



*Seminar*

# Pd/Cu协同催化的立体发散性合成 策略

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导师：张俊良 教授

2024.9.27



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1. 研究背景及意义

2.Pd/Cu协同催化的立体发散性合成策略

    2.1 直接氧化加成启动

    2.2 Heck反应启动

    2.3 PdH插入启动

3. 总结与展望



# 目录

1. 研究背景及意义

2.Pd/Cu协同催化的立体发散性合成策略

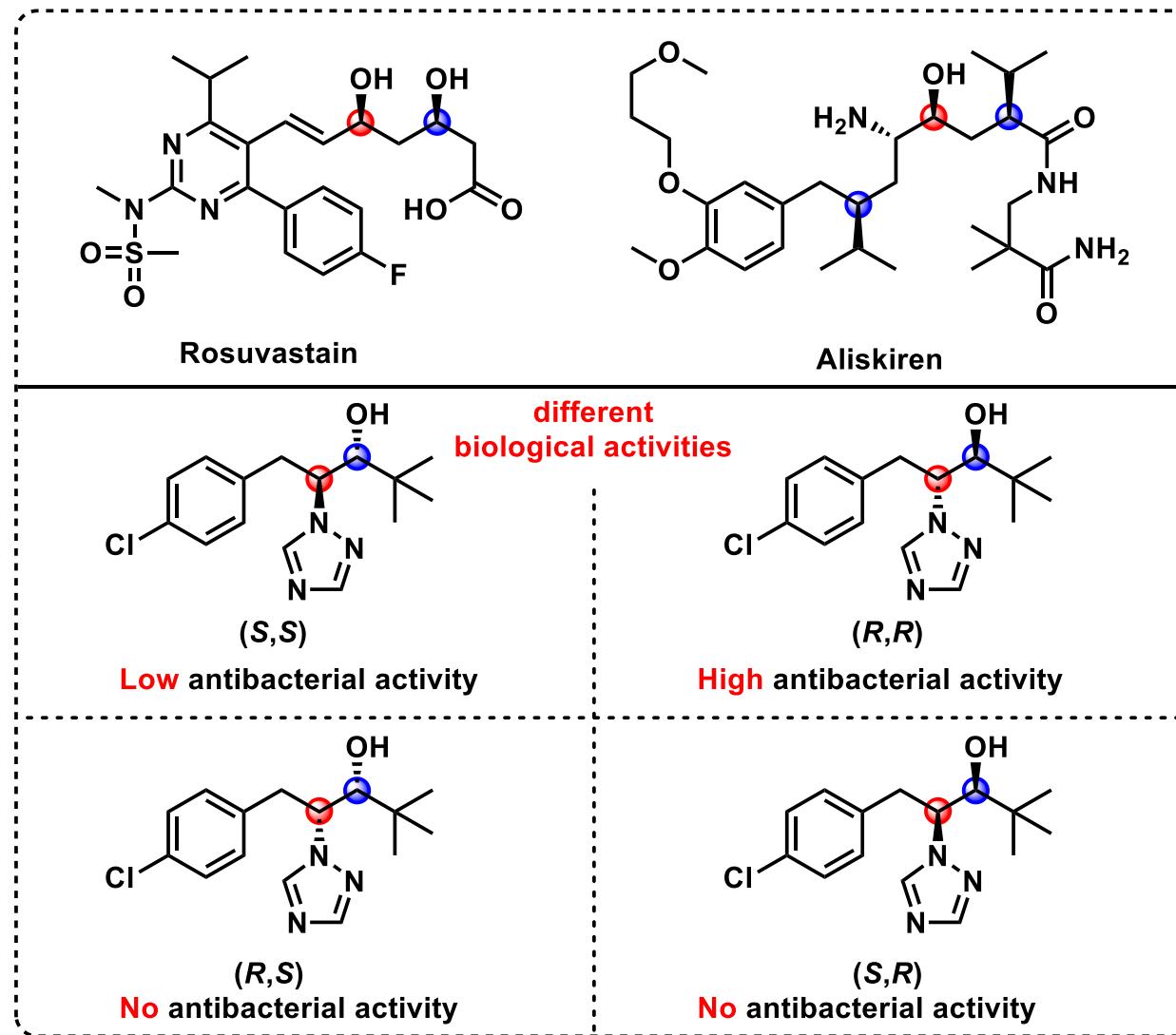
2.1 直接氧化加成启动

2.2 Heck反应启动

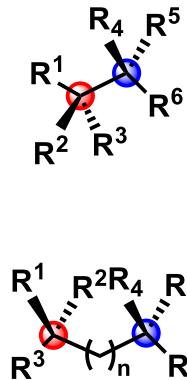
2.3 PdH插入启动

3. 总结与展望

# 1. 研究背景及意义——立体发散合成的重要性

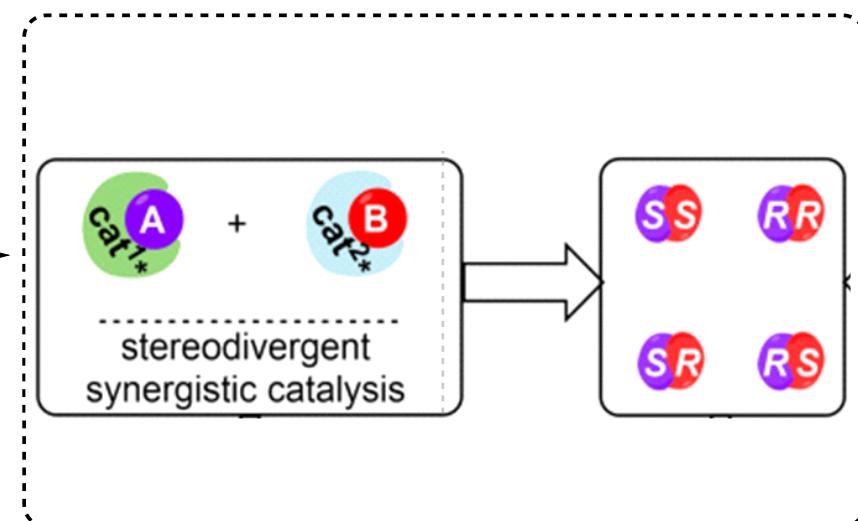


## 1) 多重手性的构建



- 多步反应构建
- 分离程序复杂
- 耗时，效率低下
- 立体选择性差

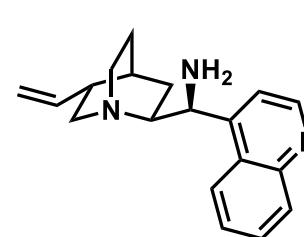
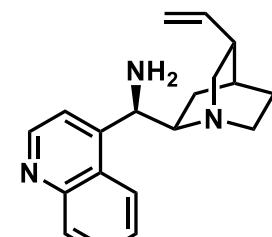
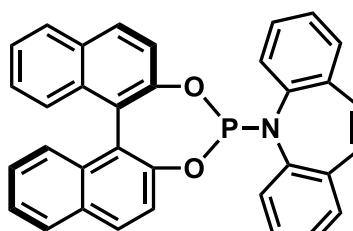
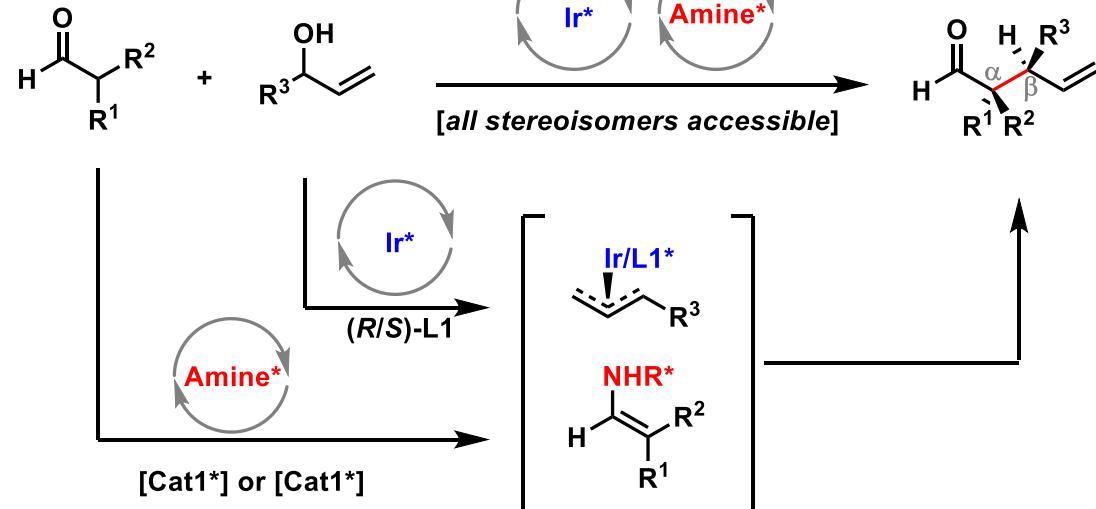
## 2) 协同催化



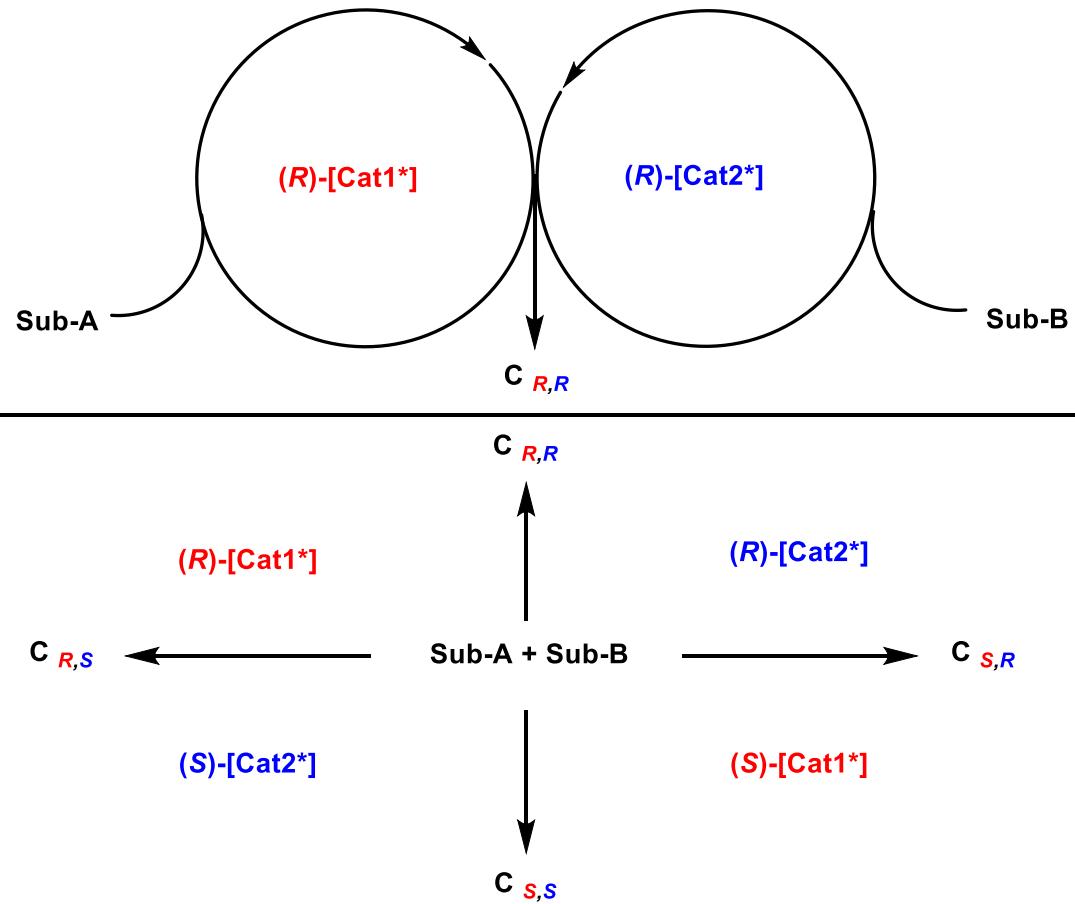
# 1. 研究背景及意义——协同催化概念

## The pioneering work

Carreia group (2013)

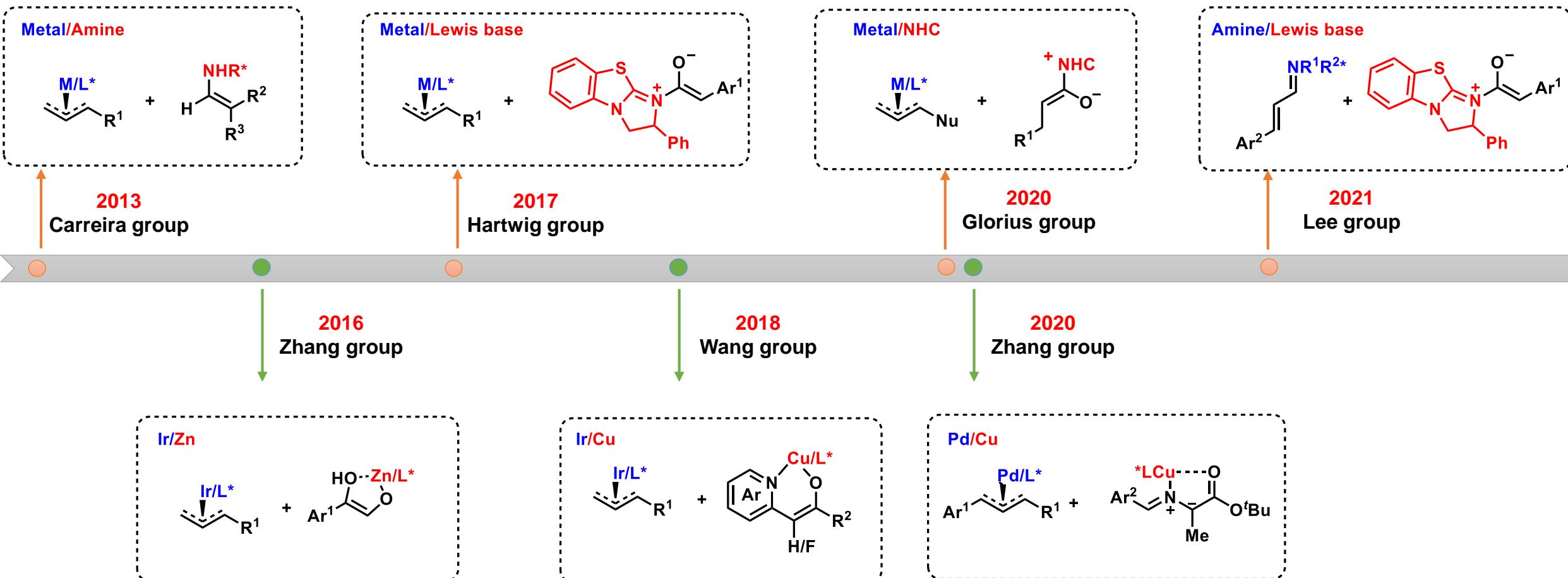


## The Catalytic Cycle



# 1.研究背景及意义——协同催化发展

## Metal/Organo catalysis



## Dual Metal catalysis

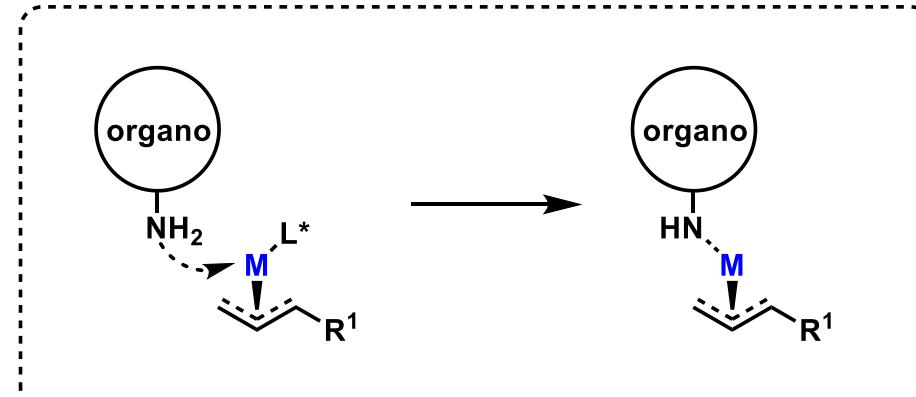
E. M. Carreira, et al. *Science*. **2013**, *340*, 1065-1068; J. F. Hartwig, et al. *J. Am. Chem. Soc.* **2017**, *139*, 87-90;

F. Glorius, et al. *Nat. Catal.* **2020**, *3*, 48-54; S. Y. Lee, et al. *J. Am. Chem. Soc.* **2021**, *143*, 73-79.

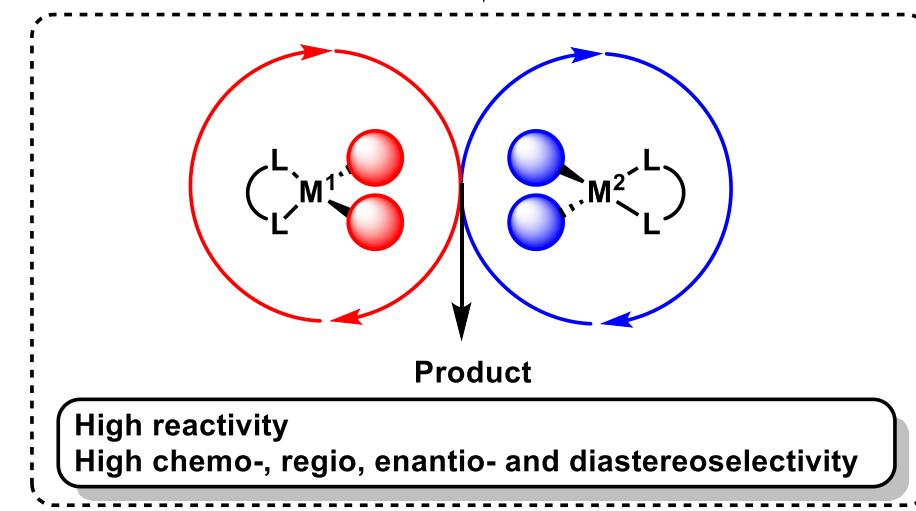
W. Zhang, et al. *J. Am. Chem. Soc.* **2016**, *138*, 11093-11096; *J. Am. Chem. Soc.* **2018**, *140*, 2080-2084; *J. Am. Chem. Soc.* **2020**, *142*, 8097-8103.

## 2. Pd/Cu协同催化

### Metal/Organo catalysis

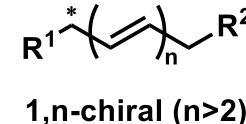
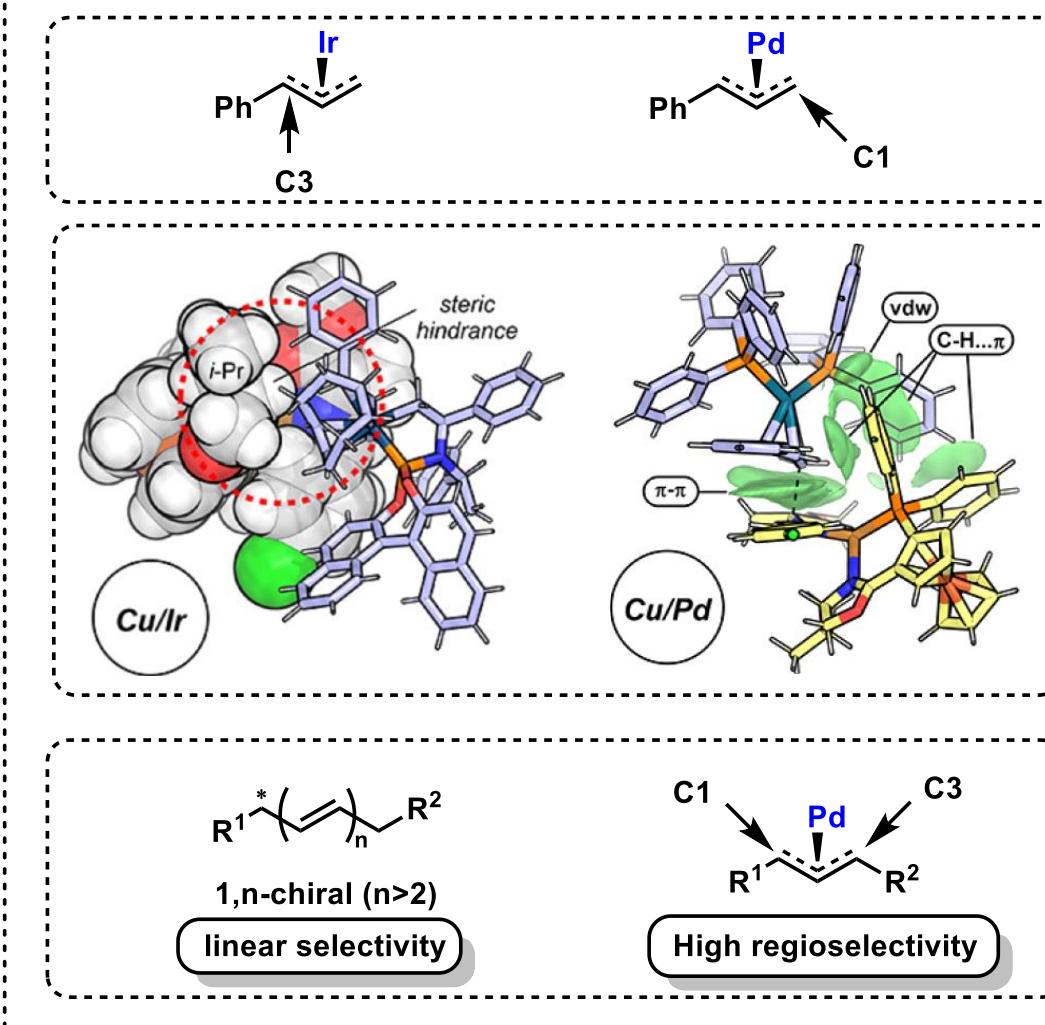


### Dual Metal catalysis

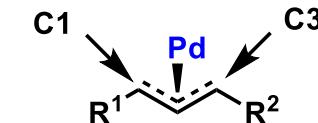


High reactivity  
High chemo-, regio, enantio- and diastereoselectivity

### Ir/Cu or Pd/Cu



linear selectivity



High regioselectivity

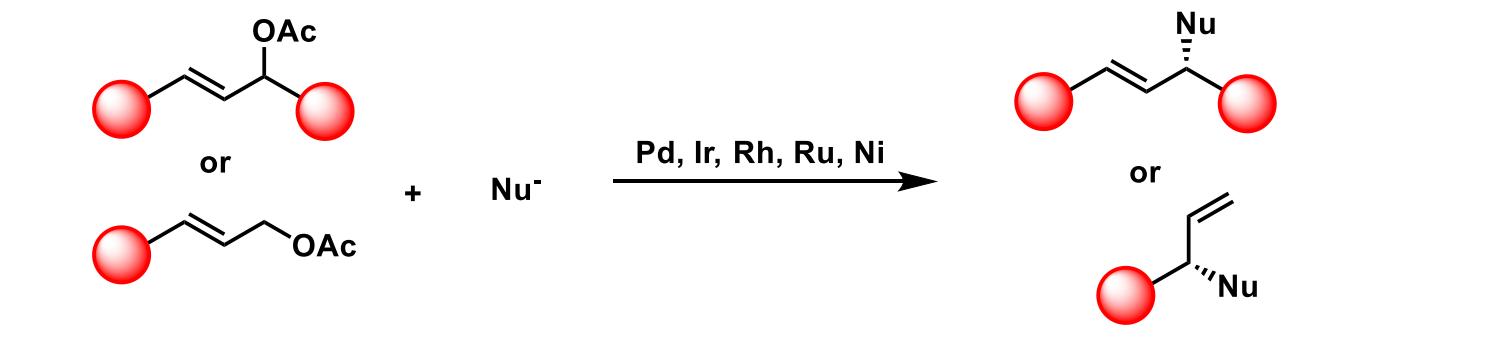


# 目录

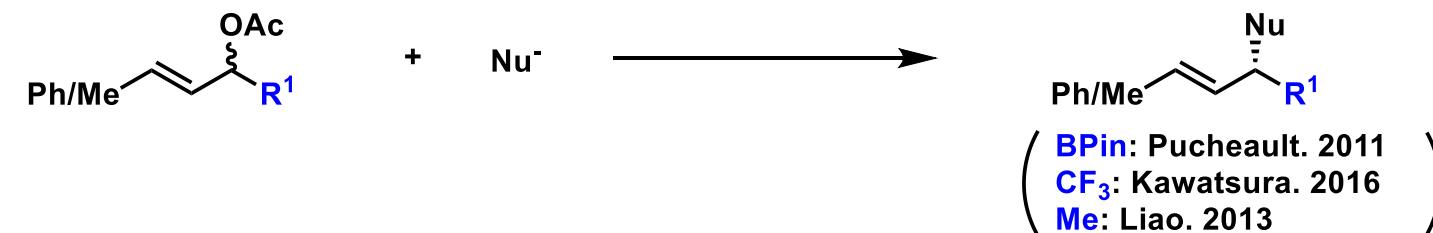
1. 研究背景及意义
- 2.Pd/Cu协同催化的立体发散性合成策略
  - 2.1 直接氧化加成启动
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  - 2.3 PdH插入启动
3. 总结与展望

## 2.1 直接氧化加成启动 (烯丙基取代)

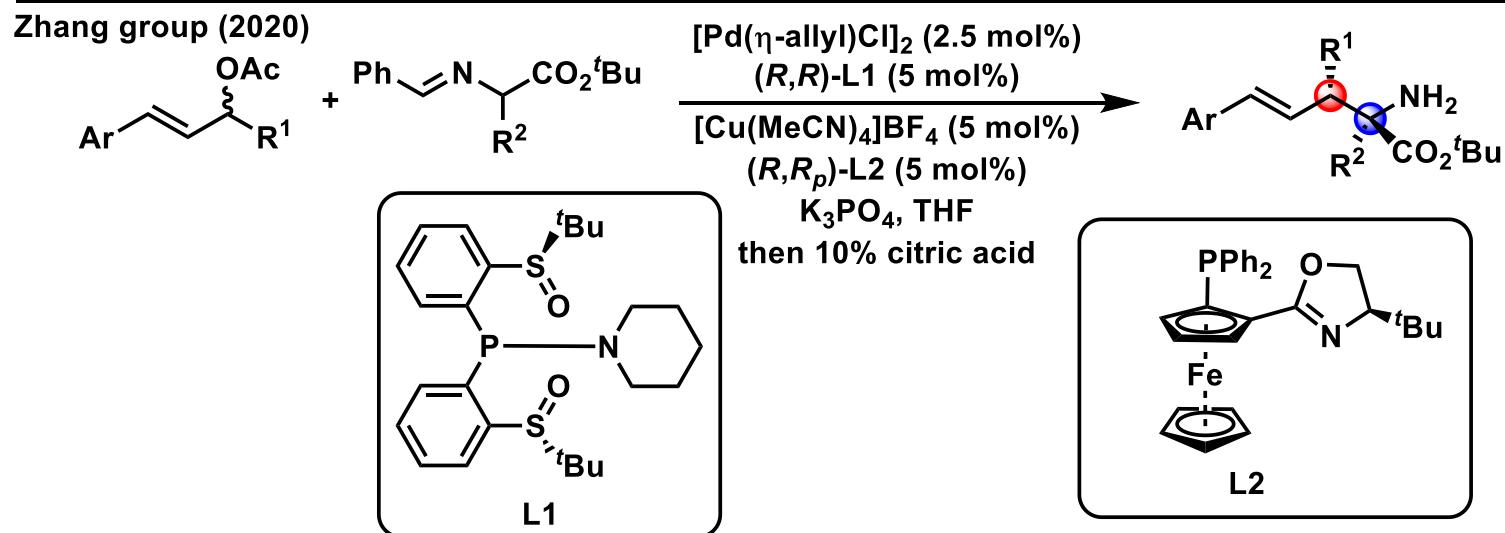
**AAA reaction**



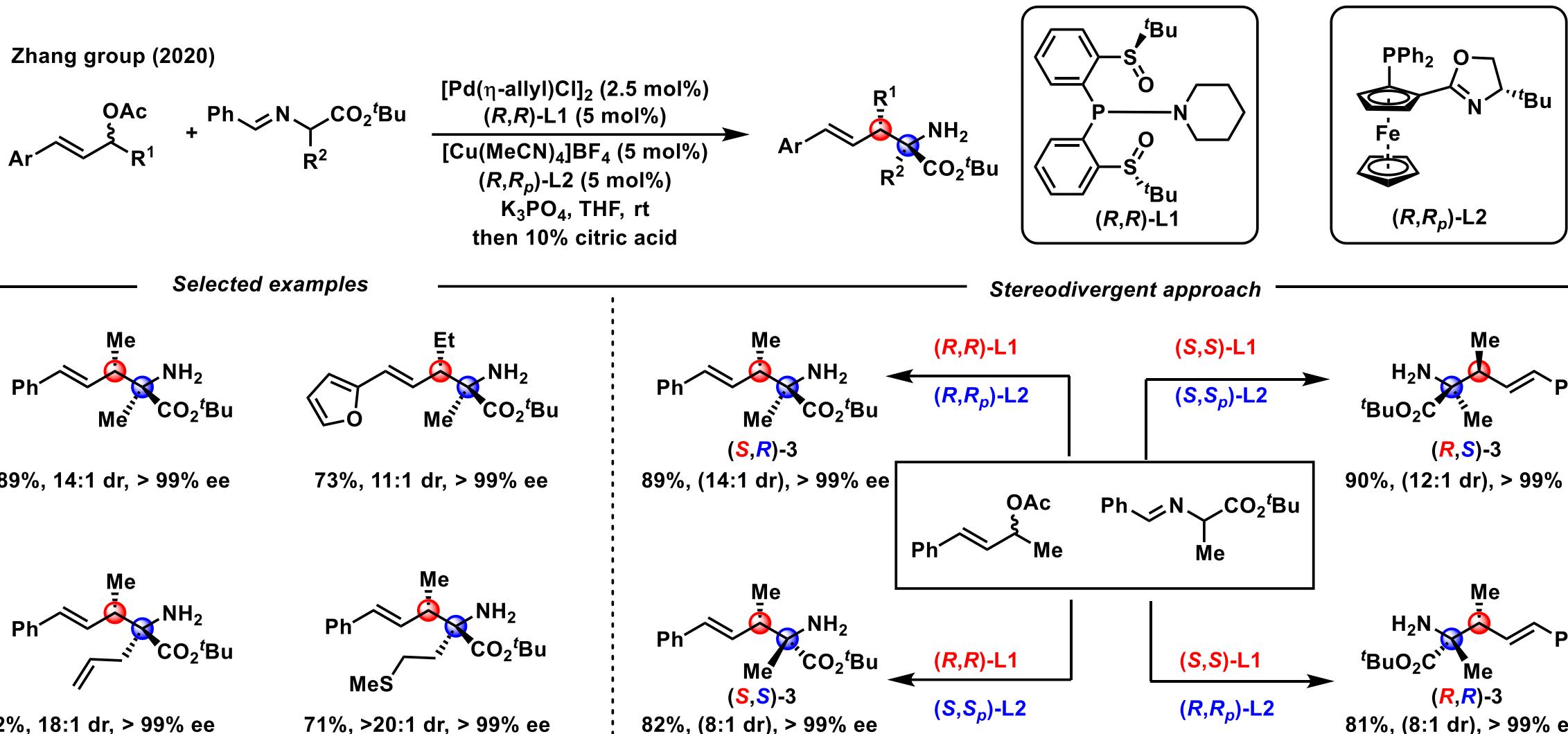
**Unsymmetrical  
1,3-disubstituted**



**1,2-adjacent**



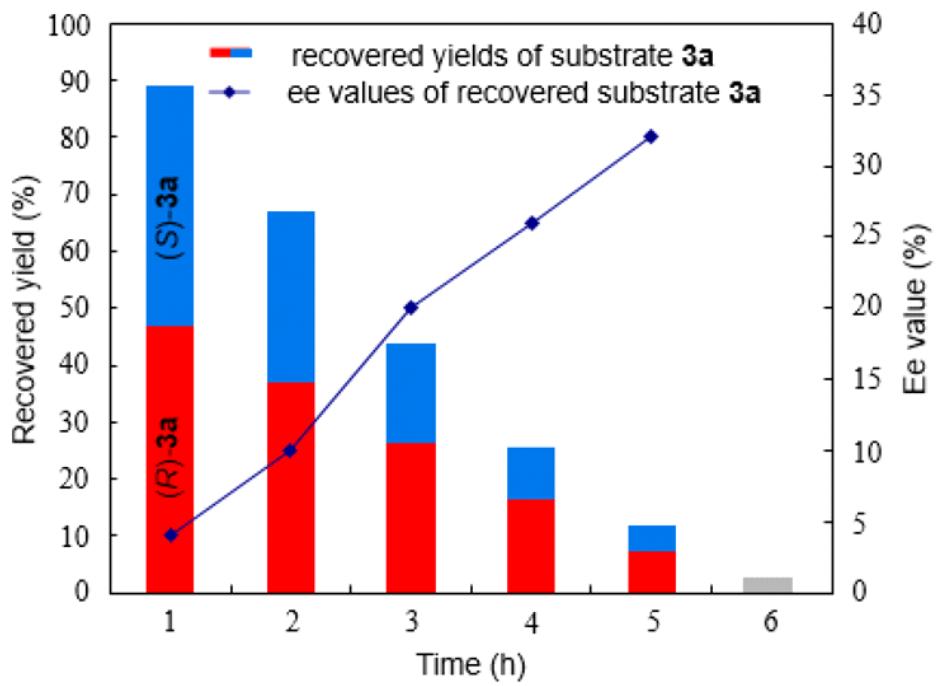
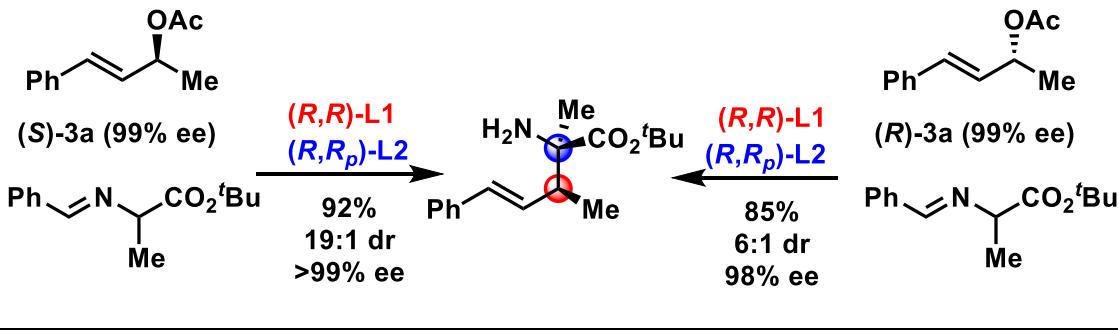
# 2.1 直接氧化加成启动 (烯丙基取代)



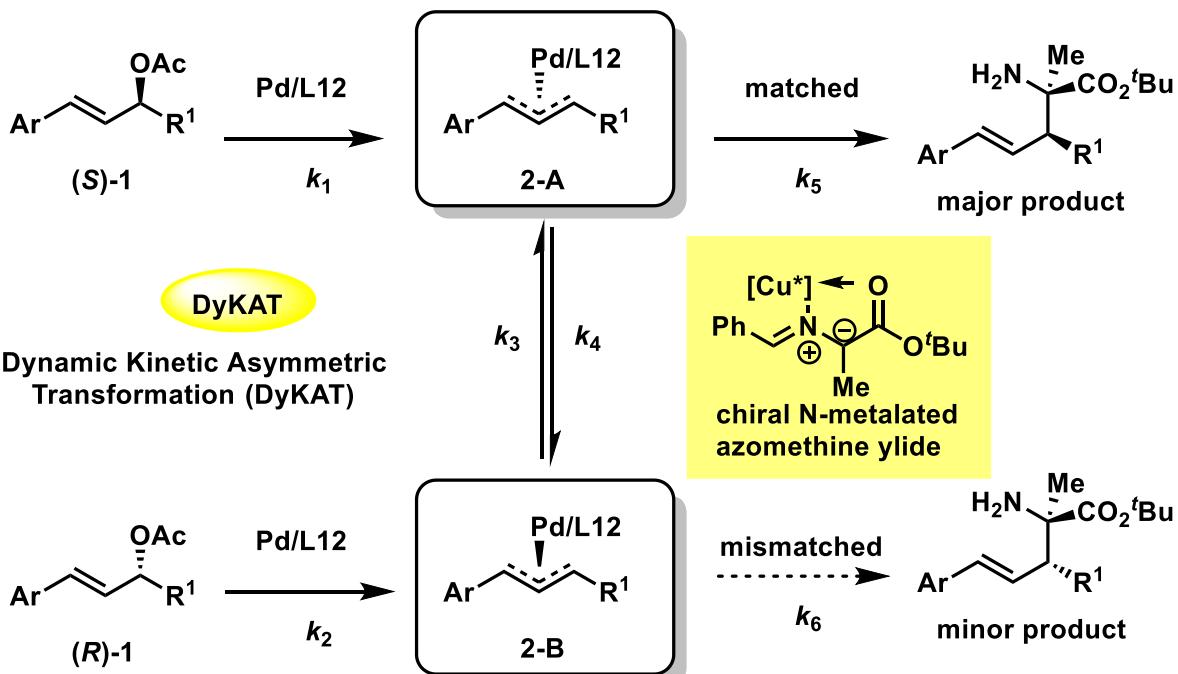
# 2.1 直接氧化加成启动 (烯丙基取代)



## The controlled experiments



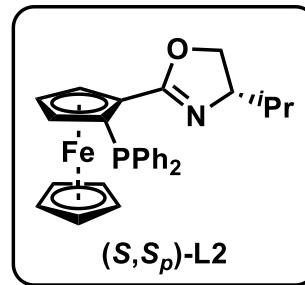
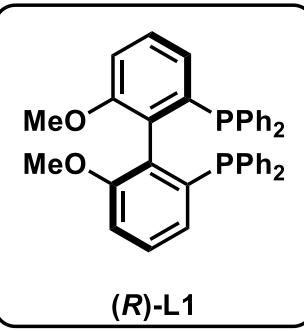
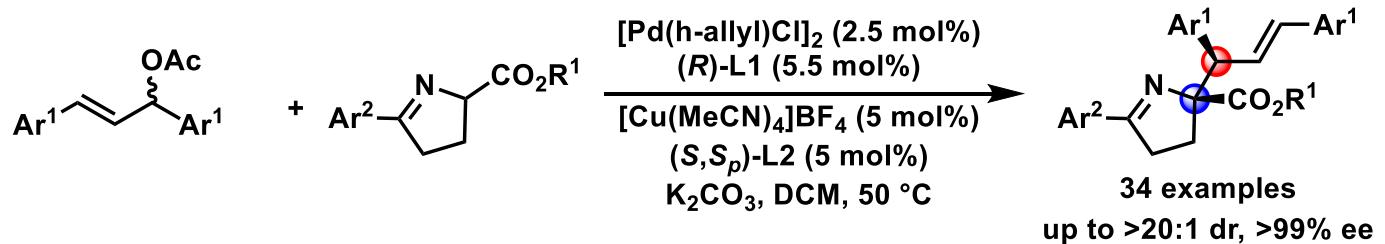
## Proposed mechanism



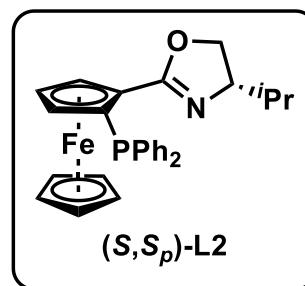
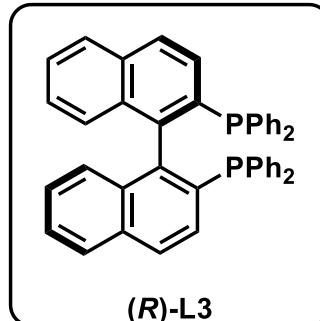
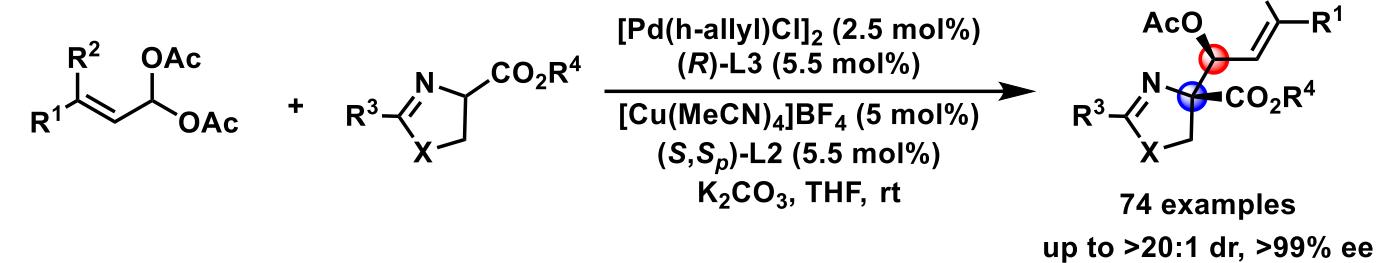
# 2.1 直接氧化加成启动 (烯丙基取代)

## The Similar Examples

Zhang group (2021)

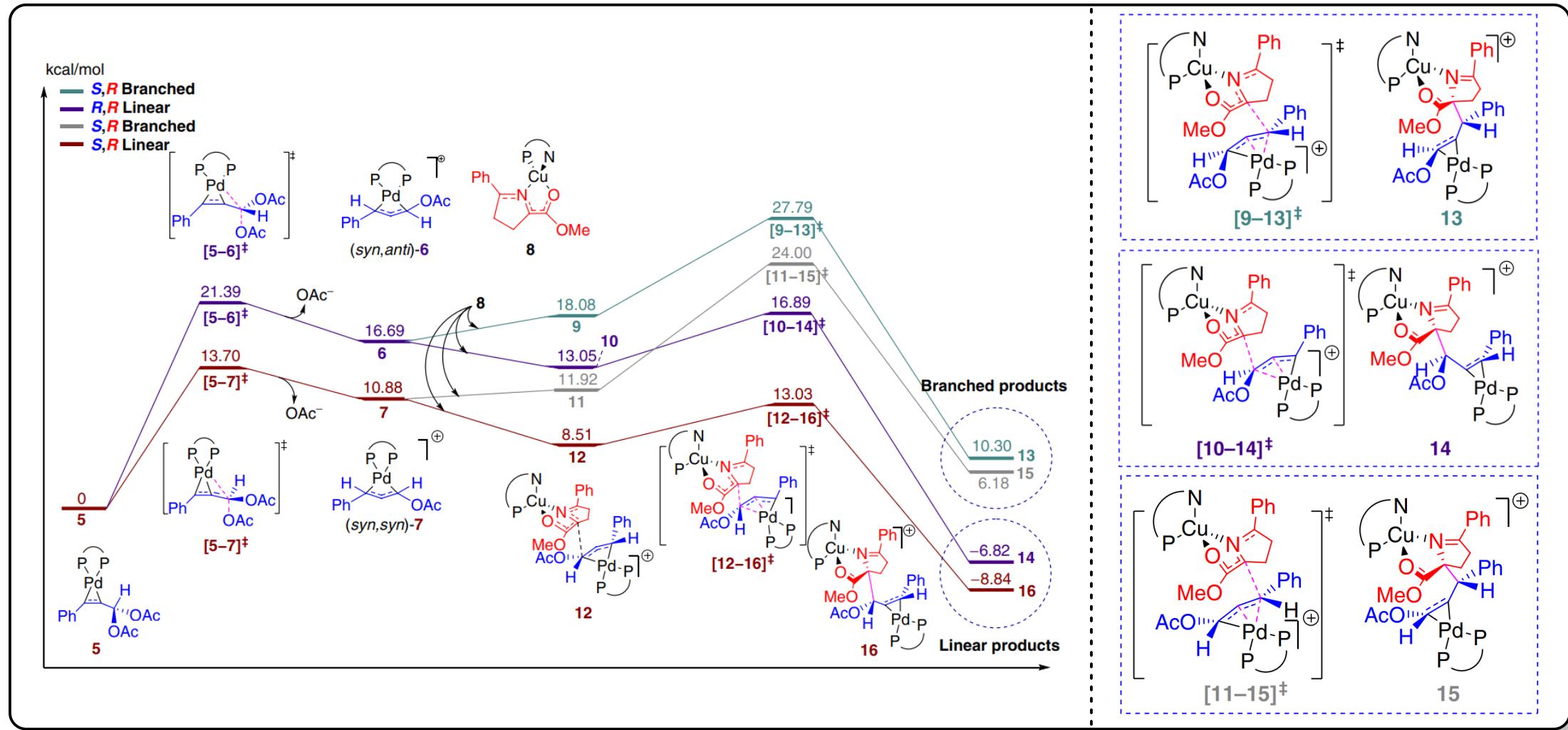


Zhang group (2022)



# 2.1 直接氧化加成启动 (烯丙基取代)

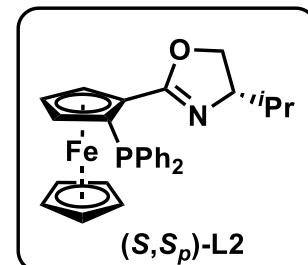
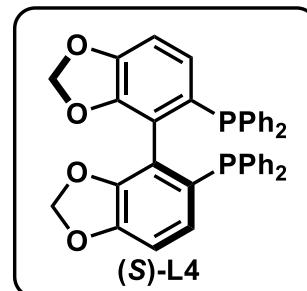
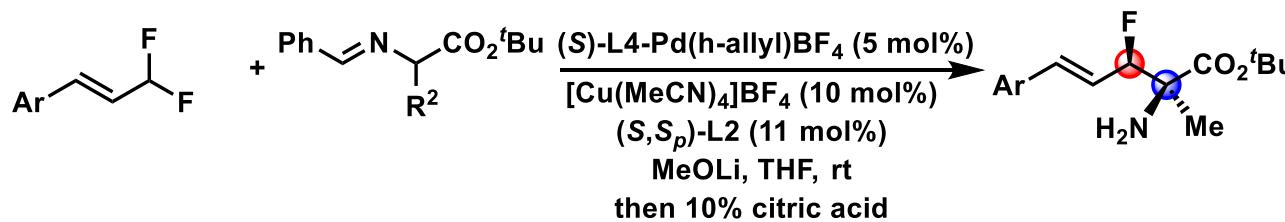
DFT calculations



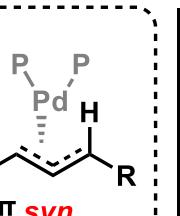
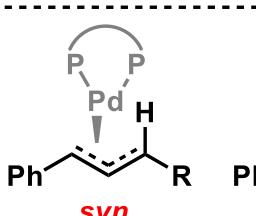
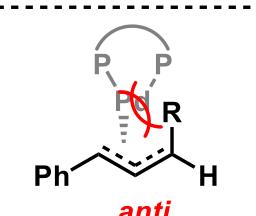
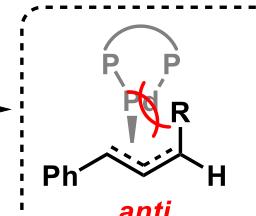
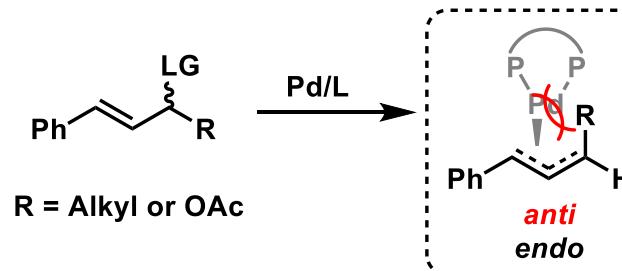
# 2.1 直接氧化加成启动 (烯丙基取代)



Zhang group (2023)

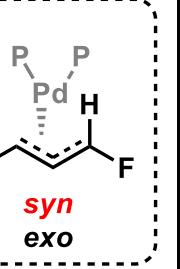
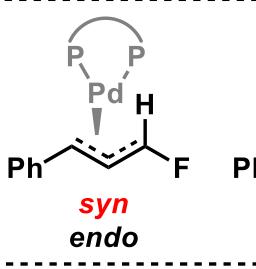
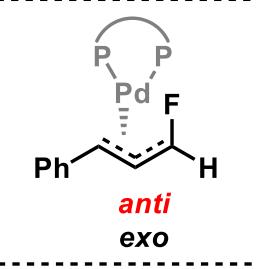
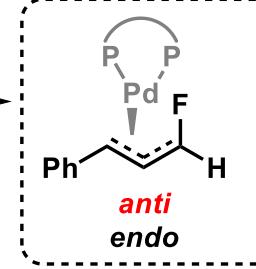
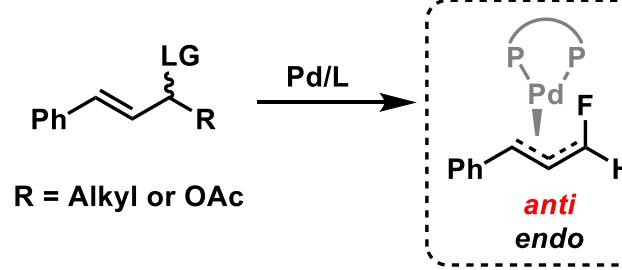


Challenges



$E_{anti} \gg E_{syn}$

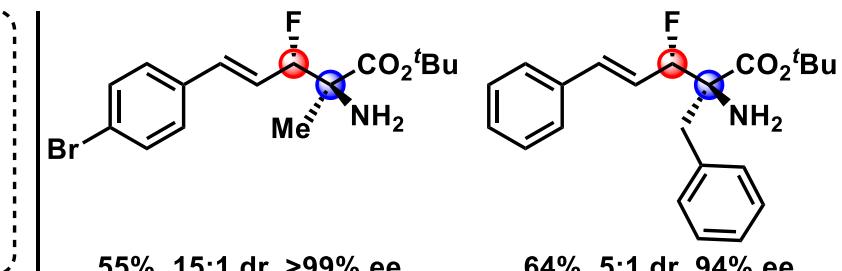
Mainly two Pd- $\pi$ -allyl-intermediates



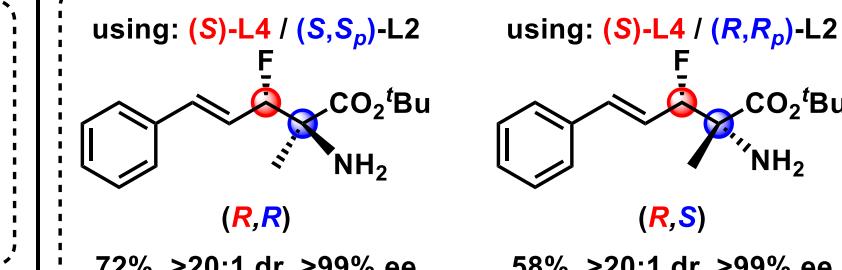
$E_{anti} \approx E_{syn}$

Four Pd- $\pi$ -allyl-intermediates

Select examples

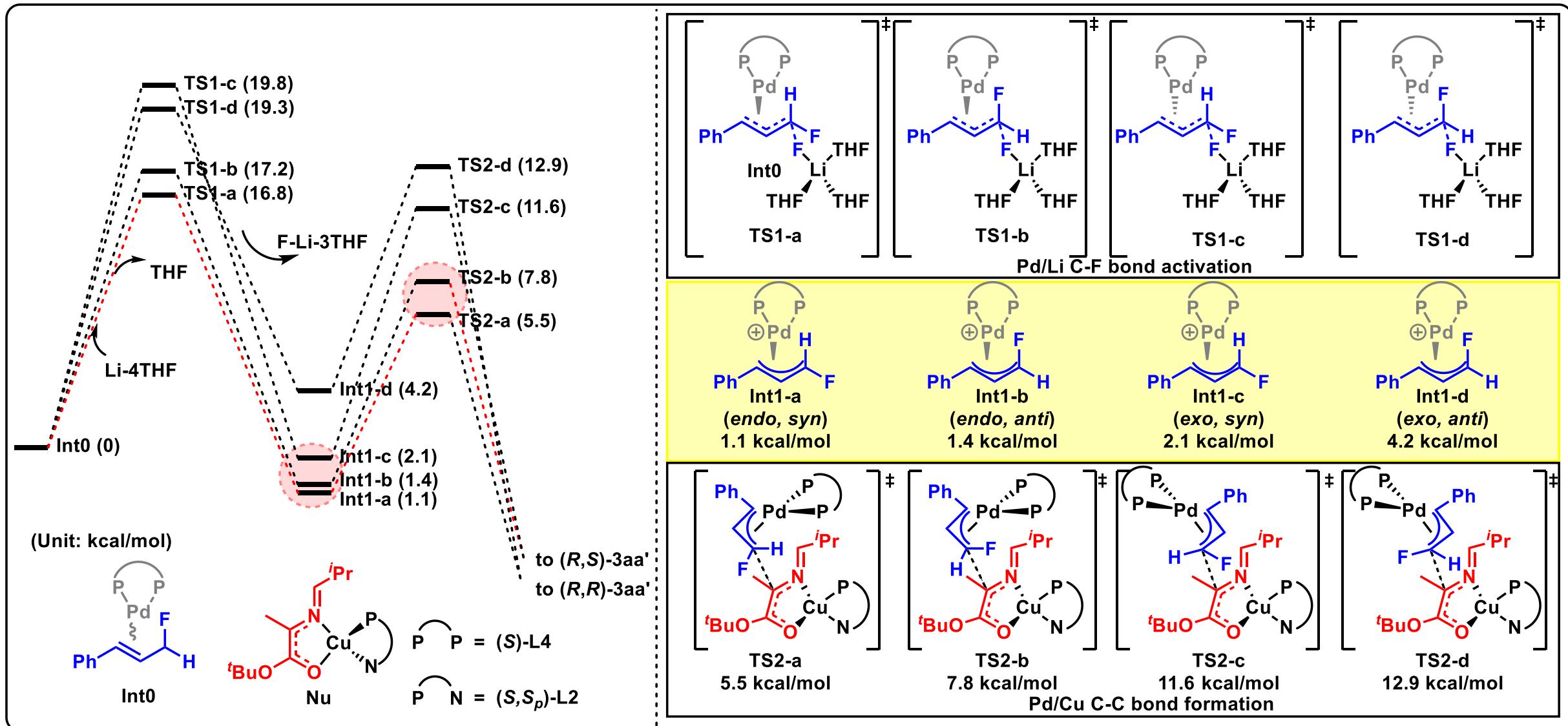


Stereodivergent approach



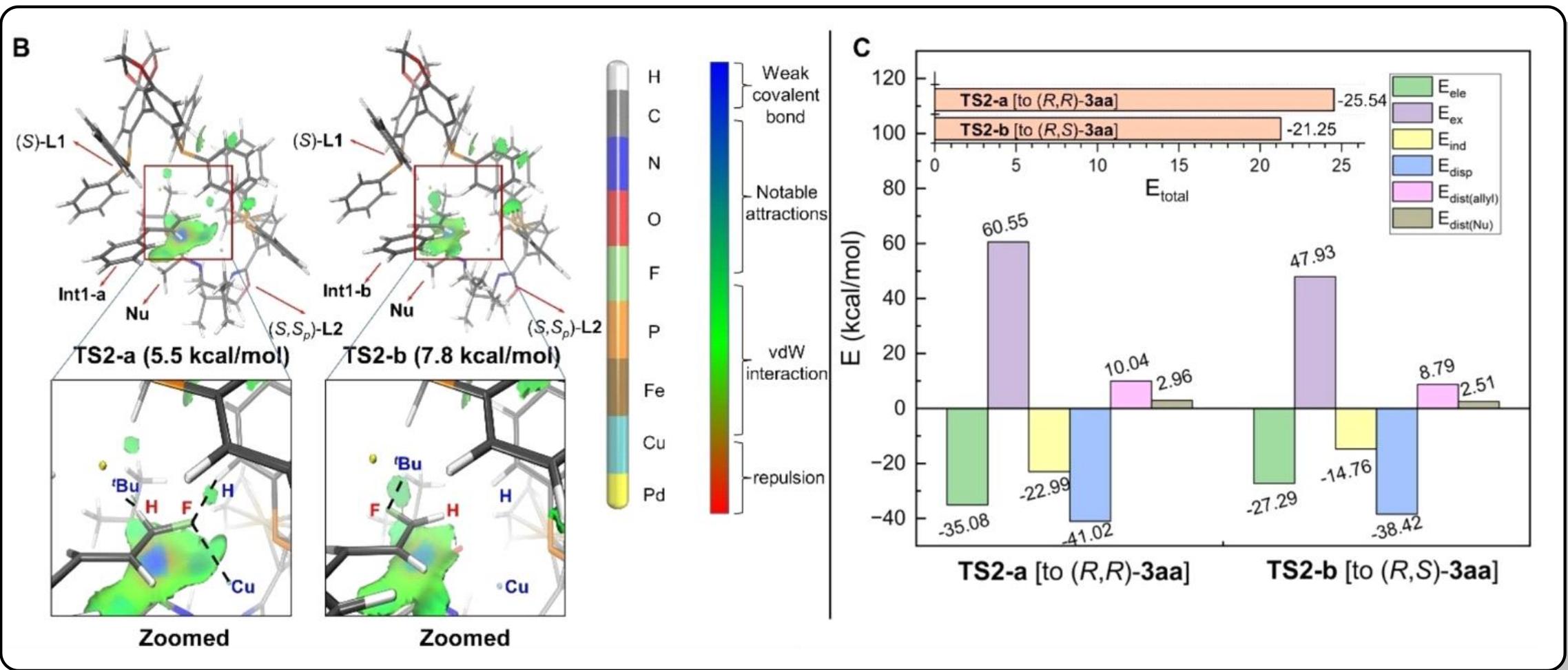
# 2.1 直接氧化加成启动 (烯丙基取代)

DFT calculations

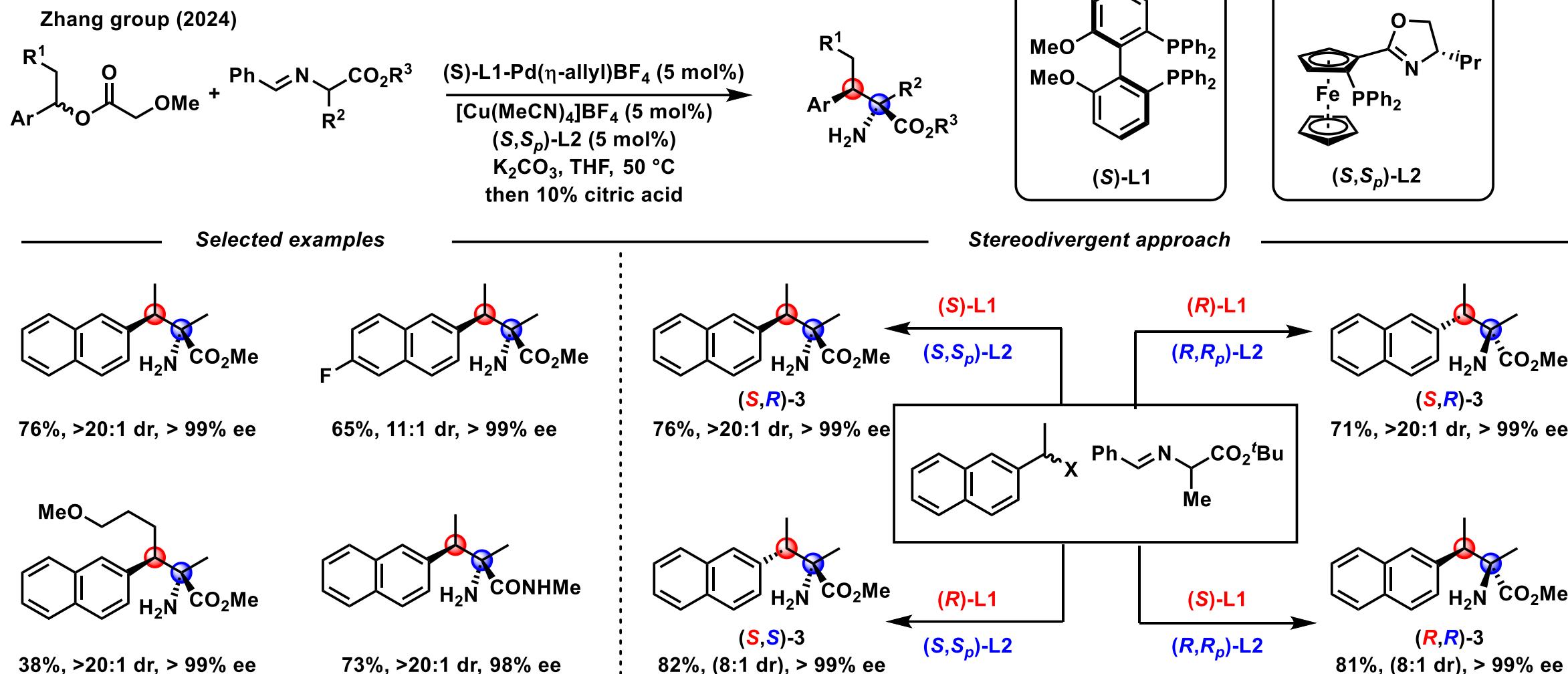


# 2.1 直接氧化加成启动 (烯丙基取代)

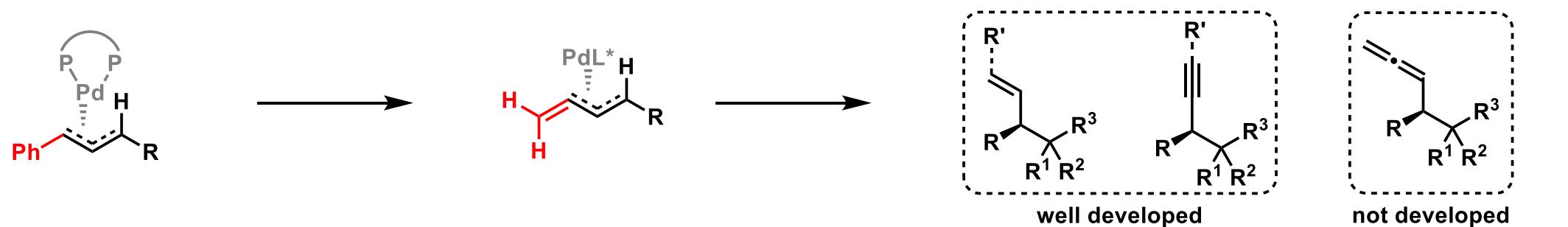
## Energy Decomposition Analyses



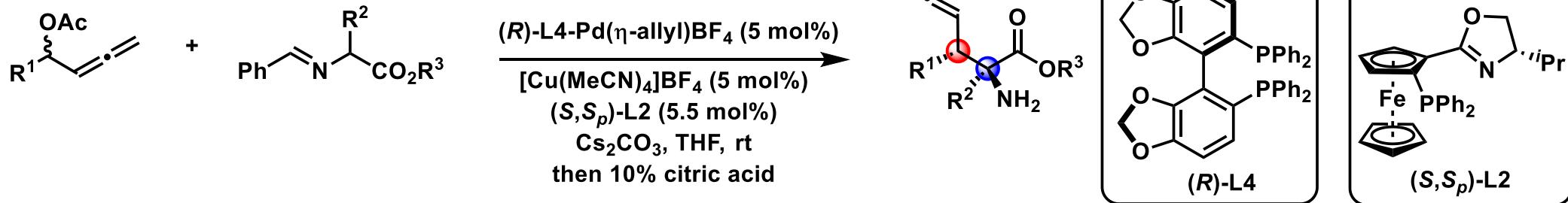
# 2.1 直接氧化加成启动 (烯丙基取代)



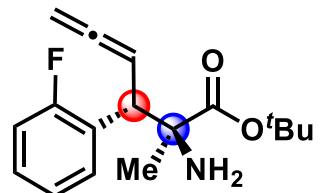
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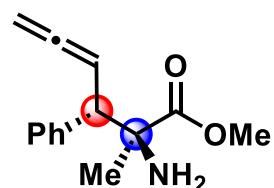
Zhang group (2023)



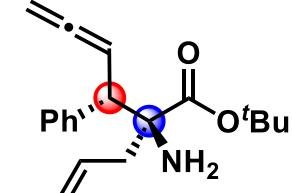
Select examples



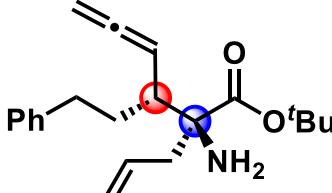
69%, >20:1 dr, > 99% ee



72%, >20:1 dr, > 99% ee



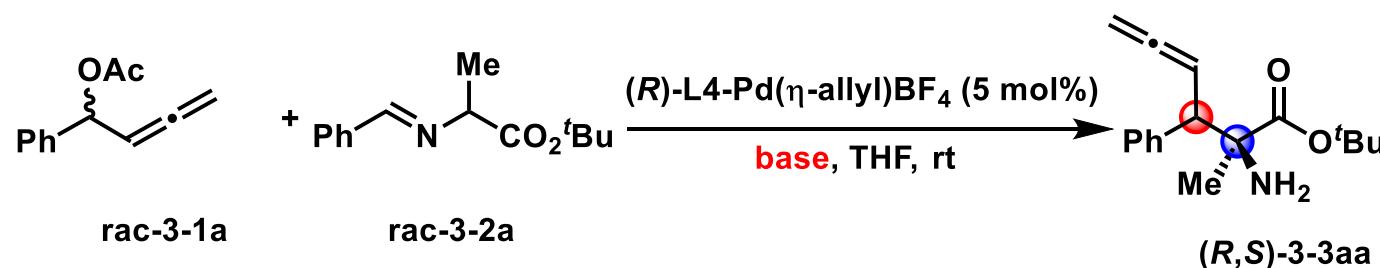
75%, >20:1 dr, > 99% ee



62%, >20:1 dr, > 99% ee

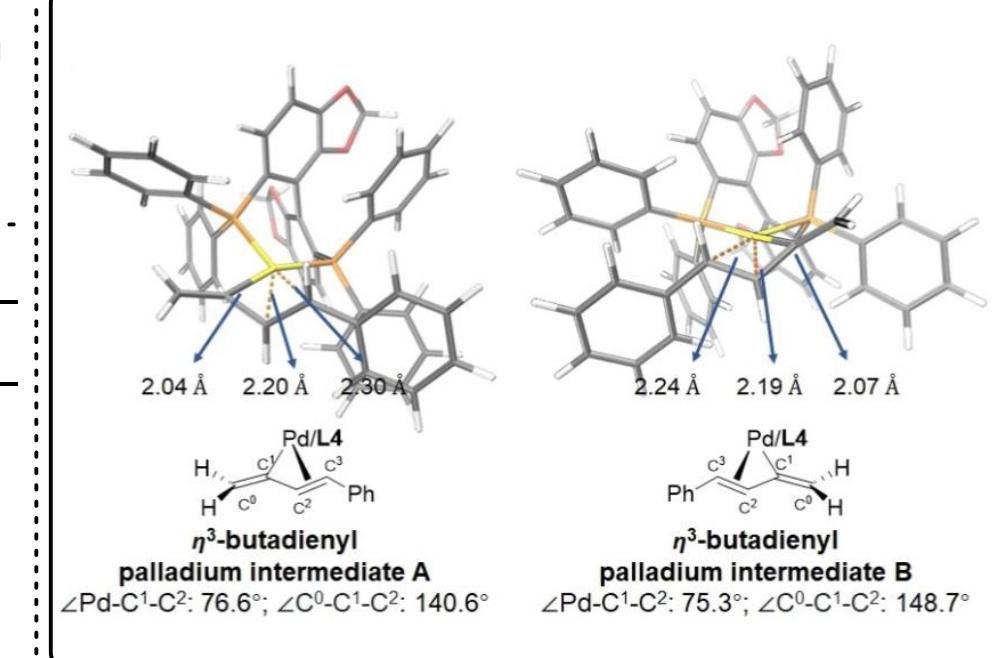
# 2.1 直接氧化加成启动 (烯丙基取代)

## The controlled experiments



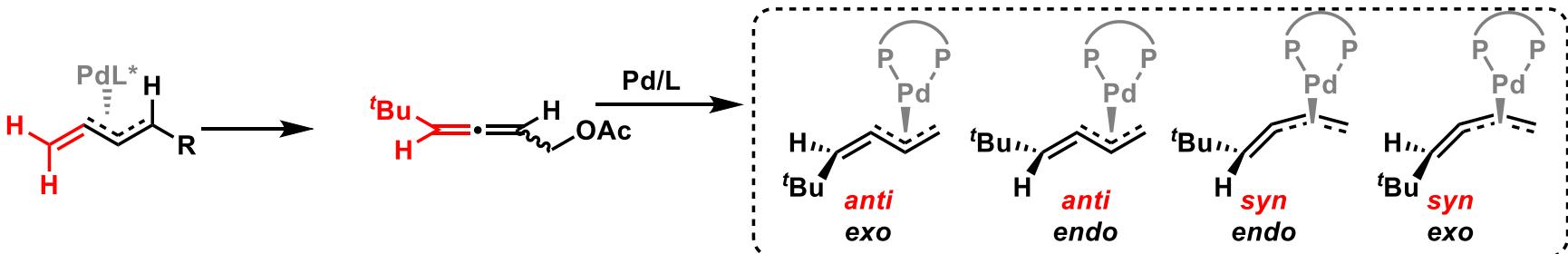
entry	base	Cat. Cu	yield (%)	dr	ee (%)
1	$\text{Cs}_2\text{CO}_3$	Cu/L1	72	> 20:1	>99
2	$\text{Cs}_2\text{CO}_3$	no Cu	nr	--	--
3	NaH	no Cu	26	1:1	82/81
4	$\text{Cs}_2\text{CO}_3$	Cu/dppf	37	2.5:1	66/14

## DFT calculations

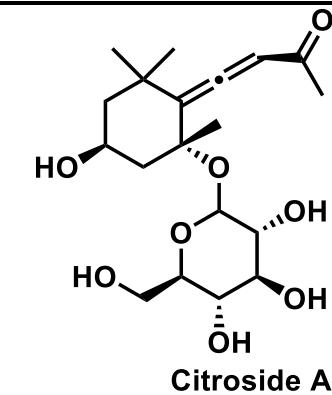
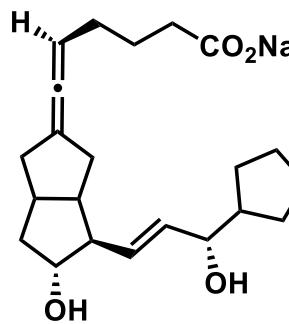
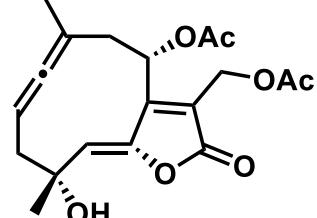
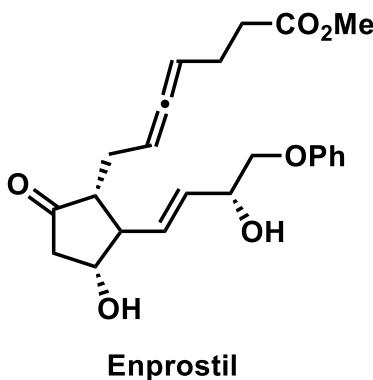


# 2.1 直接氧化加成启动 (烯丙基取代)

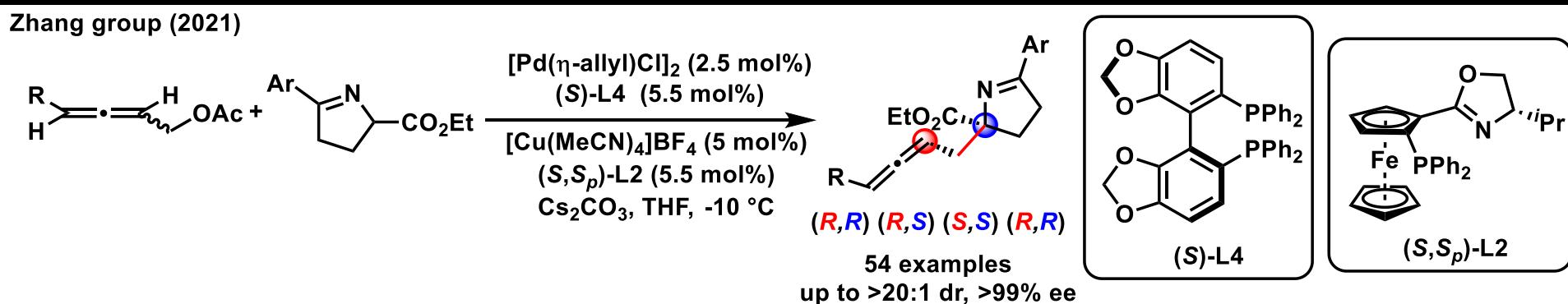
$\alpha$ -alkynylidene  
 $\pi$ -allylpalladium



Bioactive Molecules

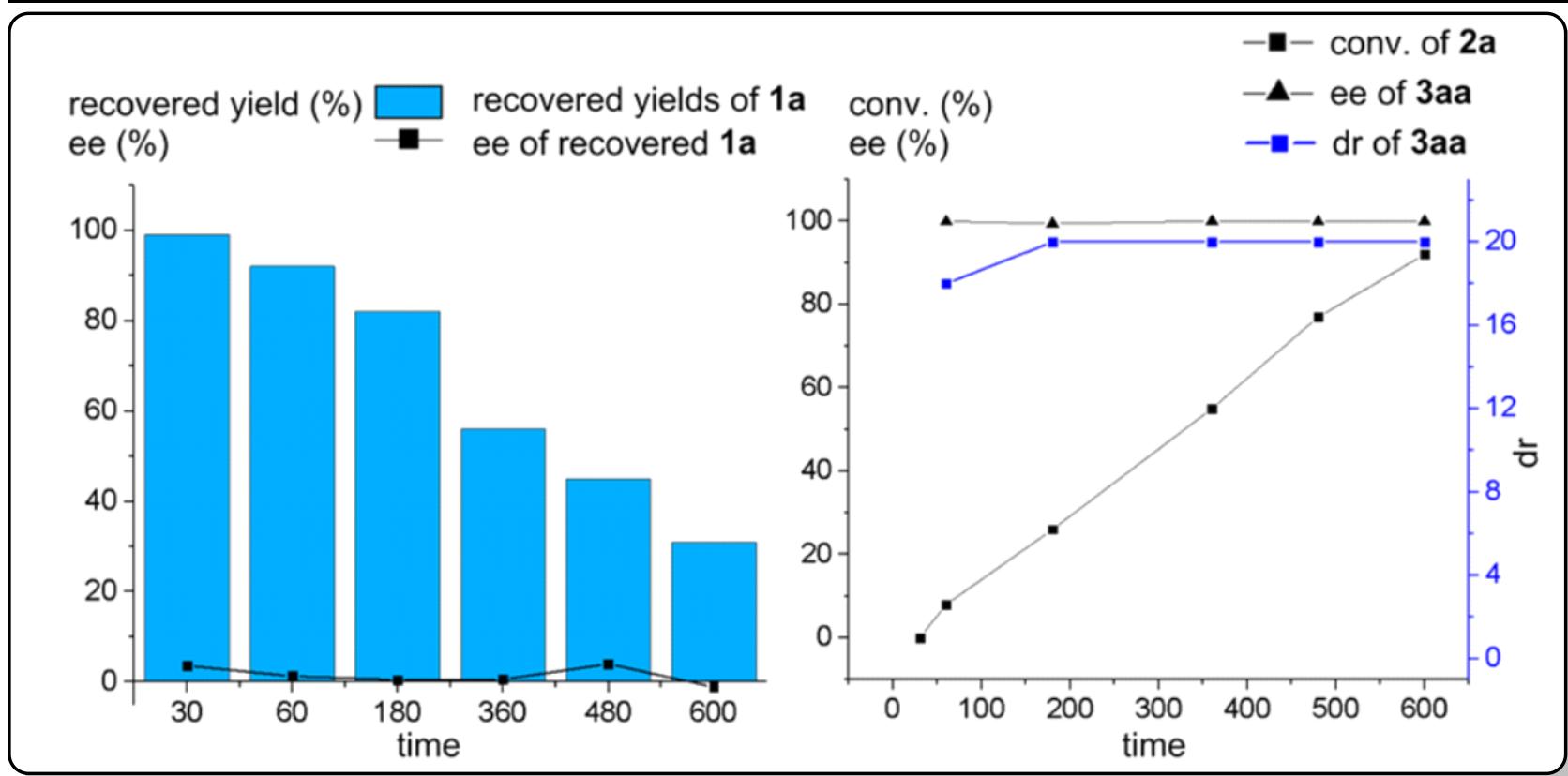
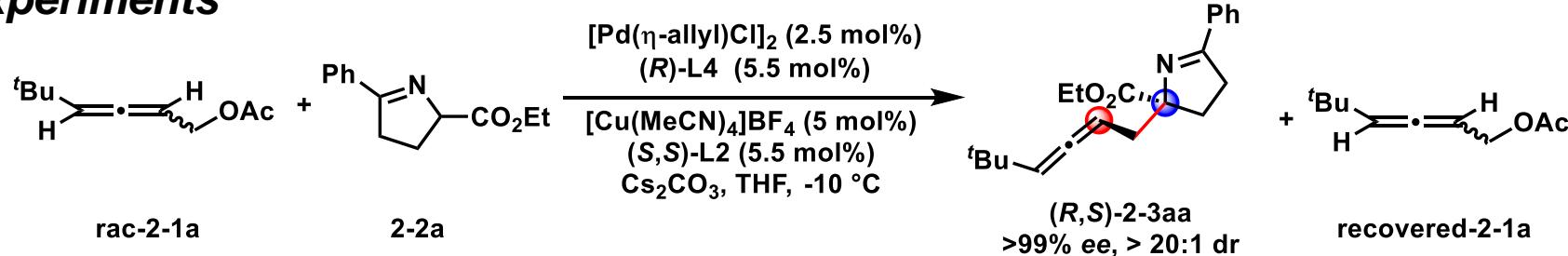


1,3-nonadjacent



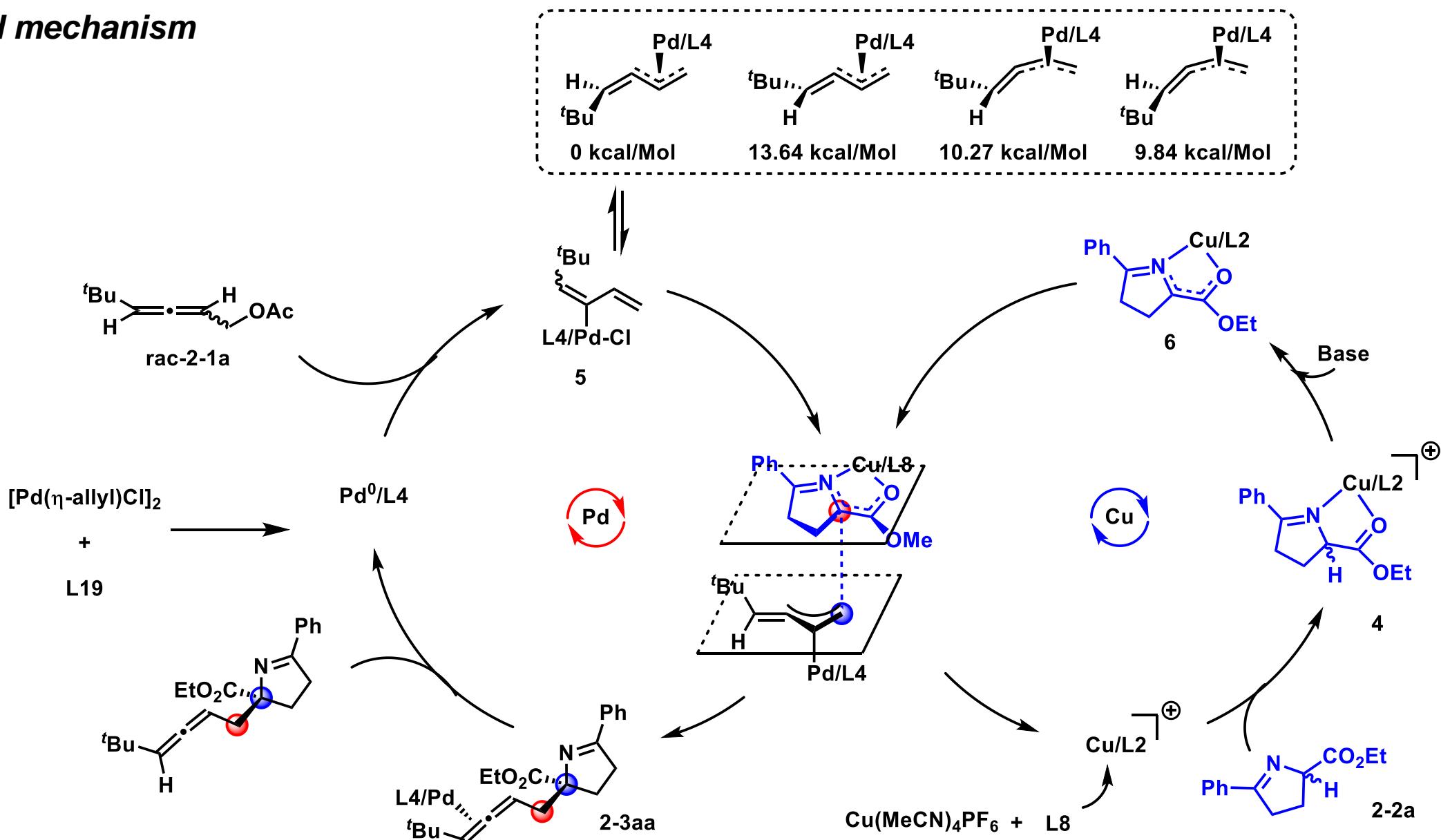
# 2.1 直接氧化加成启动 (烯丙基取代)

## The controlled experiments



# 2.1 直接氧化加成启动 (烯丙基取代)

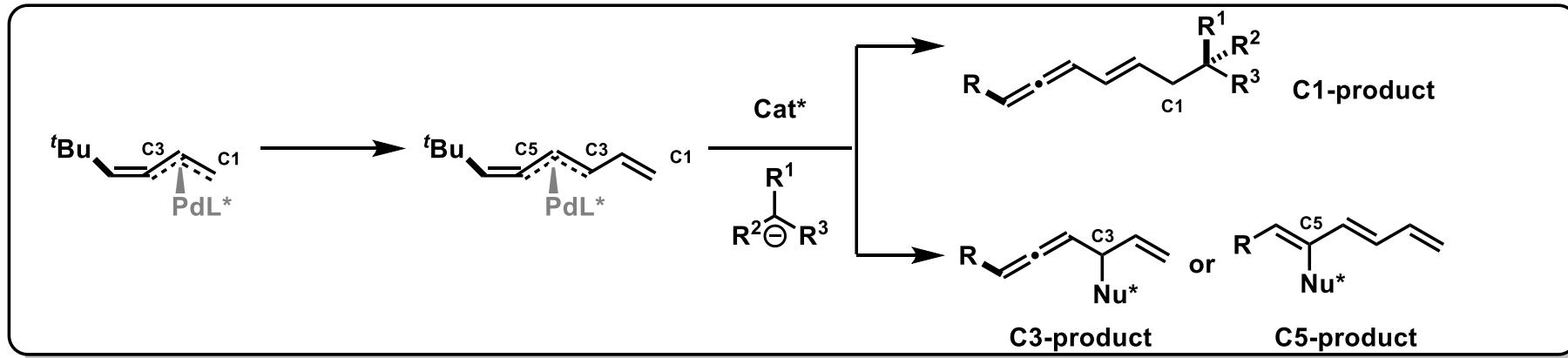
## Proposed mechanism



# 2.1 直接氧化加成启动 (烯丙基取代)

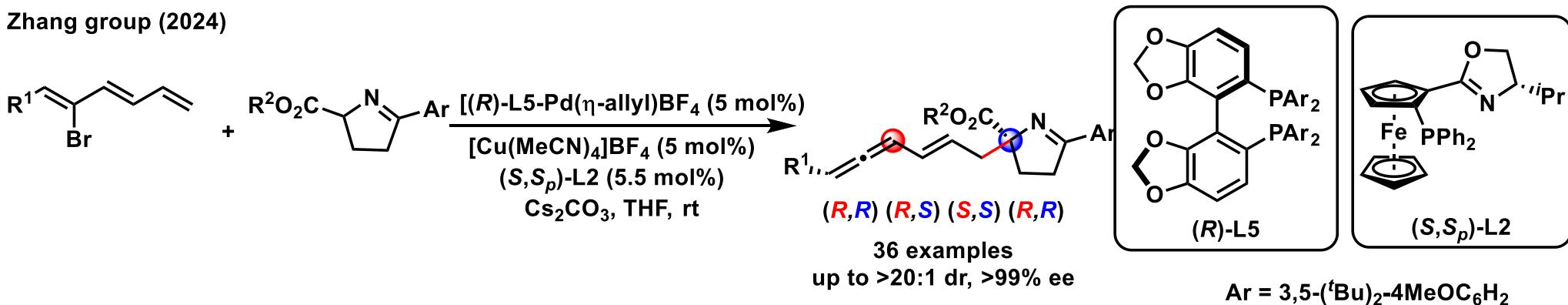


**C=C bond relay strategy**



Zhang group (2024)

**1,5-nonadjacent**



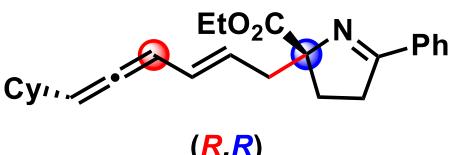
Stereodivergent approach

using: (*R*)-L5 / (*S,S<sub>p</sub>*)-L2



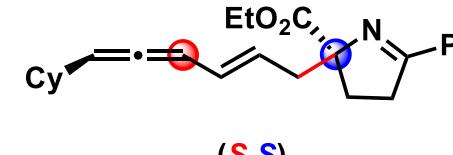
92%, >99% ee, 13:1 dr

using: (*R*)-L5 / (*R,R<sub>p</sub>*)-L2



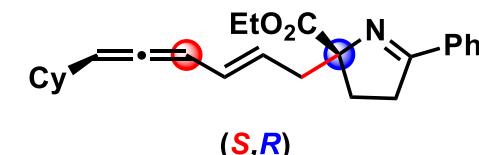
78%, >99% ee, 10:1 dr

using: (*S*)-L4 / (*S,S<sub>p</sub>*)-L2



82%, 99% ee, 14:1 dr

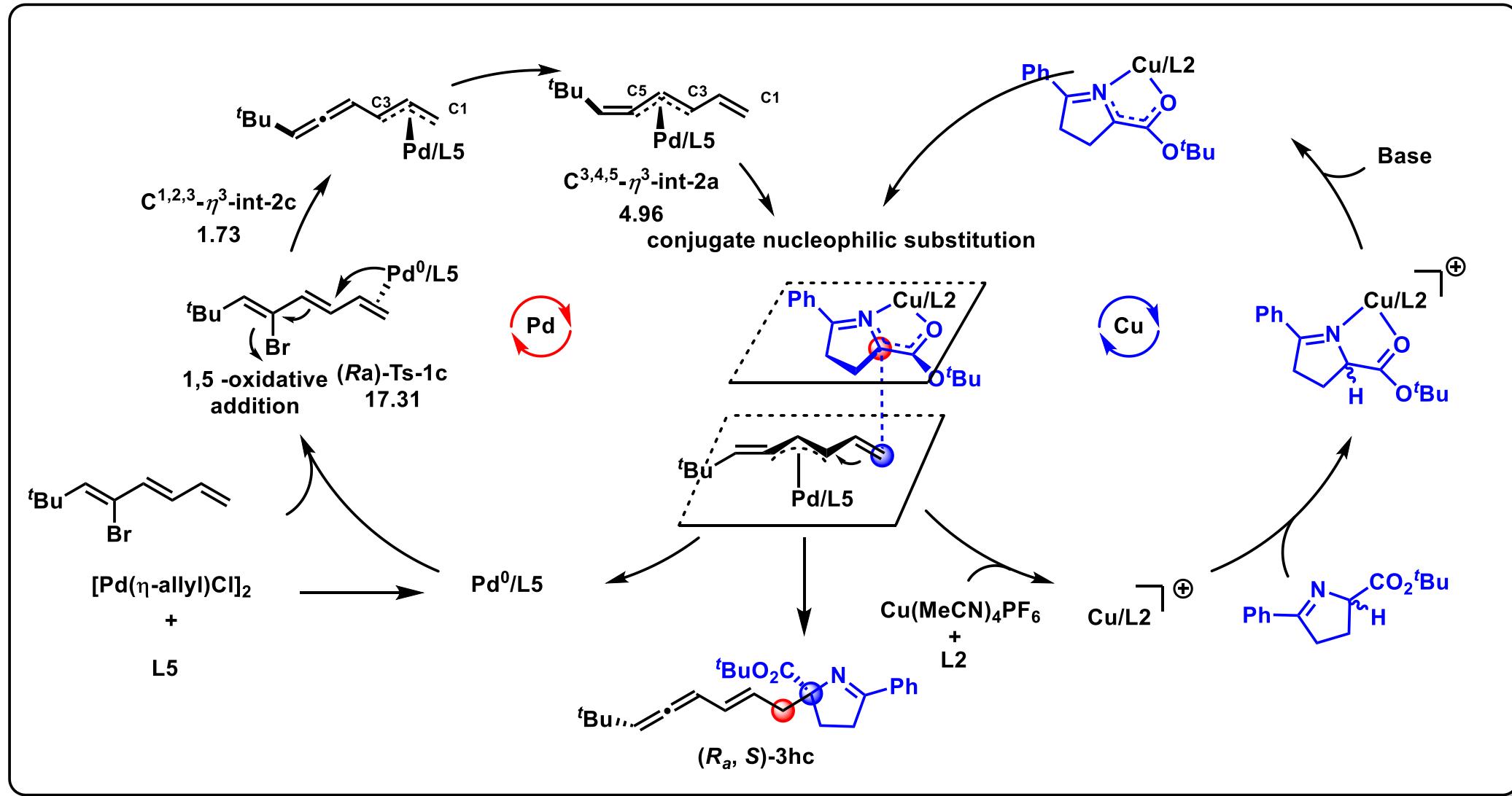
using: (*S*)-L4 / (*R,R<sub>p</sub>*)-L2



81%, 98% ee, 11:1 dr

# 2.1 直接氧化加成启动 (烯丙基取代)

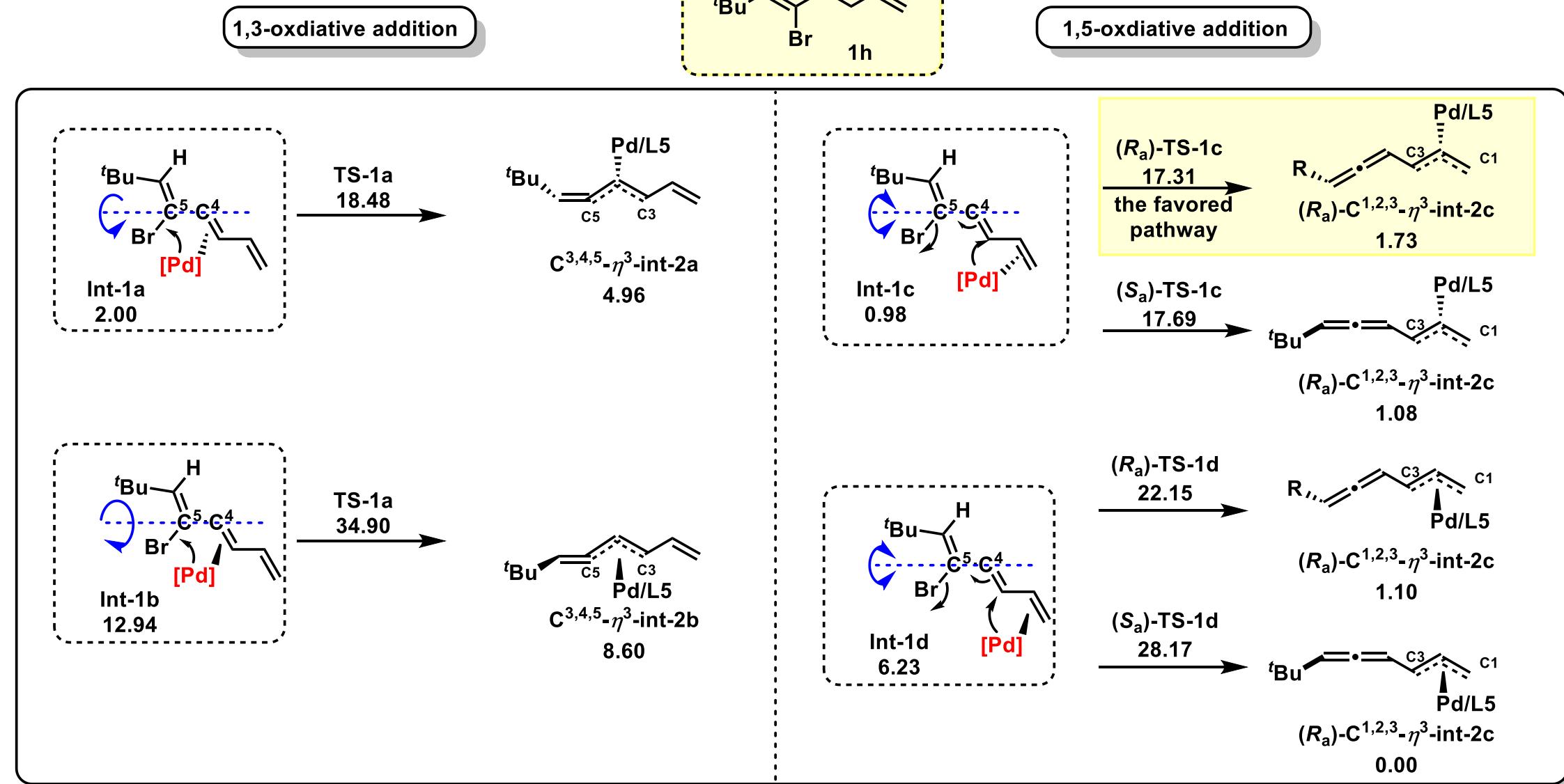
## Proposed mechanism



# 2.1 直接氧化加成启动 (烯丙基取代)

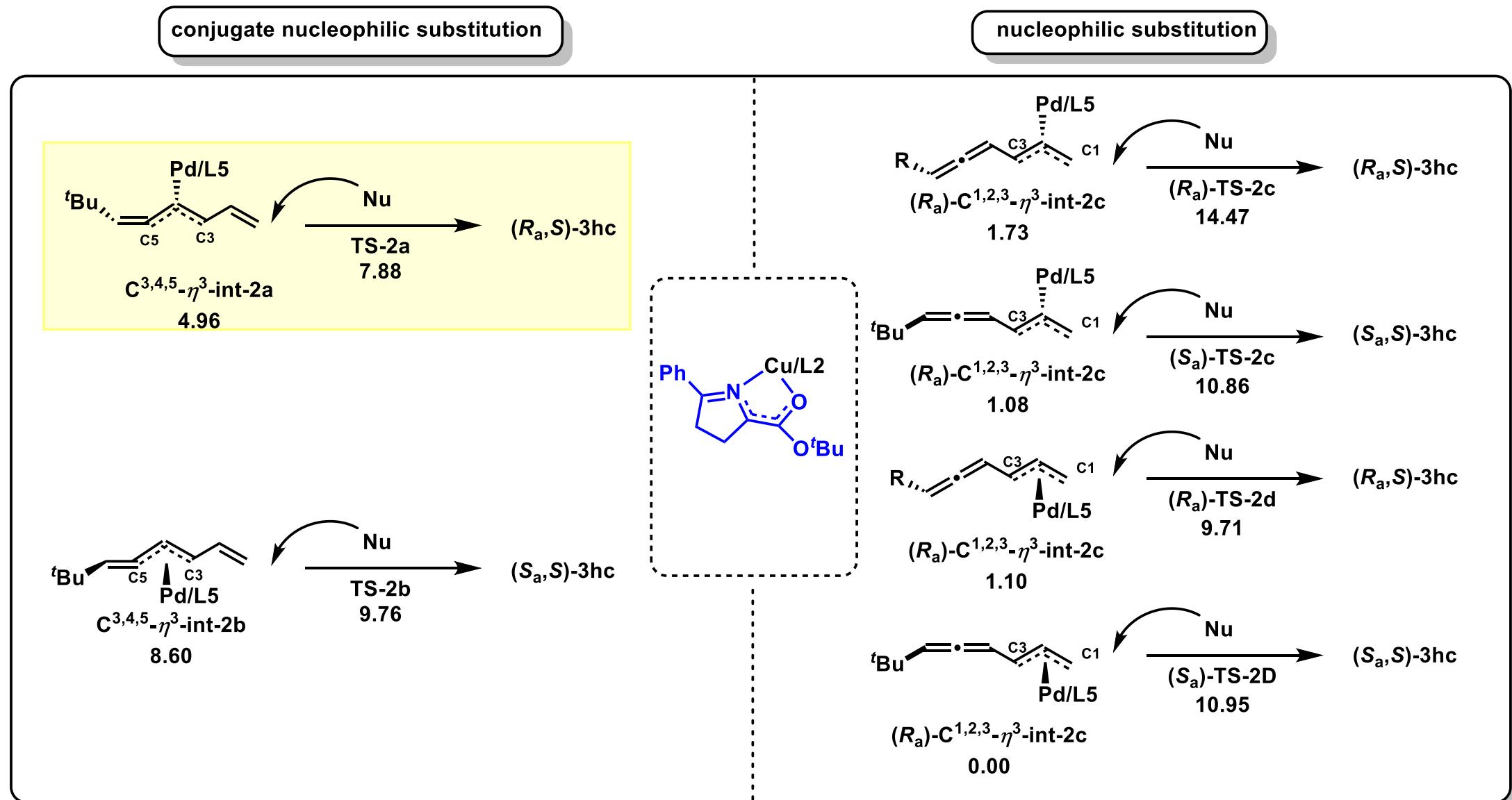


## DFT calculations



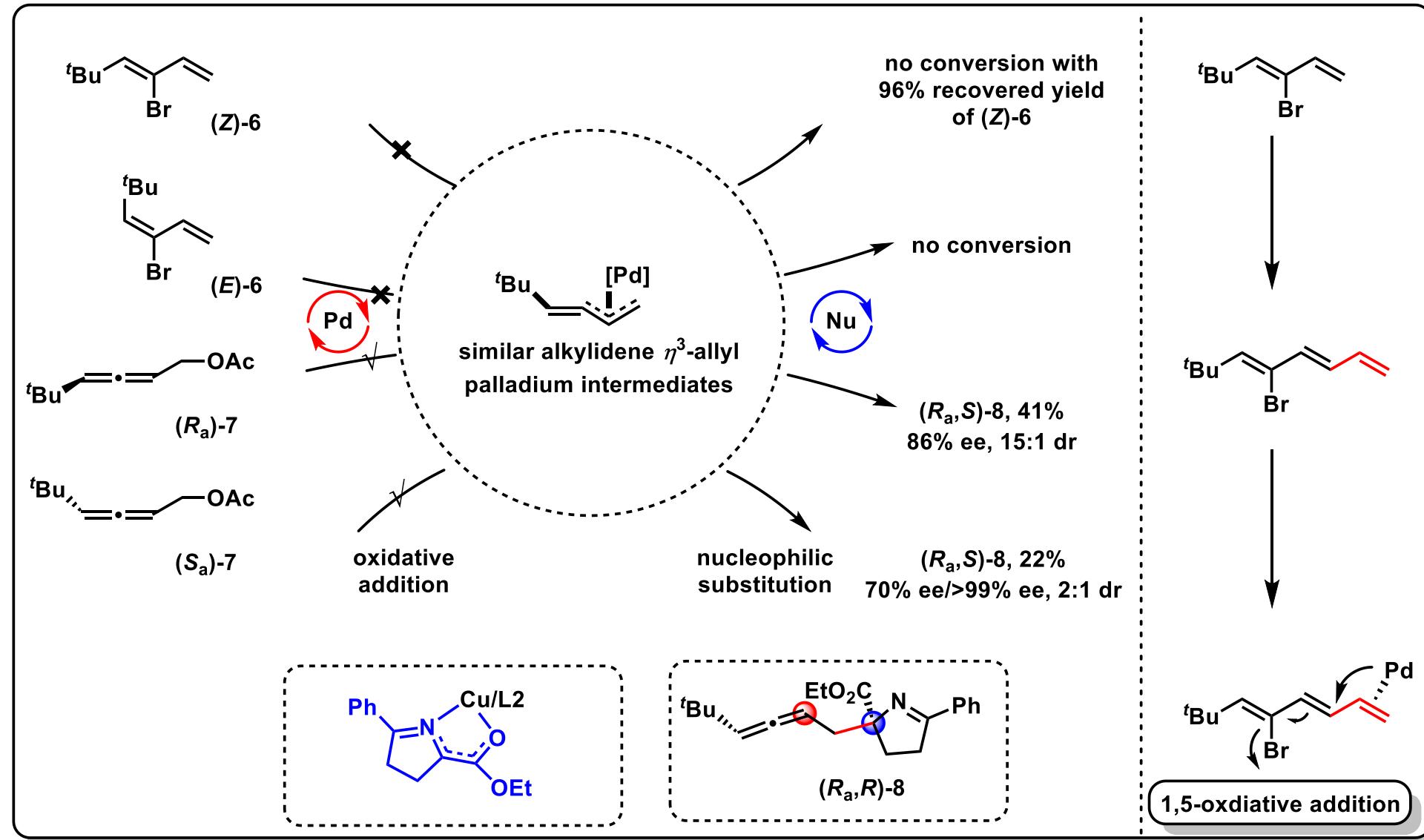
# 2.1 直接氧化加成启动 (烯丙基取代)

## DFT calculations



# 2.1 直接氧化加成启动 (烯丙基取代)

## The controlled experiments





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    2.1 直接氧化加成启动 (烯丙基取代)

    2.2 Heck反应启动

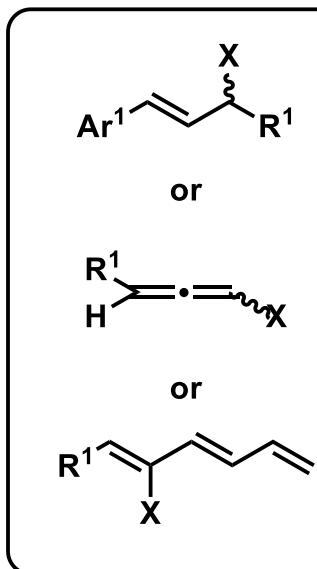
    2.1 PdH插入启动

3. 总结与展望

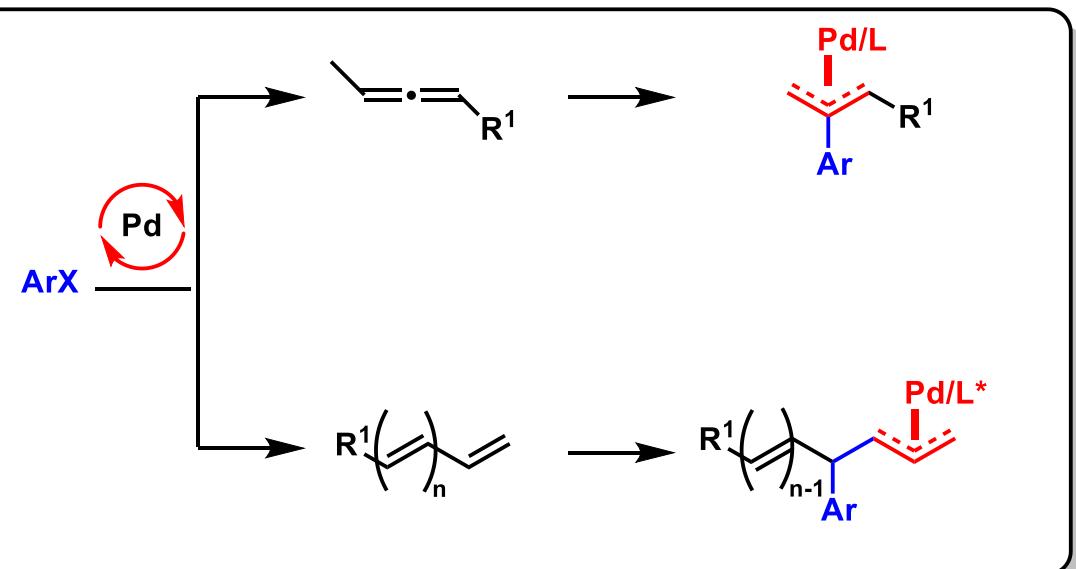
## 2.2 间接氧化加成 (Heck启动)



*Direct oxidation addition*



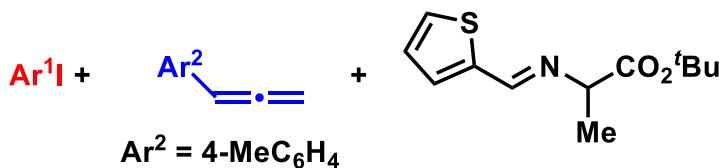
*Through Heck reaction*



## 2.2 间接氧化加成 (Heck启动)



Zhang group (2024)



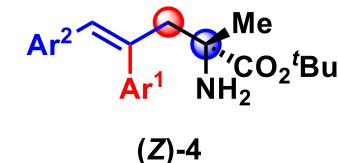
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2

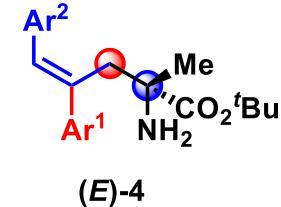
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[Pd( $\eta$ -allyl)Cl]<sub>2</sub> (5.0 mol%)  
(R)-L6 (11 mol%)

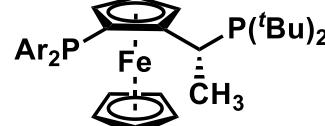
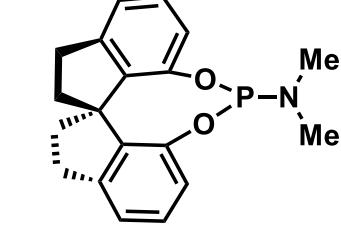
[Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> (5 mol%)  
(R,R<sub>p</sub>)-L2 (5.5 mol%)  
Cs<sub>2</sub>CO<sub>3</sub>, DCE, 50 °C  
then 10% citric acid



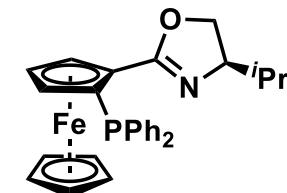
[Pd( $\eta$ -allyl)Cl]<sub>2</sub> (5.0 mol%)  
(S<sub>P</sub>, R)-L7 (11 mol%)  
[Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> (5 mol%)  
(R,R<sub>p</sub>)-L2 (5.5 mol%)  
Cs<sub>2</sub>CO<sub>3</sub>, DCE, 50 °C  
then 10% citric acid



Pd Ligand



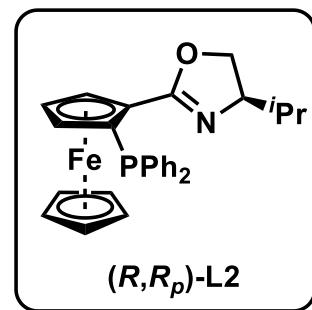
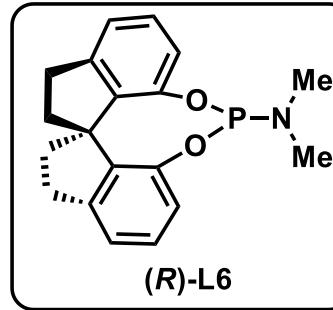
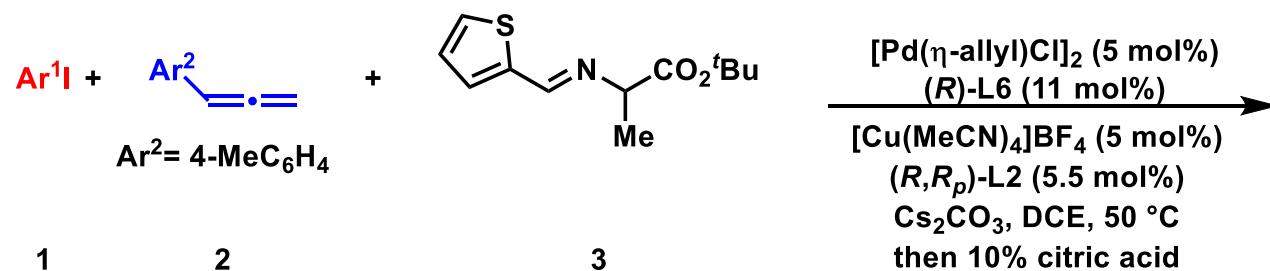
Cu Ligand



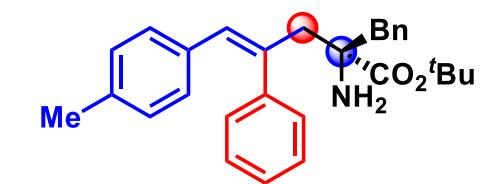
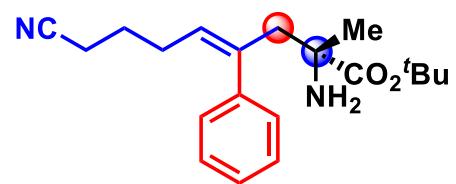
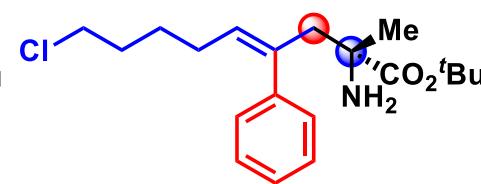
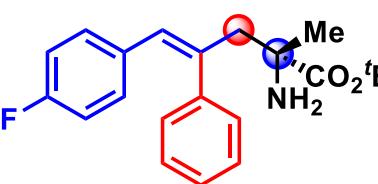
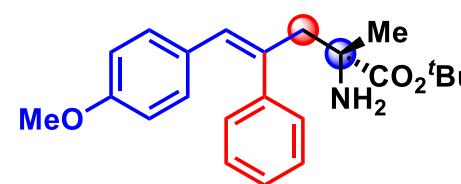
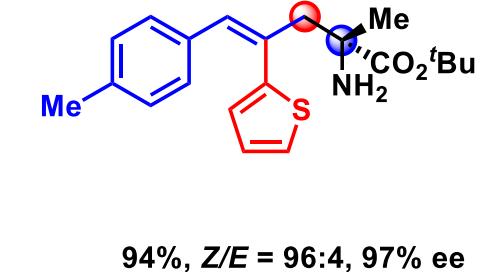
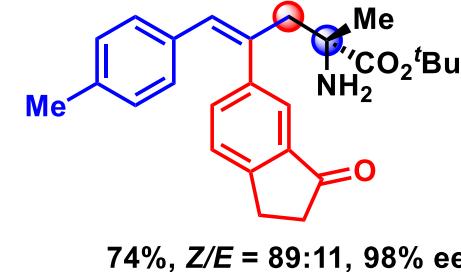
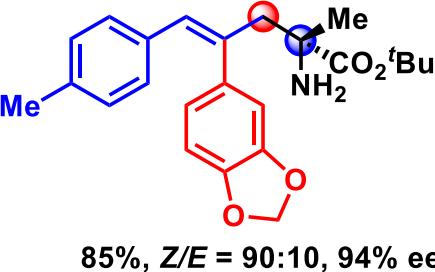
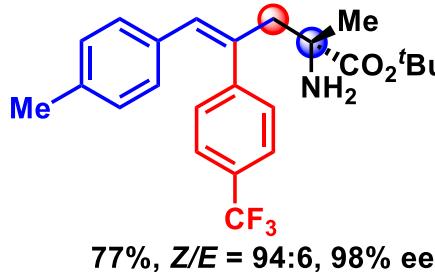
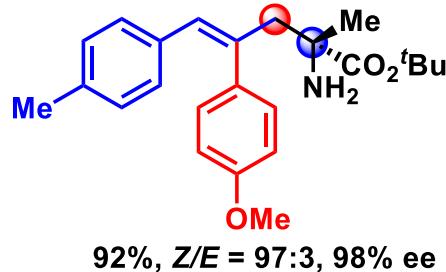
## 2.2 间接氧化加成 (Heck启动)



Zhang group (2024)



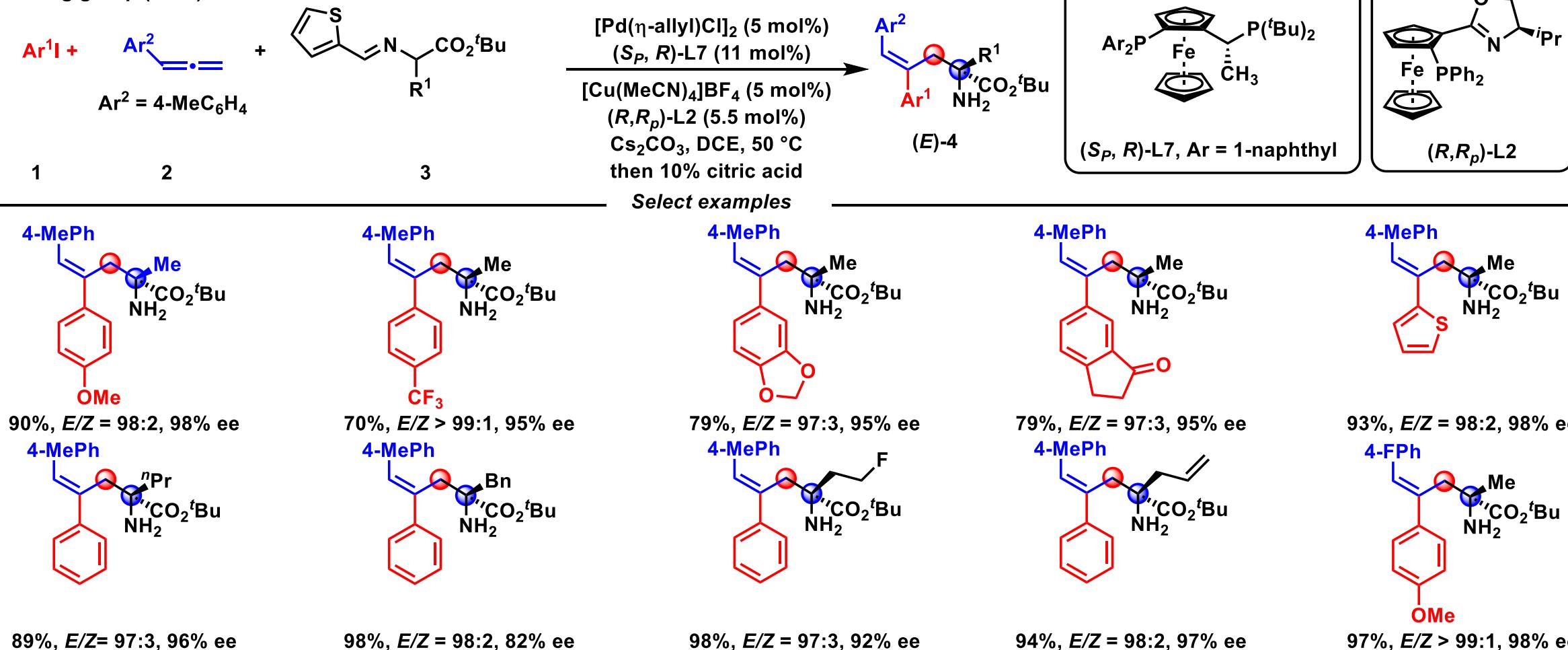
Select examples



# 2.2 间接氧化加成 (Heck启动)



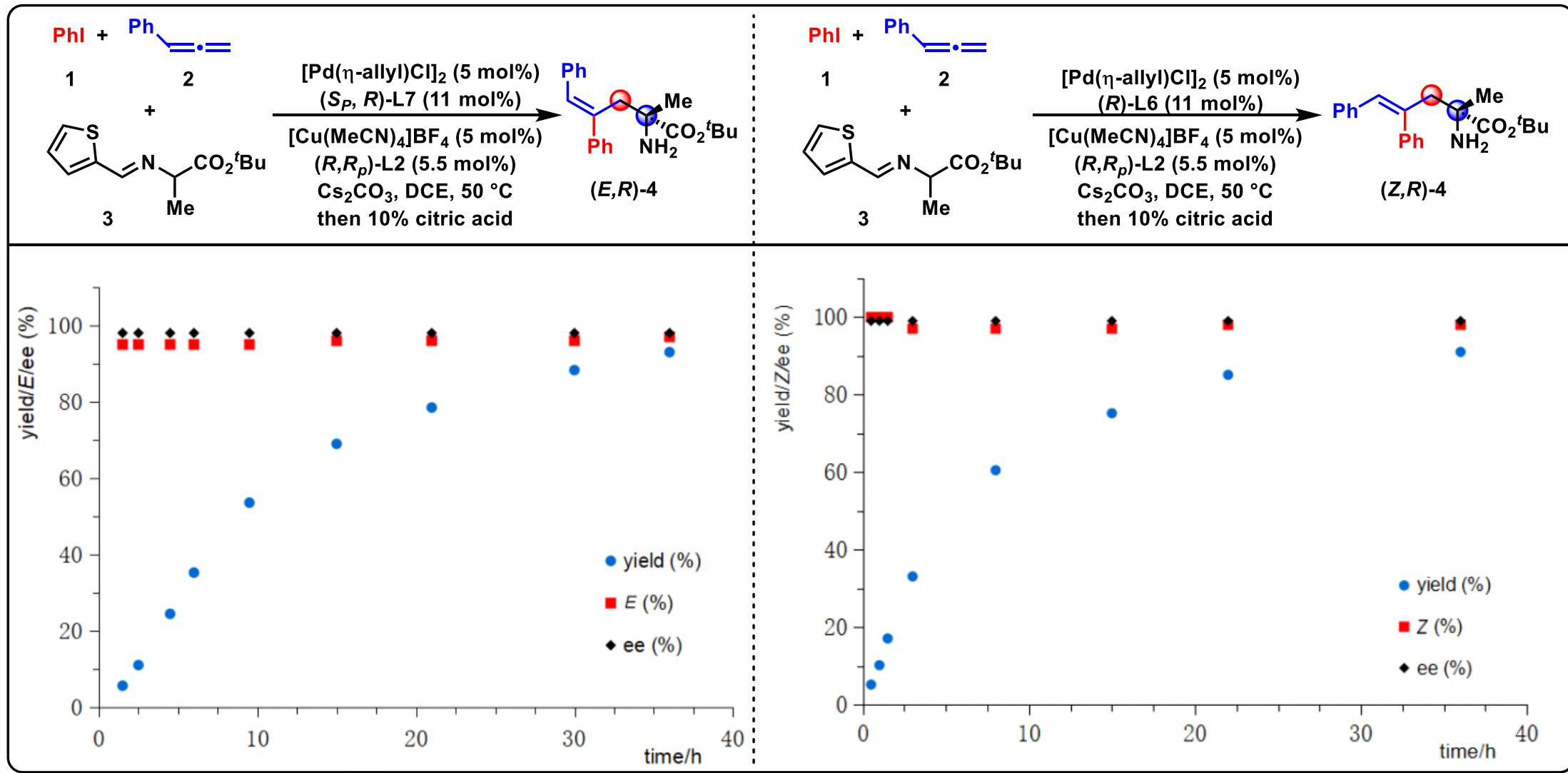
Zhang group (2024)



# 2.2 间接氧化加成 (Heck启动)

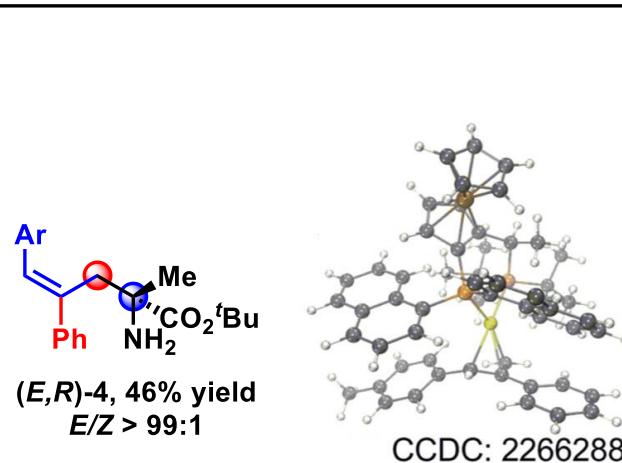
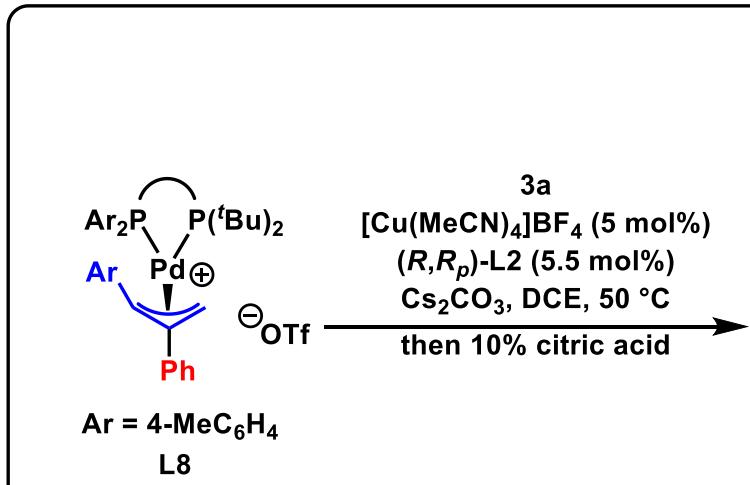


## The controlled experiments

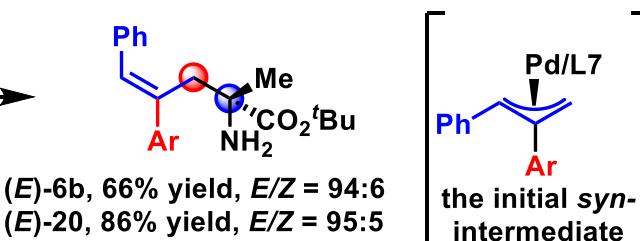
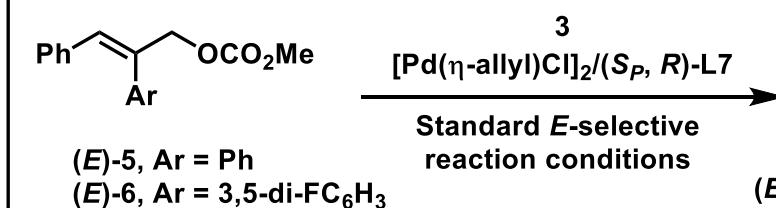
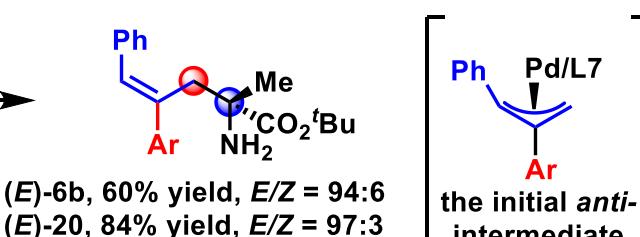
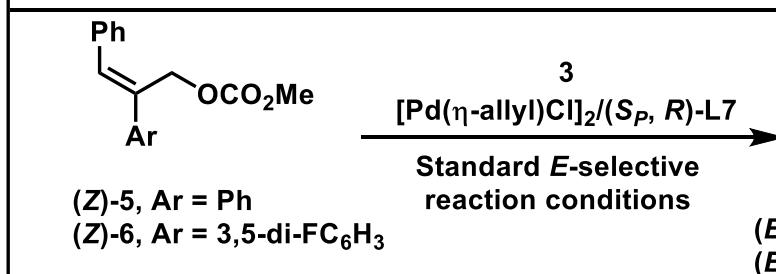
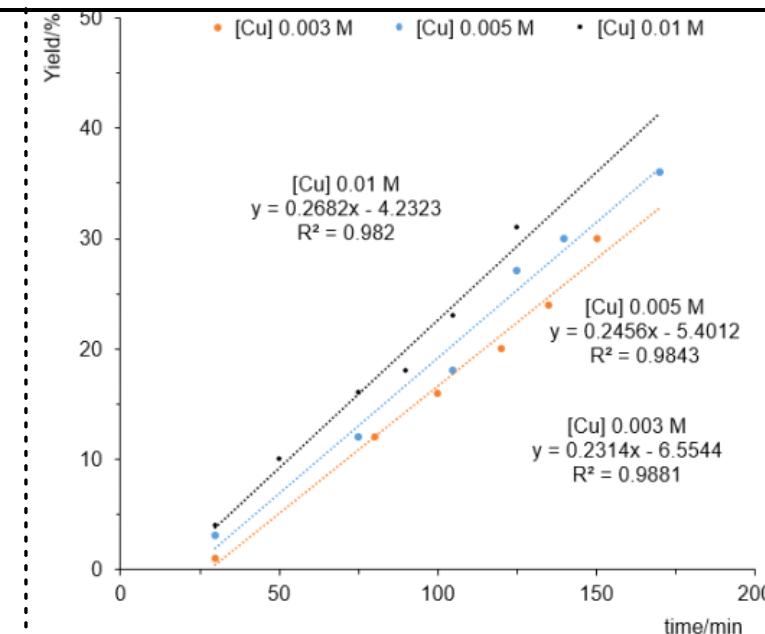
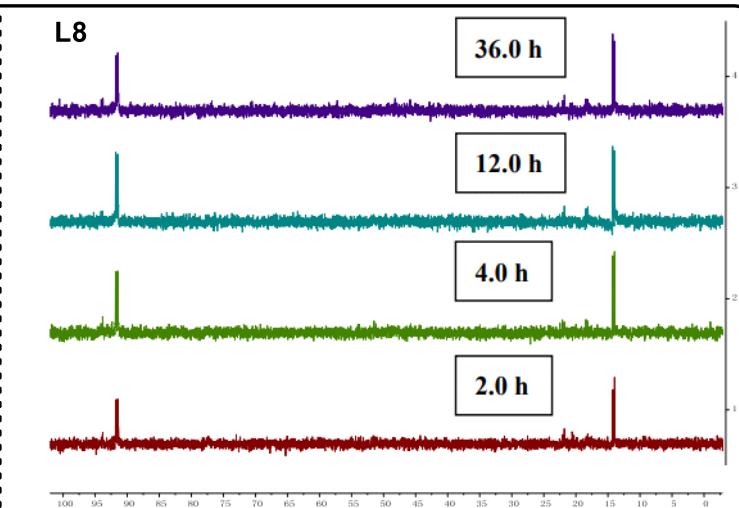


# 2.2 间接氧化加成 (Heck启动)

## The controlled experiments

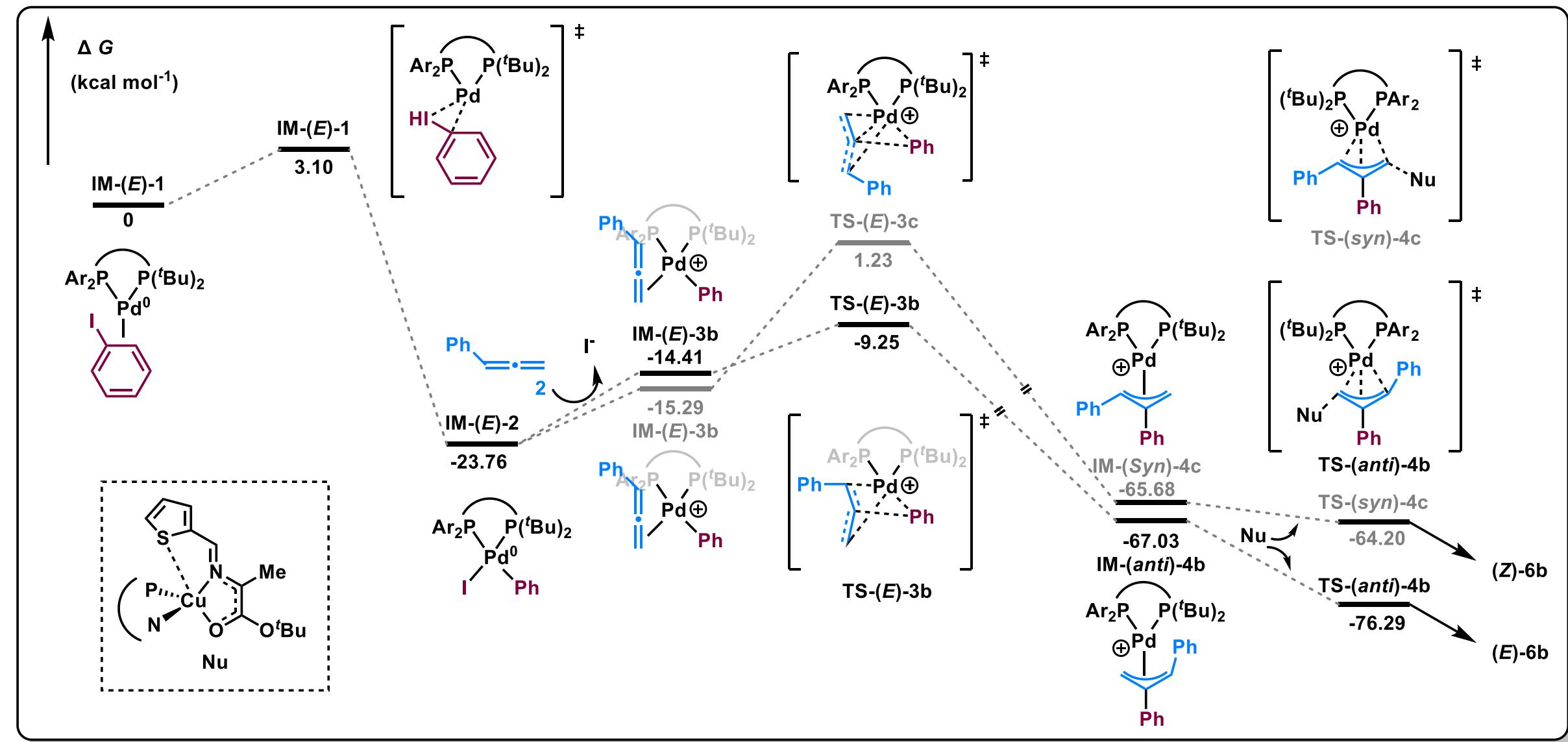


## The Kinetic studies



# 2.2 间接氧化加成 (Heck启动)

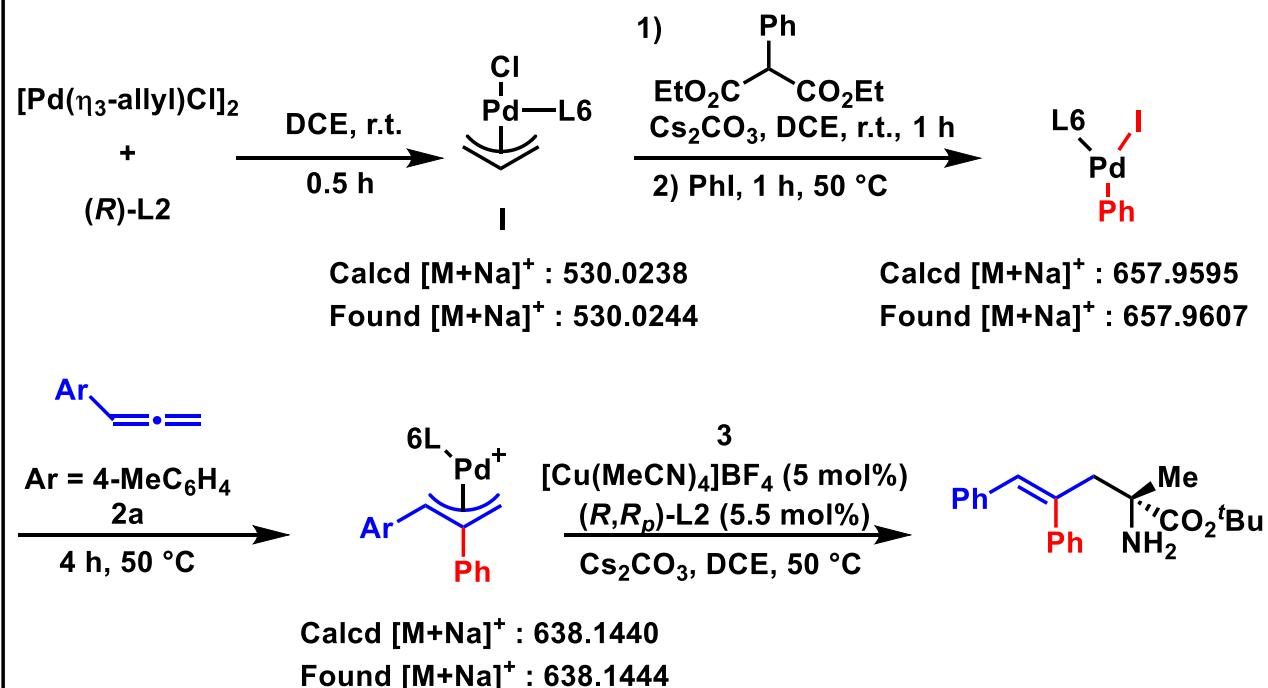
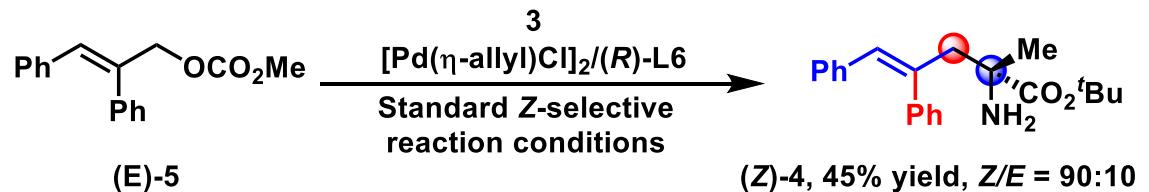
## DFT calculations



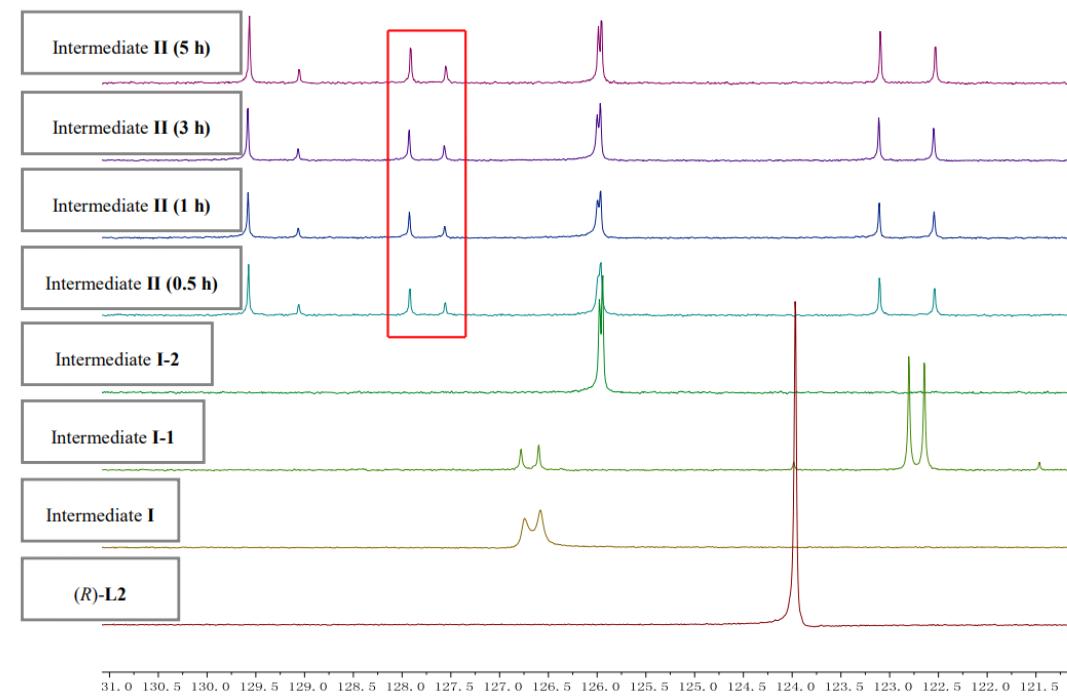
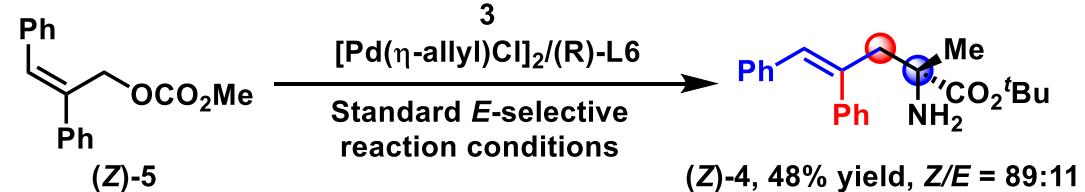
# 2.2 间接氧化加成 (Heck启动)



## The controlled experiments



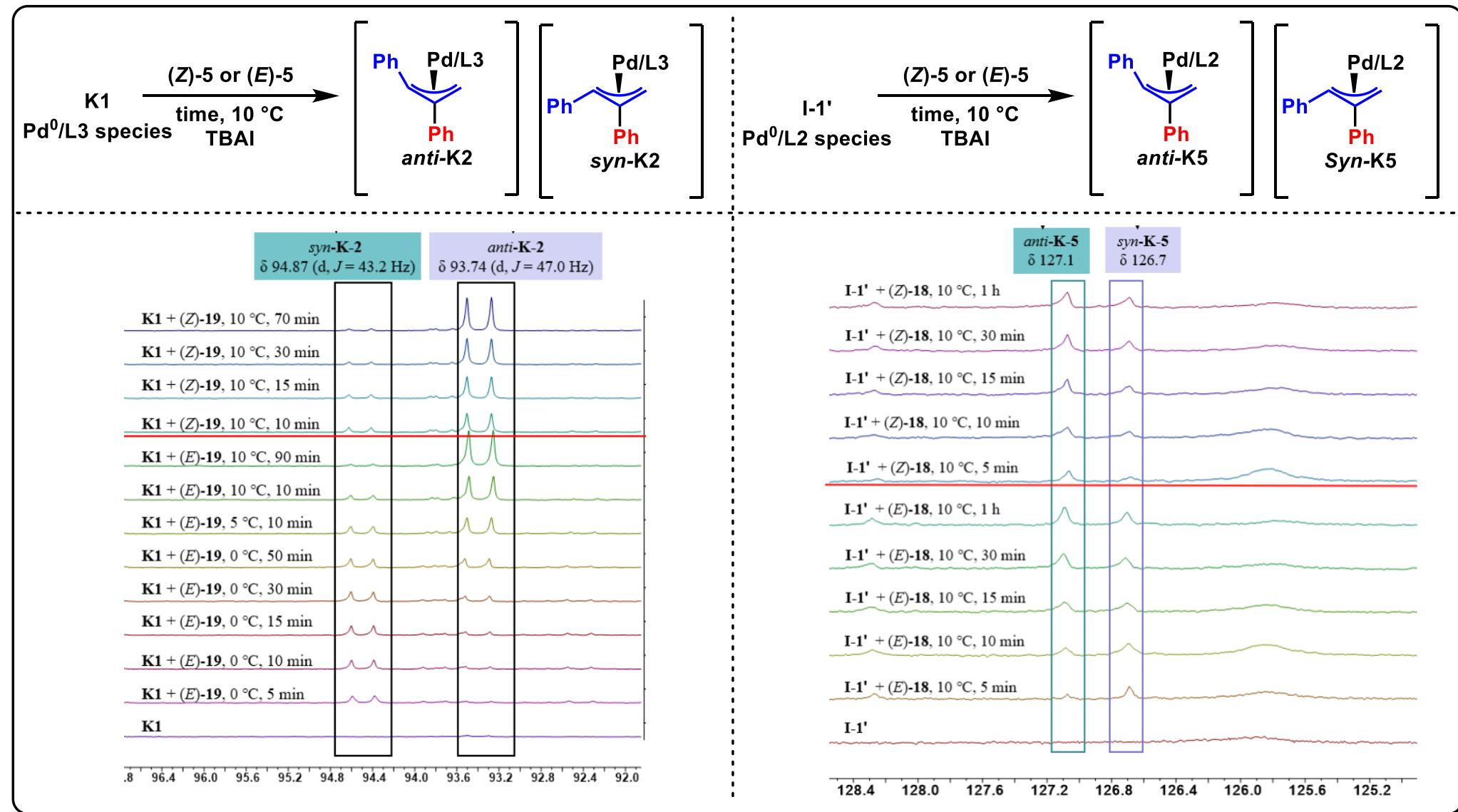
## The $\text{P}^{31}\text{-NMR}$ detected



## 2.2 间接氧化加成 (Heck启动)



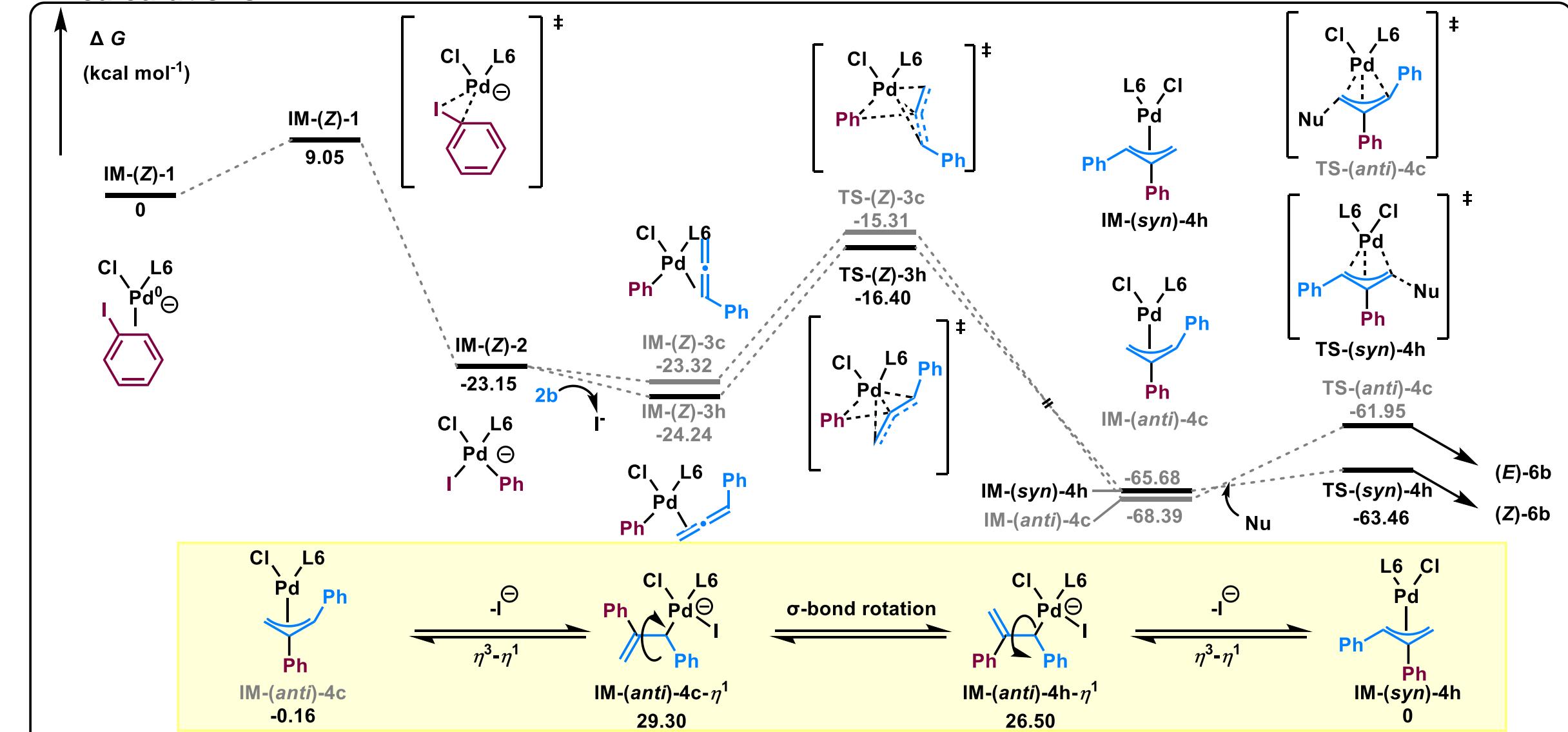
*The P<sup>31</sup>-NMR detected*



## 2.2 间接氧化加成 (Heck启动)



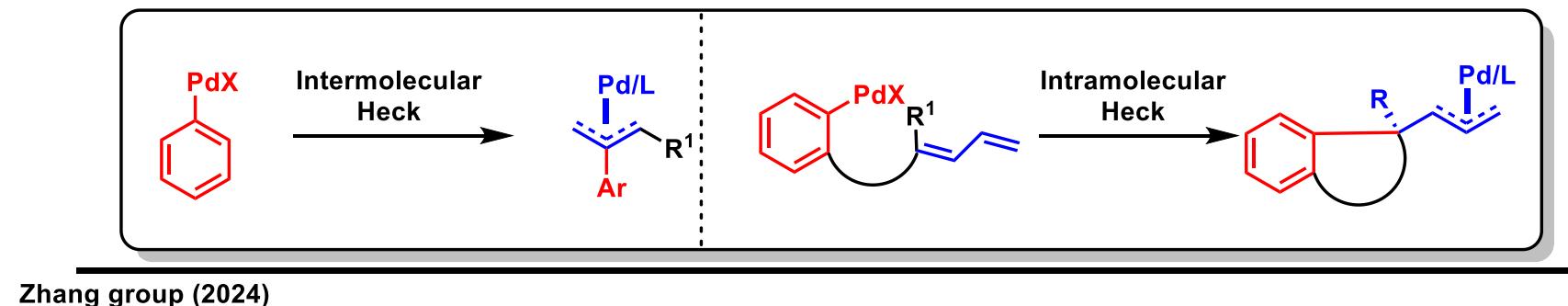
### DFT calculations



# 2.2 间接氧化加成 (Heck启动)

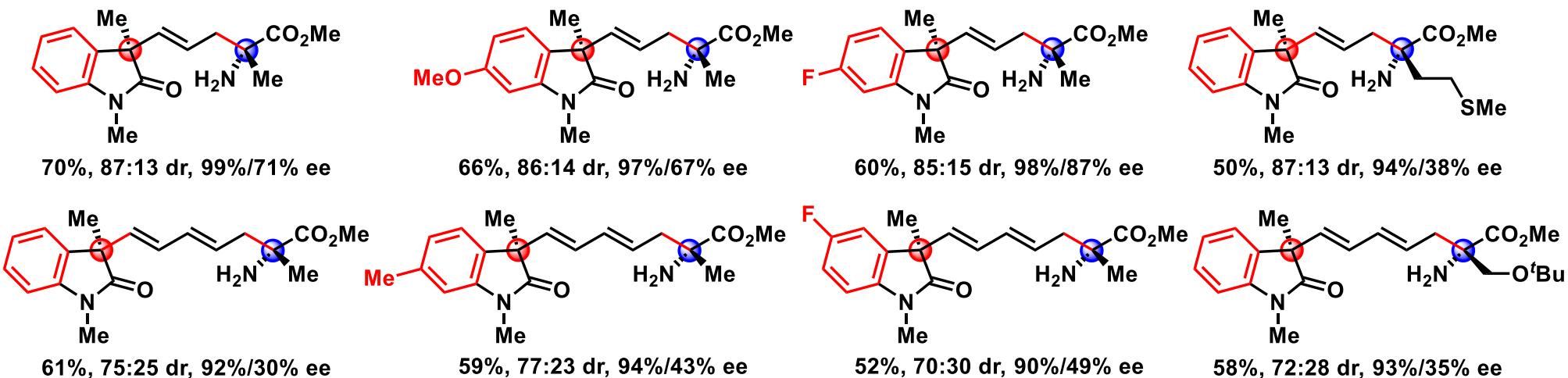
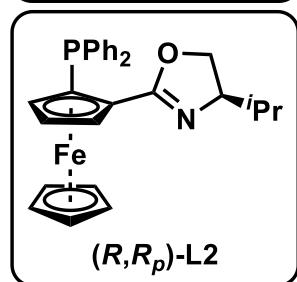
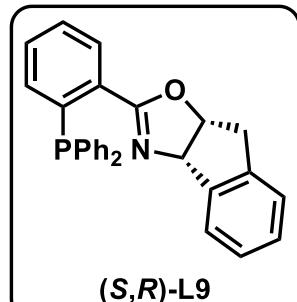
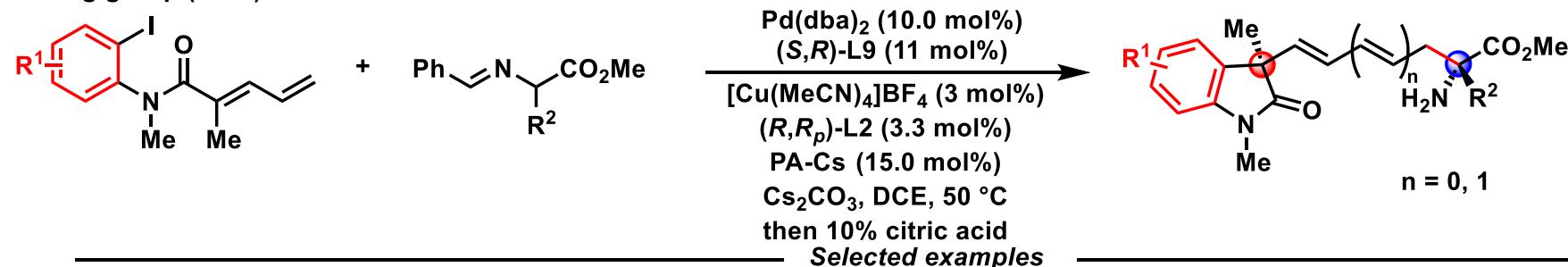


## Intramolecular Heck

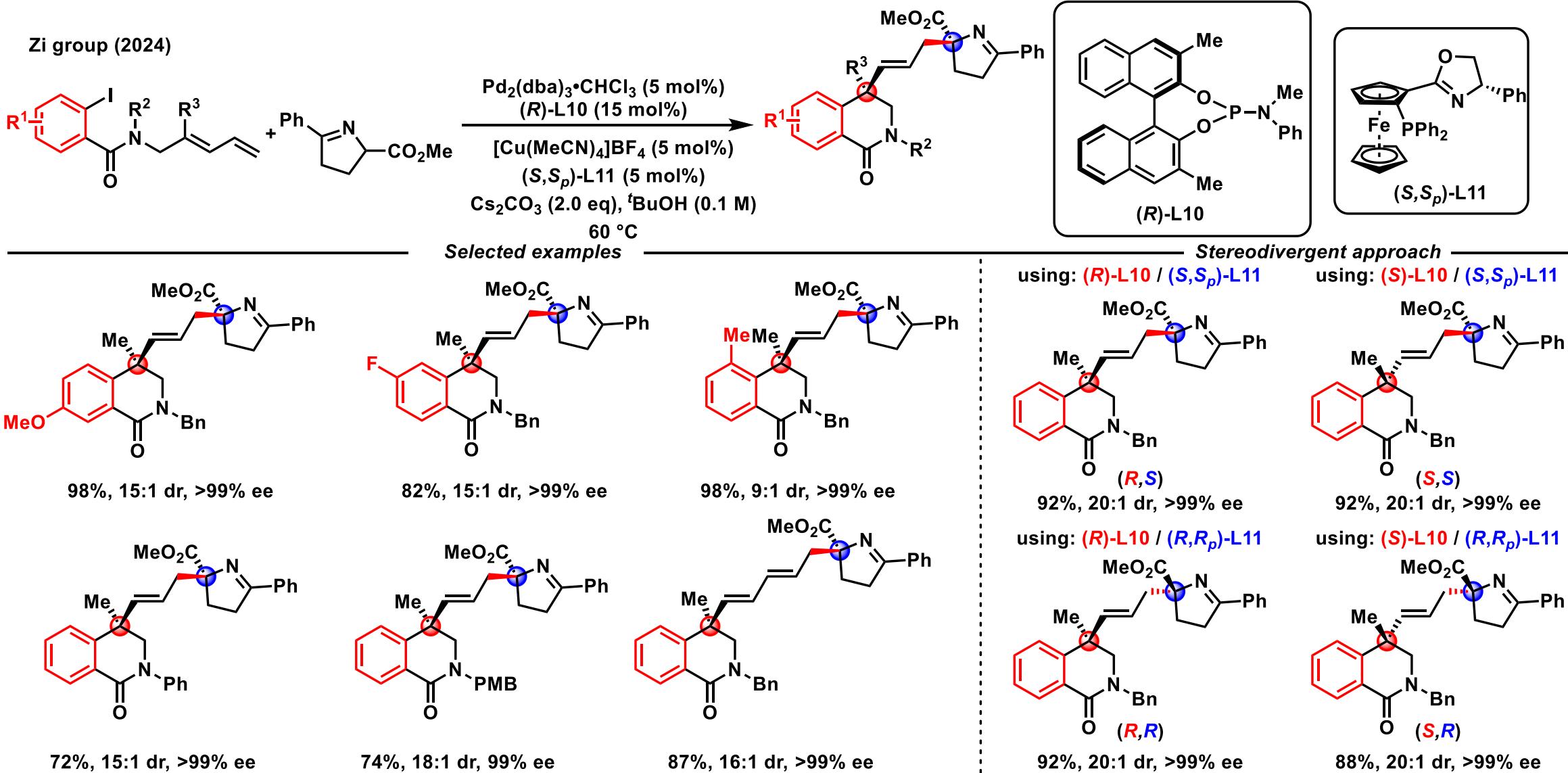


Zhang group (2024)

## 1,5-nonajacent



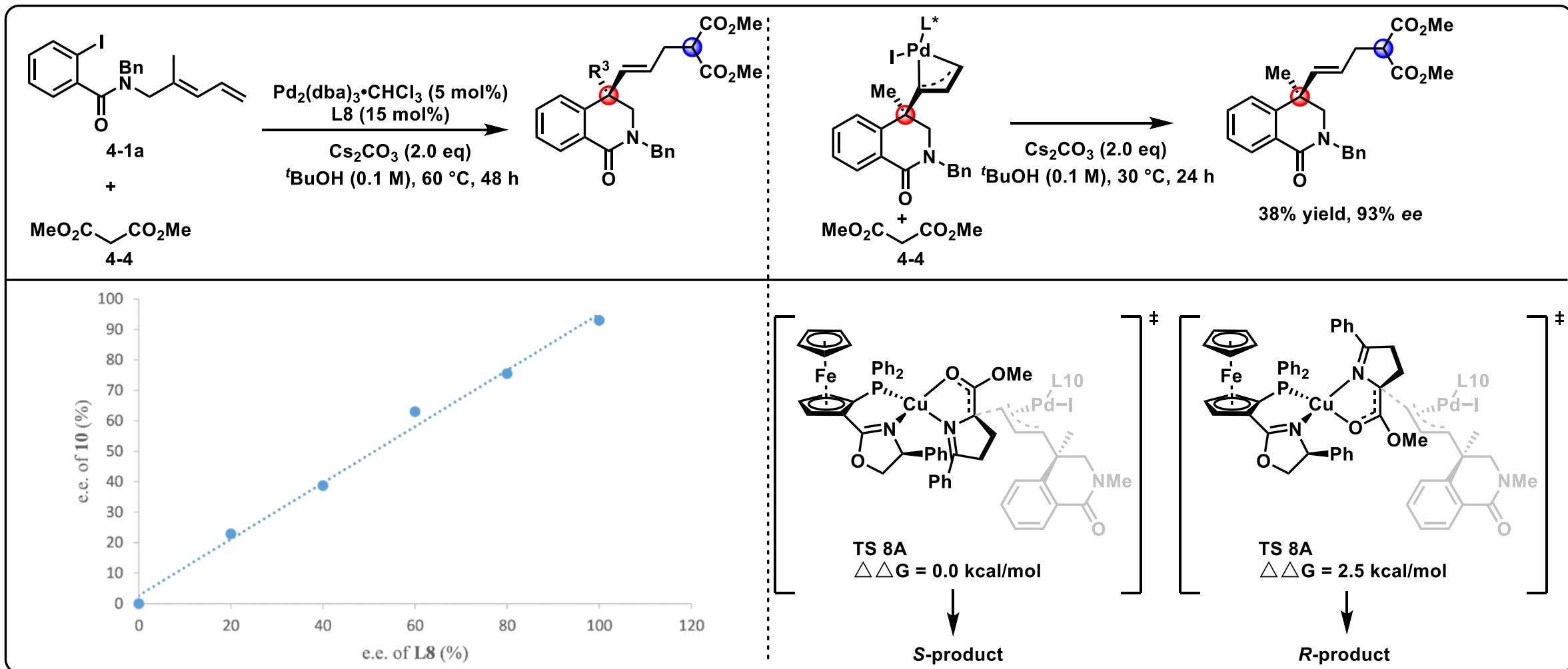
## 2.2 间接氧化加成 (Heck启动)



# 2.2 间接氧化加成 (Heck启动)



## The controlled experiments



**Nonlinear Effect**

**DFT calculations**



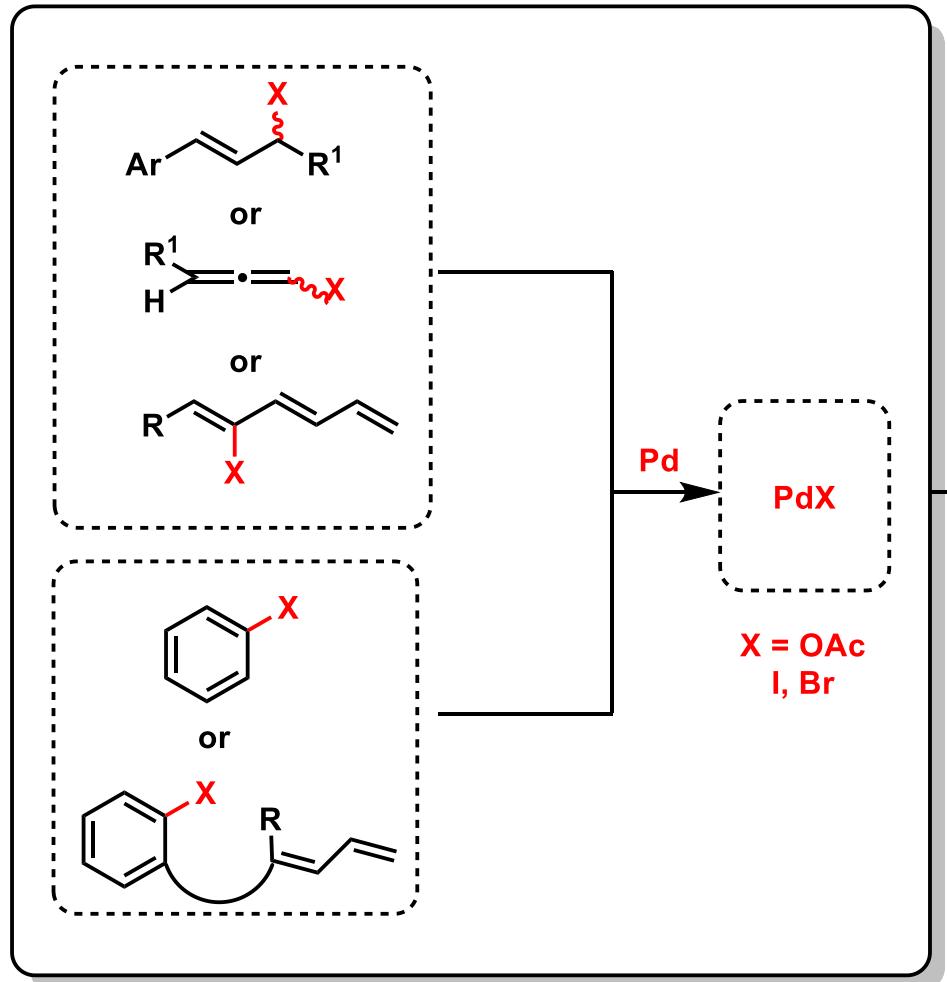
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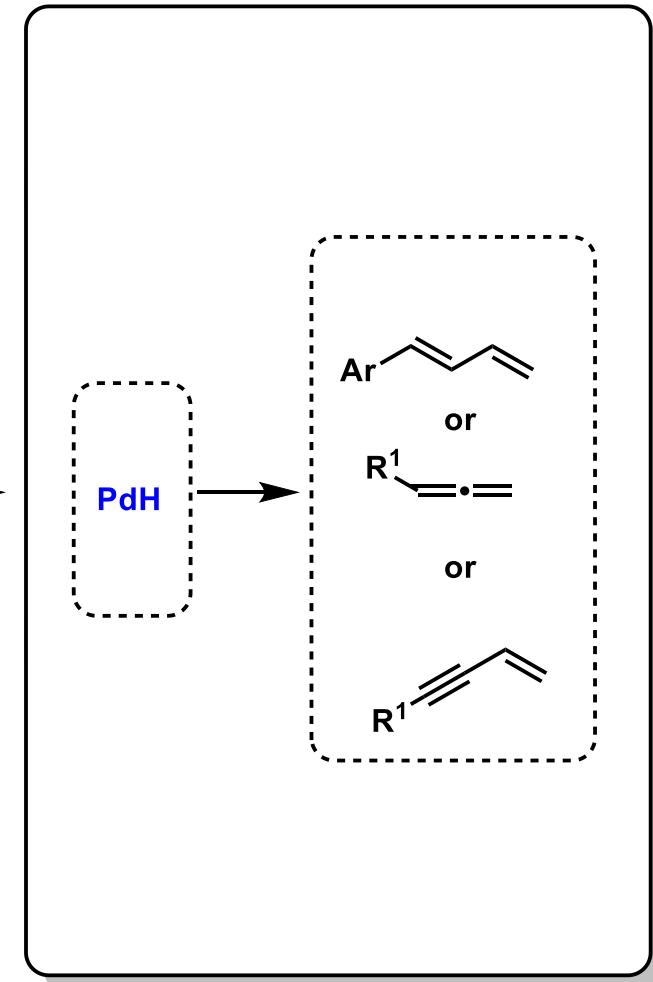
## 2.3 PdH插入启动



### Oxidation addition



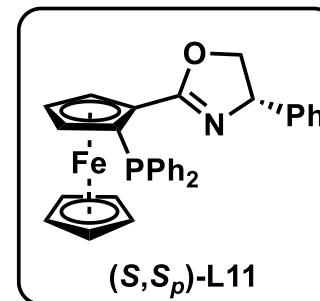
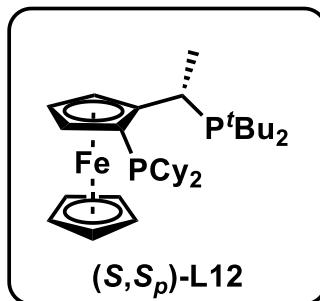
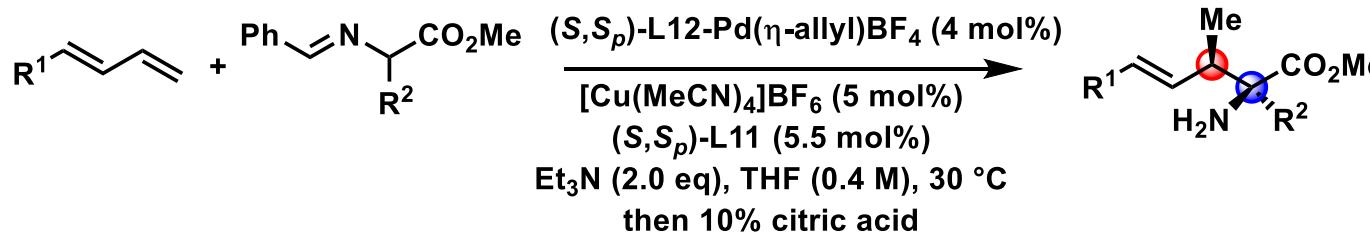
### Through [PdH] insertion



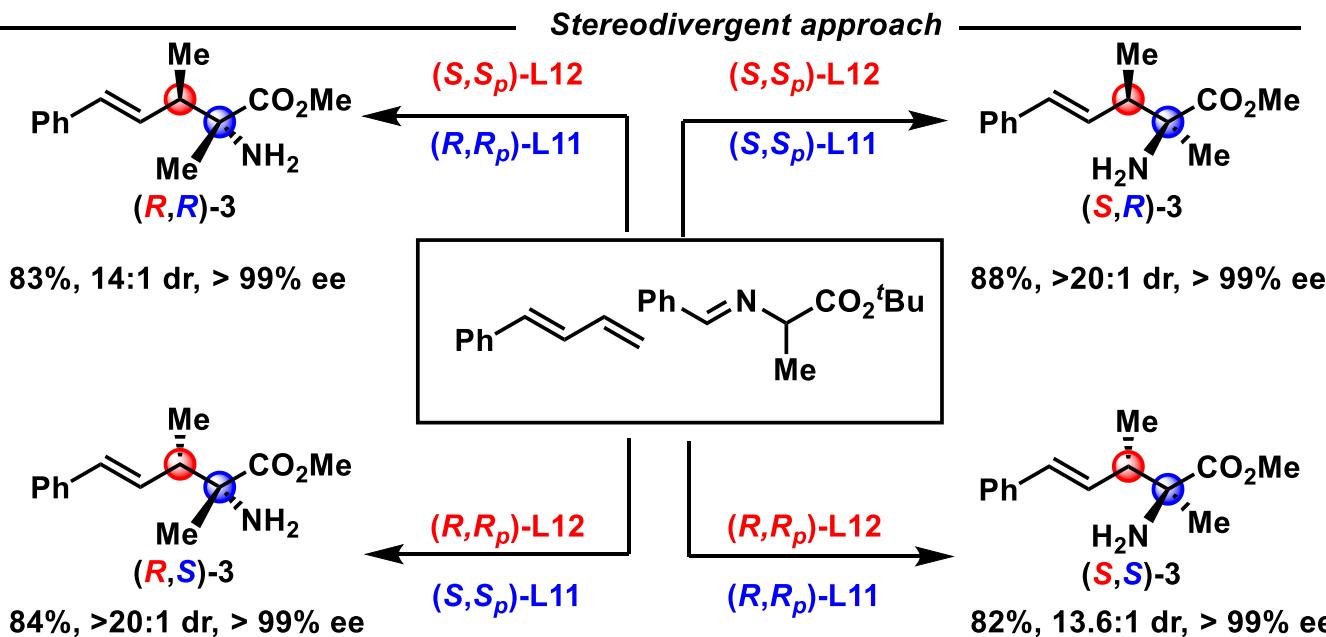
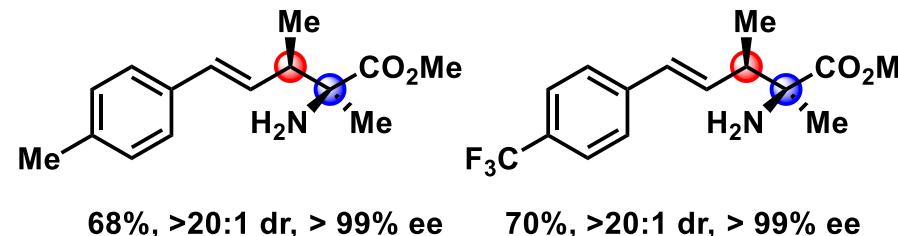
## 2.3 PdH插入启动



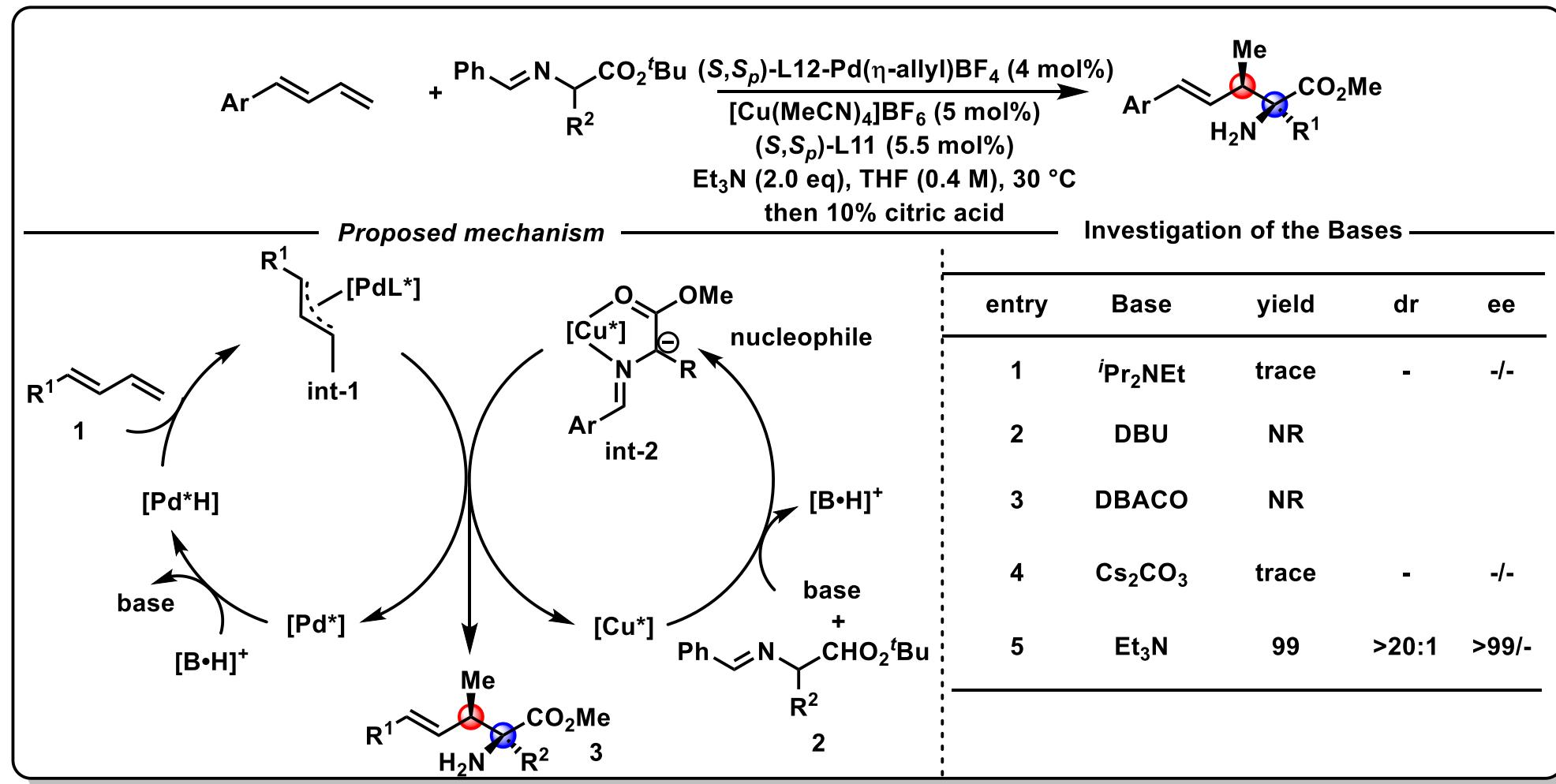
Zi group (2019)



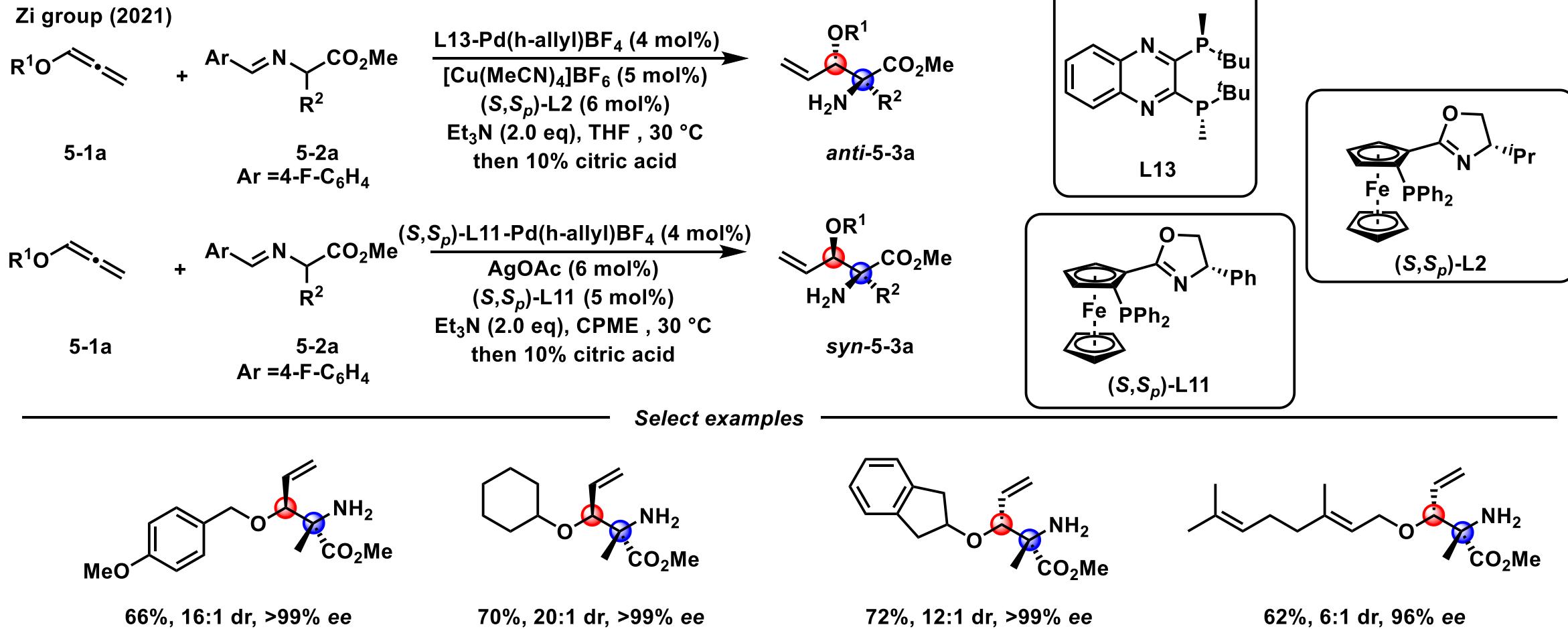
Selected examples



## 2.3 PdH插入启动



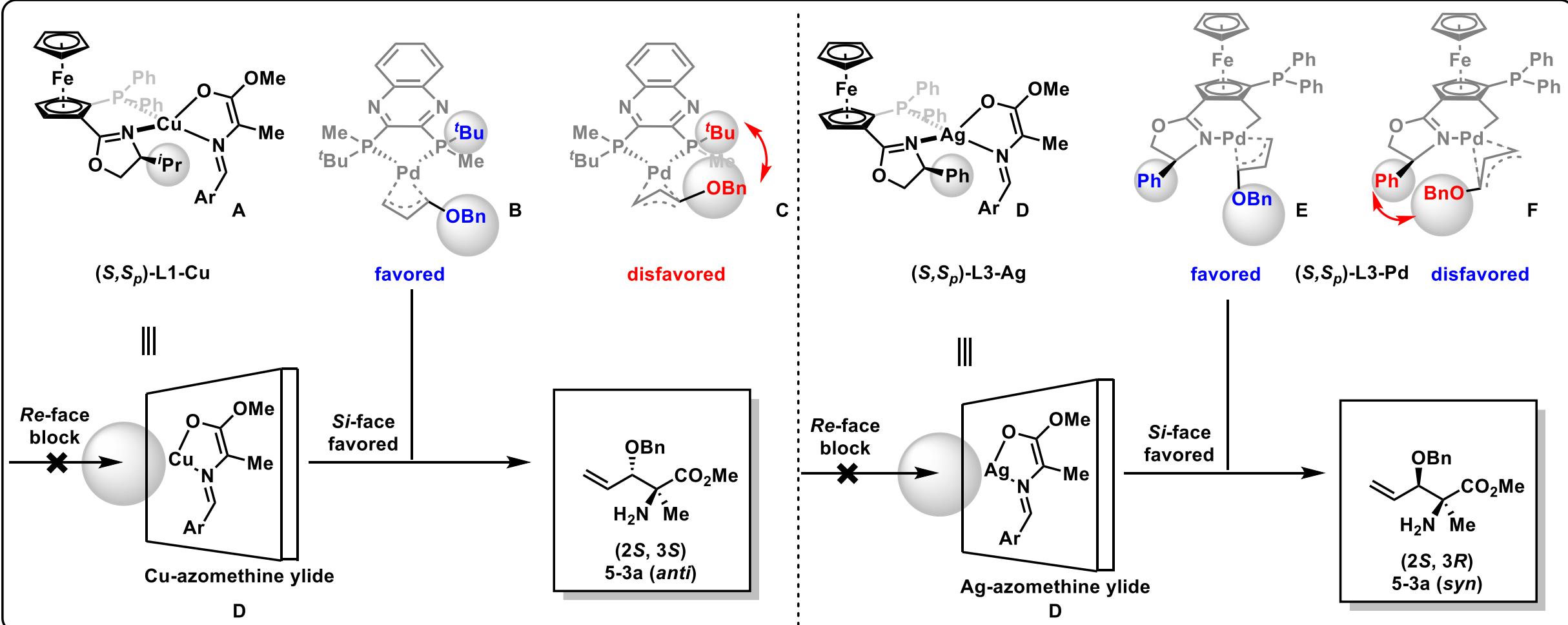
## 2.3 PdH插入启动



# 2.3 PdH插入启动



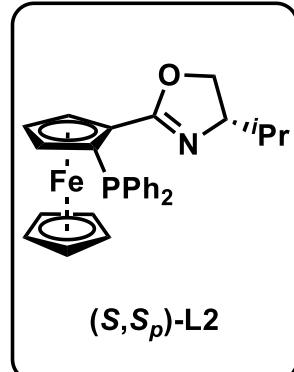
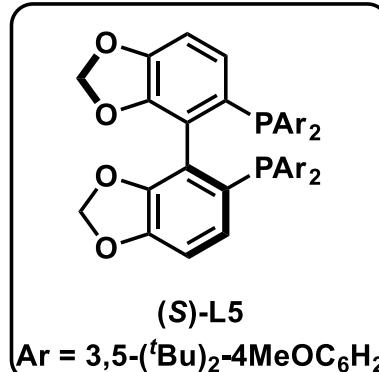
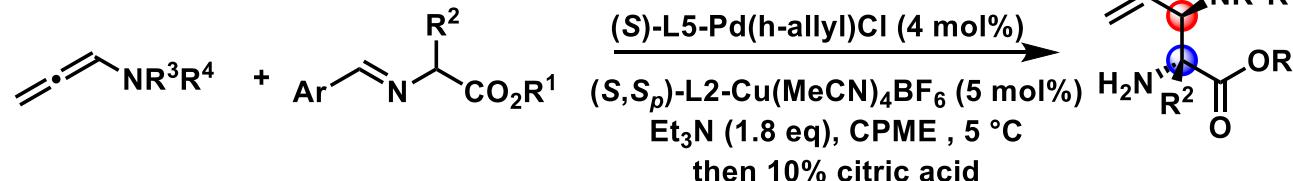
## Stereoselective model



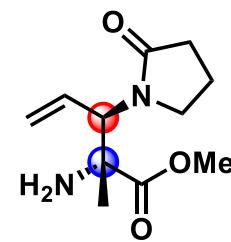
## 2.3 PdH插入启动



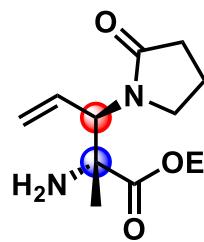
Zi group (2022)



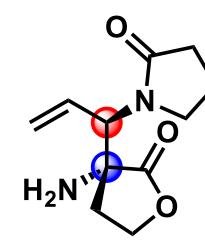
Select examples



83%, >20:1 dr, >99% ee

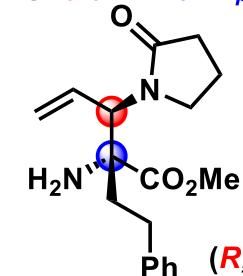


95%, >20:1 dr, >99% ee



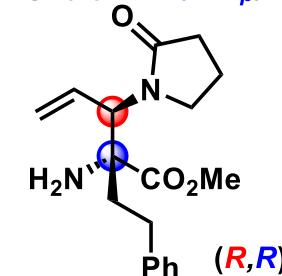
69%, >20:1 dr, >99% ee

using: (S)-L5 / (S,S<sub>p</sub>)-L2

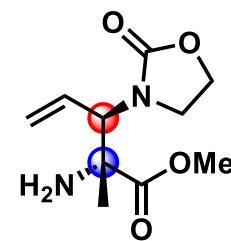


65%, >20:1 dr, >99% ee

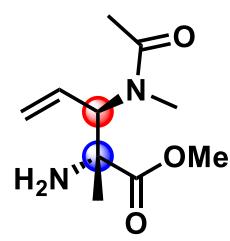
using: (S)-L5 / (R,R<sub>p</sub>)-L2



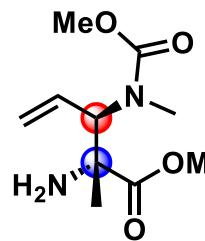
54%, 16:1 dr, >99% ee



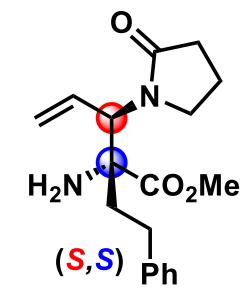
92%, >20:1 dr, >99% ee



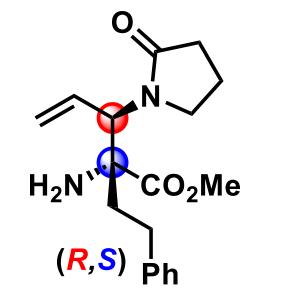
69%, 2.7:1 dr, >99% ee



79%, 10:1 dr, >99% ee



59%, 16:1 dr, >99% ee

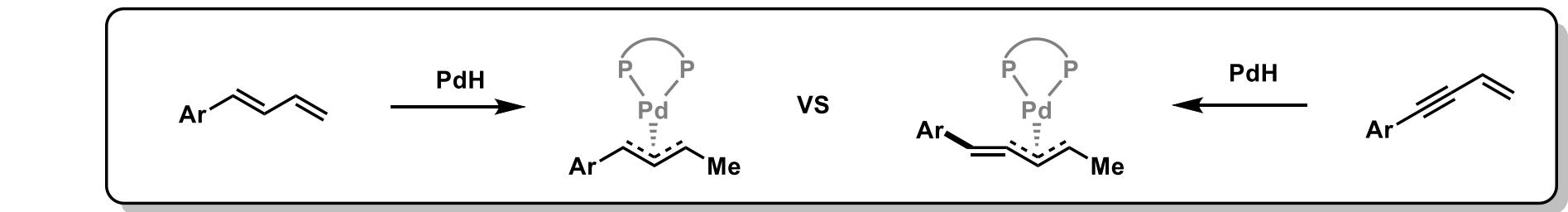


67%, >20:1 dr, >99% ee

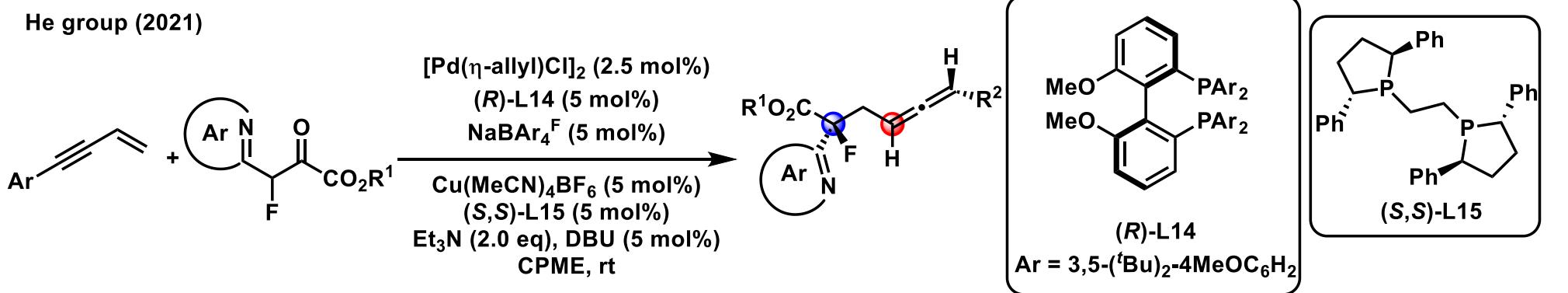
## 2.3 PdH插入启动



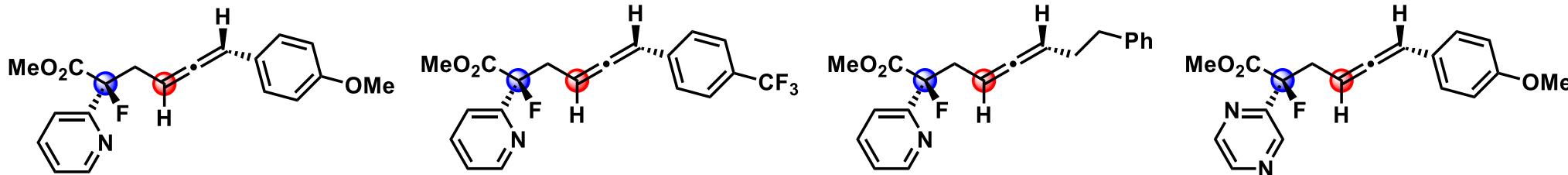
$\alpha$ -alkynylidene  
 $\pi$ -allylpalladium



1,3-nonadjacent



Select examples



20 h: 82%, 16:1 dr, >99% ee

24 h: 96%, >20:1 dr, >99% ee

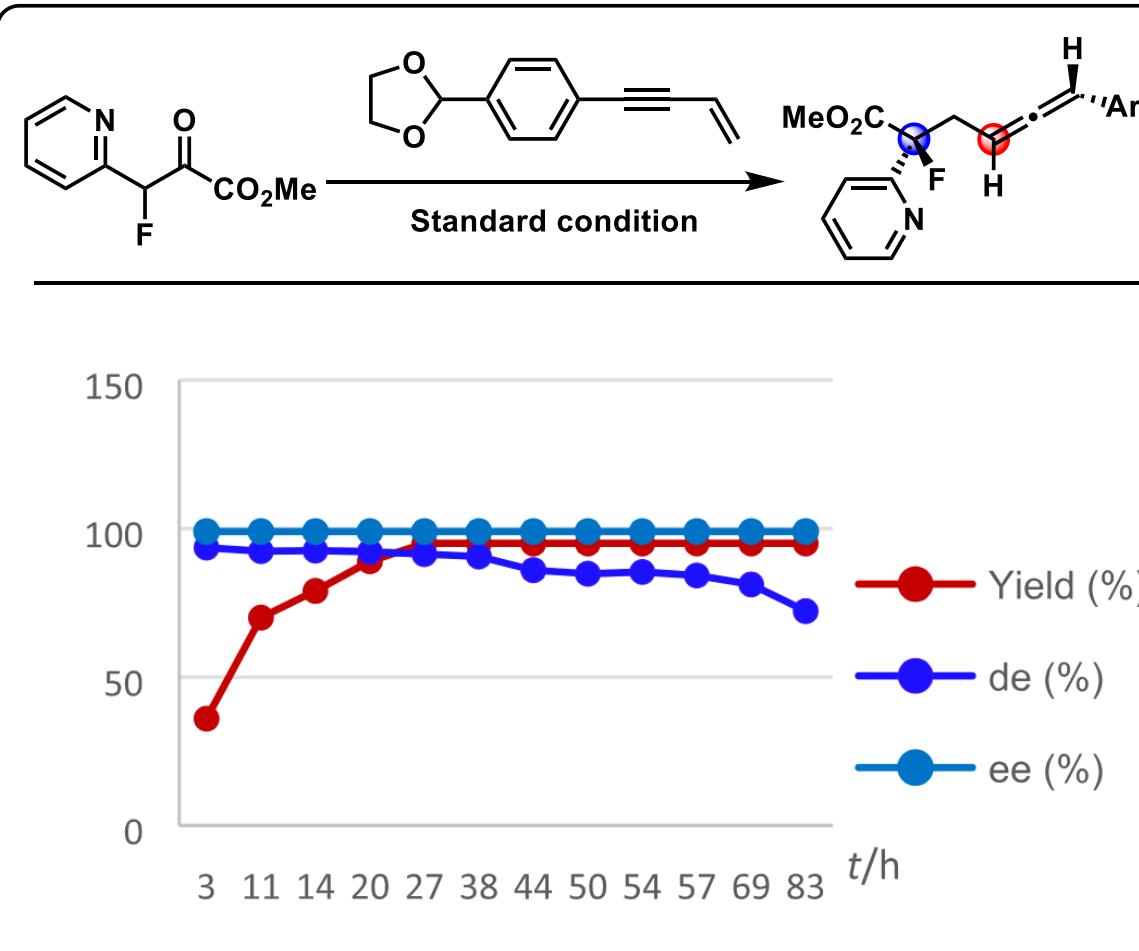
20 h: 88%, 6:1 dr, 91% ee

19 h: 79%, >20:1 dr, >99% ee

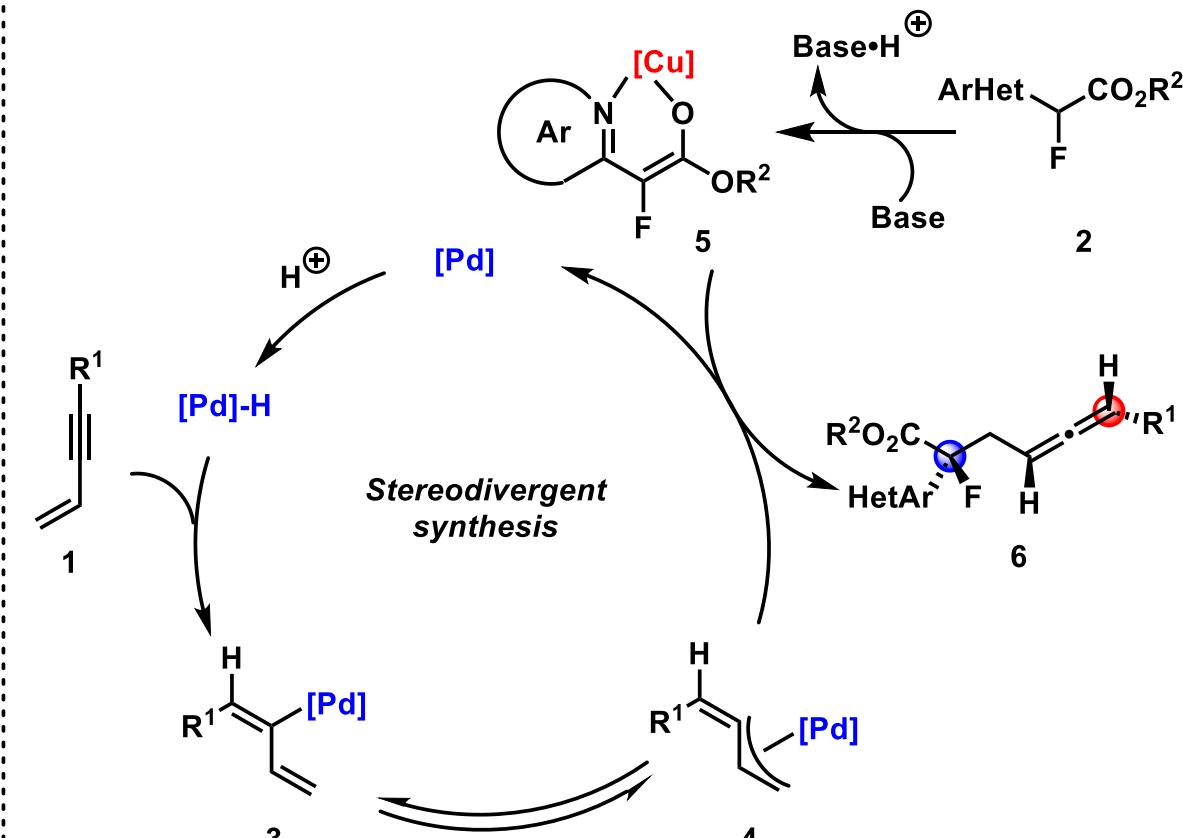
## 2.3 PdH插入启动



### The controlled experiments



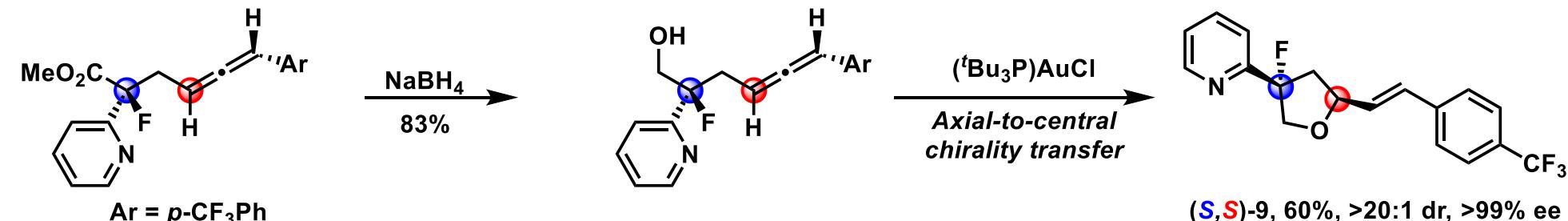
### Proposed mechanism



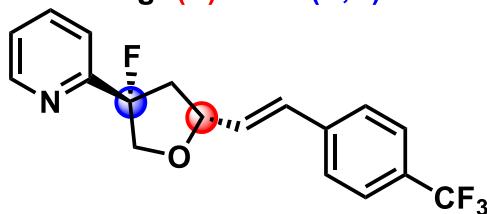
## 2.3 PdH插入启动



### Axial-to-Central



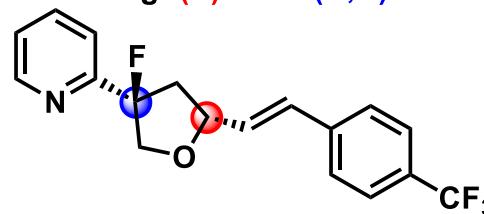
using: (S)-L14 / (S,S)-L15



(S,R)-9, 52%, >20:1 dr, >99% ee

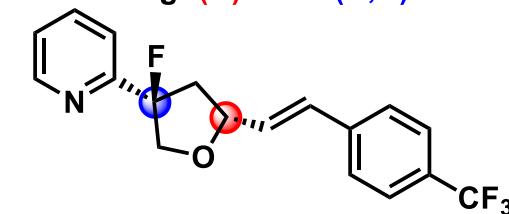
Select examples

using: (S)-L14 / (R,R)-L15

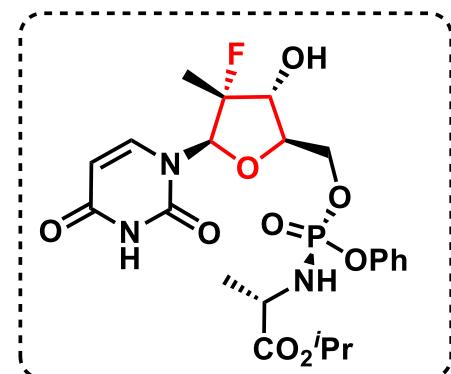


(R,R)-9, 72%, >20:1 dr, >99% ee

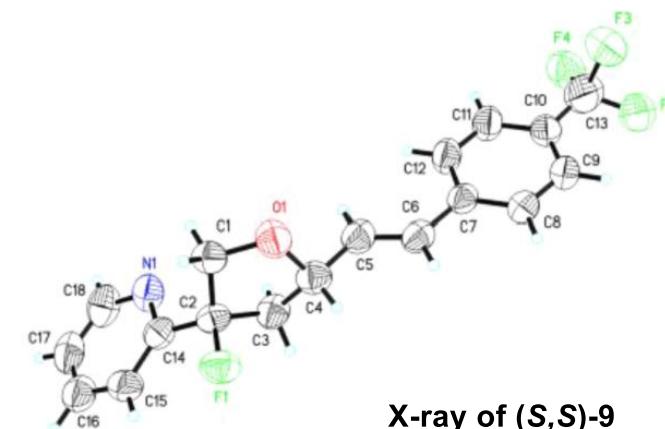
using: (R)-L14 / (R,R)-L2



(R,S)-9, 50%, >20:1 dr, >99% ee



Sofosbuvir (HCV antiviral)



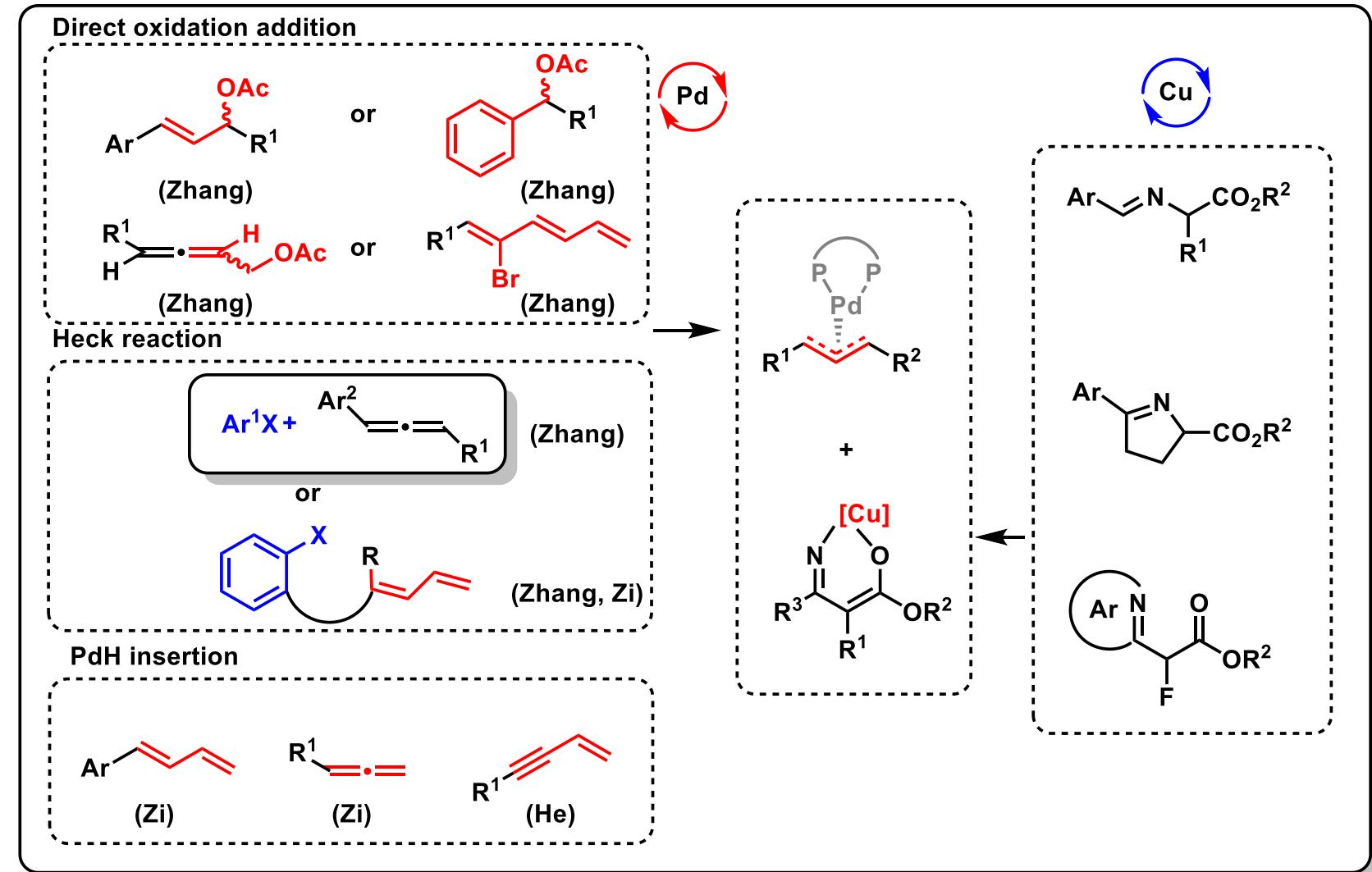
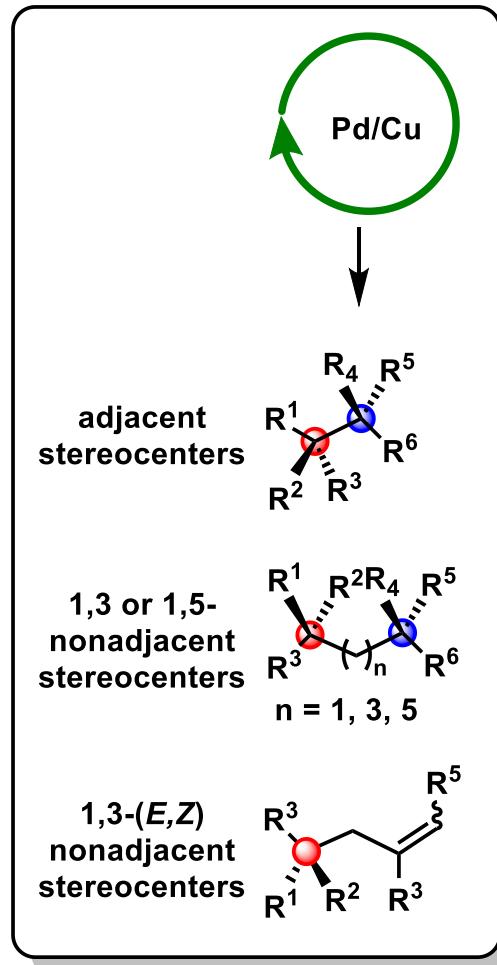
X-ray of (S,S)-9



# 目录

1. 研究背景及意义
- 2.Pd/Cu协同催化的立体发散性合成策略
  - 2.1 直接氧化加成启动 (烯丙基取代)
  - 2.2 Heck反应启动
  - 2.3 PdH插入启动
3. 总结与展望

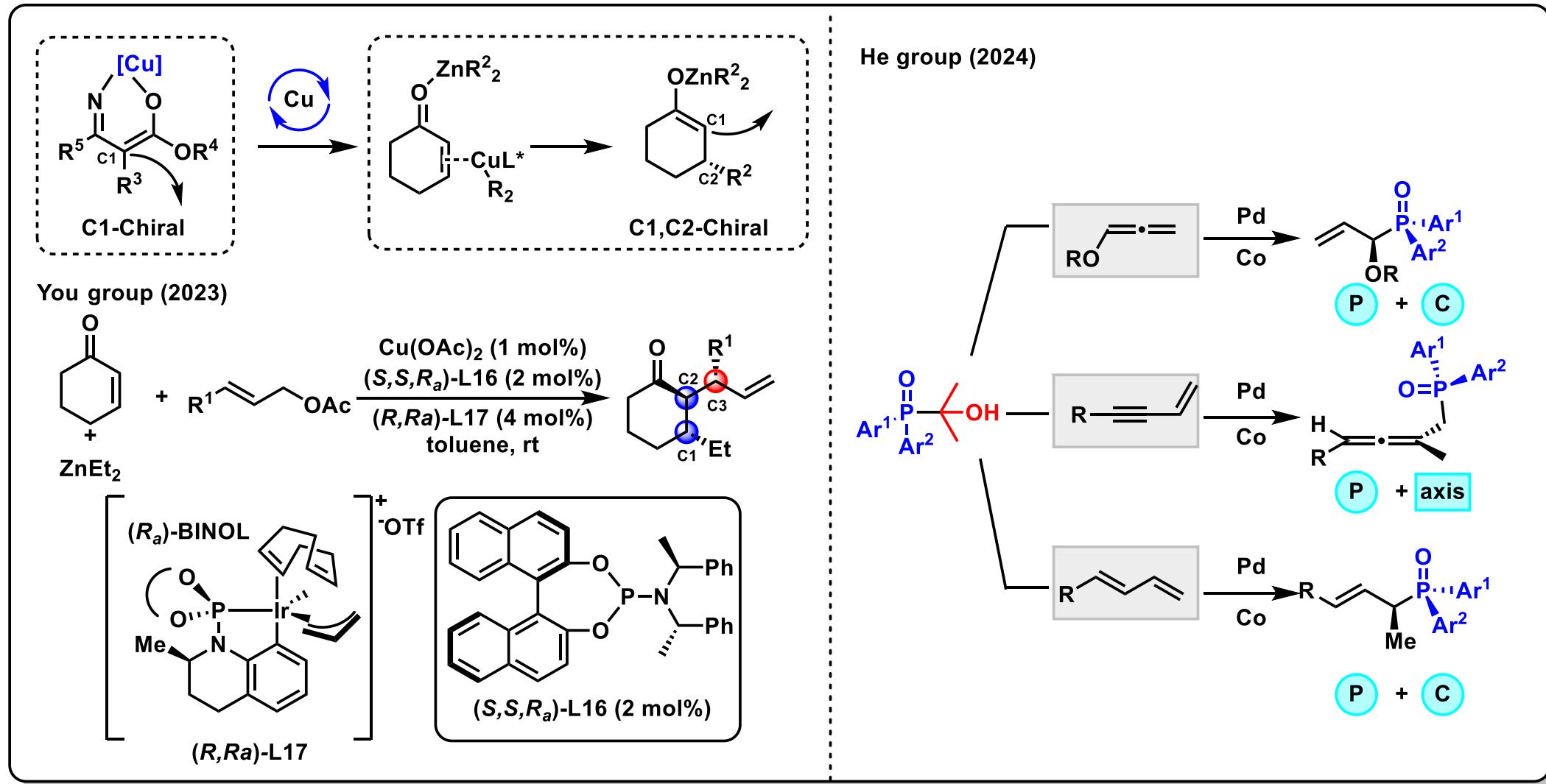
## 总结:



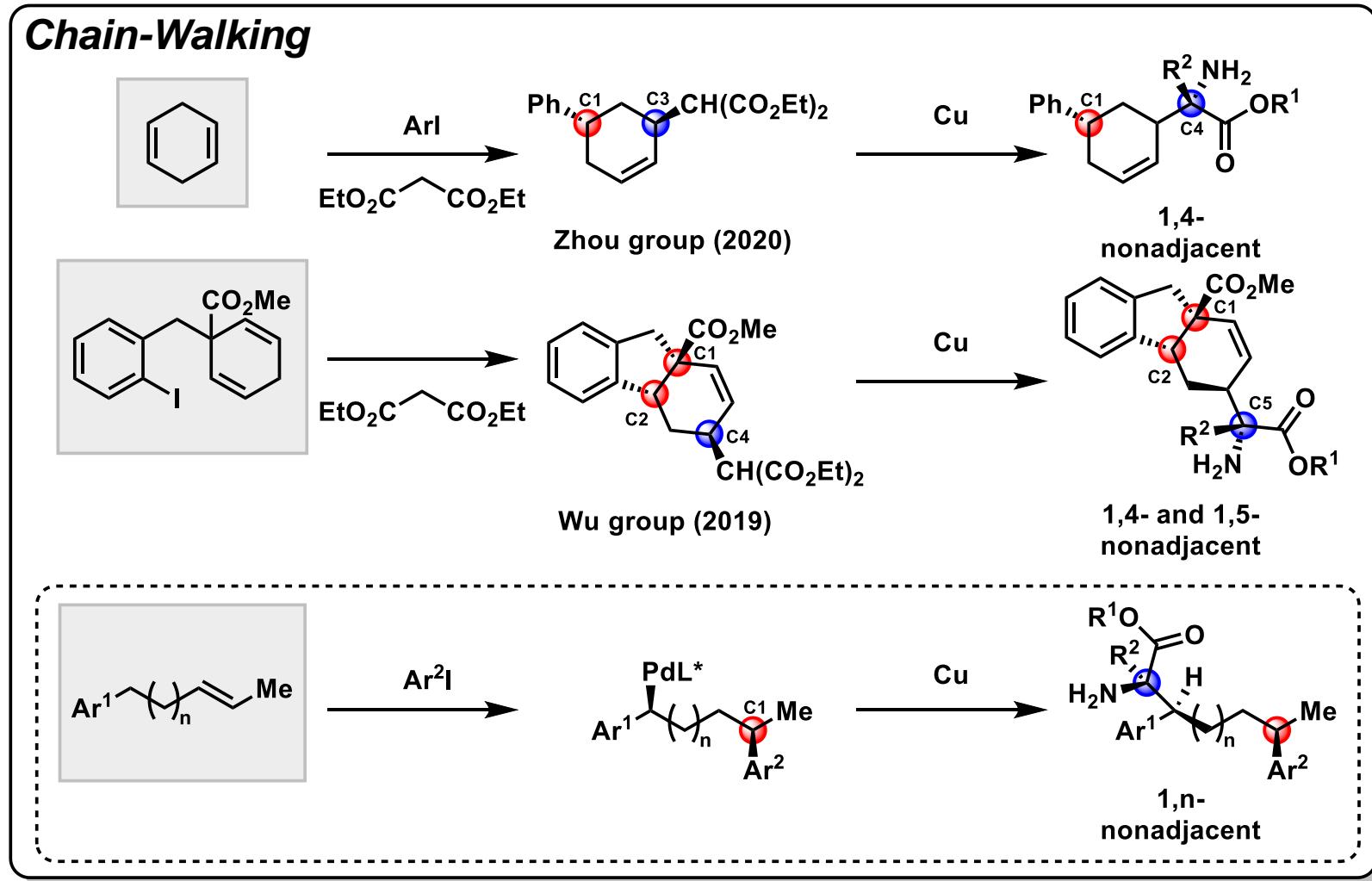
## 展望：

➤ 开发更多与Cu催化结合的亲核试剂

➤ 实现更加多样手性的发散性合成



**展望:** ➤ 开发更多的Pd催化模式实现更多样的多重手性化合物





# Seminar

谢谢大家  
请各位老师同学批评指正

2024.9.27