手性羰基催化剂在导向胺基活化的不对称转化中的应用

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导　师：朱　灿　青年研究员

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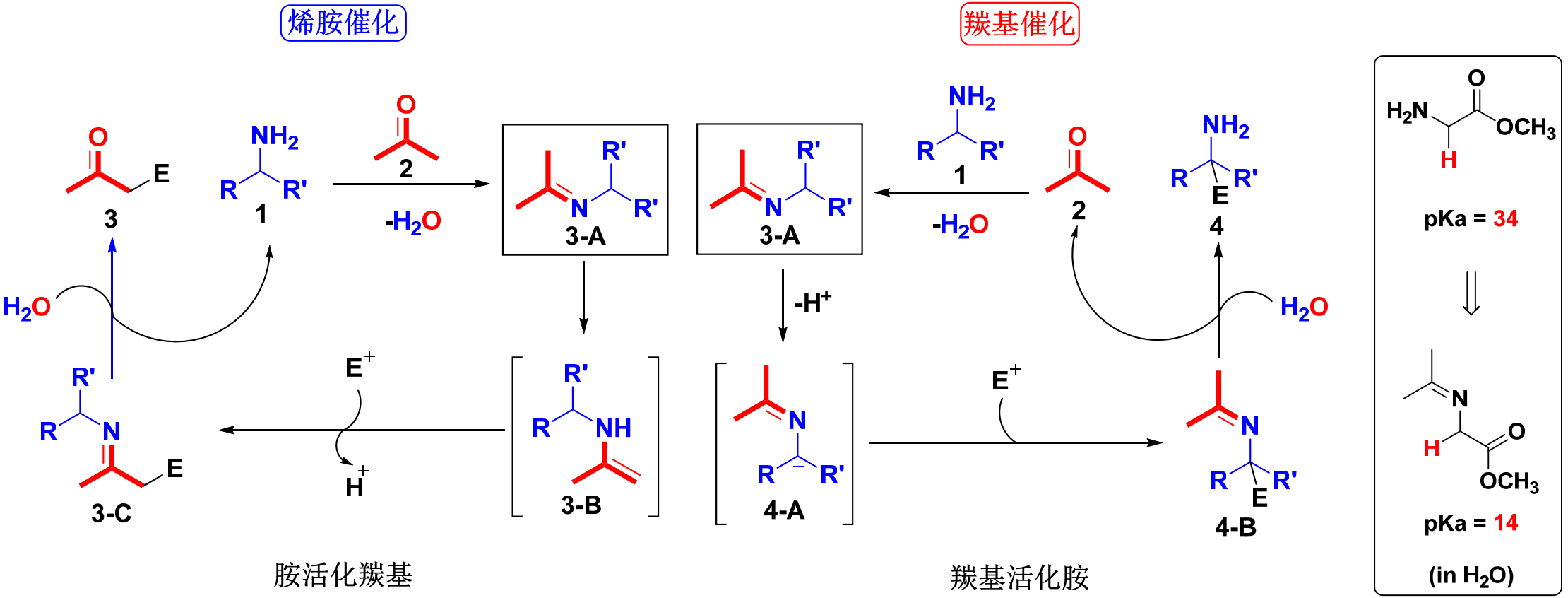
Benjamin List
David W.C. MacMillan

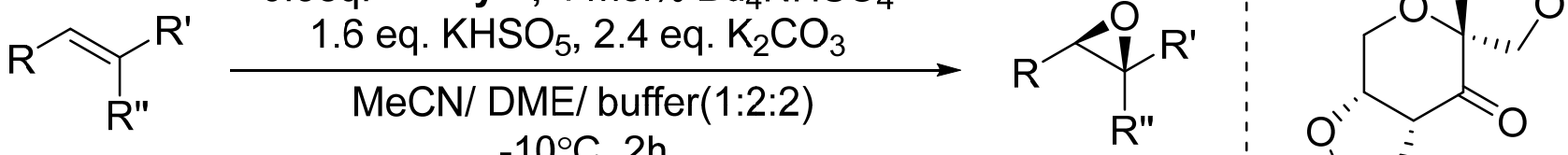
- Organocatalysis
  - Acid Catalysis
  - Base Catalysis
    - Amine Catalyst
      - Enamine（HOMO）/Iminium（LUMO）Catalysis
      - SOMO catalysis， etc
    - Phosphine Catalyst
    - Sulfur Catalyst
    - Carbene Catalyst, etc
  - Other Catalysis

1. 研究背景



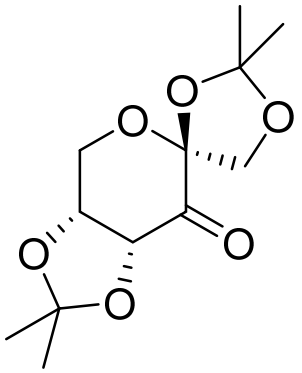
Juan Frau. J. et al. *Phys. Chem. B.* **2012**, *116*, 10665−10675

1. 研究背景

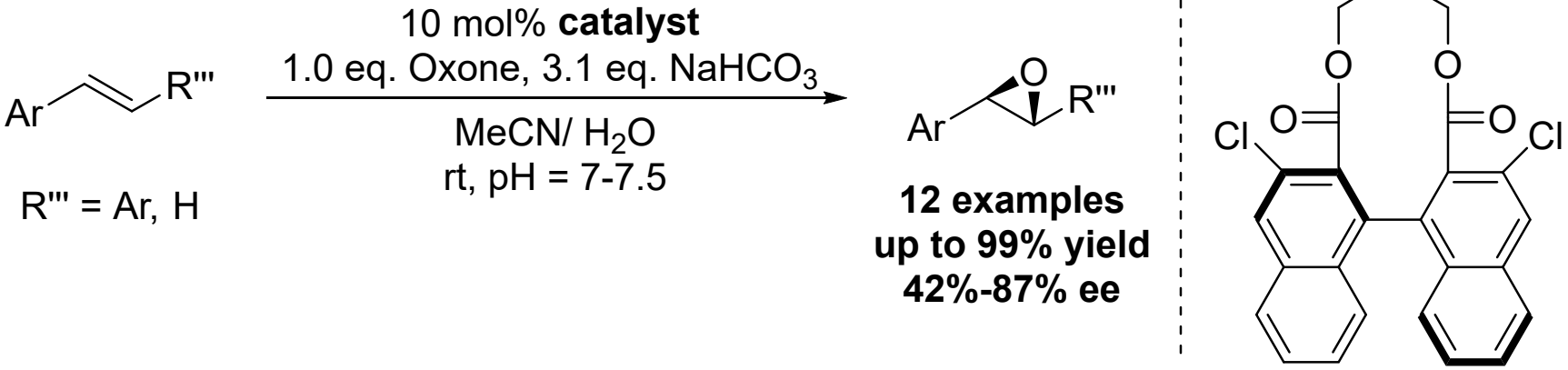


R,R' = Ar, alkyl
R" = H, alkyl, Ar

15 examples,
41-84% yield,
84-95% ee

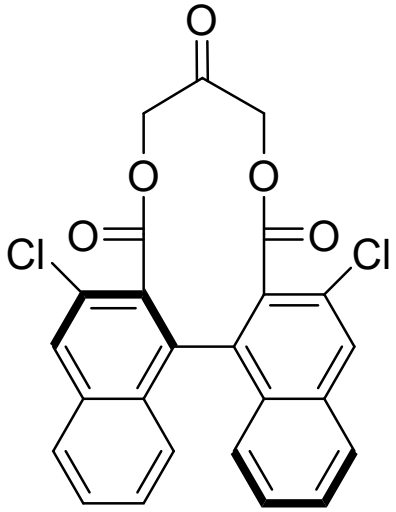


Y. Shi. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9806



R''' = Ar, H

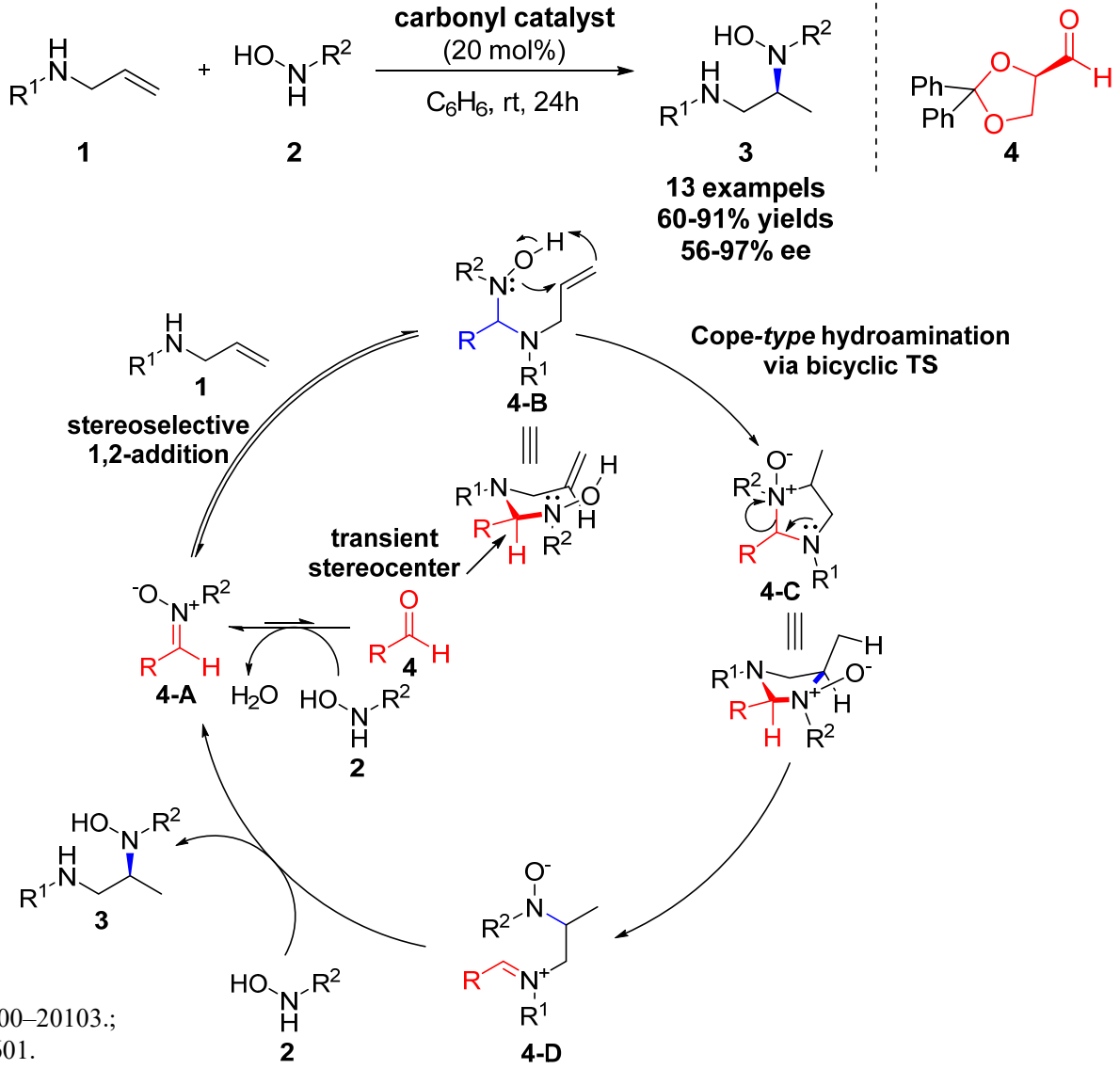
12 examples
up to 99% yield
42%-87% ee



D.Yang. et al. *J. Am. Chem. Soc.* **1998**, *120*, 24, 5943–5952

1. 研究背景

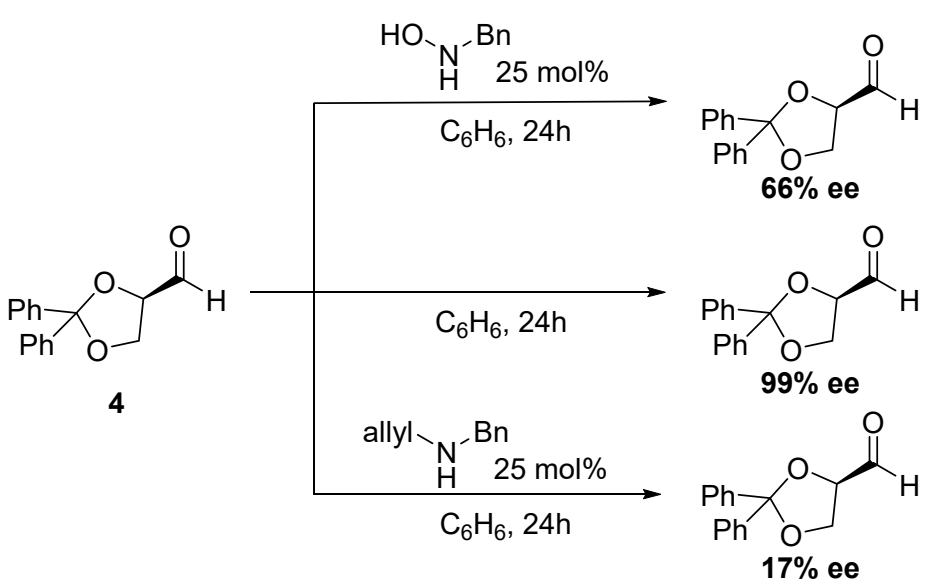
Cope-type hydroamination recation:

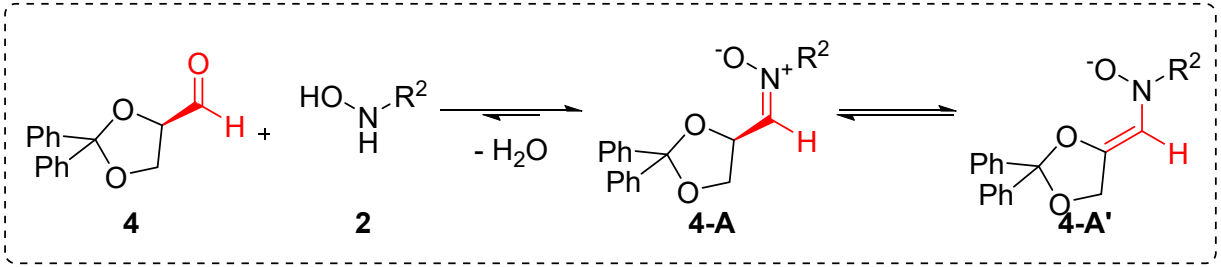


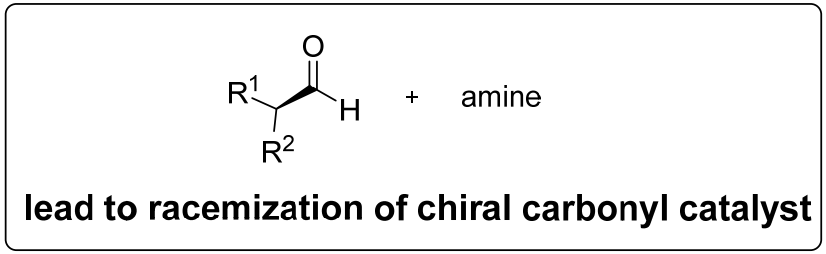
a) André M. Beauchemin. et al. *J. Am. Chem. Soc.* **2011**, *133*, 20100–20103.;
b) André M. Beauchemin. et al. *Chem. Eur. J.* **2013**, *19*, 2597 – 2601.

1. 研究背景

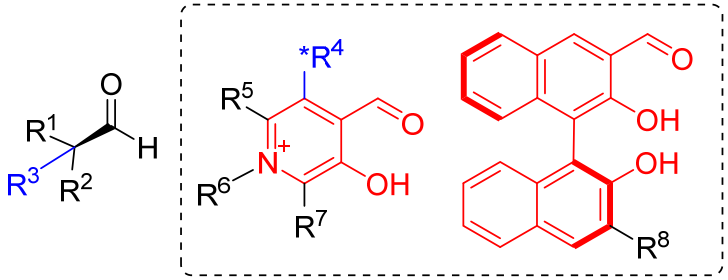
Probing the source of epimerization for catalyst:



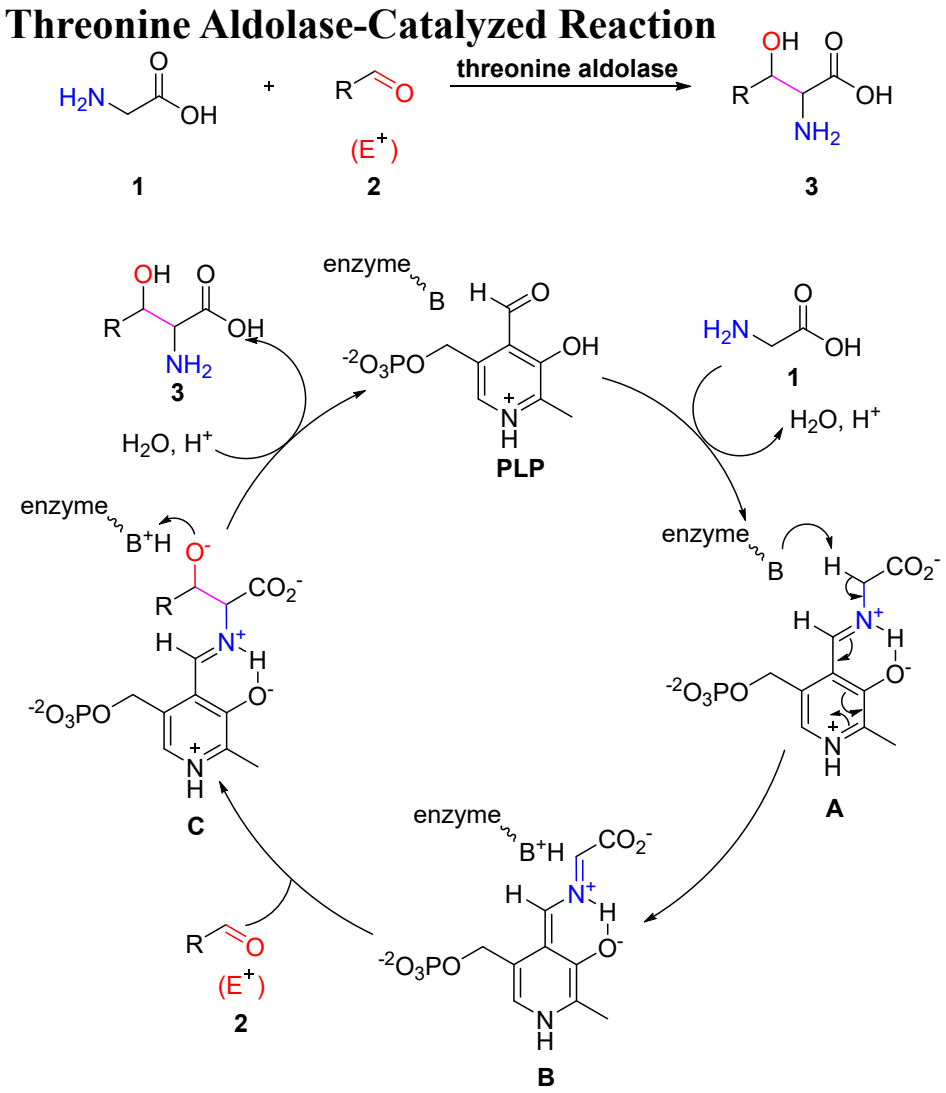




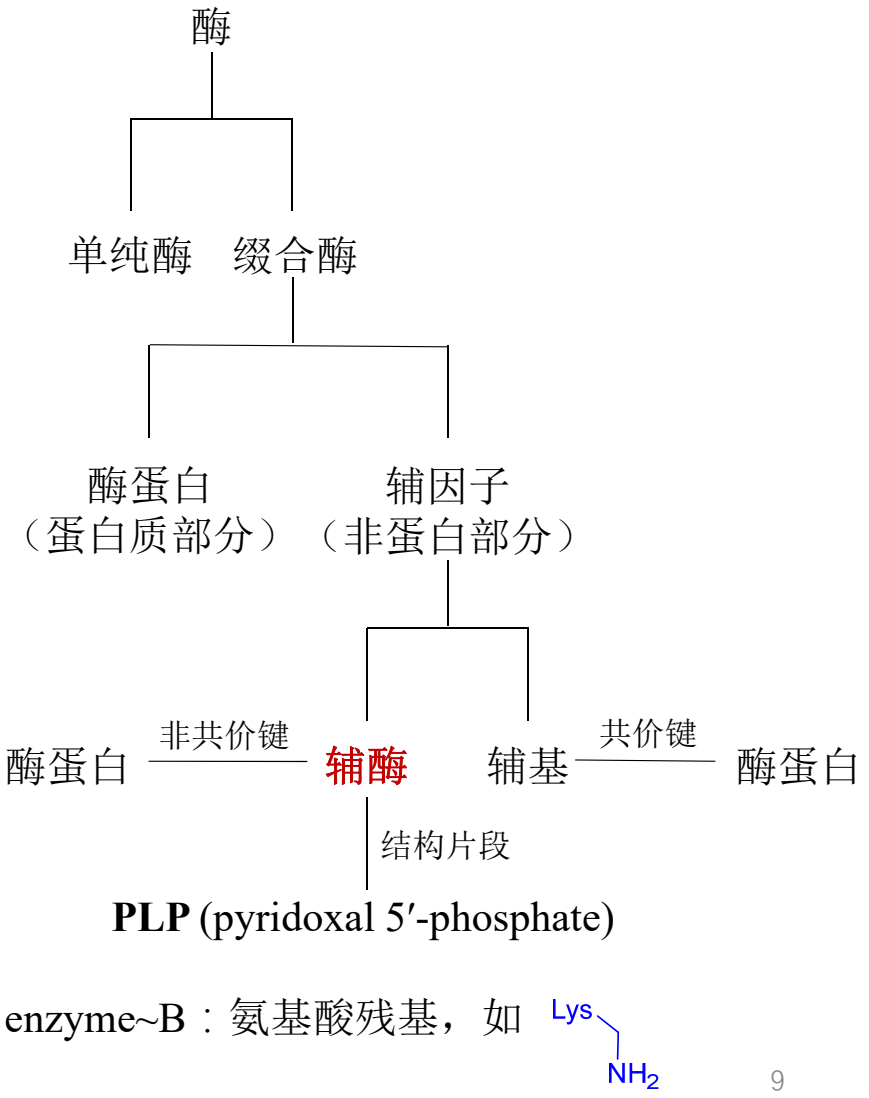
design new chiral carbonyl catalyst



1. 研究背景

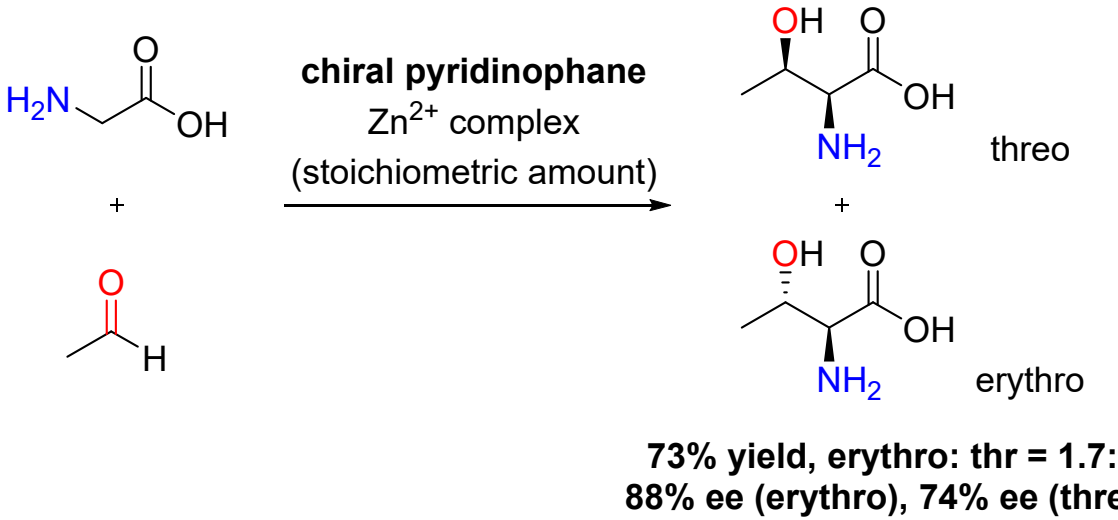


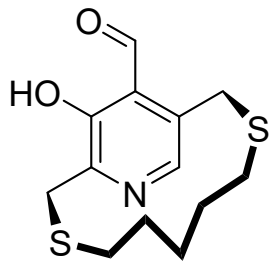
a) C.-H. Wong. et al. *J. Am. Chem. Soc.* **1997**, *119*, 11734 – 11742;
b) R. Contestabile. et al. *FEBS J.* **2014**, *281*, 129 – 145.

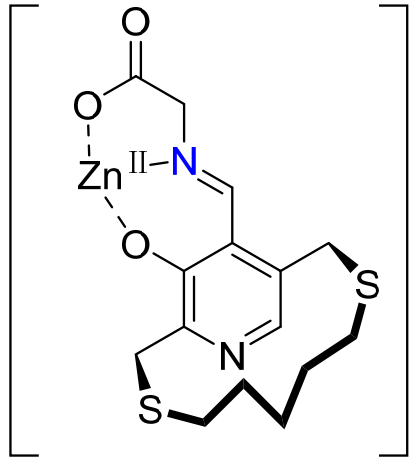


目录

2.手性羰基催化剂在胺的不对称α-C官能团化反应中的应用-不对称Aldol 反应

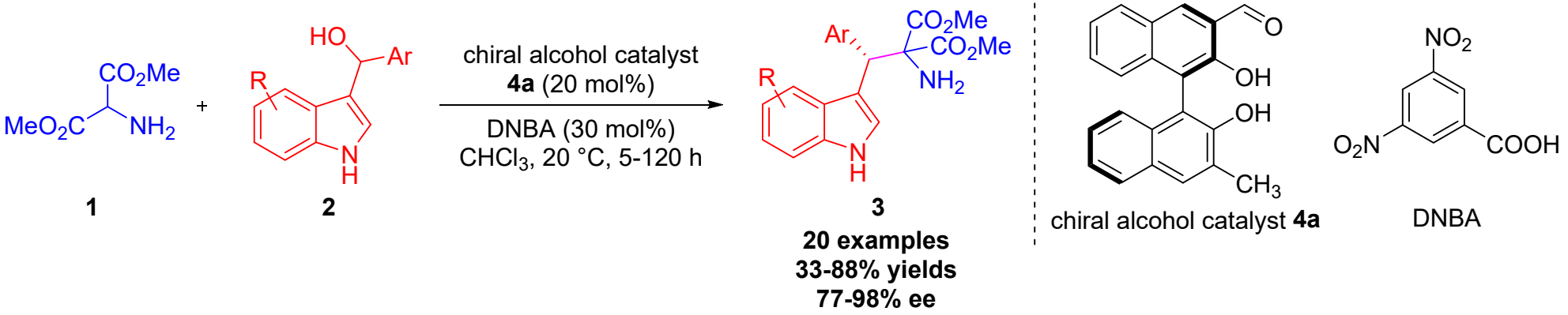


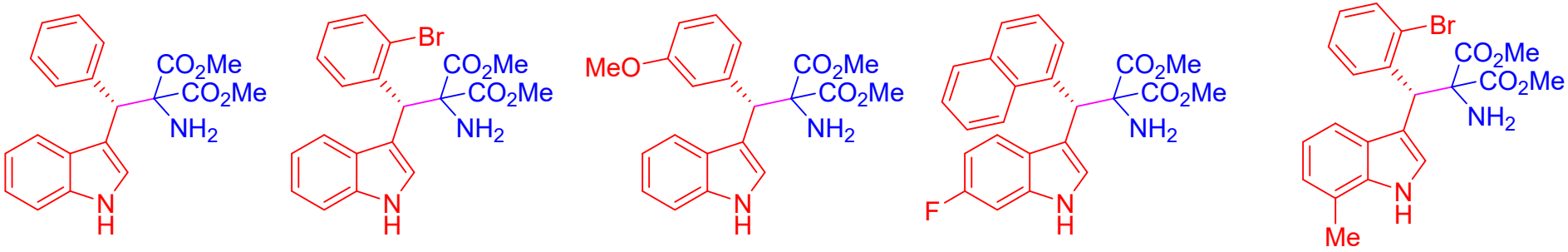




H. Kuzuhara. et al. *J. Chem. Soc. Chem. Commun.* **1987**, 95 – 96.

不对称烷基化反应



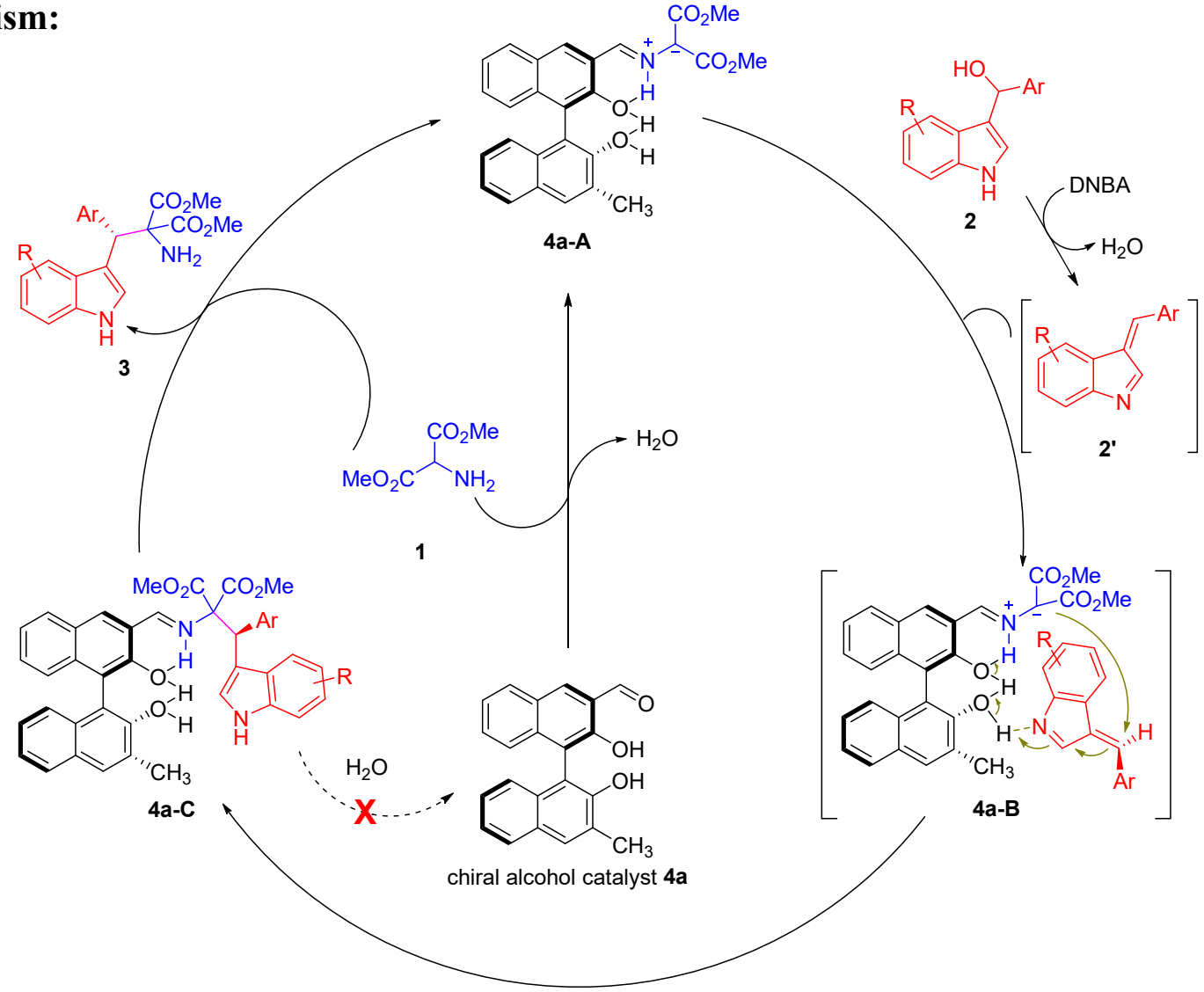


3a, 77% yield, 86% ee **3b,** 64% yield, 96% ee **3c,** 77% yield, 87% ee **3d,** 49% yield, 94% ee **3e,** 43% yield, 98% ee, at 40 °C

Q.-X. Guo. et al. *Chem. Sci.* **2014**, *5*, 1988 –1991.

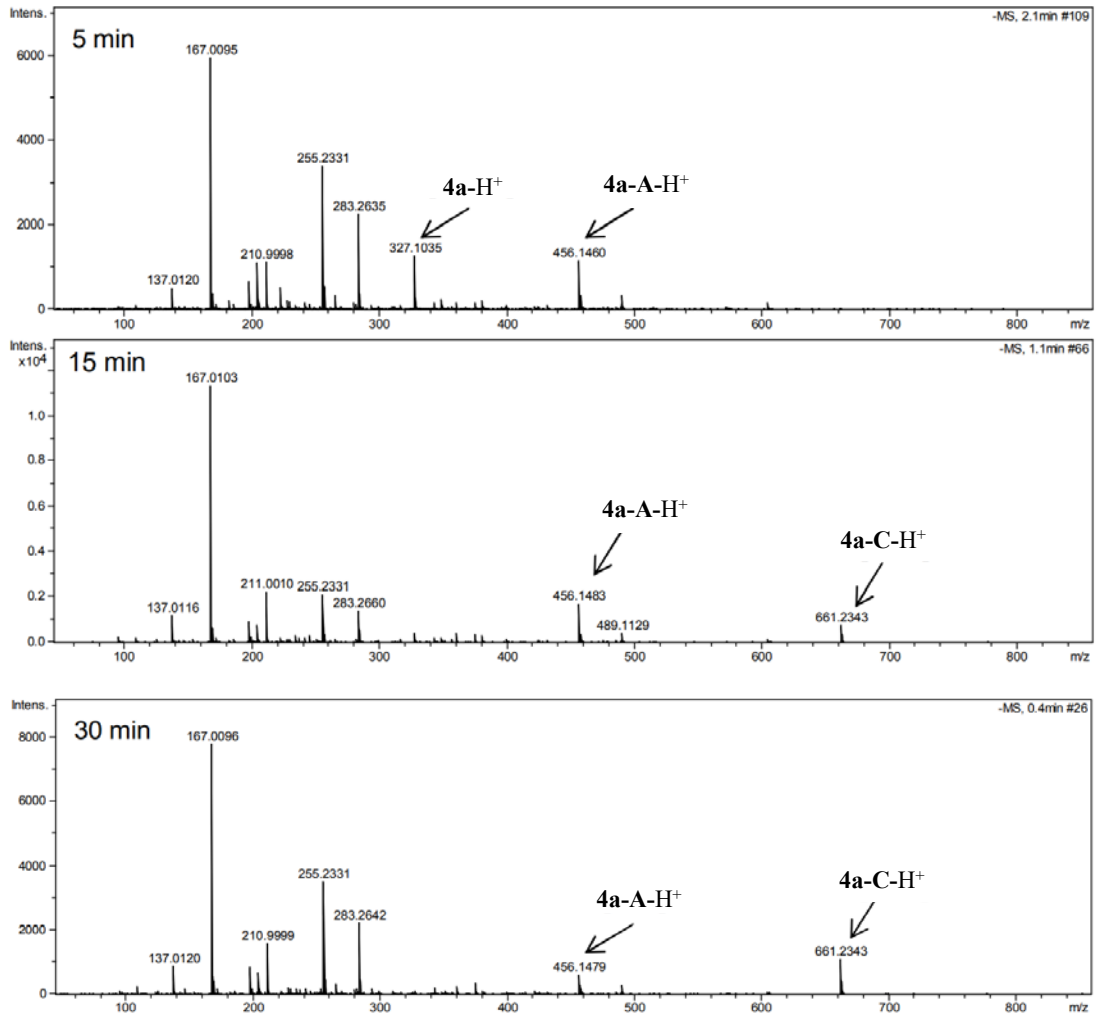
不对称烷基化反应

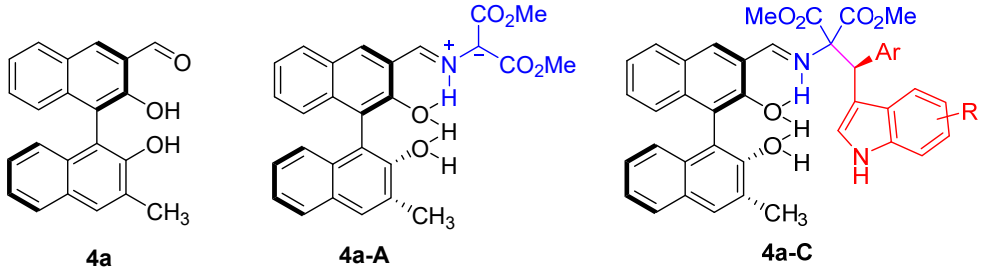
Proposed mechanism:



不对称烷基化反应

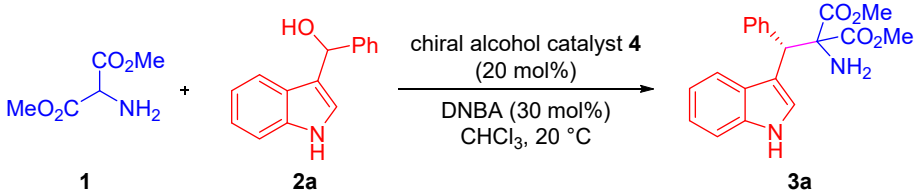
Monitor the reaction process by HRMS(In negative-ion model):

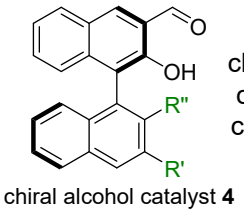




4a-H⁺：30min后完全消失，说明**4a**在反应过程中被消耗后不可再生；
4a-A-H⁺：说明**4a-A**在反应过程中被消耗后会再生

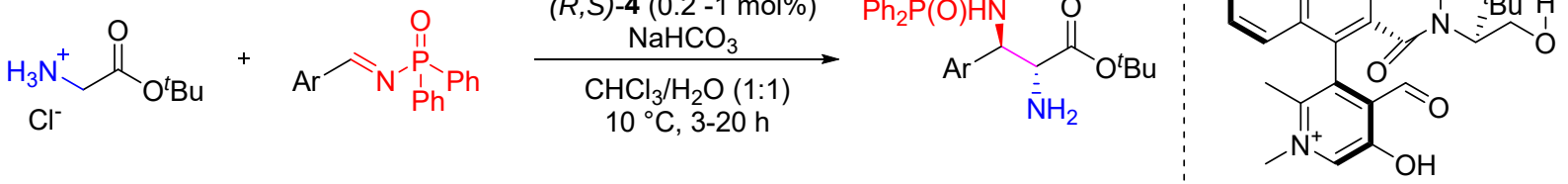
Comparison of catalytic selectivities：





chiral alcohol catalyst **4a**: R' = Me, R'' = OH, 77% yield, 86% ee
chiral alcohol catalyst **4b**: R' = H, R'' = OH, 75% yield, 74% ee
chiral alcohol catalyst **4c**: R' = H, R'' = OMe, 75% yield, -4% ee

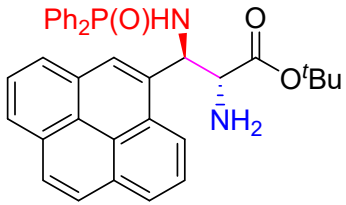
不对称Mannich反应



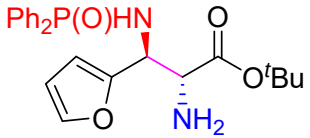
1 **2** **3**

32 exampels
47-94% yields
up to >20:1 dr
94-99% ee

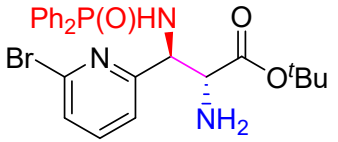
(R,S)-**4**



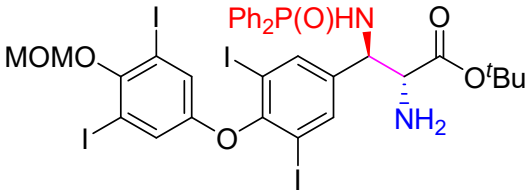
3a, 77%, >20:1 dr, 98% ee



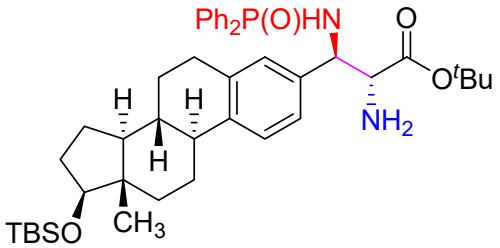
3b, 92%, >20:1 dr, 99% ee



3c, 89%, >20:1 dr, 95% ee



3d (Synthroid analogue), 86%, >20:1 dr, 94% ee

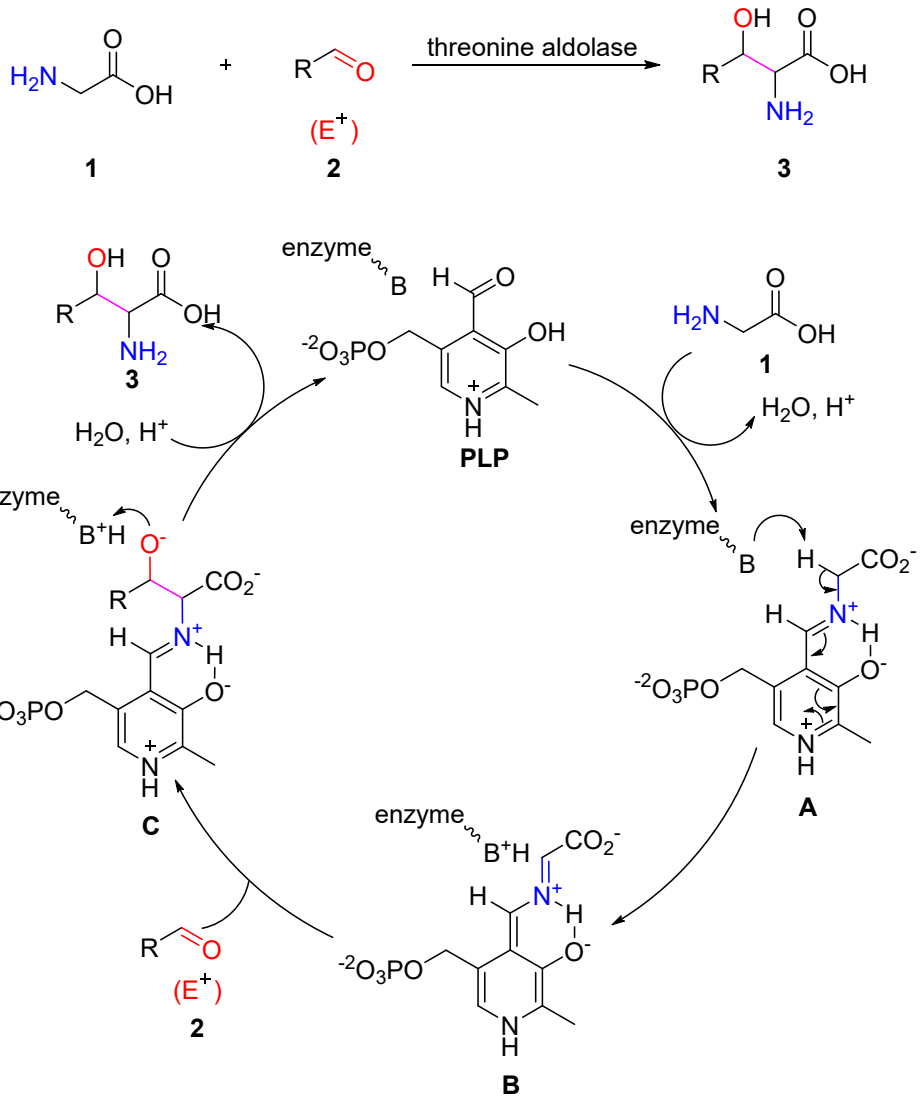


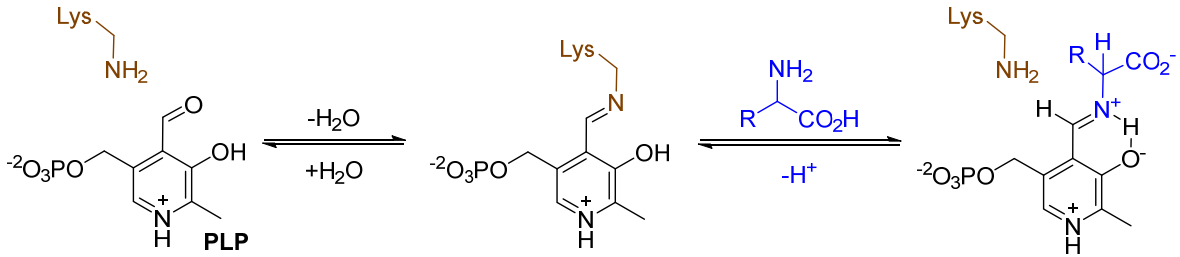
3e, 62%, >20:1 dr

W. Yuan.; B. Zhao. et al. *Science* **2018**, *360*, 1438–1442.

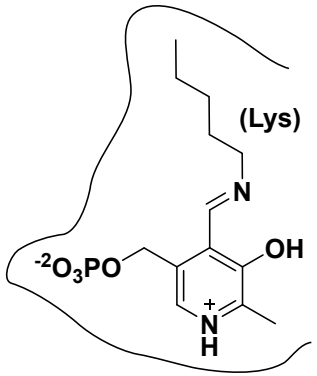
不对称Mannich反应

Threonine Aldolase-Catalyzed Reaction

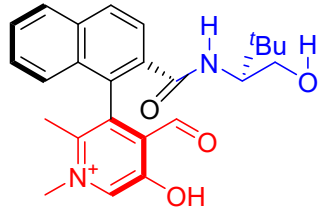




Design N-quaternized chiral pyridoxals:

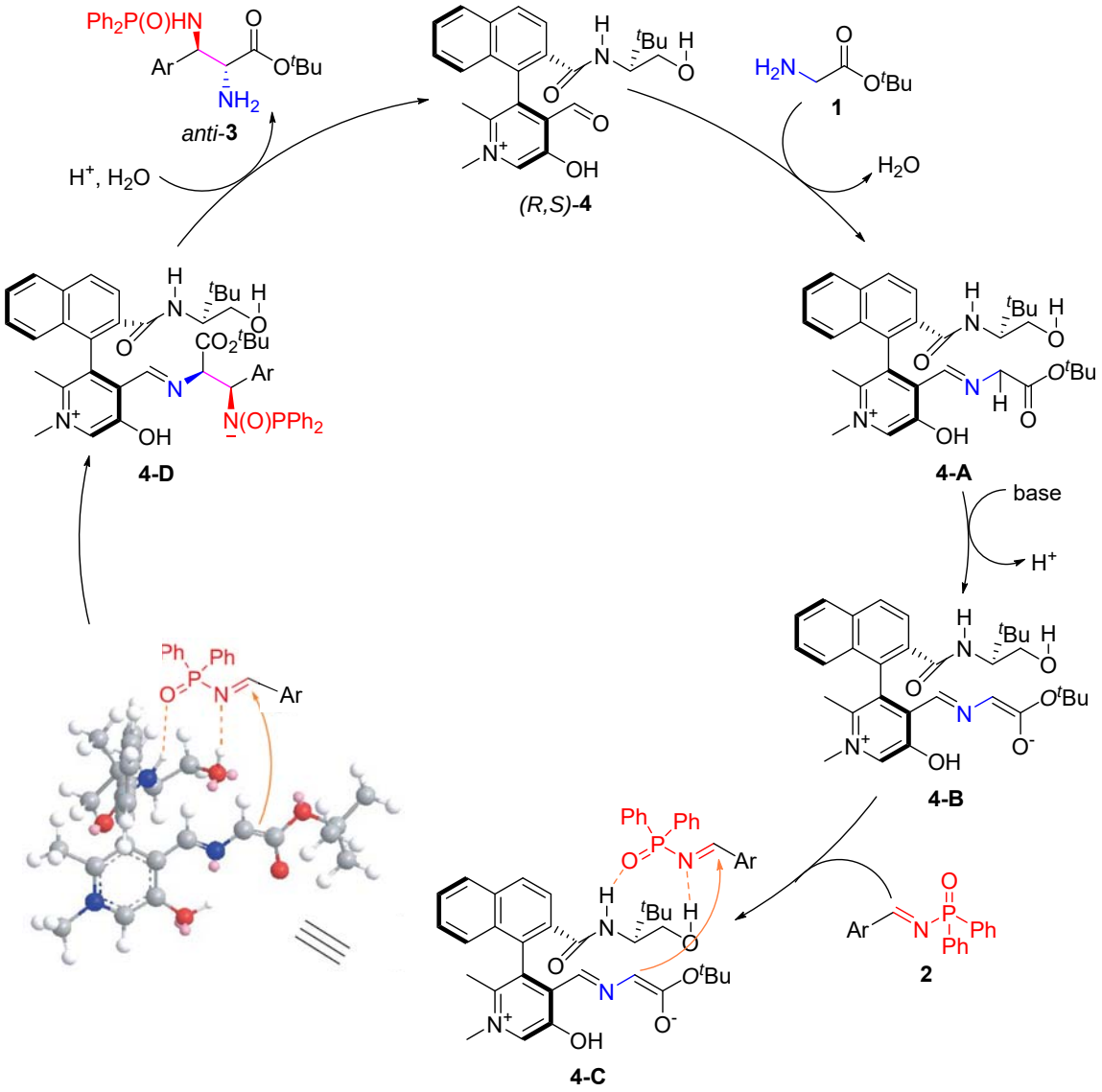


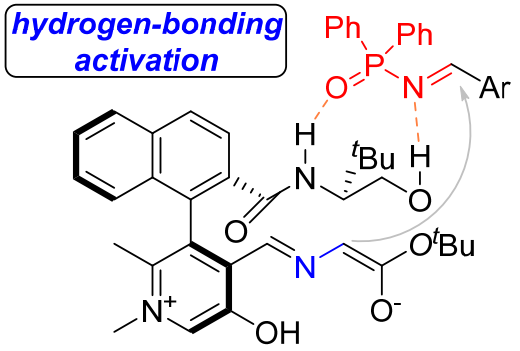
pydioxal-dependent aldolase



bioinspired carbonyl catalyst

不对称Mannich反应

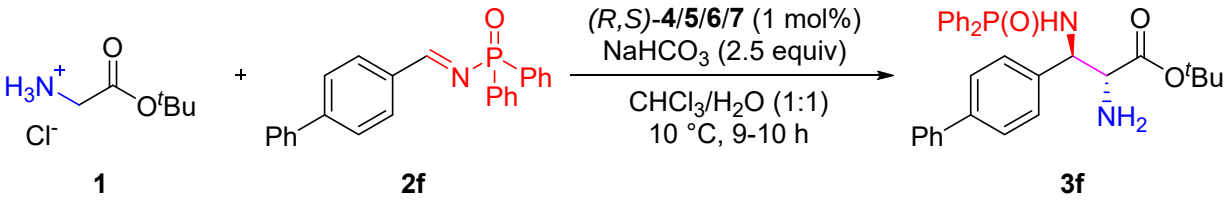


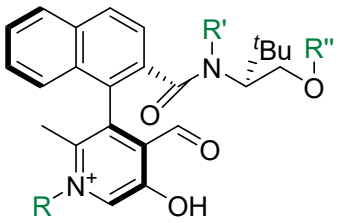


A possible transition state proposed for the Mannich reaction.

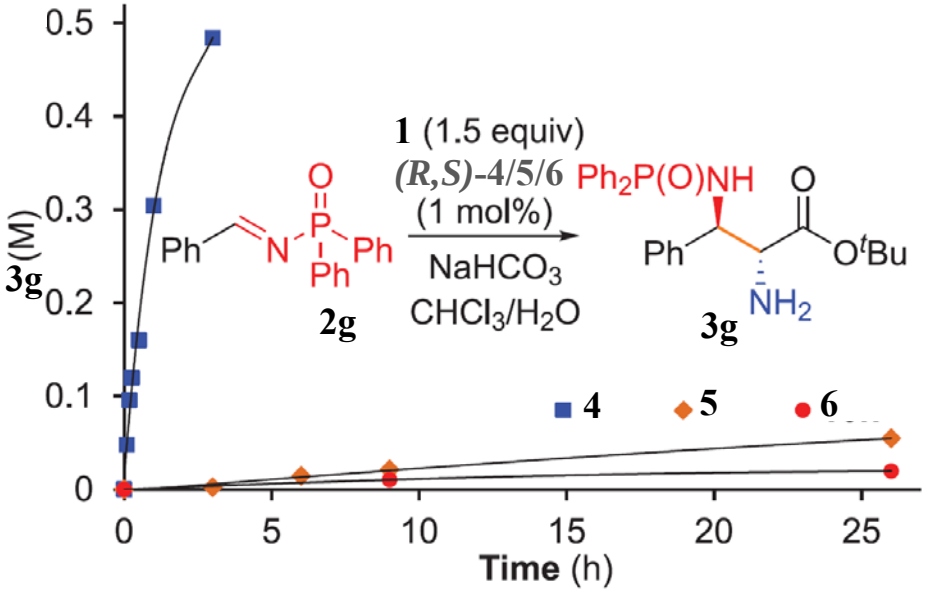
不对称Mannich反应

Comparison of catalytic selectivities：

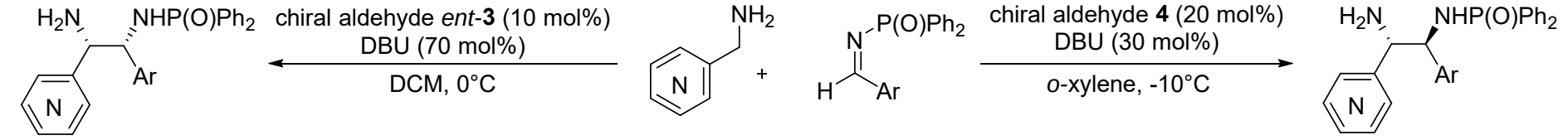




(*R,S*)-**4**(R= Me, R'= H, R"= H): 90% yield, >20:1dr, 99%ee
(*R,S*)-**5**(R= Me, R'= H, R"= Me): 27% yield, 12:1dr, -31%ee
(*R,S*)-**6**(R= Me, R'= Me, R"= H): 9% yield, 1:1dr, -87%ee
(*R,S*)-**7**(R= None, R'= H, R"= H): 0%



不对称Mannich反应

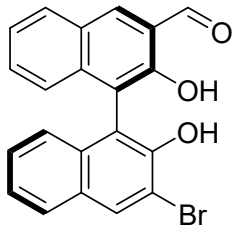


Syn-**5, up to 90% yield, >99:1 dr, 90% ee**

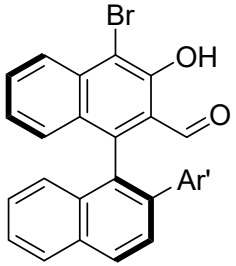
1

2

Anti-**5, up to 90% yield, 91:9 dr, 96% ee**

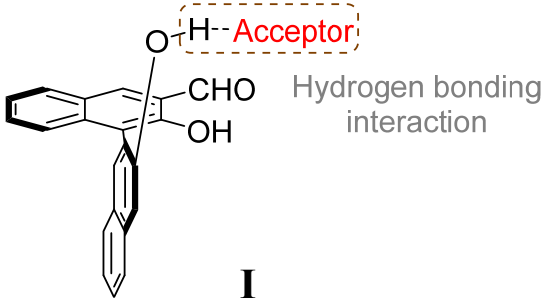


ent-**3**



4

Ar' = 4-^{t}BuC$_6$H$_4$



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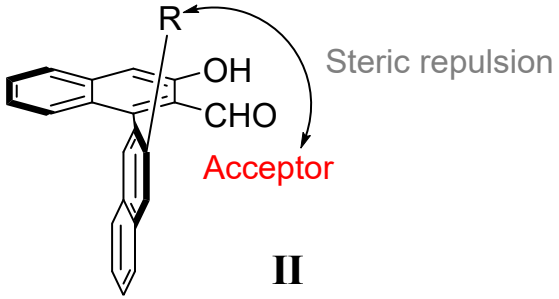
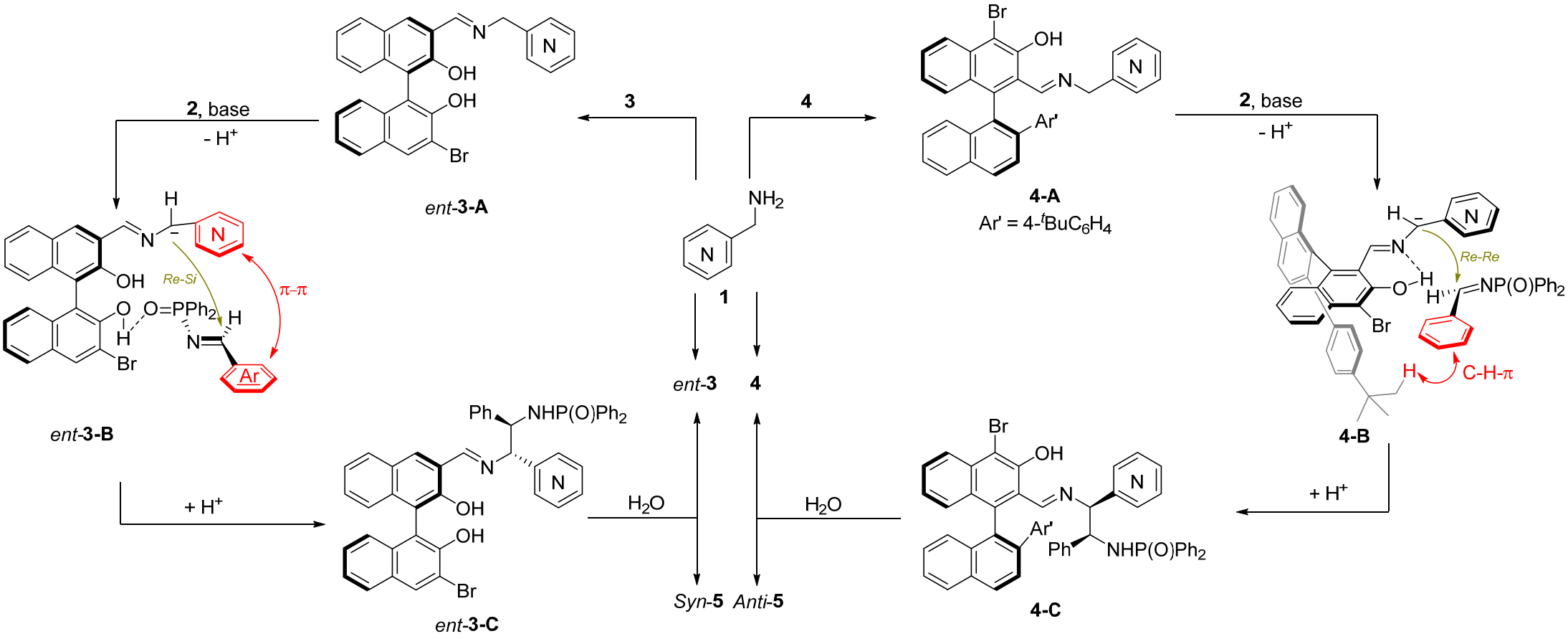


II

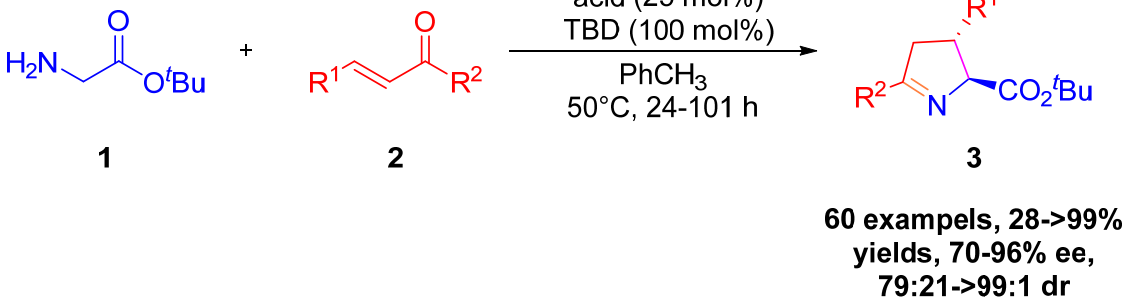
Q.-X. Guo. et al. *Nat Commun.* **2020**, *11*, 5372.

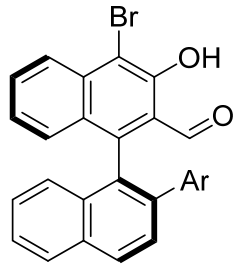
不对称Mannich反应

Proposed mechanism:

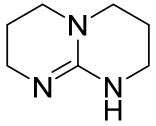


不对称Michael加成反应

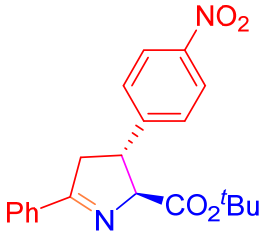




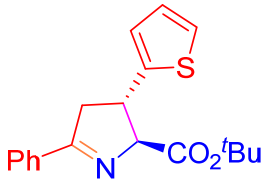
4a
Ar = 2-naphthyl



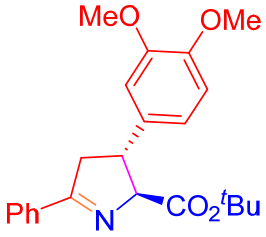
TBD



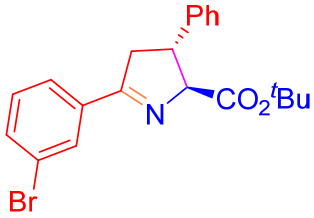
3a, 72% yield, 91:9 dr, 92% ee



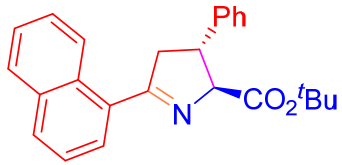
3b, 81% yield, 90:10 dr, 95% ee



3c, 64% yield, >99:1 dr, 95% ee



3d, 79% yield, 85:15 dr, 95% ee

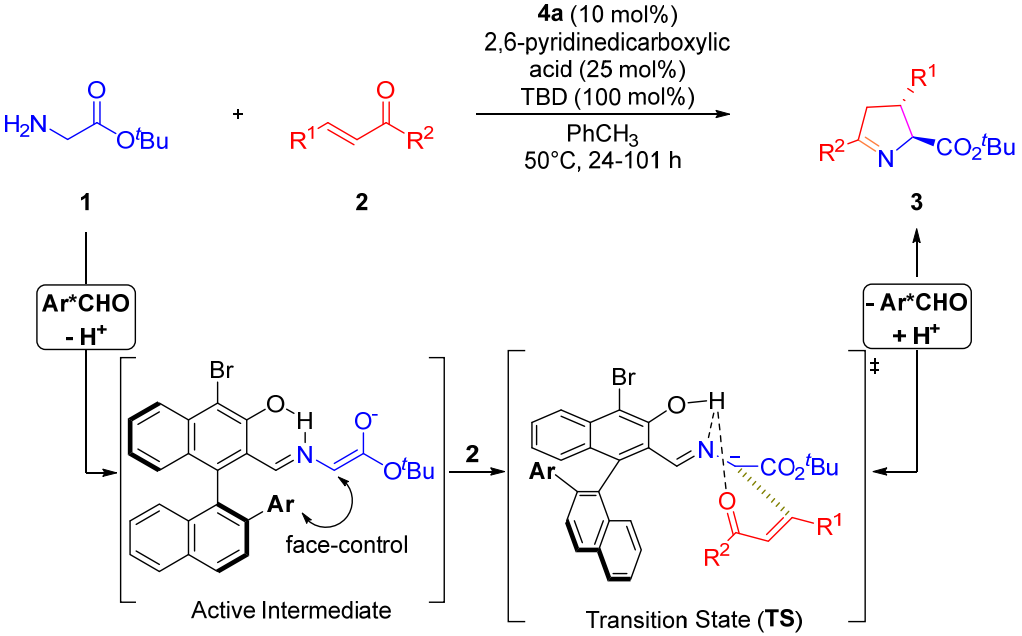


3e, >99% yield, 87:13 dr, 95% ee

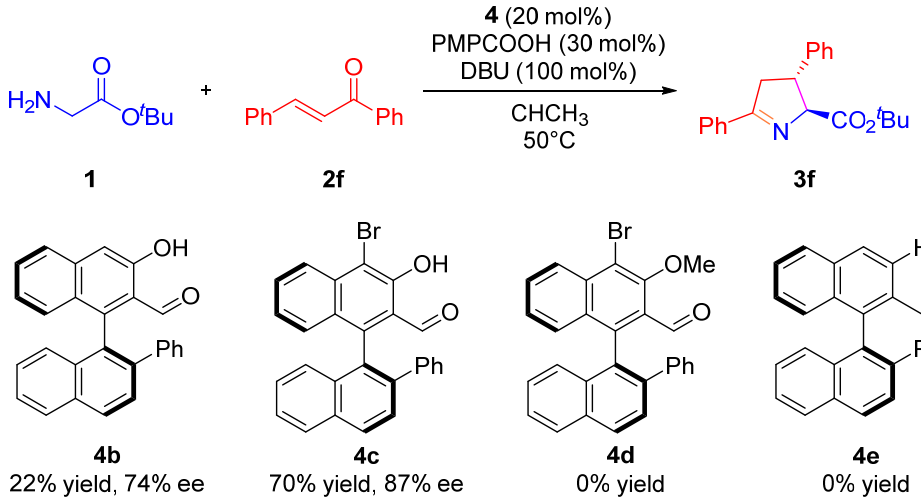
Q.-X. Guo. et al. *J. Am. Chem. Soc.* **2018**, *140*, 9774−9780

不对称Michael加成反应

Proposed mechanism:

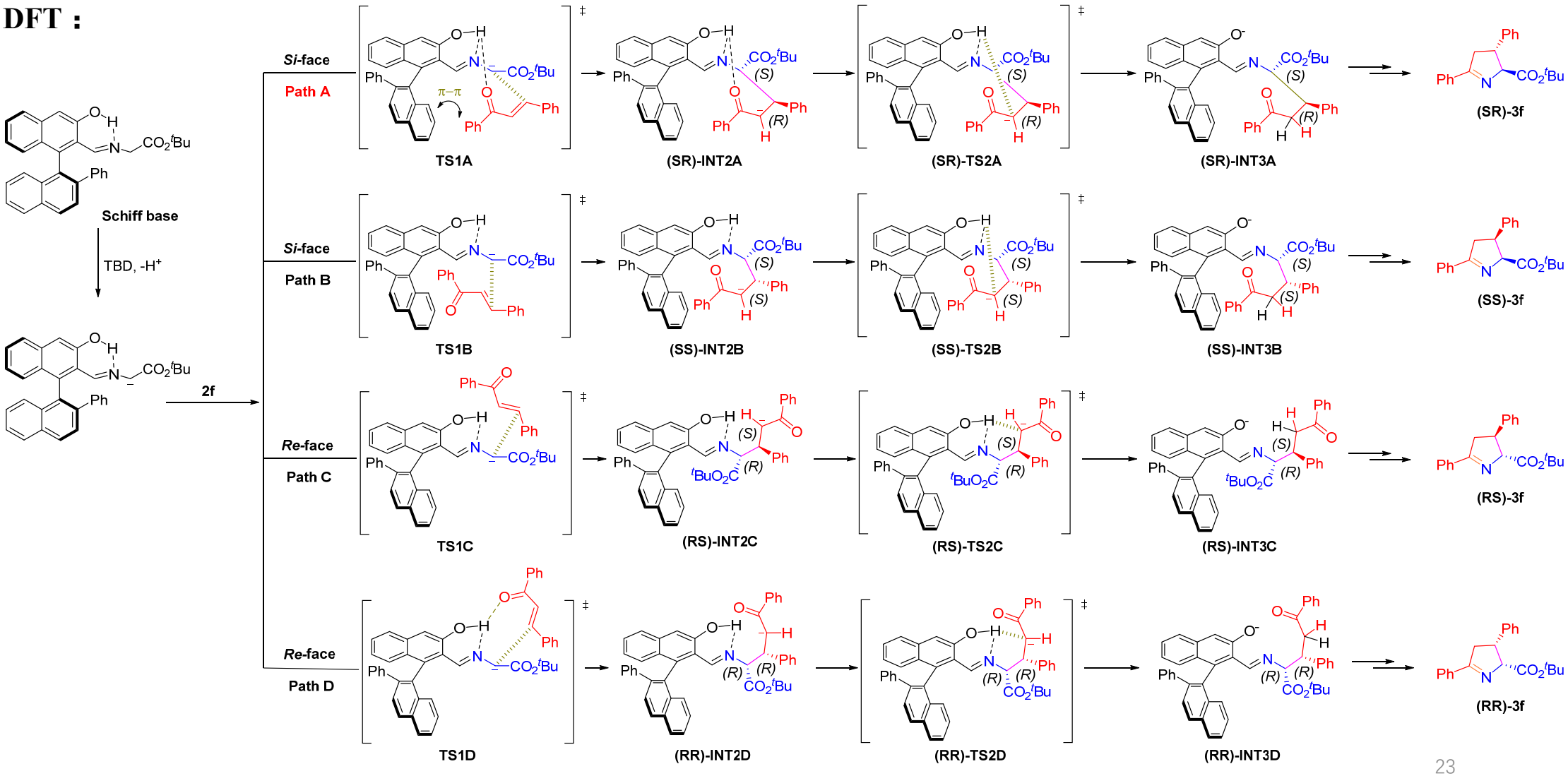


Comparison of catalytic selectivities：

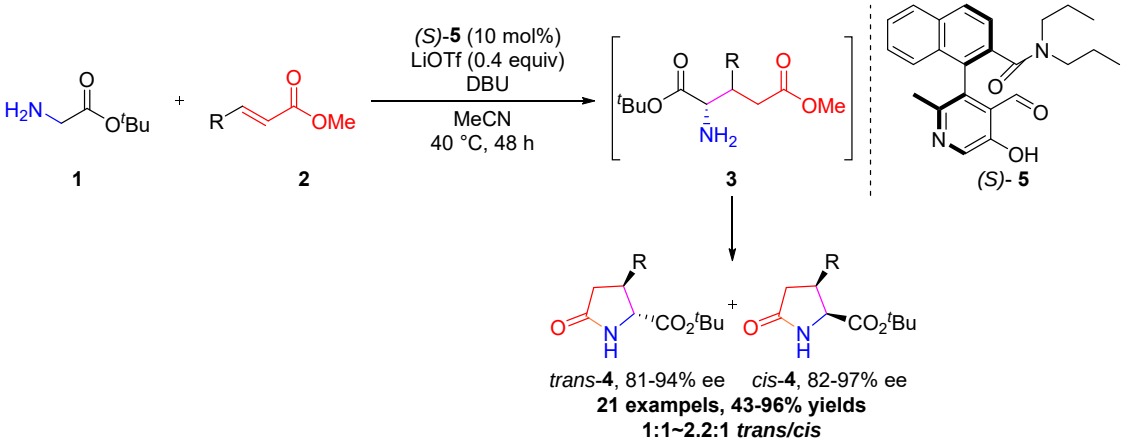


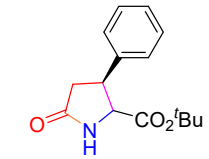
不对称Michael加成反应

DFT：

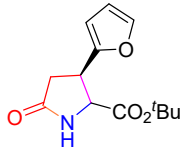


不对称Michael加成反应

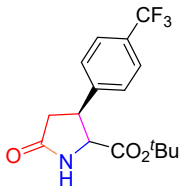




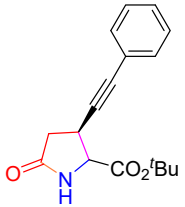
3b, 69%, 1.1:1 *trans/cis*, 86/91% ee



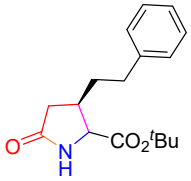
3c, 68%, 1:1 *trans/cis*, 87/90% ee



3d, 62%, 2.1:1 *trans/cis*, 90/91% ee

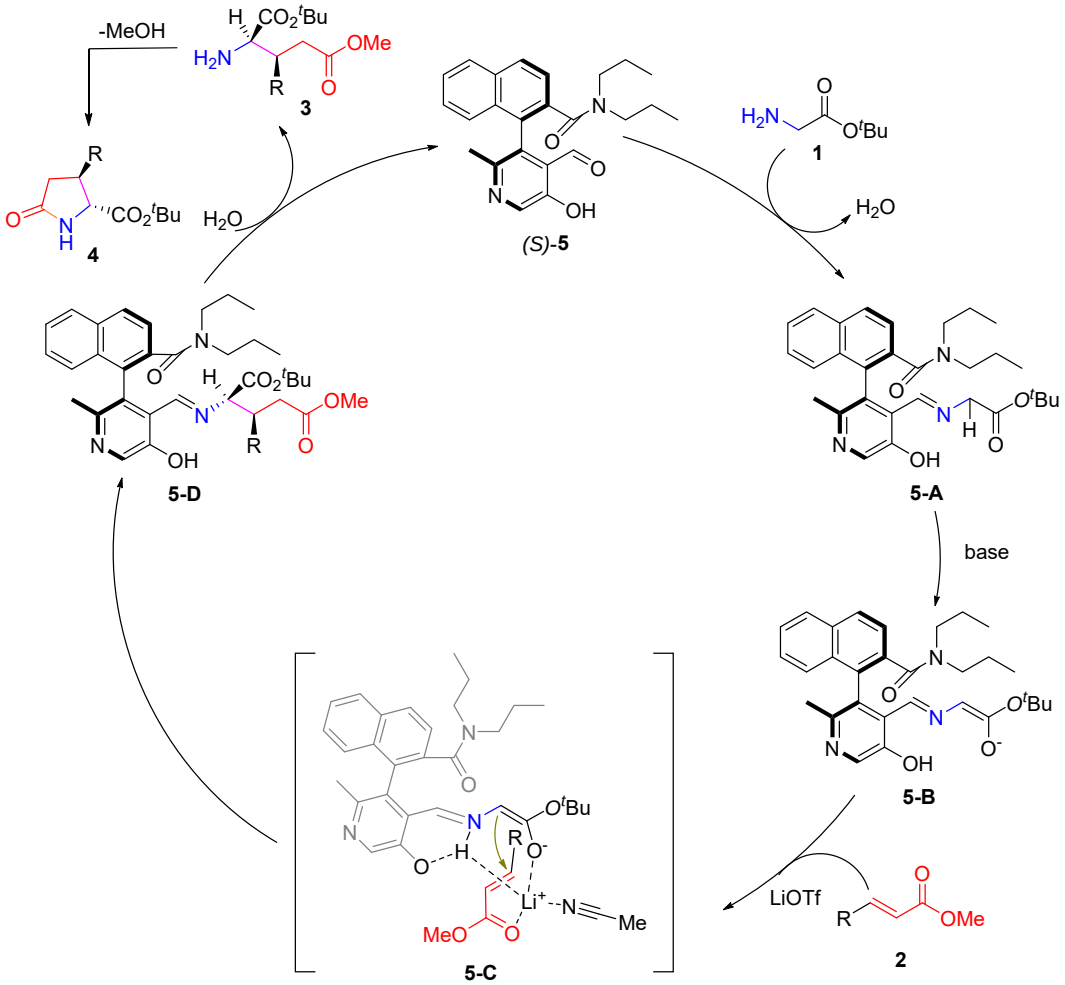


3e, 45%, 1:1.2 *trans/cis*, 88/86% ee



3f, 52%, 1:1.1 *trans/cis*, 89/86% ee

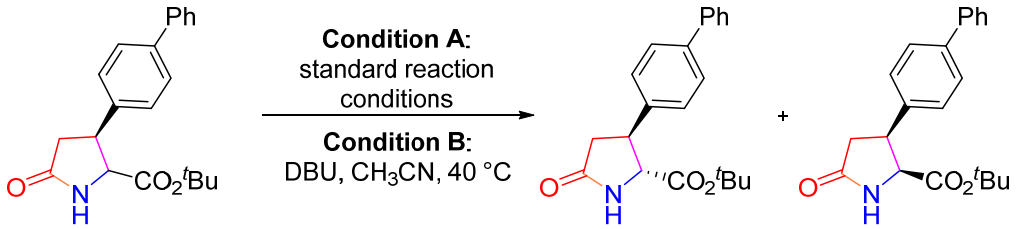
Proposed mechanism:



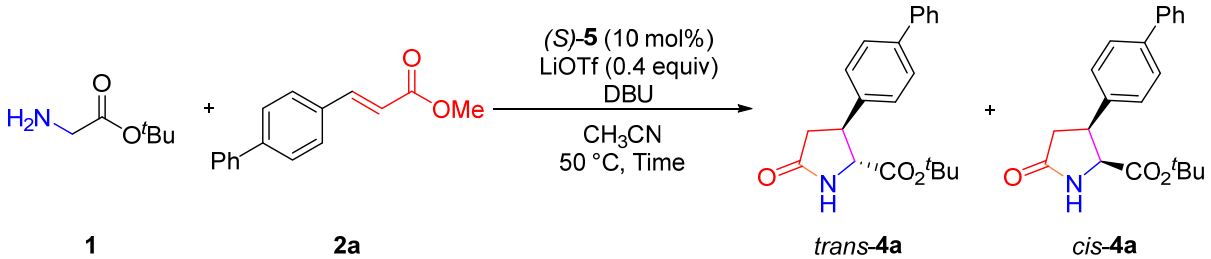
B. Zhao. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 10588 –10592

不对称Michael加成反应

Control experiments：

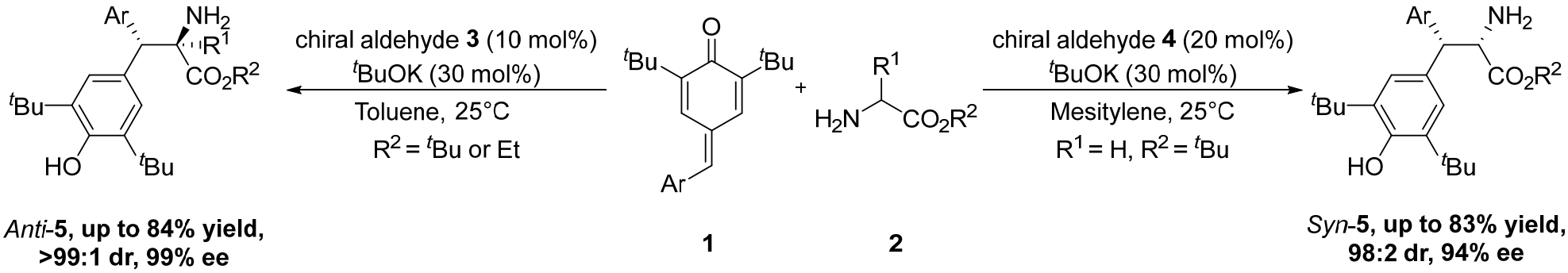


Entry	Reactant	Conditions	Time	Product
1	*trans*-**4a** (86% ee)	A	48 h	99% yield, 4.3:1 *trans/cis*, 86%/86% ee
2	*cis*-**4a** (91% ee)	A	48 h	99% yield, 1.3:1 *trans/cis*, 91%/91% ee
3	*trans*-**4a** (86% ee)	B	48 h	4.7:1 *trans/cis*, 86%/86% ee
4	*cis*-**4a** (91% ee)	B	48 h	1.2:1 *trans/cis*, 91%/91% ee



Entry	Time	Yield (%)	*trans:cis*	ee (%)
1	48 h	71	1.4:1	87/91
2	30 h	58	1.2:1	86/92
3	15 h	47	1.1:1	86/92

不对称1,6-共轭加成反应

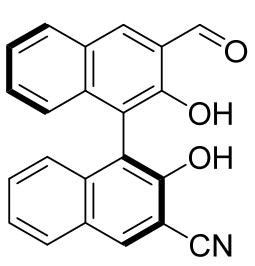


Anti-**5, up to 84% yield, >99:1 dr, 99% ee**

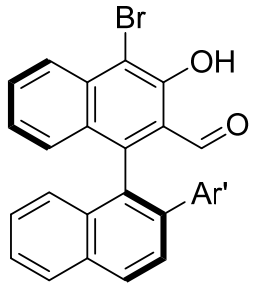
1

2

Syn-**5, up to 83% yield, 98:2 dr, 94% ee**



3



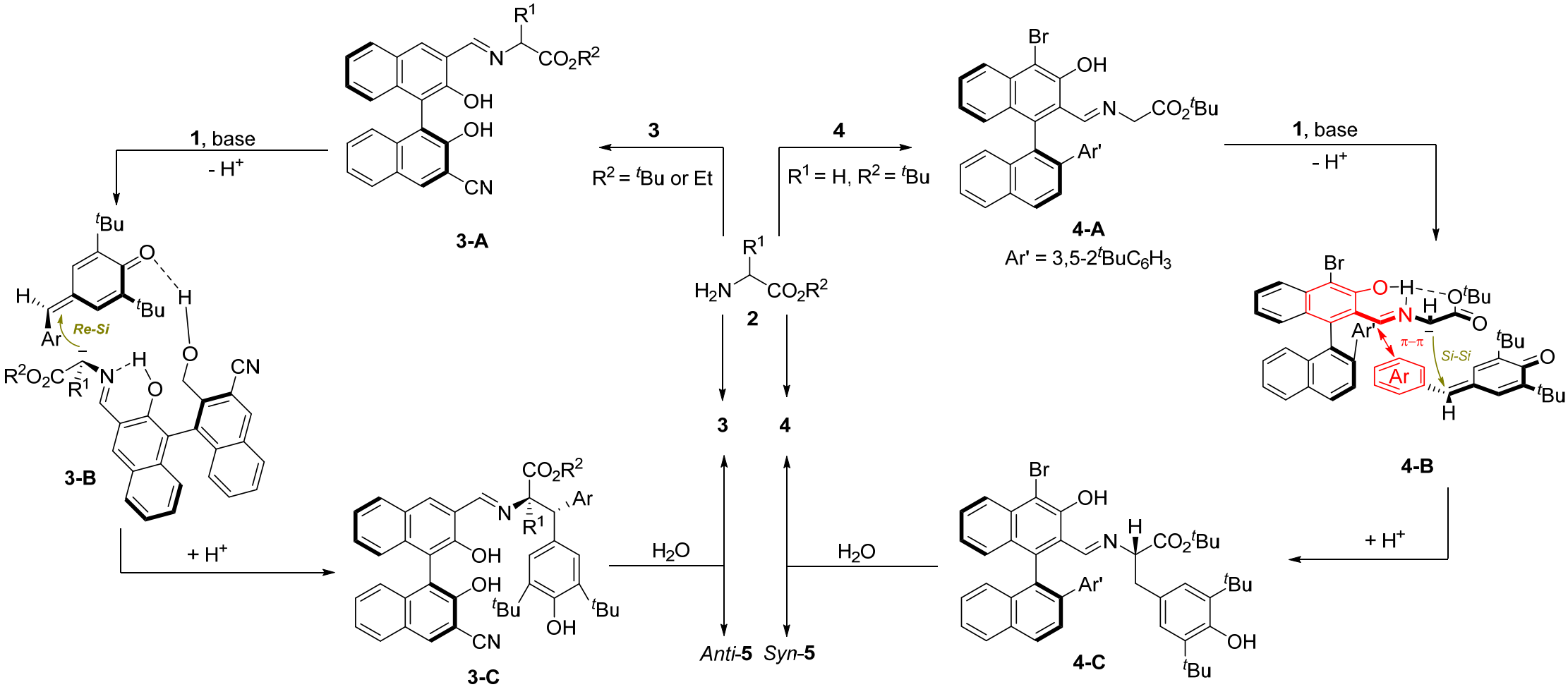
4

Ar' = 3,5-2^{t}BuC$_6$H$_3$

Q.-X. Guo. et al. *Nat Commun.* **2020**, *11*, 5372.

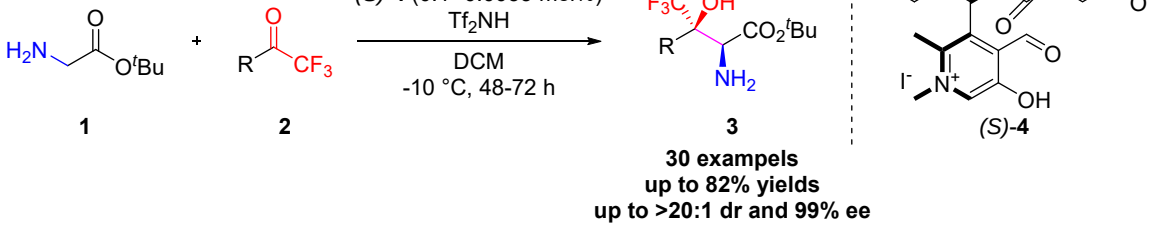
不对称1,6-共轭加成反应

Proposed mechanism:

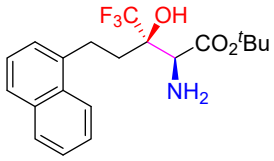


Q.-X. Guo. et al. *Nat Commun.* **2020**, *11*, 5372.

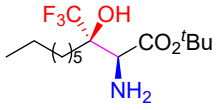
不对称Aldol 反应



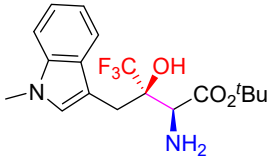
30 exampels
up to 82% yields
up to >20:1 dr and 99% ee



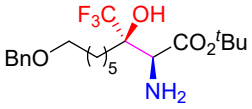
3a, 80%, 9:1 dr, 98% ee



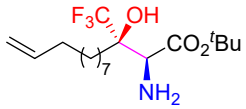
3b, 67%, 7:1 dr, 99% ee



3c, 59%, >20:1 dr, 98% ee

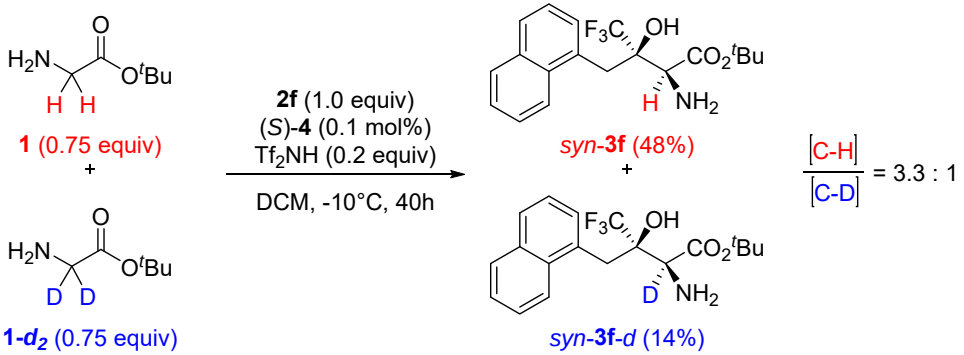


3d, 60%, 9:1 dr, 99% ee



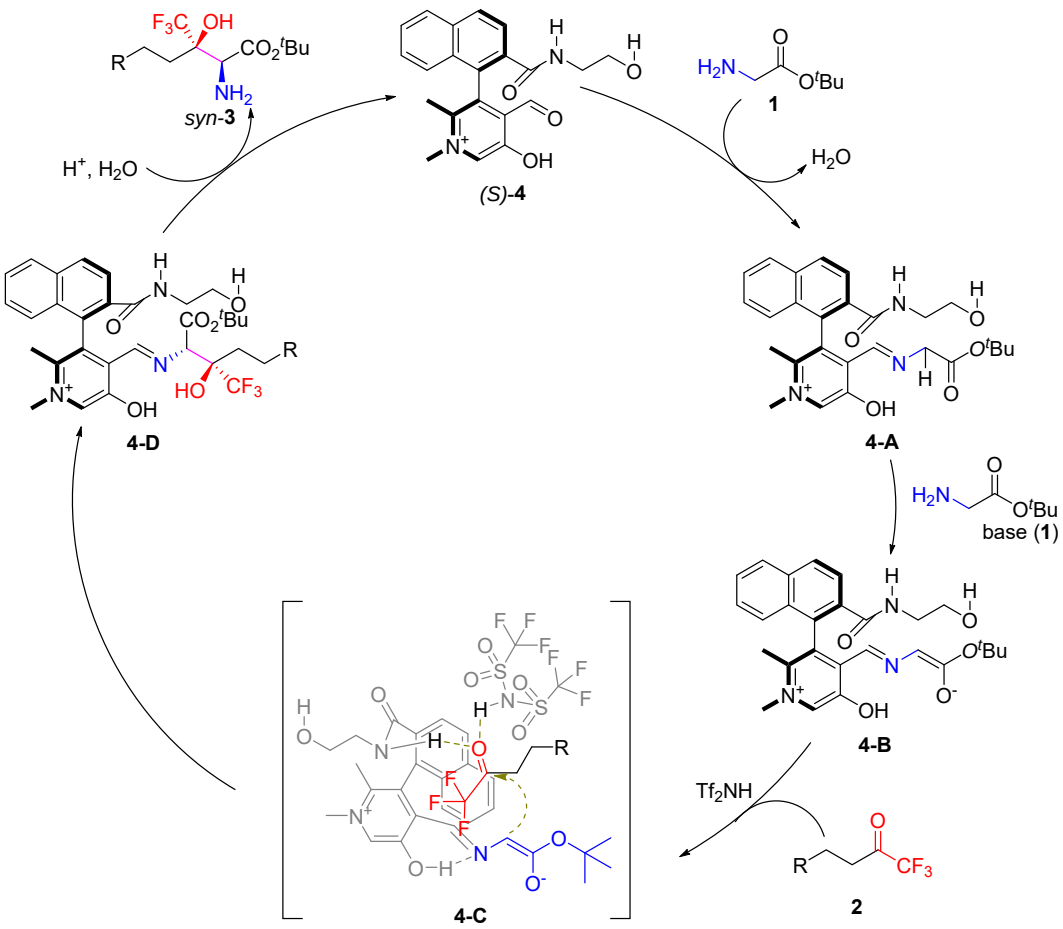
3e, 67%, 8:1 dr, 99% ee

KIE studies:

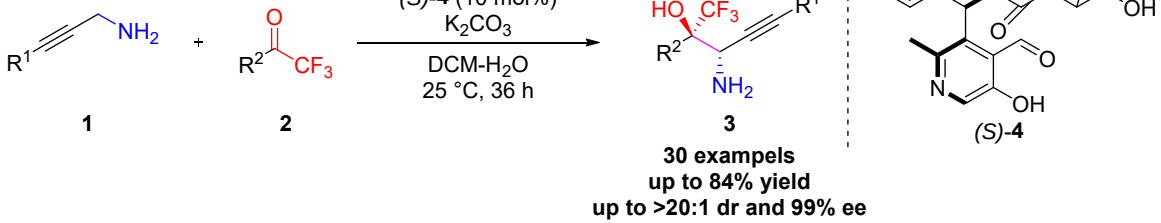


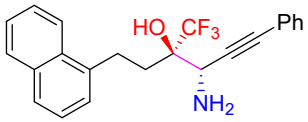
B. Zhao. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20166 –20172

Proposed mechanism:

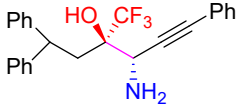


炔胺的不对称加成反应

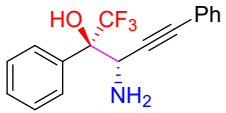




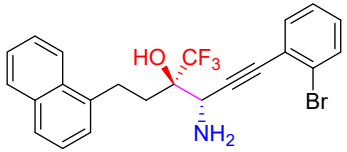
3a, 81% yield,
>20:1 dr, 95% ee



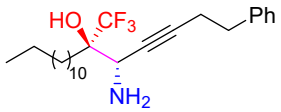
3b, 80% yield,
>20:1 dr, 97% ee



3c, 84% yield,
7:1 dr, 85% ee

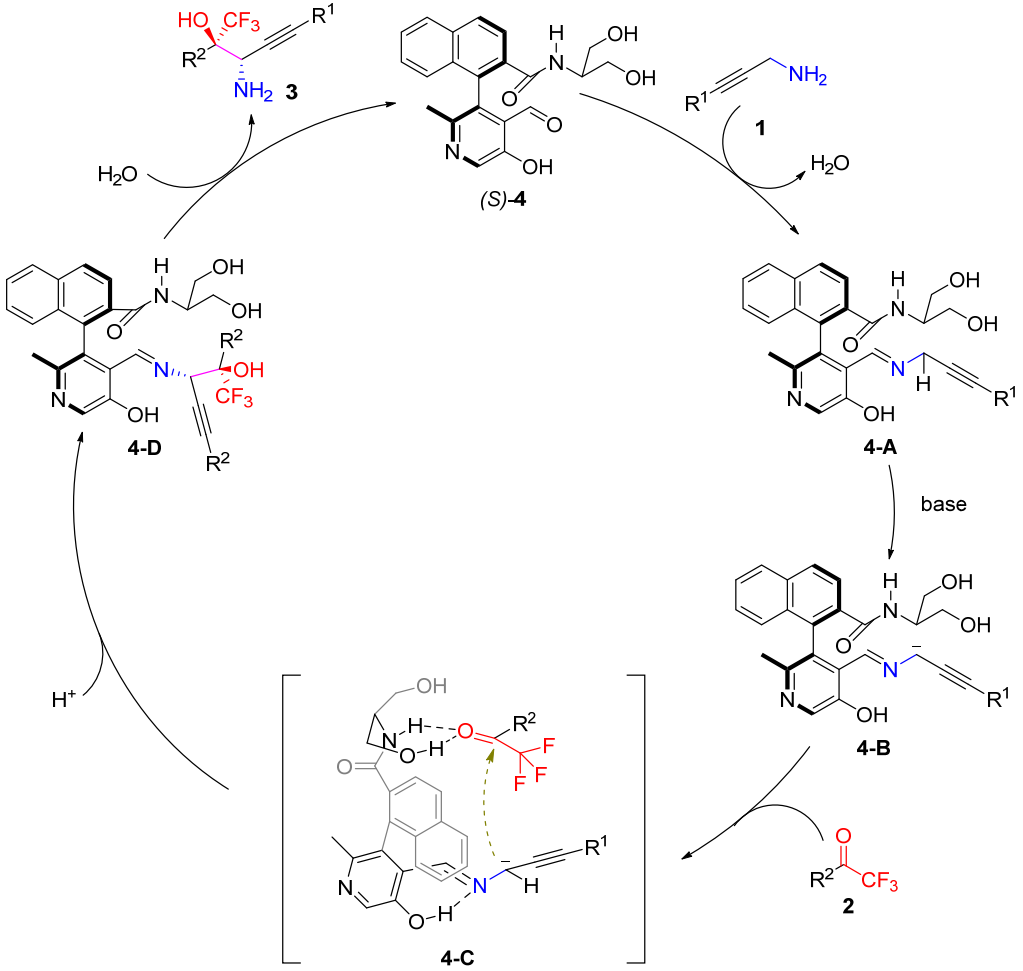


3d, 70% yield,
>20:1 dr, 94% ee



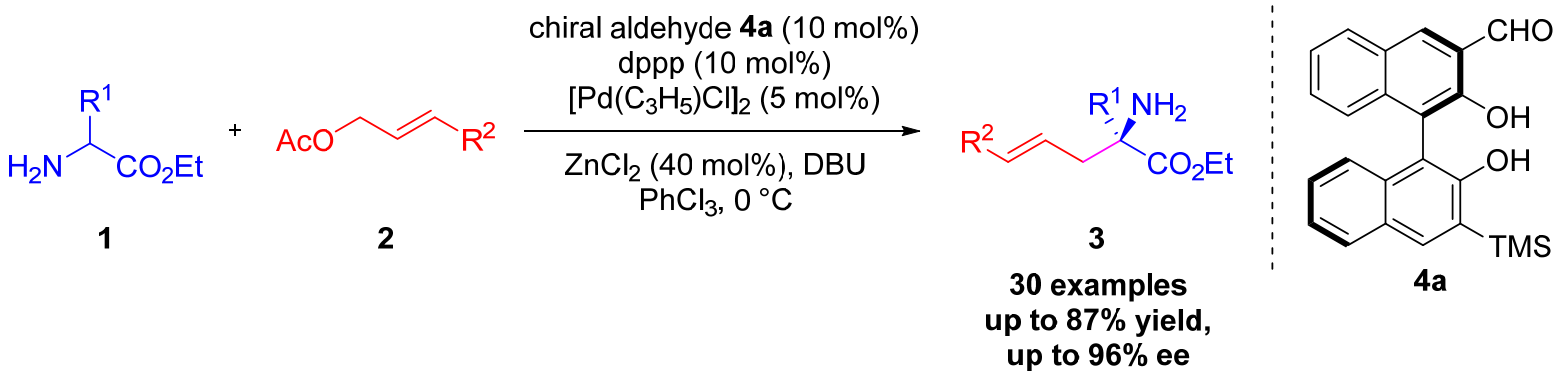
3a, 61% yield,
>20:1 dr, 94% ee

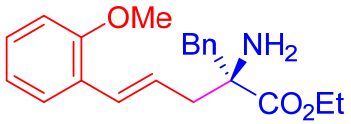
Proposed mechanism:



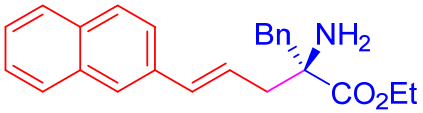
B. Zhao. et al. *Angew. Chem. Int. Ed.* **2022**, accepted.

不对称α-烯丙基化的烷基化反应

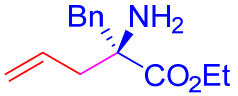




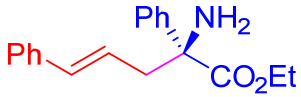
3a, 61% yield, 96% ee



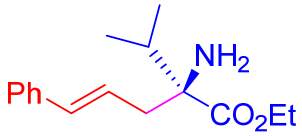
3b, 66% yield, 95% ee



3c, 62% yield, 88% ee



3d, 60% yield, 89% ee



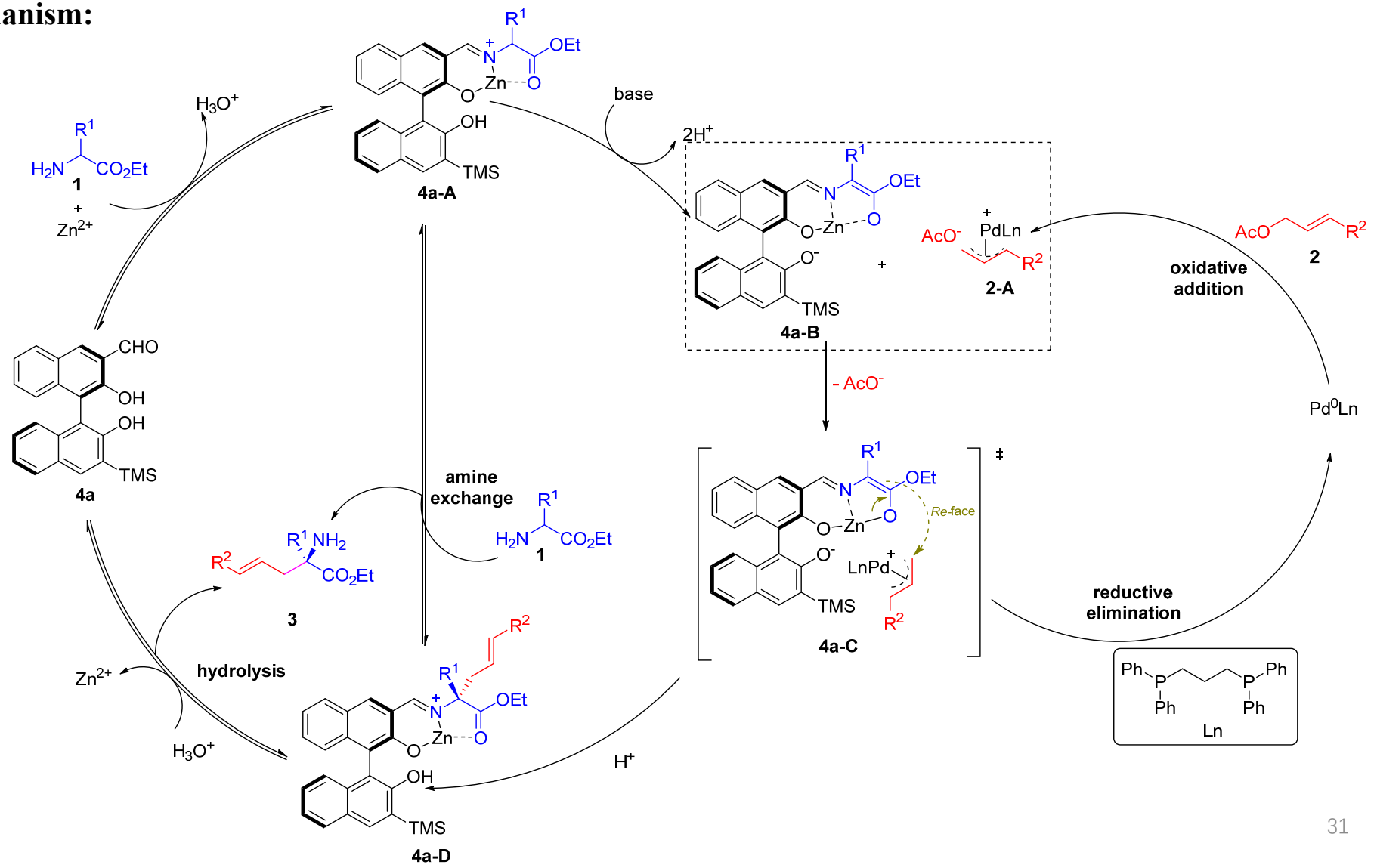
3e, 21% yield, 95% ee

反应特点：手性醛催化剂 + 过渡金属Pd + Lewis酸组成三元催化体系

Q.-X. Guo. et al. *J. Am. Chem. Soc.* **2019**, *141*, 5159−5163

不对称α-烯丙基化的烷基化反应

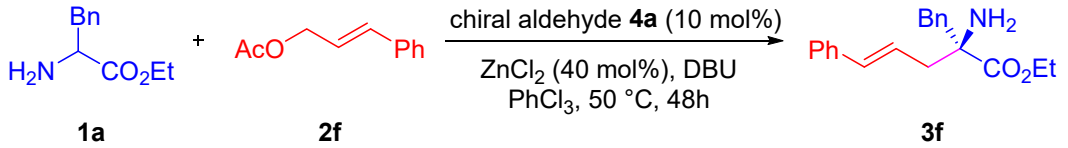
Proposed mechanism:



不对称α-烯丙基化的烷基化反应

Control Experiments：

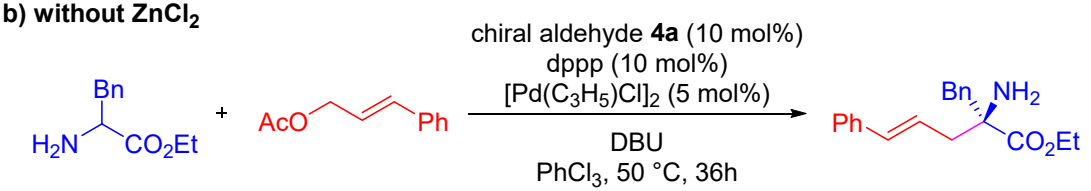
a) without palladium



1a **2f** **3f**

0% yield

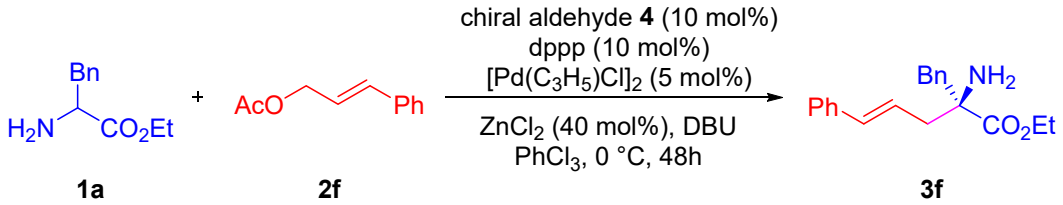
b) without $ZnCl_2$



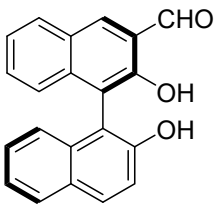
1a **2f** **3f**

14% yield, 55% ee

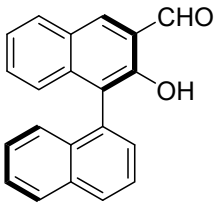
c) with modified chiral aldehyde catalyst



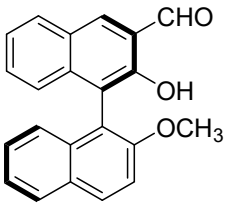
1a **2f** **3f**



4b, 18% yield, 84% ee

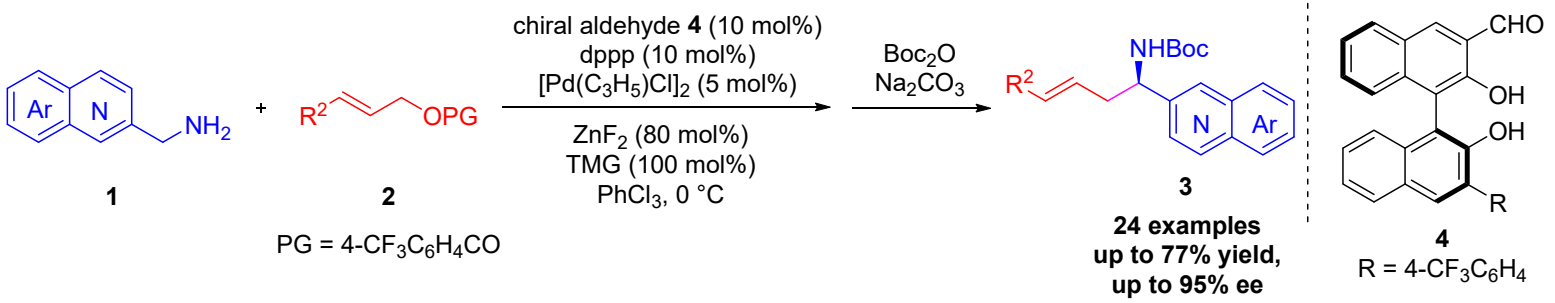


4c, 0% yield



4d, 0% yield

不对称α-烯丙基化的烷基化反应



1 **2**

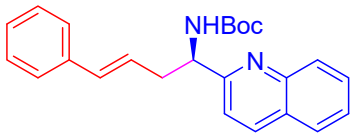
PG = 4-$CF_3C_6H_4CO$

3

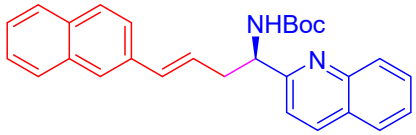
24 examples
up to 77% yield,
up to 95% ee

4

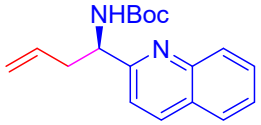
R = 4-$CF_3C_6H_4$



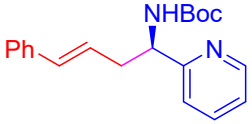
3a, 77% yield, 93% ee



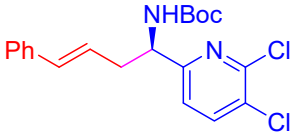
3b, 73% yield, 94% ee



3c, 55% yield, 90% ee

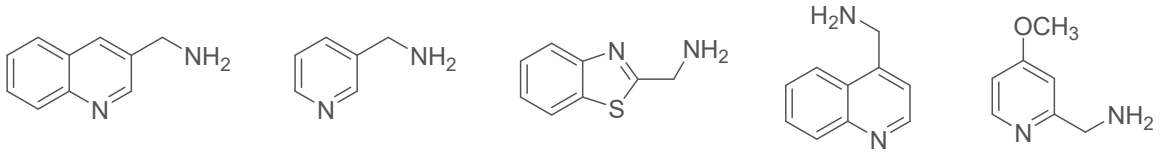


3d, 23% yield, 78% ee



3e, 45% yield, 80% ee

unsuccessful substrates:

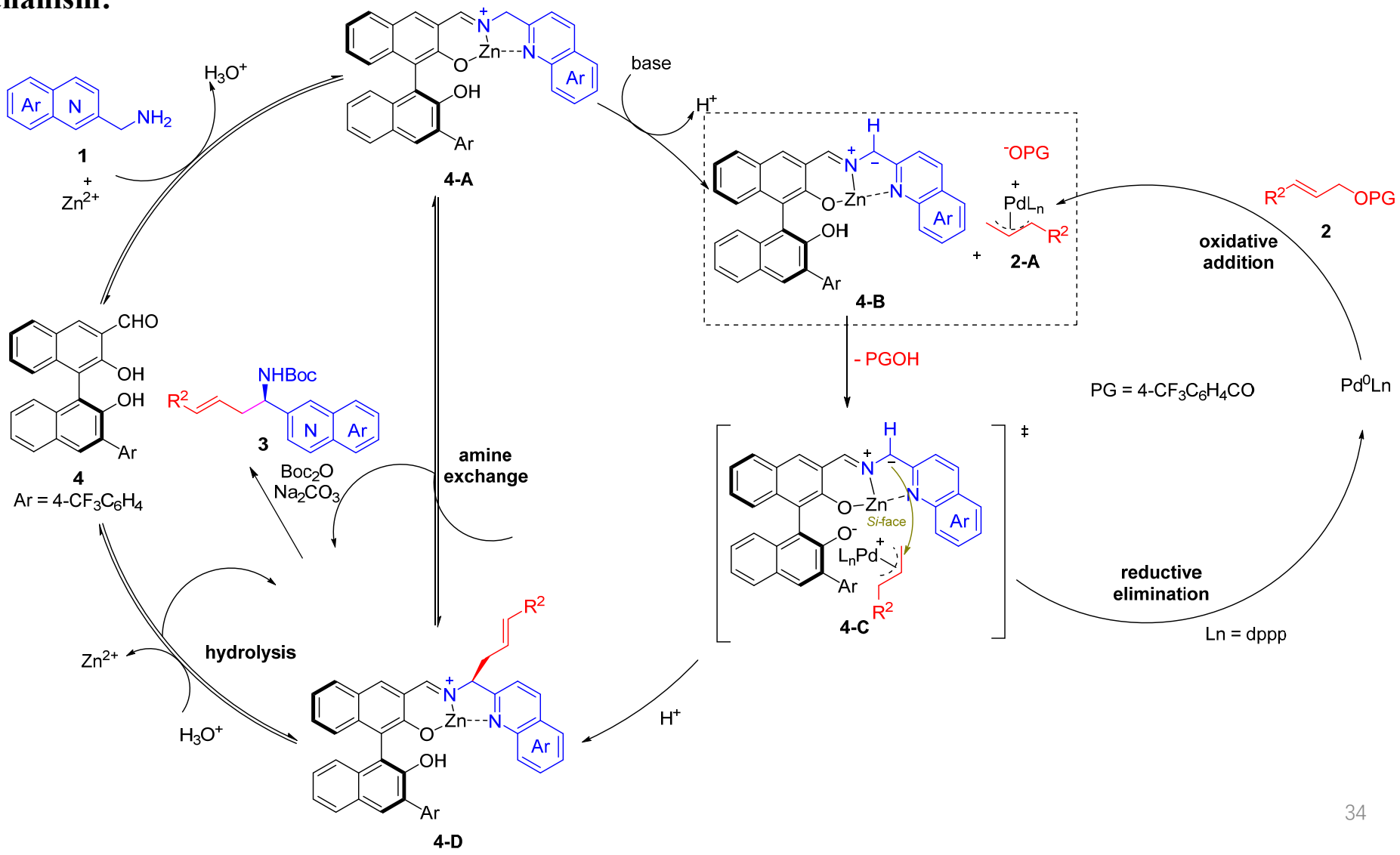


N-杂芳/烷基甲胺α-H酸性不强，易发生N-烯丙基化导致产率不高

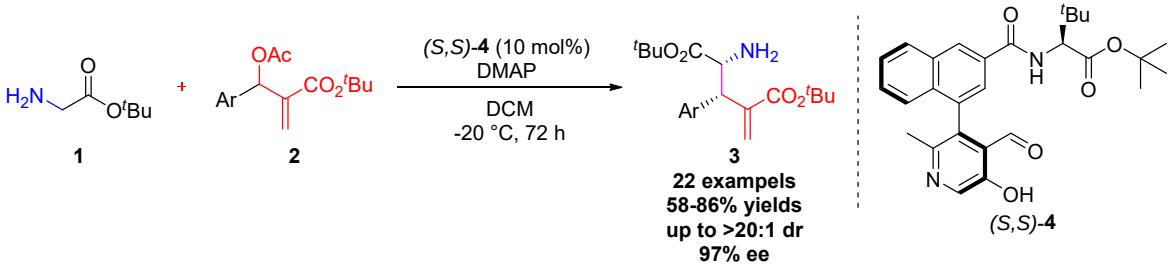
Q.-X. Guo. et al. *Org. Lett.* **2021**, *23*, 1463−1467

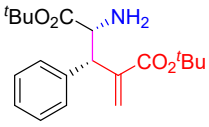
不对称α-烯丙基化的烷基化反应

Proposed mechanism:

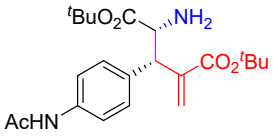


不对称α-烯丙基化的烷基化反应

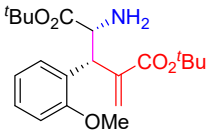




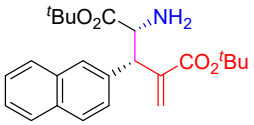
3a, 76%, 9:1 dr, 97% ee



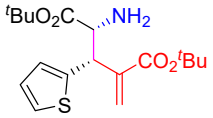
3b, 75%, >20:1 dr, 96% ee



3c, 80%, 19:1 dr, 95% ee



3d, 72%, 10:1 dr, 93% ee

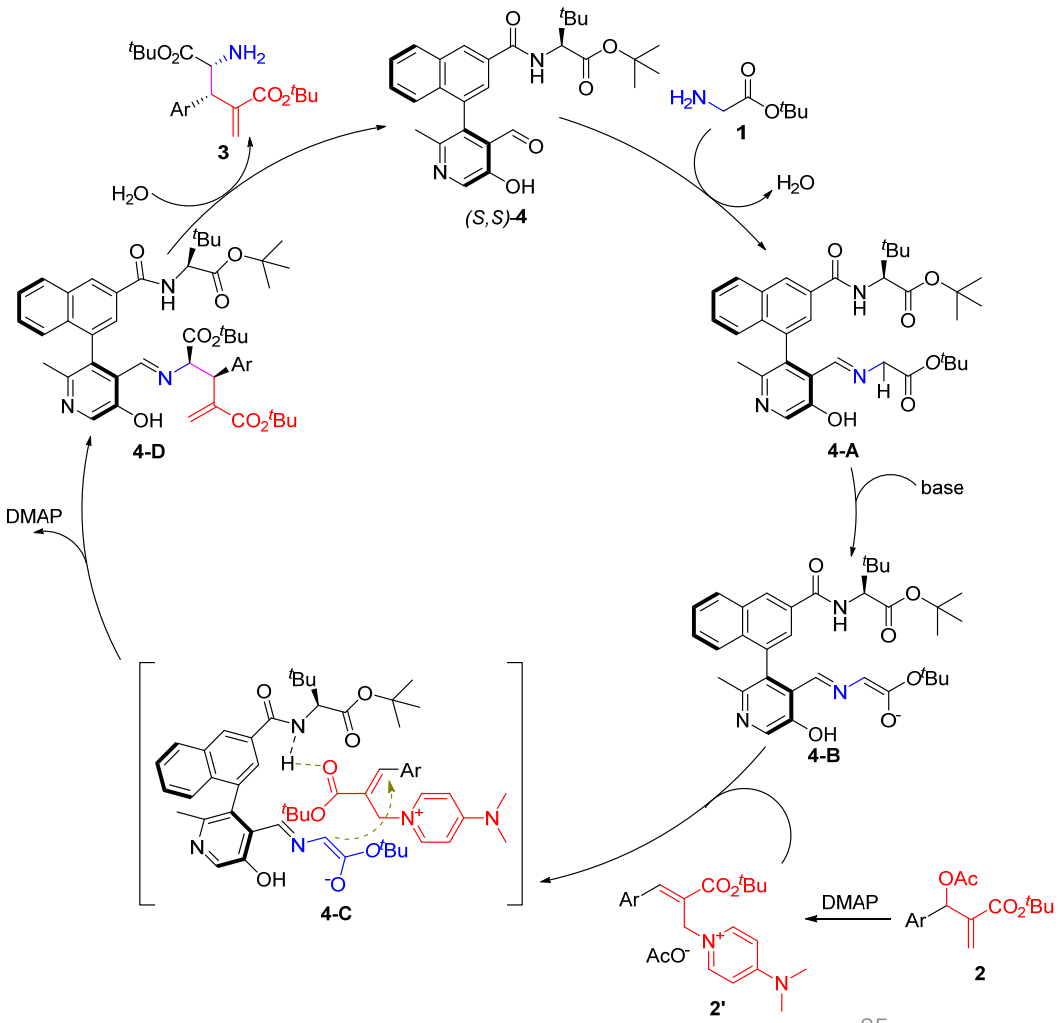


3e, 85%, 7:1 dr, 93% ee

反应特点：

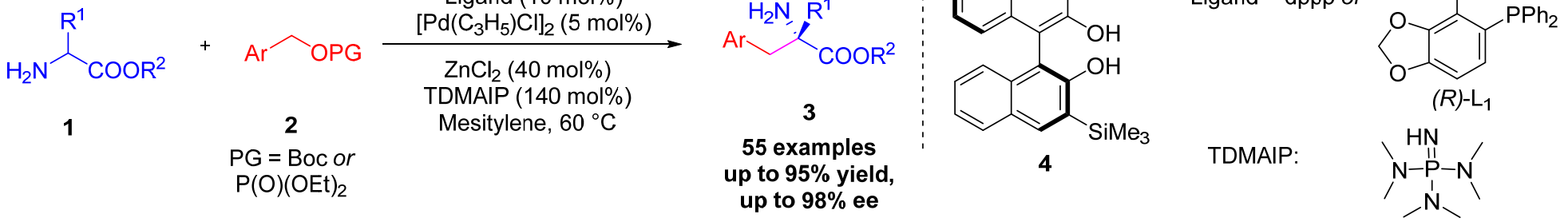
1. 设计合成了包含大催化空腔的手性羰基催化剂
2. 1和2的反应由N-烯丙基化转变为α-C的烯丙基化（-NH_2未保护）

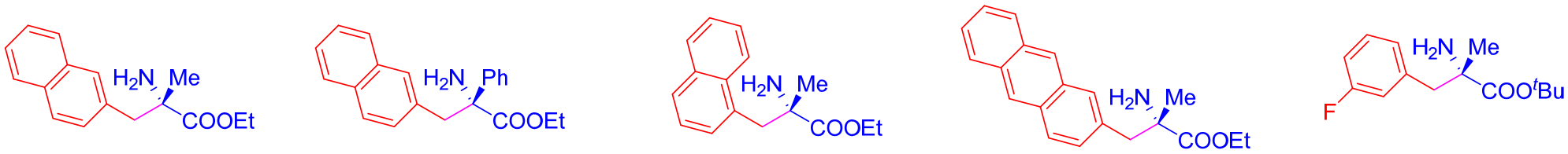
Proposed mechanism:



B. Zhao. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200850

不对称α-芳基化的烷基化反应





3a, 93% yield, 90% ee

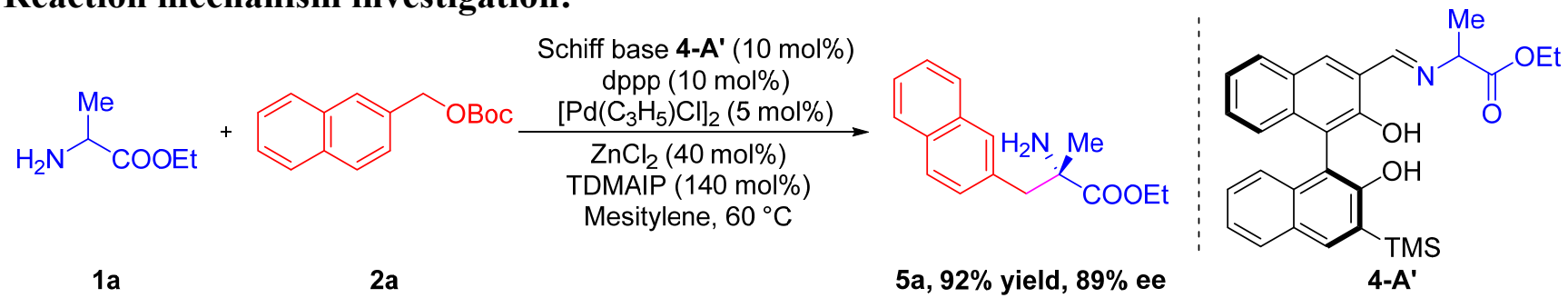
3b, 85% yield, 78% ee

3c, 85% yield, 81% ee

3d, 82% yield, 88% ee

3f, 83% yield, 98% ee

Reaction mechanism investigation:

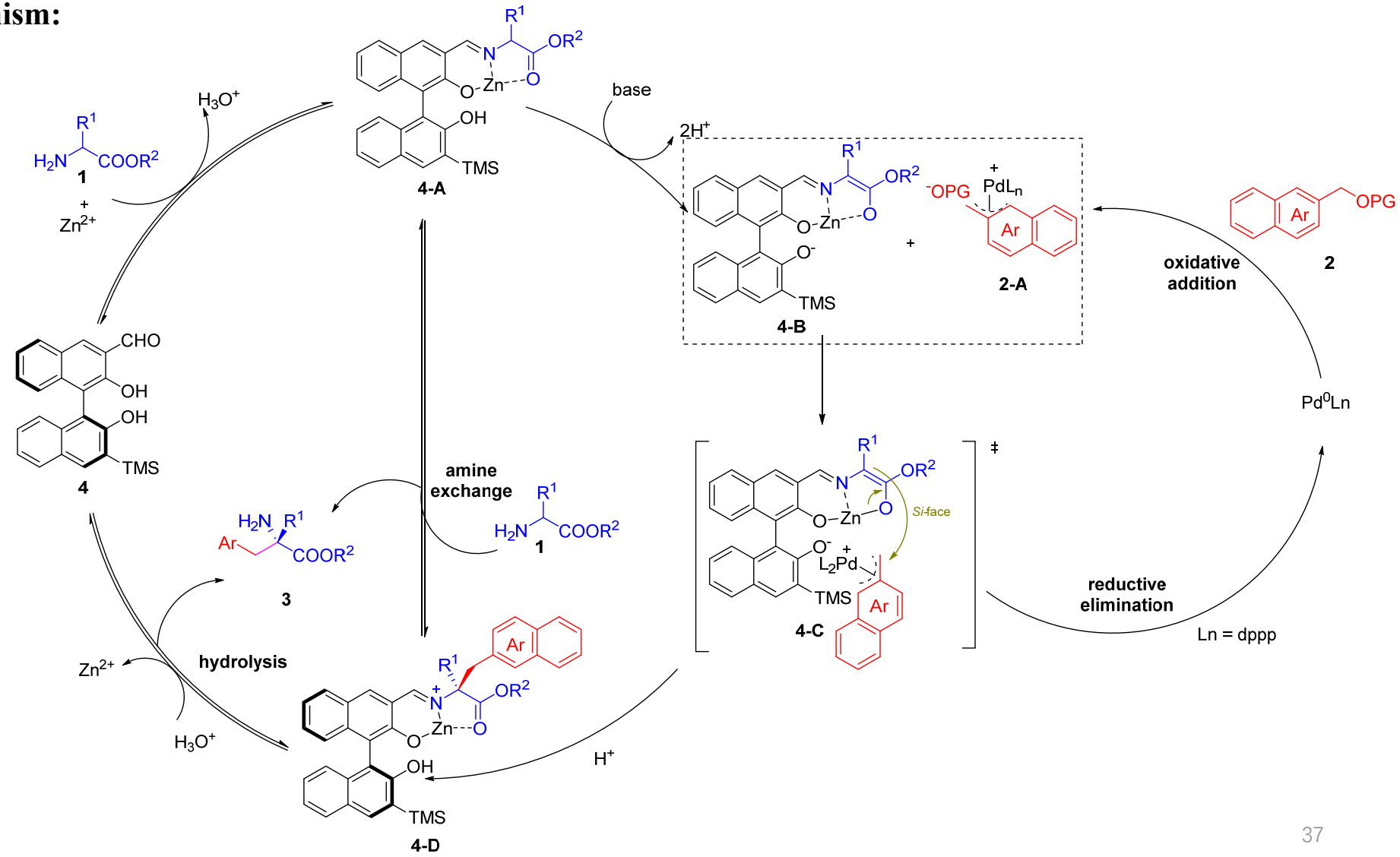


可能存在胺交换过程

Q.-X. Guo. et al. *Nat Commun.* **2022**, *13*, 2509.

不对称α-芳基化的烷基化反应

Proposed mechanism:



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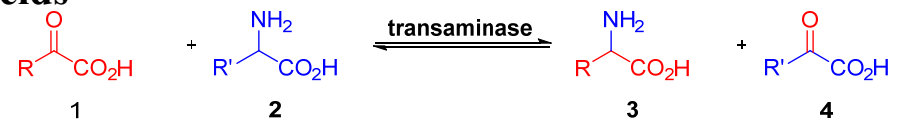
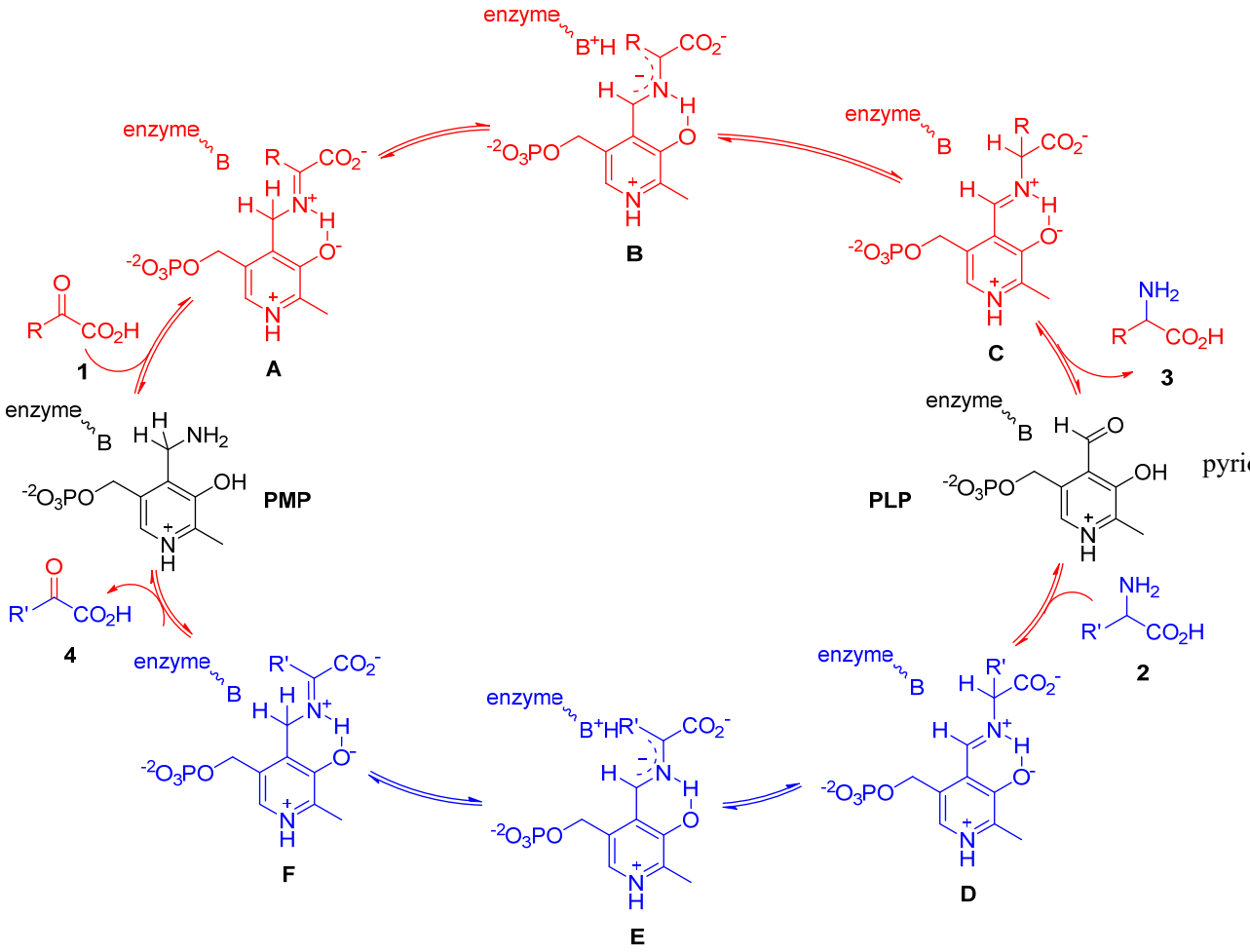
3.手性羰基催化剂在α-酮酸的转胺化反应中的应用

Biological Transamination of α-Keto Acids

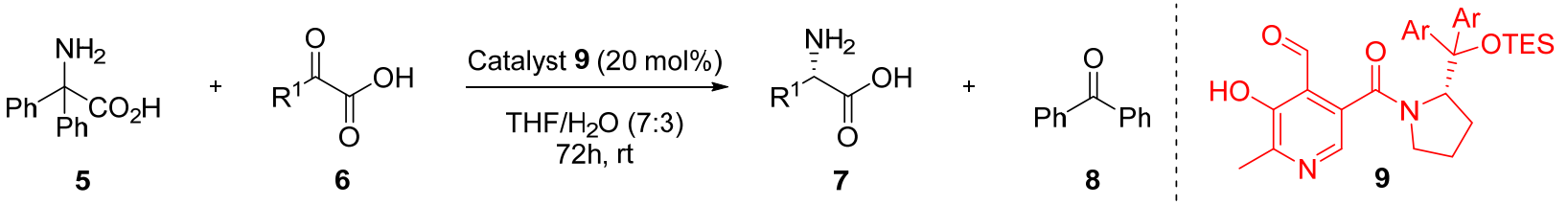


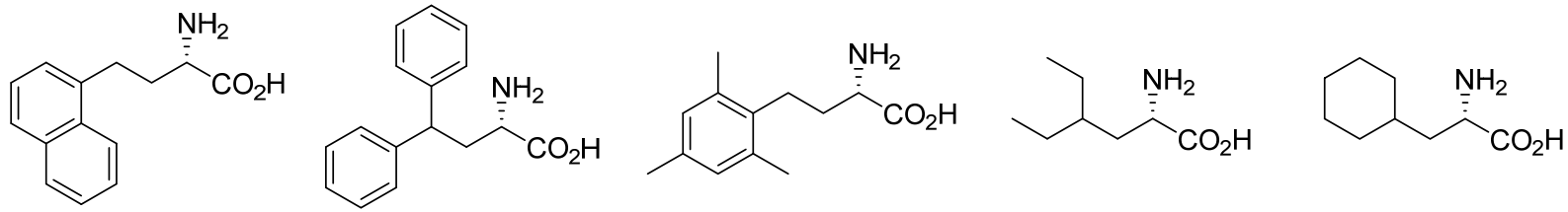
pyridoxamine 5′-phosphate (**PMP**)

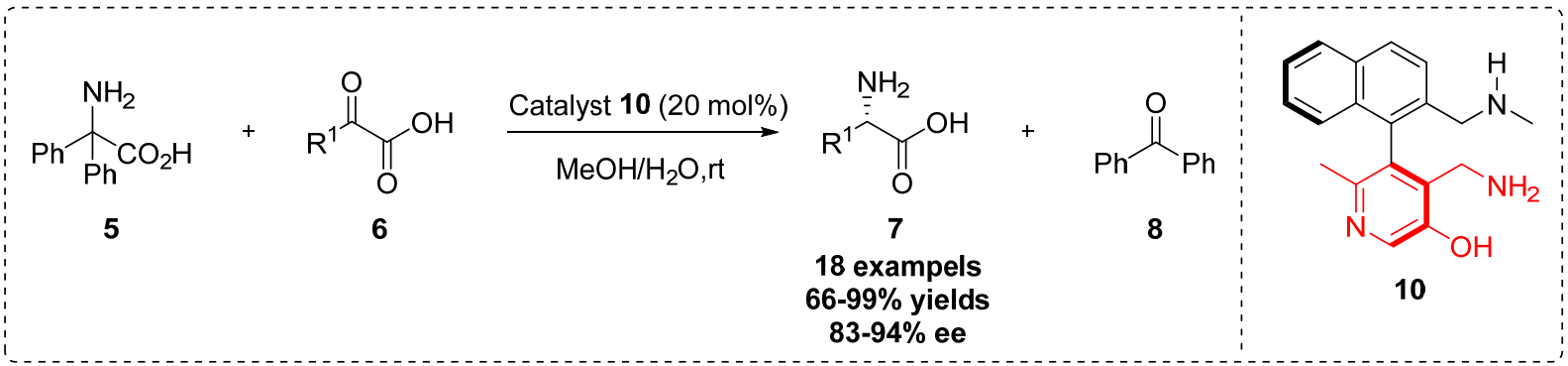


pyridoxal 5′-phosphate (**PLP**)

α-酮酸的转移胺化反应



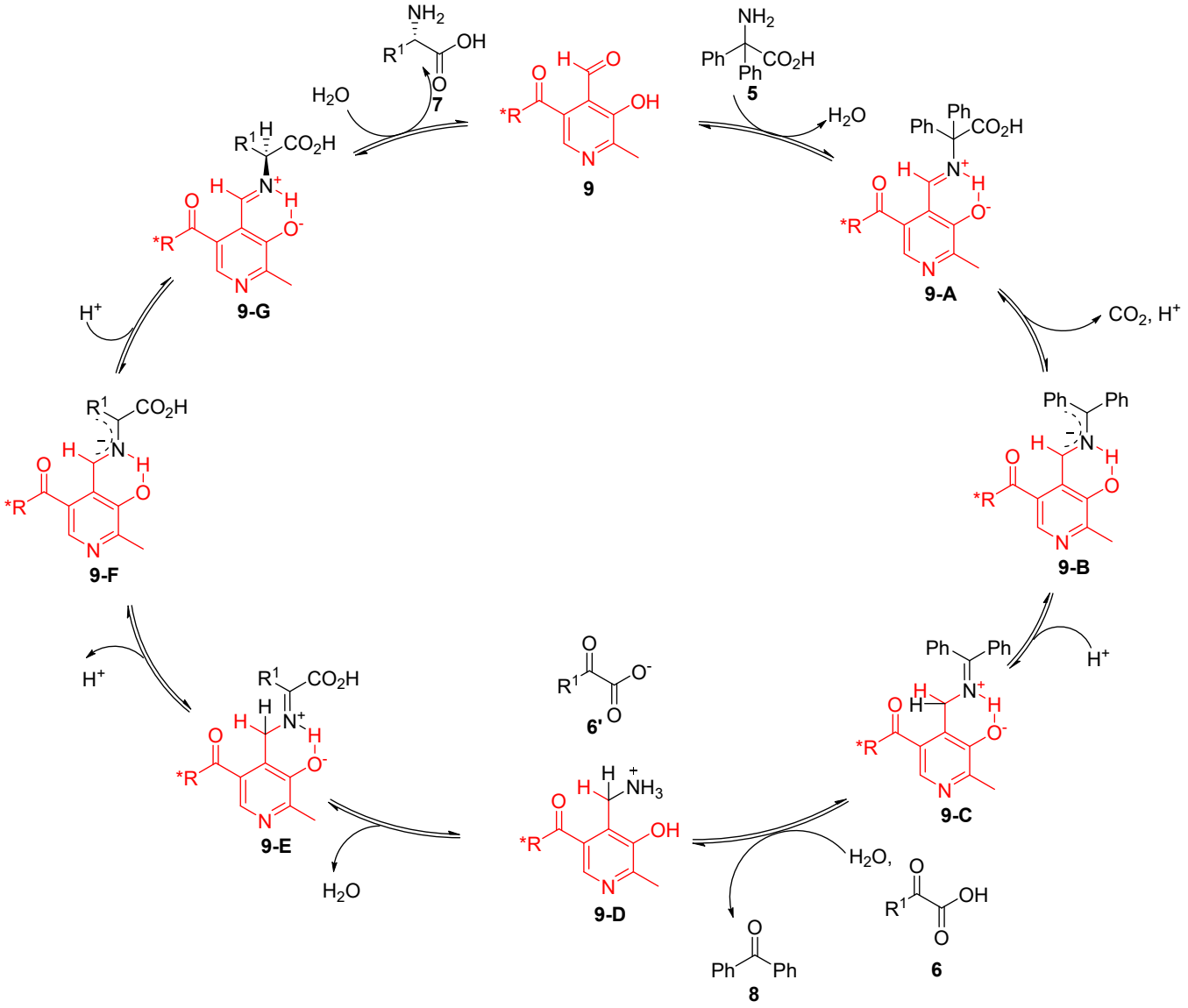




B. Zhao. et al. *Org. Lett.* **2015**, *17*, 5784–5787;
B. Zhao. et al. *J. Am. Chem. Soc.* **2016**, *138*, 34, 10730–10733.

α-酮酸的转移胺化反应

Proposed mechanism:



目录

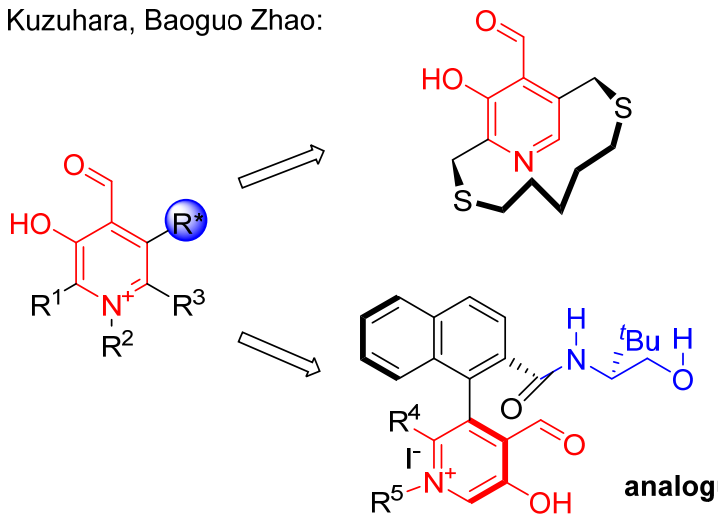
3. 总结与展望

总结：

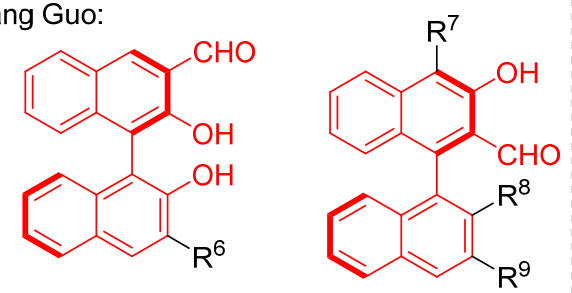
a) 手性羰基催化剂在胺的不对称α-C官能团化反应中的应用

手性羰基催化剂种类：

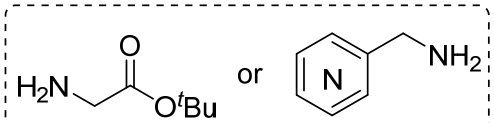
Kuzuhara, Baoguo Zhao:



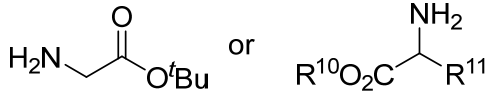
Qixiang Guo:



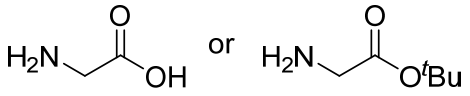
不对称催化反应类型：



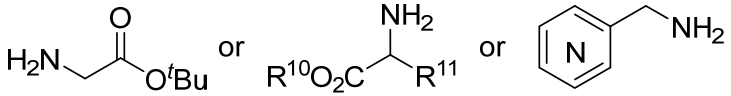
Mannich反应



共轭加成反应(Michael加成, 1,6-共轭加成)

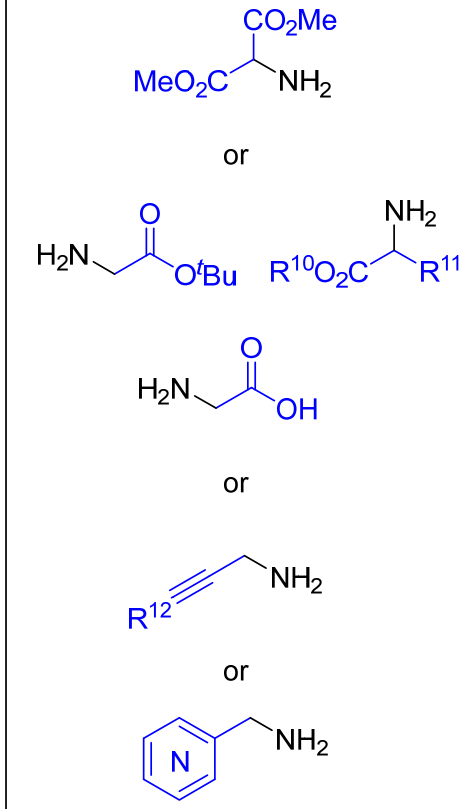


Aldol反应



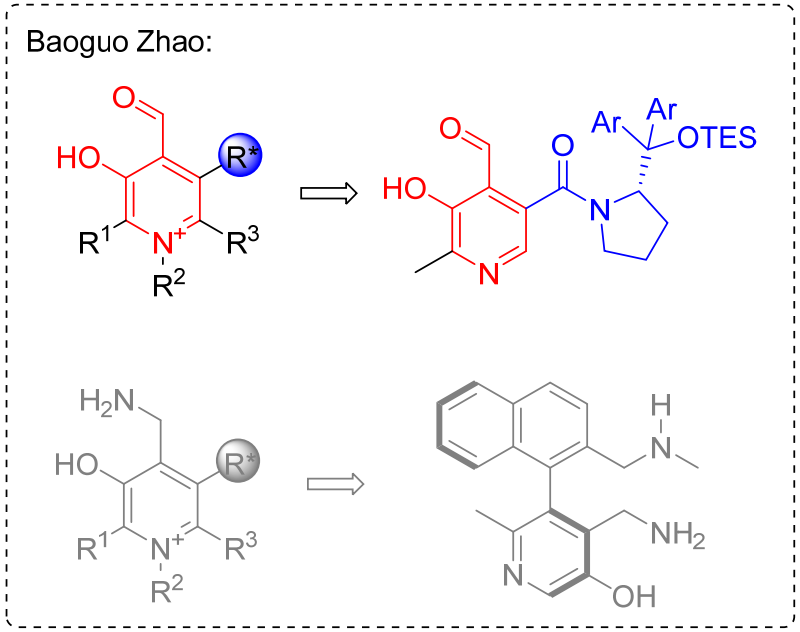
烷基化反应(α-烯丙基化, α-苄基化等)

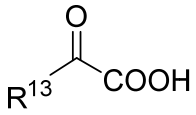
反应底物：



3. 总结与展望

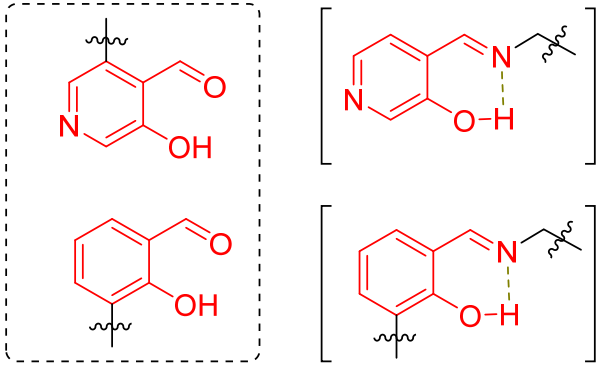
b) 手性羰基催化剂在α-酮酸的转移胺化反应中的应用





转移胺化反应

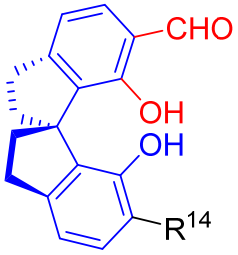
c) 手性羰基催化剂的关键结构



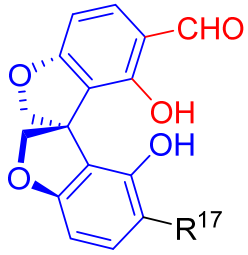
3. 总结与展望

展望：

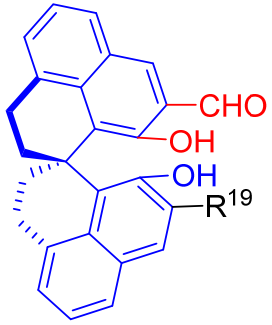
(1) 设计合成新的基于螺/轴结构的手性羰基催化剂



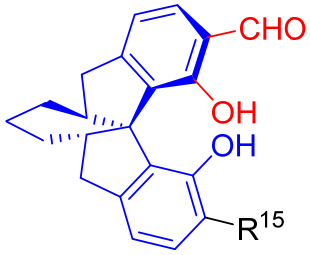
SPINOL



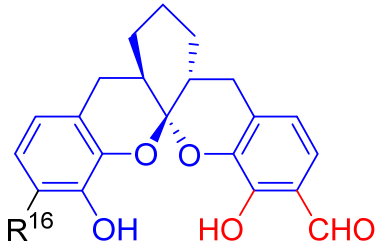
O-SPINOL



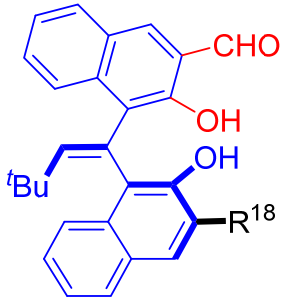
SPHENOL



chf-SPINOL



SKP



EBINOL

(2) 拓展胺类底物范围

请各位老师和同学

批评指正！