Literature Report VII

Construction of Axially Chiral Dialdehydes *via* Rhodium-Catalyzed Enantioselective C−H Amidation

Reporter: Bao-Qian Zhao
Checker: Gao-Wei Wang
Date: 2025-03-10

Yang, J.-Y.; Du, Y.-R.; Cheng, F.-Q.; Hu, Y.; Li, Z.-Y. *Angew. Chem. Int. Ed.* **2025**, *62*, e202421412

CV of Prof. Zhong-Yuan Li (李忠原)

Research:

Asymmetric catalysis and synthesis & Transition metal catalysis

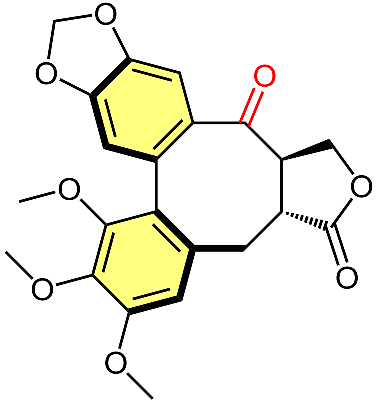
Background:

- **2008-2012** B.S., Anhui Normal University
- **2012-2017** Ph.D., University of Science and Technology of China
- **2017-2021** Postdoc., University of Michigan
- **2021-Now** Associate Professor, Anhui Normal University

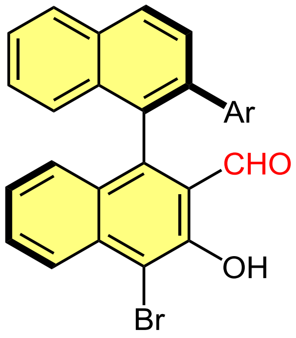
Contents

Introduction

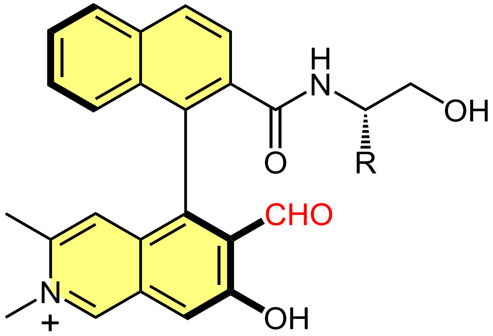
Axially Chiral Biaryl Compounds in Natural Products



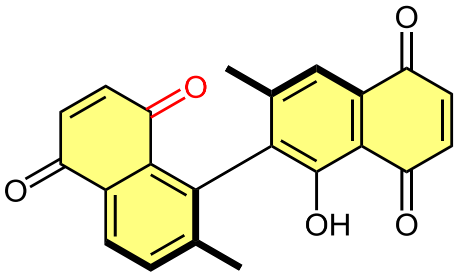
(-)-Steganone



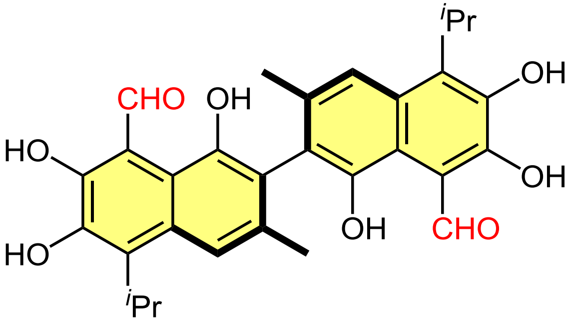
Chiral catalyst



Chiral catalyst



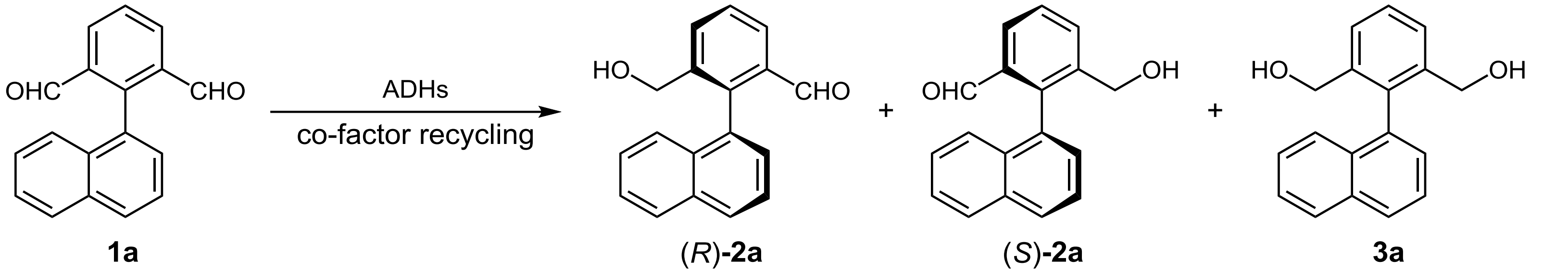
Isodiospyrin



(-)-Gossypol

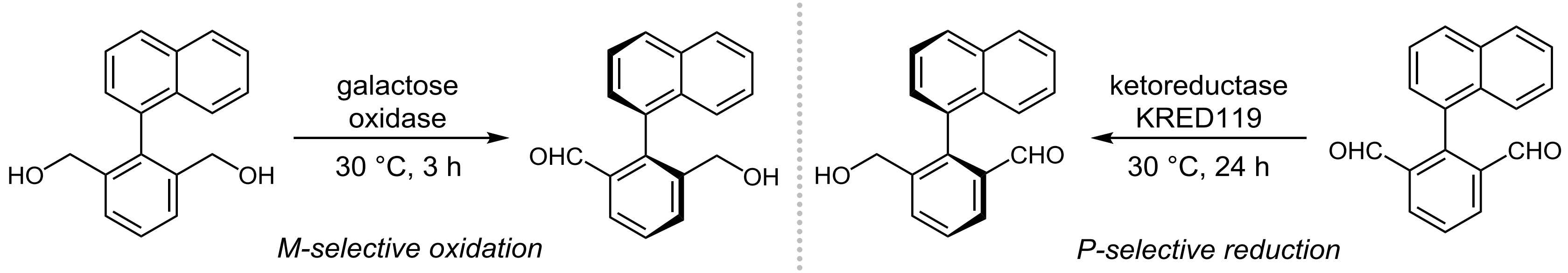
Introduction

Enzymatic Desymmetrization of Biaryl Dialdehydes



Ye, M.; Li, C.; Xiao, D.; Qu, G.; Yuan, B. Sun, Z. *JACS Au* **2024**, *4*, 411

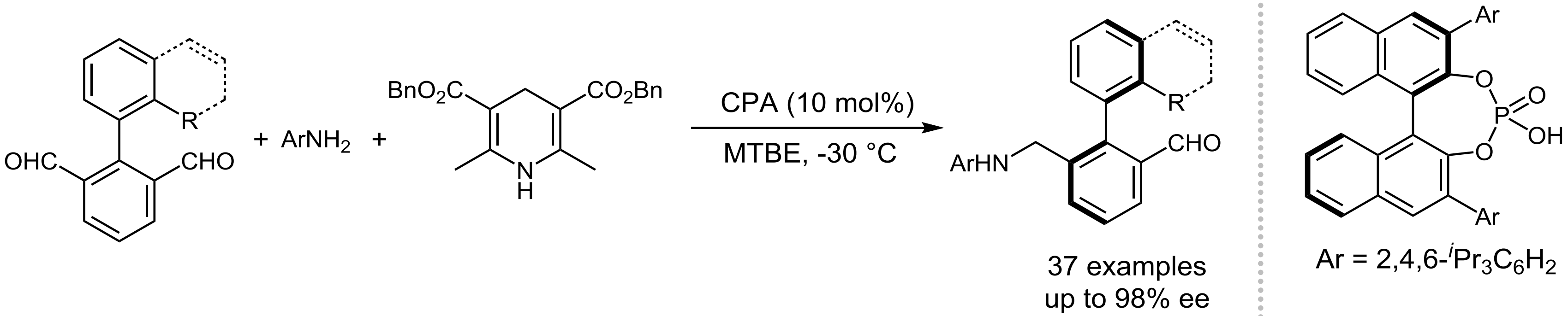
Enzymatic Desymmetrization of Aldehyde or Diol



Staniland, S.; Yuan, B.; Willies, S.; Grainger, D. M.; Turner, N. J.; Clayden, J. *Chem. Eur. J.* **2014**, *20*, 13084

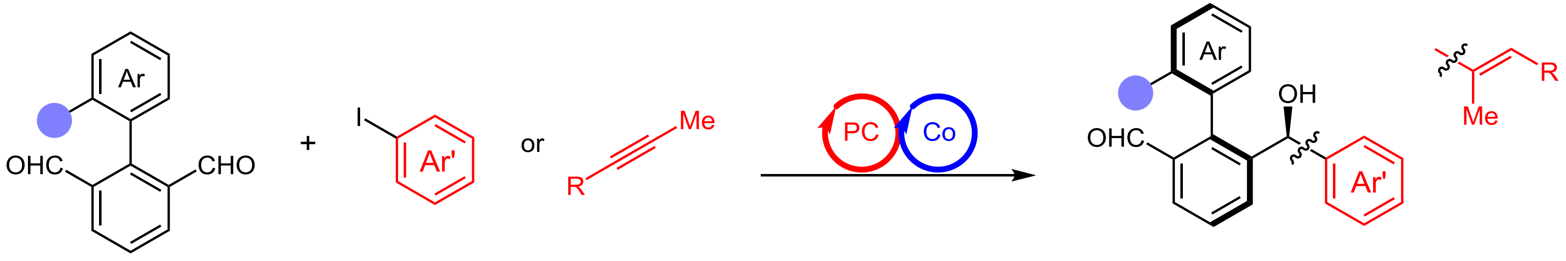
Introduction

CPA-Catalyzed ARA of Biaryl Dialdehydes



Wang, Y.; Song, R.-P.; Chen, W.-L.; Zhang, S.-H.; Shao, Y.-D.; Cheng, D.-J. *Org. Lett.* **2024**, *26*, 7161

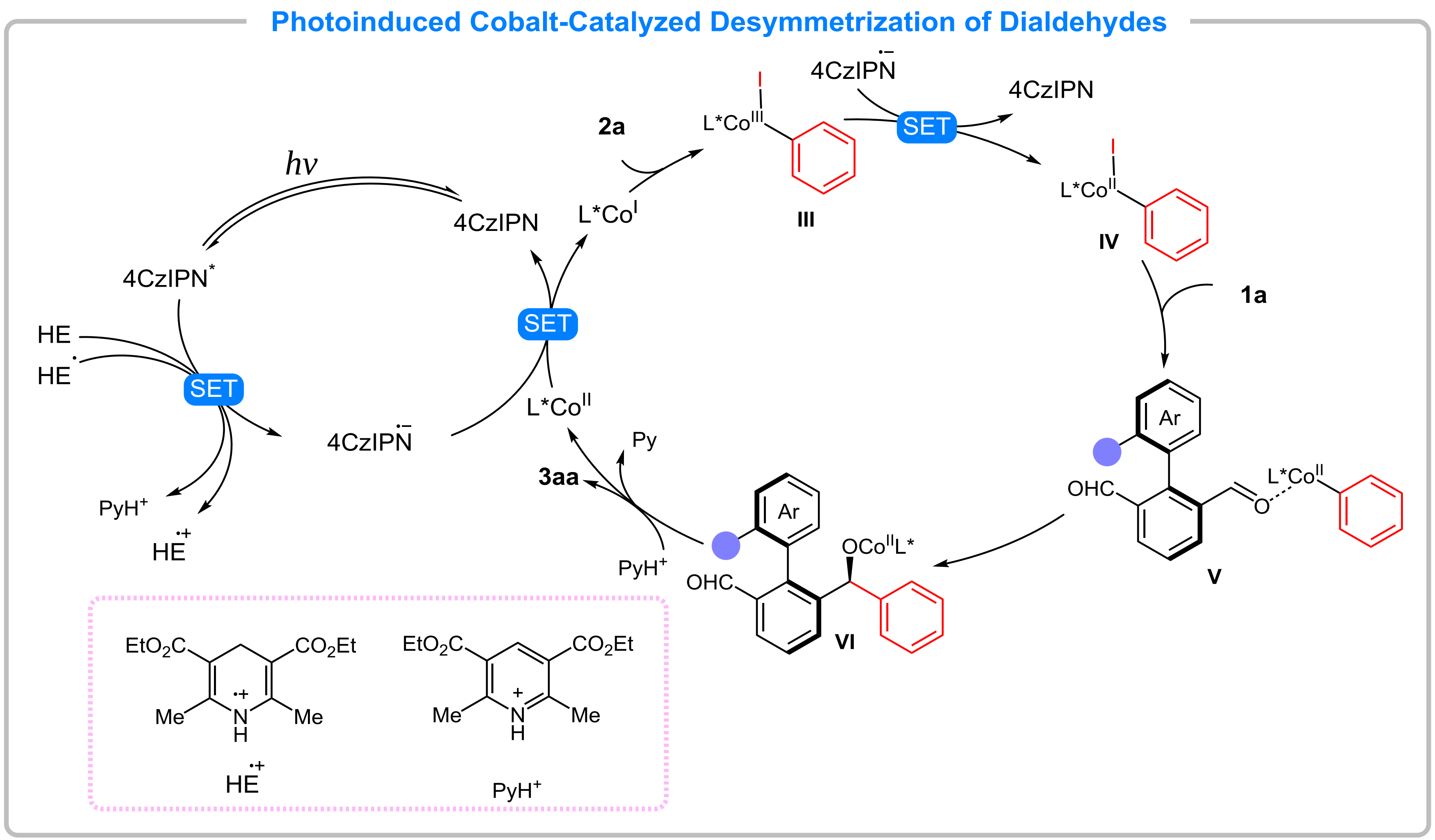
Photoinduced Cobalt-Catalyzed Desymmetrization of Dialdehydes



1a **2a** **3aa** 60 examples
>99% ee, > 19:1 dr

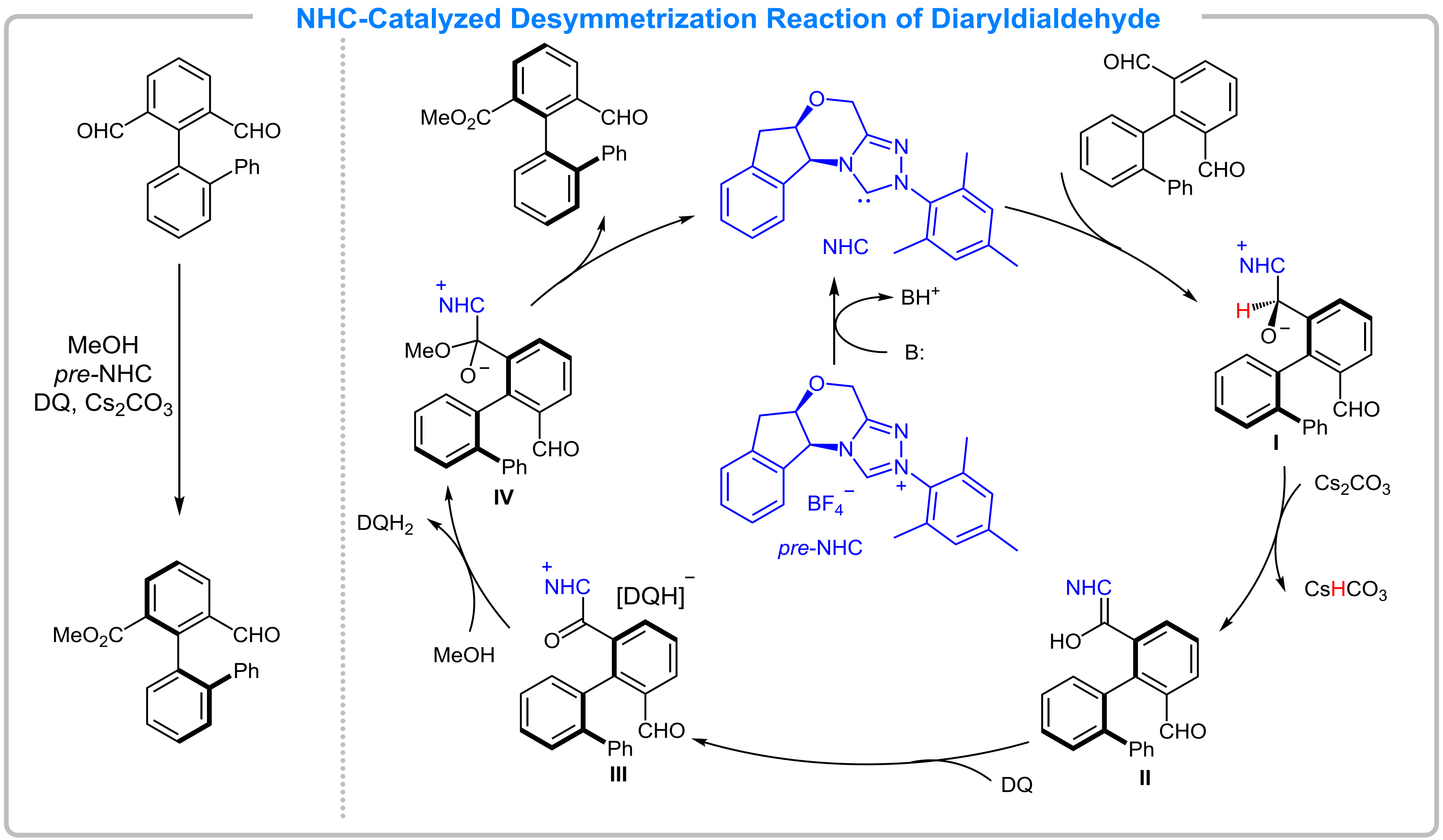
Jiang, H.; He, X.-K.; Jiang, X.; Zhao, W.; Lu, L.-Q.; Cheng, Y.; Xiao, W.-J. *J. Am. Chem. Soc*. **2023**, *145,* 6944

Introduction



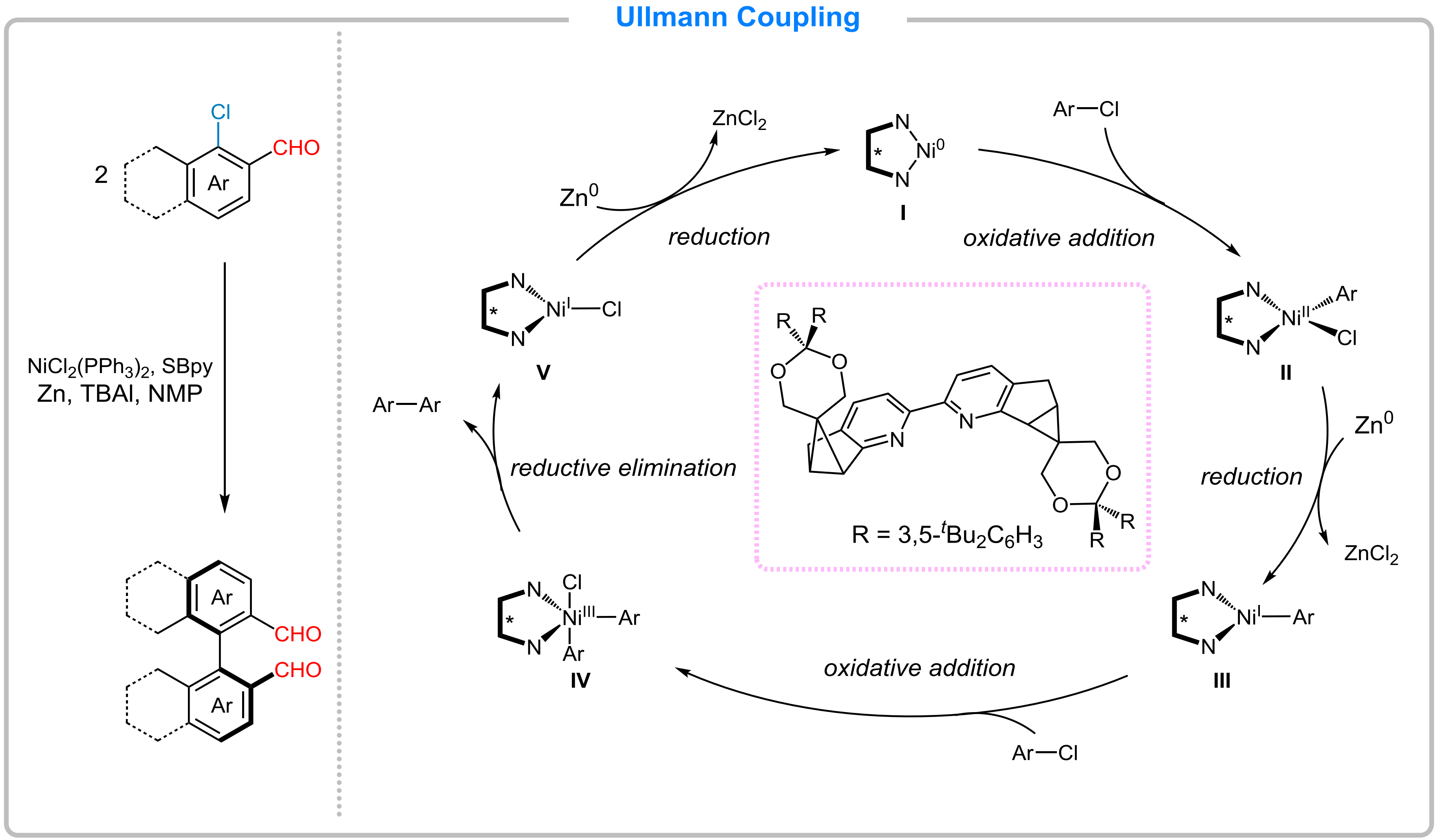
Jiang, H.; He, X.-K.; Jiang, X.; Zhao, W.; Lu, L.-Q.; Cheng, Y.; Xiao, W.-J. *J. Am. Chem. Soc*. **2023**, *145,* 6944

Introduction



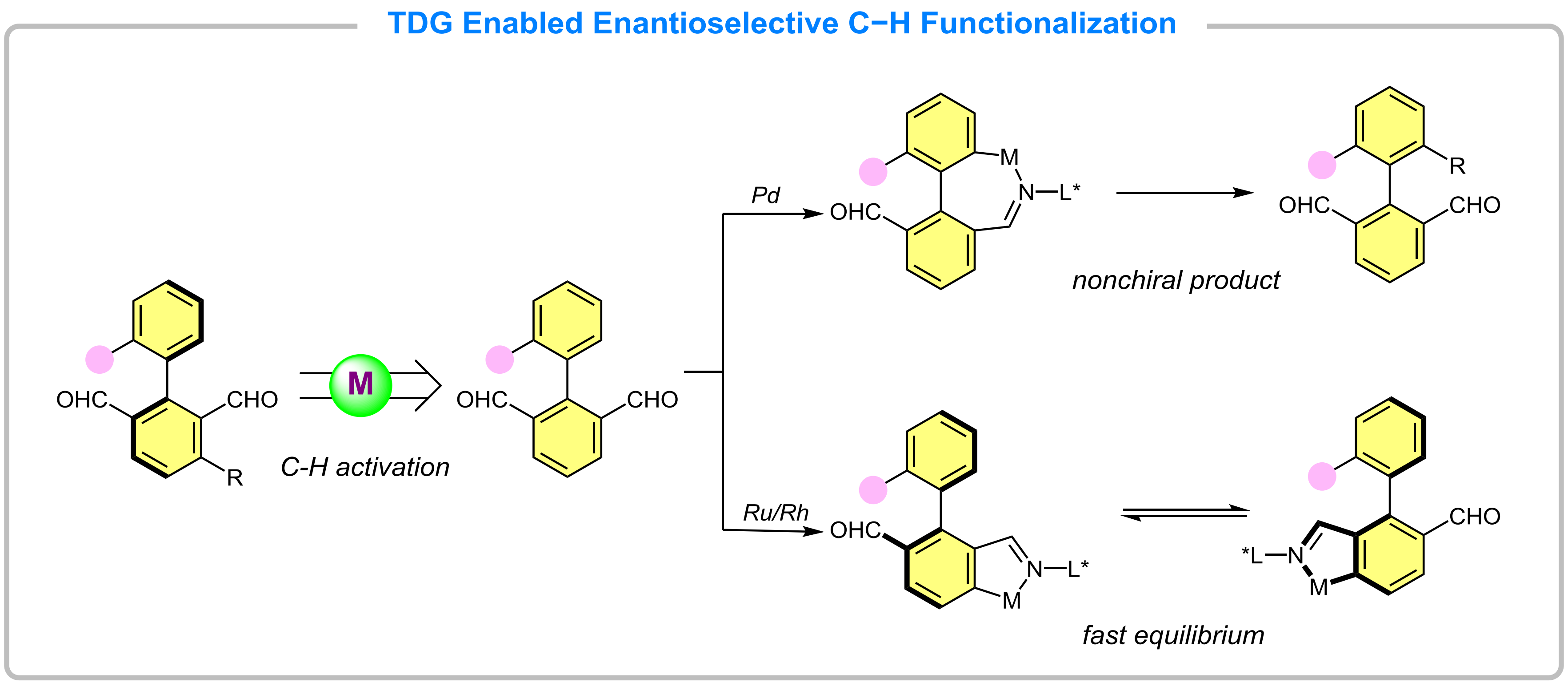
Hou, X.-X.; Wei, D. *J. Org. Chem*. **2024**, *89*, 3133

Introduction



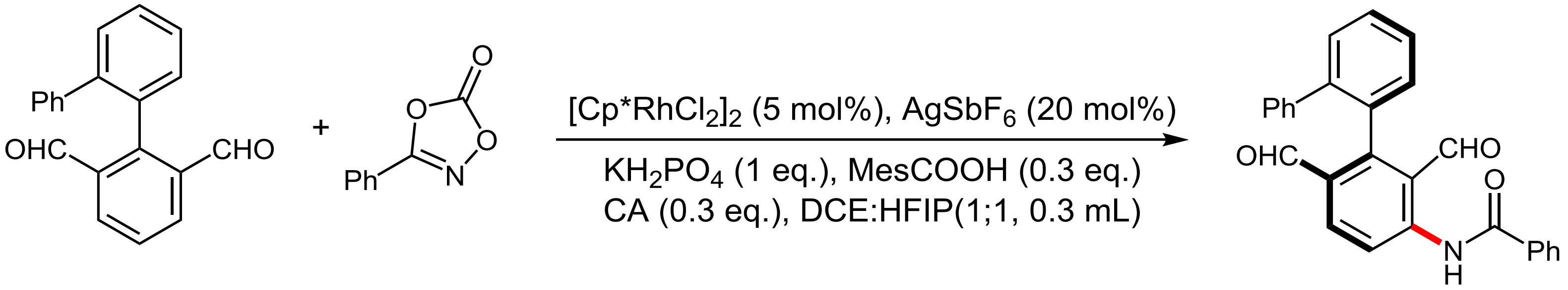
Perveen, S.; Wang, L.; Song, P.; Jiao, J.; Duan, X.; Li, P. *Angew. Chem. Int. Ed.* **2022**, *61*, e202212108.

Introduction

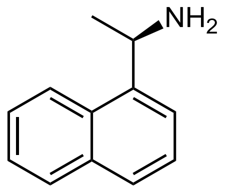


Optimazation Conditions

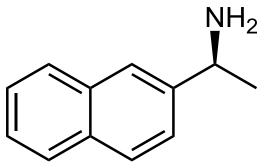
Optimazation of Reaction Conditions



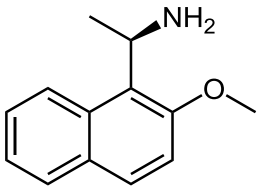
1a **2a** **3aa**



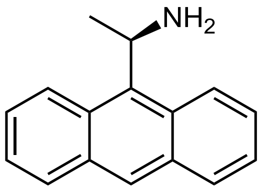
CA1
26%; 64:36 er



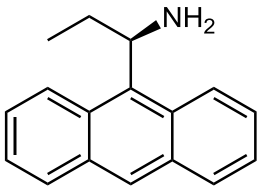
CA2
29%; 58:42 er



CA3
32%; 61:39 er



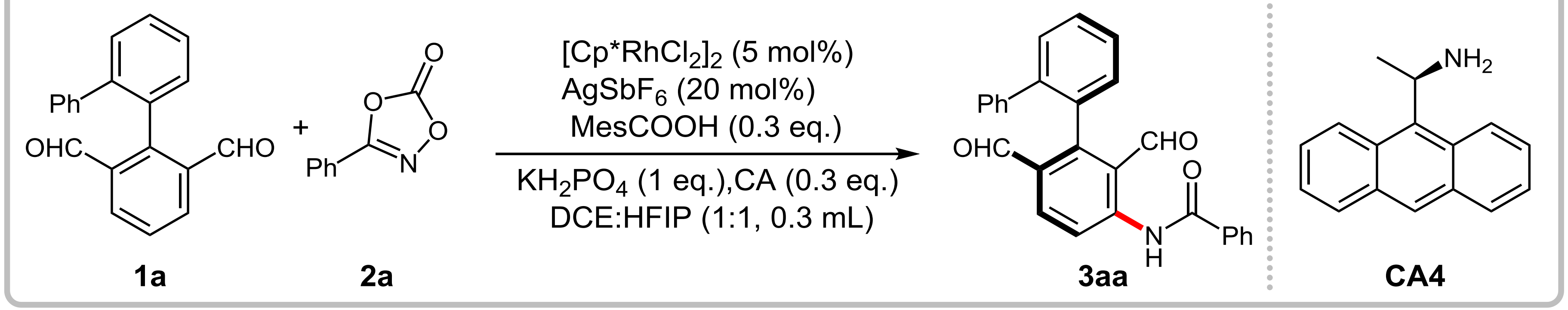
CA4
44%; 94:6 er



CA5
45%; 85:15 er

Optimazation Conditions

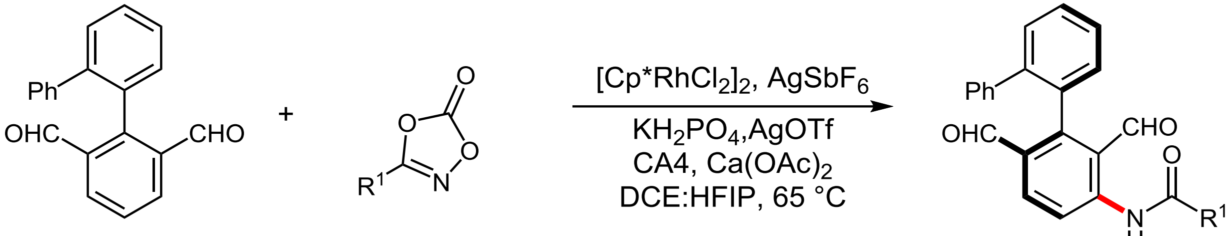
Optimazation of Reaction Conditions



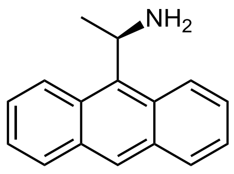
Entry	Additive	Solvent	Yield (%)	*Er*
1	MesCOOH	HFIP	42	70:30
2	MesCOOH	PhMe:HFIP	11	80:20
3	MesCOOH	PhCl:HFIP	6	70:30
4	MesCOOH	DCE:HFIP	44	94:6
5	1-AdCOOH	DCE:HFIP	68	79:21
6	AcOH	DCE:HFIP	70	89:11
7	KOAc	DCE:HFIP	31	82:18
8	CsOAc	DCE:HFIP	15	72:28
9	$Mg(OAc)_2$	DCE:HFIP	66	94:6
10	$Ca(OAc)_2$	DCE:HFIP	78	98.5;1.5

Substrate Scope

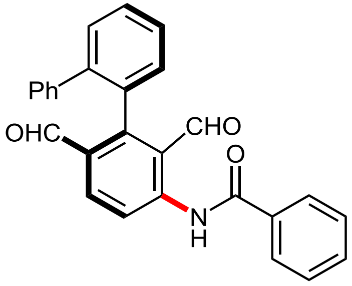
Scope of 3-Substituted-1,4,2-Dioxazol-5-One



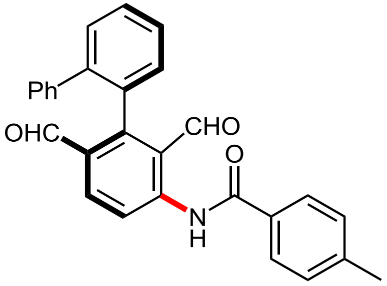
1a **2** **3**



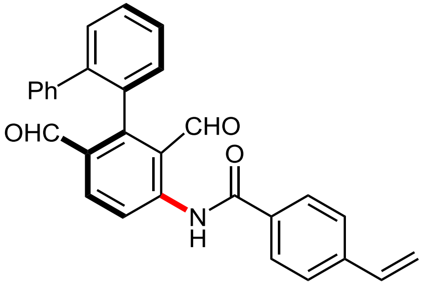
CA4



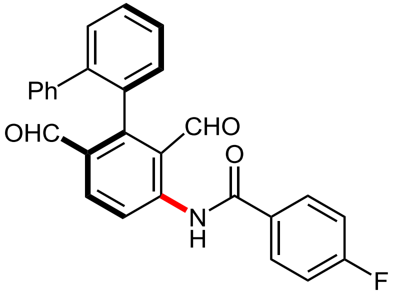
3aa, 76%; 98.5:1.5 er



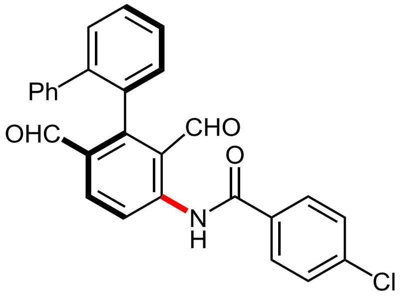
3ba, 78%; 99.5:0.5 er



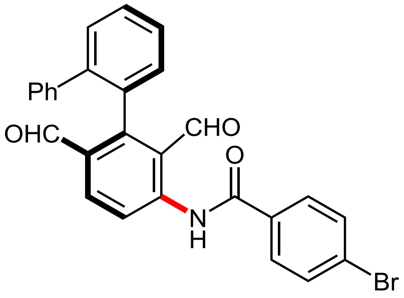
3ca, 56%; 95.5:4.5 er



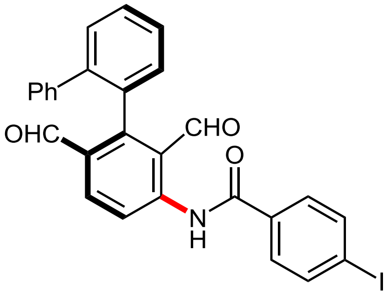
3da, 74%; 97:3 er



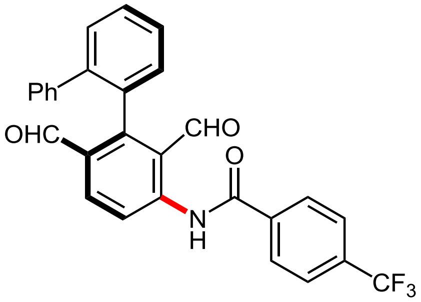
3ea, 75%; 99:1 er



3fa, 74%; 98:2 er

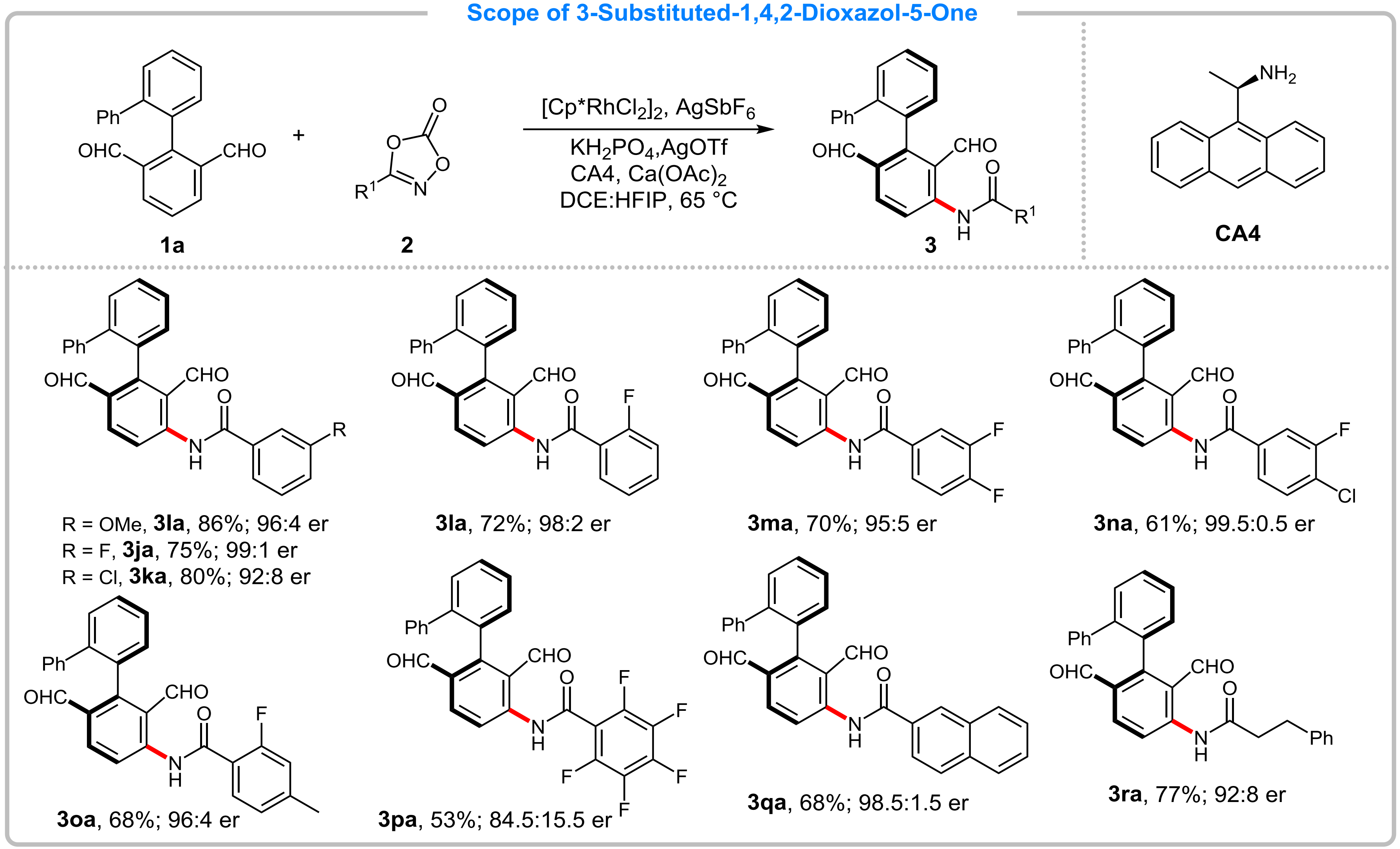


3ga, 76%; 94.5:5.5 er

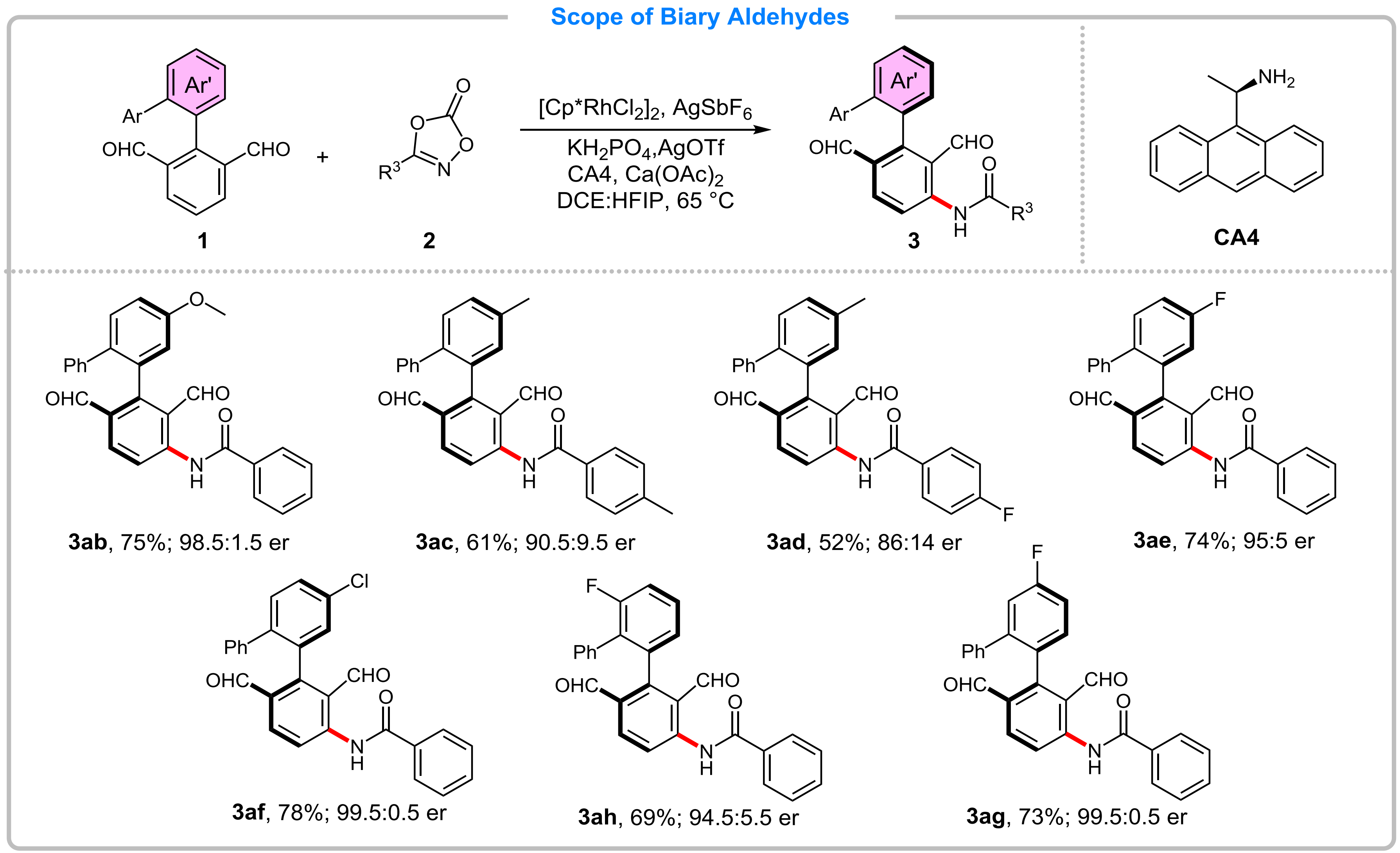


3ha, 71%; 86.5:13.5 er

Substrate Scope

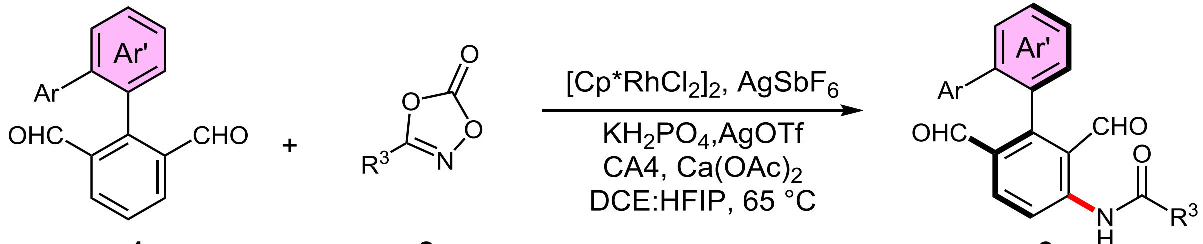


Substrate Scope

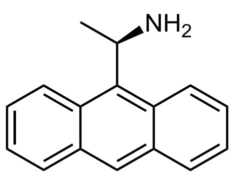


Substrate Scope

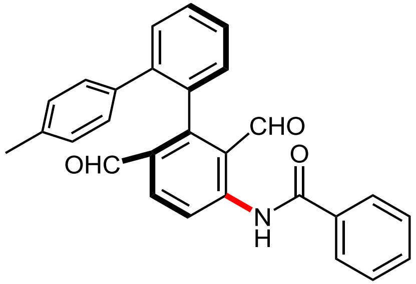
Scope of Biary Aldehydes



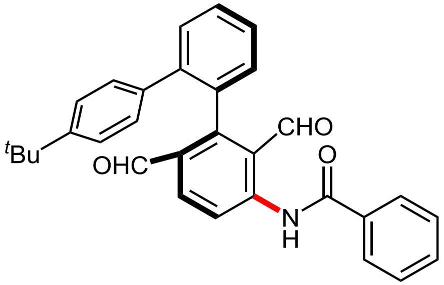
1 **2** **3**



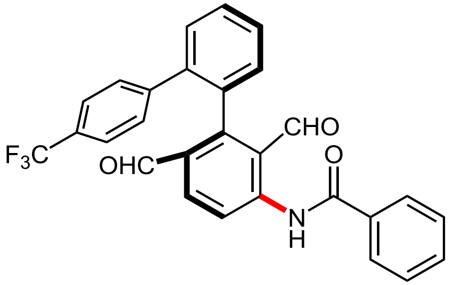
CA4



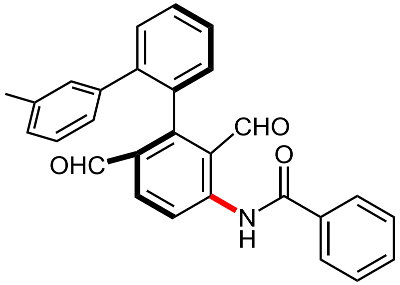
3ai, 71%; 93.5:6.5 er



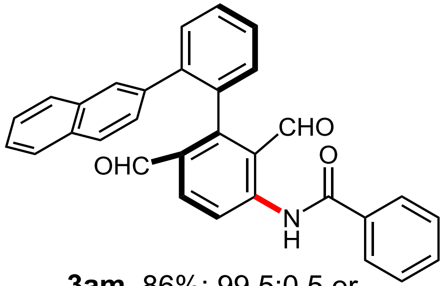
3aj, 66%; 62.5:37.5 er



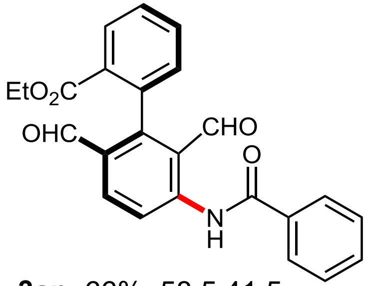
3ak, 77%; 52.5:47.5 er



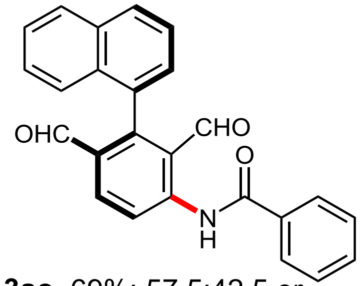
3al, 76%; 99:1 er



3am, 86%; 99.5:0.5 er

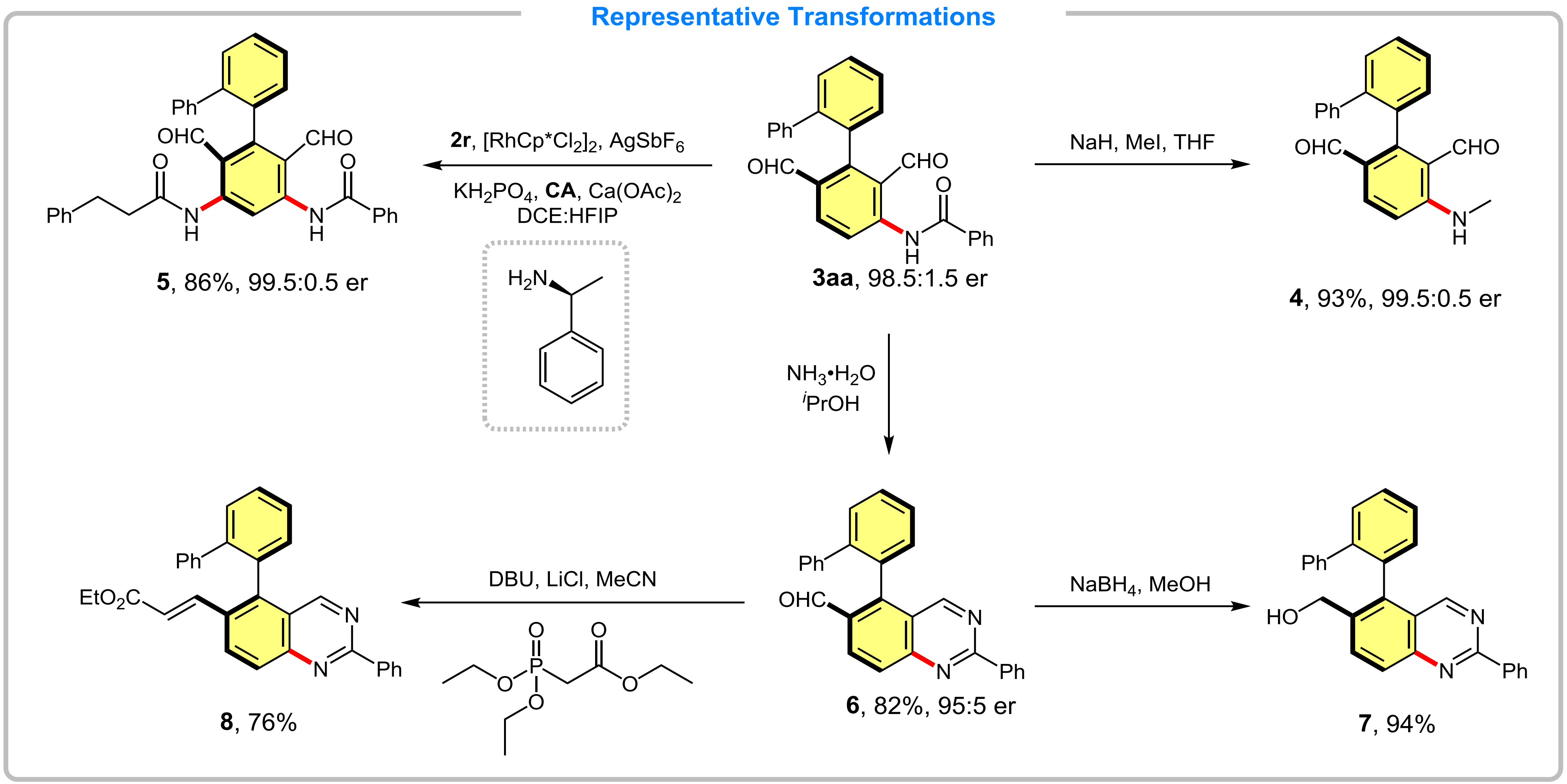


3an, 66%; 58.5:41.5 er



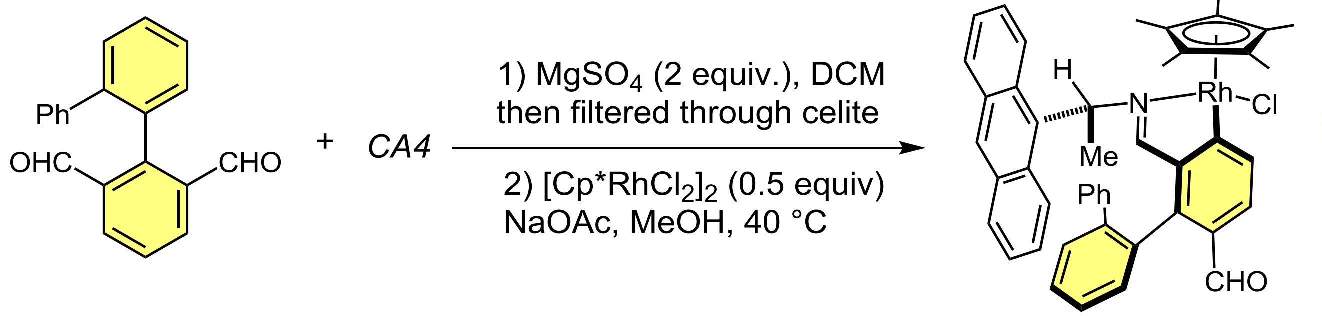
3ao, 69%; 57.5:42.5 er

Representative Transformations



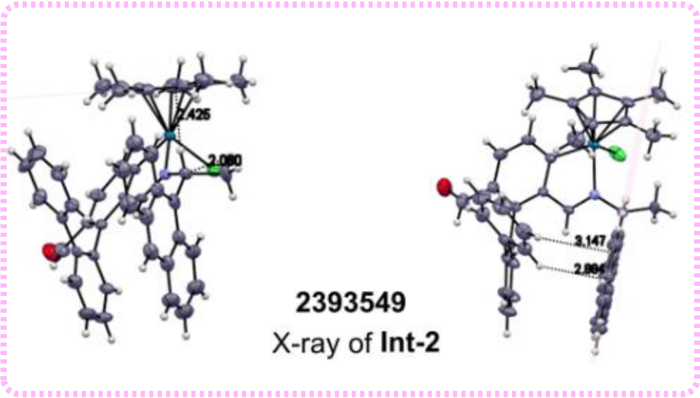
Mechanism Experiment

Synthesis and Single Crystal Structure of Int-2

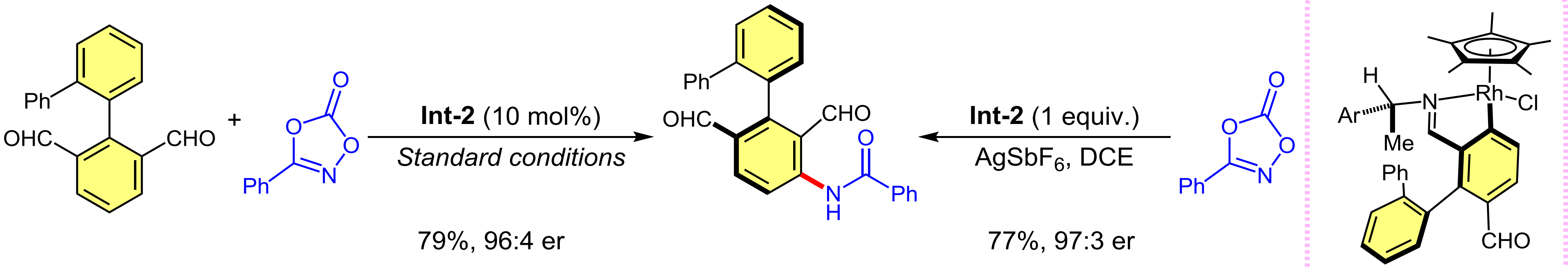


1a

Int-2 71%, >20:1 dr



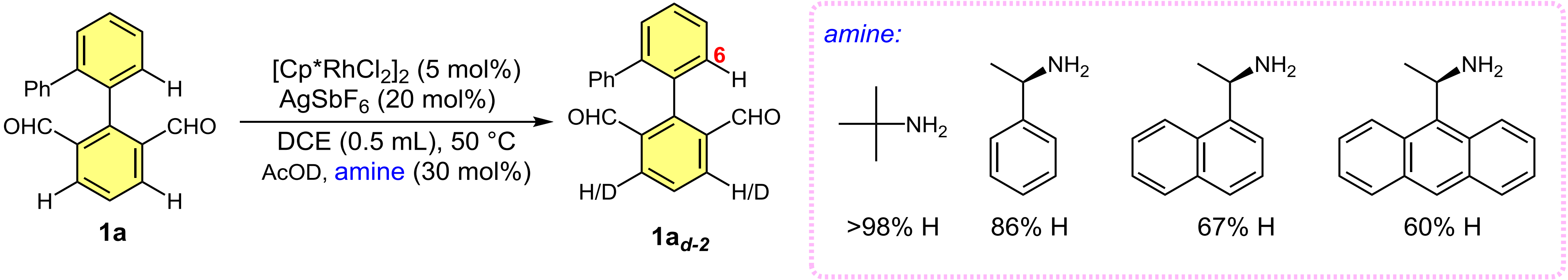
Catalytic and Stoichiometric Activity Evaluation of Int-2



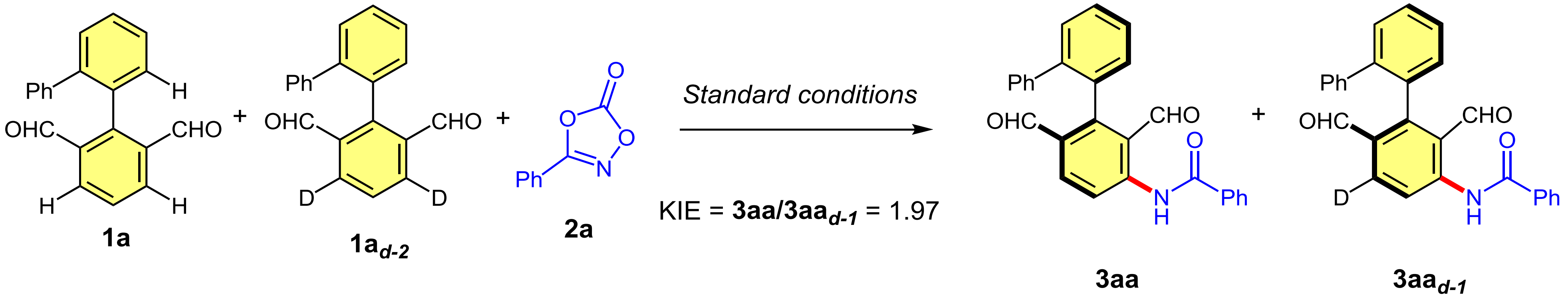
1a **2a** **3aa** **2a** **Int-2**

Mechanism Experiment

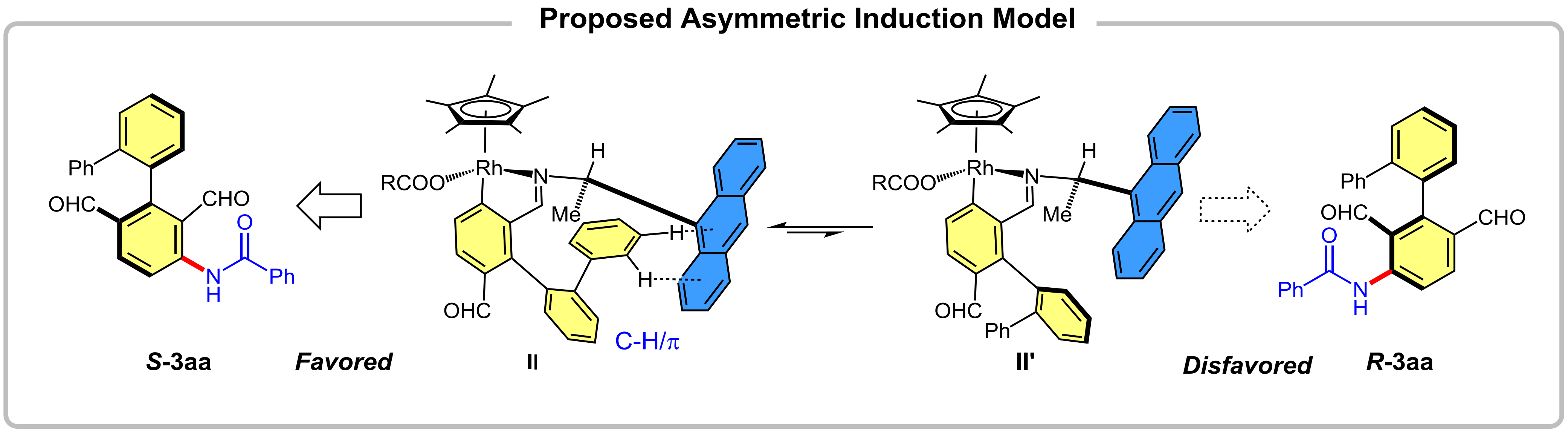
H/D Scrambling Experiments



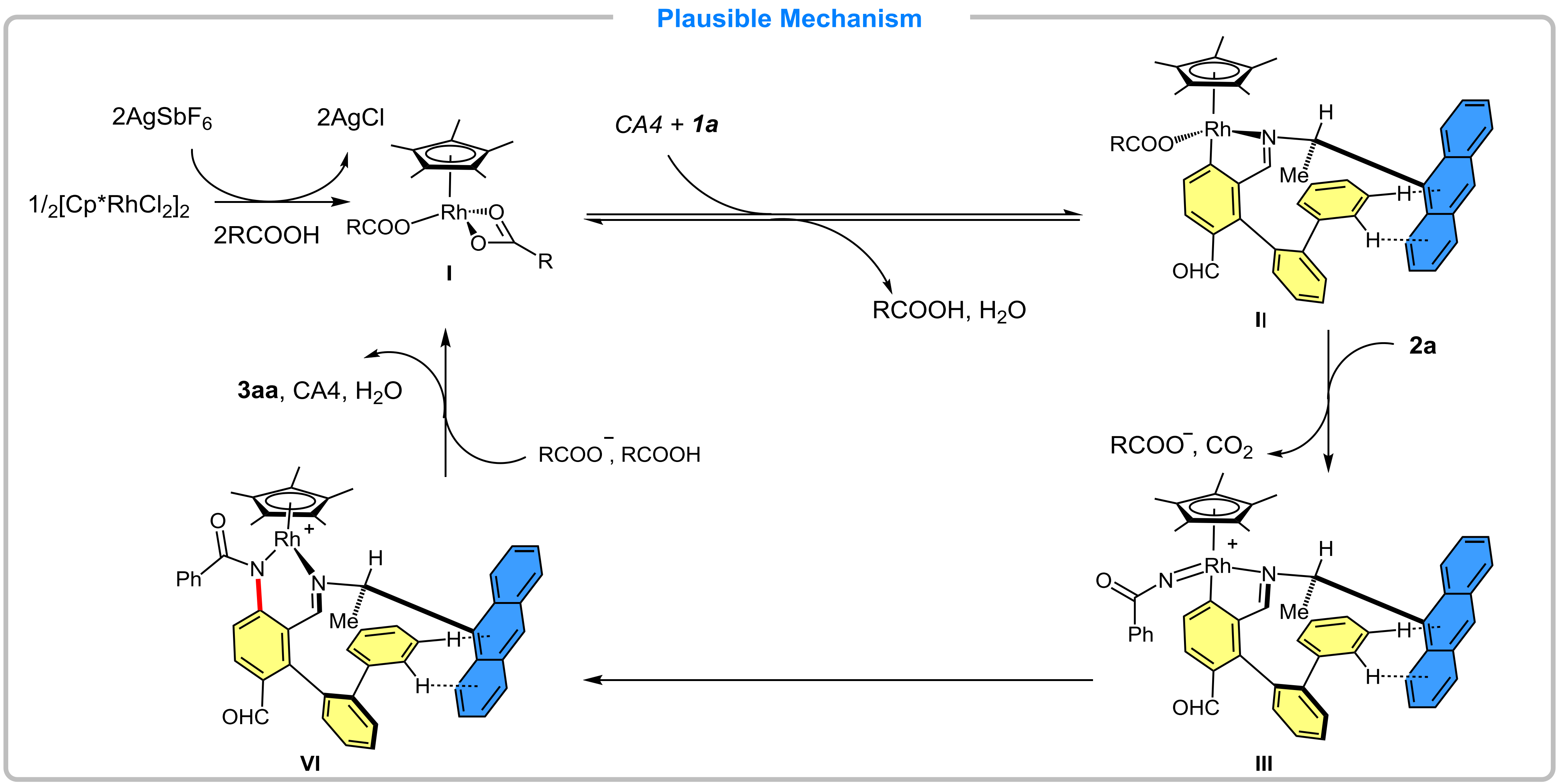
KIE Experiment



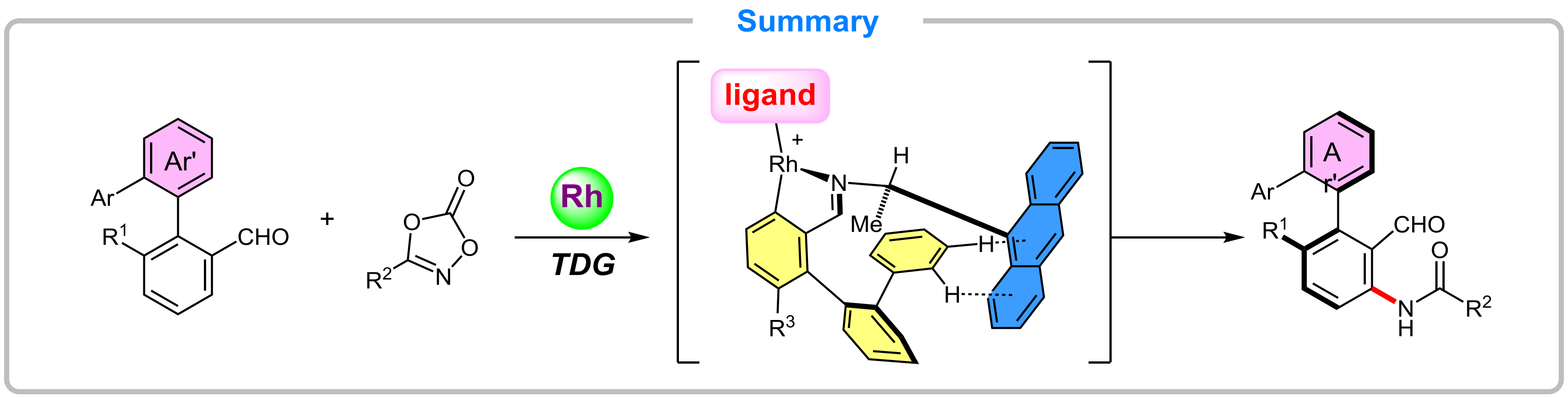
Mechanism Experiment



Plausible Mechanism



Summary



- Transient and Noncovalent Synergistic Interactions
- Achieving Axially Chiral Biaryl Dialdehydes

Writing Strategies

☐ The First Paragraph

The importance of
axially chiral scaffolds

↓

Few reports about
axially biaryl dialdehydes

- ✓ Axially chiral scaffolds are one of the most ubiquitous structural motifs in natural products, bioactive molecules, and materials science, as well as essential frameworks as chiral ligands and catalysts. Particularly, axially chiral aldehydes attract increasing interest owing to their excellent catalytic performance, which were pioneered by the Guo and the Zhao groups, respectively.

- ✓ Among various strategies, desymmetrization of biaryl dialdehydes has emerged as a straightforward method from readily accessible substrates. A couple of delicate strategies have been developed to achieve the synthesis of axially chiral aldehydes by desymmetrization during the last decade.

Writing Strategies

☐ The Last Paragraph

Summary
of this work

- ✓ We have developed a novel and practical strategy for the construction of axially chiral amido dialdehydes in moderate to good yields with commendable enantioselectivities. Furthermore, the confirmed absolute structure of intermediate as well as detailed control experiments indicated that the asymmetric induction might start from a sterically rigidified chiral amine moiety, and followed by C−H/π interaction to facilitate the favored pathway.

↓

Outlook
of this work

- ✓ The new transient and C−H/π synergistic interactions might bring up opportunities for not only synthesizing novel axially chiral amido dialdehydes, but also providing a new tool to stimulate asymmetric catalysis.

Representative Examples

- ✓ **In stark contrast** (**形成鲜明对比的是**) , basic conditions K_2CO_3/MeOH resulted in significant erosion of the ee, the observed racemization could be presumably attributed to the facile silyl-transferring reaction.

- ✓ Various NCIs have been **exploited** (**被利用**) in enantioselective C−H functionalization in recent years, including hydrogen bond, ion pair, and π interactions et al.

- ✓ Nevertheless, II could be more stable than II’ because of the intramolecular C−H/π interaction, thus producing ***S*-3 aa** as the **ascendant** (**优势，占支配地位**) product through subsequent nitrene insertion and protonation. .

Acknowledgment

Thanks for your attention!