Literature Report 6

Direct Enantioselective *α*-C−H Conjugate Addition of Propargylamines to *α,β*-Unsaturated Ketones *via* Carbonyl Catalysis

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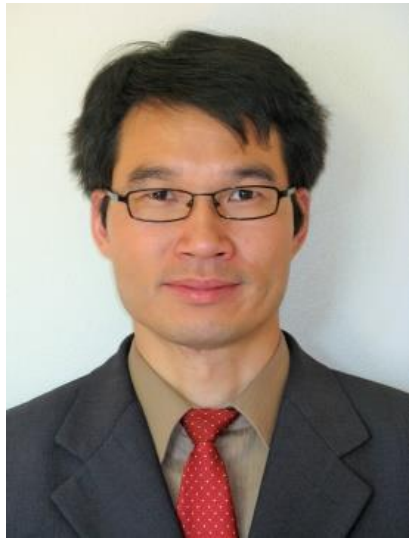
Checker: Yan-Jiang Yu
Date: 2024-10-21

Zhang, R.; Xu, J.; Liu, S.; Si, S.; Chen, J.; Wang, L.; Chen, W.-W.; Zhao, B.
J. Am. Chem. Soc. **2024**, *146,* 25927

CV of Prof. Baoguo Zhao (赵宝国)



Education & Experience:

- **1992-1996** B.S., Wuhan University
- **1999-2002** M.S., Nanjing University
- **2003-2006** Ph.D., Shanghai Institute of Organic Chemistry
- **2006-2011** Postdoc., Colorado State University
- **2011-Present** Professor, Shanghai Normal University

Research:

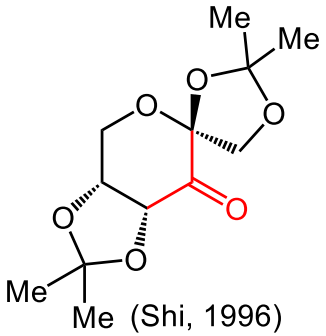
- **Biomimetic Asymmetric Catalysis**
- **Biomimetic Total Synthesis**
- **Development of New Reaction**

Contents

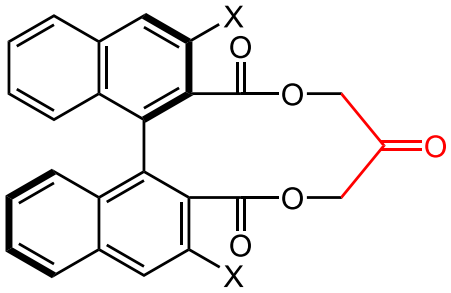
Introduction

Representative Chiral Ketone and Chiral Aldehyde Catalysts

a) Chiral ketones for catalytic asymmetric epoxidation

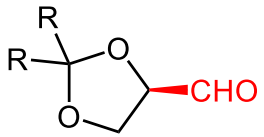


(Shi, 1996)

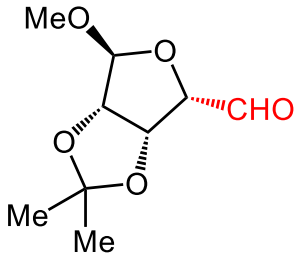


(Yang, 1996)

b) Chiral aldehydes as tethering catalysts

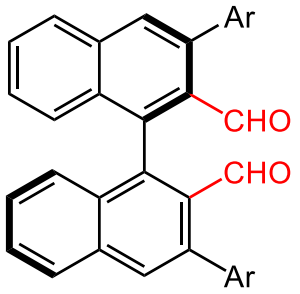


(Beauchemin, 2011)

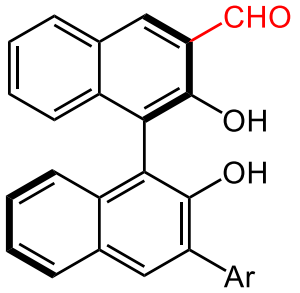


(Beauchemin, 2013)

c) Chiral aldehydes for catalytic asymmetric α-functionalization of primary amines



(Guo, 2014)



(Guo, 2014)

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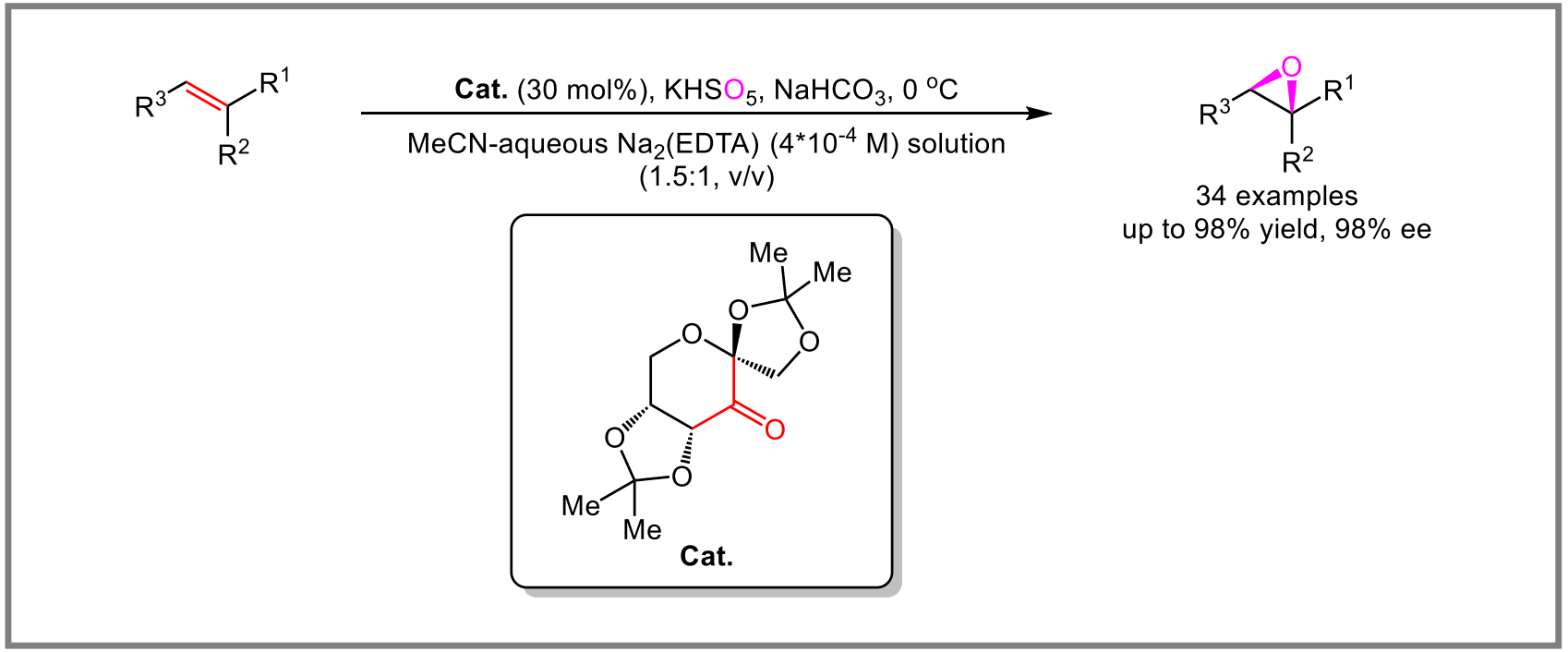
Introduction

Chiral Ketones for Catalytic Asymmetric Epoxidation



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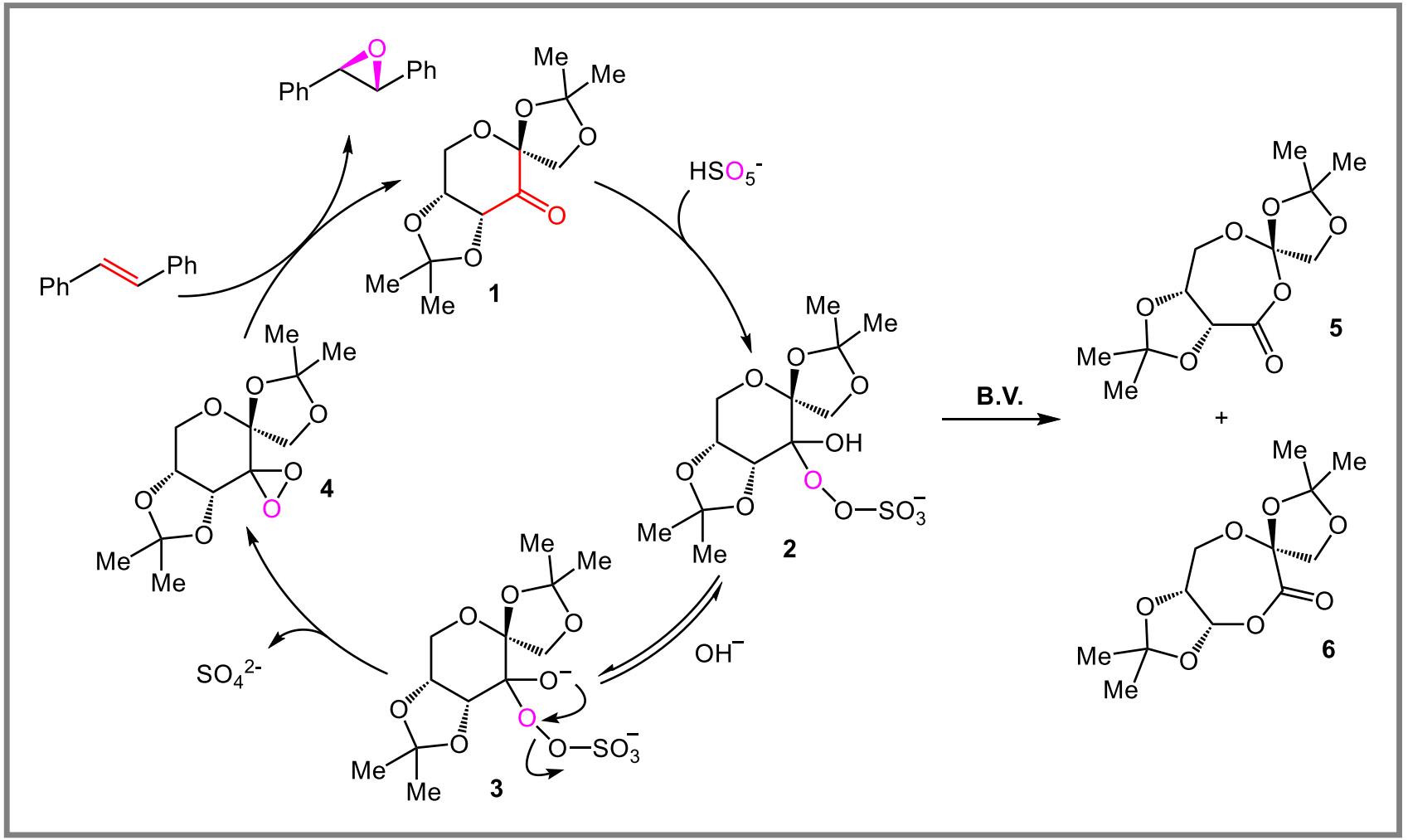

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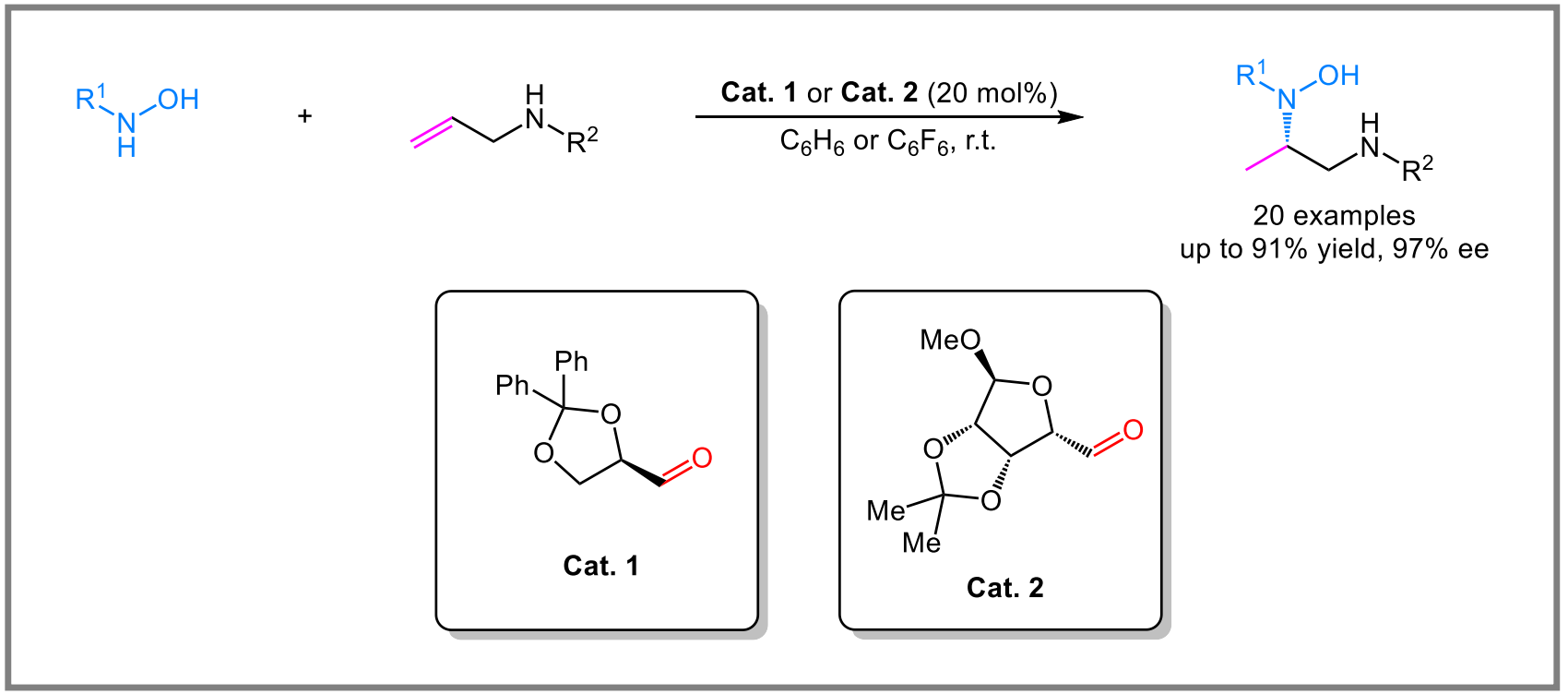
Chiral Aldehydes as Tethering Catalyst



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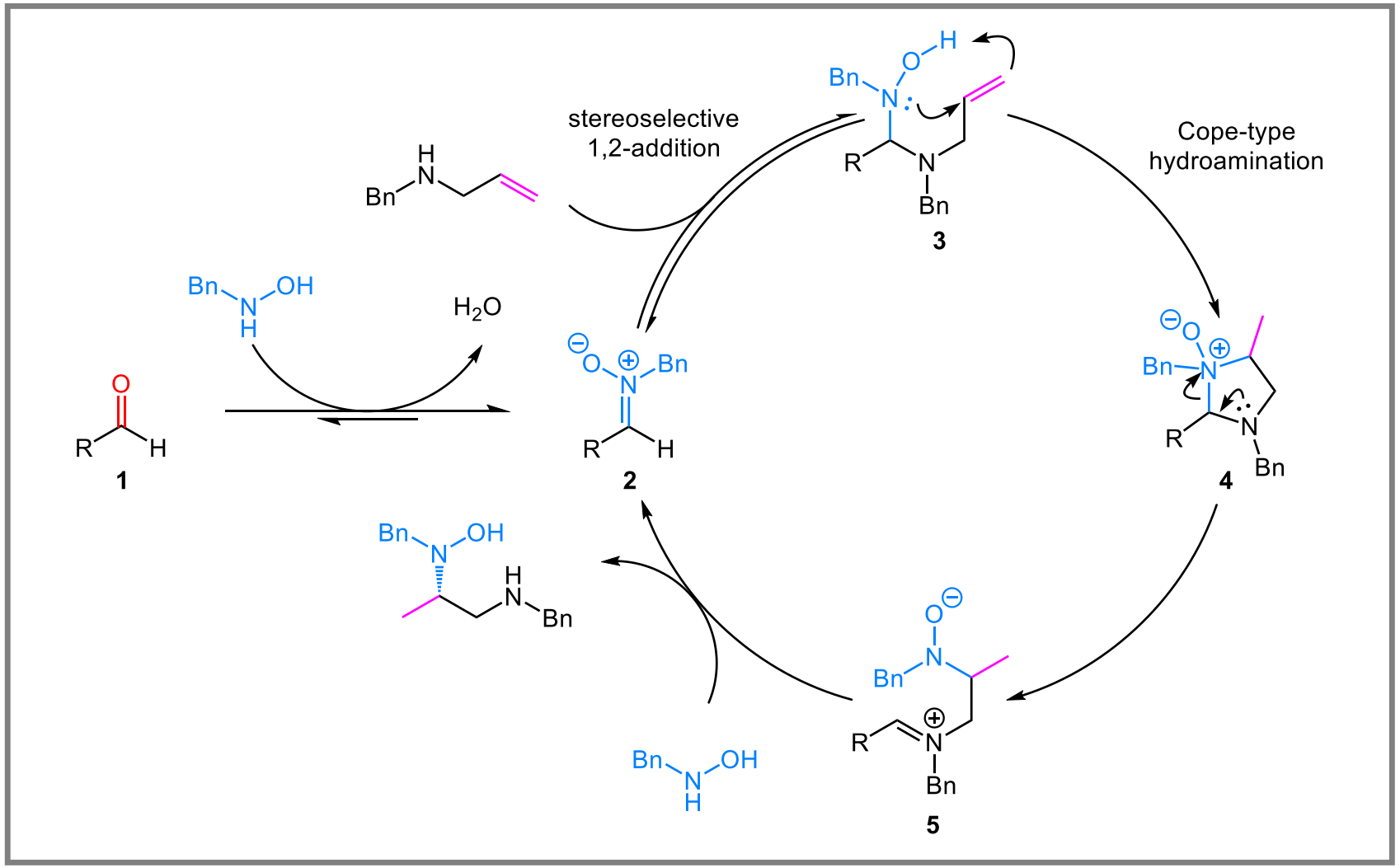

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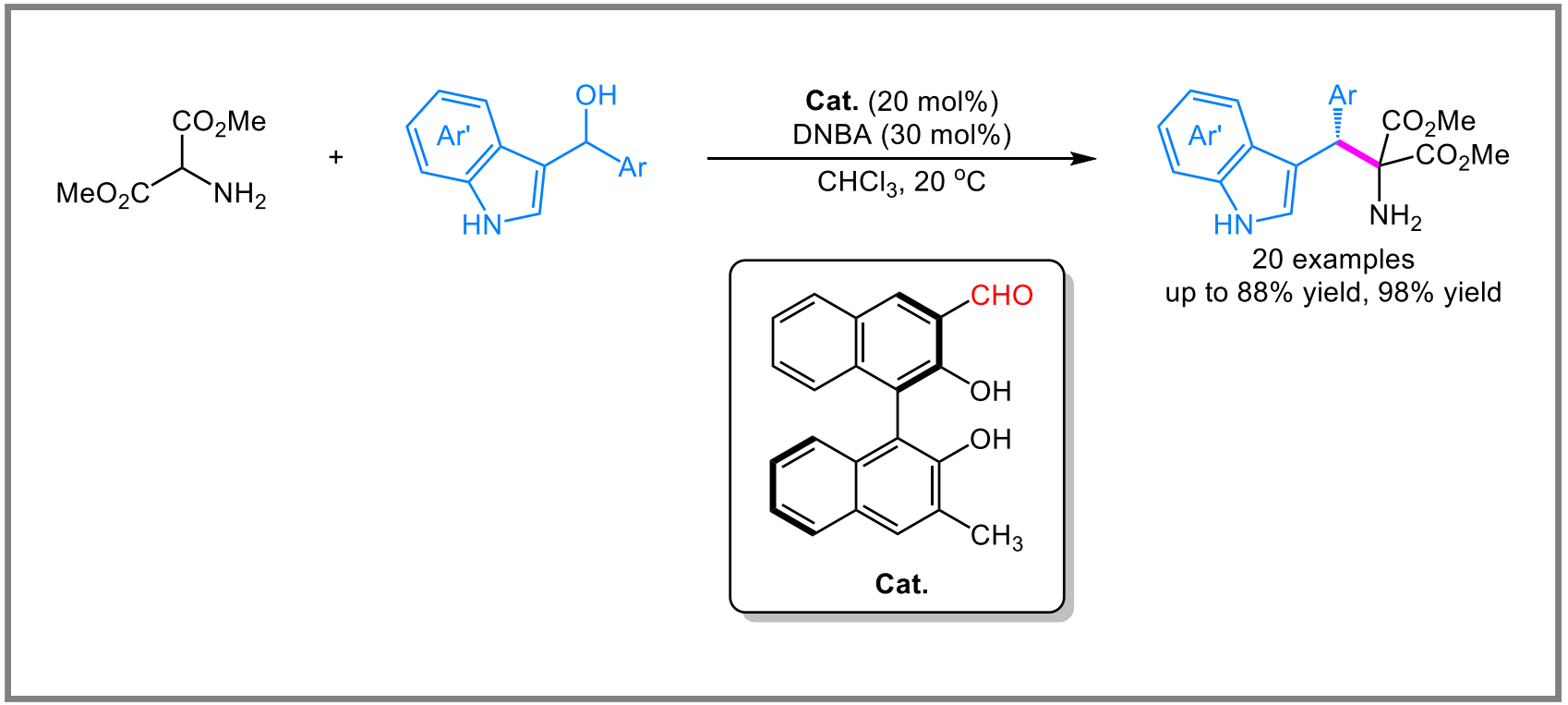
Chiral Aldehydes for Catalytic Asymmetric *a*-Functionalization of Primary Amines



Xu, B.; Shi, L.-L.; Zhang, Y.-Z.; Wu, Z.-J.; Fu, L.-N.; Luo, C.-Q.; Peng, Y.-G.; Guo, Q.-X. *Chem. Sci.* **2014**, *5*, 1988

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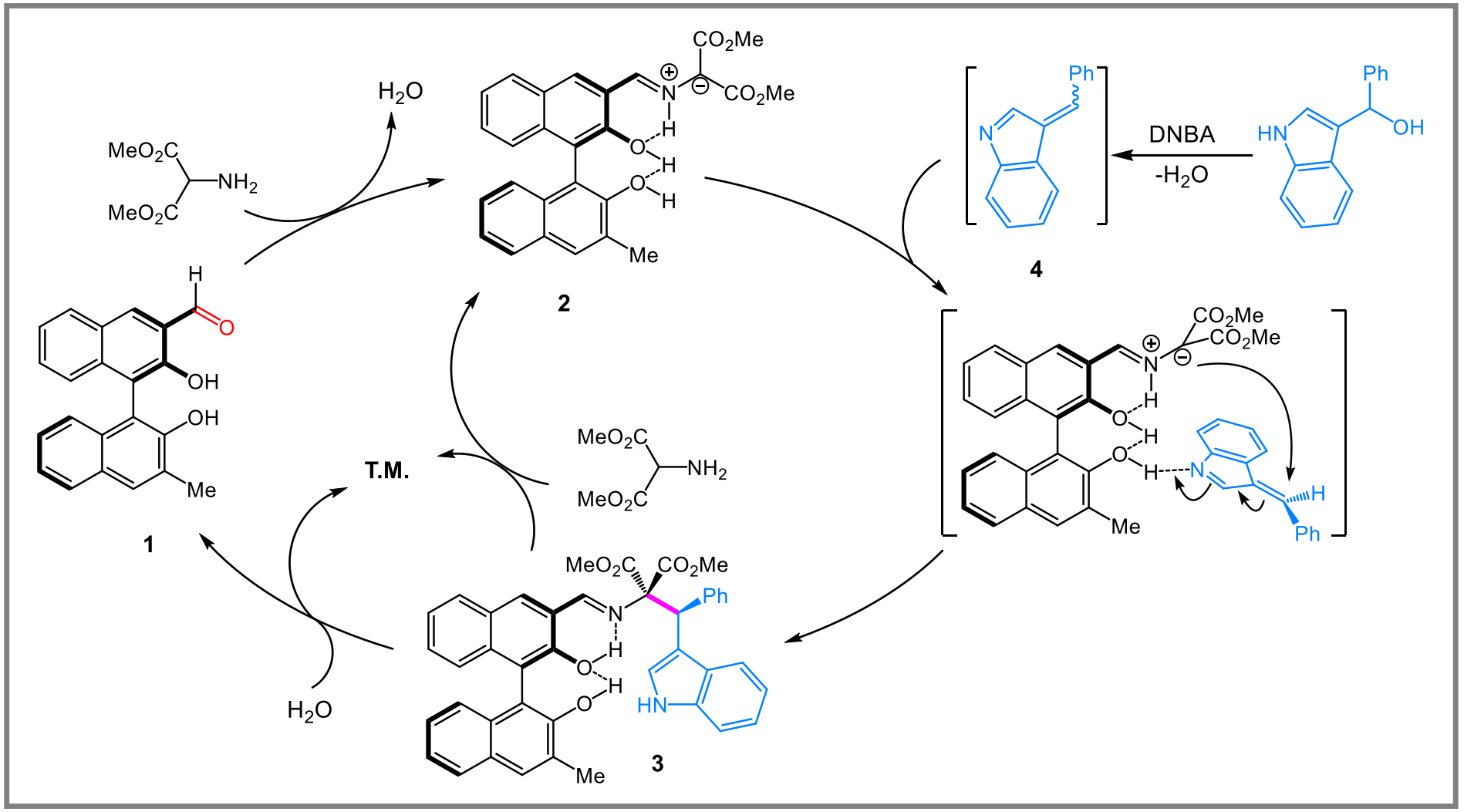

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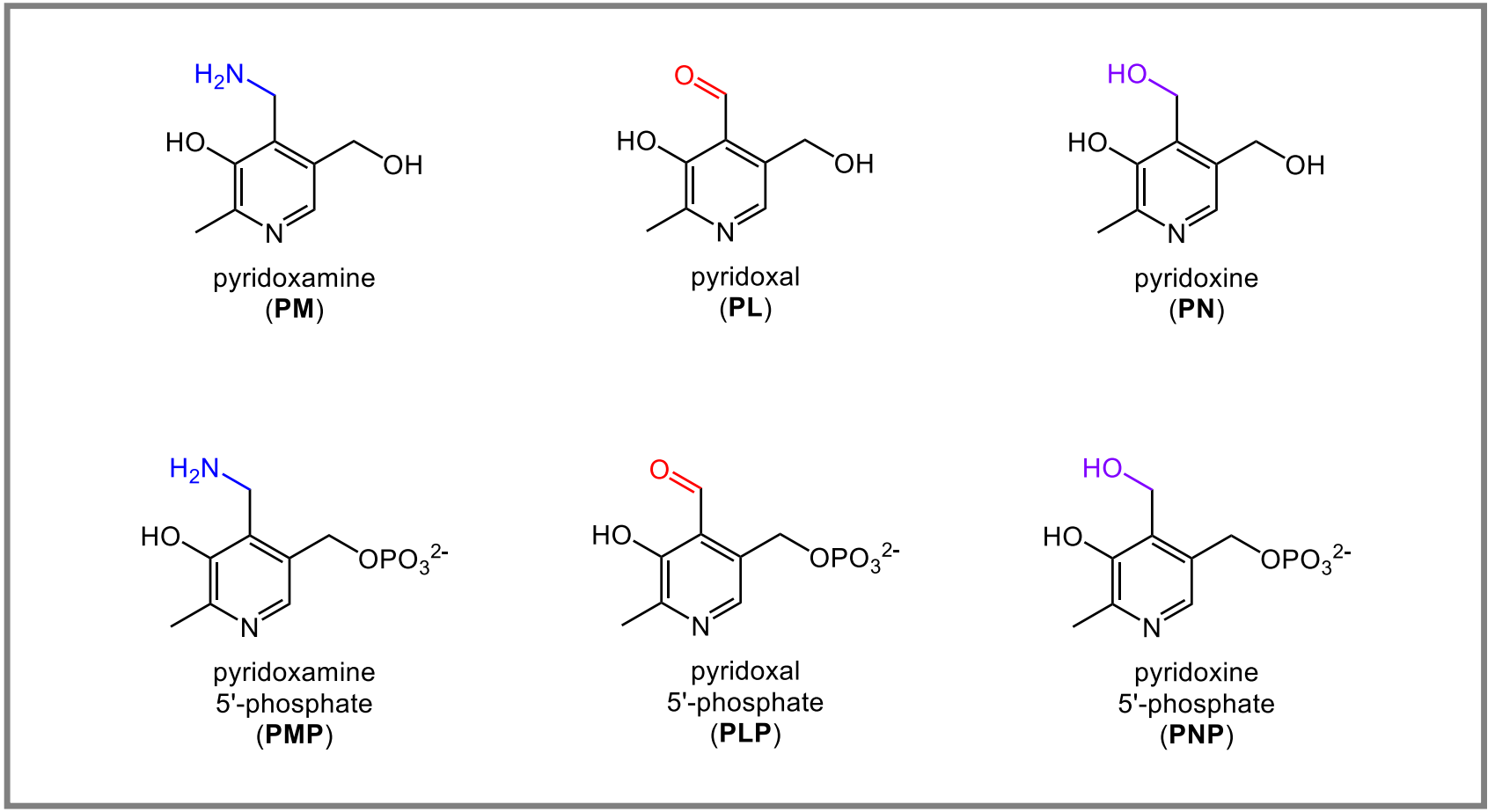
Vitamin B_6 Family



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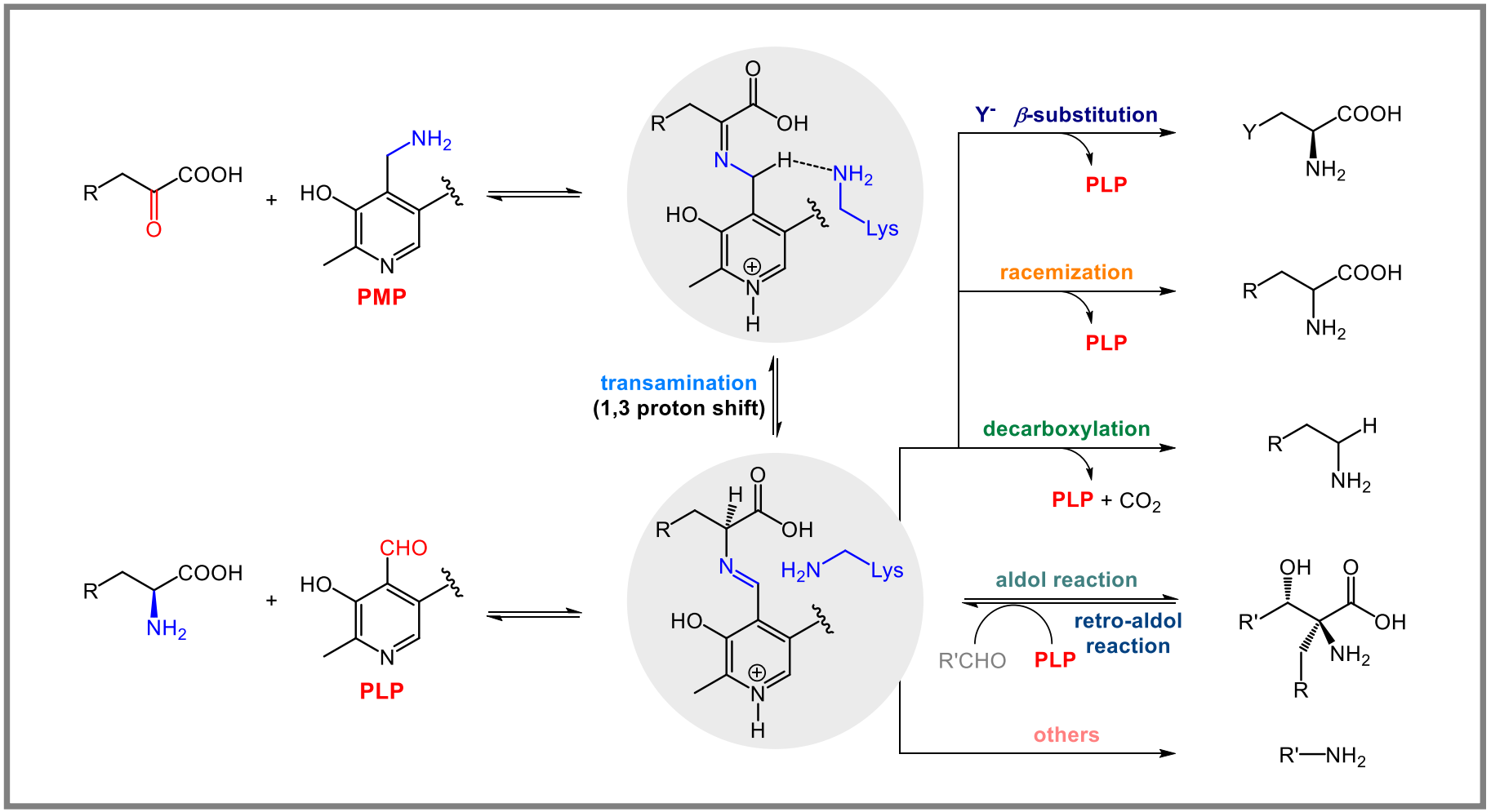
Vitamin B_6 Mediated Biological Transformations



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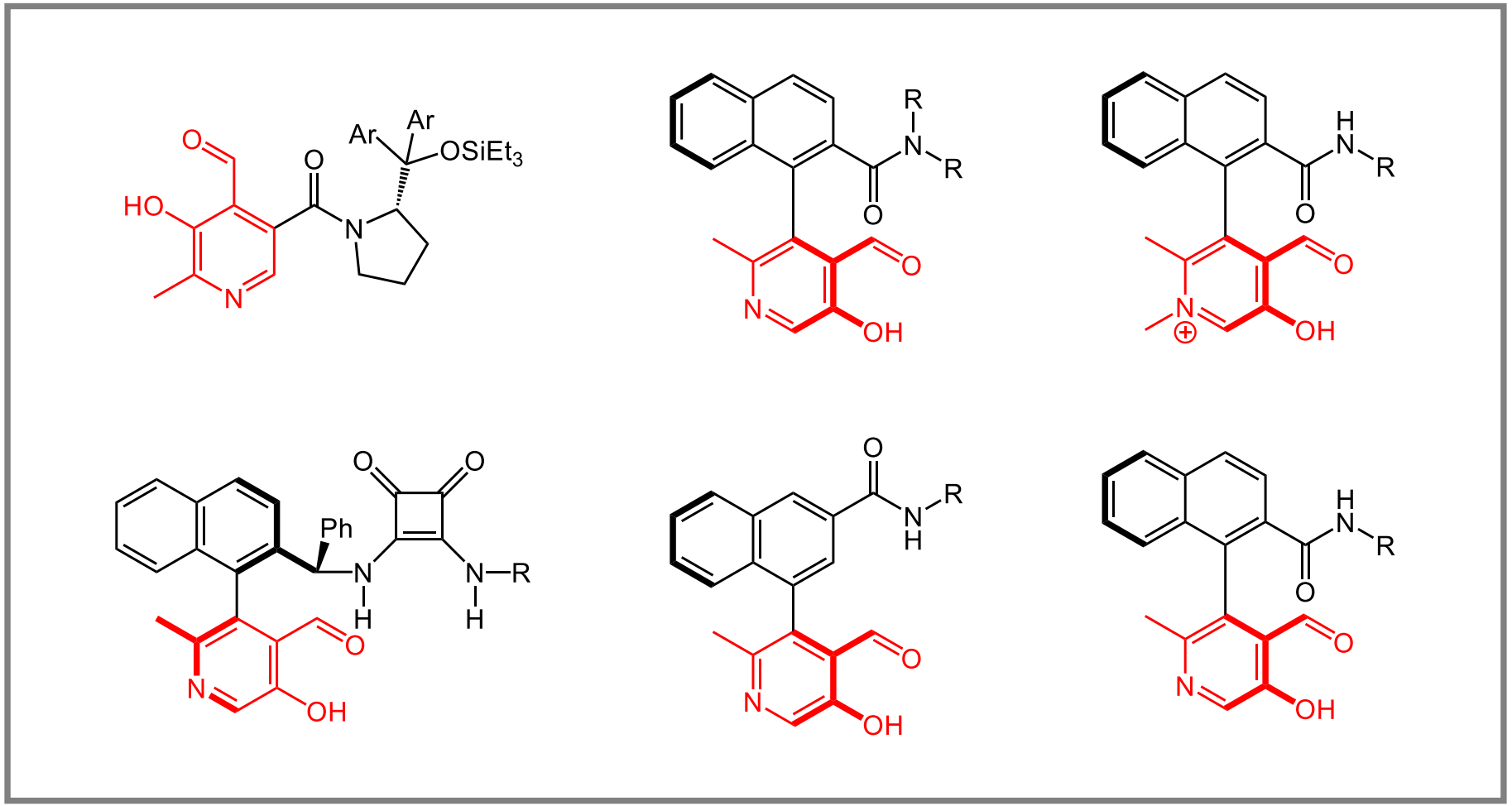
Introduction

Representative Vitamin B_6 Based Catalysts



Xiao, X.; Zhao, B. *Acc. Chem. Res.* **2023**, *56,* 1097

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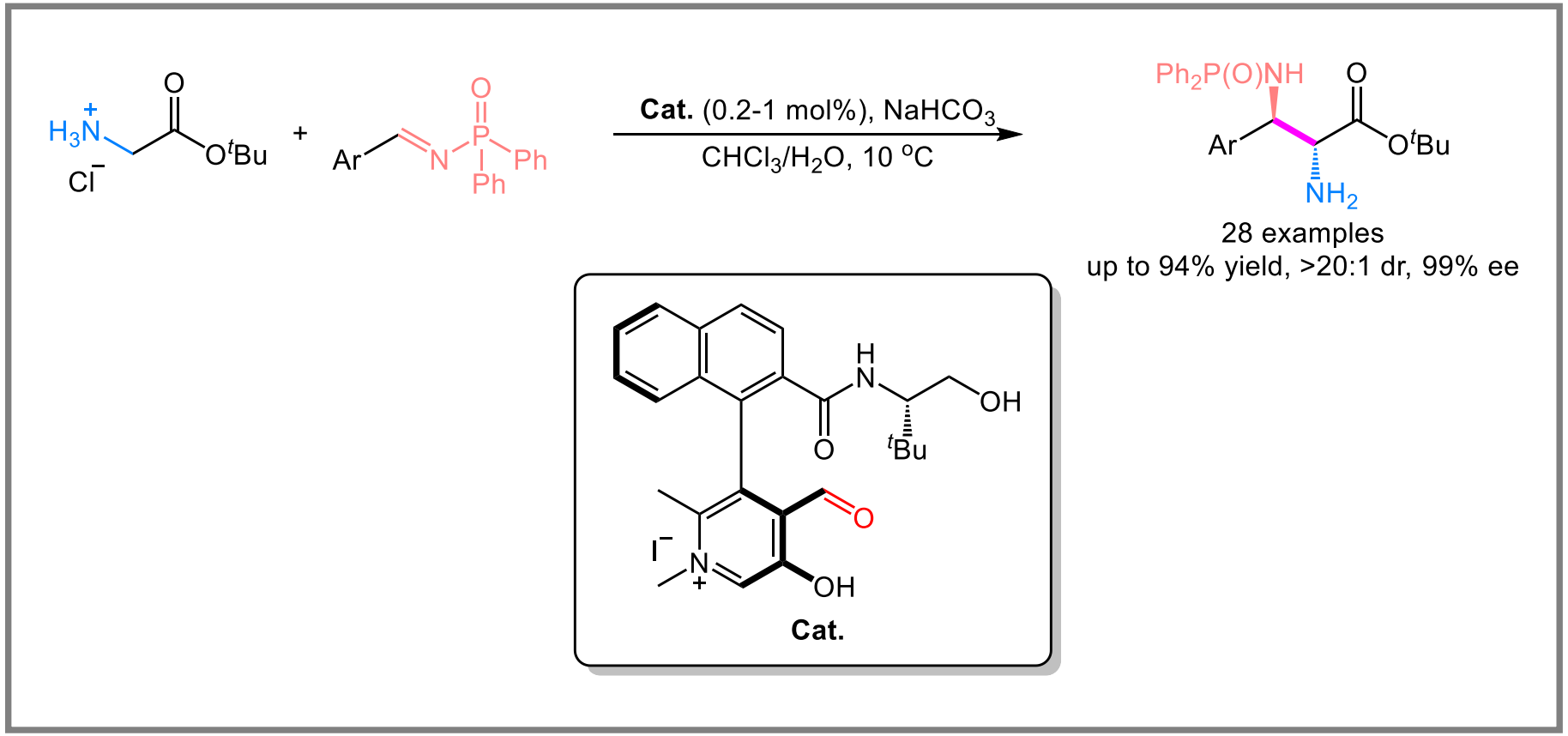
Asymmetric Biomimetic Carbonyl Catalysis



Chen, J.; Gong, X.; Li, J.; Li, Y.; Ma, J.; Hou, C.; Zhao, G.; Yuan, W.; Zhao, B. *Science* **2018**, *360,* 1438

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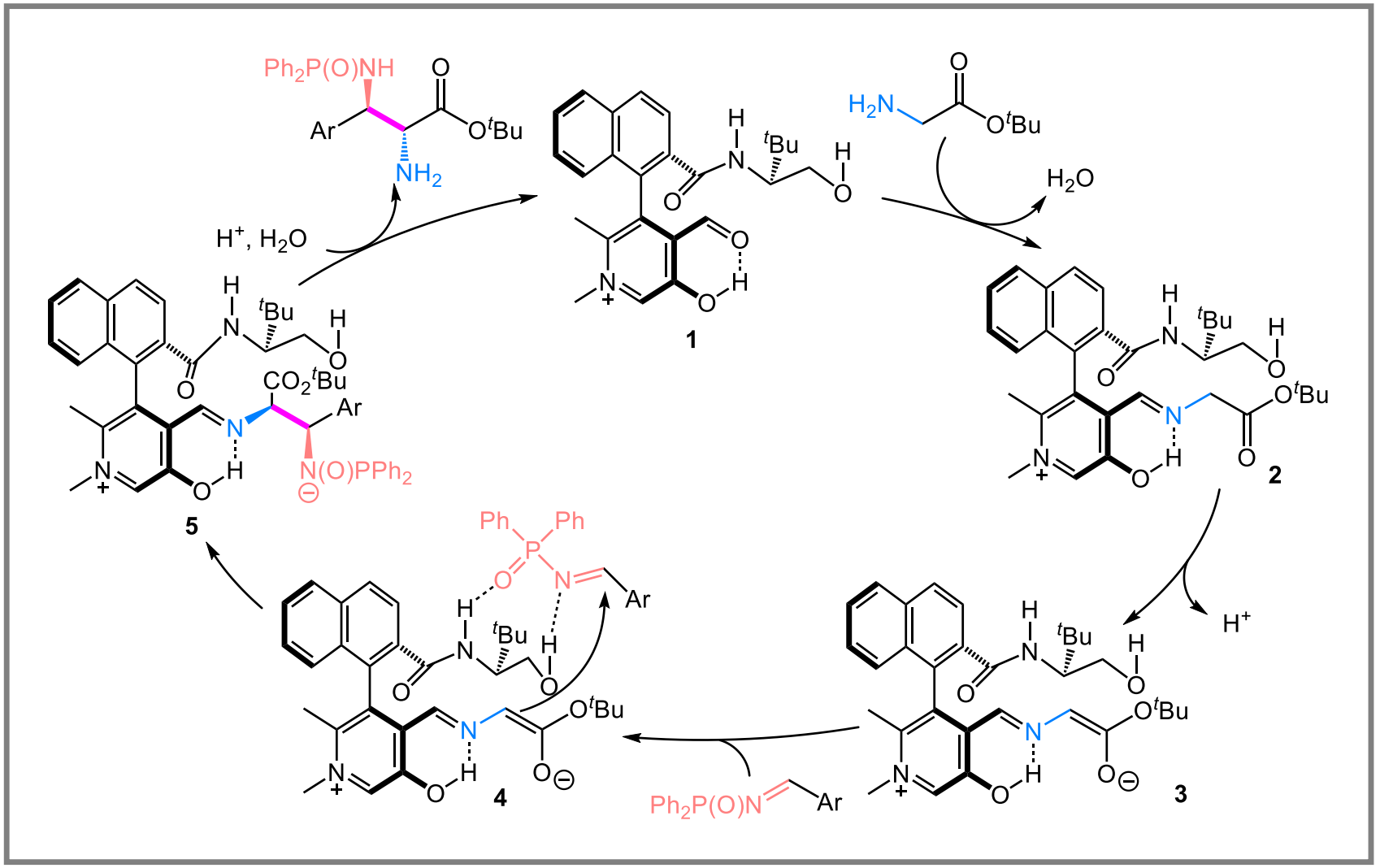

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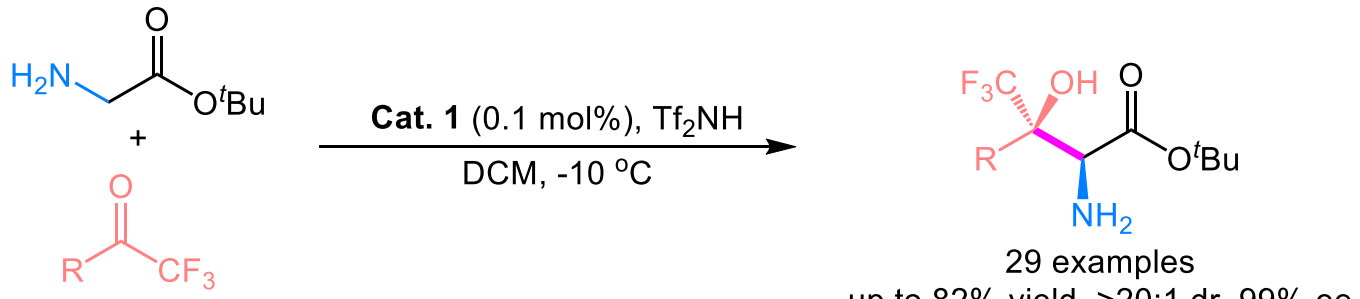
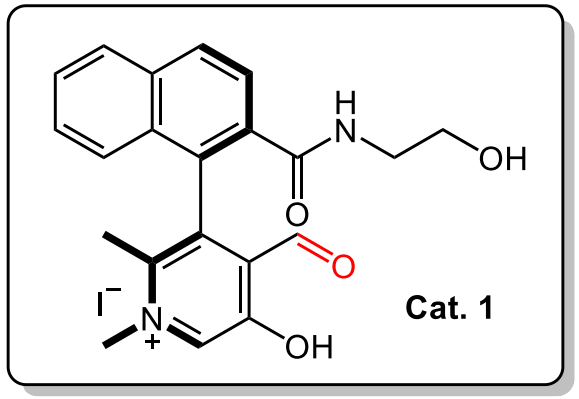
Asymmetric Biomimetic Carbonyl Catalysis





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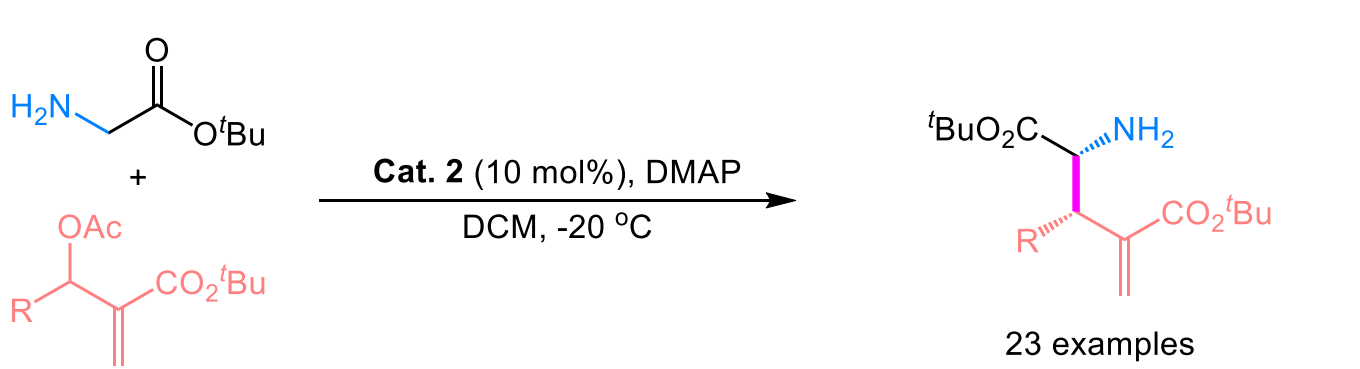

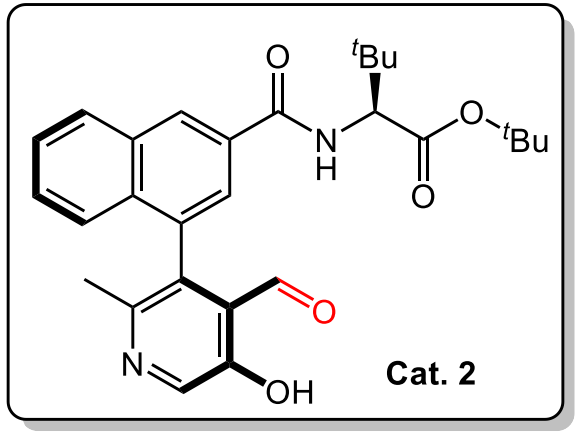

Ma, J.; Gao, B.; Song, G.; Zhang, R.; Chen, W.-W.; Zhao, B. *Angew. Chem. Int. Ed.* **2022**, *61*, e202200850

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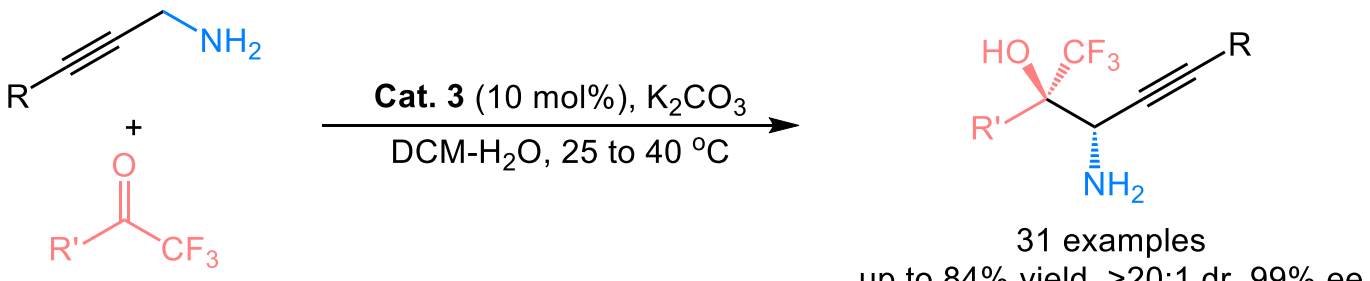
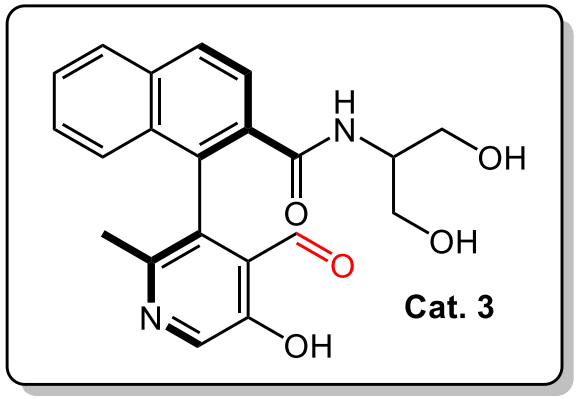
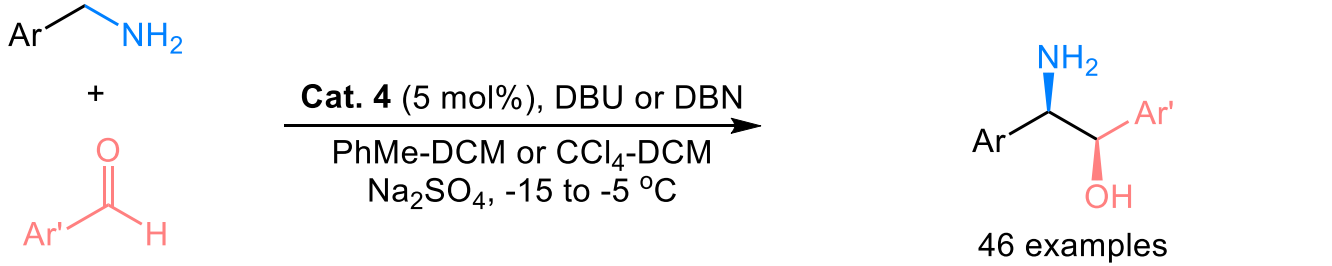
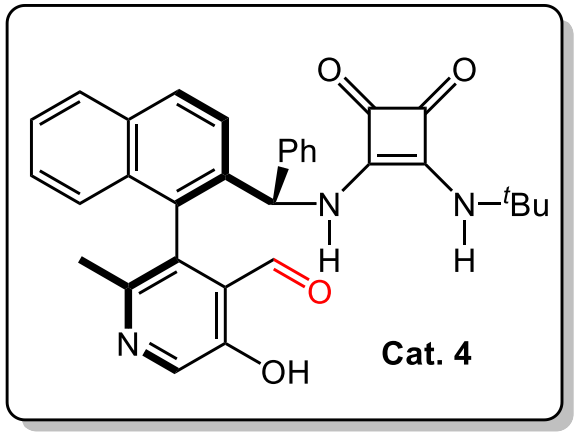
Asymmetric Biomimetic Carbonyl Catalysis





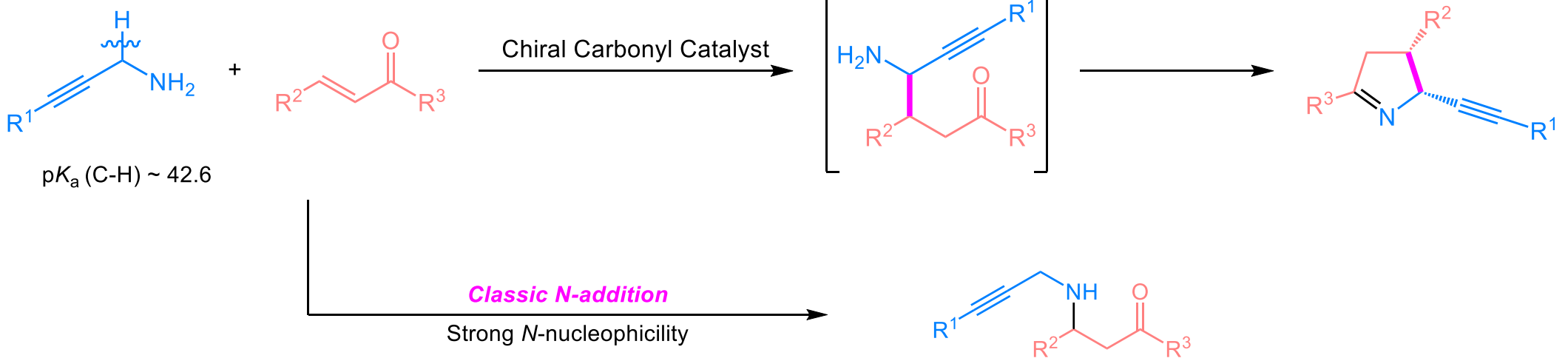
Ji, P.; Liu, X.; Xu, J.; Zhang, X.; Guo, J.; Chen, W.-W.; Zhao, B. *Angew. Chem. Int. Ed.* **2022,** *61*, e202206111





Hou, C.; Peng, B.; Ye, S.; Yin, Z.; Cao, J.; Xiao, X.; Zhao, B. *Nat. Catal.* **2022**, *5,* 1061

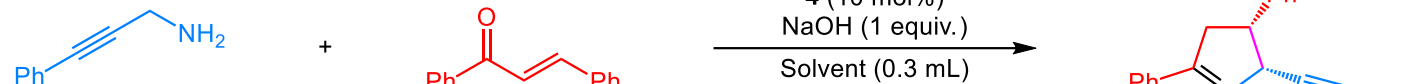
Project Synopsis



Two Challenges:

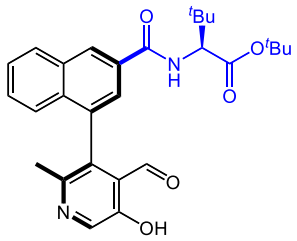
1. ***Low acidity of a C-H bonds***
2. ***Interference of classic N-addition***

Optimization of the Reaction Conditions

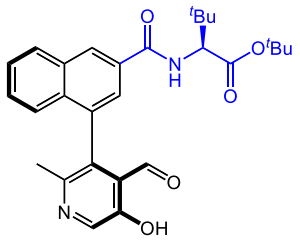


Entry	4	Solvent	Yield (%)	Dr	Ee (%)
1	**4a**	DCM	41	10:1	83
2	**4a**	Hexane	80	>20:1	81
3[b]	-	Hexane	-	-	-
4	**4b**	Hexane	61	19:1	-69
5	**4c**	Hexane	55	>20:1	39
6	**4d**	Hexane	42	>20:1	66
7	**4e**	Hexane	51	5:1	94
8	**4f**	Hexane	55	>20:1	98
9	**4g**	Hexane	45	>20:1	95
10	**4h**	Hexane	50	>20:1	98

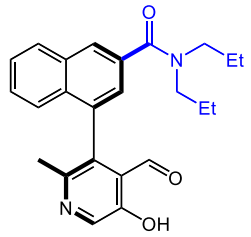
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.10 mmol), **4** (0.010mmol), H_2O (40 μL) and NaOH (0.10 mmol) in solvent (0.30 mL) at 35 °C for 24 h unless otherwise stated. The ee values were determined by chiral HPLC analysis. The dr values were determined by ^{1}H NMR. [b]Only *N*-addition product was observed. [c]2 equivalents of **1a**. [d]20 μL of H_2O. [e]80 μL of H_2O.



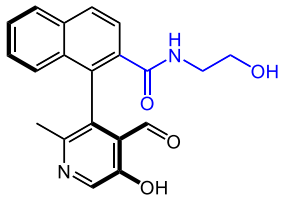
(*R*,*S*)-**4a**



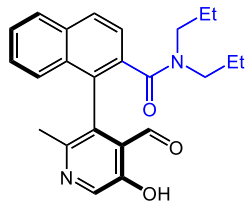
(*S*,*S*)-**4b**



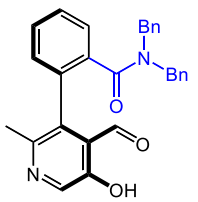
(*R*)-**4c**



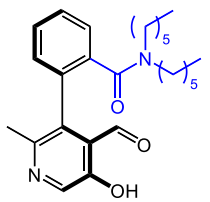
(*R*)-**4d**



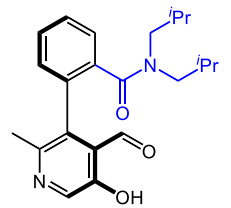
(*R*)-**4e**



(*R*)-**4f**

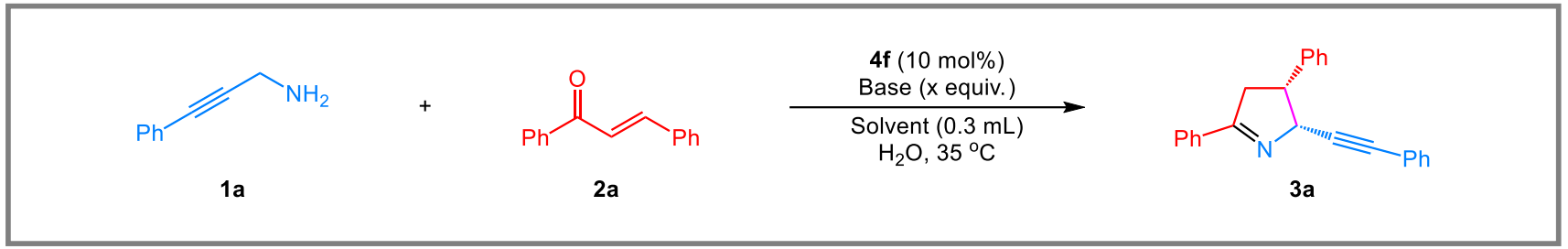


(*R*)-**4g**



(*R*)-**4h**

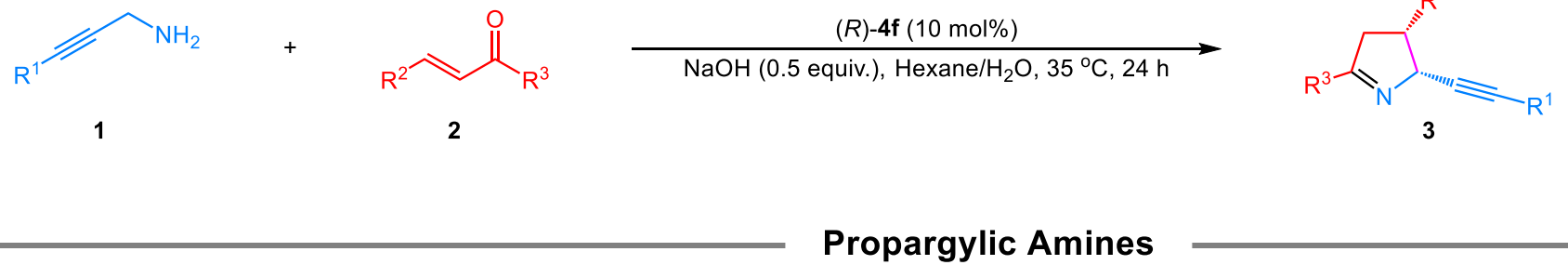
Optimization of the Reaction Conditions



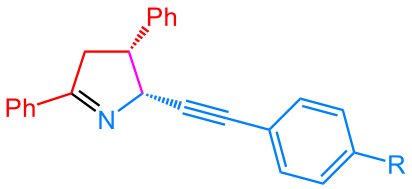
Entry	Solvent	Base (eq.)	H_2O (μL)	Yield (%)	Dr	Ee (%)
11	Hexane	NaOH (1.0)	40	55	>20:1	98
12	Toluene	NaOH (1.0)	40	44	>20:1	98
13	THF	NaOH (1.0)	40	35	>20:1	92
14	Hexane	NaOH (0.5)	40	72	>20:1	98
15	Hexane	LiOH (0.5)	40	57	>20:1	98
16	Hexane	KOH (0.5)	40	70	13:1	98
17	Hexane	CsOH (0.5)	40	68	10:1	98
18[c]	Hexane	NaOH (0.5)	40	83	>20:1	98
19[c]	Hexane	NaOH (0.5)	20	70	19:1	97
20[c]	Hexane	NaOH (0.5)	80	86	>20:1	98

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.10 mmol), **4** (0.010mmol), H_2O (40 μL) and base (0.10 mmol) in solvent (0.30 mL) at 35 °C for 24 h unless otherwise stated. The ee values were determined by chiral HPLC analysis. The dr values were determined by ^{1}H NMR. [b]Only *N*-addition product was observed. [c]2 equivalents of **1a**.

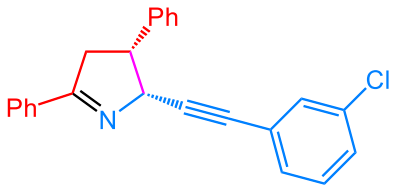
Substrate Scope



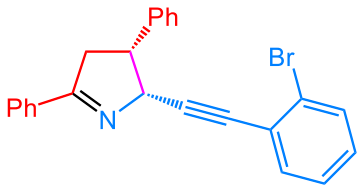
Propargylic Amines



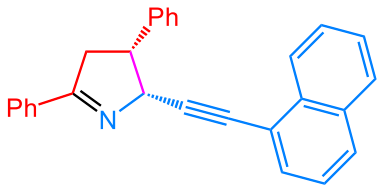
3a (R = H): 86%, >20:1 dr, 98% ee
3b (R = Me): 78%, >20:1 dr, 98% ee
3c (R = F): 92%, >20:1 dr, 99% ee



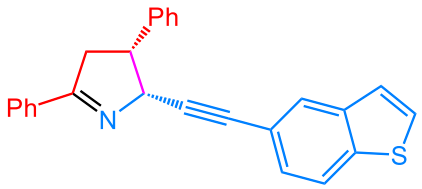
3d: 92%, >20:1 dr, 99% ee



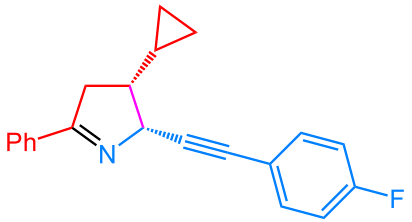
3e: 91%, >20:1 dr, 98% ee



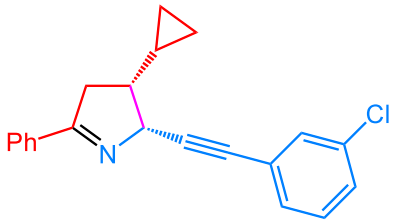
3f: 62%, >20:1 dr, 98% ee



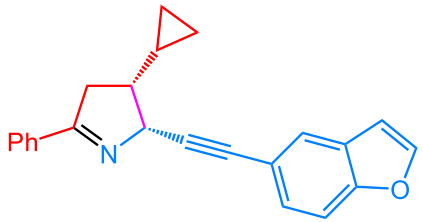
3g: 62%, >20:1 dr, 98% ee



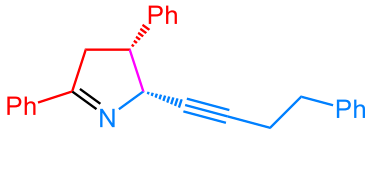
3h: 68%, >20:1 dr, 92% ee



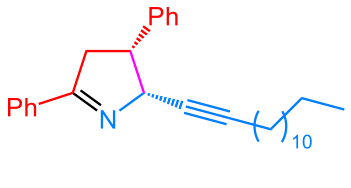
3i: 65%, >20:1 dr, 92% ee



3j: 66%, >20:1 dr, 93% ee



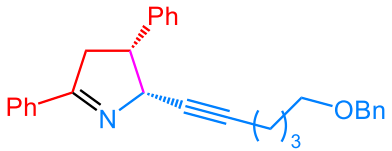
3k: 68%, >20:1 dr, 99% ee



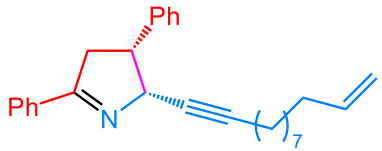
3l: 65%, >20:1 dr, 99% ee

Substrate Scope

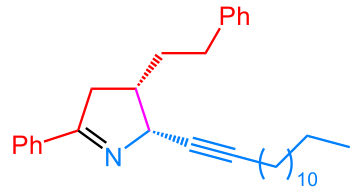
Propargylic Amines



3m[b]: 65%, >20:1 dr, 98% ee

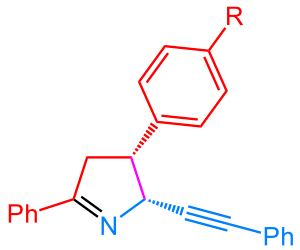


3n[b]: 60%, >20:1 dr, 98% ee

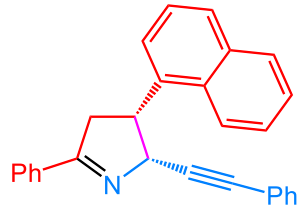


3o[c]: 62%, >20:1 dr, 98% ee

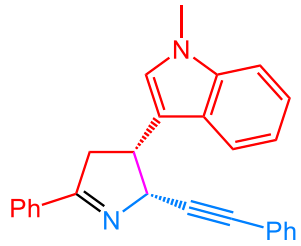
α,β-Unsaturated Ketones



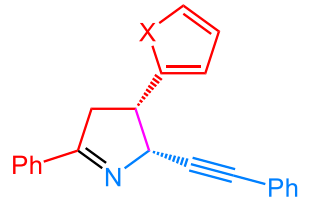
3p (R = F): 88%, >20:1 dr, 98% ee
3q (R = Cl): 82%, >20:1 dr, 98% ee
3r (R = Br): 78%, >20:1 dr, 98% ee
3s (R = NO_2): 43%, >20:1 dr, 97% ee
3t (R = OH): 35%, >20:1 dr, 31% ee



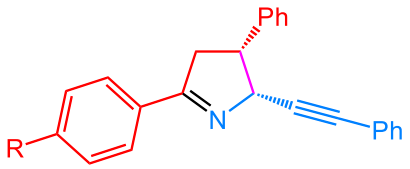
3u: 81%, >20:1 dr, 98% ee



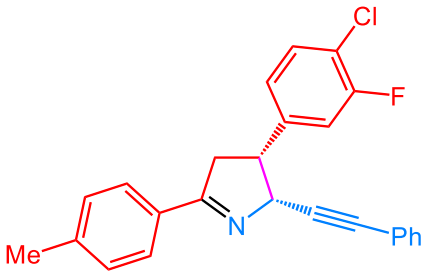
3v: 72%, >20:1 dr, 98% ee



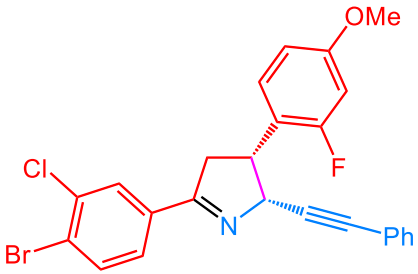
3w (X = O): 91%, >20:1 dr, 99% ee
3x (X = S): 90%, >20:1 dr, 98% ee



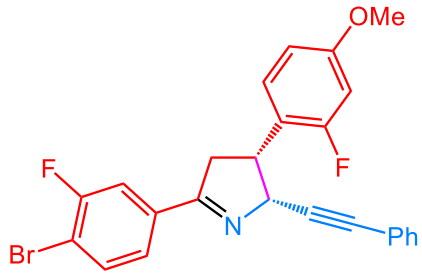
3y (R = F): 86%, >20:1 dr, 98% ee
3z (R = OMe): 70%, >20:1 dr, 98% ee



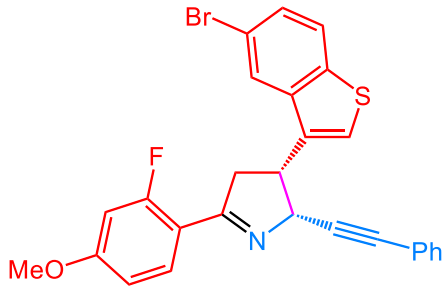
3aa: 75%, >20:1 dr, 99% ee



3ab[b]: 84%, >20:1 dr, 98% ee



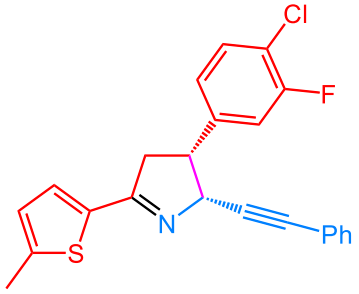
3ac[b]: 83%, >20:1 dr, 98% ee



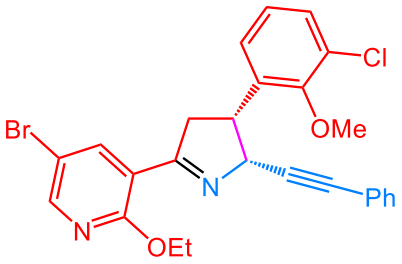
3ad[b]: 74%, >20:1 dr, 98% ee

Substrate Scope

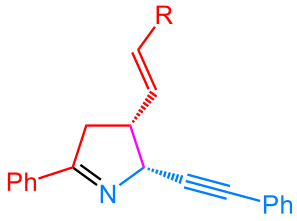
α,β-Unsaturated Ketones



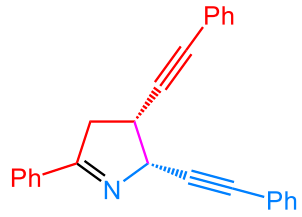
3ae: 76%, >20:1 dr, 99% ee



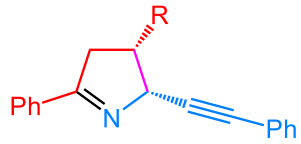
3af: 71%, >20:1 dr, 98% ee



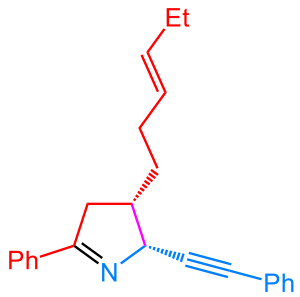
3ag (R = Ph): 60%, >20:1 dr, 97% ee
3ah (R = ^{n}Pr): 68%, >20:1 dr, 99% ee



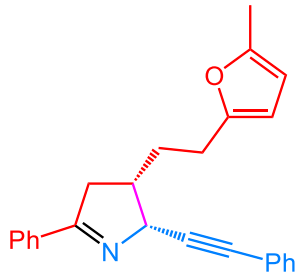
3ai: 68%, >20:1 dr, 97% ee



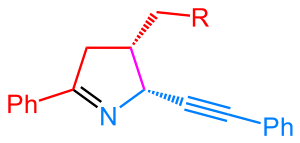
3aj (R = ^{i}Pr): 56%, >20:1 dr, 92% ee
3ak (R = cyclobutyl): 64%, >20:1 dr, 91% ee
3al (R = ^{n}Bu): 62%, >20:1 dr, 92% ee



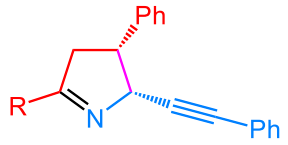
3am: 61%, >20:1 dr, 91% ee



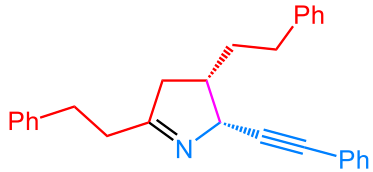
3an: 60%, >20:1 dr, 92% ee



3ao (R = OBn): 61%, >20:1 dr, 92% ee
3ap (R = Bn): 70%, >20:1 dr, 98% ee



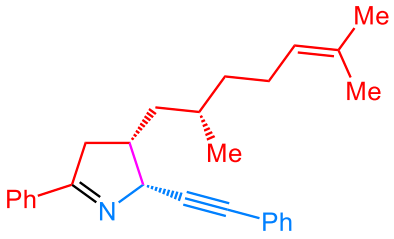
3aq (R = Me): 68%, >20:1 dr, 94% ee
3ar (R = ^{n}Pr): 67%, >20:1 dr, 95% ee



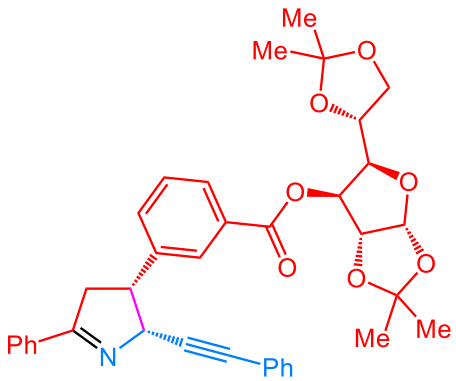
3aq: 40%, >20:1 dr, 98% ee

Substrate Scope

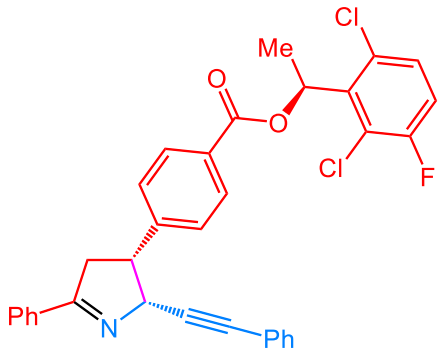
Chiral α,β-Unsaturated Ketones



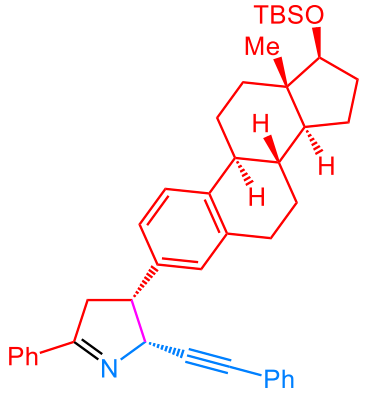
3at[a]: 61%, 96:4 dr
from **Citronellal**



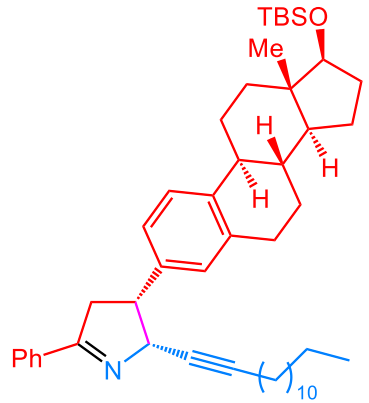
3au[d]: 75%, 99:1 dr
from ***D*-Glucose**



3av[d]: 64%, 99:1 dr
from **Crizotinib intermediate**



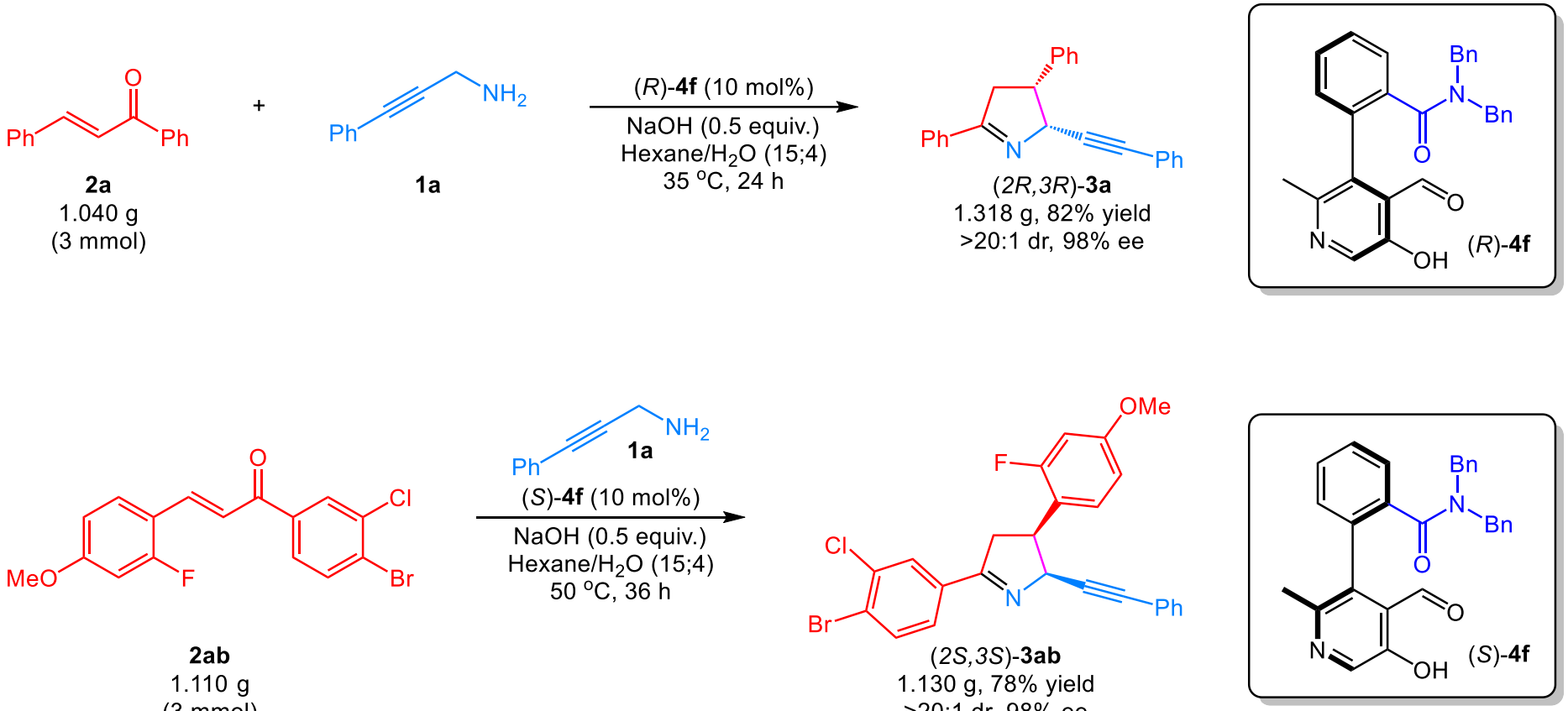
3aw[d]: 74%, 99:1 dr
from **Estradiol**



3ax[d]: 63%, 99:1 dr
from **Estradiol**

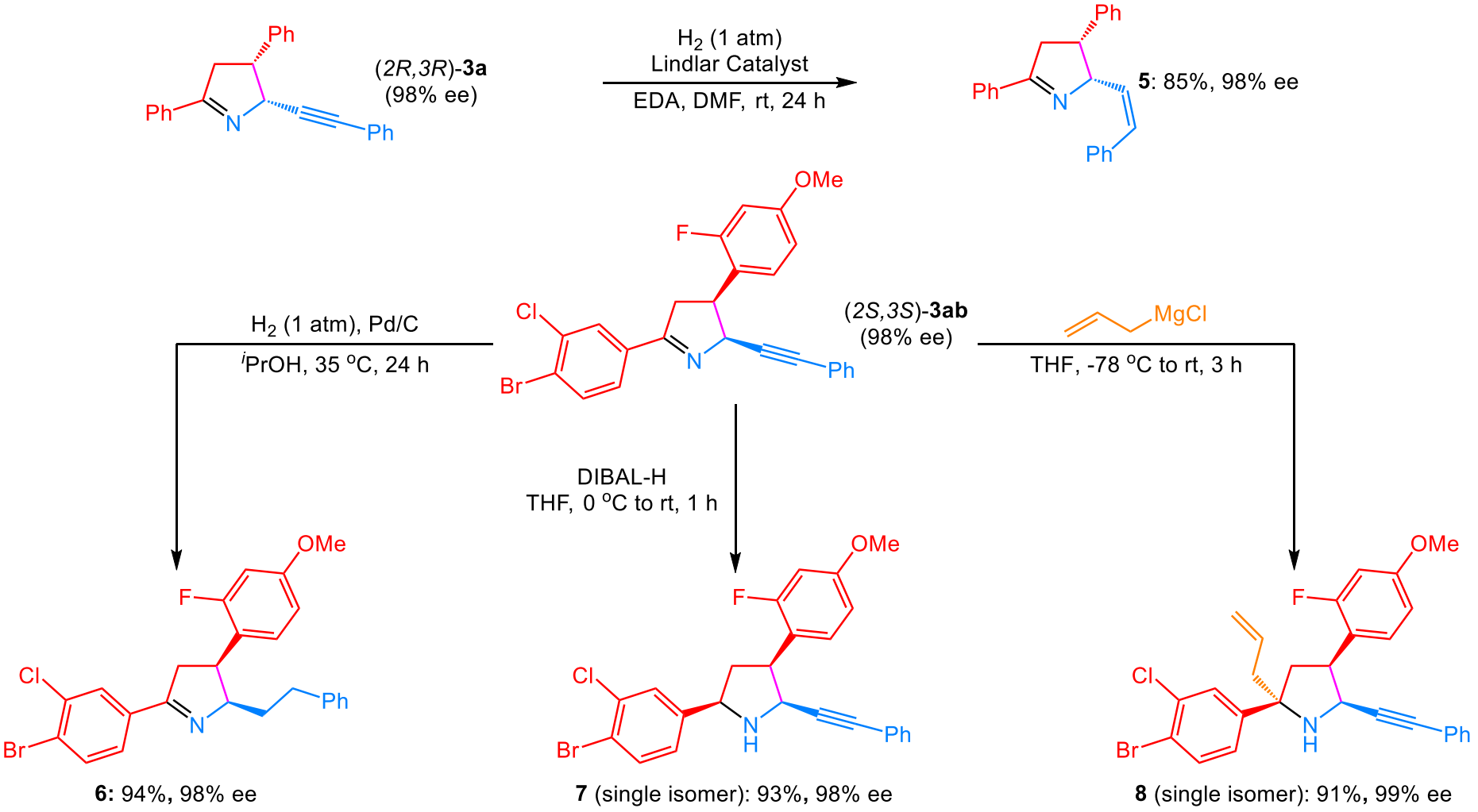
Synthetic Applications

Gram-Scale Reactions

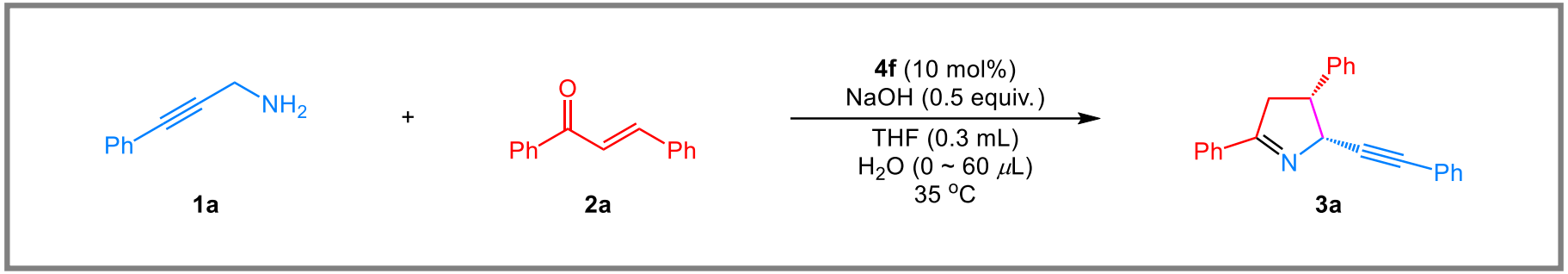


Synthetic Applications

Synthetic Transformations



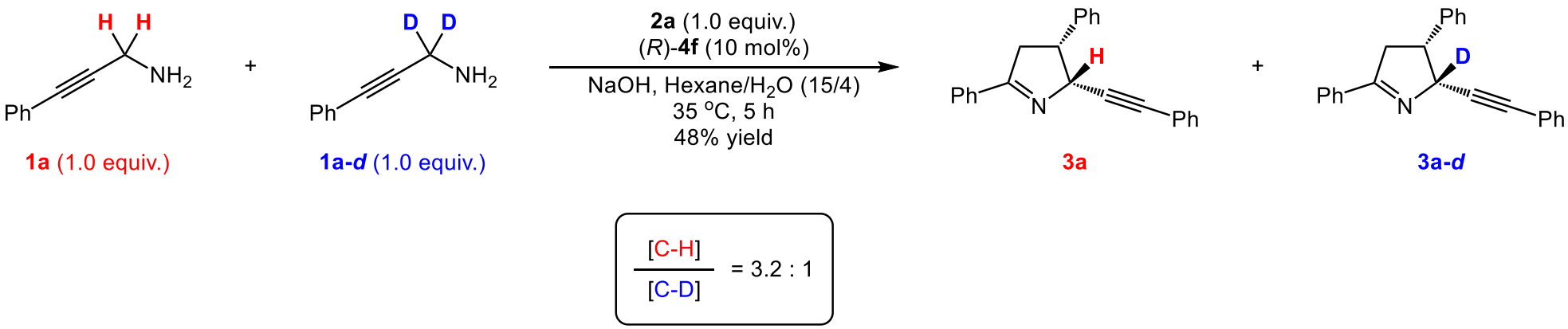
Mechanistic Investigation: Impact of Water



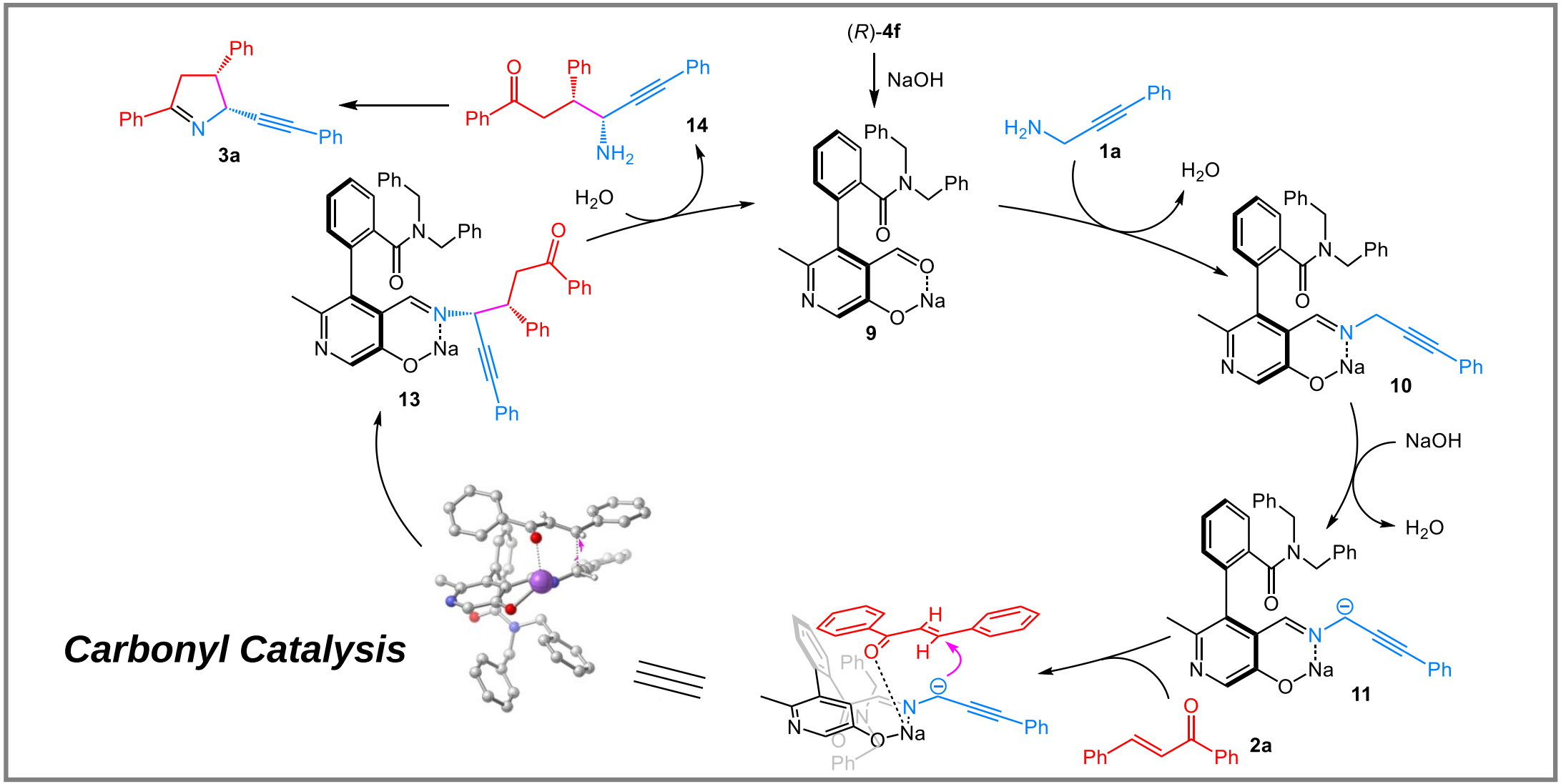
Entry	Additive	Yield (%)	Dr	Ee (%)
1	H_2O (0 μL)	-	-	-
2	Bu_4NCl (0.2 eq.), H_2O (0 μL)	trace	-	-
3[b]	18-Crown-6 (0.2 eq.), H_2O (0 μL)	-	-	-
4	H_2O (10 μL)	trace	-	-
5	H_2O (20 μL)	23	>20:1	92
6	H_2O (40 μL)	40	>20:1	92
7	H_2O (60 μL)	49	>20:1	92

[a]The reactions were carried out with **1a** (0.20 mmol, 2.0 equiv.), **2a** (0.10 mmol, 1.0 equiv.), NaOH (0.05 mmol, 0.5 equiv.), (*R*)-**4f** (0.01 mmol, 10 mol%) and additive in THF (0.3 mL) at 35 °C for 24 h unless otherwise stated. Isolated yields were based on **2a**. The ee values were determined by chiral HPLC analysis. The dr values were determined by crude ^{1}H NMR. [b]KOH (0.2 equiv.) was employed instead of NaOH.

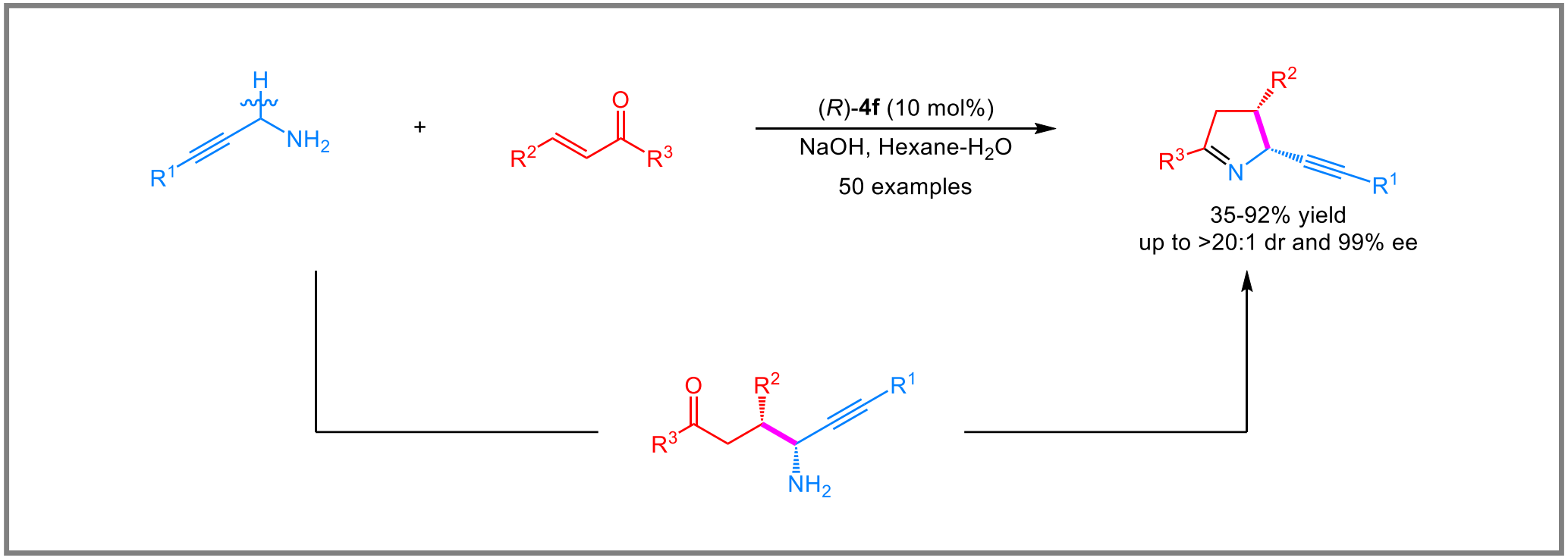
Mechanistic Investigation: KIE Studies



Proposed Reaction Mechanism



Summary



- ***Mild Reaction Conditions***
- ***Broad Substrate Scope***
- ***Outstanding Diastereo- and Excellent Enantioselectivities***

Writing Strategy

首段写作思路

惰性氨基α位C-H键直接官能化的重要性

↓

惰性氨基α位C-H键直接官能化面临的挑战

↓

引出本文工作

Writing Strategy

末段写作思路

总结工作

↓

强调亮点：高选择性合成手性1-吡咯啉衍生物

↓

提出展望：发展新的基于维生素B_6的仿生催化剂

Representative Examples

- Second, the classical *N*-addition may disrupt the desired *α*-C conjugate addition. (disrupt, v. 中断，扰乱)
- The synthetic transformations of products **3a** and **3ab** are depicted in Scheme 3. (depict, v. 描述，描绘)
- For the step from intermediate **13** to **14**, control experiments indicated that hydrolysis dominated the process and amine exchange between **13** and **1** played a negligible role for the conversion. (negligible, adj. 微不足道的，不值一提的，反义词：nonnegligible)

Acknowledgement

Thanks for your attention