Literature Report IV

Modular Construction of Heterobiaryl Atropisomers and Axially Chiral Styrenes *via* All-Carbon Tetrasubstituted VQMs

Reporter: Yan-Jiang Yu

Checker: Xiang Li

2022-10-26

Gou, B.-B.; Chen, J.; Zhou, L. *Angew*. *Chem*. *Int*. *Ed*. **2022**, *61*, *e202208174*.

CV of Prof. Ling Zhou

Research Interests:

- Synthetic Methodology Development
- Asymmetric Catalysis
- Efficient Synthesis of Natural Products

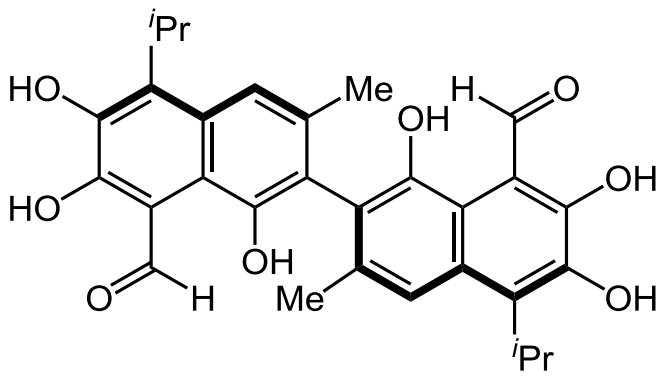
Education:

- **1998-2002** B.S., Lanzhou University
- **2002-2007** Ph.D., Lanzhou University, (Prof. Cao, X.; Prof. Ye, X.)
- **2007-2009** Basilea Pharmaceutica China Ltd.
- **2009-2011** Postdoctor, NUS, (Prof. Yeung, Y.-Y.)
- **2012-Present** Professor, Northwest University

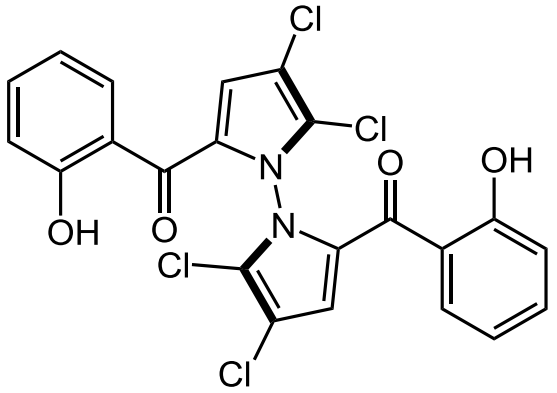
Contents

Introduction

Natural Products and Bioactive Molecules

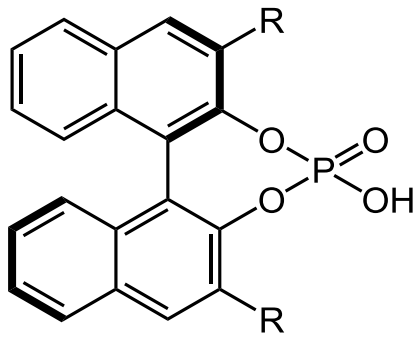


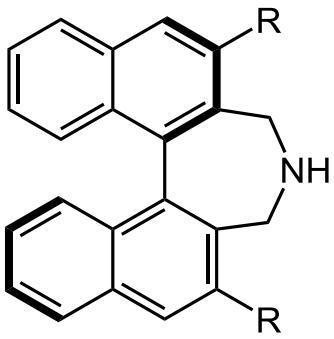
Gossypol

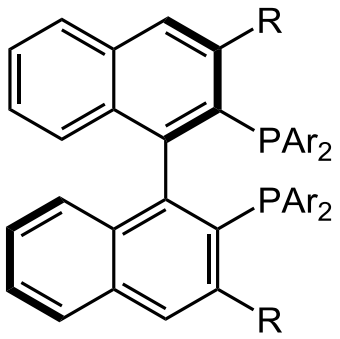


Marinopyrrole

Organocatalysts and Metal Ligands

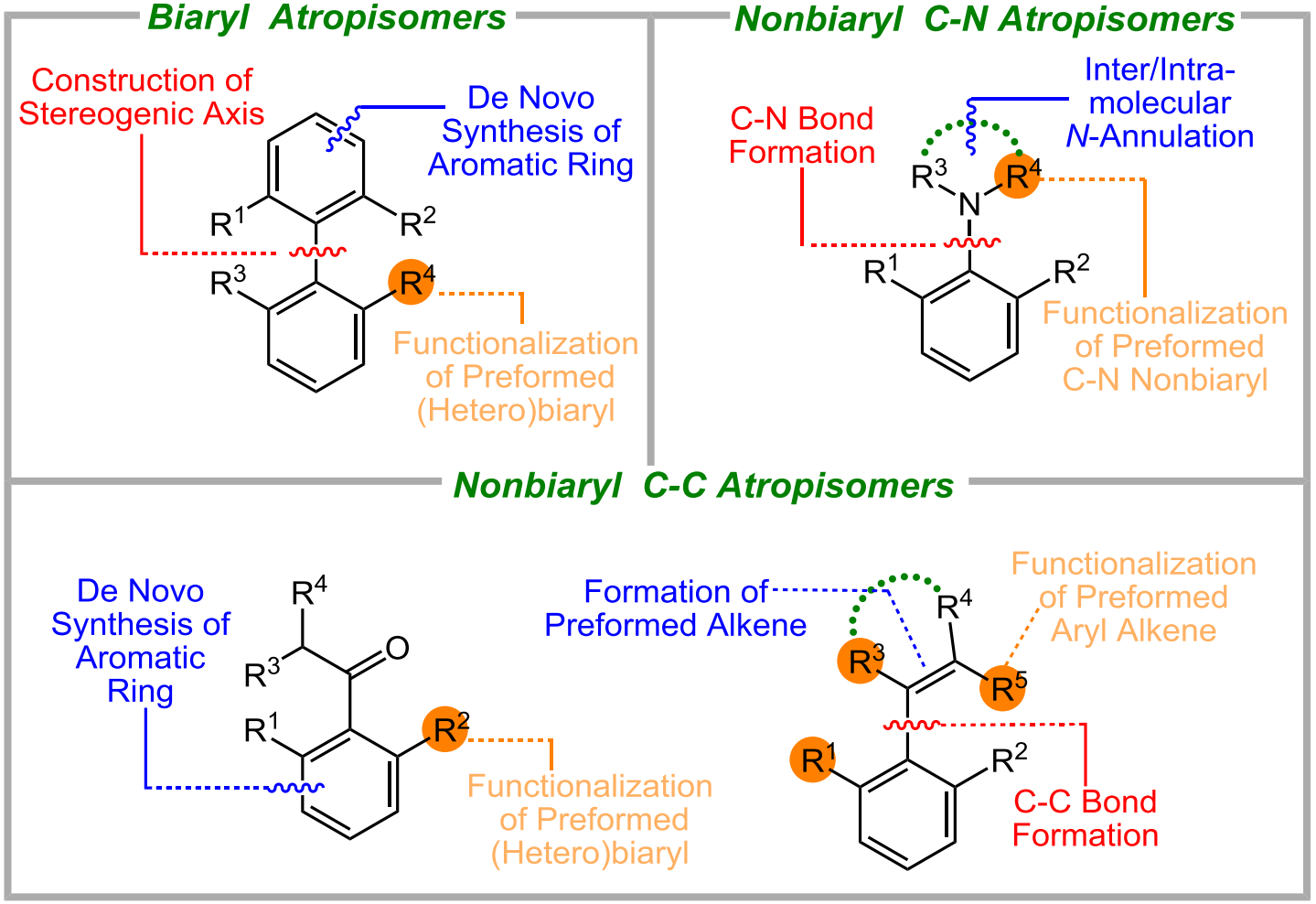






Introduction

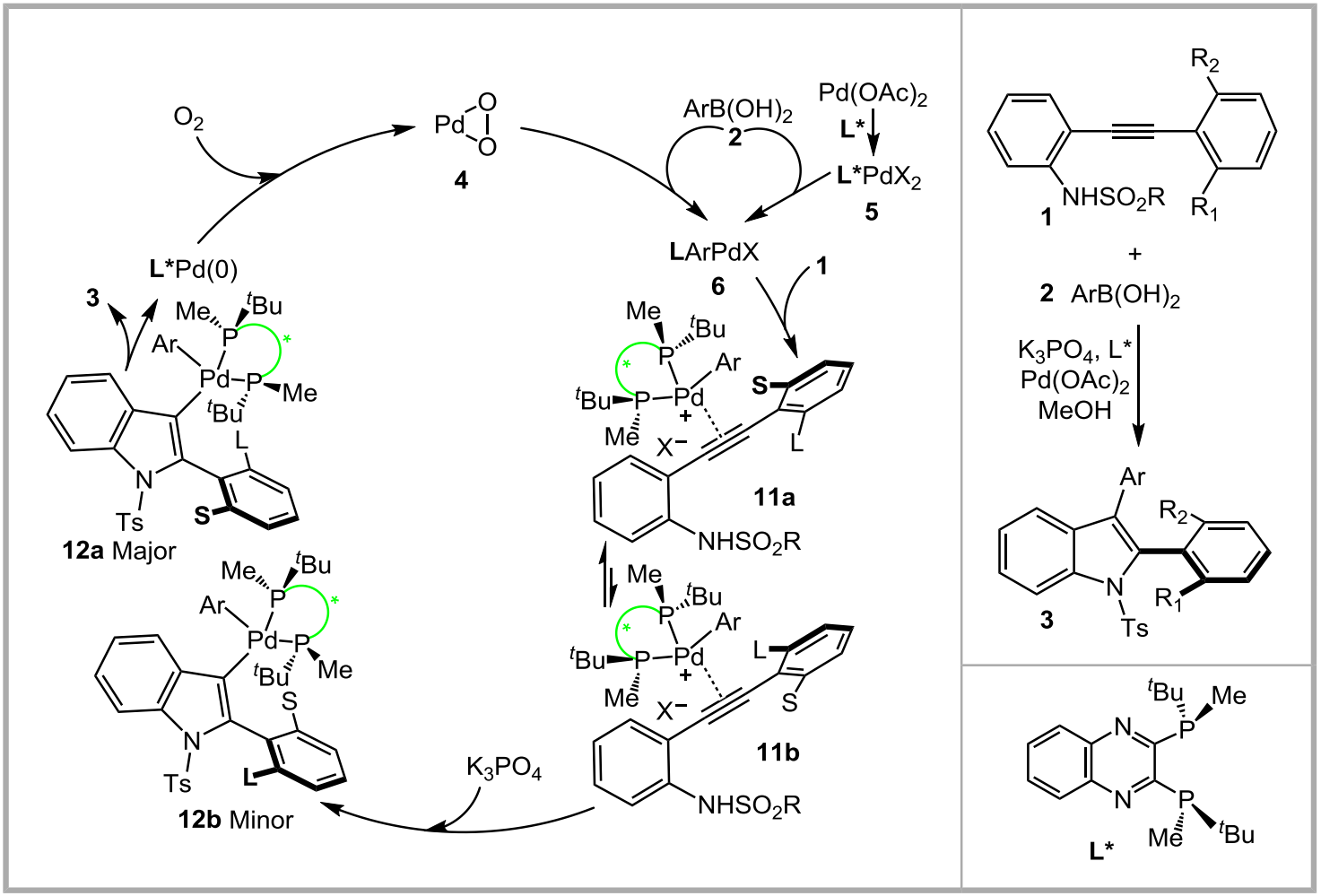
Presentation of Atroposelective Synthetic Strategies



Cheng, J.-K.; Ye, L.; Tan, B. *Chem. Rev.* **2021**, *121*, 4805-4902.

Introduction

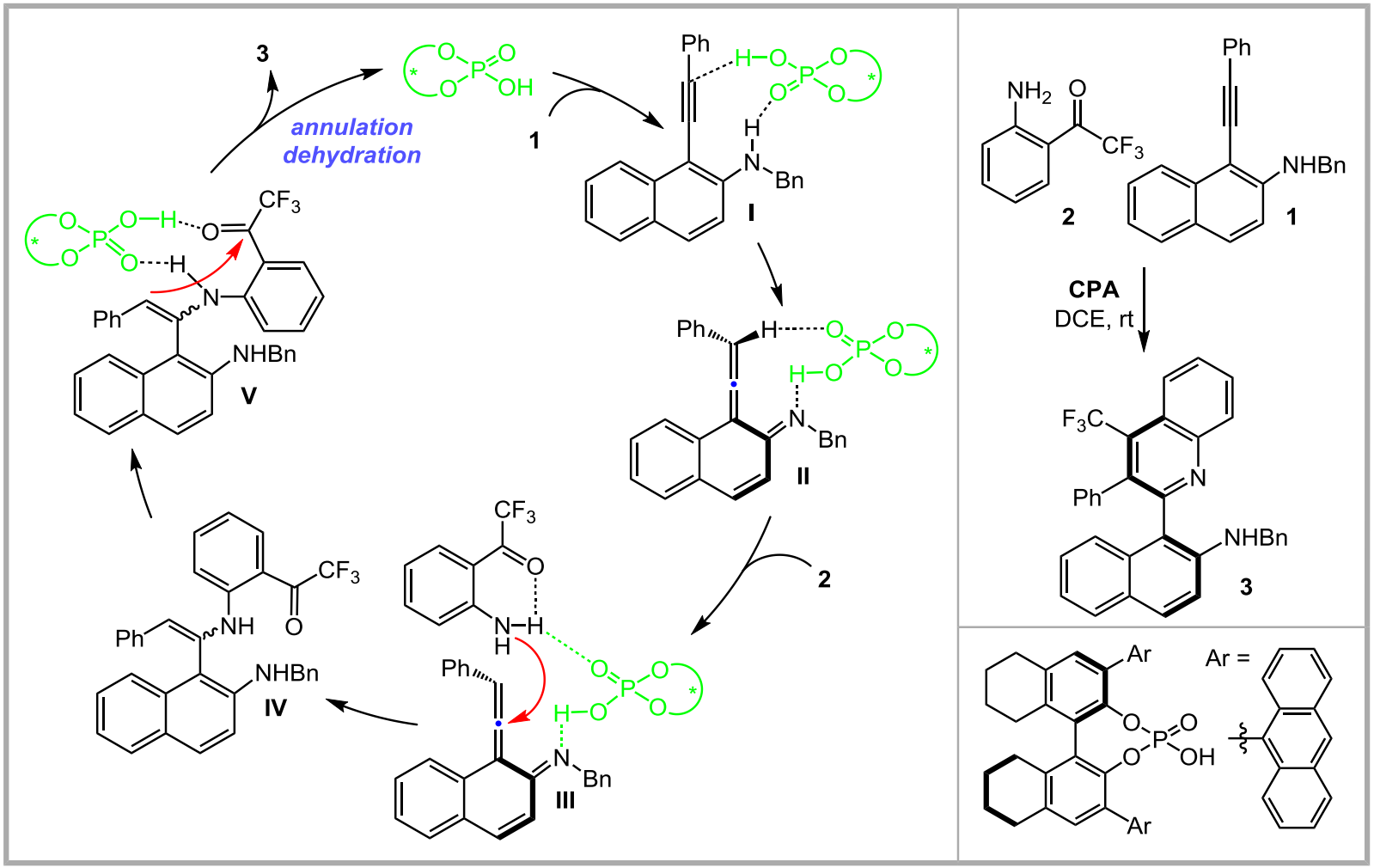
Transition-Metal-Catalyzed Transformation of Alkynyl Arenes



He, Y.-P.; Wang, J.; Zhu, J. *Angew. Chem. Int. Ed*. **2020**, *59*, 23077-23082.

Introduction

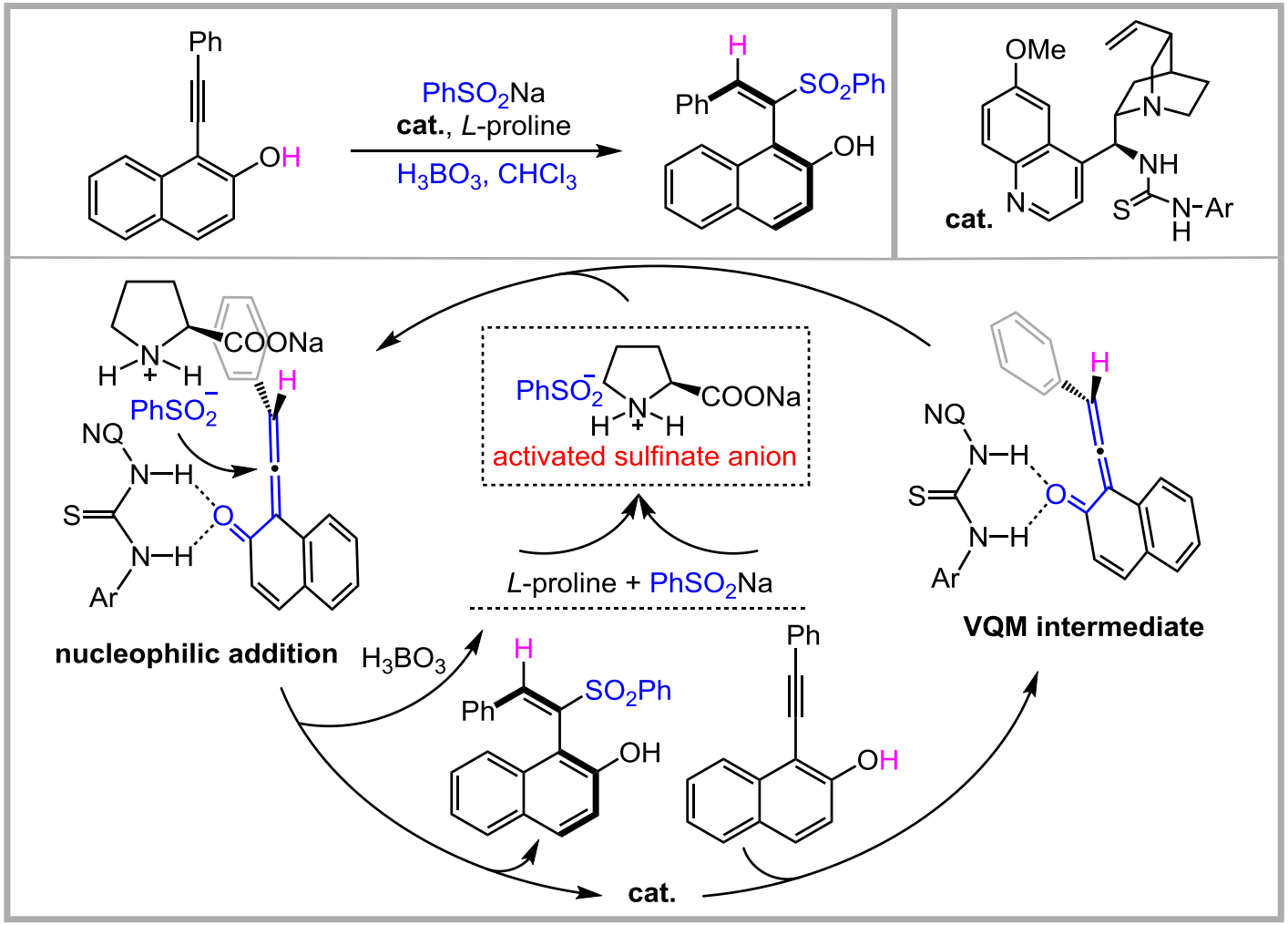
Chiral H-Based VQMs: Nucleophilic Addition



Zhang, L.; Zhong, G.; Tan, B. *Angew. Chem. Int. Ed*. **2020**, *59*, 23077-23082.

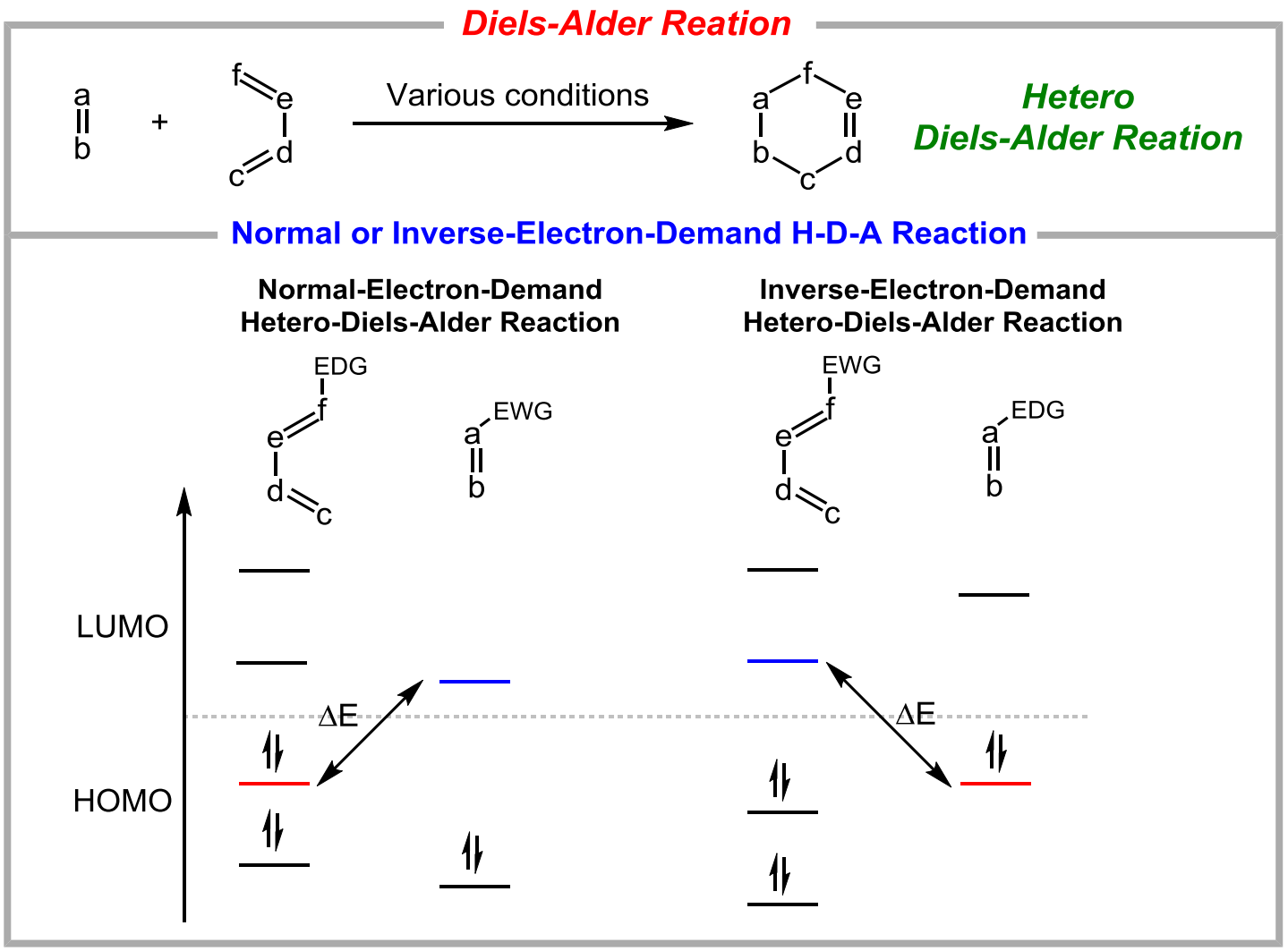
Introduction

Chiral H-Based VQMs: Nucleophilic Addition



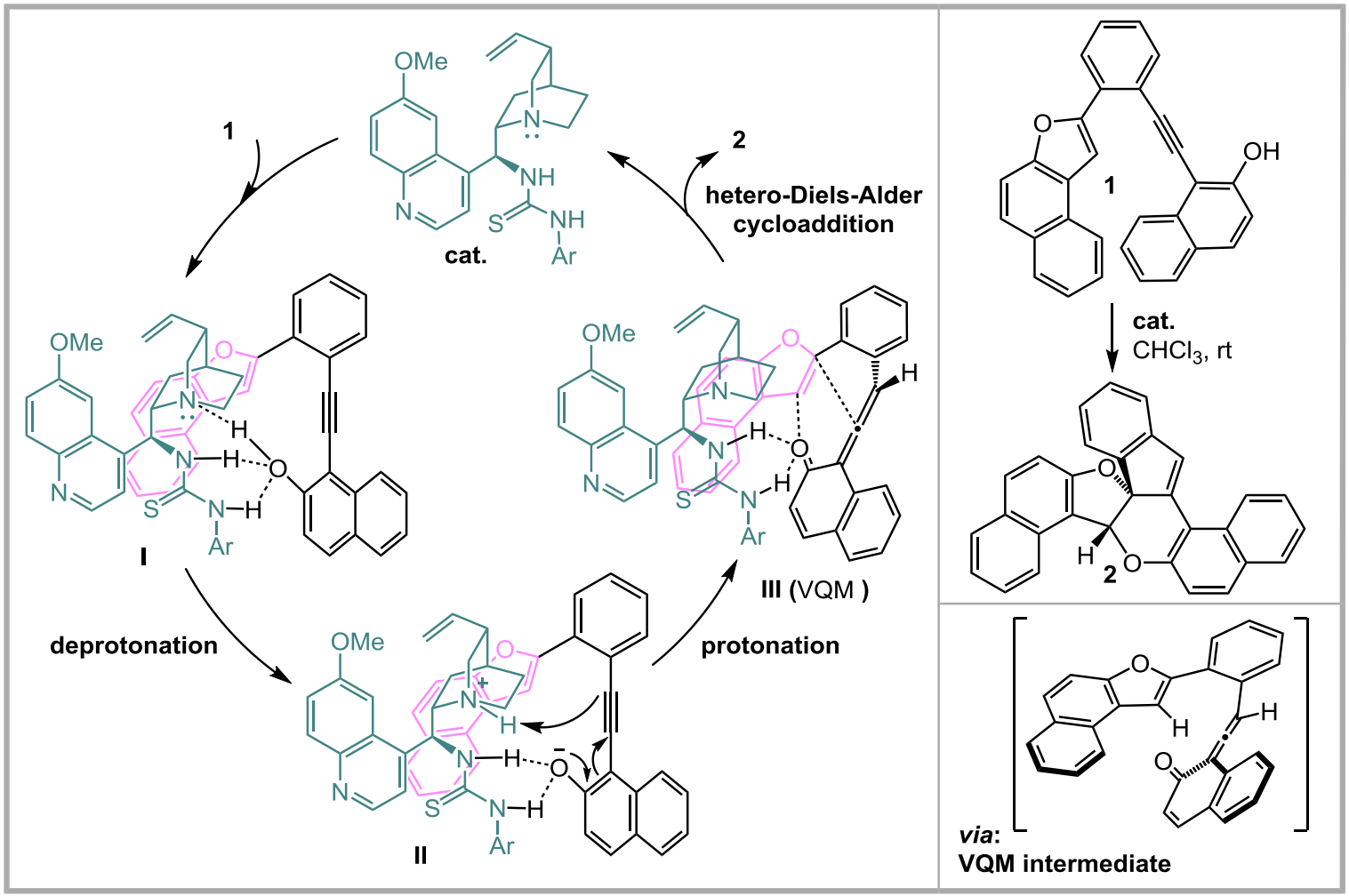
Jia, S.; Deng, J.; Yan, H. *J. Am. Chem. Soc*. **2018**, *140*, 7056-7060.

Introduction



Introduction

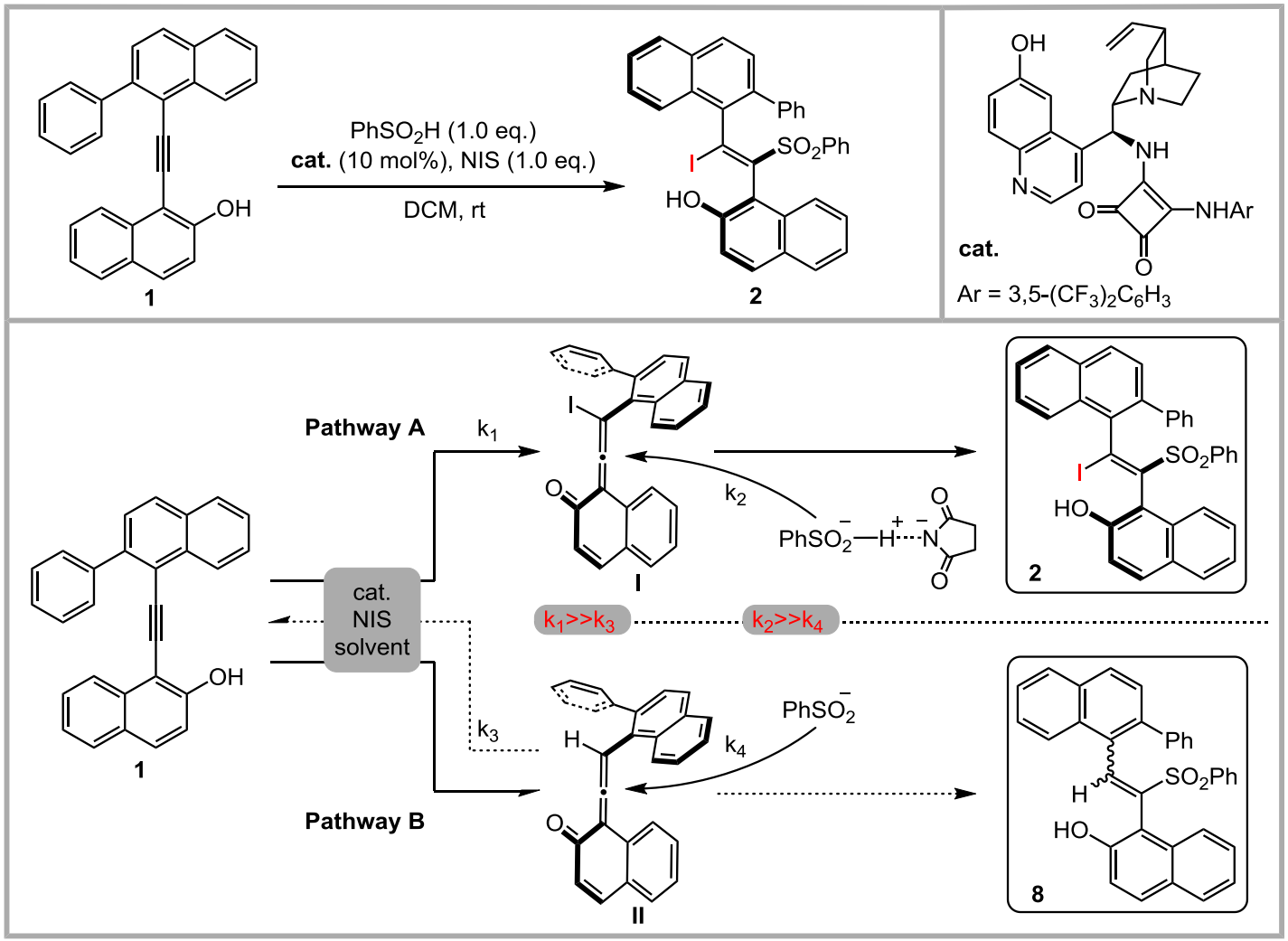
Chiral H-Based VQMs: Hetero-Diels-Alder Reaction



Wu, X.; Deng, J.; Yan, H. *Angew. Chem. Int. Ed*. **2017**, *56*, 13722-13726.

Introduction

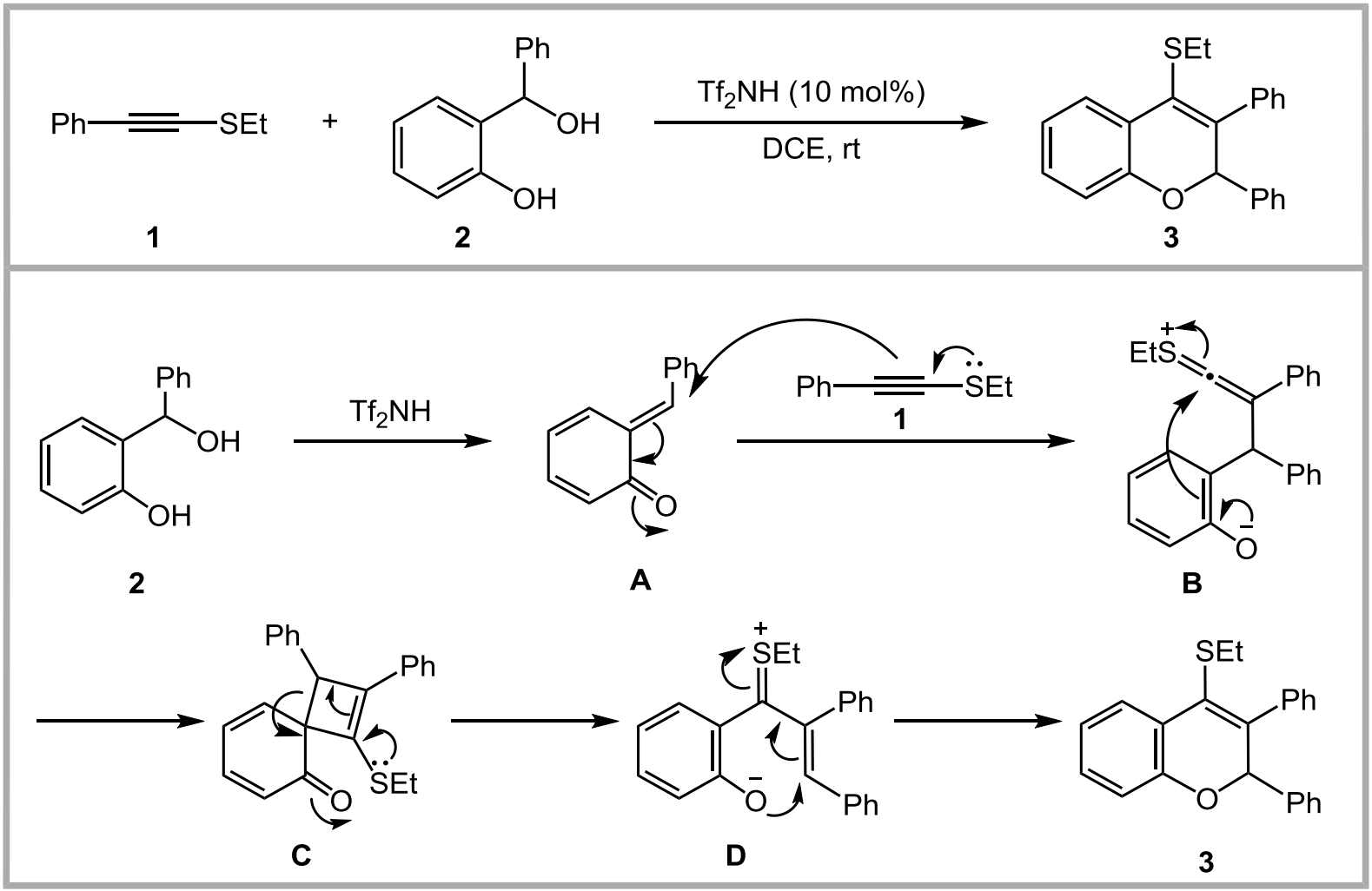
Chiral Halogen-Based VQMs: Nucleophilic Addition



Tan, Y.; Li, D.; Yan, H. *J. Am. Chem. Soc*. **2018**, *140*, 16893-16898.

Introduction

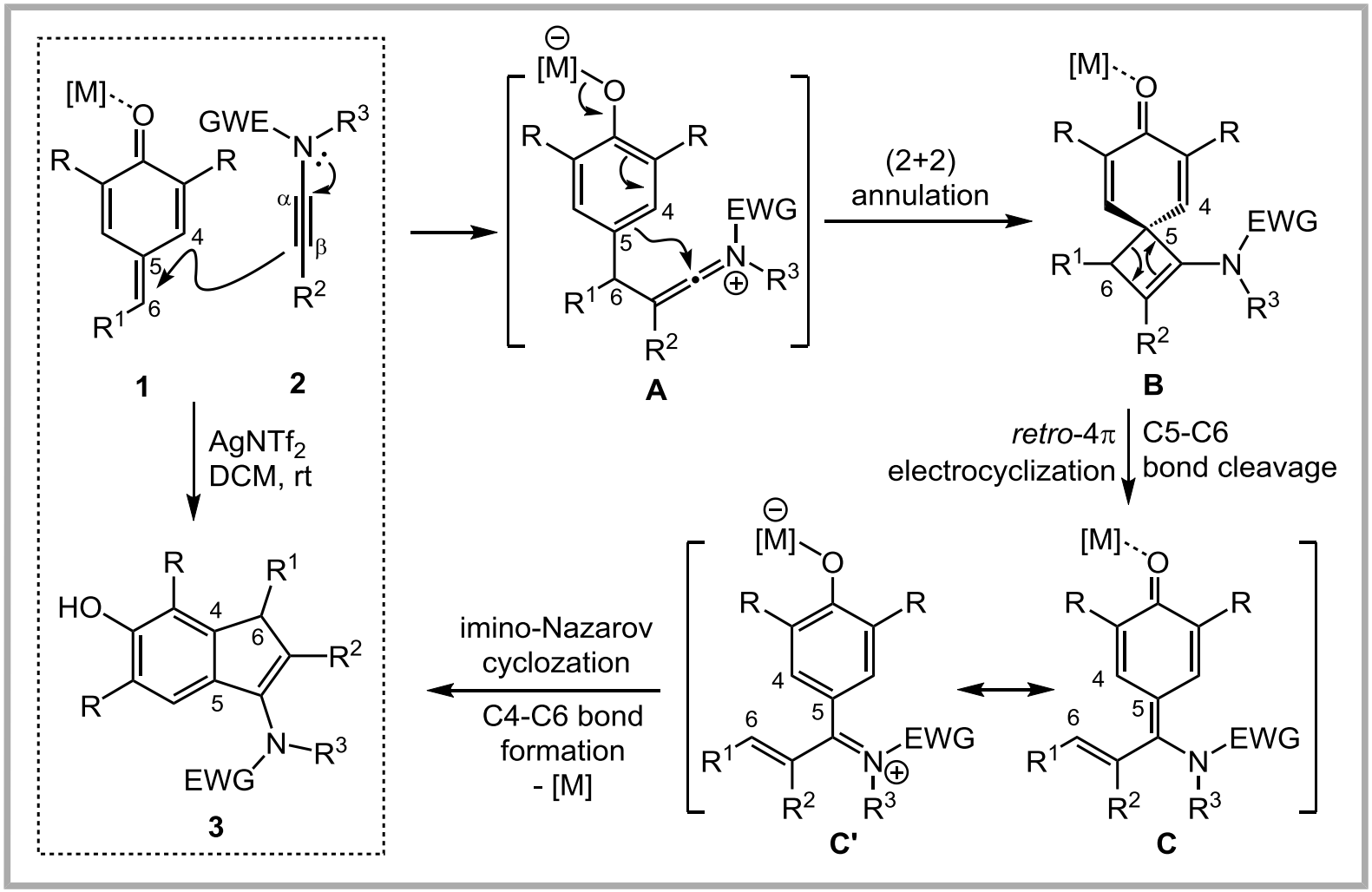
Brønsted Acid Catalyzed Reaction of *o*-QMs with Alkynes



Hu, H.-Z.; Qian, P.-C.; Ye, L.-W. *Org. Lett.* **2020**, *22*, 648-652.

Introduction

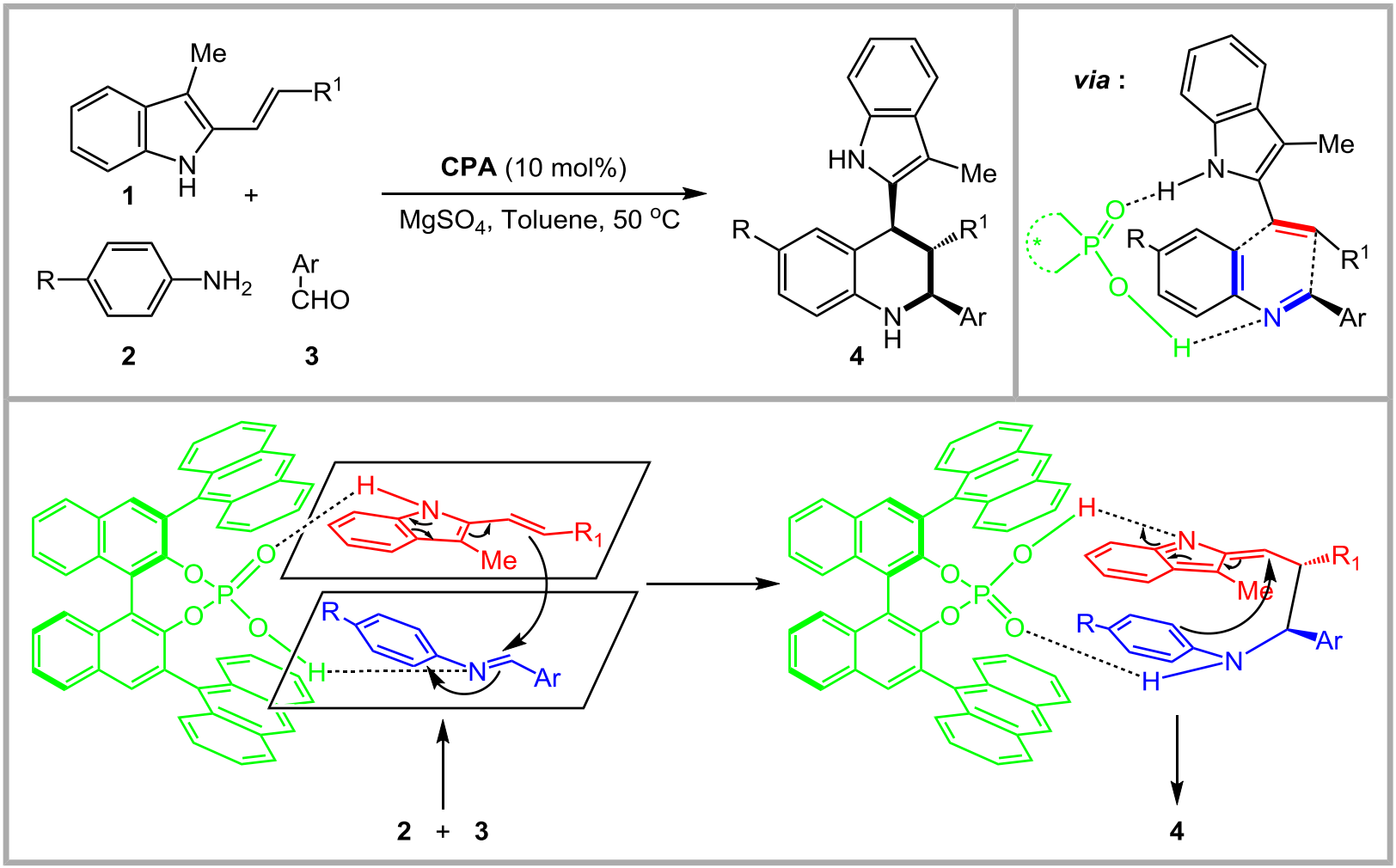
Lewis Acid Catalyzed Reaction of *p*-QMs with Alkynes



Yu, K.-Y.; Zhao, X.-H.; Fan, C.-A. *Org. Lett.* **2021**, *23*, 5885-5890.

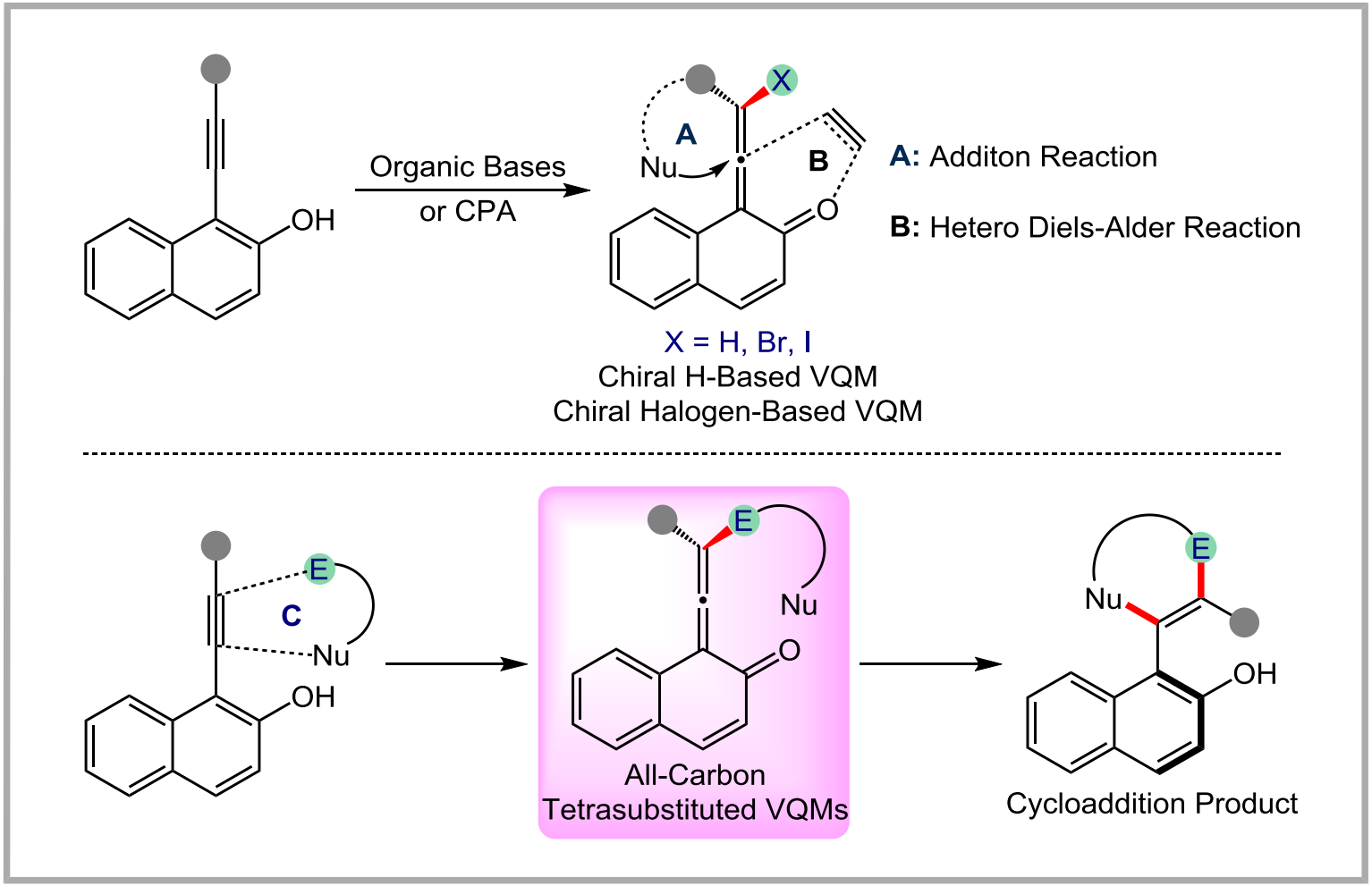
Introduction

CPA Catalyzed Reaction of Aryl Imines with Alkenes



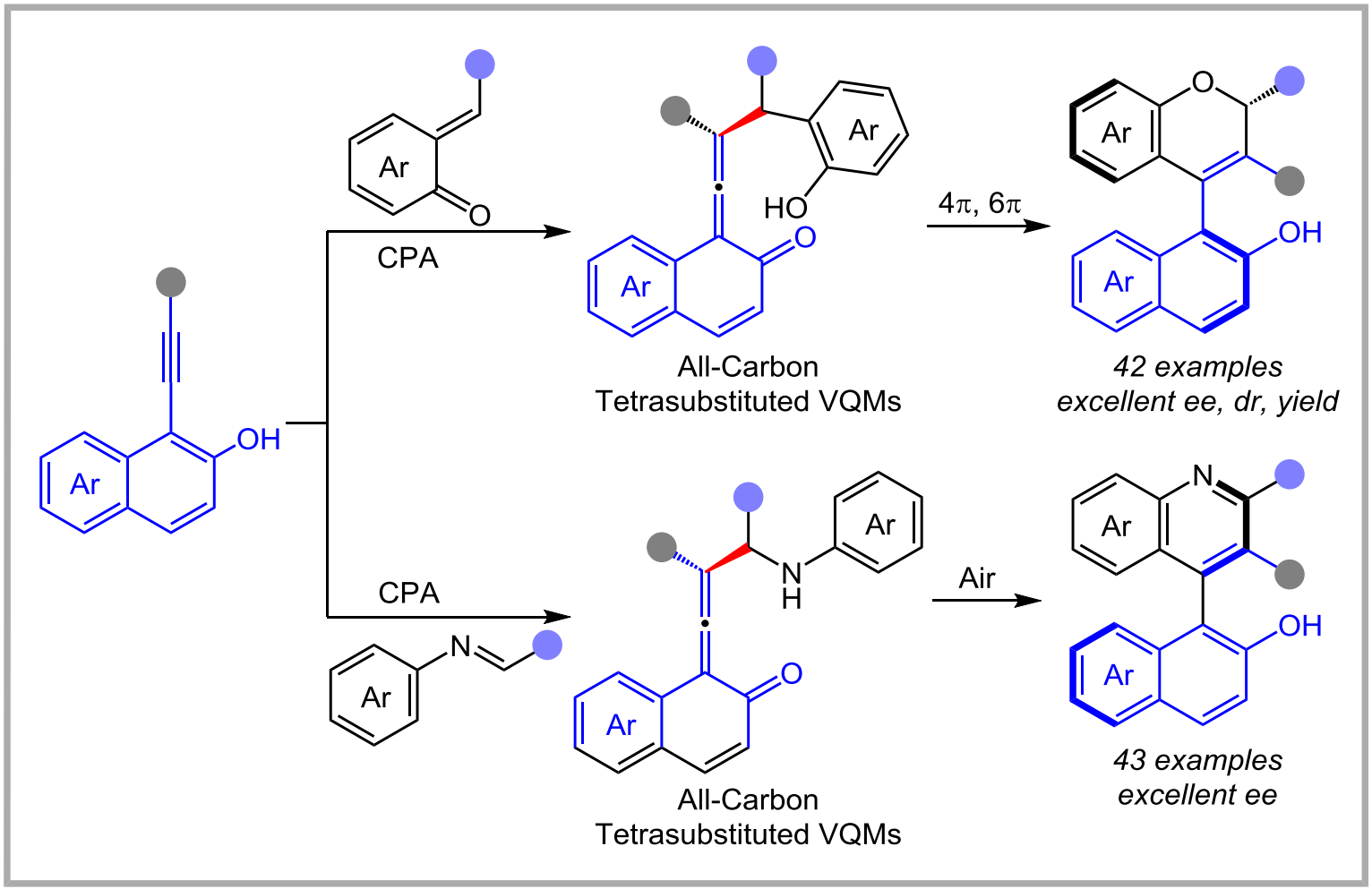
Dai, W.; Tao, J.-Y.; Shi, F. *J. Org. Chem*. **2016**, *81*, 185-192.

Introduction



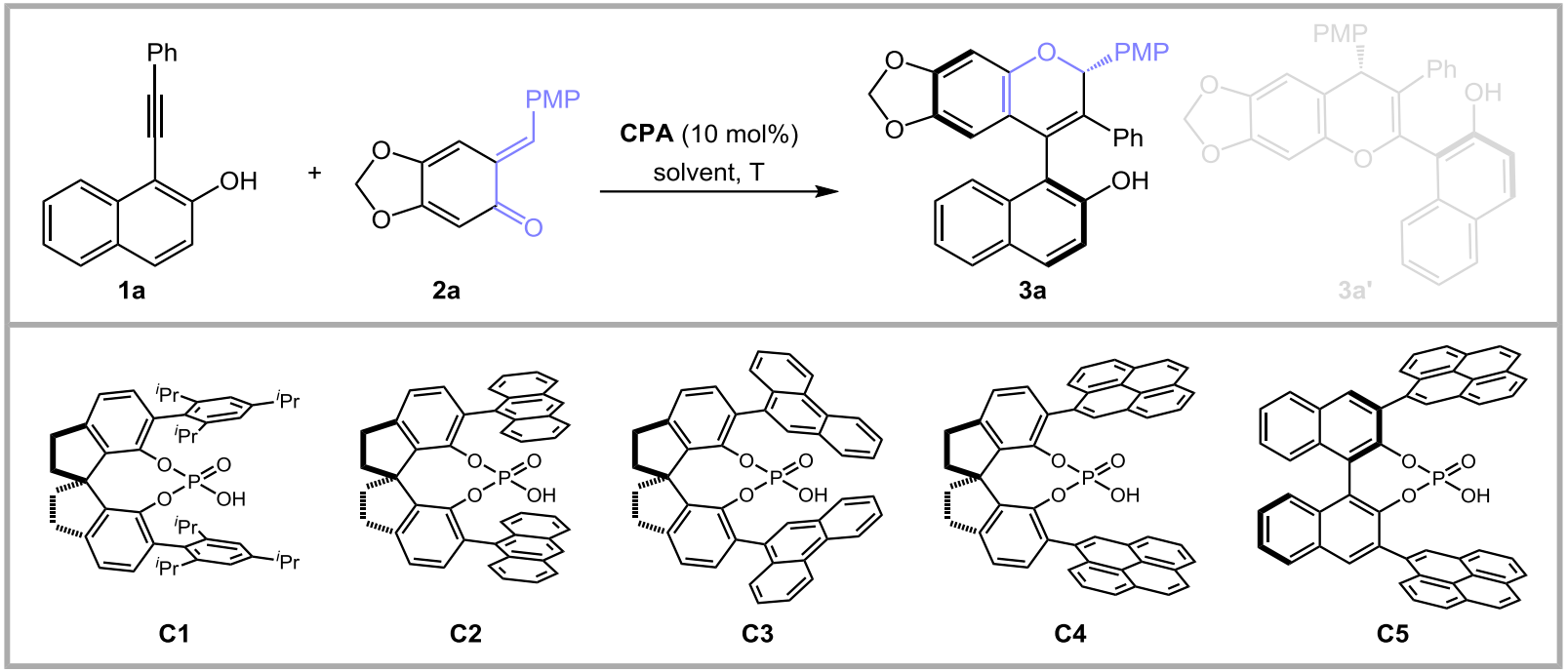
Go, B.-B.; Chen, J.; Zhou, L. *Angew. Chem. Int. Ed*. **2022**, *61, e202208174*.

Introduction



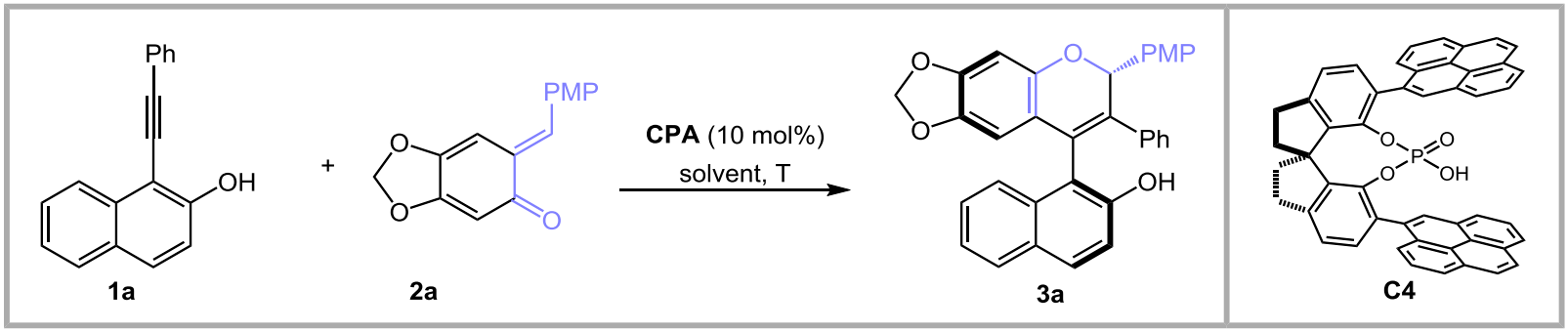
Go, B.-B.; Chen, J.; Zhou, L. *Angew. Chem. Int. Ed*. **2022**, *61, e202208174*.

Introduction



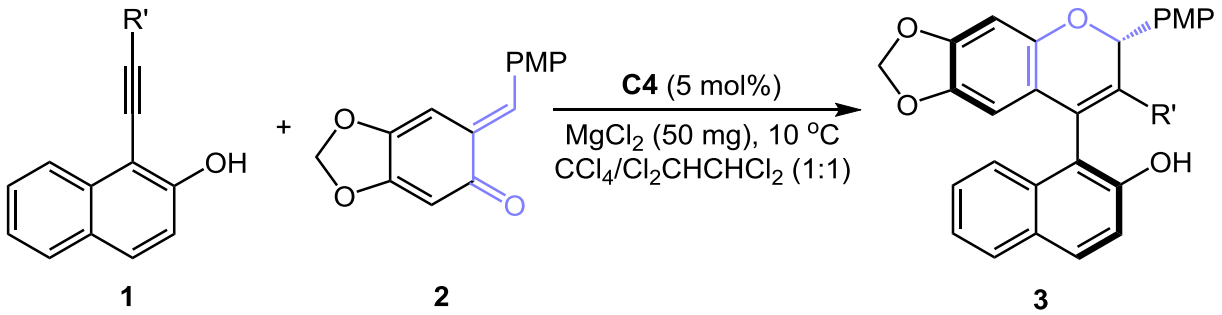
Entry	CPA	Solvent	T (°C)	Yield (%)	Ee (%)
1	**C1**	CCl_4	25	43	62
2	**C2**	CCl_4	25	70	60
3	**C3**	CCl_4	25	72	61
4	**C4**	CCl_4	25	81	84
5	**C5**	CCl_4	25	60	20

Introduction

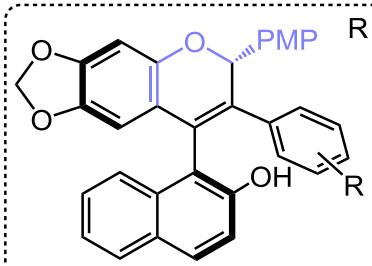


Entry	CPA	Solvent	$MgCl_2$	T(°C)	Yield (%)	Ee(%)
6	**C4**	**CH_2Cl_2**	-	25	82	79
7	**C4**	**$C_6H_5CH_3$**	-	25	80	82
8	**C4**	**C_6H_5F**	-	25	85	81
9	**C4**	**$Cl_2CHCHCl_2$**	-	25	80	89
10	**C4**	**$CCl_4/Cl_2CHCHCl_2$ (1:1)**	**-**	25	94	90
11	**C4**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	**50**	**25**	89	92
12	**C4**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	50	**40**	82	91
13	**C4**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	50	**10**	92	93
14	**C4**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	50	**-10**	93	92
15	**C4 (5 mol%)**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	50	10	93	92
16	**C4 (2 mol%)**	$CCl_4/Cl_2CHCHCl_2$ (1:1)	50	10	88	89

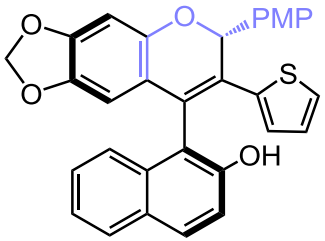
Substrate Scope



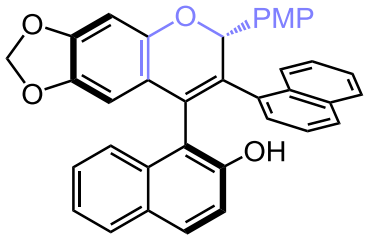
1 2 3 C4



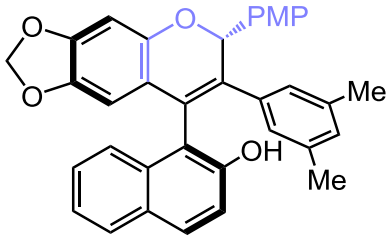
R = 2-Me, **3a**, 94%, 93% ee
2-Br, **3b**, 98%, 96% ee
3-Br, **3c**, 97%, 92% ee
3-CO_2Et, **3d**, 98%, 88% ee
4-Me, **3e**, 92%, 93% ee
4-^{t}Bu, **3f**, 98%, 90% ee
4-CO_2Et, **3g**, 95%, 91% ee
4-NO_2, **3h**, 95%, 90% ee (dr, 9:1)



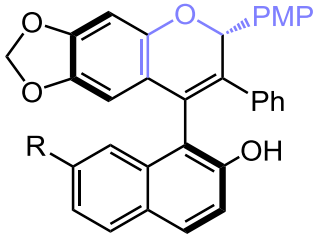
3i, 79%, 86% ee



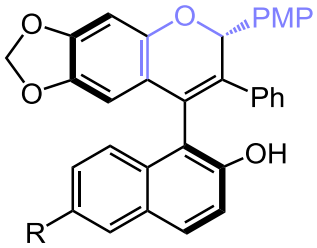
3j, 92%, 93% ee



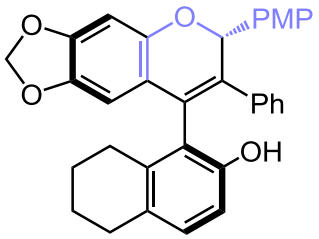
3k, 95%, 90% ee



R = Me, **3m**, 99%, 95% ee
Ph, **3n**, 98%, 93% ee
Br, **3p**, 92%, 95% ee

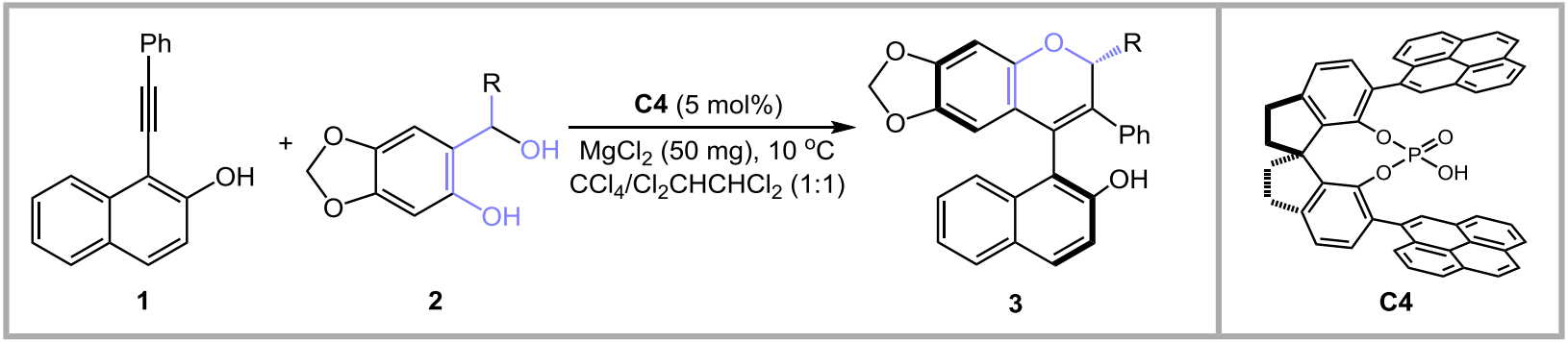


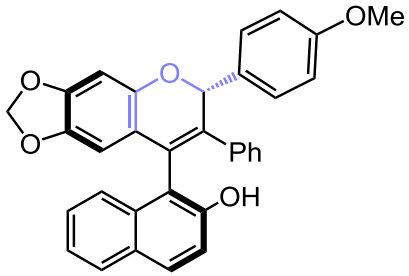
R = Me, **3q**, 99%, 95% ee
Ph, **3r**, 97%, 92% ee
Br, **3s**, 93%, 93% ee



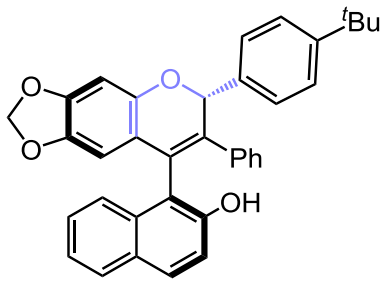
3t, 77%, dr, 1:1
85% ee, 90% ee

Substrate Scope

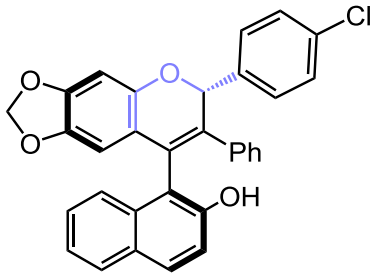




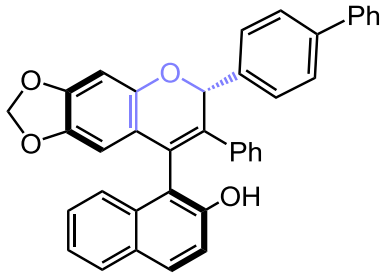
3aa, 91%, dr, 20:1, 92% ee



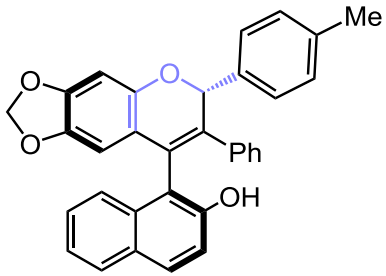
3ab, 85%, dr, 13:1, 92% ee



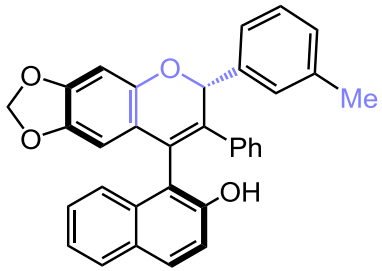
3ac, 85%, dr, 9:1, 95% ee



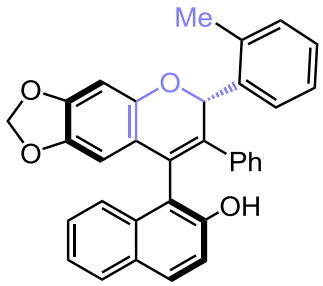
3ad, 95%, dr, 16:1, 99% ee



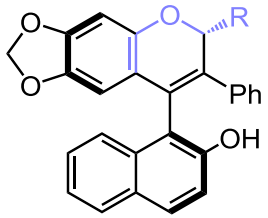
3ae, 88%, dr, 16:1, 94% ee



3af, 72%, dr, 17:1, 96% ee

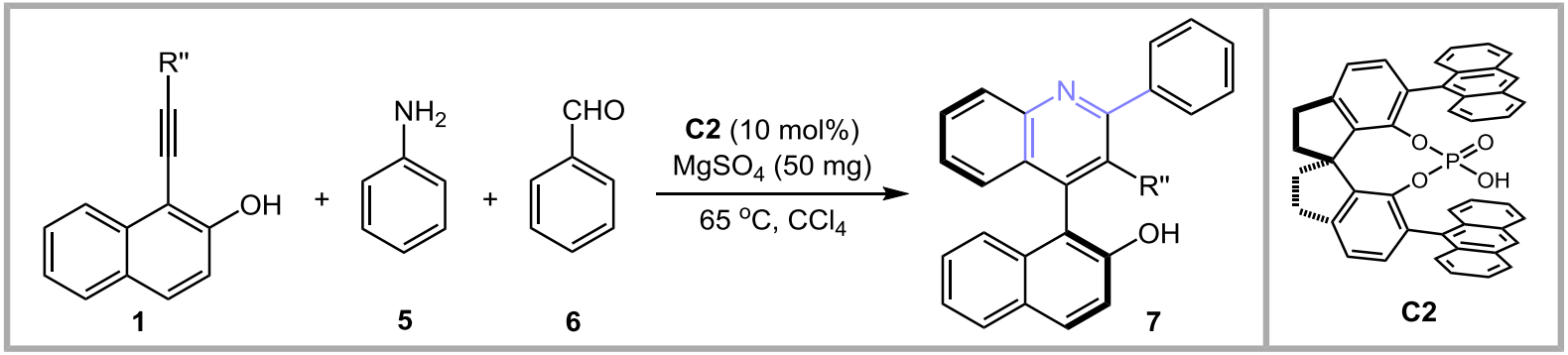


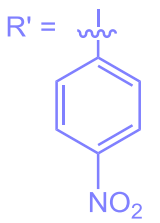
3ag, 85%, dr, 12:1, 98% ee

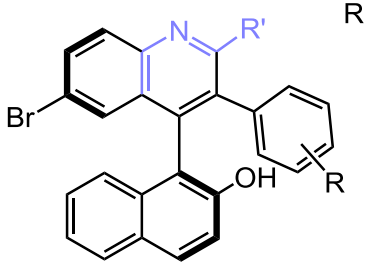


2-Naphthyl, **3ah**, 92%, dr, 16:1, 96% ee

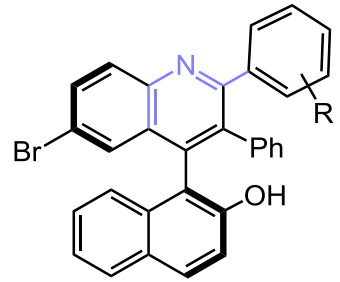
Substrate Scope



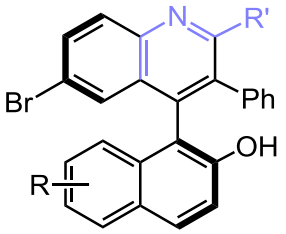




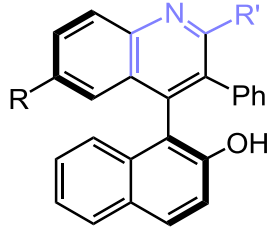
R = 2-Me, **7a**, 58%, dr, 12:1, 94% ee
2-F, **7b**, 60%, dr, 5:1, 89% ee
3-Br, **7c**, 59%, 99% ee
3-CO_2Me, **7d**, 44%, 99% ee
4-Me, **7e**, 70%, 99% ee
4-^{t}Bu, **7f**, 67%, 99% ee
4-CO_2Et, **7g**, 67%, 99% ee
4-NO_2, **7h**, 59%, 99% ee



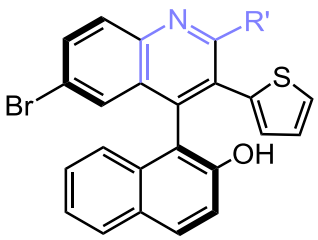
R = 4-NC, **7j**, 55%, 97% ee
4-CO_2Me, **7k**, 55%, 97% ee



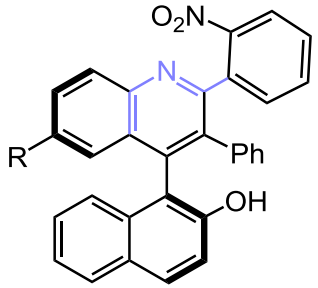
R = 2-Me, **7m**, 58%, 94% ee
3-Me, **7n**, 60%, 89% ee



R = Cl, **7p**, 68%, 99% ee
Me, **7q**, 46%, 90% ee
PhO, **7r**, 48%, 92% ee

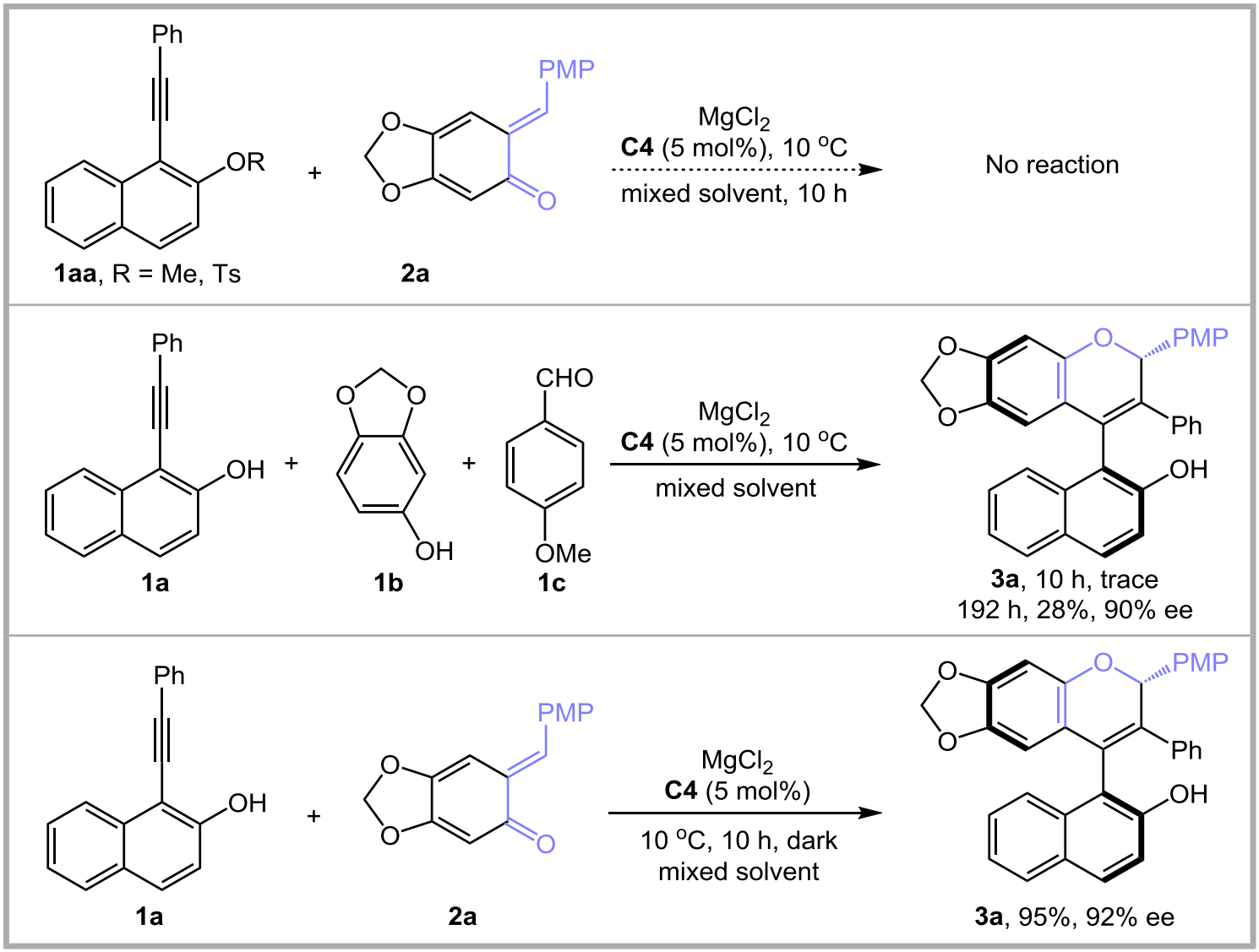


7s, 79%, 86% ee

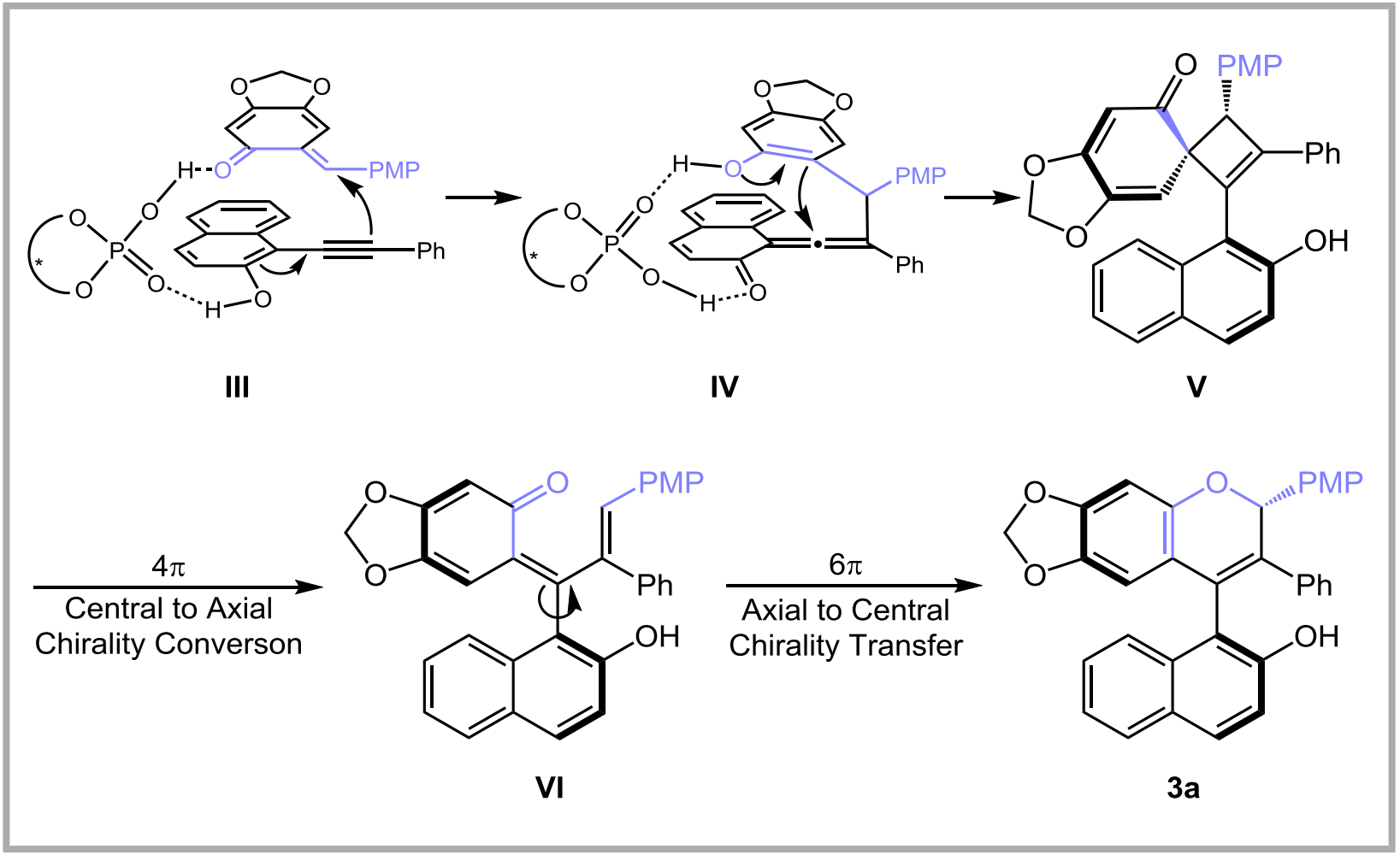


R = Br, **7t**, 55%, 97% ee
PhO, **7u**, 55%, 97% ee

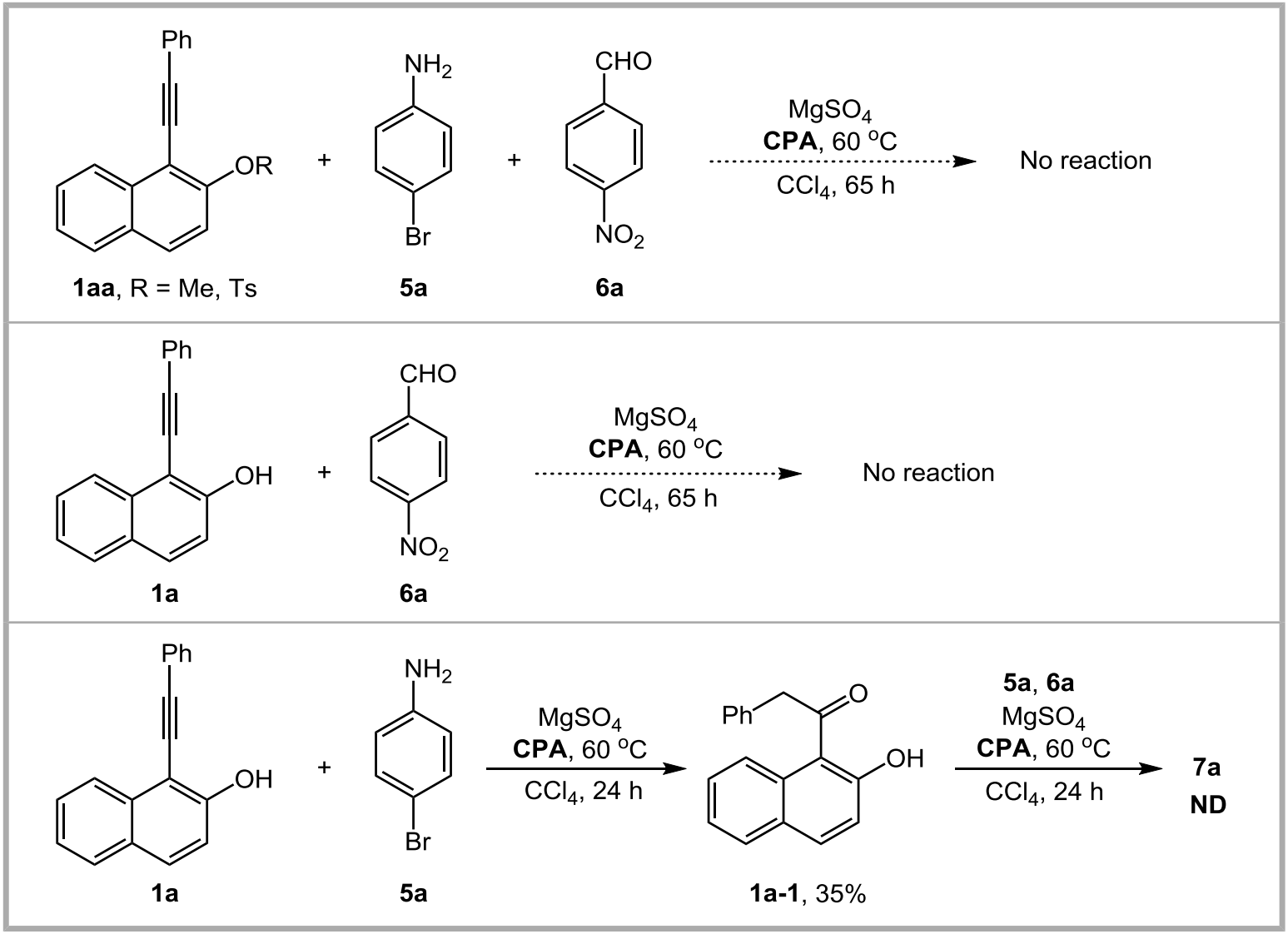
Mechanistic Experiments



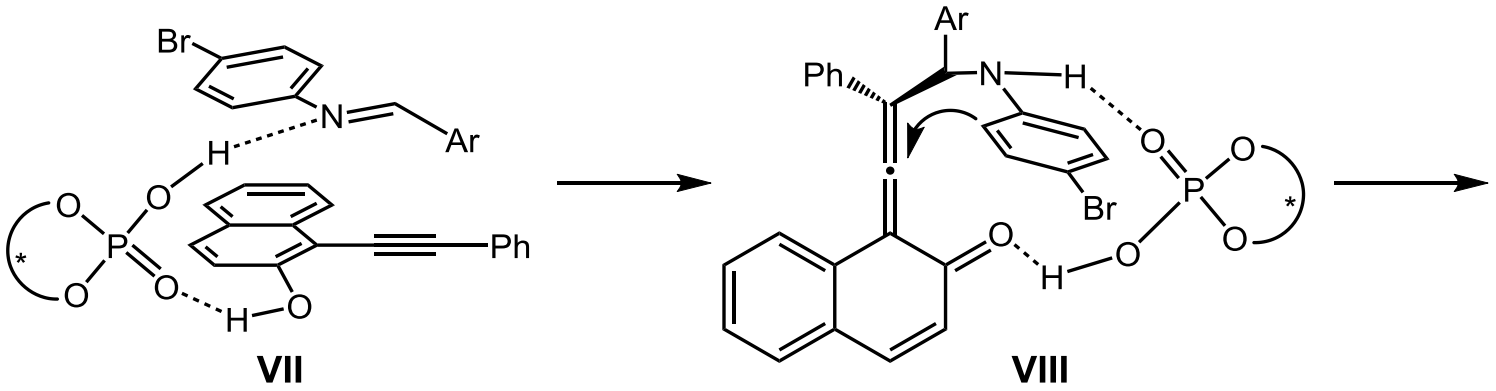
Proposed Mechanis

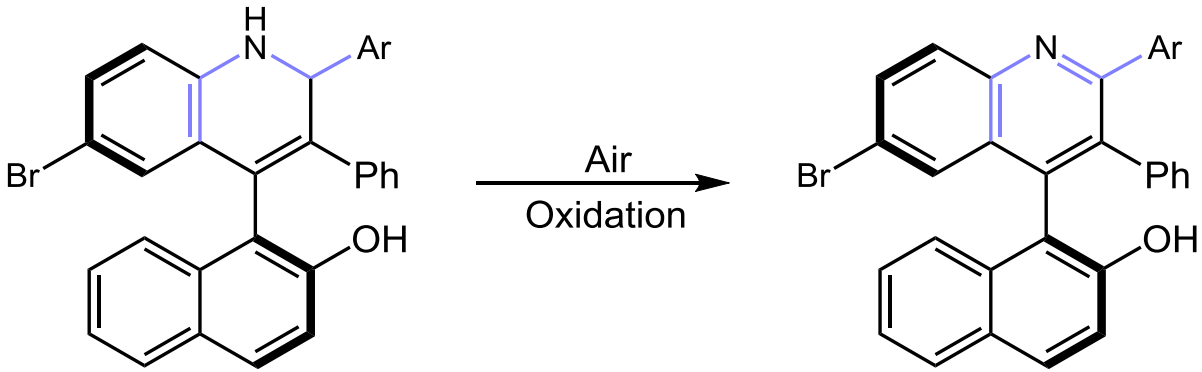


Mechanistic Experiments



Proposed Mechanis

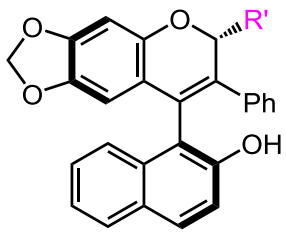




7a-INT (Ar = 4-NO_2Ph)
$[M+H]^+$ m/z: 549.0808
found: 549.0802

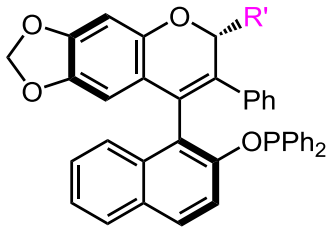
7a

Synthetic Transformations



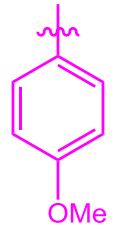
3a, 99% ee, crystallization

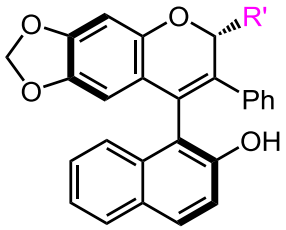
Ph_2PCl, Et_3N, DMAP, Et_2O, 25 °C



9, 75%, 99% ee

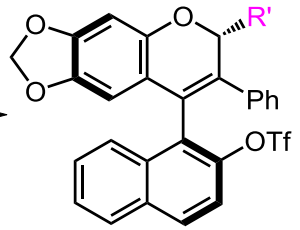
R' =





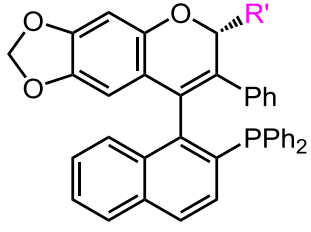
3a, 99% ee
crystallization

K_2CO_3
4-$NO_2C_6H_4OTf$
DMF, 25 °C

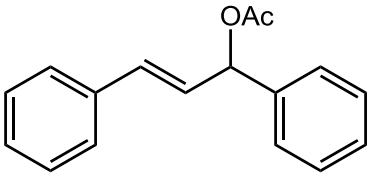


3a-OTf, 91%, 99% ee

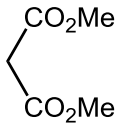
$Ph_2P(O)H$
$Pd(OAc)_2$, dppp
DIPEA, DMSO, 120 °C
then **3a-P(O)Ph_2**, 52%, dr, 1:1
$HSiCl_3$, PhMe, 120 °C



8a (*R, aS*), 72%, dr, 6:1, 97% ee
8b (*R, aR*), 70%, dr, 2:3, 98% ee

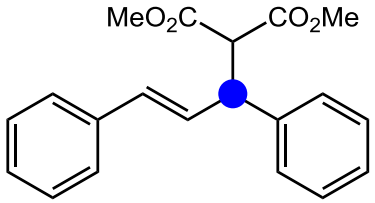


+

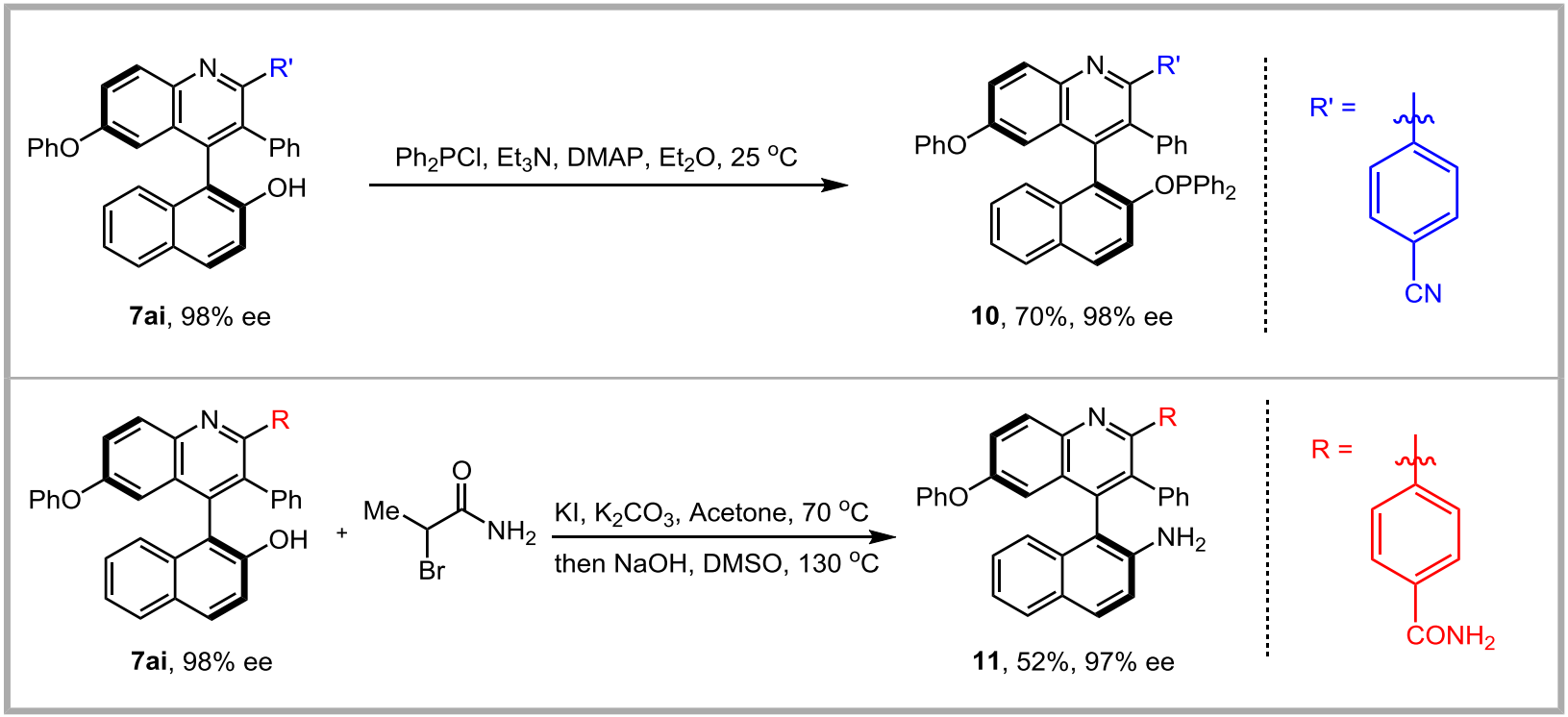


L* (2 mol%)
$[Pd(allyl)Cl]_2$ (1 mol%)
BSA, K_2CO_3, DCM, 0 °C

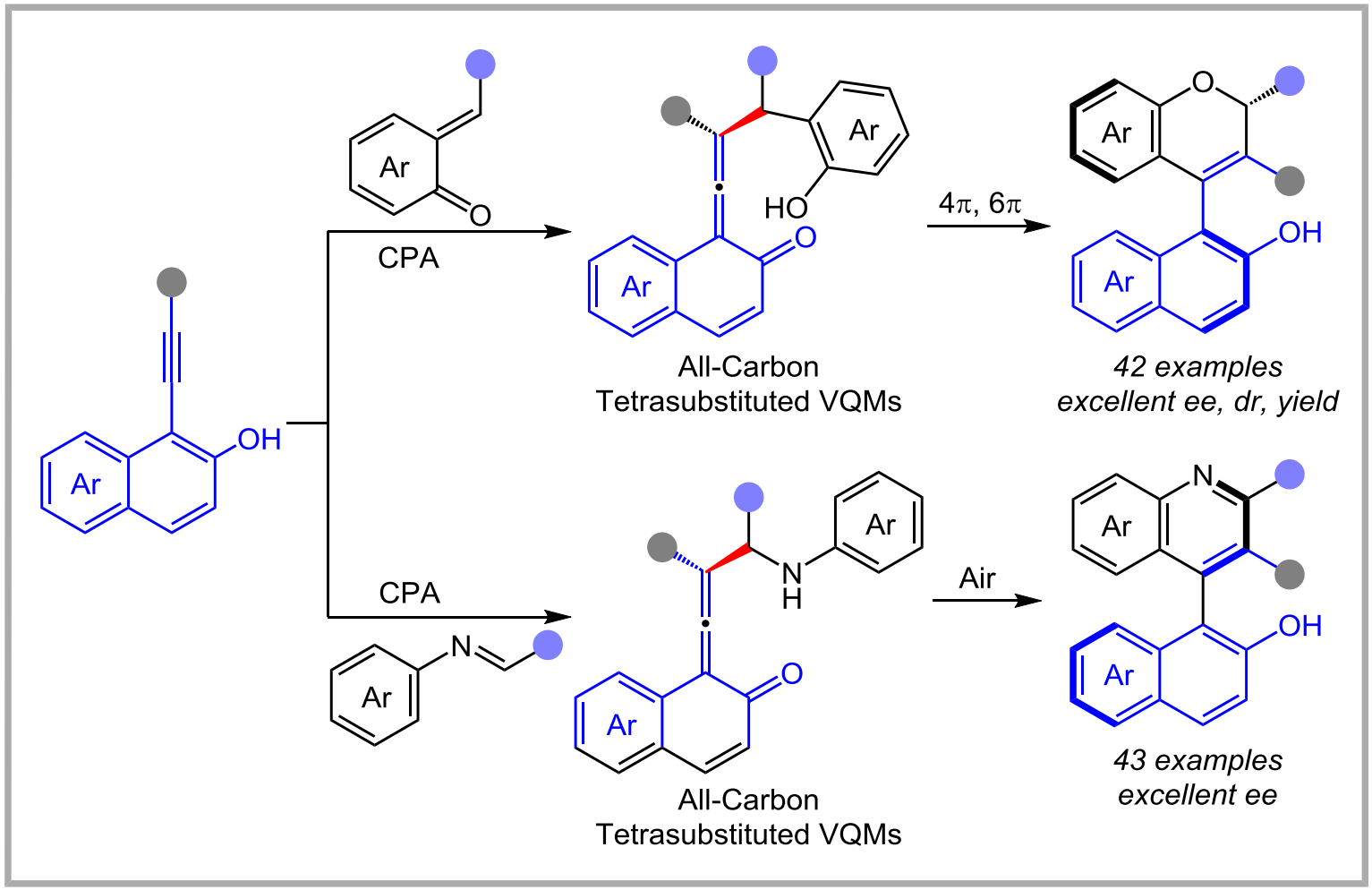
8a (*R, aS*), 76%, 82% ee
8b (*R, aR*), 90%, 57% ee



Synthetic Transformations



Summary


Ar
OH
CPA
Ar
O
Ar
HO
O
Ar
All-Carbon
Tetrasubstituted VQMs
4π, 6π
Ar
O
OH
Ar
42 examples
excellent ee, dr, yield
CPA
Ar
N
Ar
N
H
Ar
O
Ar
All-Carbon
Tetrasubstituted VQMs
Air
Ar
N
OH
Ar
43 examples
excellent ee

The First Paragraph

写作思路

轴手性化合物的重要性

↓

概述轴手性化合物的合成策略

↓

由有机催化经联烯醌
中间体合成轴手性化合物

The First Paragraph

Axially chiral compounds are present in a lot of **natural products**, **biologically active compounds**, and privileged **chiral ligands and catalysts**. **(轴手性化合物的重要性)**

Numerous **metal-catalyzed** or **organocatalytic strategies** have been developed to access axially chiral molecules. Various arene deravitives are employed as starting materials because steric congestions at the **ortho-positions** could **prevent rotate around the axis**. Among them, the **transition-metal-catalyzed nucleophilic addition** or **cycloaddition reactions** of **alkynyl arenes** have been well documented during past decades. **(轴手性化合物的合成策略)**

Organocatalyzed transformation of 2-alkynylnaphthols have attracted a great deal of interest in synthetic chemistry, because the **vinylidene-quinone methides (VQMs)** could be formed as active. **Chiral VQMs** can be captured by a series of nucleophiles to **give axially chiral compounds**. **(CPA催化手性联烯醌中间体构建轴手性化合物)**

The Last Paragraph

写作思路

总结工作

↓

指出工作特征以及意义

↓

进一步工作展望

The Last Paragraph

In summary, we have developed the first enantioselective cycloaddition of alkynylnaphthols with *o*-quinone methides and imines. **(总结工作)**

A new class of naphthyl-2H-chromenes bearing axially and centrally chiral elements and axially chiral quinone-naphthols were prepared efficiently. The obtained products can be converted into valuable phosphine ligands and other functional molecules. The mechanistic experiments and theory calculations indicated that a **[2+2] cycloaddition, 4π-electrocyclic ring opening** and **6π-electrocyclization** are involved in the **cycloaddition of alkynylnaphthols with *o*-quinone methides**. The newly generated all-carbon tetrasubstituted VQMs will **open up avenues for more conversions**. **(工作特征以及意义)**

Further studies on the application of such enantioselective cycloaddition reaction for the synthesis of other chiral molecules **are currently underway. (工作展望)**

Representative Examples

The enantioselective intermolecular cycloaddition of alkynylnaphthols is an unmet synthetic challenge, only one preliminary result with 20% ee was reported at the allene ketone part. (unmet: /ʌn'met/ *adj.* 未满足的；一个尚未解决的挑战)

Several challenges associated with such intermolecular cycloaddtion reaction can be envisaged. (与…相关的若干挑战)

The asymmetric synthesis of such compounds has attracted a great deal of interest among researchers. (…引起了研究人员的极大兴趣)

The newly generated all-carbon tetrasubstituted VQMs will open up avenues for more conversions. (为…开辟道路)

Acknowledgement

Thanks
for your attention