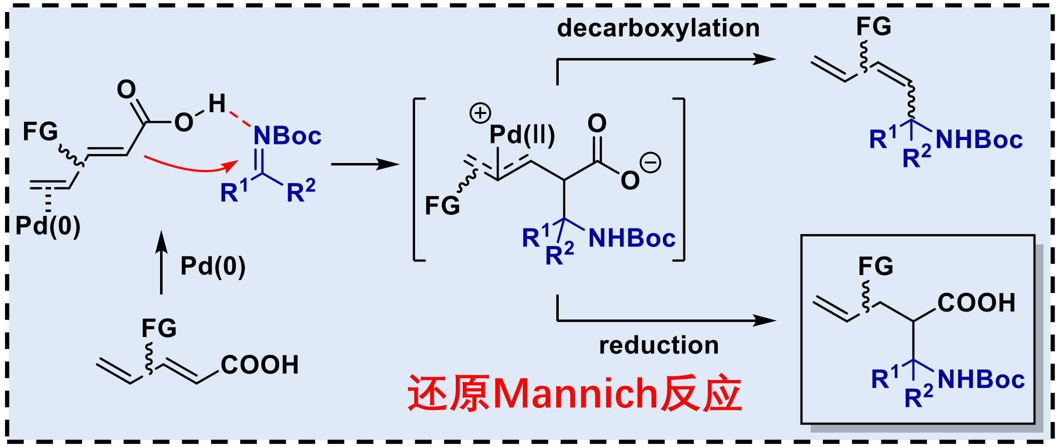
TU9 >99%
17:1 *dr*, 93% *ee*

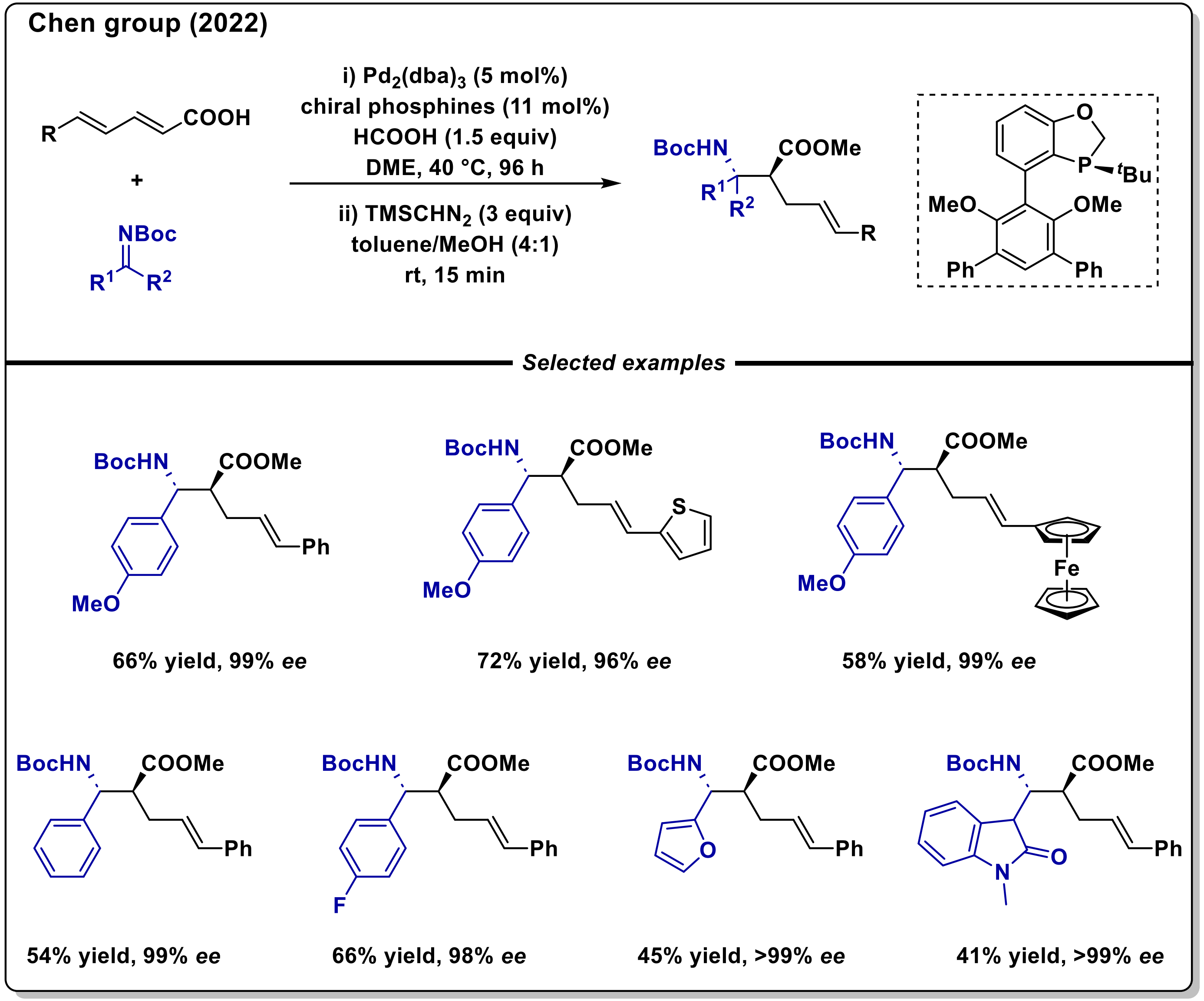
➢ 可能的机理



2.1 传统Mannich反应





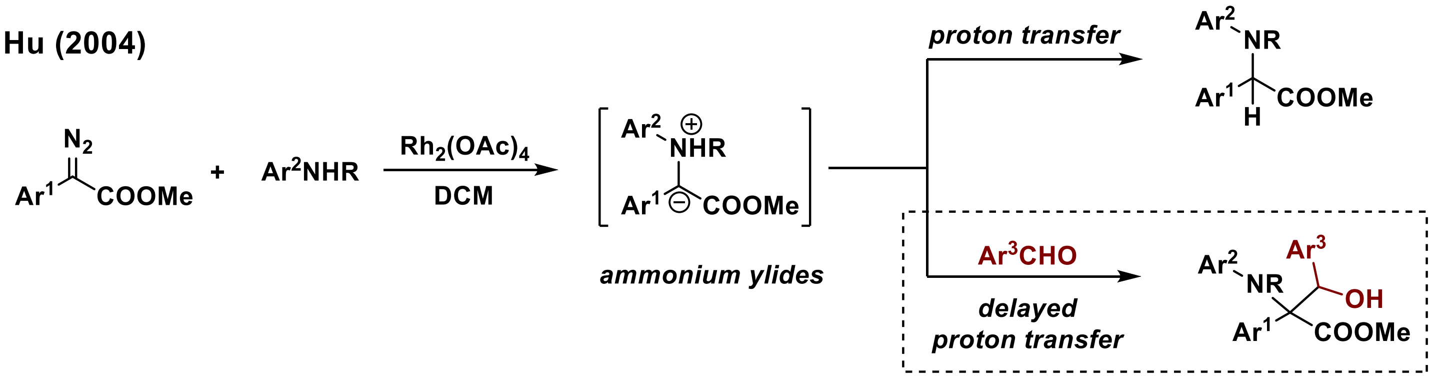


Chen, Y.-C.; et al. *J. Am. Chem. Soc.* **2022**, *144* (49), 22689-22697

目　录

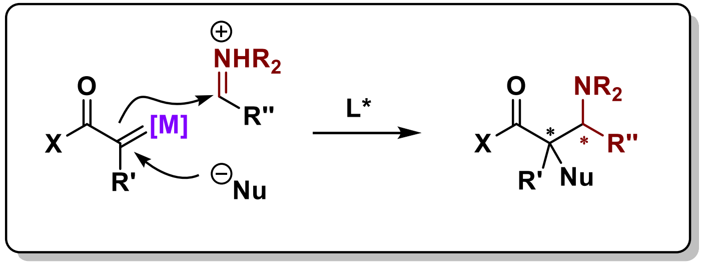
2.2 金属卡宾参与的三组分偶联

Hu (2004)

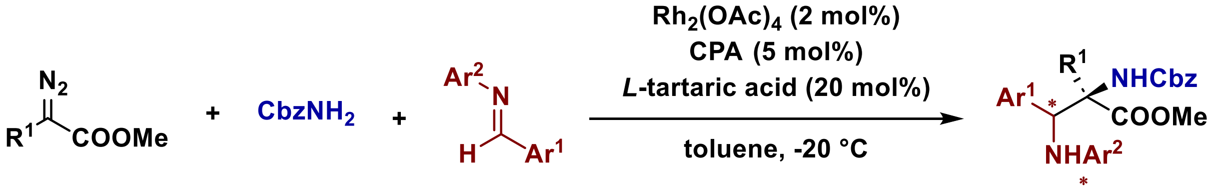


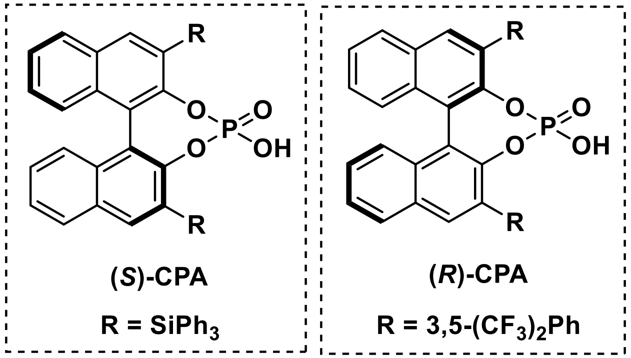
亲电试剂捕获活泼中间体

金属卡宾参与的三组分偶联



Hu (2011)

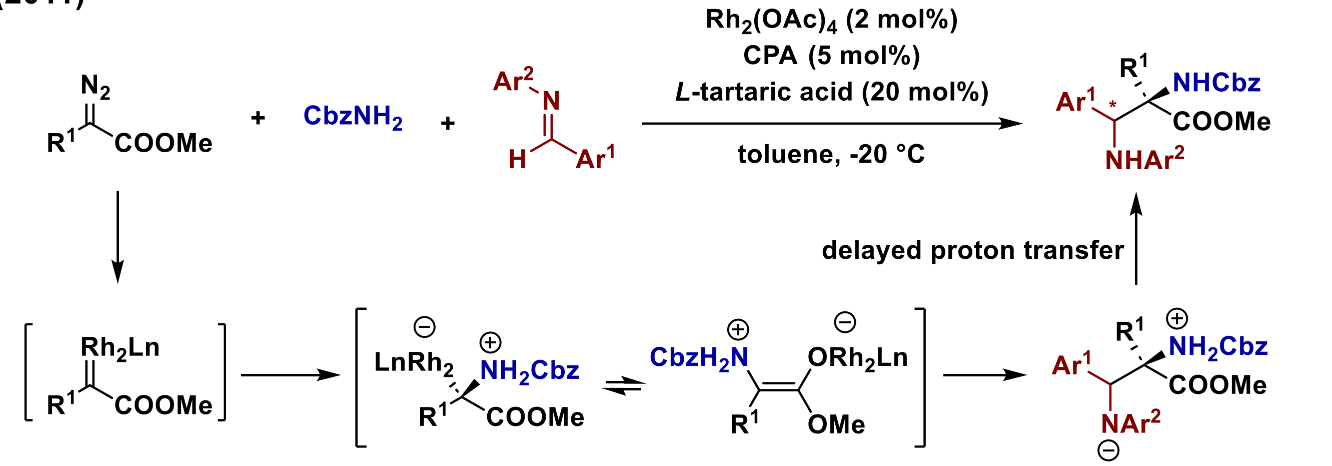




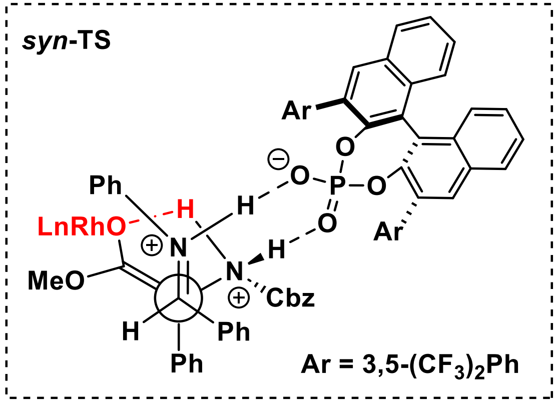
(1) Hu, W.-H.; et al. *Chem. Commun.*. **2004**, 2486-2487 (2) Hu, W.-H.; et al. *J. Am. Chem. Soc.* **2011**, *133* (22), 8428-8431

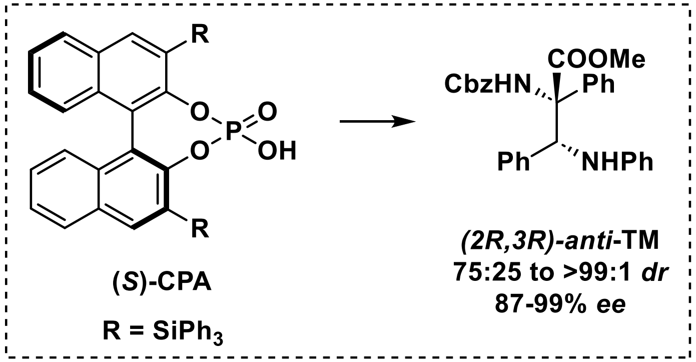
2.2 金属卡宾参与的三组分偶联

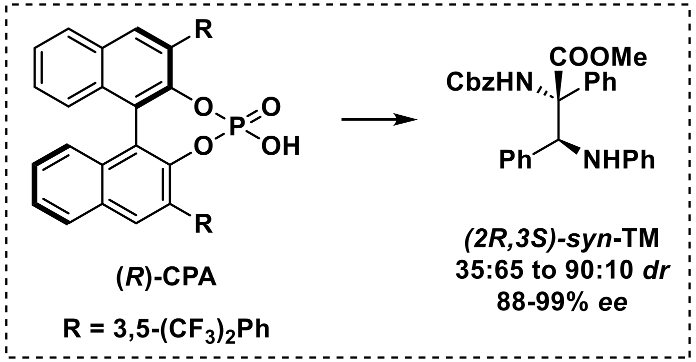
Hu (2011)

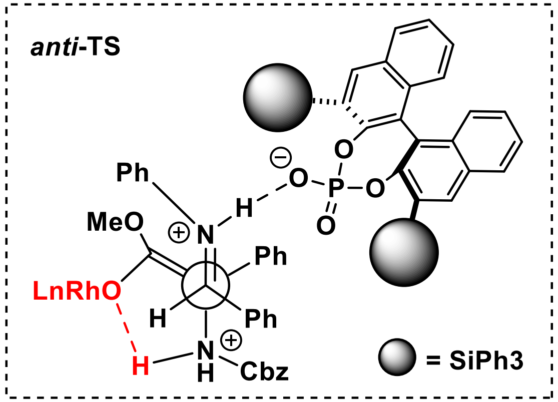


➢ 可能的过渡态







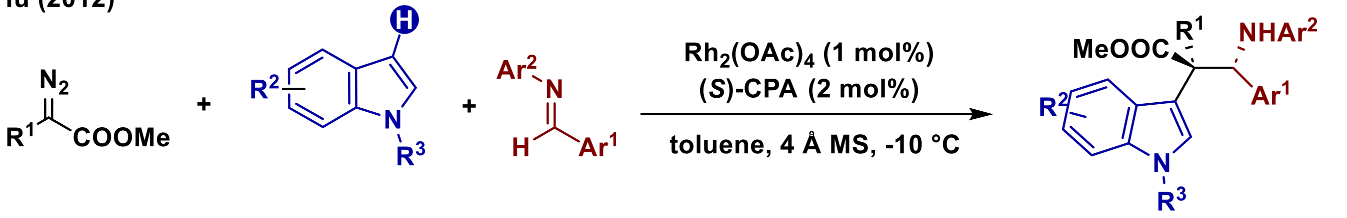


Hu, W.-H; et al. *J. Am. Chem. Soc.* **2011**, *133* (22), 8428-8431

2.2 金属卡宾参与的三组分偶联

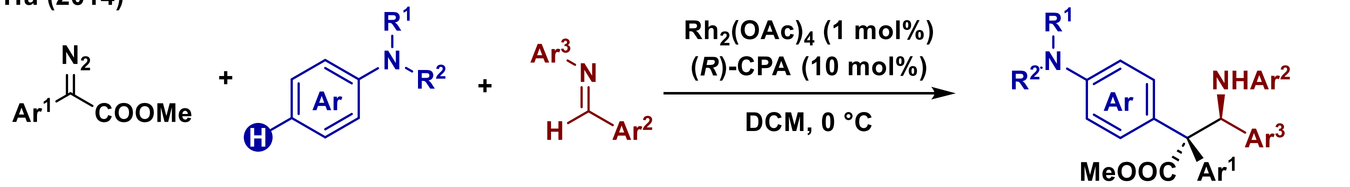
亲核物种拓展：芳环/芳杂环C-H不对称官能团化

Hu (2012)

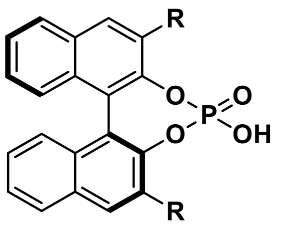


30 examples, 58-98% yield,
>20:1 *dr*, 84-99% *ee*

Hu (2014)

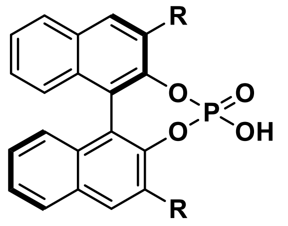


24 examples, 40-84% yield,
80:20 to 95:5 *dr*, 90-99% *ee*



(*S*)-CPA

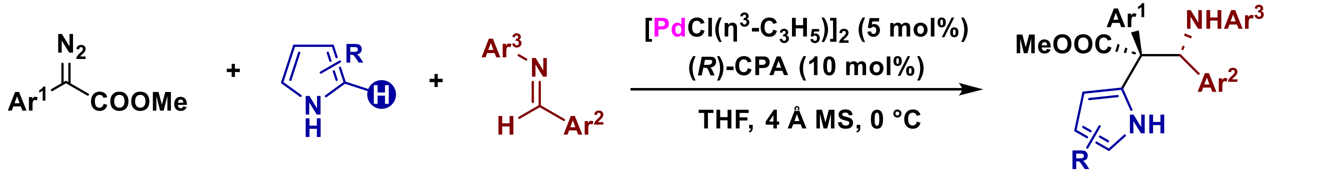
R = $SiPh_3$



(*R*)-CPA

R = = 2,4,6-$^{i}Pr_3C_6H_2$

Hu (2013)

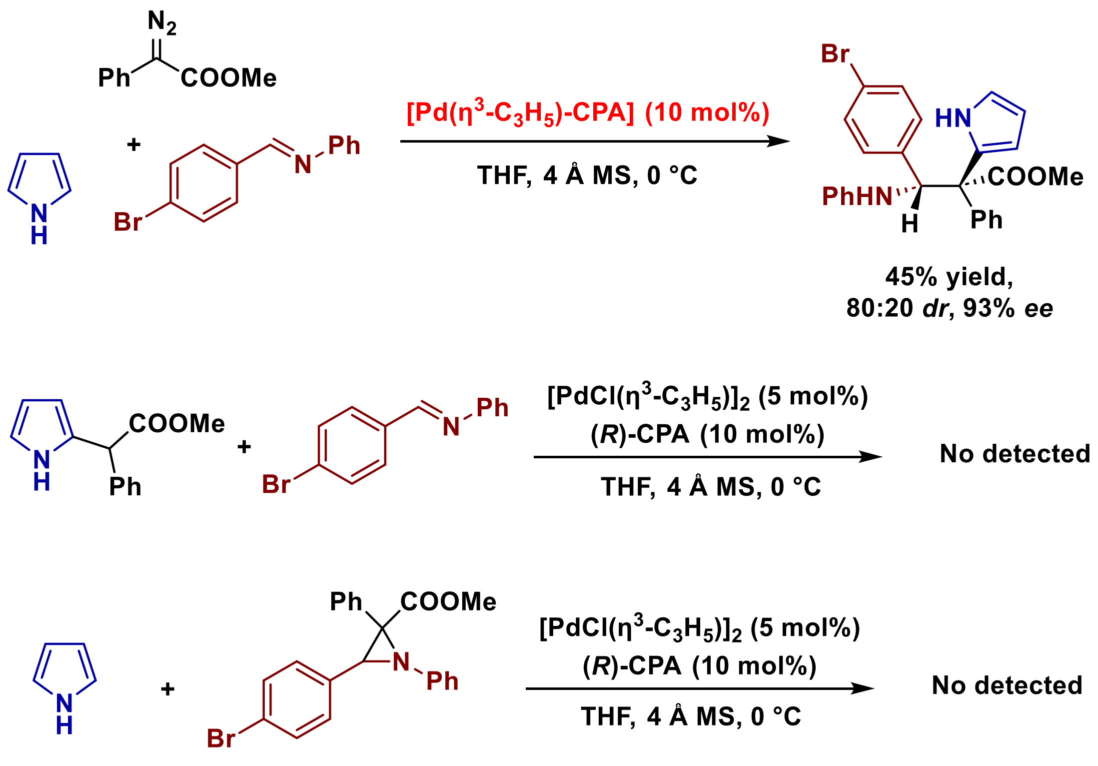


26 examples, 40-84% yield,
72:28 to 95:5 *dr*, 58-99% *ee*

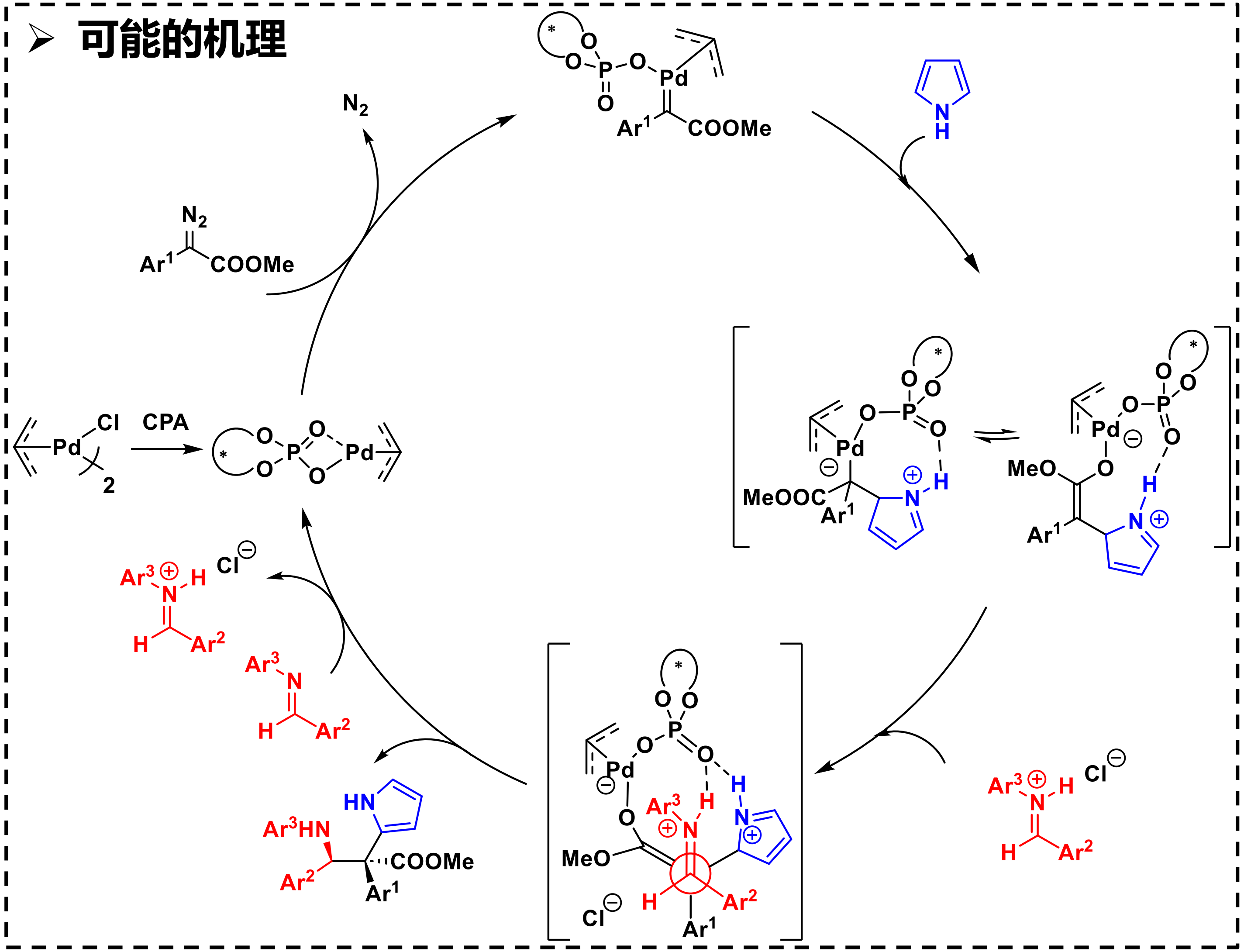
(1) Hu, W.-H; et al. *Nat. Chem.* **2012**, *4*, 733–738. (2) Hu, W.-H; et al. *Angew. Chem. Int. Ed.* **2014**, *53* (48), 13098-13101.
(3) Hu, W.-H; et al. *Angew. Chem. Int. Ed.* **2013**, *52* (50), 13356-13360.

2.2 金属卡宾参与的三组分偶联

➢ 控制实验



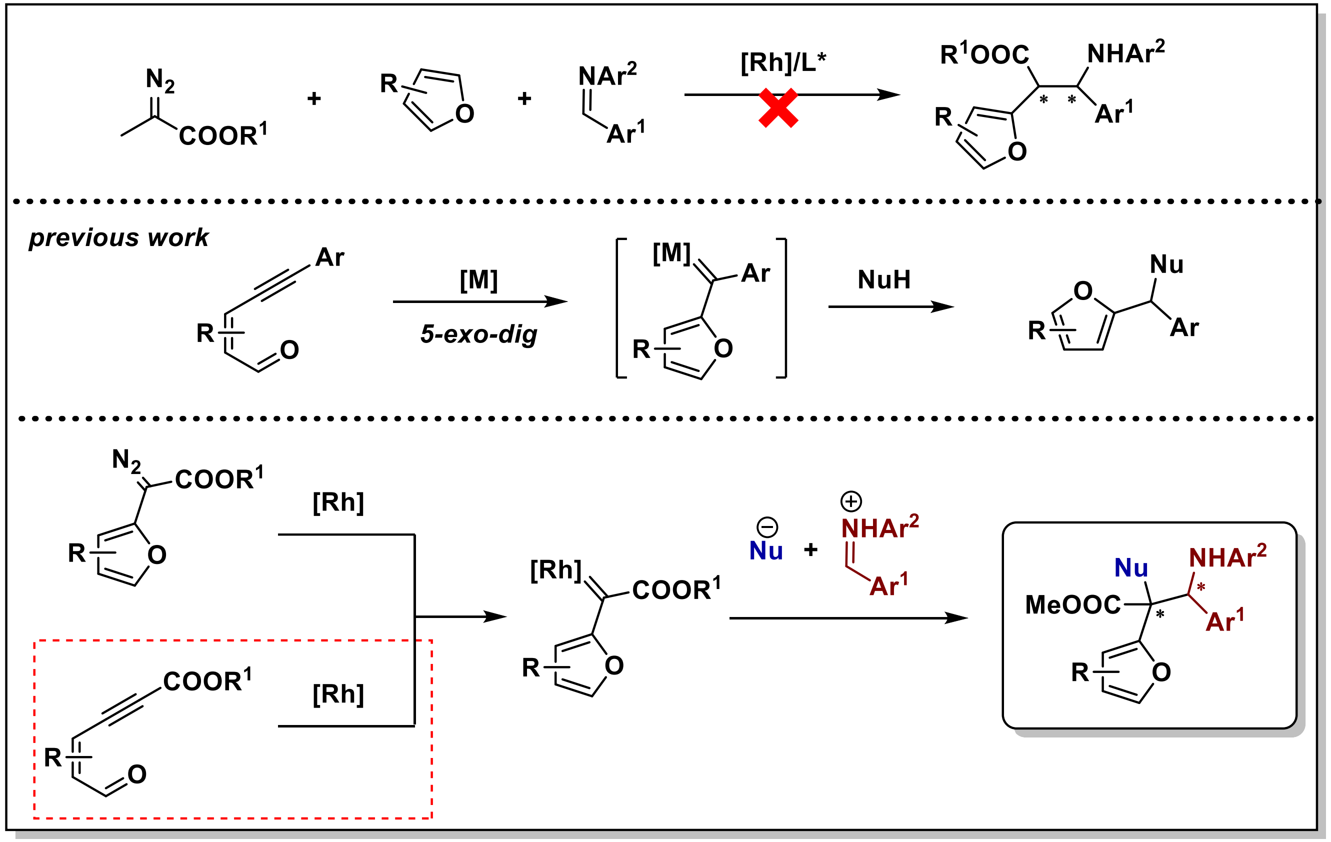
➢ 可能的机理



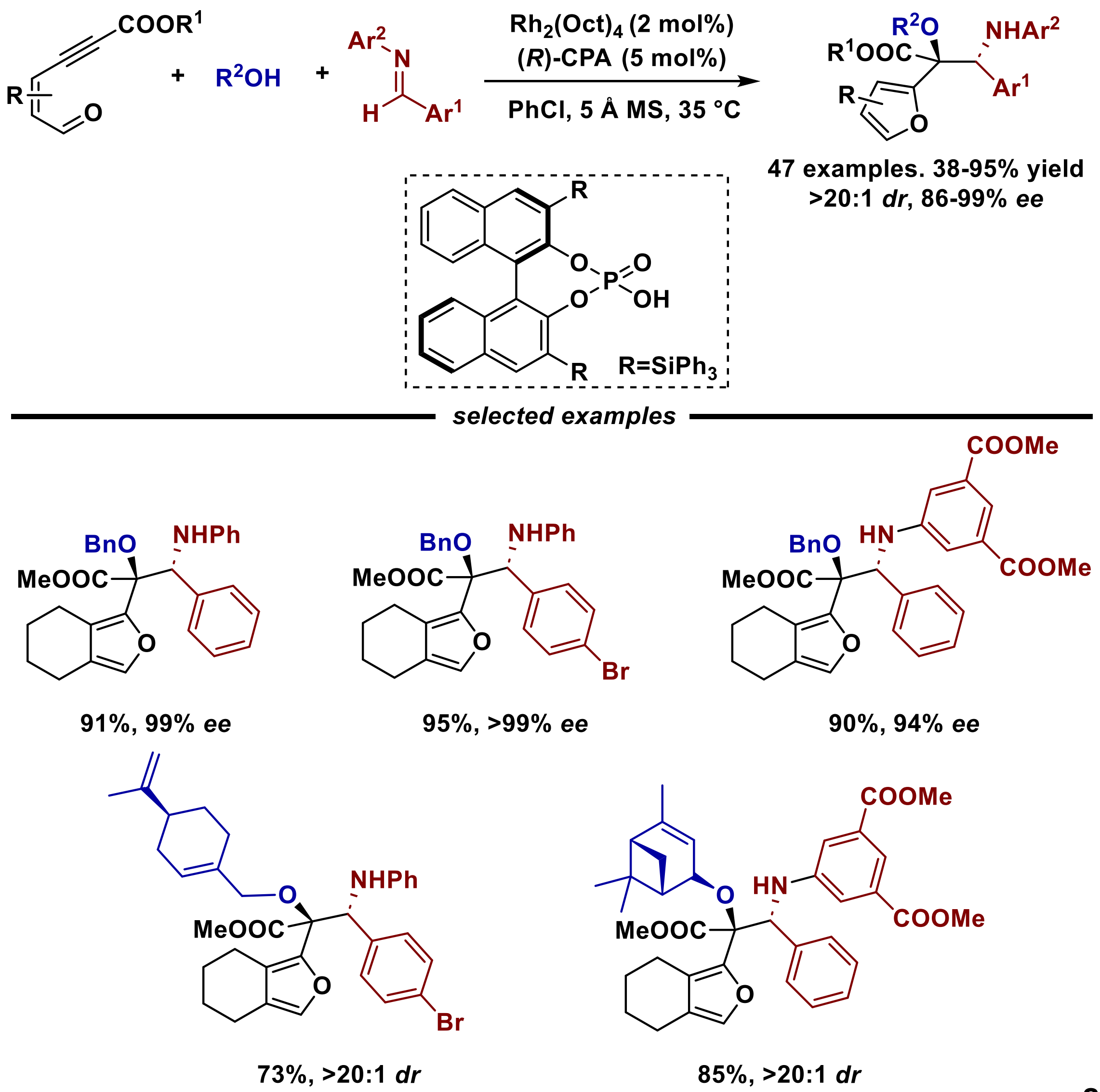
Hu, W.-H; et al. *Angew. Chem. Int. Ed.* **2013**, *52* (50), 13356-13360.

2.2 金属卡宾参与的三组分偶联

底物拓展：呋喃环的引入



Xu (2021)

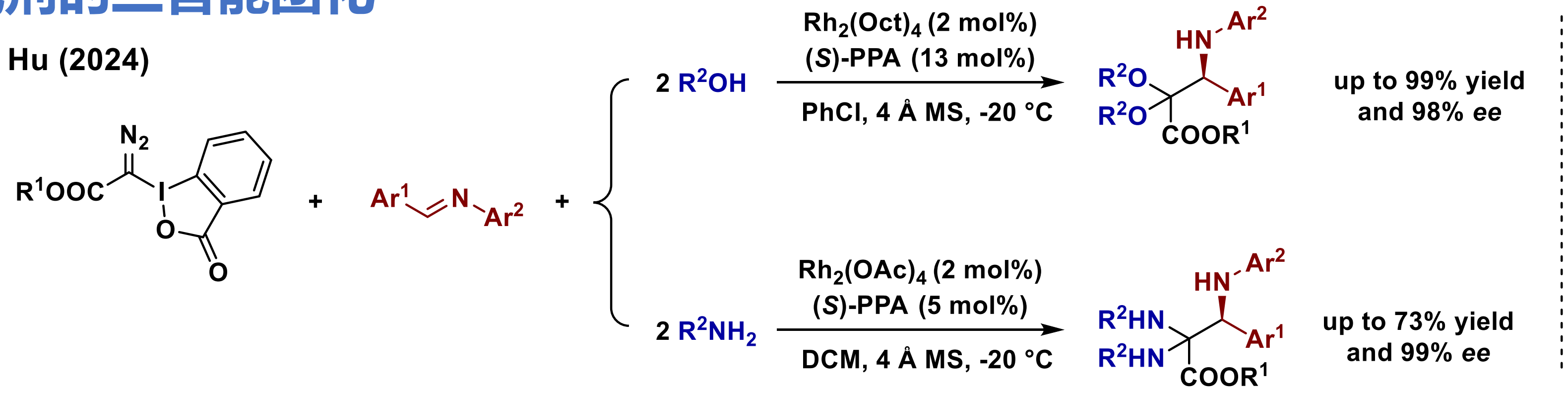


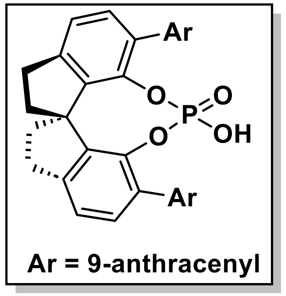
Xu, X.; et al. *ACS Catal.* **2021**, *11* (12), 6750-6756

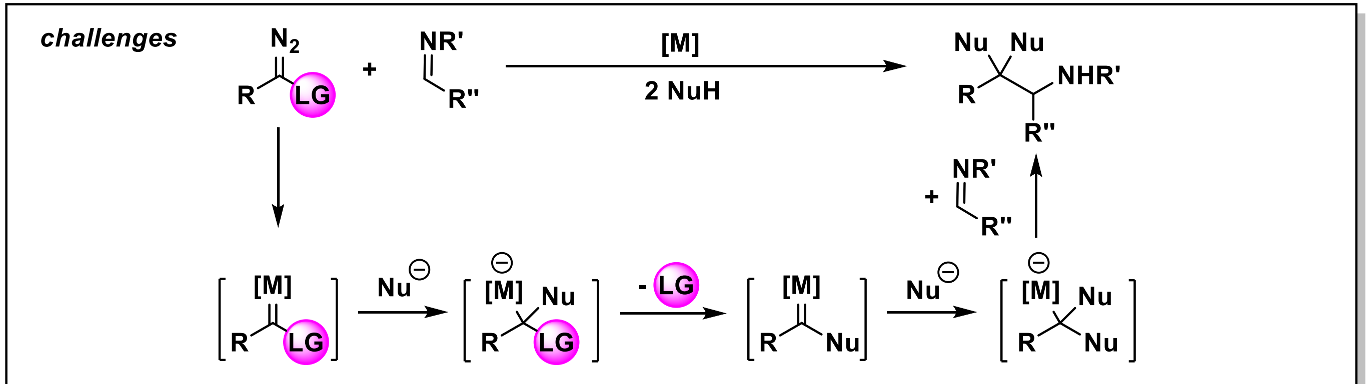
2.2 金属卡宾参与的三组分偶联

引入双亲核试剂的三官能团化

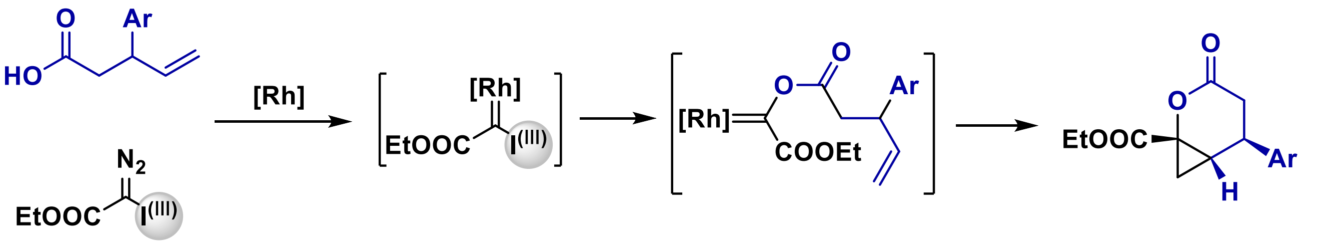
Hu (2024)



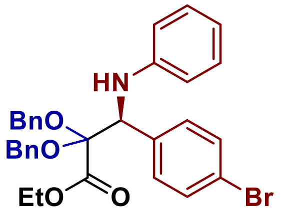




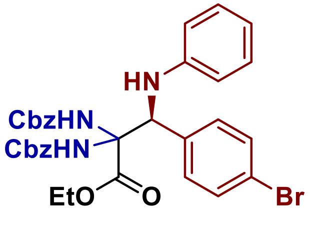
Suero (2023)



selected examples



95% yield, 92% ee



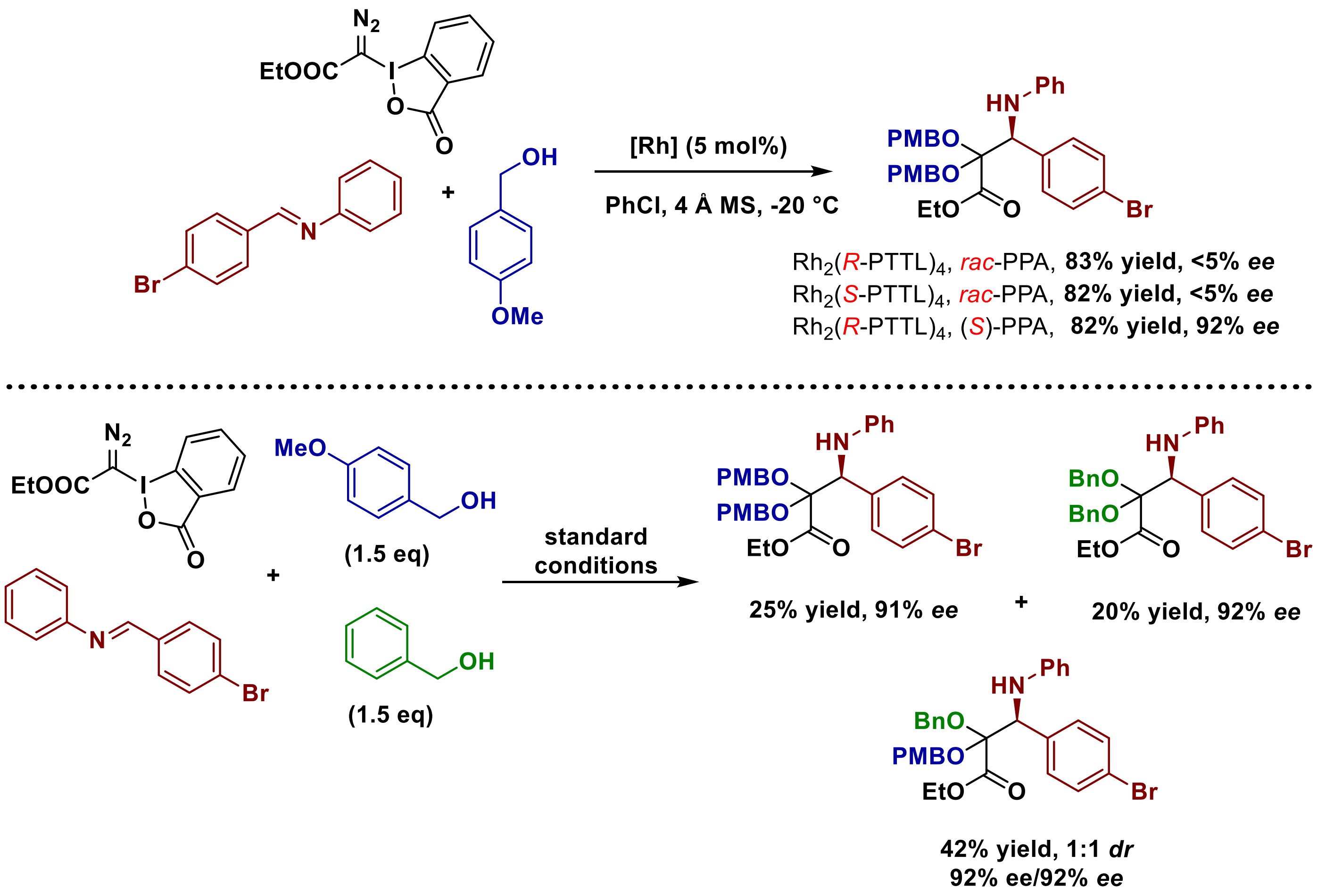
72% yield, 97% ee

(1) Hu, W.-H.; et al. *ACS Catal.* **2024**, *11* (12), 6750-6756 (2) Suero, M. G.; et al. *J. Am. Chem. Soc.* **2023**, *145* (9), 4975-4981

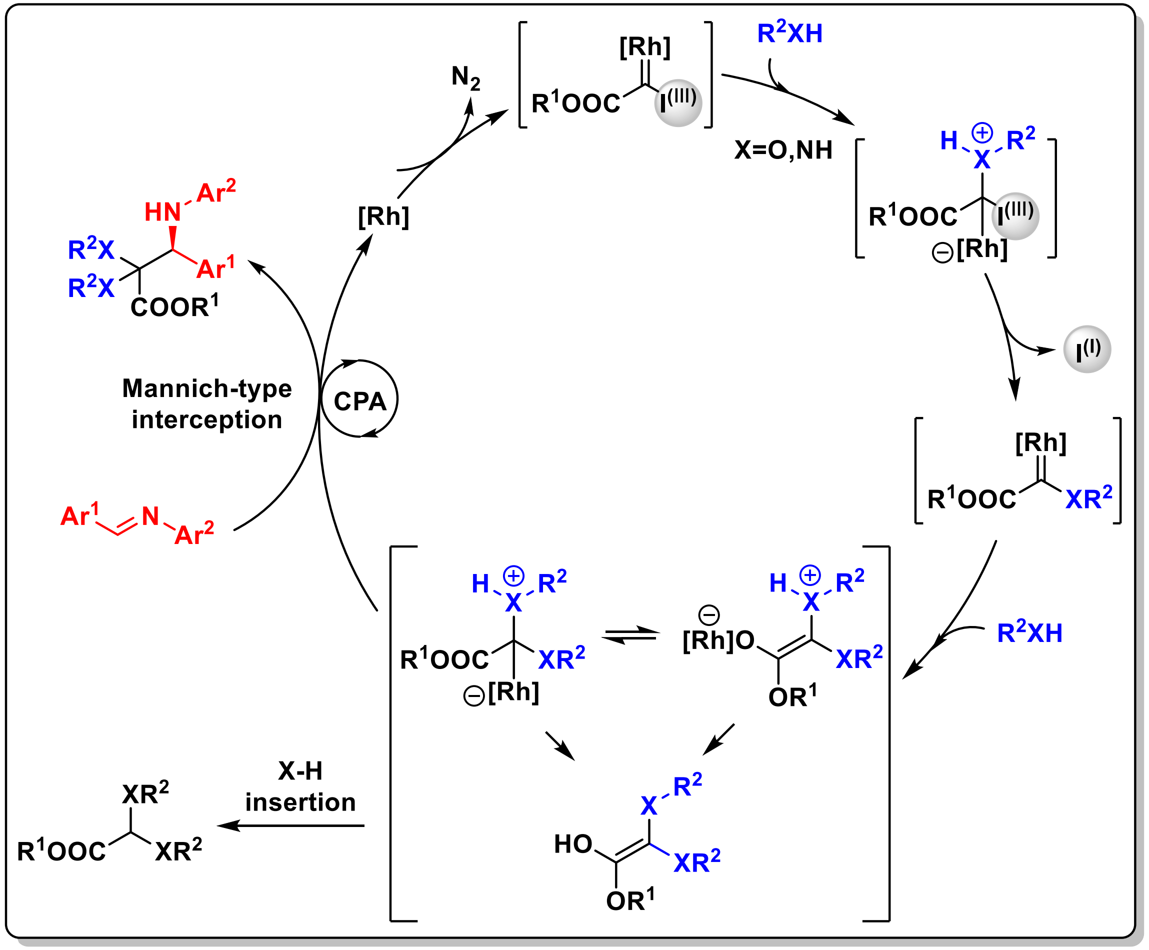
2.2 金属卡宾参与的三组分偶联

> 复旦大学 FUDAN UNIVERSITY 1905

➢ 控制实验

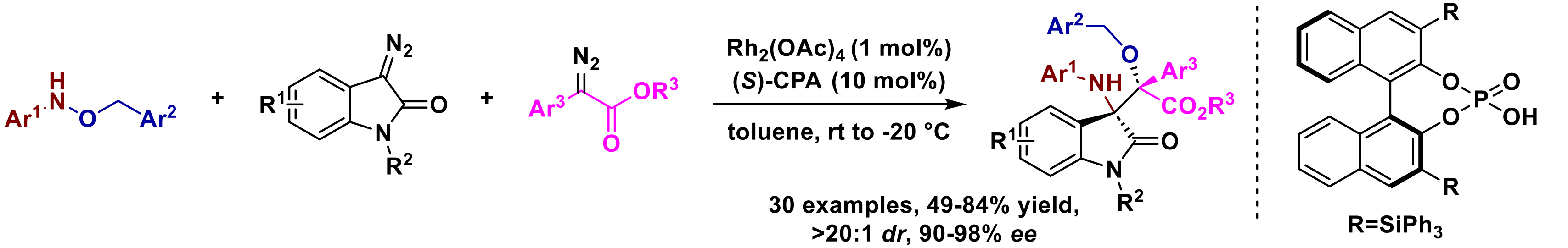


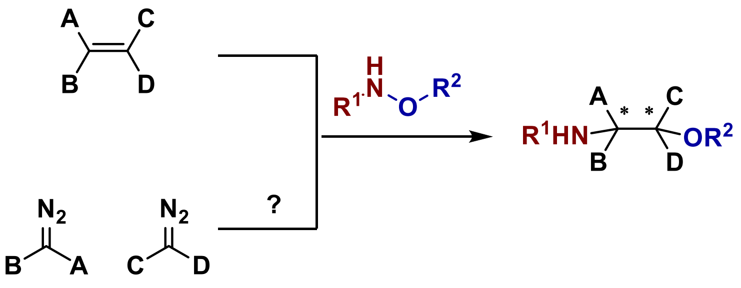
➢ 可能的机理



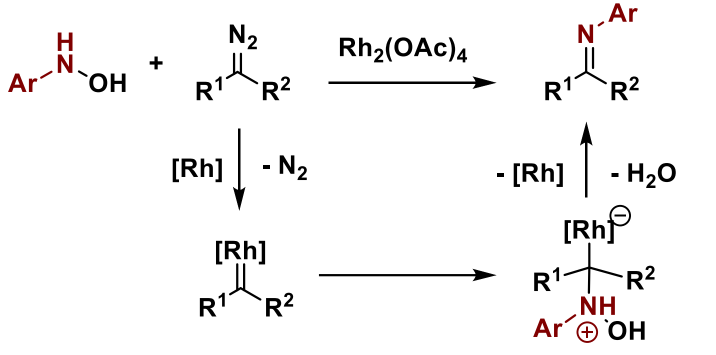
2.2 金属卡宾参与的三组分偶联

Hu (2022)

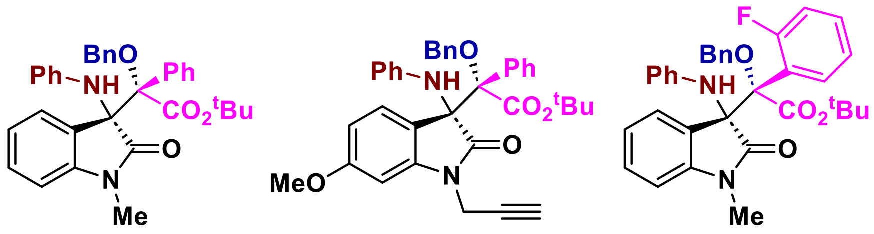




Sun (2019)

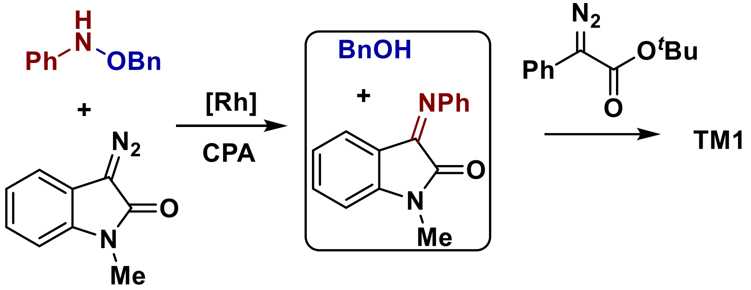


selected examples



(TM1) 77%, 96% *ee*　　73%, 90% *ee*　　75%, 98% *ee*

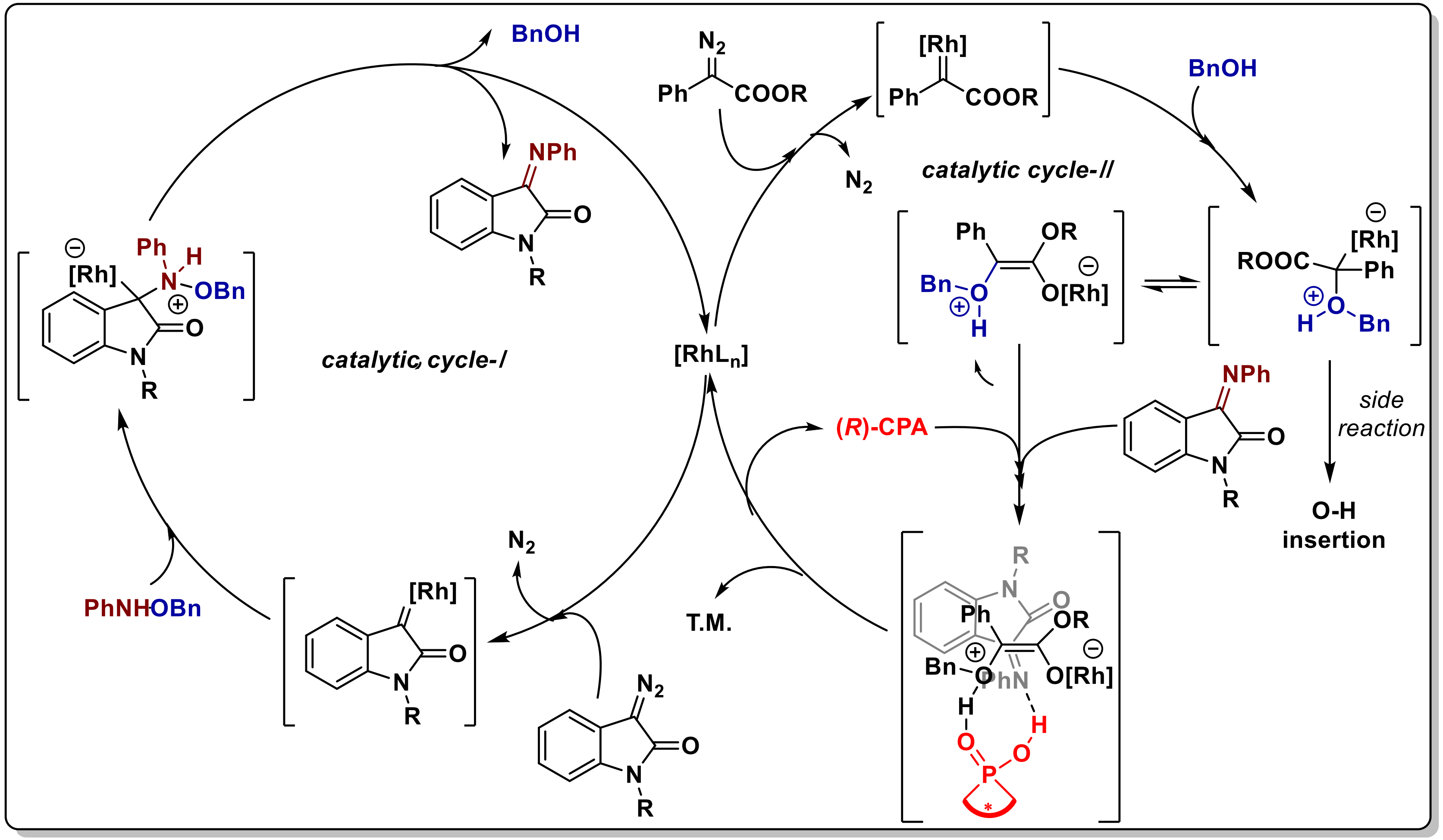
➢ 控制实验



Hu, W.-H.; et al. *ACS Catal.* **2022**, *12* (19), 12302-12309

2.2 金属卡宾参与的三组分偶联

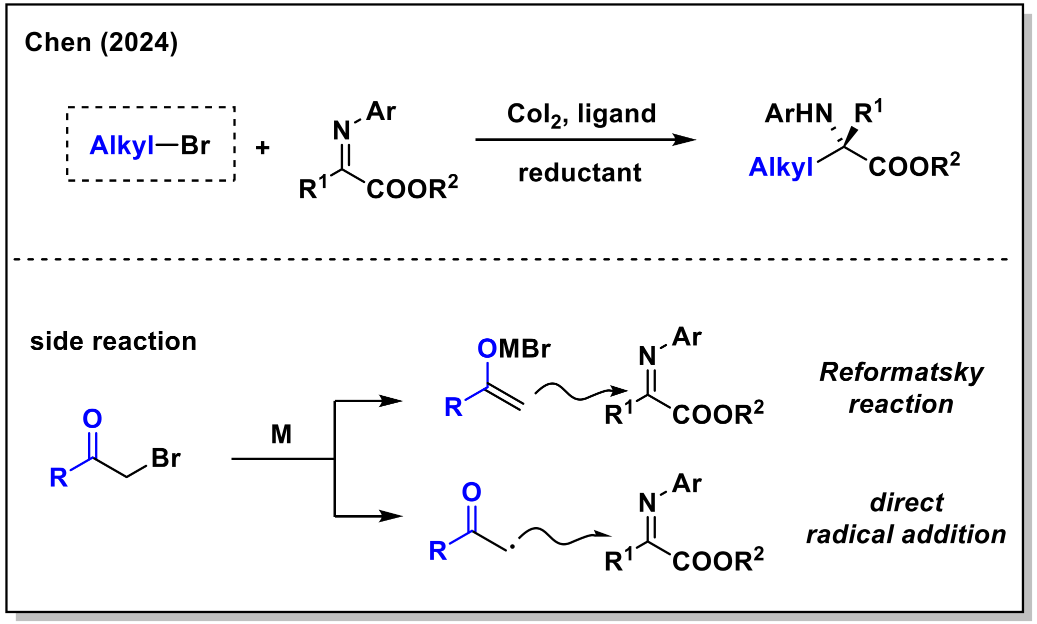
➢ **可能的机理**



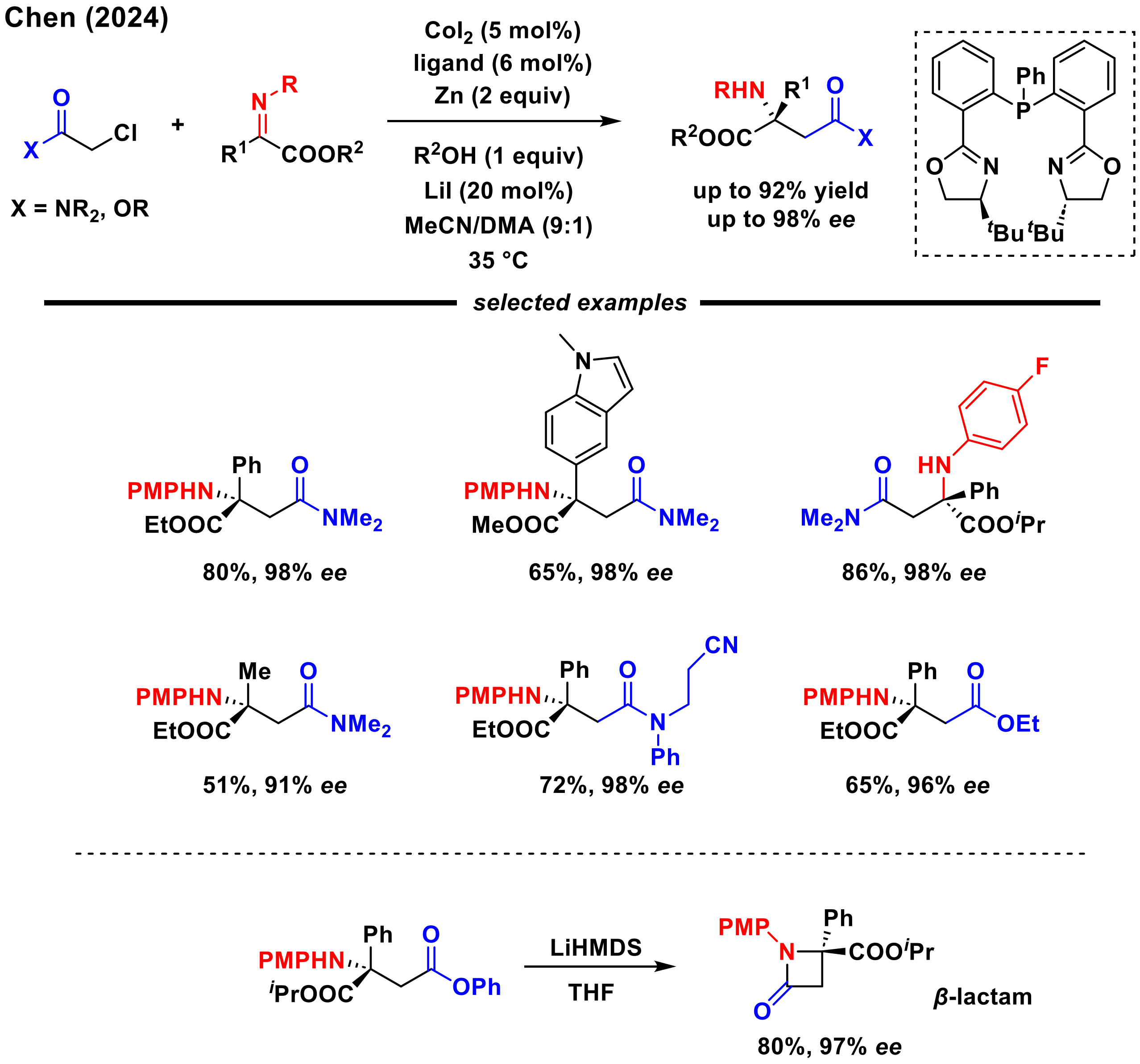
Hu, W.-H.; et al. *ACS Catal.* **2022**, *12* (19), 12302-12309

目　录

2.3 自由基Mannich反应



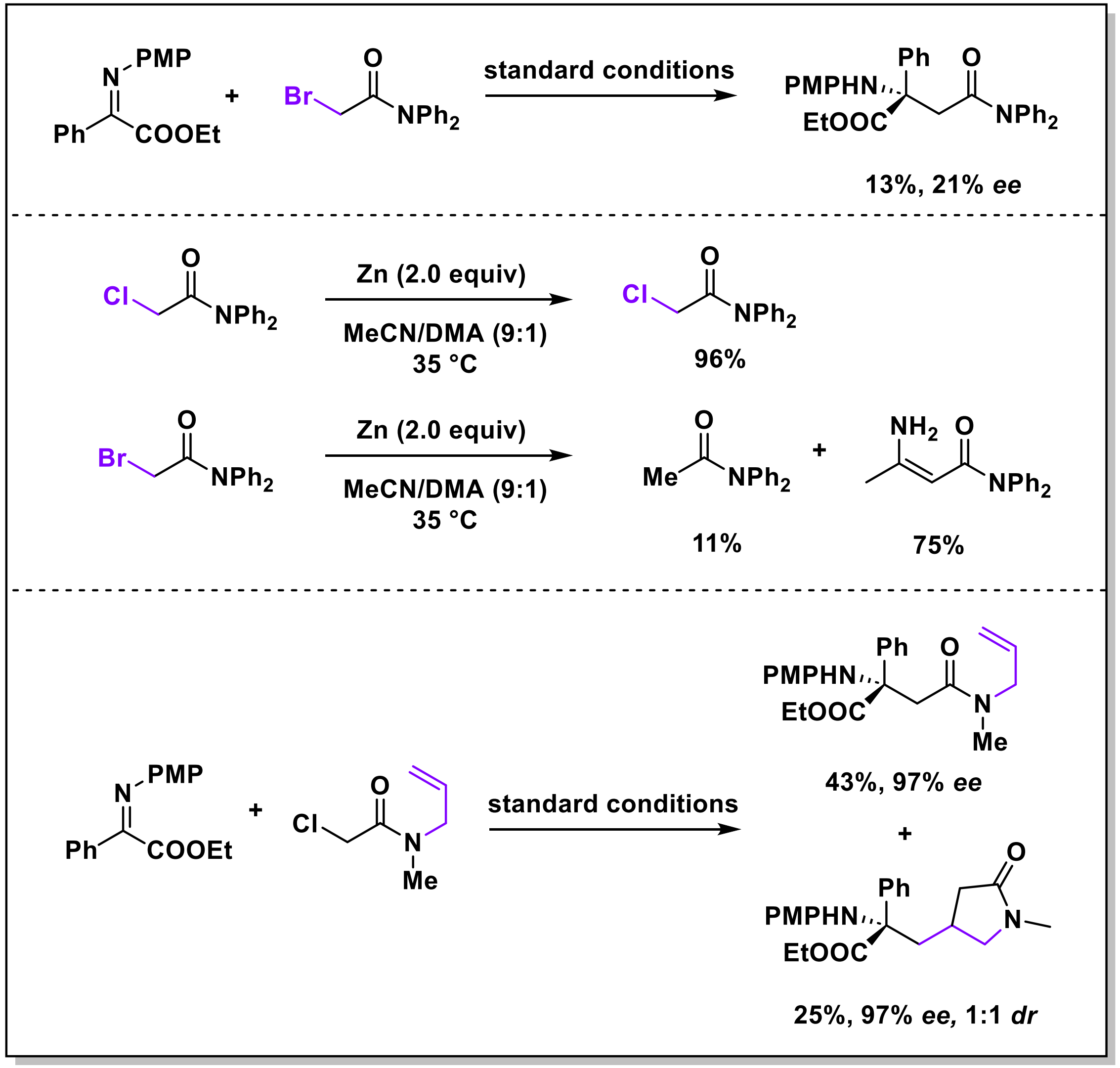
抑制副反应，提高对映选择性



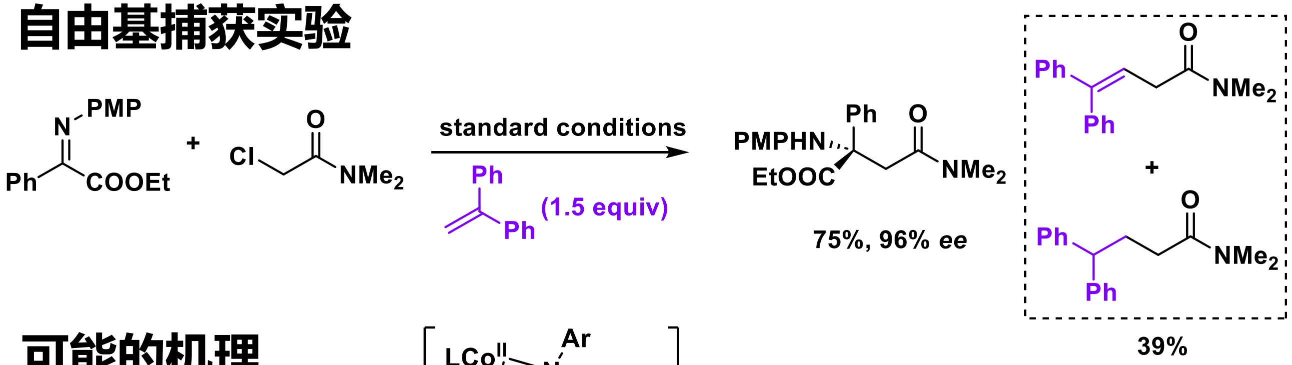
(1) Chen, Y; et al. *Nat. Chem.* **2024**, *63*, 398–407 (2) Chen, Y; et al. *Angew. Chem. Int. Ed.* **2024**, *63* (25), e202318991

2.3 自由基Mannich反应

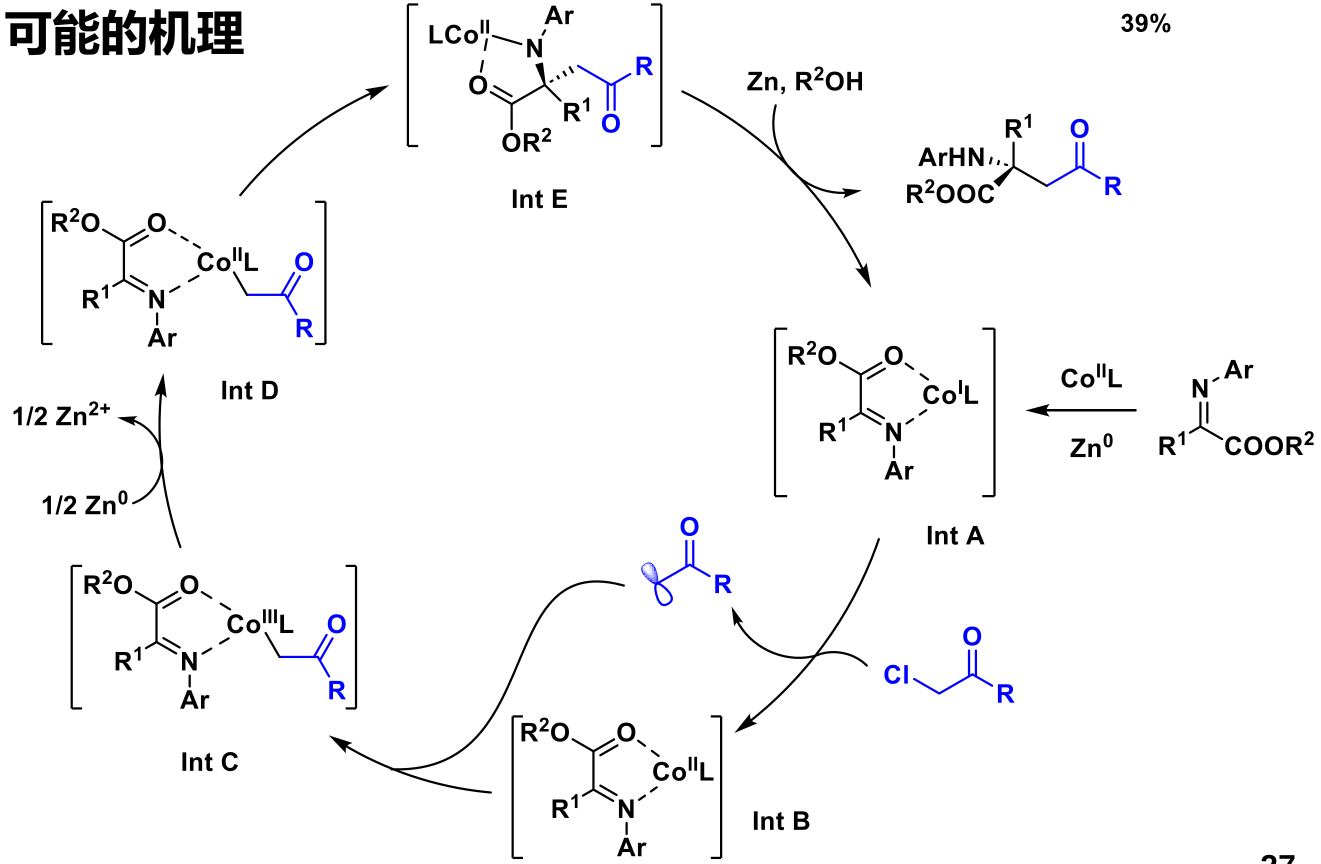
➢ 控制实验



➢ 自由基捕获实验



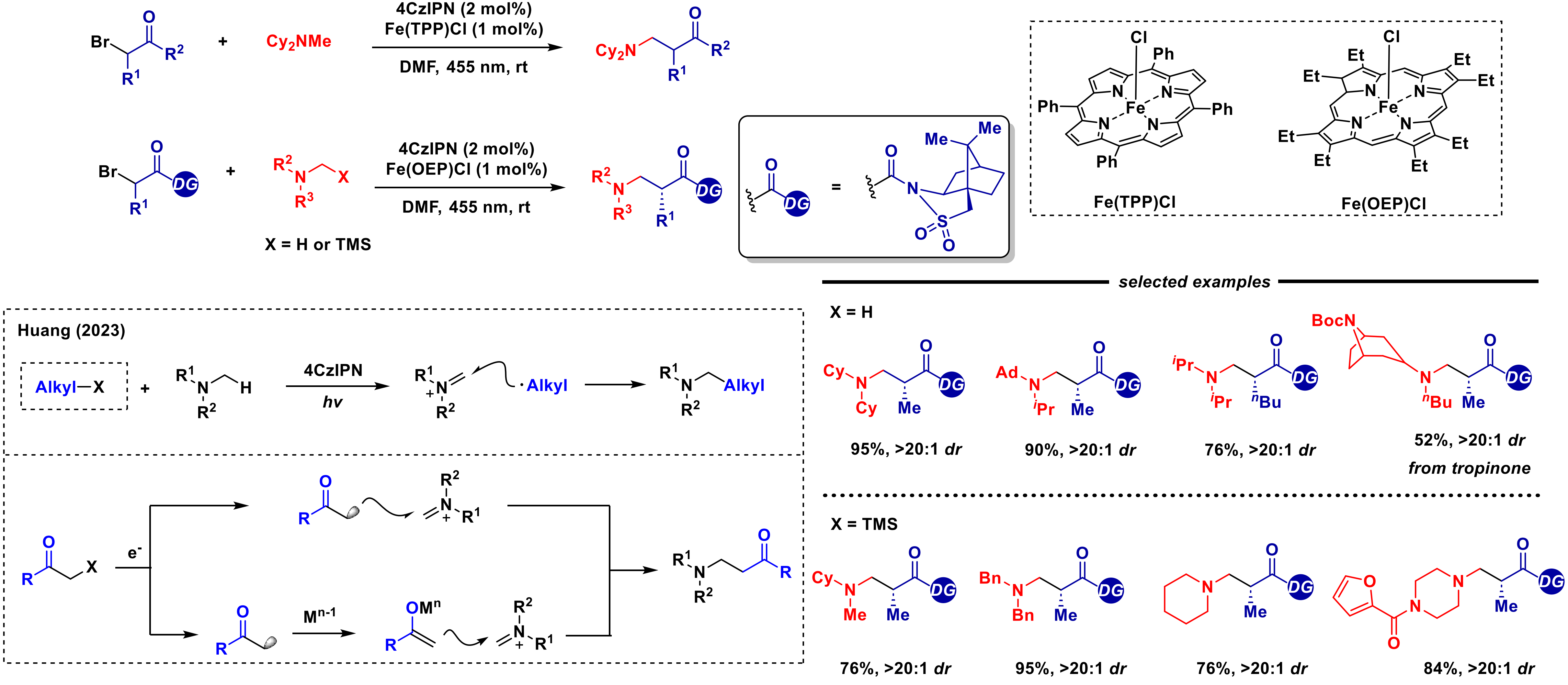
➢ 可能的机理



Chen, Y; et al. *Angew. Chem. Int. Ed.* **2024**, *63* (25), e202318991

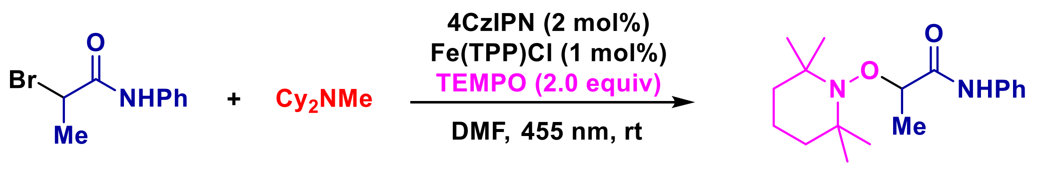
2.3 自由基Mannich反应

Huang group (2025)

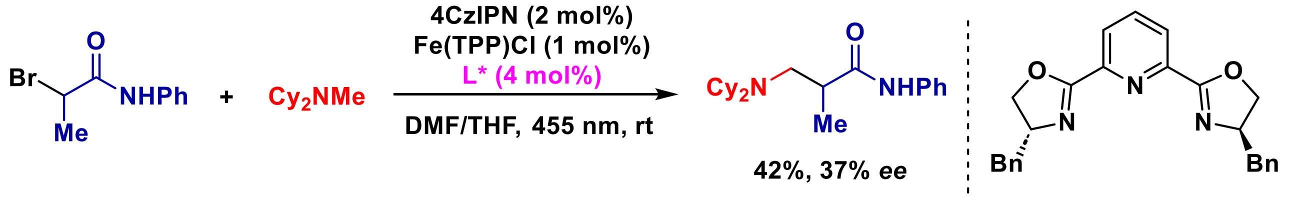


2.3 自由基Mannich反应

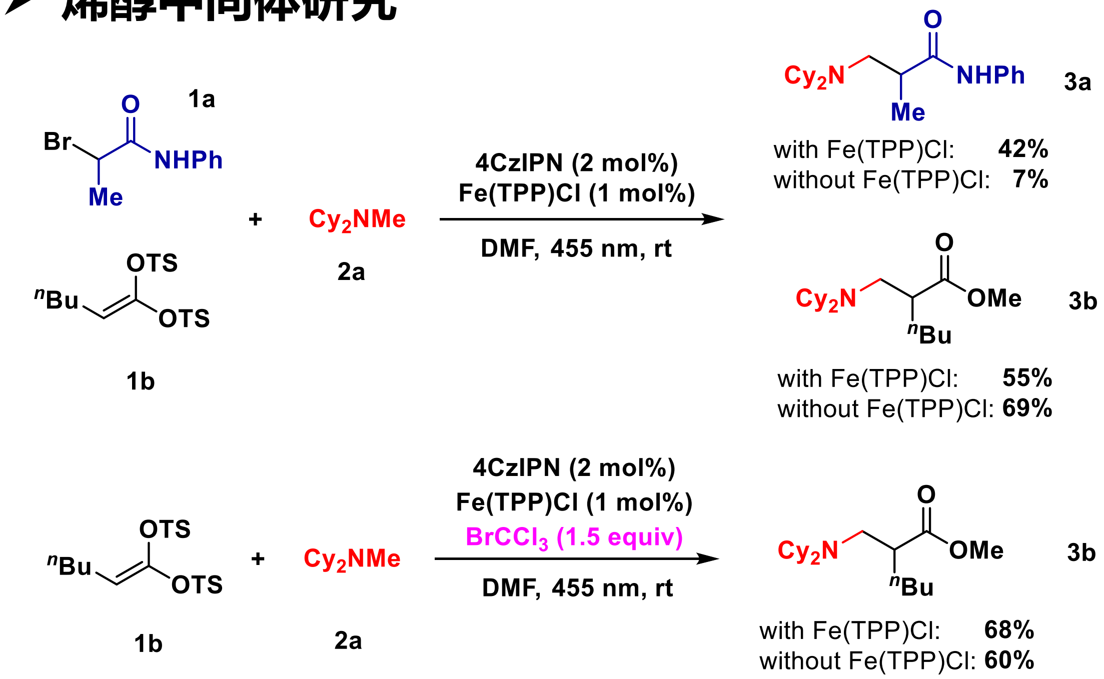
➢ 自由基捕获实验



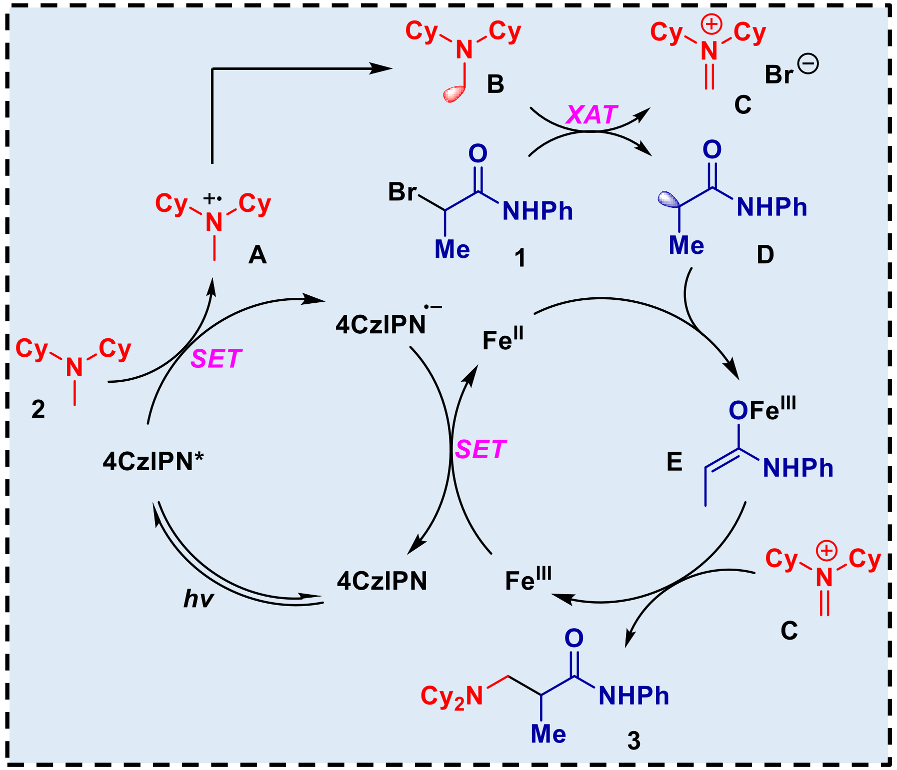
21%, TM not detected



➢ 烯醇中间体研究



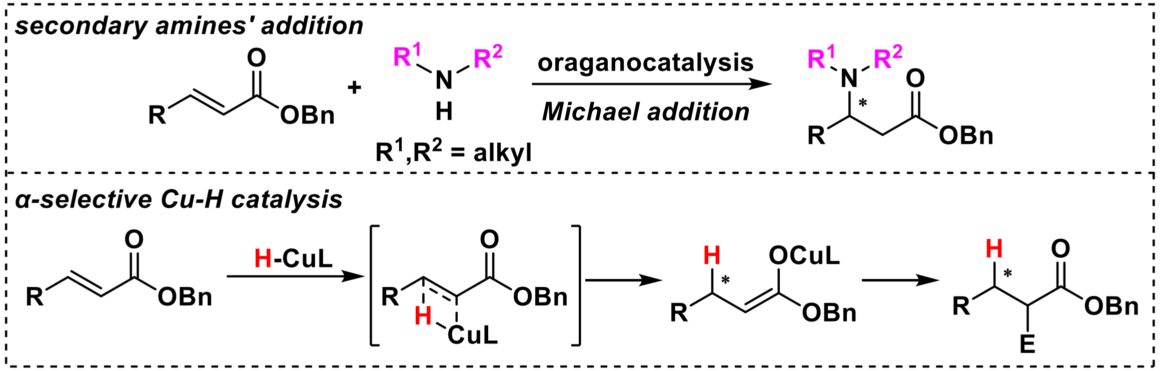
➢ 可能的机理



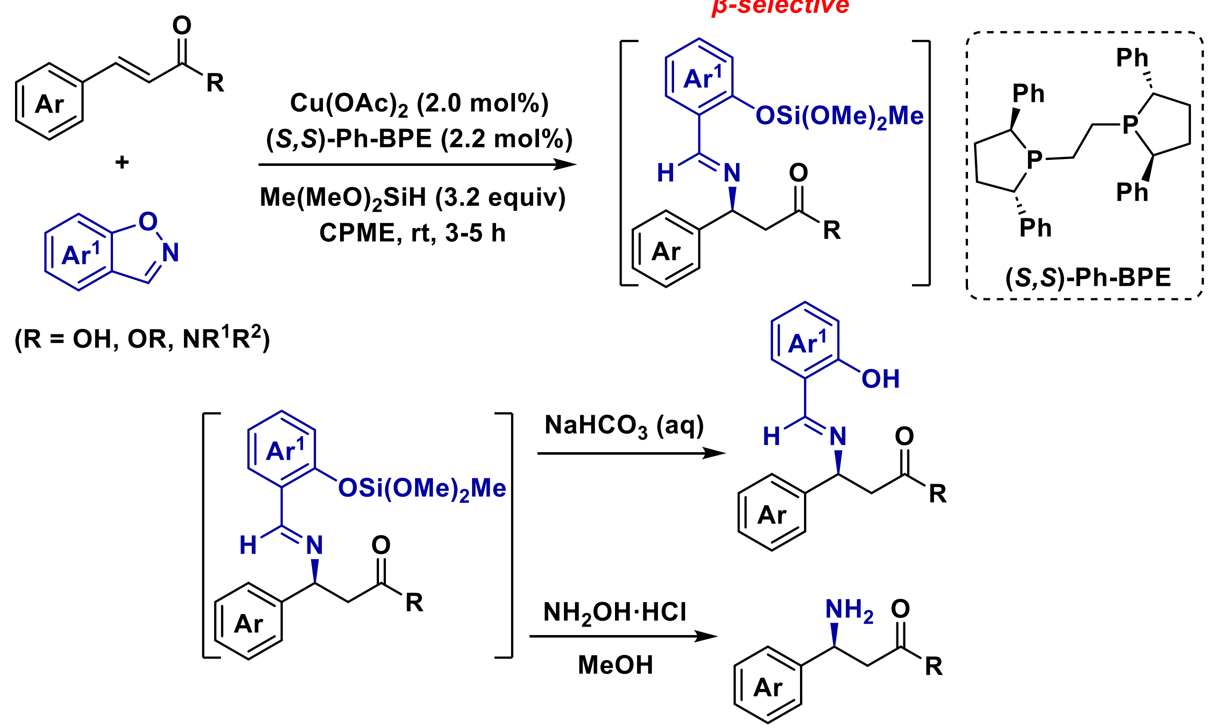
Huang, H.; et al. *J. Am. Chem. Soc.* **2025**, *147* (41), 37565-37575

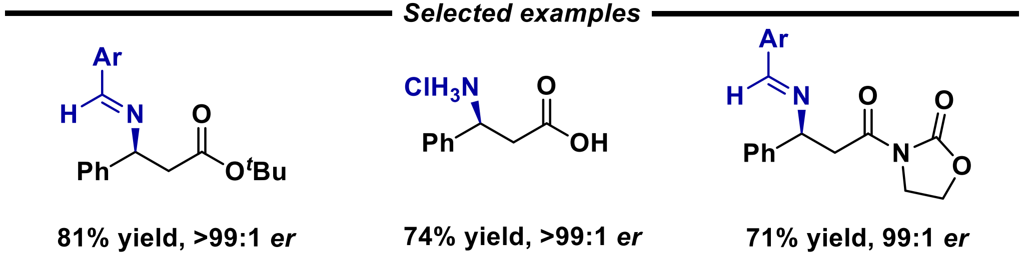
目　录

3 烯烃的不对称氢胺化

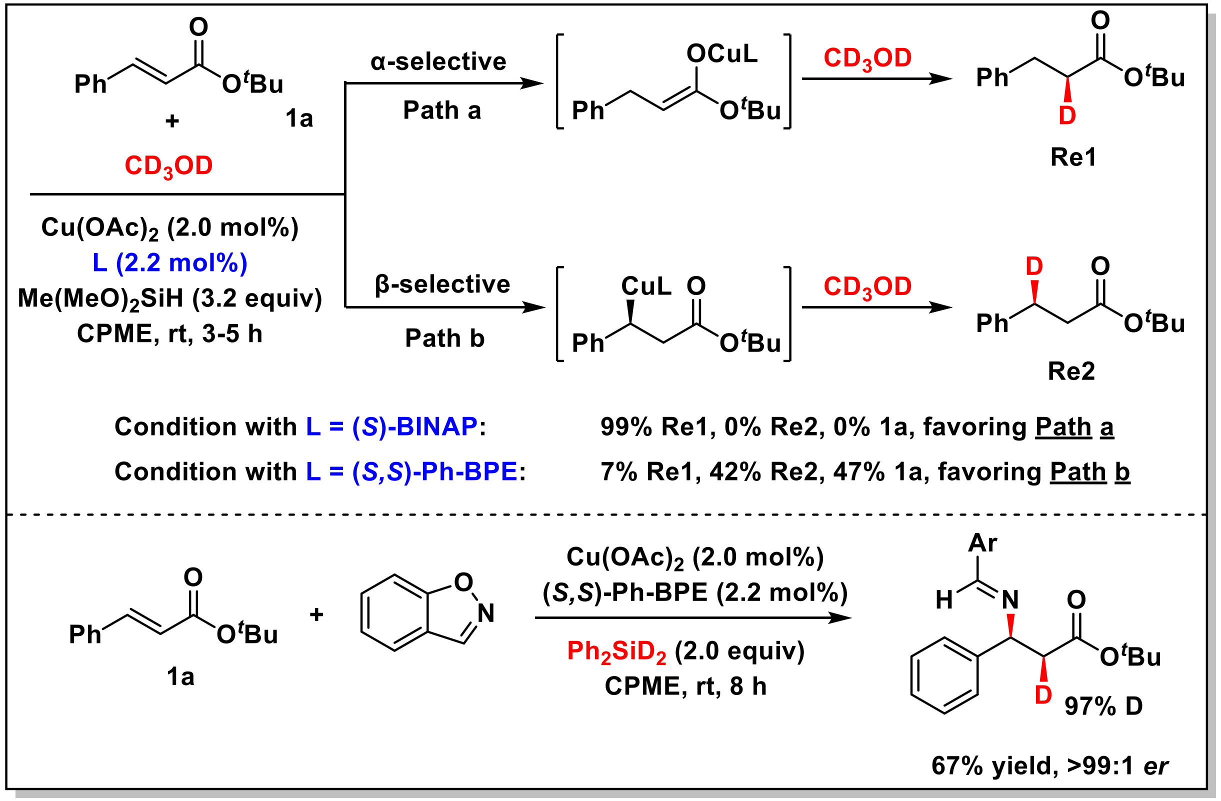


Buchwald (2020)





➢ 机理研究

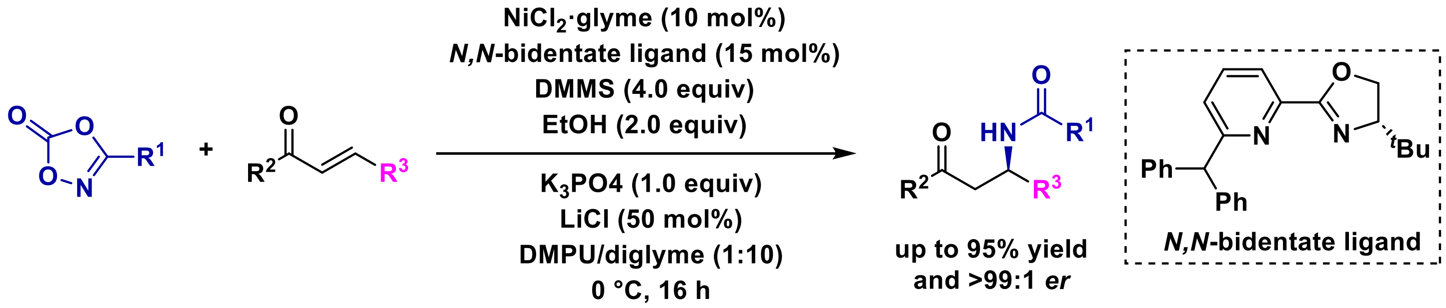


Buchwald, S.L.; et al. *Angew. Chem. Int. Ed.* **2020**, *132* (47), 21027-21031

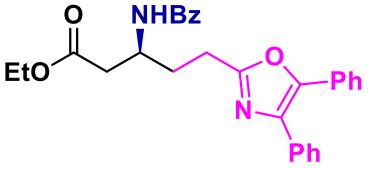
3 烯烃的不对称氢胺化

Chang group (2024)

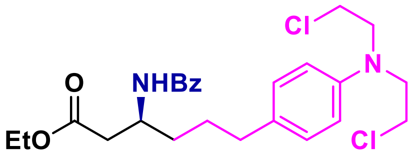
底物拓展：
β-烷基-α,β-不饱和酯



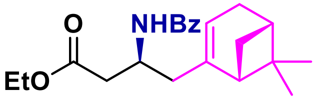
Biorevelant derivatives



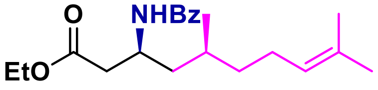
79%, 91:9 *er*
from Oxaprozin



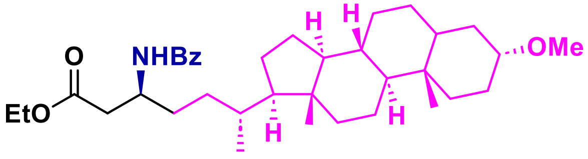
82%, 99:1 *er*
from Chiorambucil



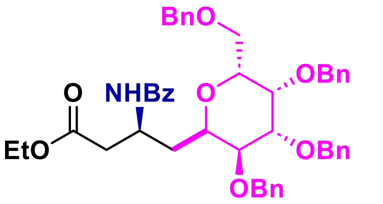
61%, >20:1 *dr*
from (-)-Nopol



58%, >20:1 *dr*
from (-)-Citronellal

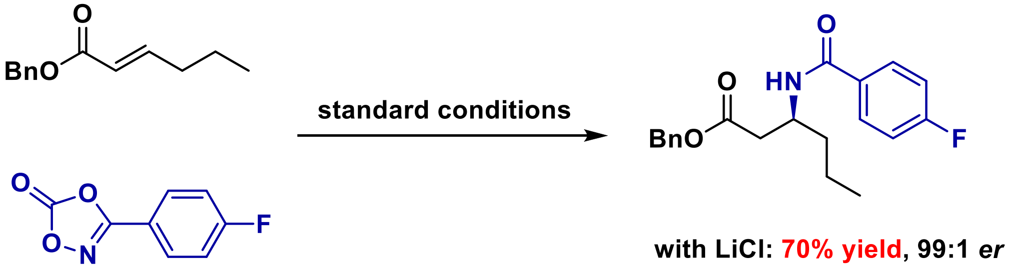


68%, 99:1 *dr*
from Lithocholic acid



43%, >20:1 *dr*
from α-d-Galactopyranoside

Addition of LiCl influenced hydroamidation

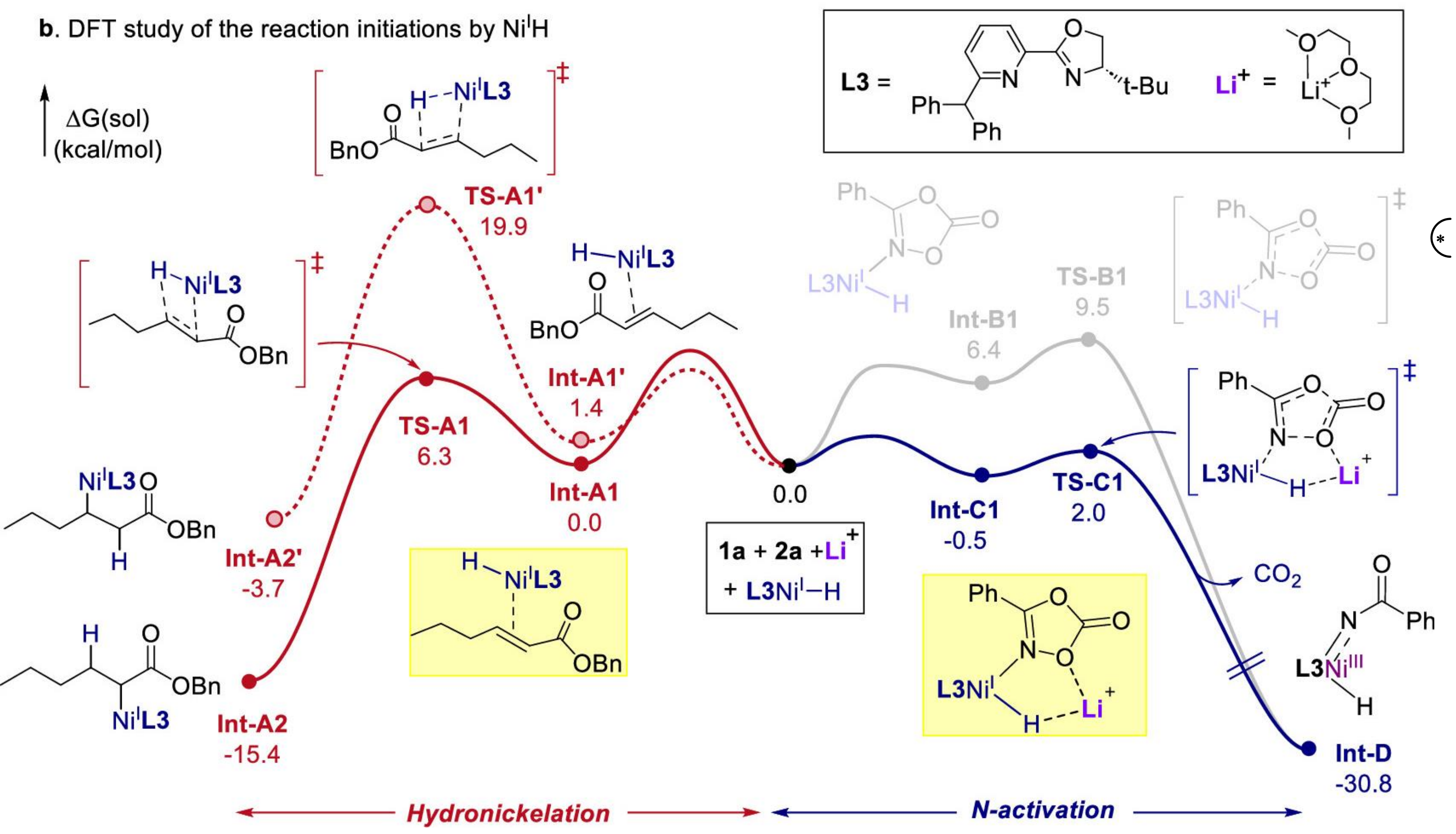


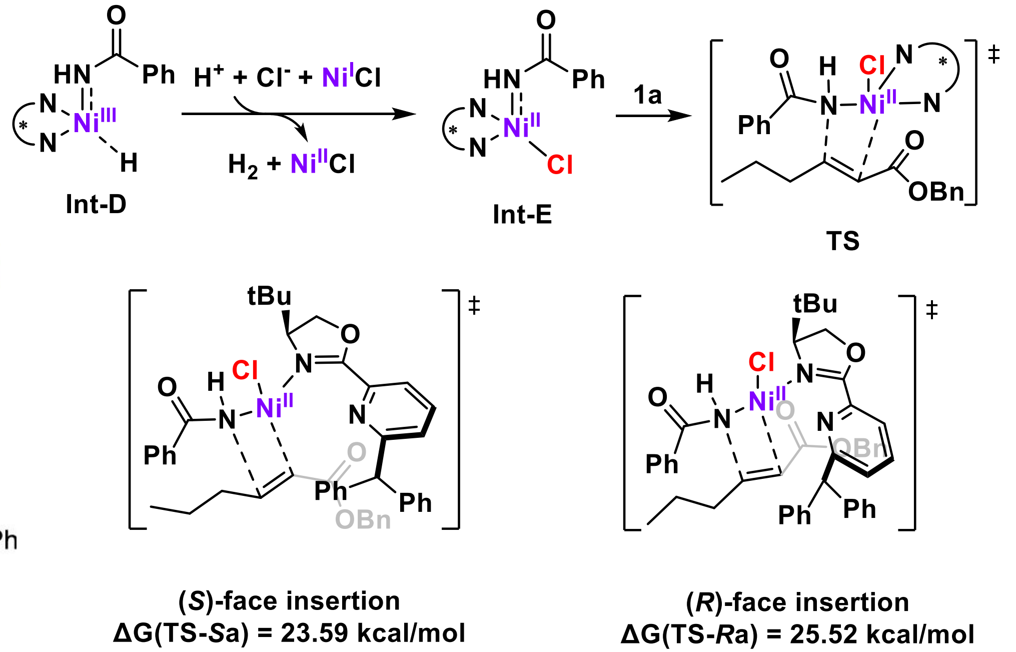
with LiCl: 70% yield, 99:1 *er*
w/o LiCl: 11% yield, 99:1 *er*

Chang, S.; et al. *J. Am. Chem. Soc.* **2024**, *146* (21), 14745-14753

3 烯烃的不对称氢胺化

➢ DFT计算

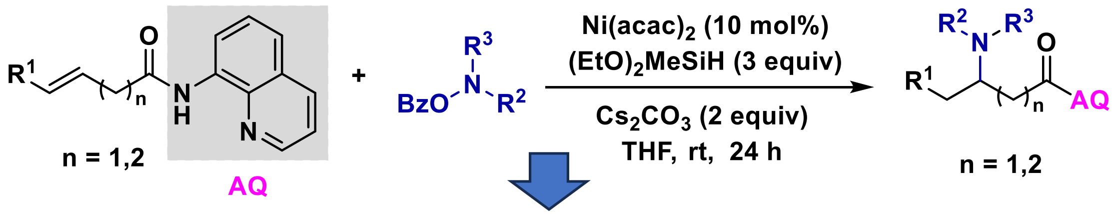




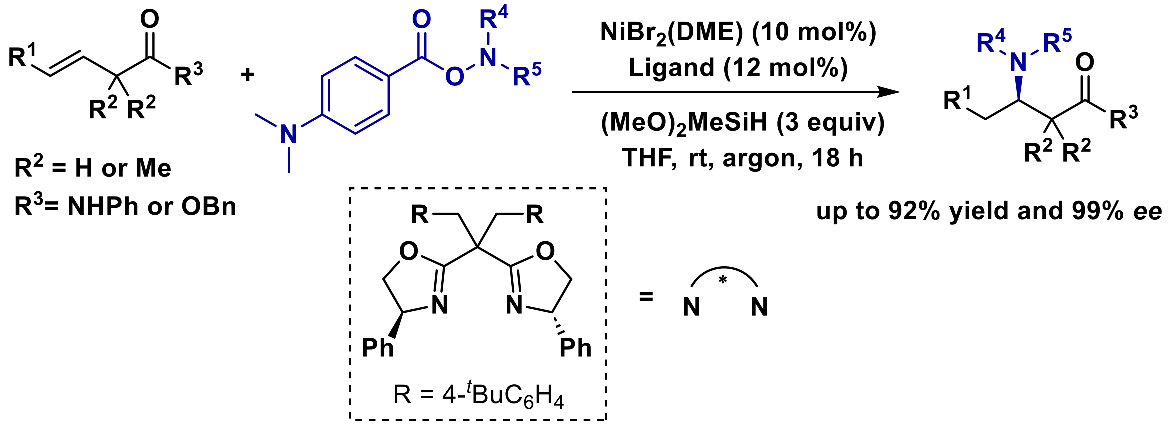
Chang, S.; et al. *J. Am. Chem. Soc.* **2024**, *146* (21), 14745-14753

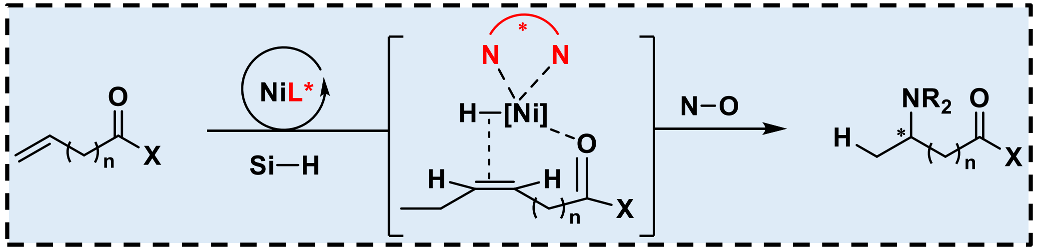
3 烯烃的不对称氢胺化

Hong (2020)

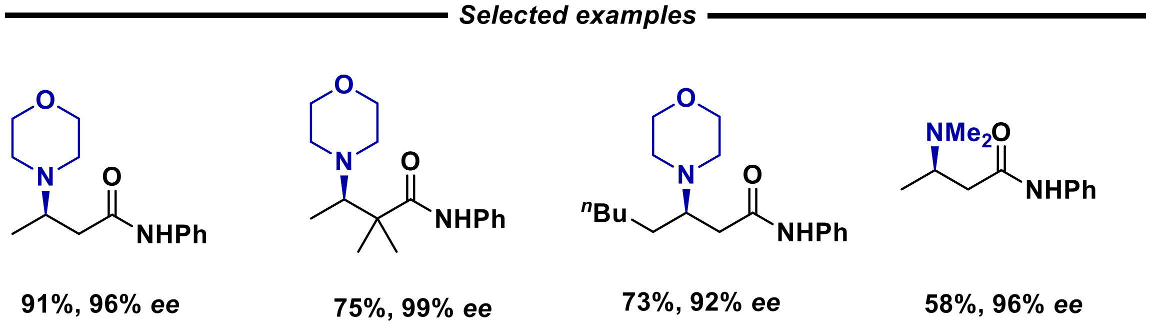


Hong (2022)

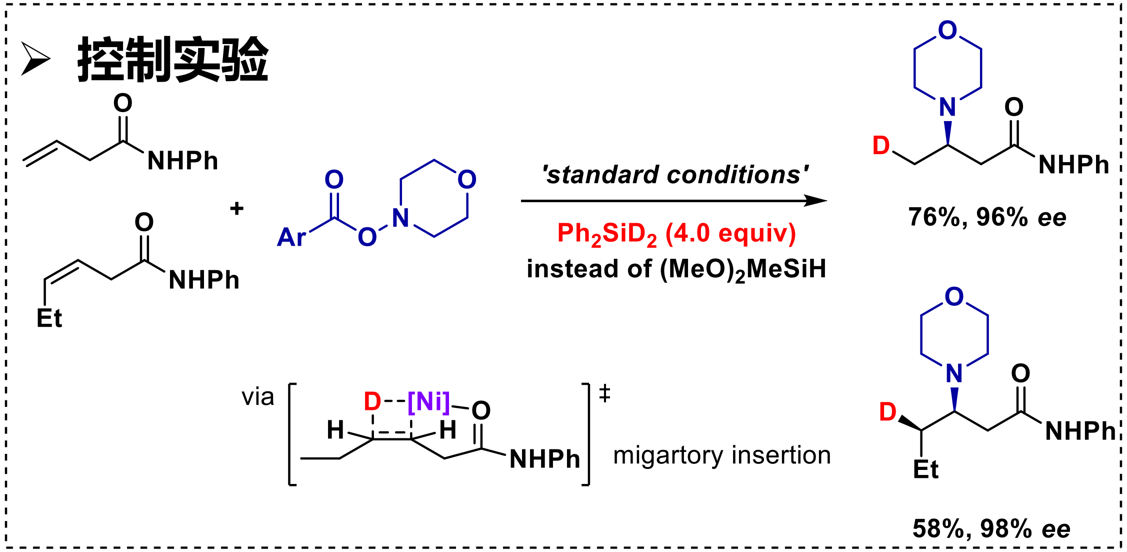




• 非活化烯烃 • 无导向基 • 手性控制



➢ 控制实验

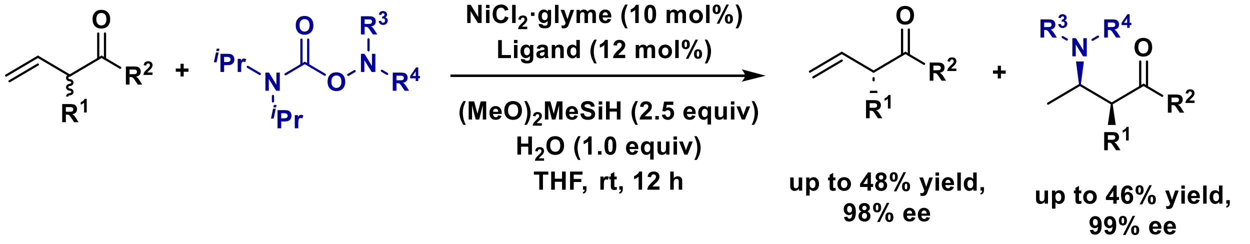


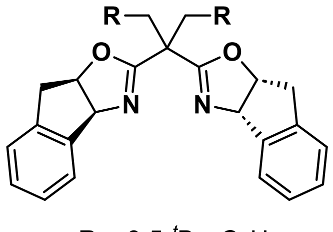
(1) Hong, S.; et al. *J. Am. Chem. Soc.* **2020**, *142* (48), 20470-20480 (2) Hong, S.; et al. *J. Am. Chem. Soc.* **2022**, *144* (20), 9091-9100

3 烯烃的不对称氢胺化

Hong group (2023)

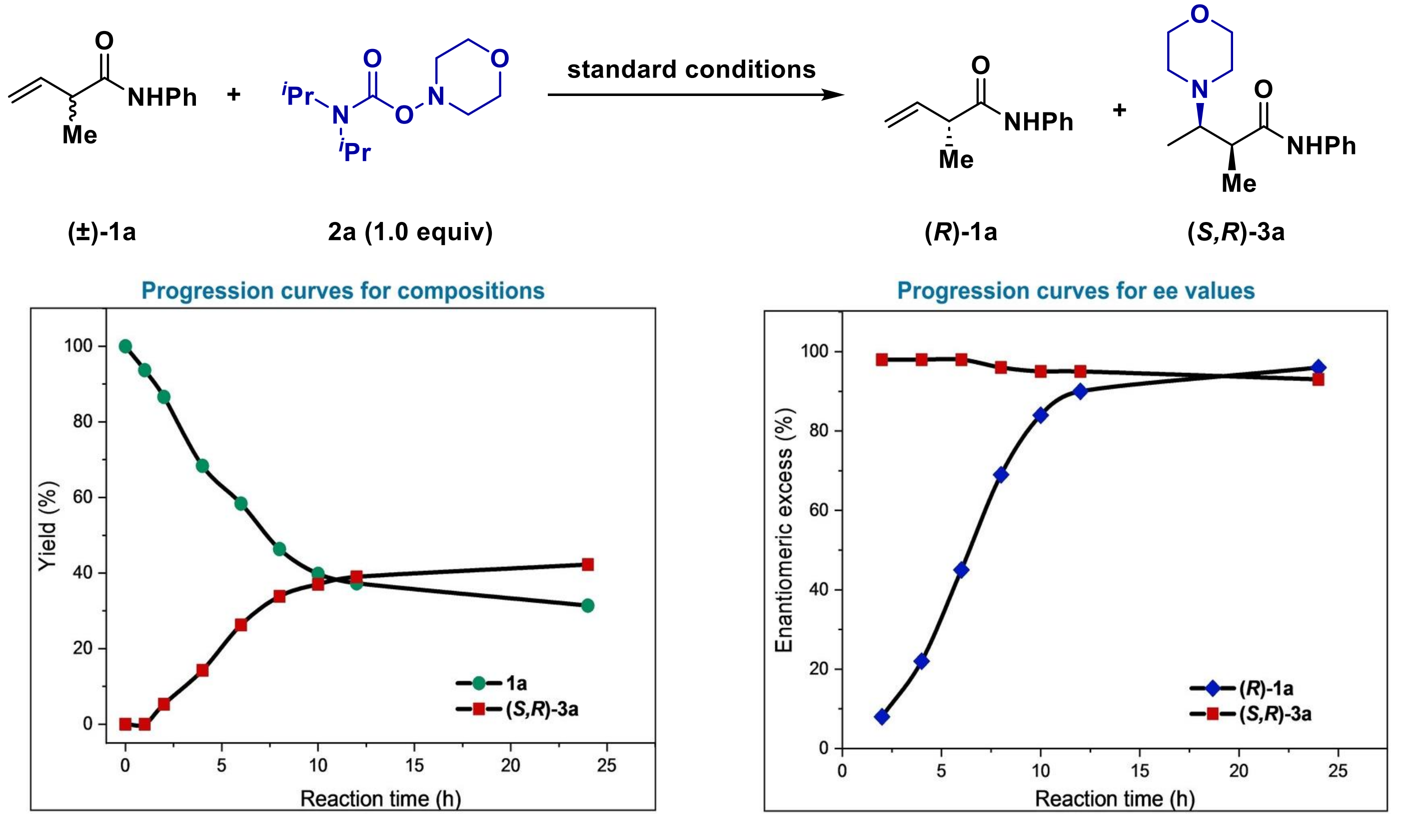
不对称拆分





R = 3,5-$^{t}Bu_2C_6H_3$

➢ **拆分过程追踪**

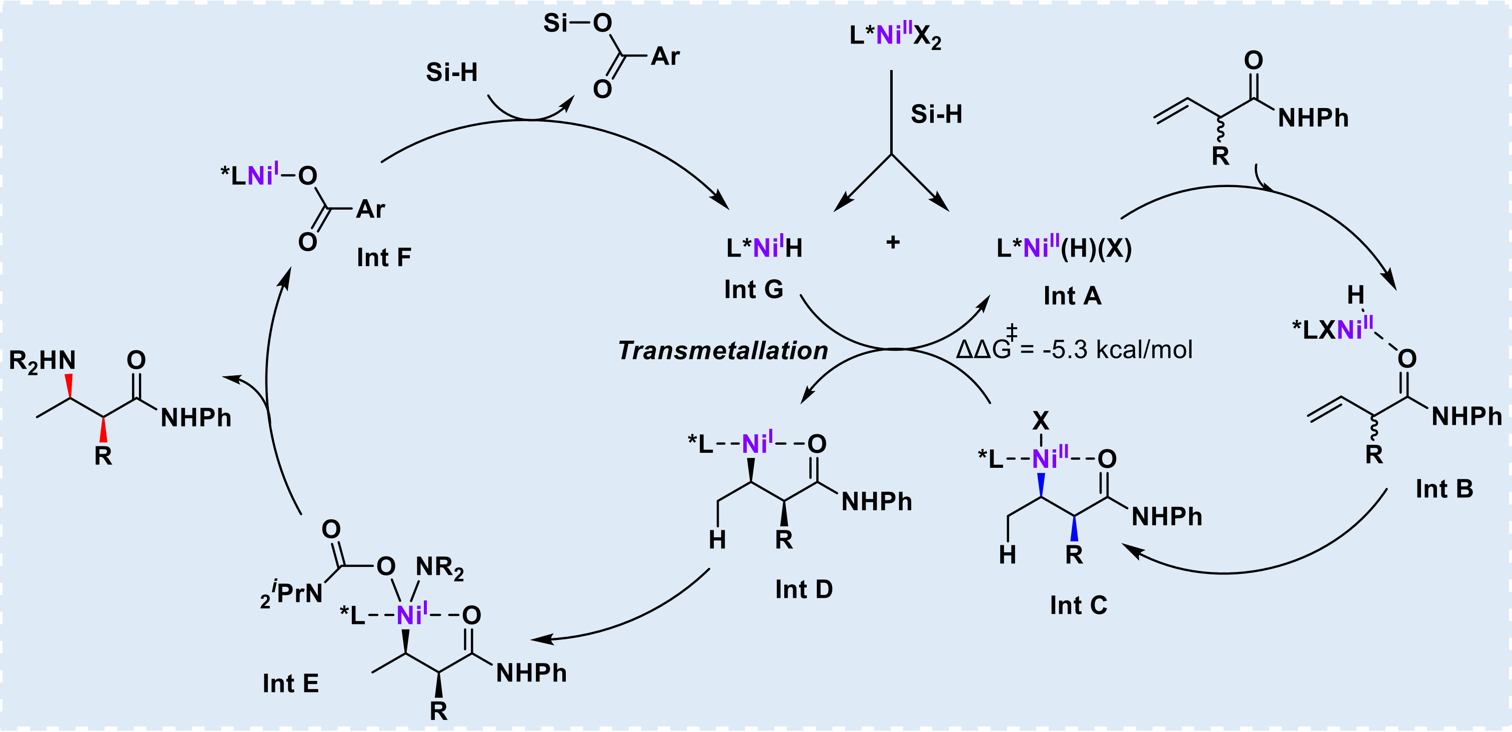


The composition of **1a** and **(*S*,*R*)-3a** and ee values of **(*R*)-1a** and **(*S*,*R*)-3a** were analyzed by HPLC.

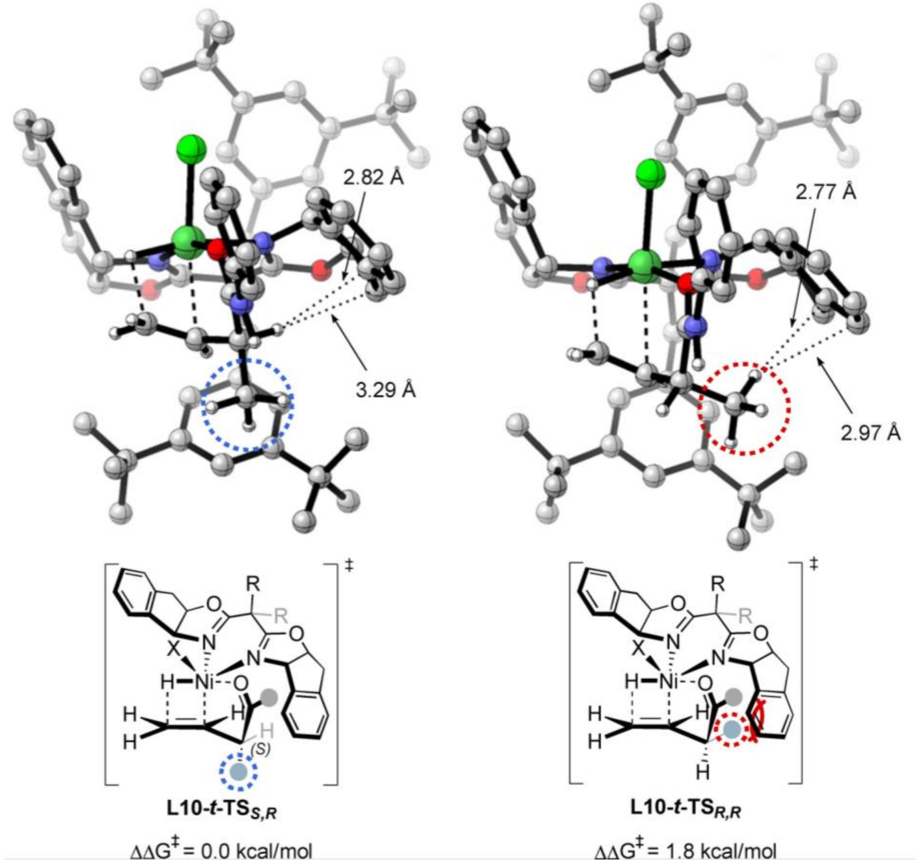
Hong, S.; et al. *Angew. Chem. Int. Ed.* **2023**, *62* (24), e202305042

3 烯烃的不对称氢胺化

➢ 可能的机理



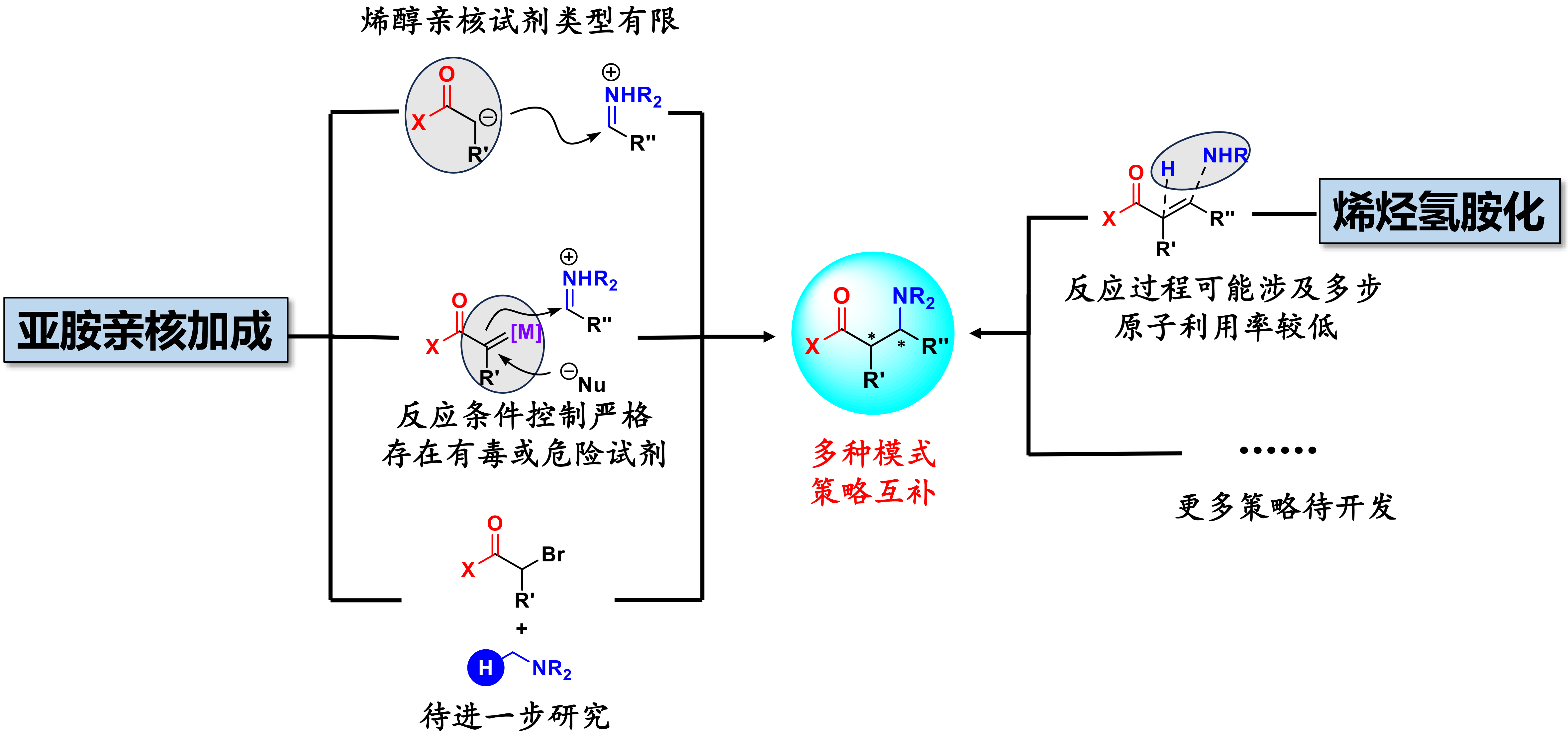
➢ 过渡态DFT计算



Hong, S.; et al. *Angew. Chem. Int. Ed.* **2023**, *62* (24), e202305042

目 录

3 总结与展望

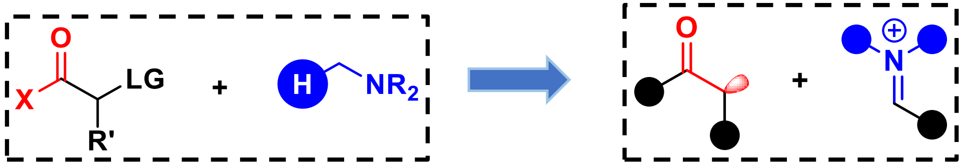


烯醇亲核试剂类型有限
NHR2
R''
R'
X
O
[M]
Nu
反应条件控制严格
存在有毒或危险试剂
Br
H
NR2
待进一步研究
亚胺亲核加成
多种模式
策略互补
NHR
烯烃氢胺化
反应过程可能涉及多步
原子利用率较低
……
更多策略待开发

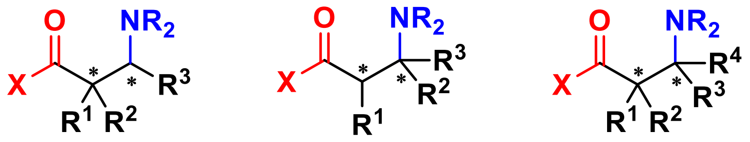
3 总结与展望

反应模式拓展

自由基过程



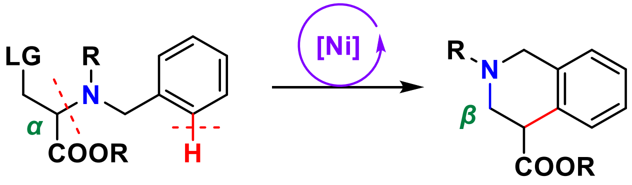
• 光催化 • 电催化



季碳手性中心尝试

实现不对称催化

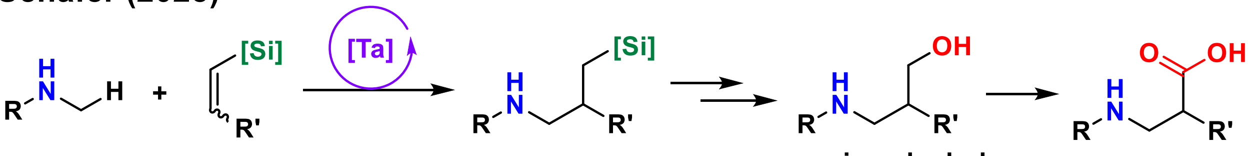
Tang (2023)



β-amino acid ester

••••••

Schafer (2025)



γ-amino alcohol

(1)Tang, S.; et al. *ACS Catal.* **2024**, *14* (8), 5491-5502 (2) Schafer, L. L.; et al. *J. Am. Chem. Soc.* **2025**, *147* (16), 13415-13423

谢谢大家

请各位老师同学批评指正