

# Literature Report 3

## Asymmetric Construction of Aryl-Alkene Axis by Palladium-Catalyzed Suzuki–Miyaura Coupling Reaction

---

**Reporter:** Qing-Xian Xie

**Checker:** Xiang Li

2022-11-09

Qiu, S.-Q.; Tan, B.\* *Angew. Chem. Int. Ed.* **2022**, 61, e202211211

# CV of Prof. Bing Tan

---

## *Background:*



- **1997-2001** B. S., Hunan University of Science and Technology
- **2001-2005** M. S., Xiamen University
- **2005-2010** Ph. D., Nanyang Technological University
- **2010-2012** Postdoc., The Scripps Research Institute
- **2012-2018** Tenure-Track Associate Professor, SUSTC
- **2018-Now** Professor, SUSTC

---

## *Research:*

- Asymmetric axis chiral chemistry
- Organocatalytic multicomponent reactions
- Discovery and synthesis of chiral drug molecules

# Contents

---

**1** Introduction

---

**2** Main Strategies to Construct Axially Chiral Alkenes

---

**3** Atroposelective Suzuki-Miyaura Coupling

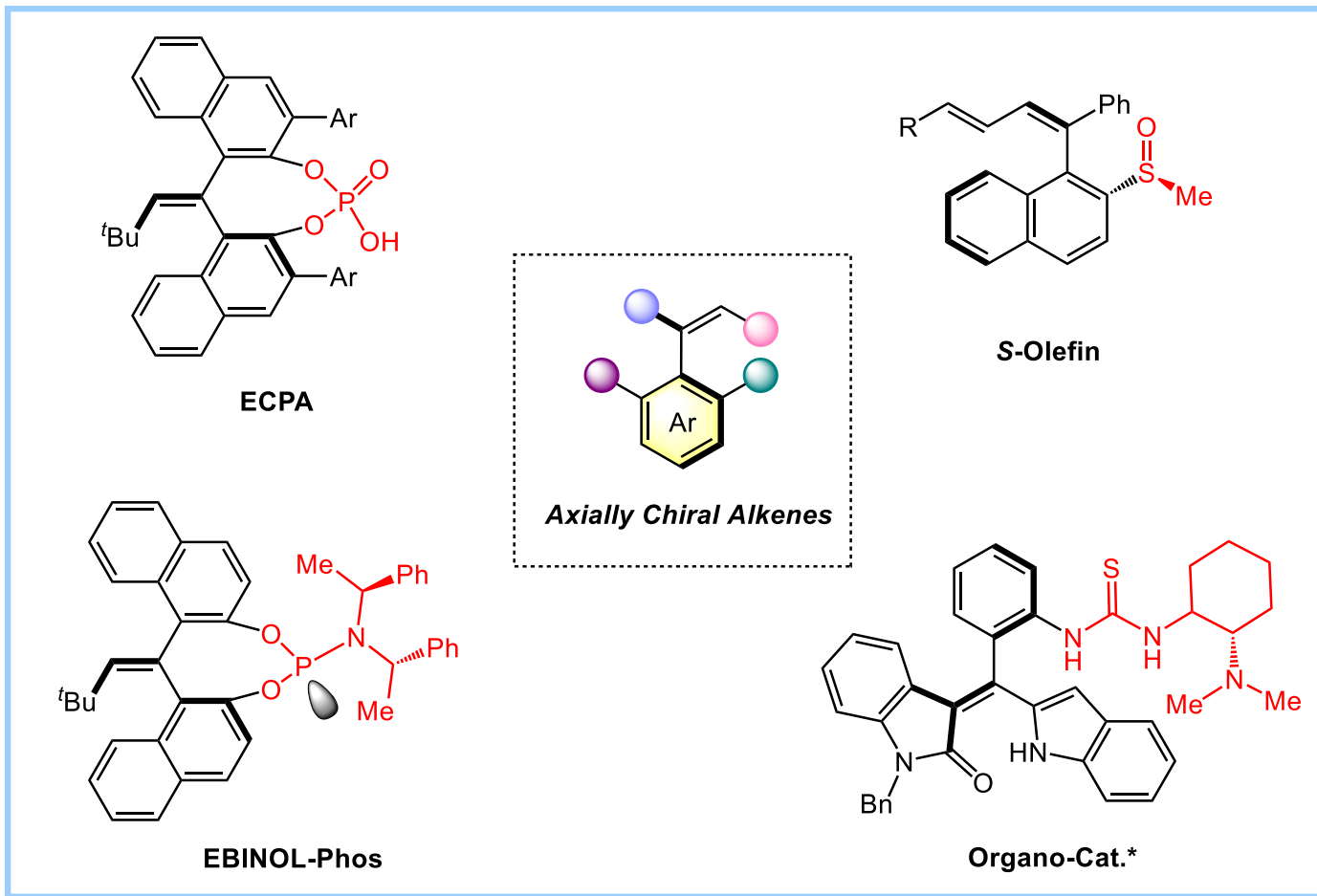
---

**4** Summary

---

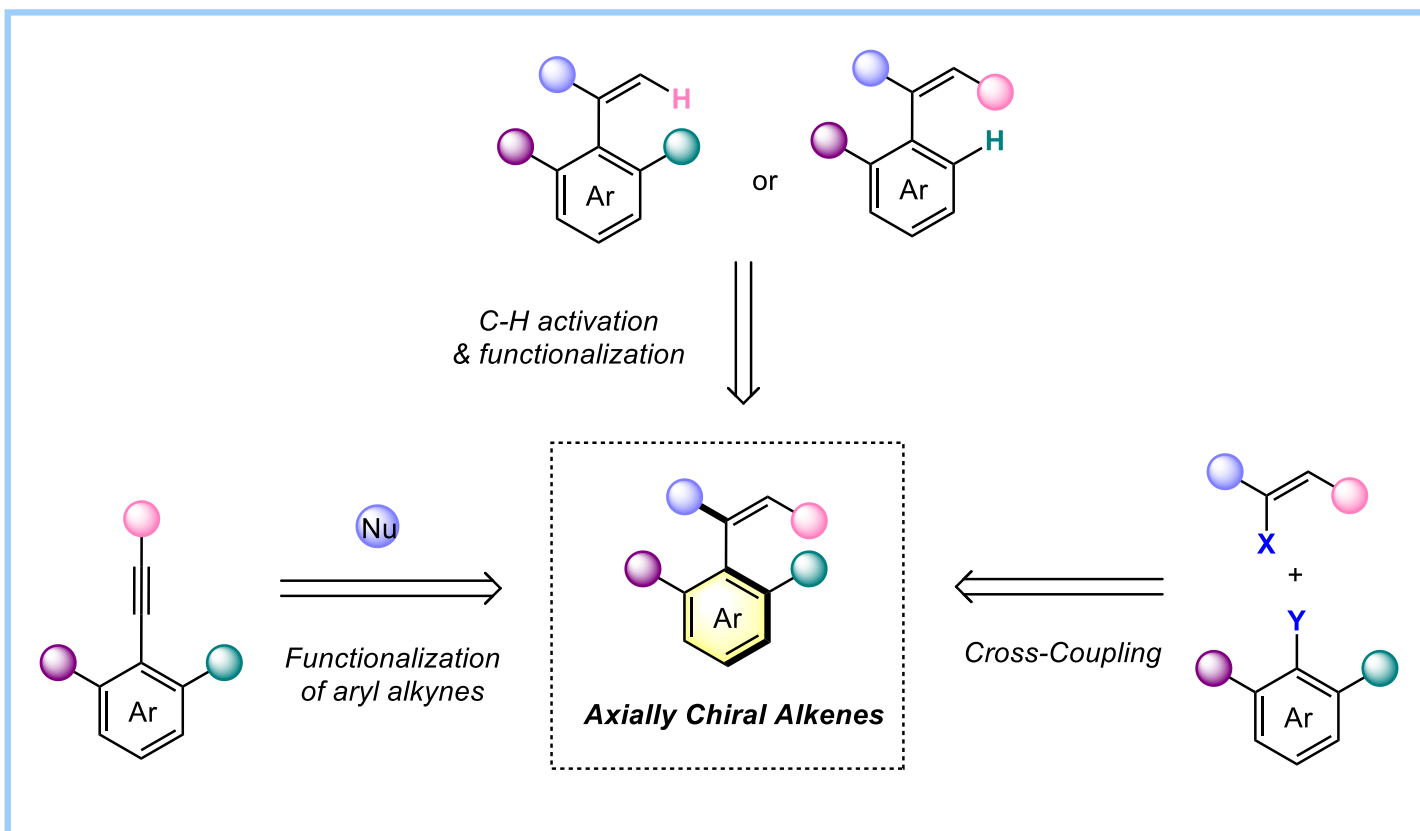
# Introduction

## Potential Utility of Axially Chiral Alkenes



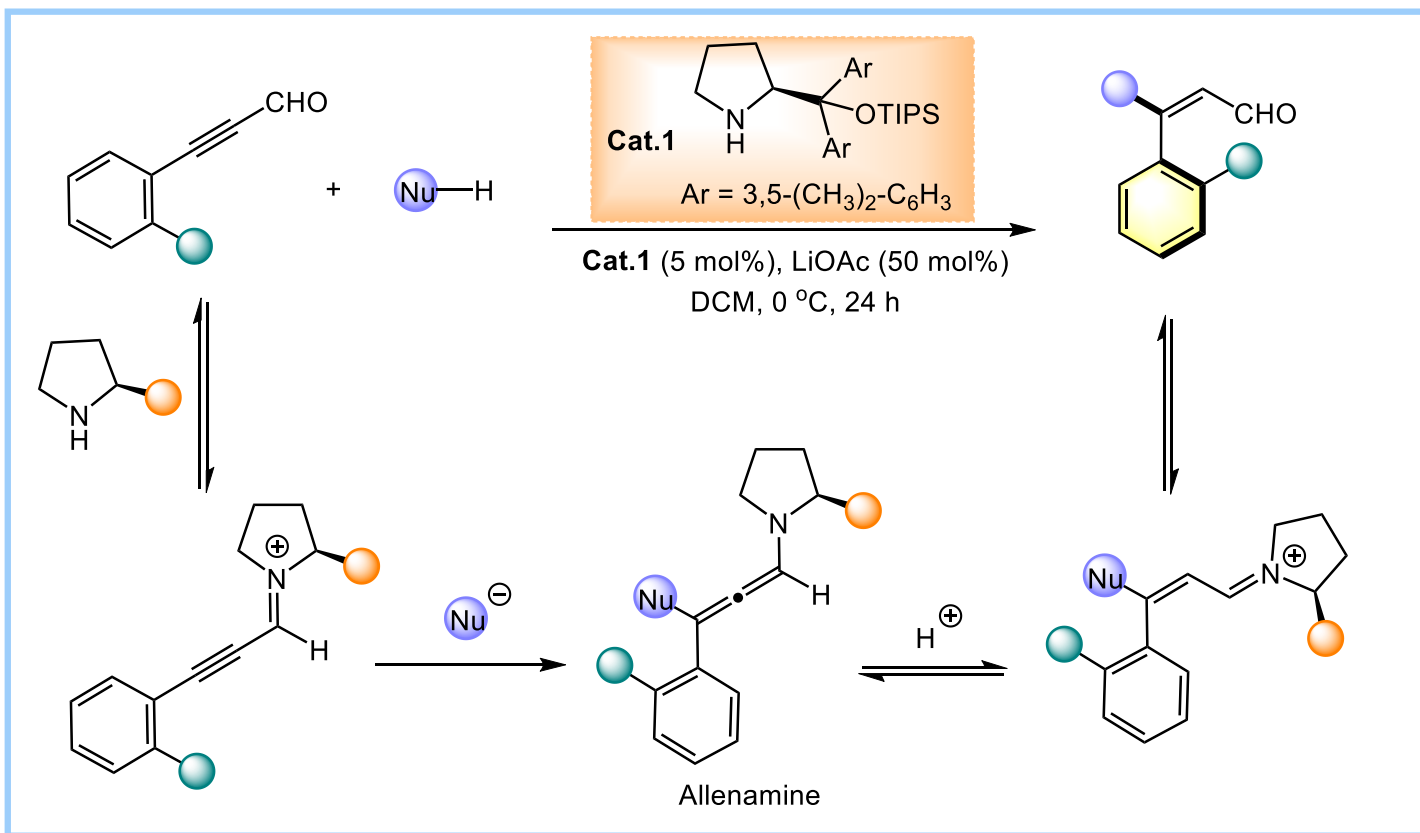
# Introduction

## Main Strategies to Construct Axially Chiral Alkenes



# Organocatalytic Atroposelective Functionalization of Alkynes

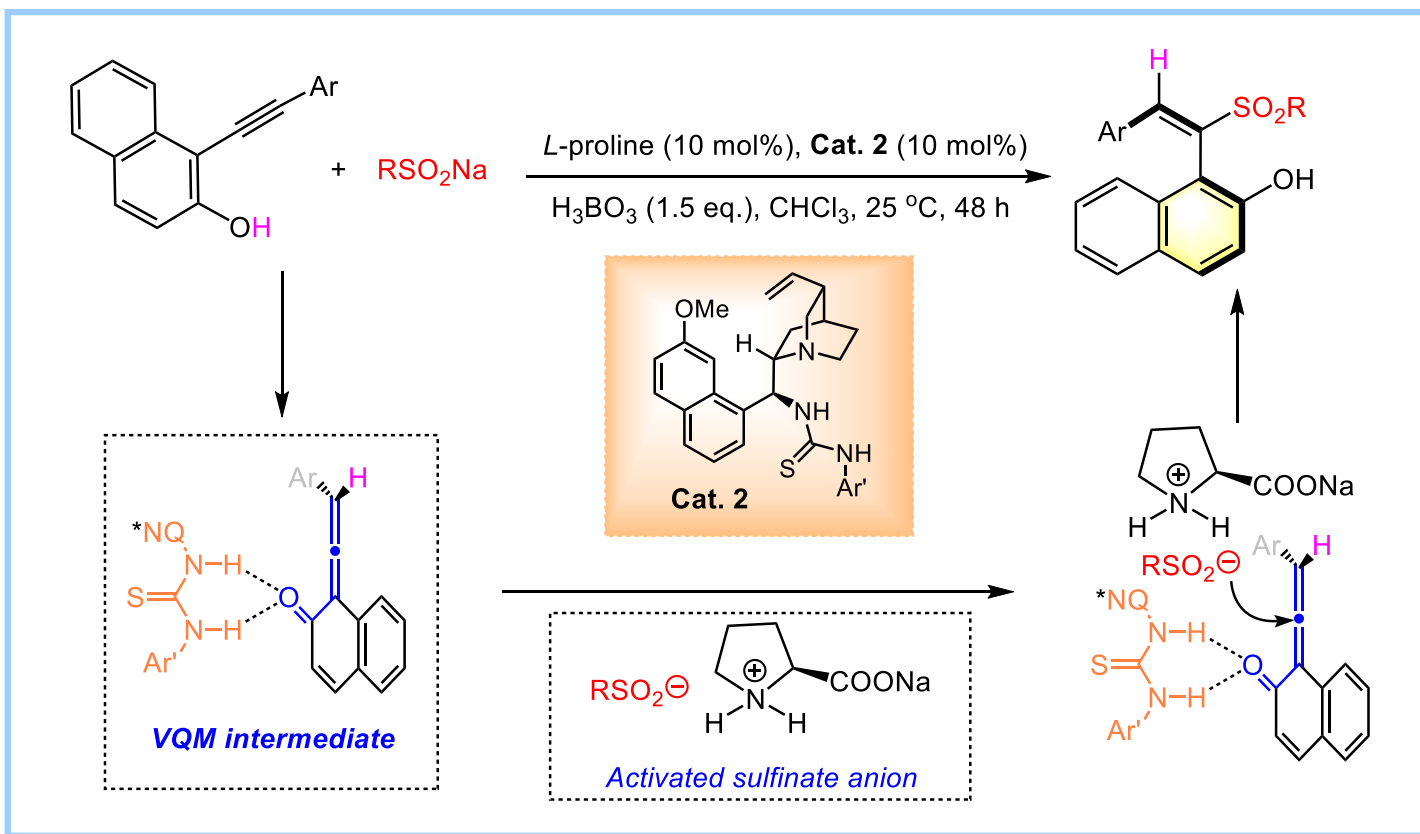
## Asymmetric Michael Addition Strategy



Zhang, S.-C.; Tan, B.\* *Nat. Commun.* **2017**, *8*, 15238

# Organocatalytic Atroposelective Functionalization of Alkynes

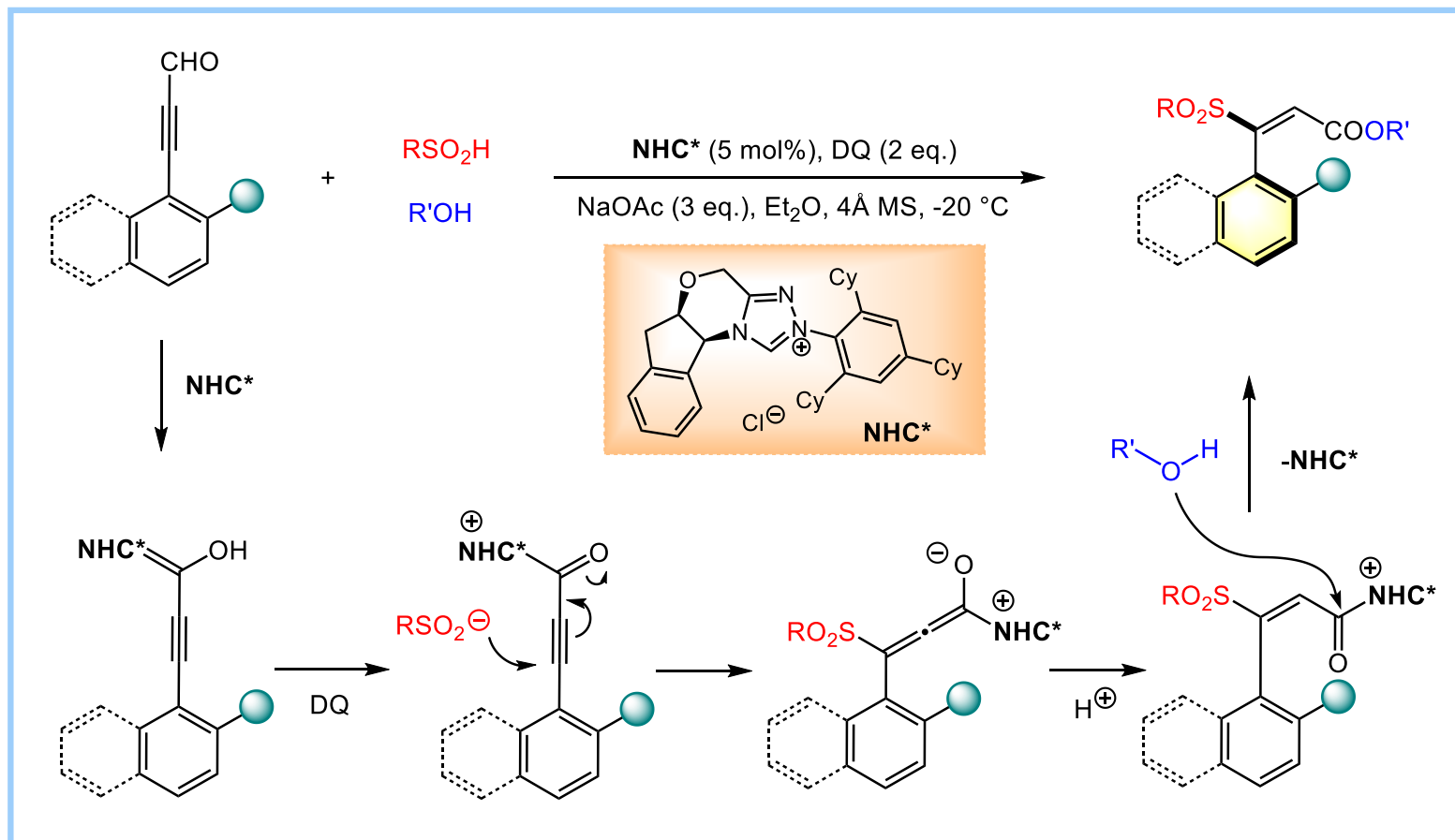
## VQM Intermediates Strategy



Jia, S.; Yan, H.\* *J. Am. Chem. Soc.* **2018**, *140*, 7056

# Organocatalytic Atroposelective Functionalization of Alkynes

## NHC Catalytic Strategy

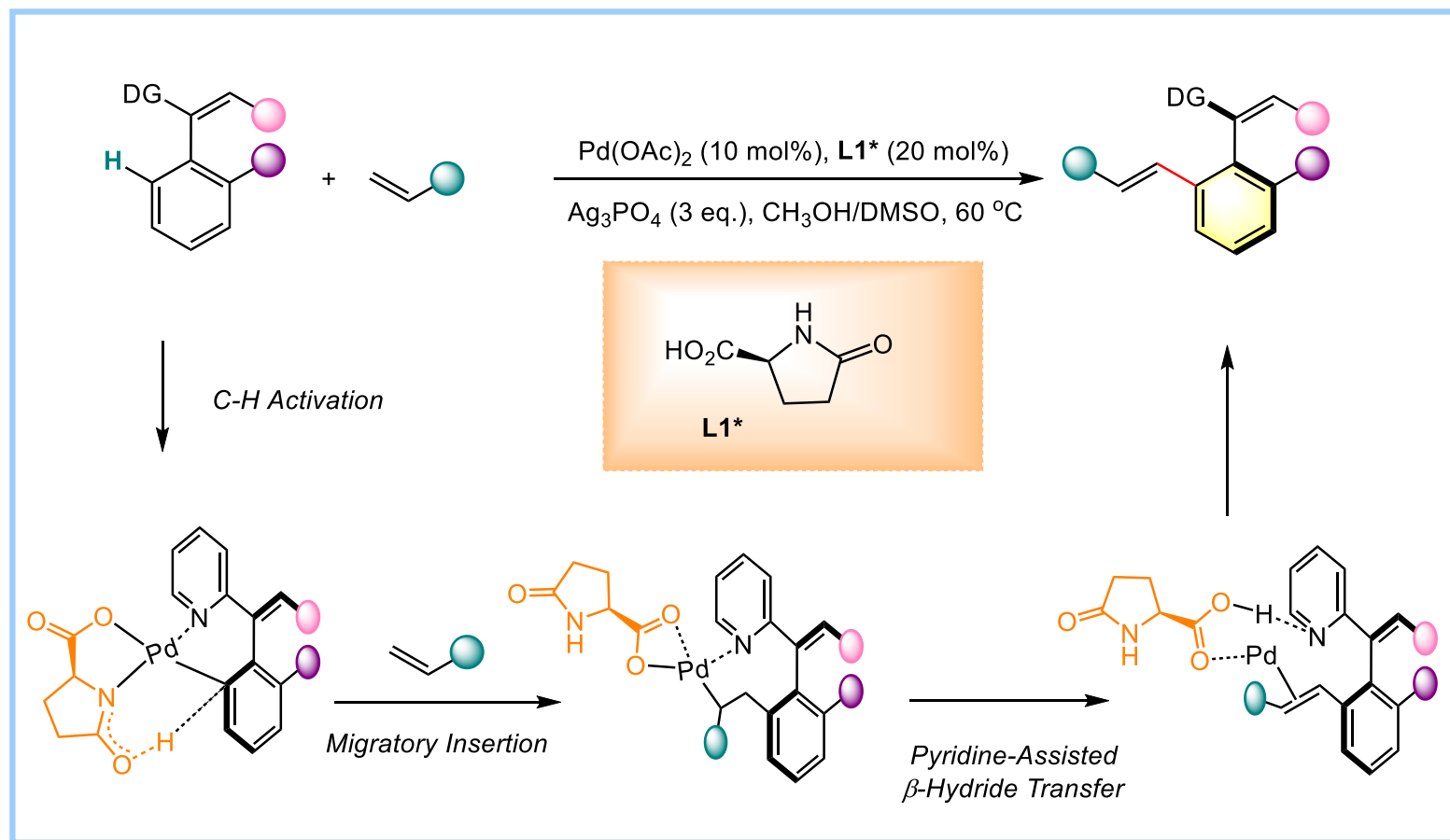


Yan, J.-L.; Chi, Y. R.\* *Nat. Commun.* **2022**, 13, 84



# Transition-Metal-Catalyzed Synthesis of Aryl-Alkenes

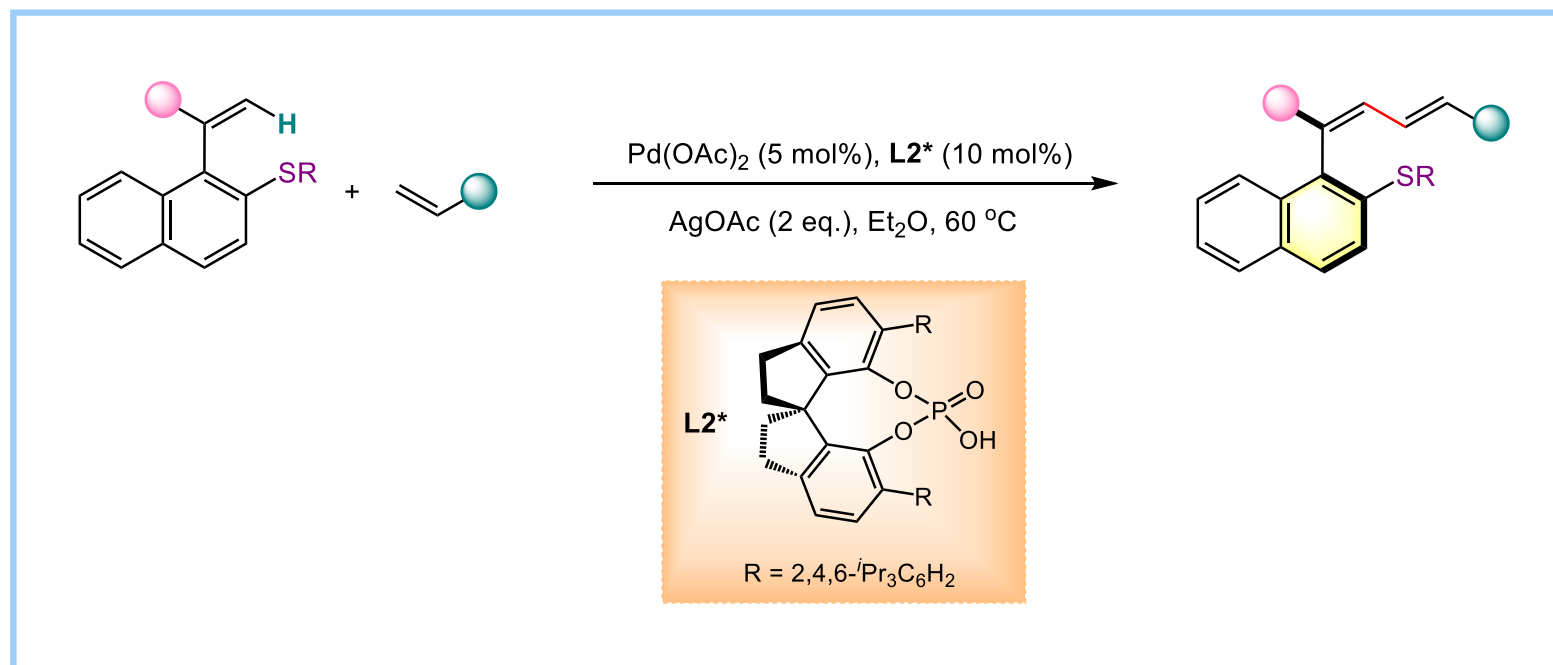
## Asymmetric C-H Functionalization Strategy



Jin., L.; Shi, B.-F.\* *Chem* **2020**, *6*, 497

# Transition-Metal-Catalyzed Synthesis of Aryl-Alkenes

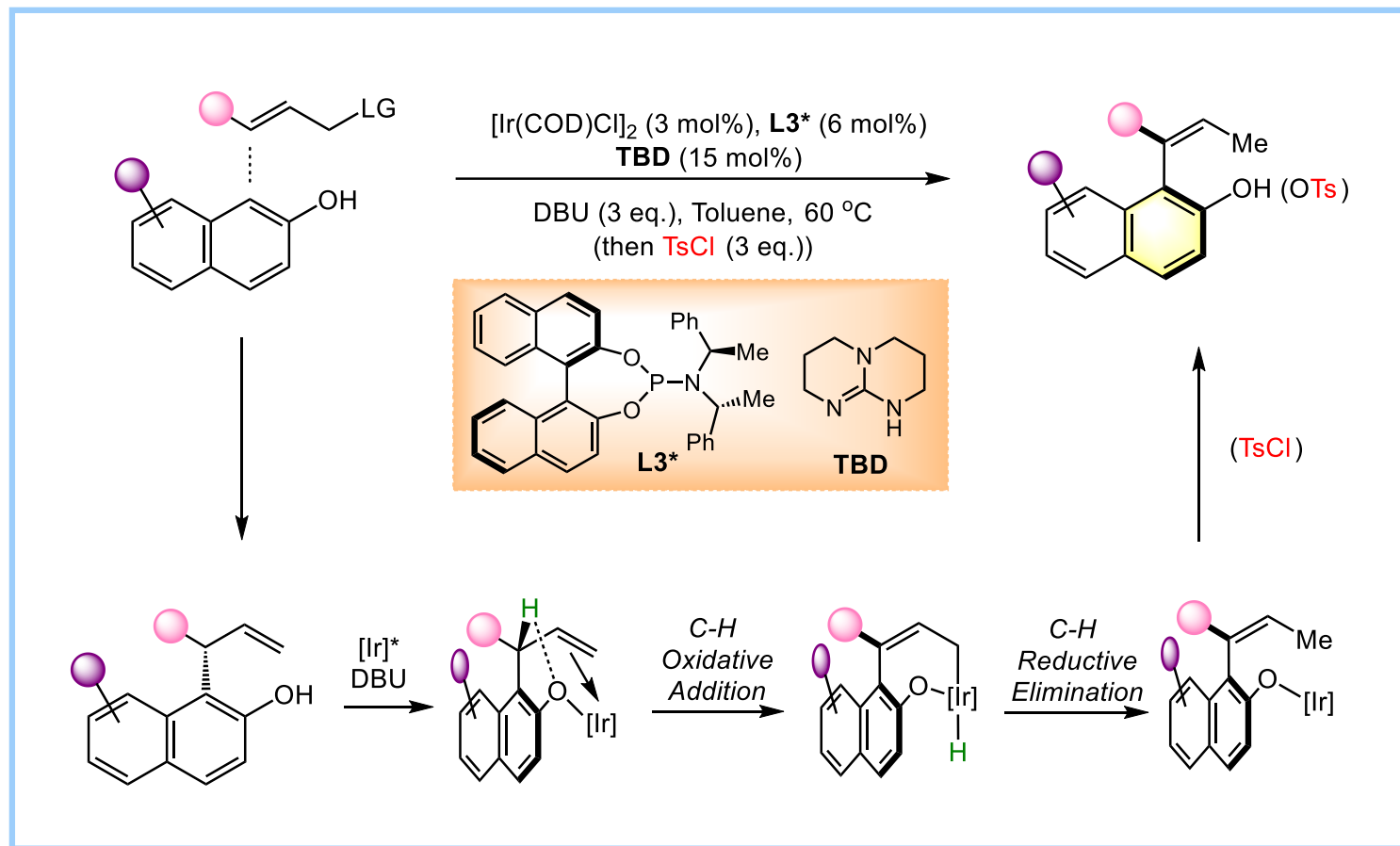
## Asymmetric C-H Functionalization Strategy



Jin, L.; Shi, B.-F.\* *J. Am. Chem. Soc.* **2021**, *143*, 12335

# Transition-Metal-Catalyzed Synthesis of Aryl-Alkenes

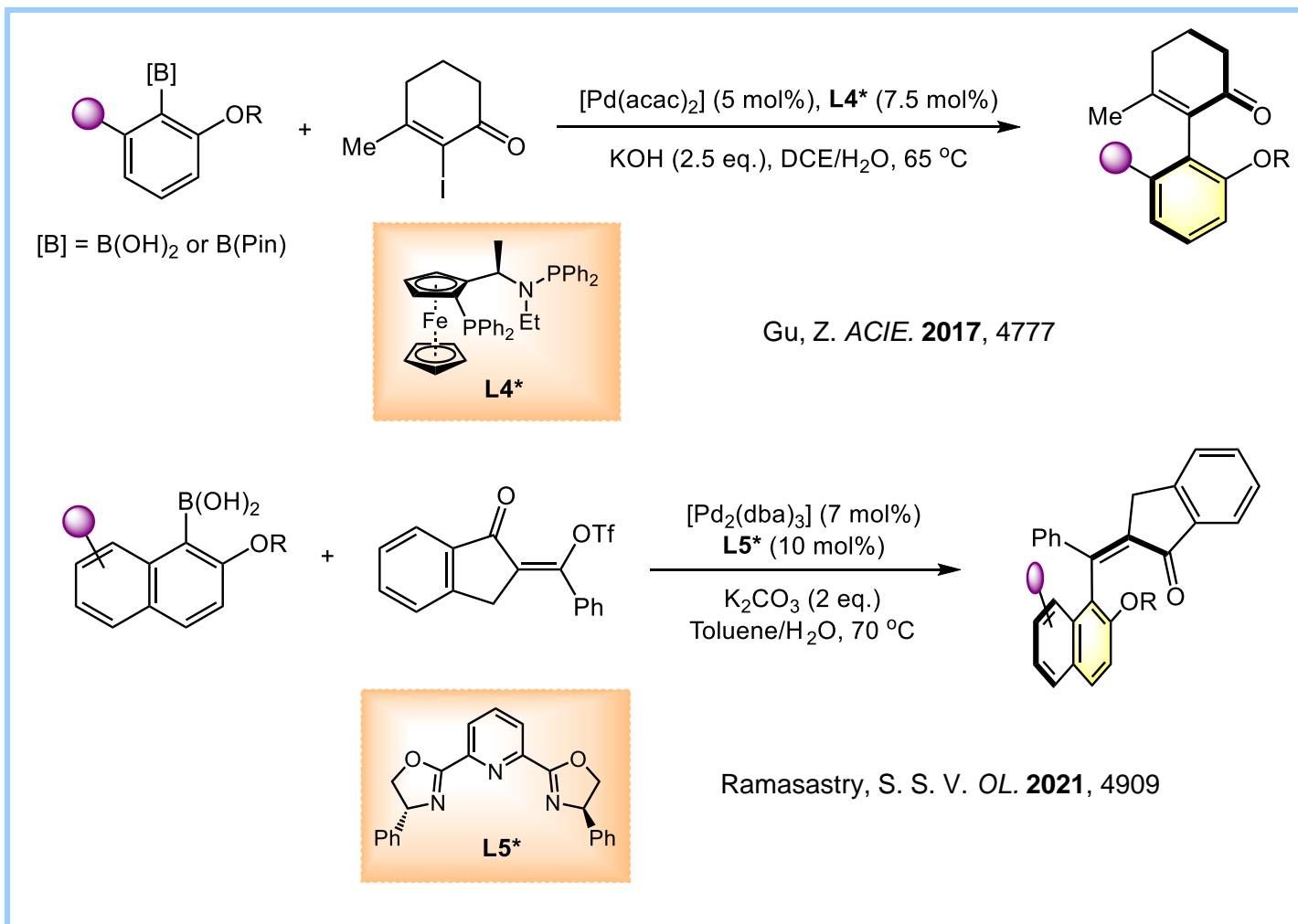
## Asymmetric Allylic Substitution-Isomerization Strategy



Wang, J.; He, Y.\* *J. Am. Chem. Soc.* **2021**, *143*, 10686

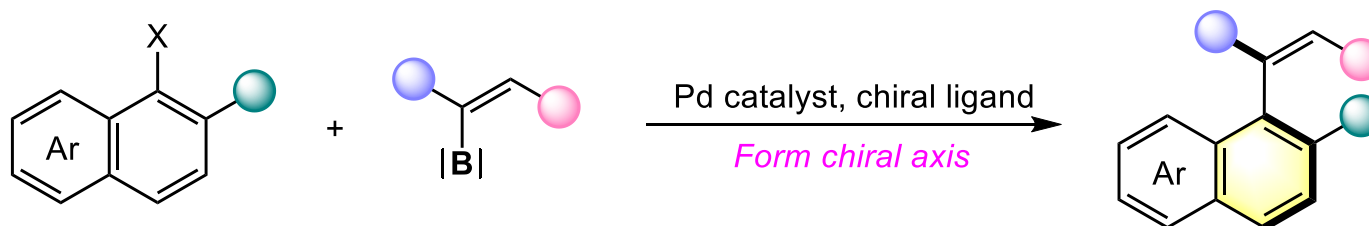
# Transition-Metal-Catalyzed Synthesis of Aryl-Alkenes

## Atroposelective Suzuki-Miyaura Coupling Strategy



# Project Synopsis

## Palladium-Catalyzed Atroposelective Suzuki-Miyaura Coupling

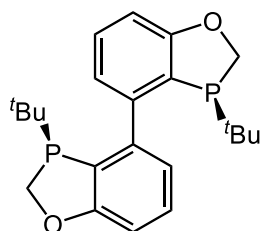
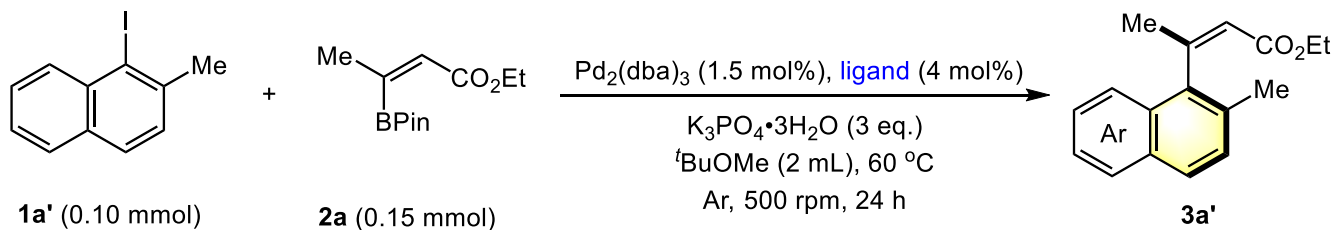


### Challenges

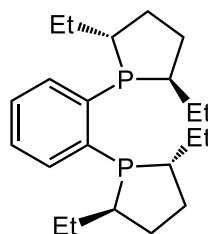
- ◆ Limited catalytic systems for reference
- ◆ Weak interaction between substrates and catalyst
- ◆ *Z/E* Inversion during chiral axis formation
- ◆ Antagonism between reactivity and atropostability

# Optimization of Reaction Conditions

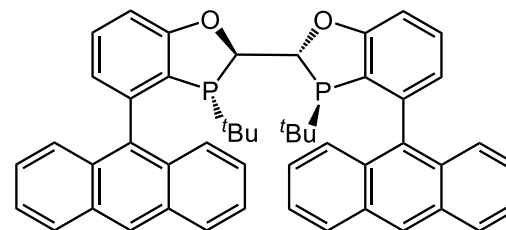
## a) Initial screening of various types of chiral ligands



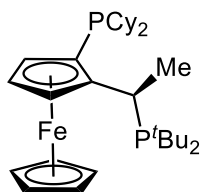
**L1**, no reaction



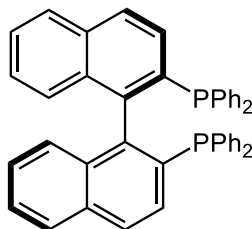
**L2**, no reaction



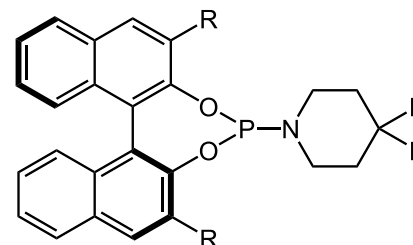
**L3**, no reaction



**L4**, 14%, 6% ee



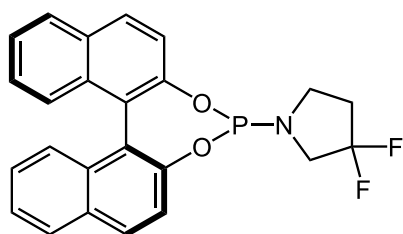
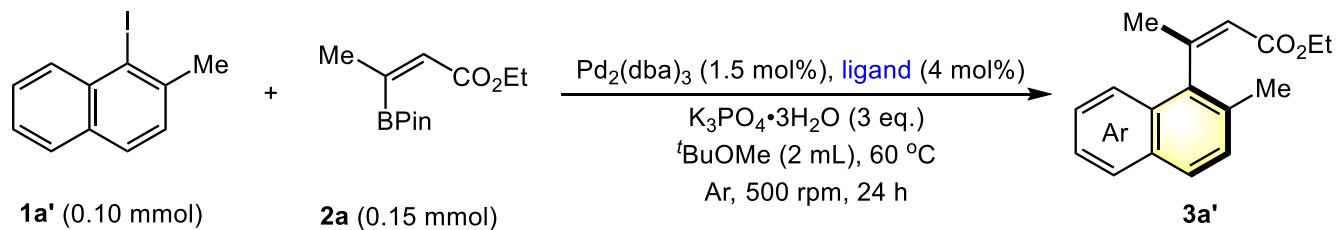
**L5**, 31%, 5% ee



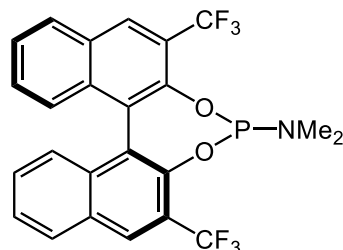
**L6**, R = 9-anthryl, 90%, -40% ee

# Optimization of Reaction Conditions

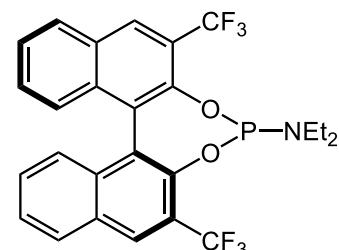
## a) Initial screening of various types of chiral ligands



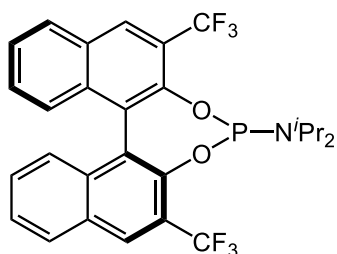
**L7**, 17%, 13% ee



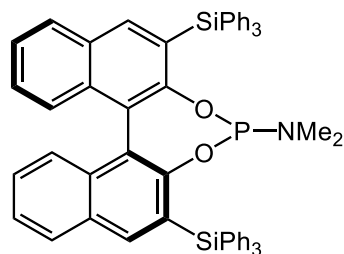
**L8**, 88%, -59% ee  
74%, -69% ee<sup>a</sup>



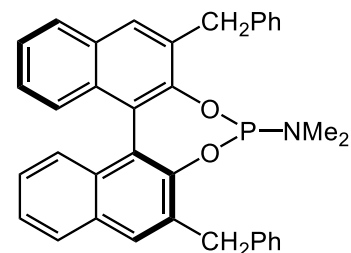
**L9**, 64%, -37% ee



**L10**, 88%, 30% ee



**L11**, 88%, 8% ee<sup>b</sup>

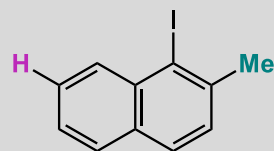
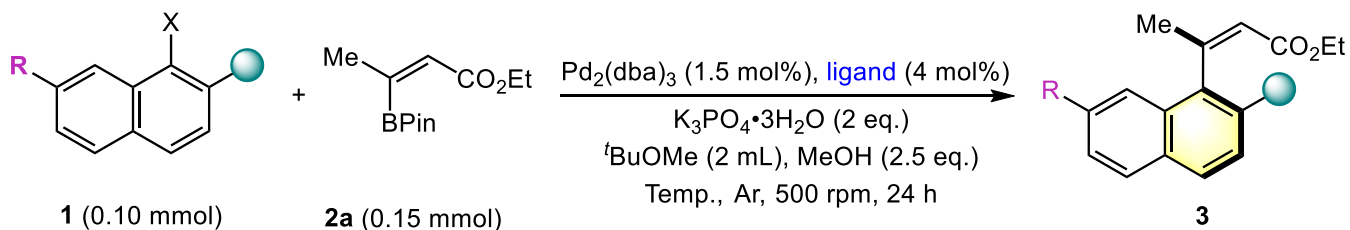


**L12**, 35%, 43% ee

[a] Methanol (2.5 equiv) and  $\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$  (2 equiv). [b] The reaction was conducted at  $30\text{ }^\circ\text{C}$

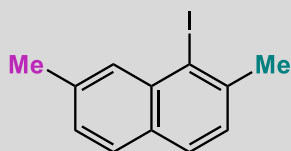
# Optimization of Reaction Conditions

## b) Modification of substrate and screening of 3,3'-triphenylsilyl substituted ligands



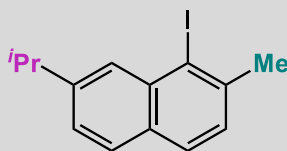
**1a'**

**L8**, 60 °C, -69% ee  
**L11**, 30 °C, 8% ee



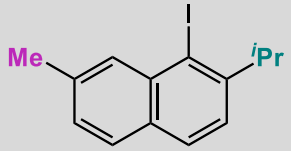
**1b'**

**L8**, 60 °C, -51% ee  
**L11**, 30 °C, 16% ee



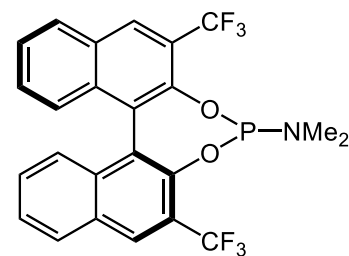
**1c'**

**L8**, 60 °C, < -10% ee  
**L11**, 30 °C, 40% ee

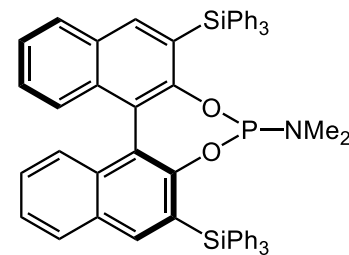


**1d'**

**L8**, 60 °C, < 10% ee  
**L11**, 30 °C, 72% ee



**L8**

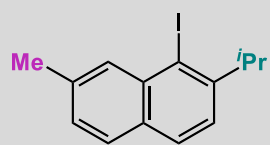
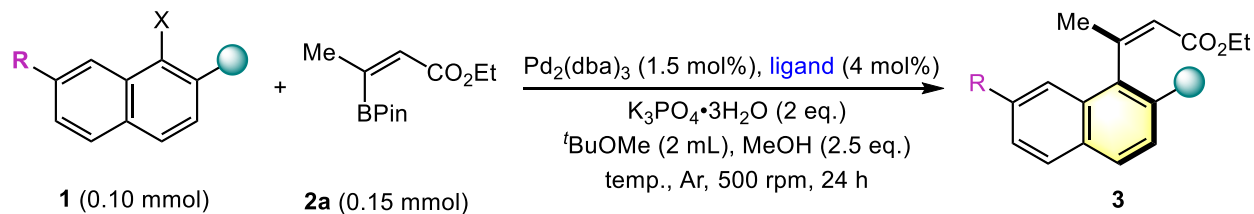


**L11**



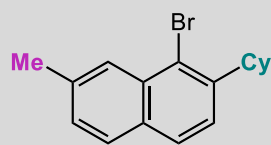
# Optimization of Reaction Conditions

## b) Modification of substrate and screening of 3,3'-triphenylsilyl substituted ligands



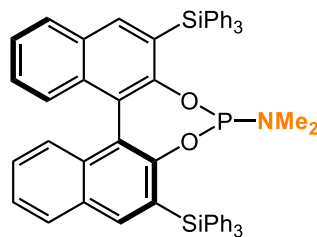
**1d'** (30 °C)

**L11**, 72% ee; **L13**, 42% ee  
**L14**, 43% ee; **L15**, -28% ee

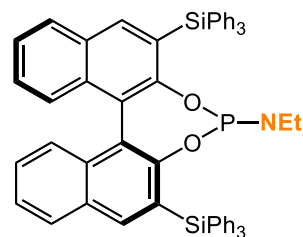


**1a** (30 °C)

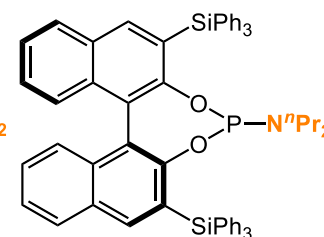
**L11**, 59% ee; **L16**, 65% ee  
**L17**, 66% ee; **L18**, 89% ee



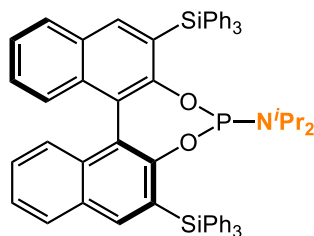
**L11**



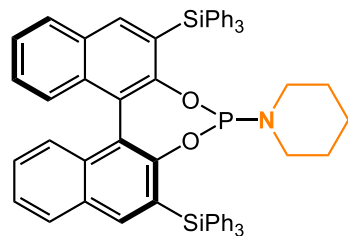
**L13**



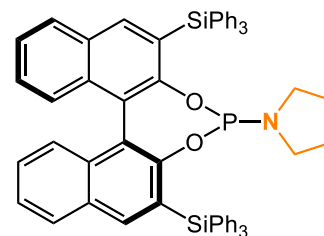
**L14**



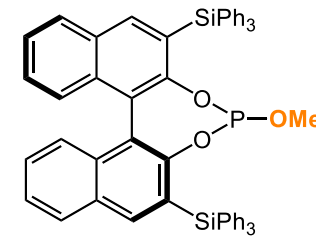
**L15**



**L16**



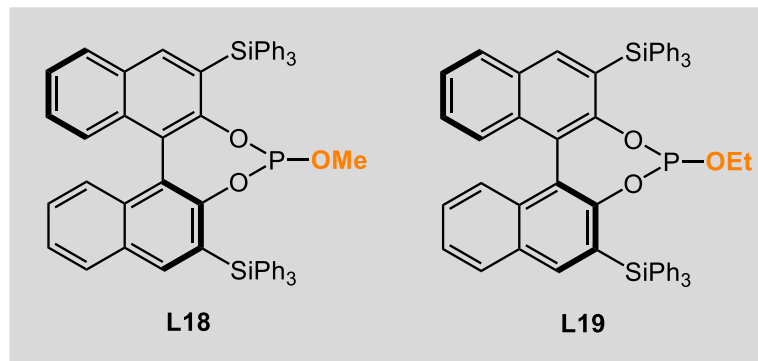
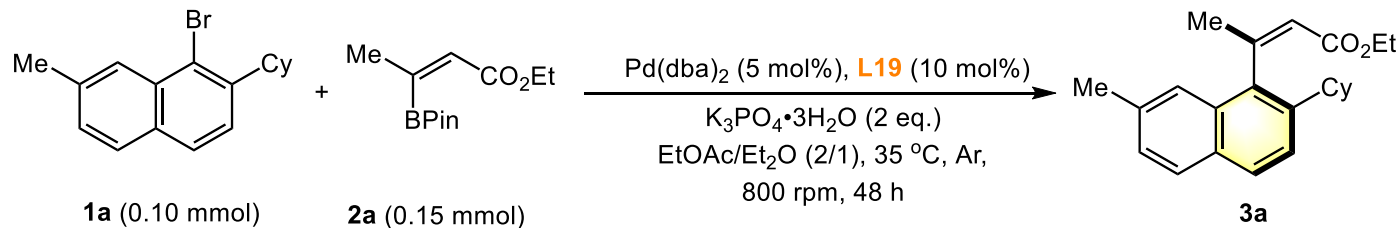
**L17**



**L18**

# Optimization of Reaction Conditions

## c) Further optimization of other reaction parameters

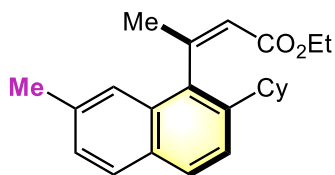
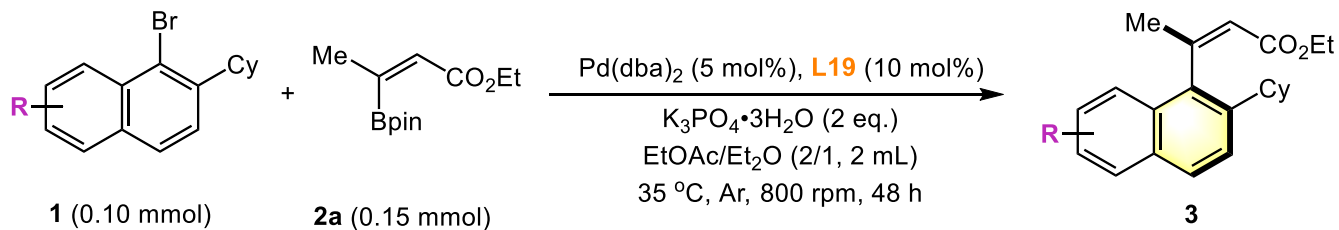


Yield of **Z-3a** = 94%  
Z/E = 94/6  
Ee of **Z-3a** = 91%

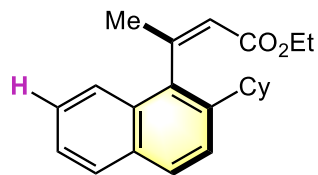
**Enantiomerization**  
energy barrier of **3a**  
 $\Delta G^\ddagger = 34.4$  kcal/mol  
(120 °C, toluene,  $t_{1/2} = 163$  h)

# Substrate Scope

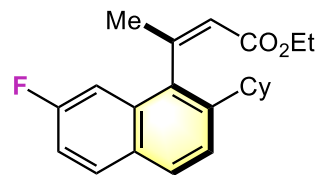
## a) Substrate generality of the *ortho*-substituted ary bromides



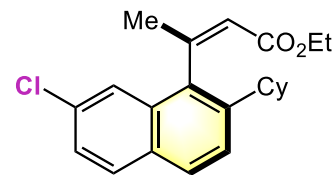
**3a**, 94% yield  
91% ee, Z/E = 94/6



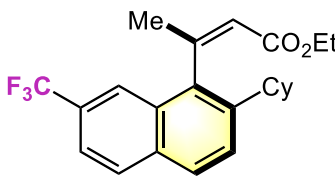
**3b**, 66% yield  
91% ee, Z/E = 91/9



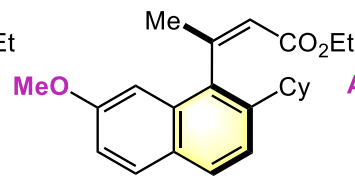
**3c**, 78% yield  
94% ee, Z/E = 93/7



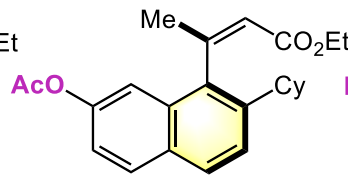
**3d**, 64% yield  
94% ee, Z/E = 93/7



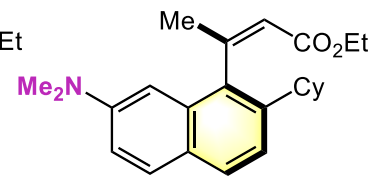
**3e**, 56% yield<sup>a</sup>  
87% ee, Z/E = 91/9



**3f**, 75% yield  
87% ee, Z/E = 93/7



**3g**, 71% yield  
96% ee, Z/E = 88/12

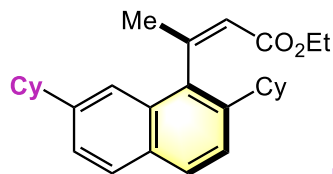
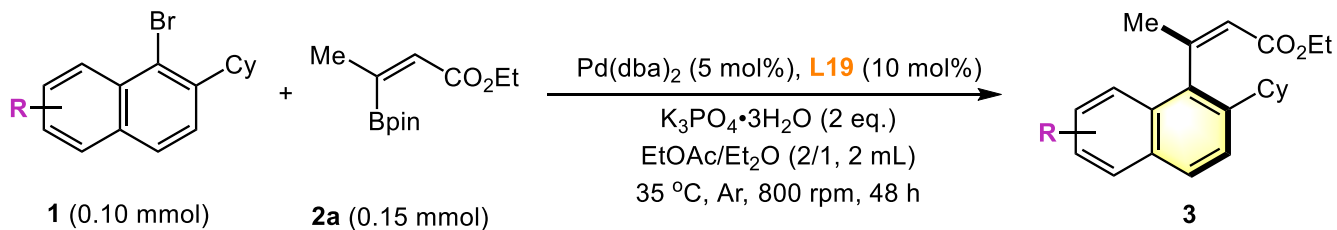


**3h**, 60% yield  
81% ee, Z/E = 87/13

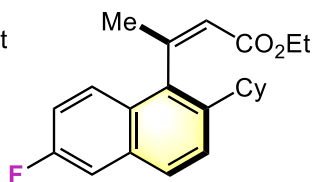
[a] Reacted for 6 days.

# Substrate Scope

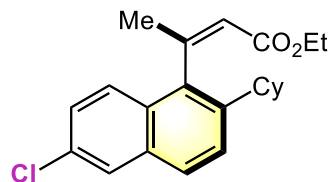
## a) Substrate generality of the *ortho*-substituted ary bromides



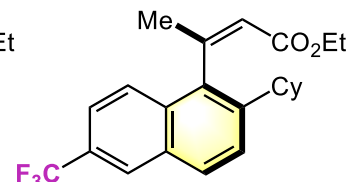
**3i**, 80% yield  
80% ee, Z/E = 93/7



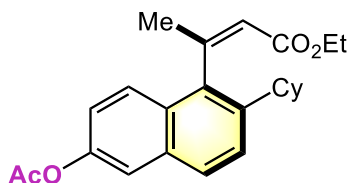
**3j**, 85% yield  
88% ee, Z/E = 93/7



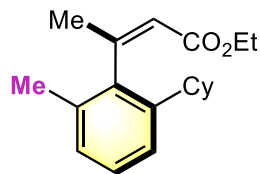
**3k**, 81% yield  
86% ee, Z/E = 88/12



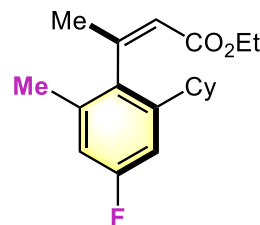
**3l**, 59% yield<sup>a</sup>  
85% ee, Z/E = 89/11



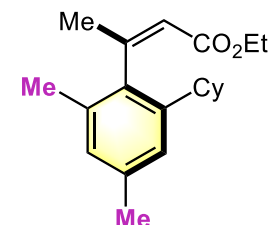
**3m**, 60% yield  
88% ee, Z/E = 87/13



**3n**, 62% yield<sup>b</sup>  
69% ee, Z/E = 89/11



**3o**, 29% yield<sup>b</sup>  
69% ee, Z/E = 74/26

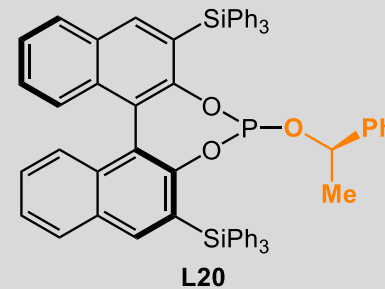
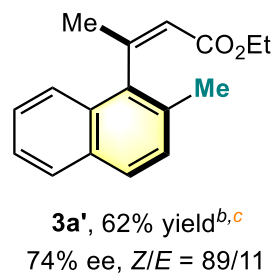
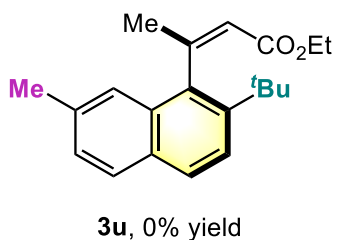
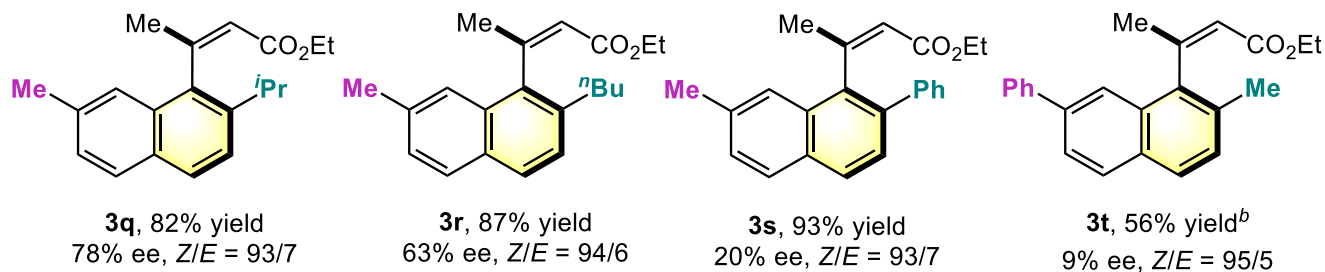
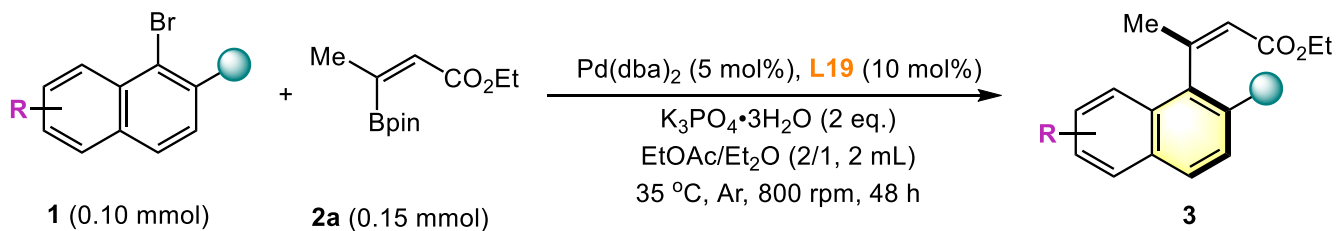


**3p**, 59% yield<sup>b</sup>  
68% ee, Z/E = 89/11

[a] Reacted for 6 days. [b] Reaction using aryl iodide as starting material.

# Substrate Scope

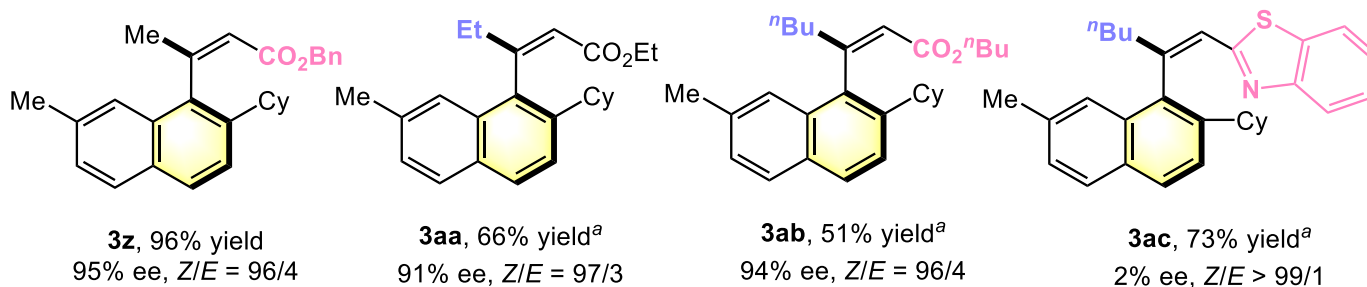
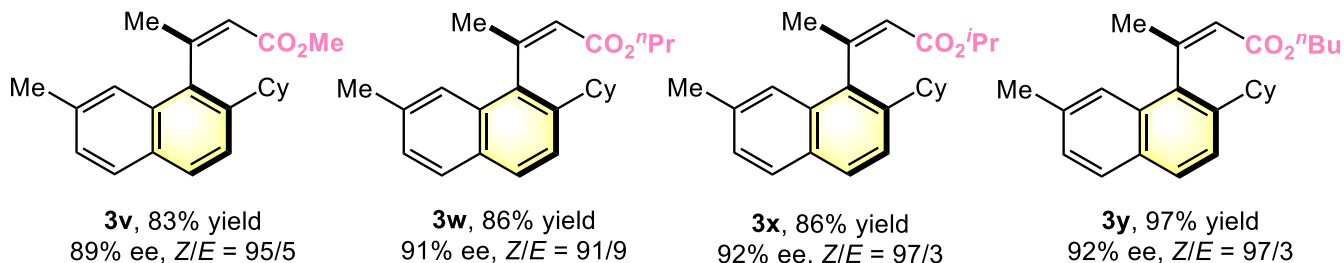
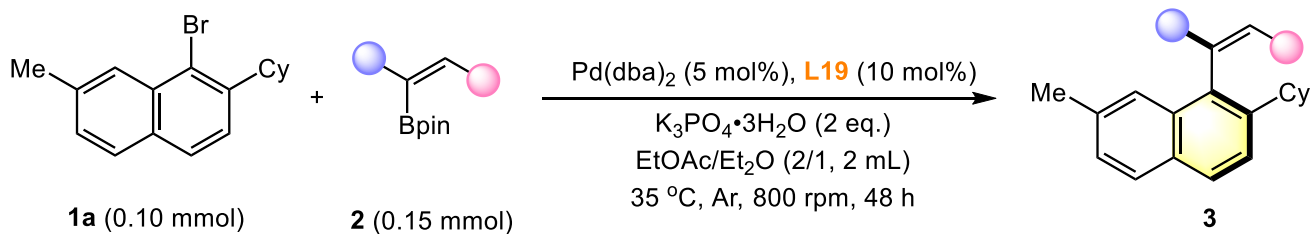
## a) Substrate generality of the *ortho*-substituted ary bromides



[a] Reacted for 6 days. [b] Reaction using aryl iodide as starting material. [c] Reaction using **L20** as ligand.

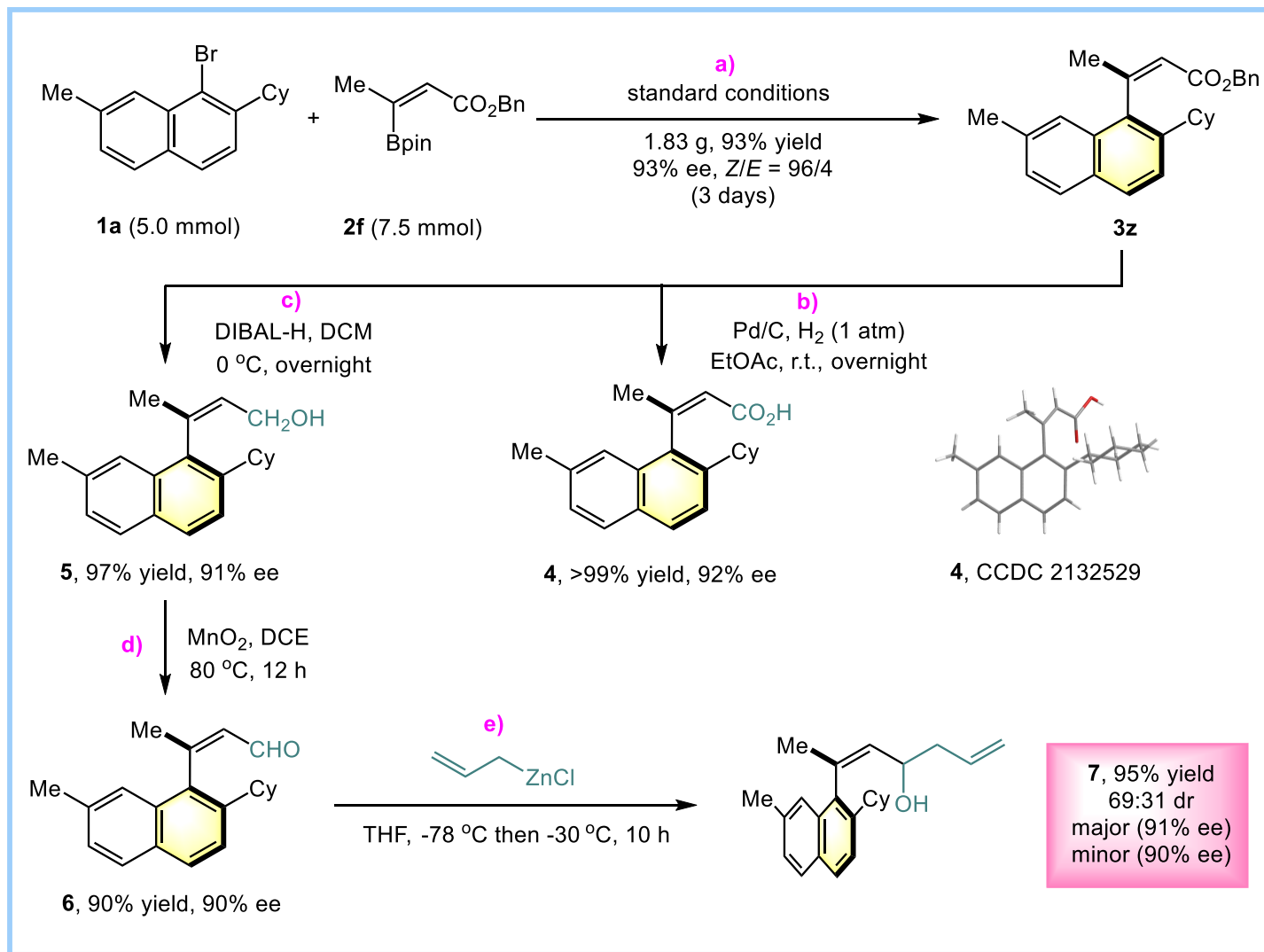
# Substrate Scope

## b) Substrate generality of the vinyl boronates

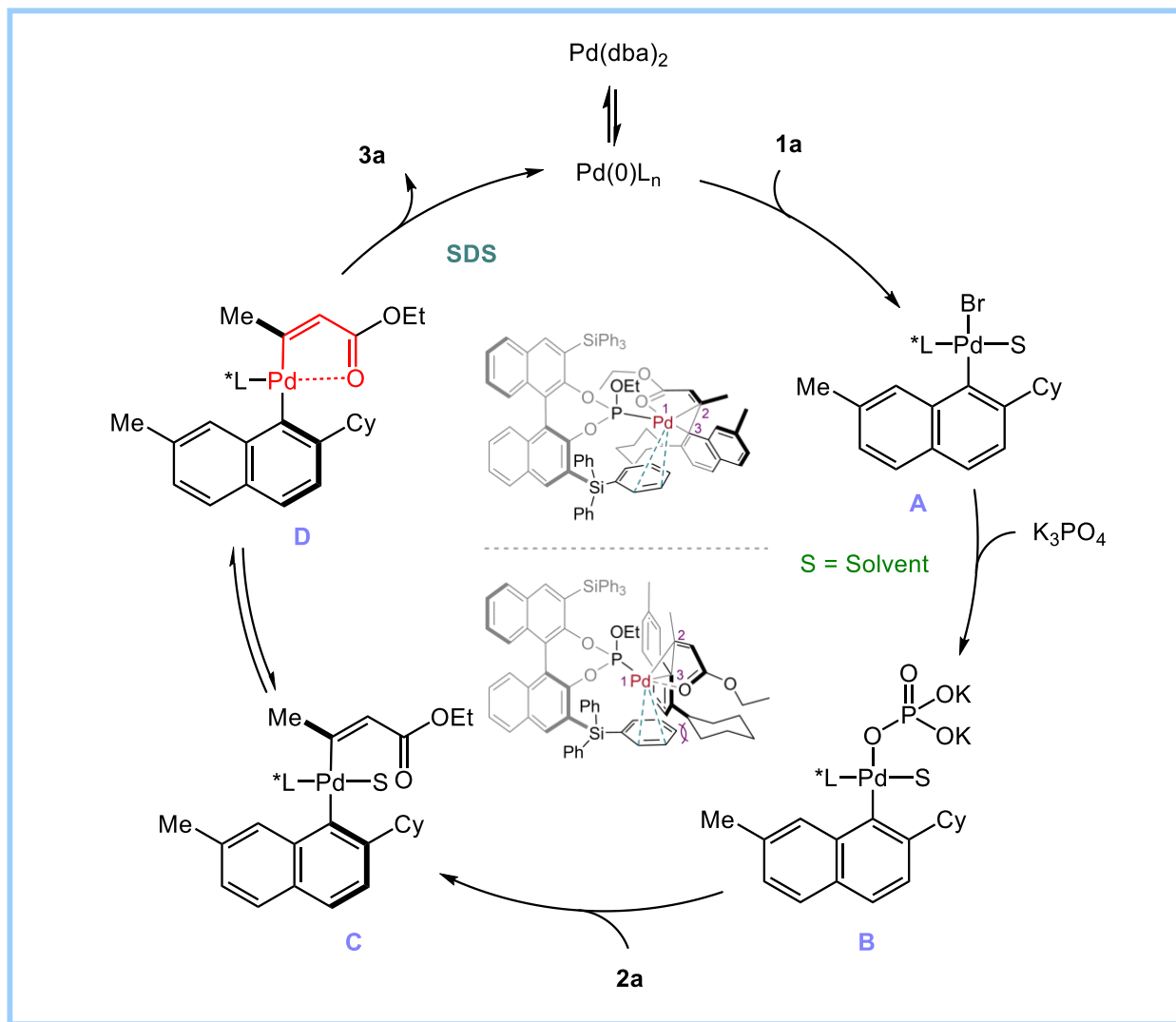


[a] Reacted for 6 days.

# Gram-scale Synthesis and Transformations of Products

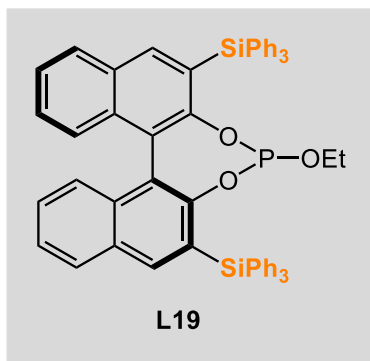
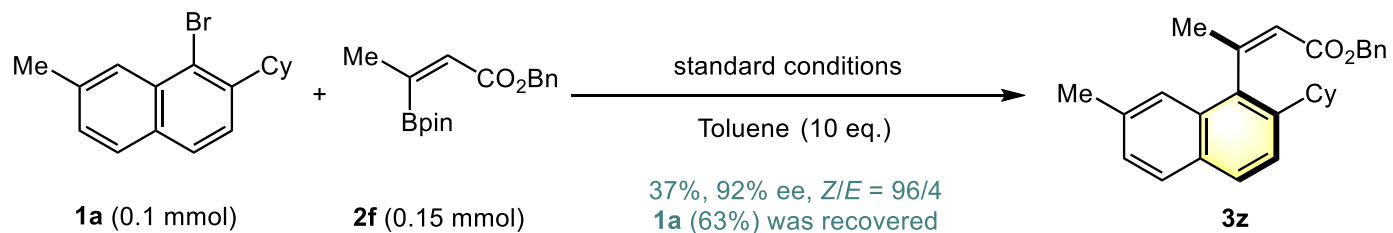


# Proposed Mechanism

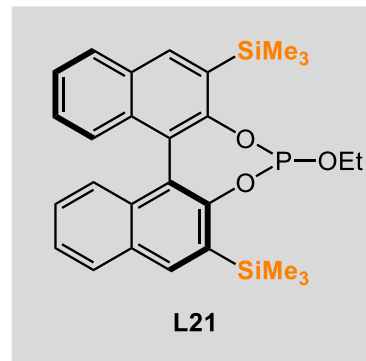




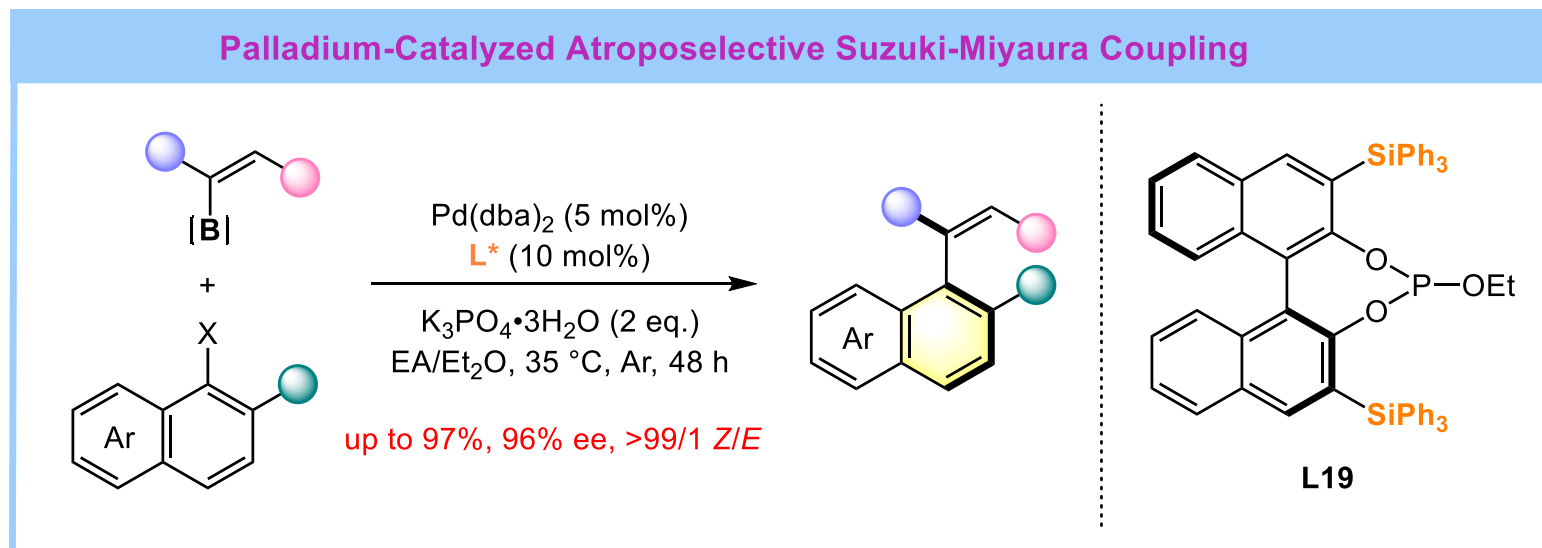
# Control Experiments



vs



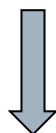
# Summary



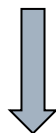
- ♥ Novel catalytic system
- ♥ Applicable to sterically hindered substrates
- ♥ Mild reaction conditions
- ♥ Good *Z/E* selectivity and enantioselectivity

## 写作思路

轴手性化合物重要性



轴手性烯烃化合物的发展和应用



介绍发展较好的一种合成策略

# The First Paragraph

---

Having been established as a distinct subclass of molecular chirality, axial chirality is increasingly identified in strikingly many natural products and is incorporated more readily in drug development. In synthetic science, development and application of axially chiral ligands and catalysts are one of the cornerstones of asymmetric synthesis. Beyond the prototypical biaryl atropisomerism, chirality could be exhibited also by an alkene-tethered bond axis. There is however an initial negligence in research of axially chiral aryl-alkenes owing to their perceived instability which would hinder their synthesis and productive use. Early synthetic studies were mainly contributed by Gu's group who envisioned using Pd-catalyzed cross-coupling reactions to derive dihydronaphthalene- and cyclohex-2-enone-type atropisomers with enclosed double bond in the 6-membered ring.

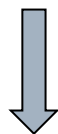
# The First Paragraph

---

The report on catalytic asymmetric synthesis of axially chiral acyclic aryl-alkenes came in 2017 and since then, expanding knowledge on atroposelective synthesis has advanced various methods to prepare axially chiral arylalkenes. These studies create avenues to investigate the potential utility of these chiral frameworks in asymmetric catalysis as ligands and organocatalysts. One major strategy involves nucleophilic addition to alkyne precursors, which was seminally demonstrated by our group in an aminocatalytic stereoselective addition to alkynals. Subsequently, the versatility of chiral vinylidene ortho-quinone methide (VQM) intermediates was studied in atroposelective nucleophilic addition reactions by Yan, Zhang and our group, opening up a robust pathway to diverse axially chiral acyclic aryl-alkenes.

## 写作思路

总结工作：钯催化偶联方式一步构建轴手性无环烯烃



成功关键：合适的配体

# The Last Paragraph

---

In conclusion, a palladium-catalyzed asymmetric cross-coupling of *ortho*-substituted aryl halides and vinyl boronates has been developed as a new approach to the synthesis of axially chiral acyclic alkenes. The triphenylsilyl-substituted ligand identified could afford high activity and selectivity control for cross-coupling of aryl halides and vinyl boronates in good to high yields, good enantioselectivities and *E/Z* ratios under mild conditions. Further studies to expand the application of this synthetic approach are in progress.

# Representative Examples

---

- Metal catalysis establishes complementary reactivity domain in the synthesis of atropisomeric aryl-alkenes.

反应性领域上的互补

- ... play predominant roles in controlling the stereoselectivity in aryl-aryl coupling.

占据主导角色

- Altogether, these highlighted the key design considerations in ligand optimization and substrate choice to ...

总的来说（代替In conclusion）



# Acknowledgement

---

*Thanks for Your Attention*