



# Non-Covalent Interactions (NCIs) between Ligand and Substrate in Enantioselective Transition Metal Catalysis

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指导老师：陆平 青年研究员

2021年11月19日

# CATALOGUE

1

Background

2

Hydrogen Bond Interactions

- a. Quinine-Derived Ligands
- b. Prolinol-Derived Ligands
- c. Chiral Lactam Scaffolds

3

Ion-Pairing Interactions

4

$\pi-\pi$  Stacking Interactions

# PART 1

Background



## Background

# Non-Covalent Interactions (NCIs)

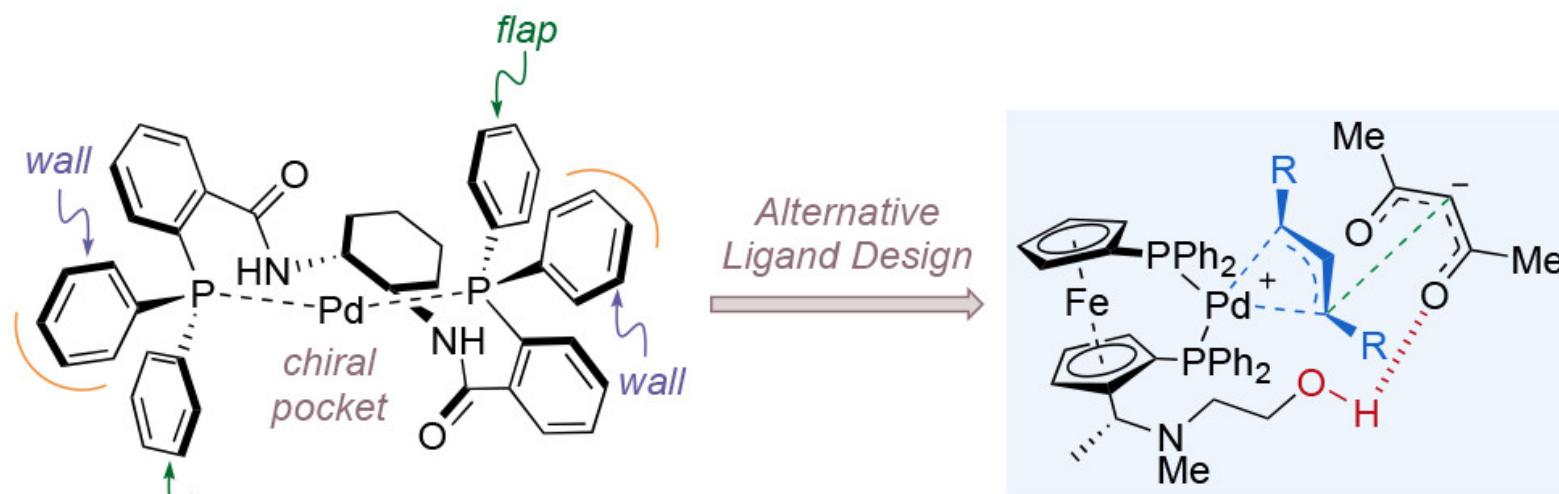
Steric repulsion	
Hydrogen bond	
Halogen bond	 $R-X \cdots X-R' / R-X \cdots \text{Lewis base}$
Ion pair	
Dispersion	
$\pi-\pi$ stacking	
Ion- $\pi$ interaction	
XH- $\pi$ interaction	



# Background

## NCIs between Chiral Ligands and Substrates

### Asymmetric Allylation



*Control Based on  
Steric Repulsion Alone*

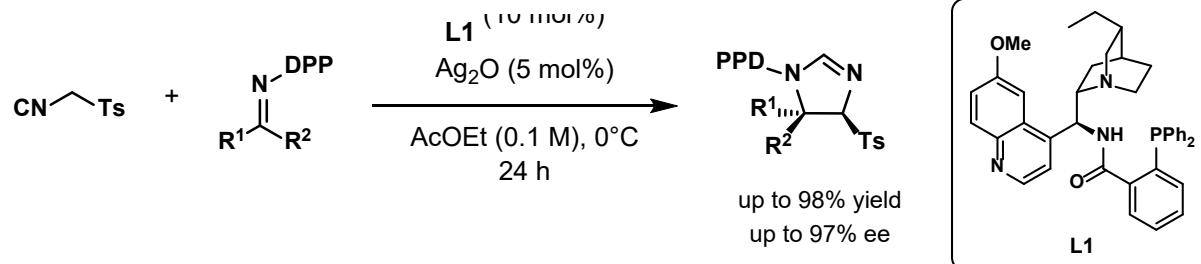
*Attractive Interactions  
Incorporated*



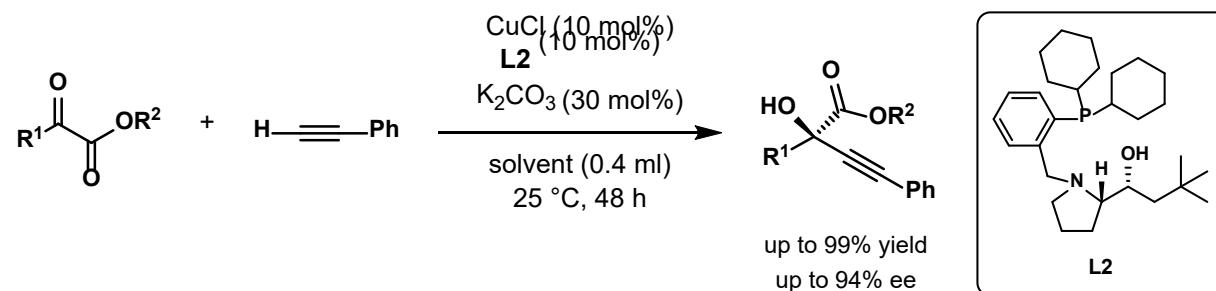
# Background

## NCIs between Chiral Ligands and Substrates

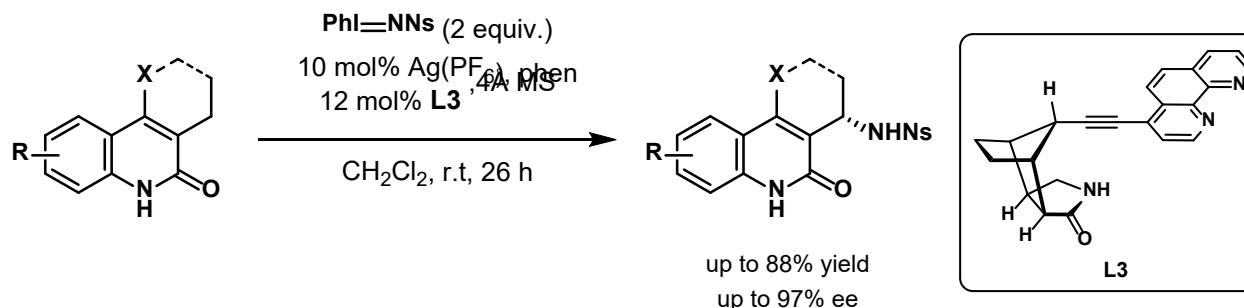
### Hydrogen Bond Interactions:



Dixon, D. J. et al. *Chem. - Eur. J.* **2018**, *24*, 17660–17664

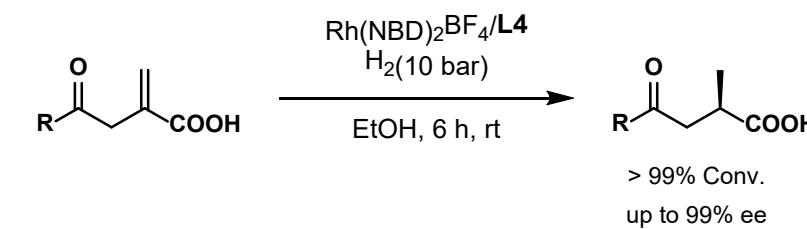


Sawamura, M. et al. *Chem. Sci.* **2018**, *9*, 3484–3493



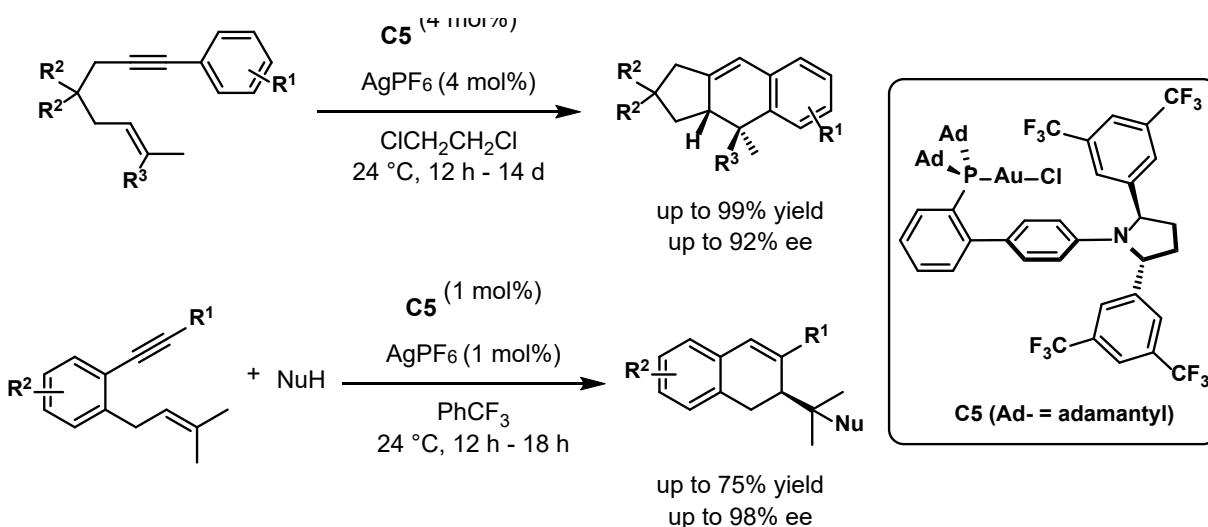
Bach, T. et al. *J. Am. Chem. Soc.* **2020**, *142*, 7374–7378

### Ion-Pairing Interactions:



Zhang, X. et al. *Angew. Chem., Int. Ed.* **2017**, *56*, 6808–6812

### $\pi-\pi$ Stacking Interactions:



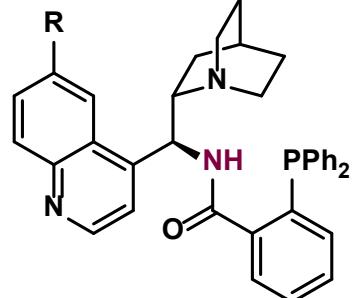
Echavarren, A. M. et al. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863

# PART 2

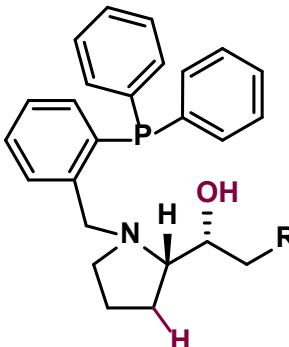
## Hydrogen Bond Interactions



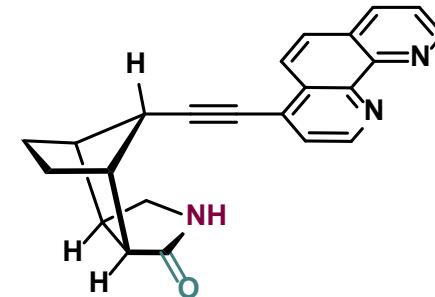
# Common Ligands & Catalysts



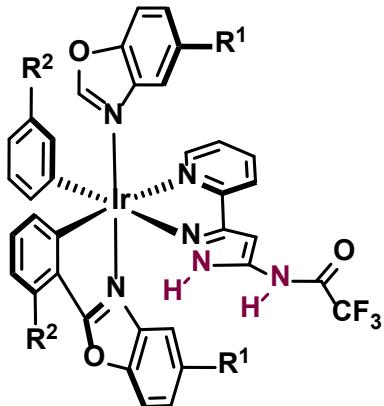
Quinine-Derived Ligands



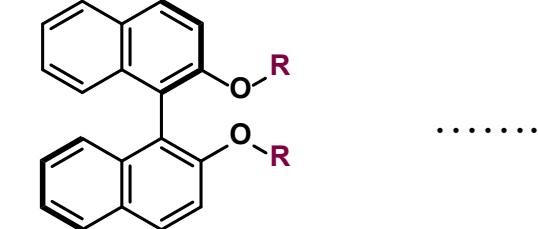
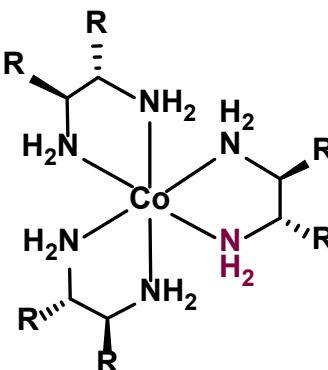
Prolinol-Derived Ligands



Chiral Lactam Ligands



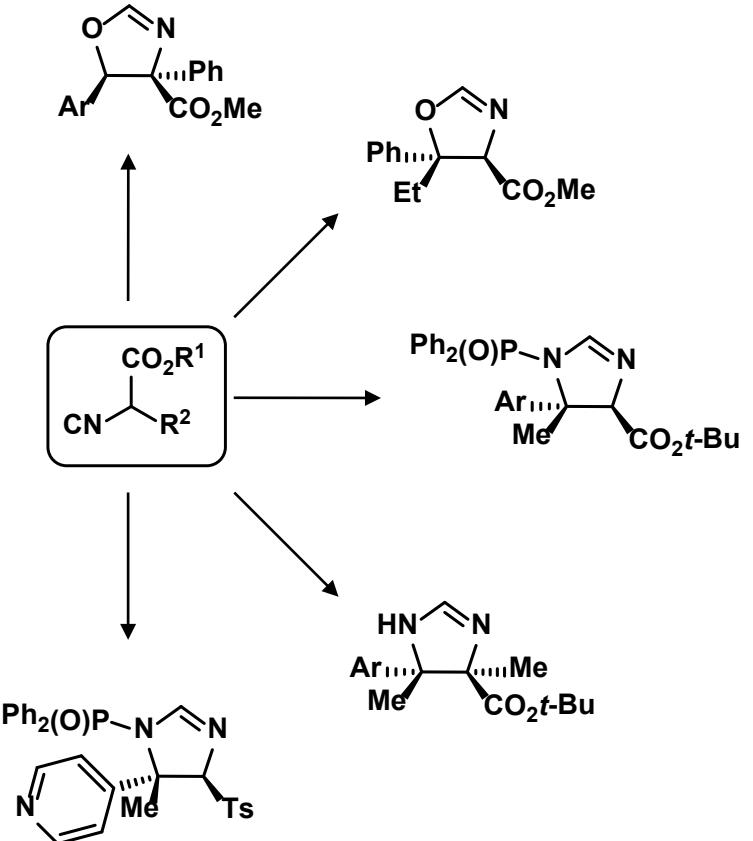
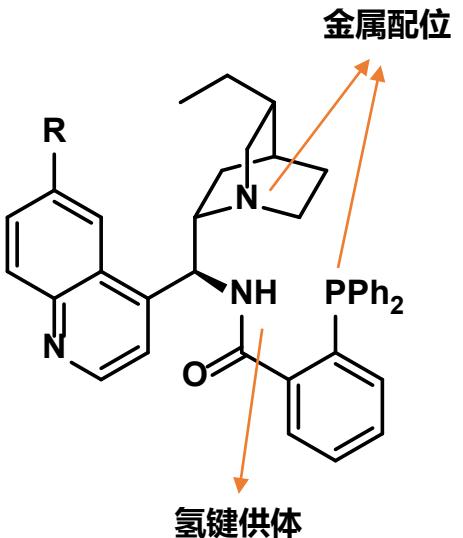
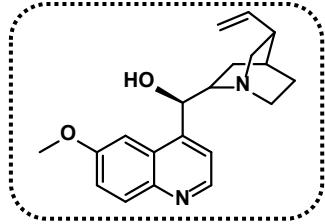
Chiral-at-metal Catalysts



BINOL-Derived Ligands



# Quinine-Derived Ligands

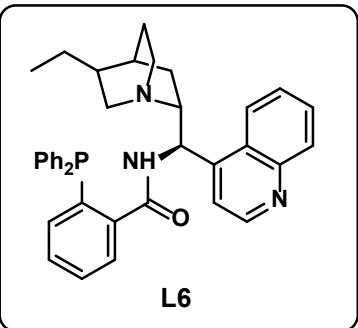
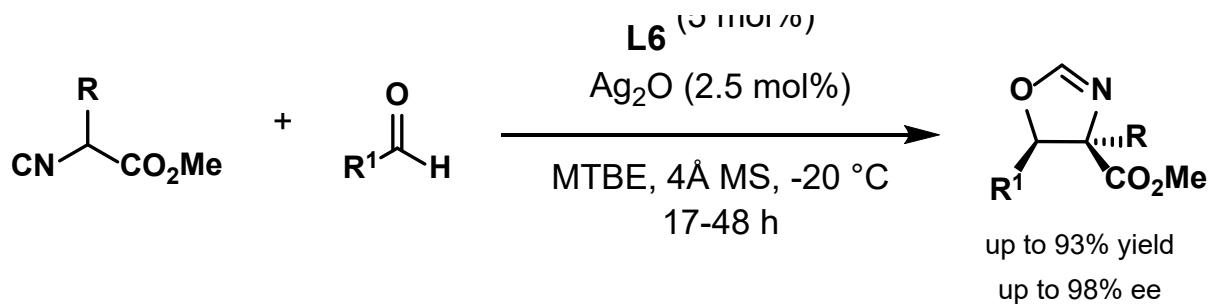
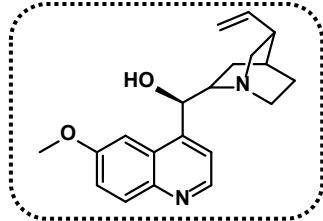


Aldol reaction / Mannich reaction

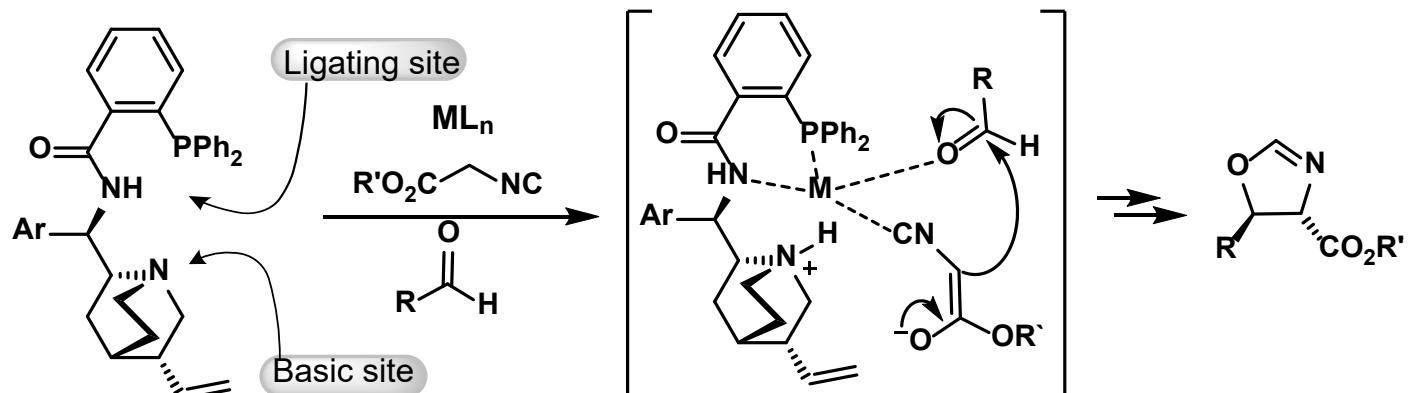
- Dixon, D. J. et al. *J. Am. Chem. Soc.* **2011**, *133*, 1710–1713  
Dixon, D. J. et al. *Angew. Chem., Int. Ed.* **2014**, *53*, 3462–3465  
Dixon, D. J. et al. *Angew. Chem., Int. Ed.* **2015**, *54*, 4895–4898  
Dixon, D. J. et al. *Chem. Commun.* **2016**, *52*, 10632–10635  
Dixon, D. J. et al. *Chem. - Eur. J.* **2018**, *24*, 17660–17664



# Quinine-Derived Ligands—Initial Work



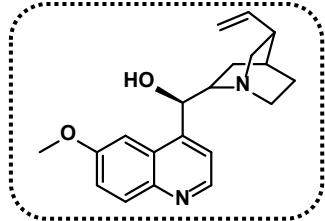
Postulated Catalyst Activation Mode:



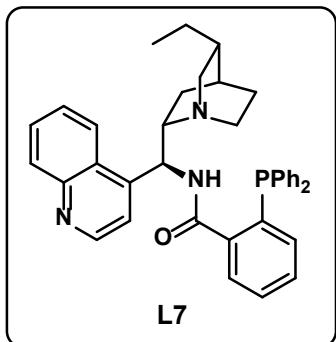
配位模型存在问题



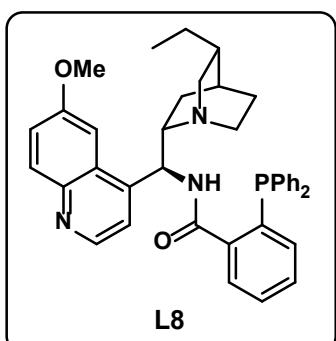
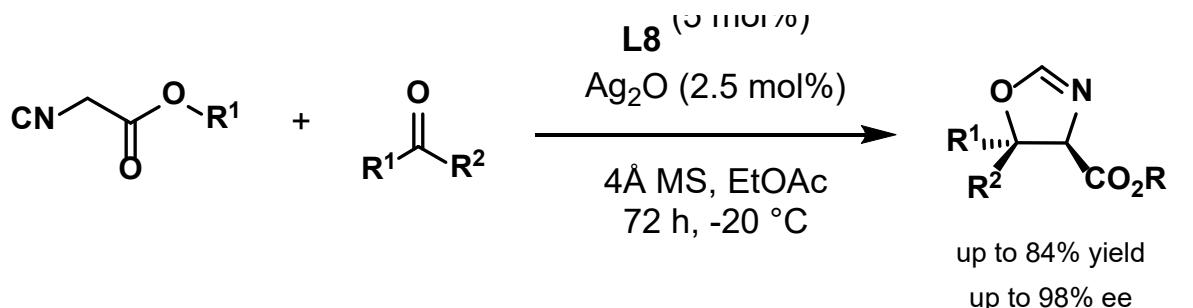
# Quinine-Derived Ligands—Possible Interactions



Dixon, D. J. et al. (2014):

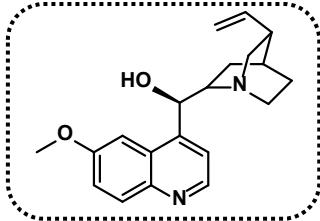


Dixon, D. J. et al. (2015):

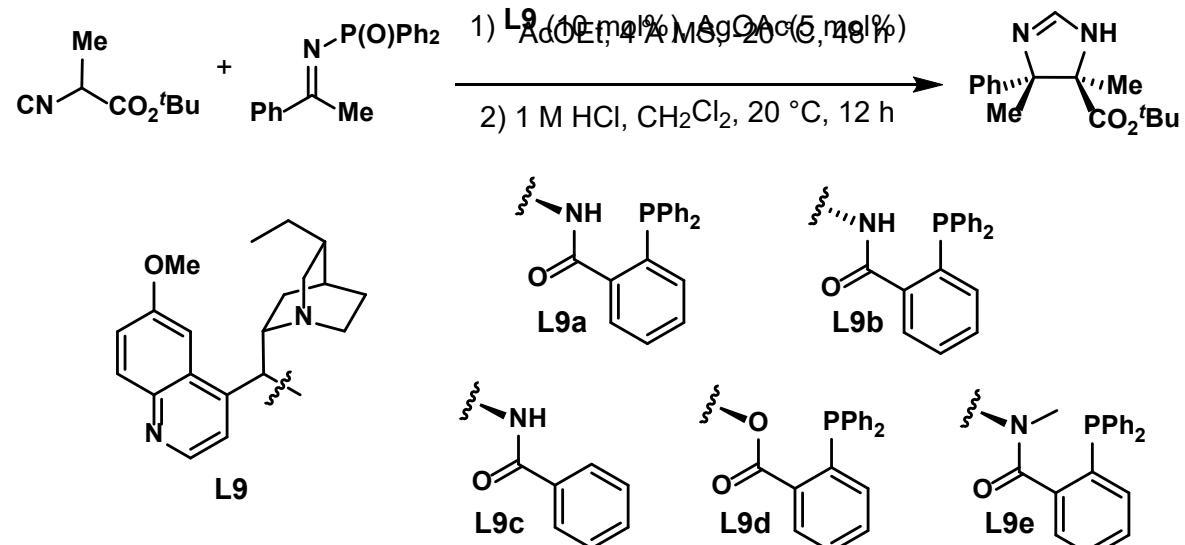




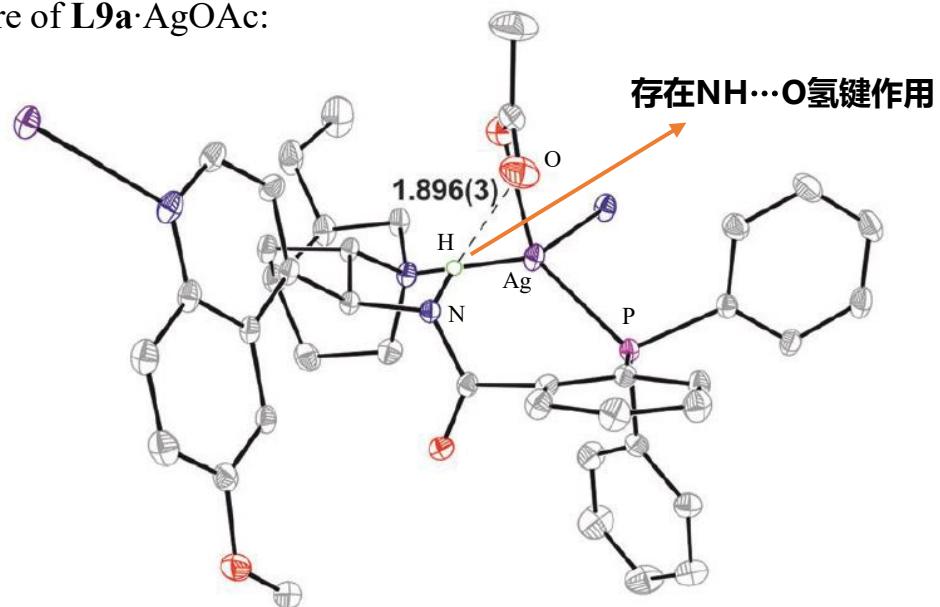
# Quinine-Derived Ligands—Hydrogen Bond



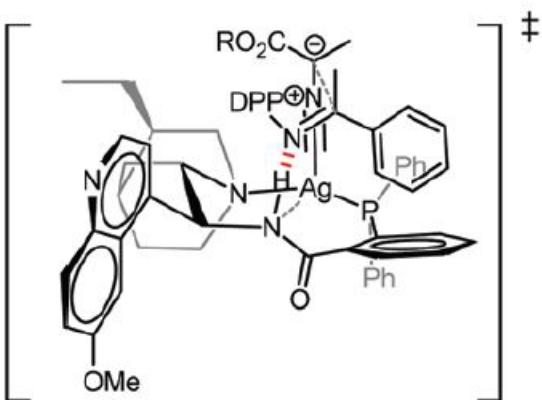
Control Experiments:



Structure of **L9a·AgOAc**:

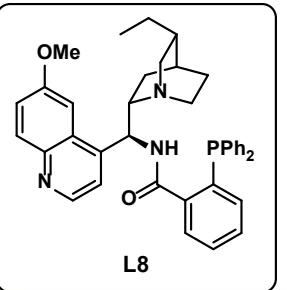
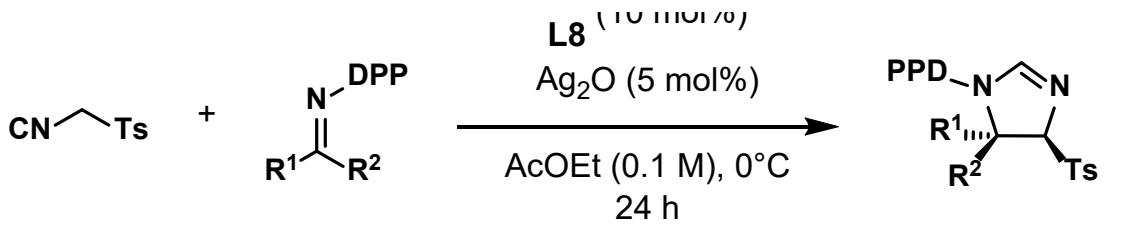
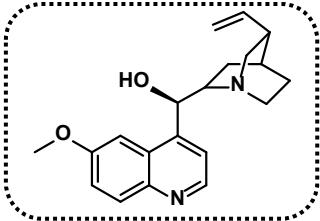


Proposed Transition Structure:

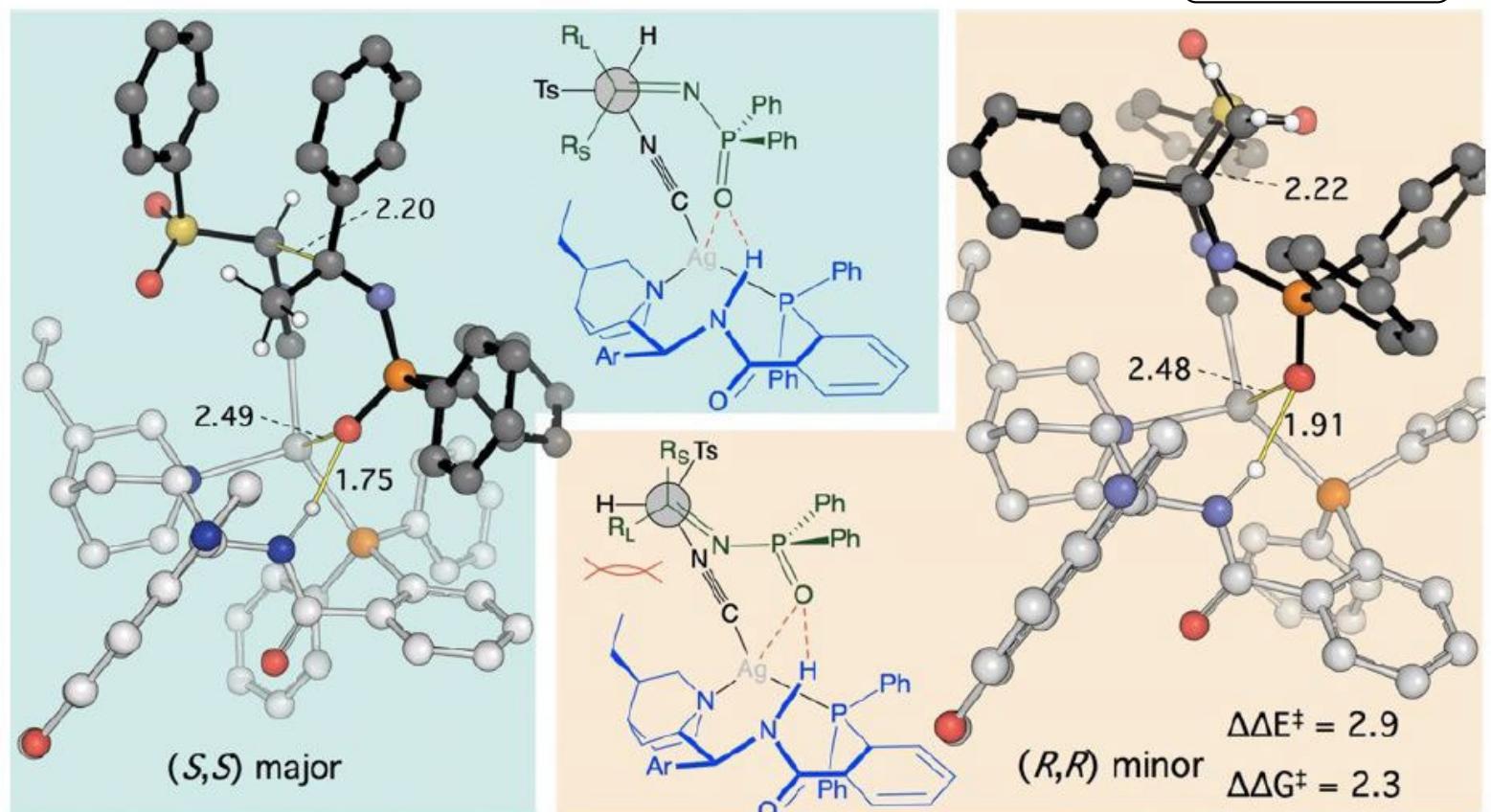




# Quinine-Derived Ligands—DFT Calculations

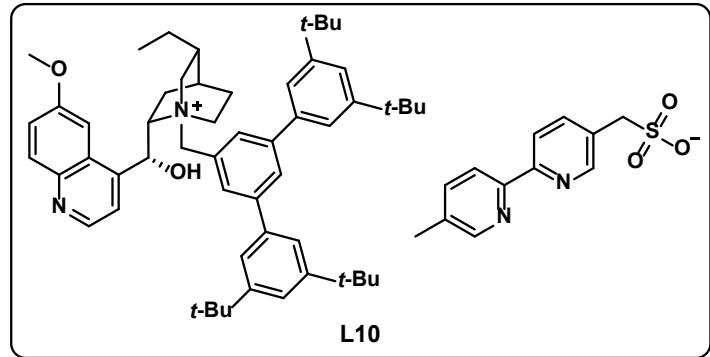
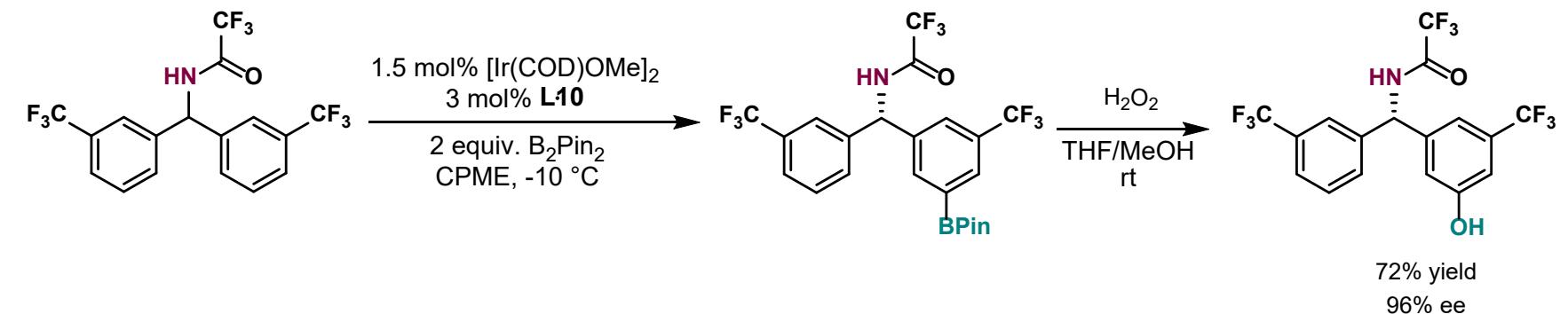
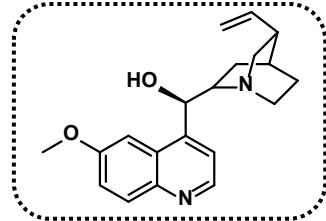


证实配体-底物间  
氢键作用

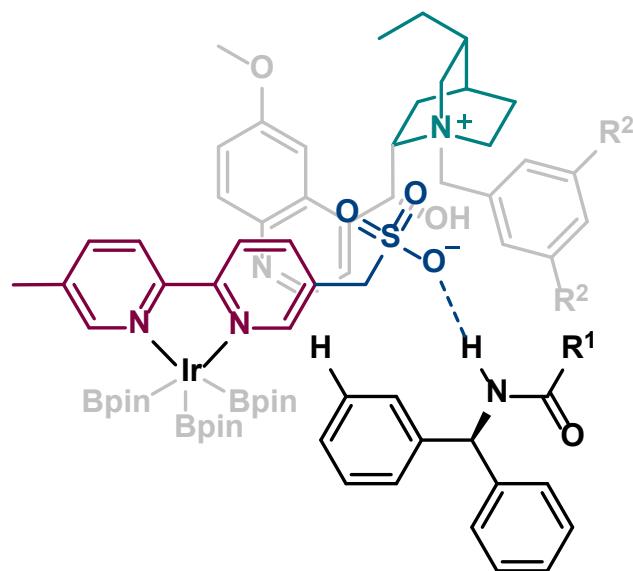




# Quinine-Derived Ligands—Chiral Cation



Proposed Interactions:

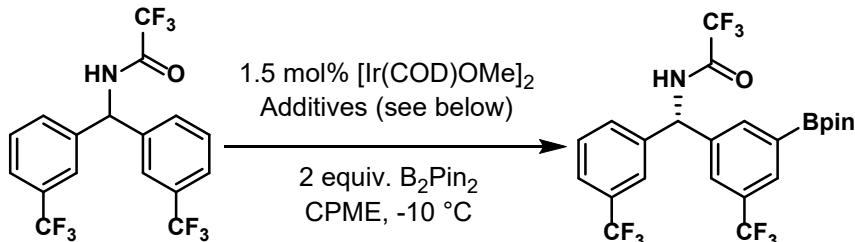


Probing ligand-substrate interactions:

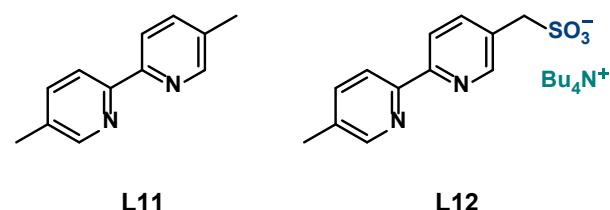
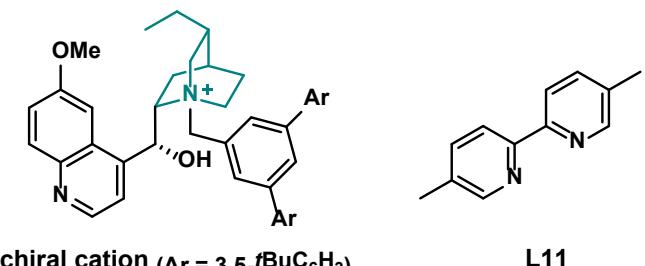
	Temp (°C)	conv. (%)	ee (%)
a	-10	91	91
b	-10	0	-
a	10	> 95	73
b	10	> 95	8

R = H, **a**; R = Me, **b**

Probing ligand-cation interactions:

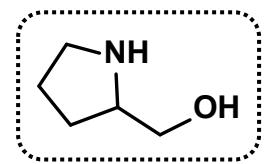


With 3 mol% **chiral cation** and 3 mol% **L11**: Racemic  
With 3 mol% **chiral cation** and 3 mol% **L12**: 58% ee

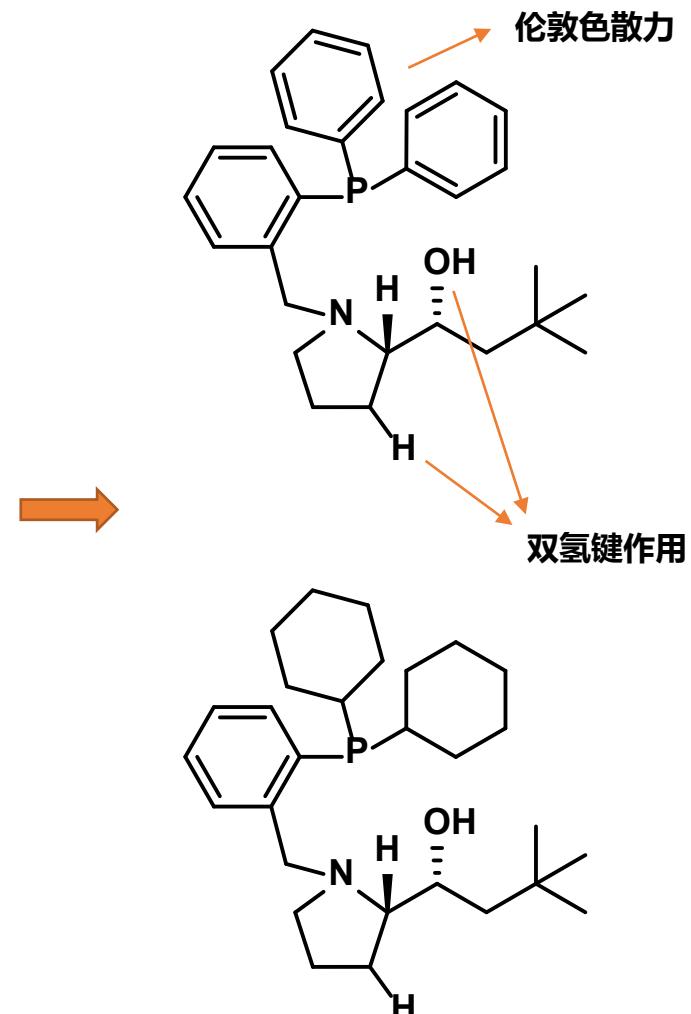




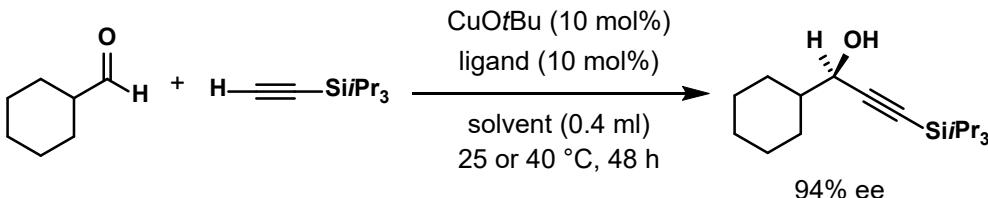
# Prolinol-Derived Ligands



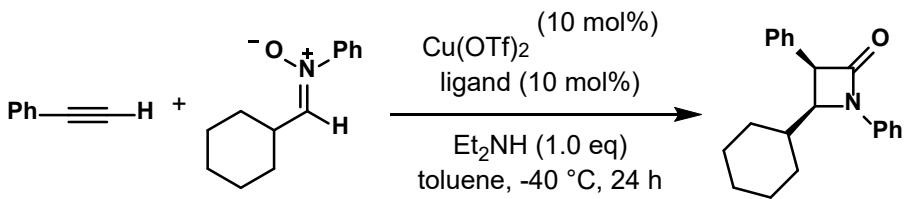
Masaya Sawamura  
(Hokkaido University)



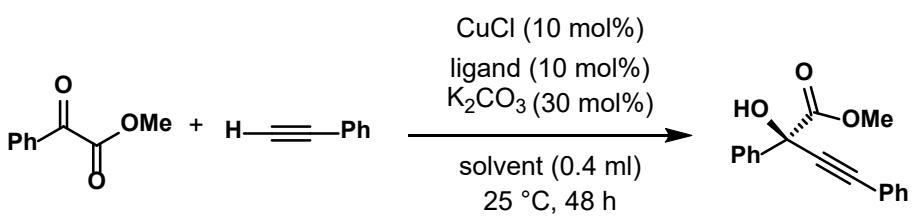
In 2013



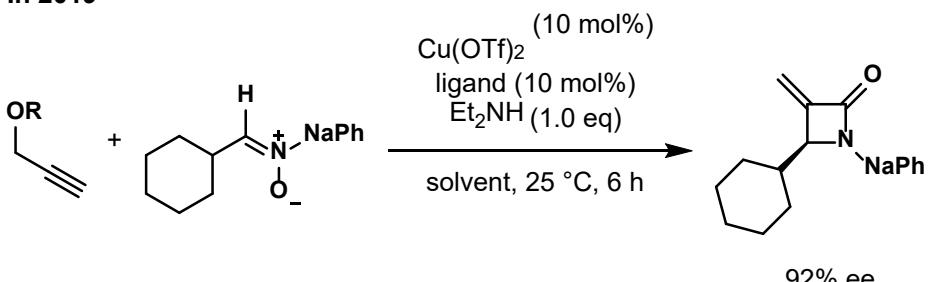
In 2017



In 2018



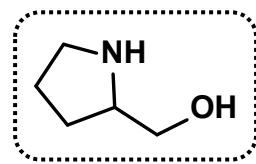
In 2019



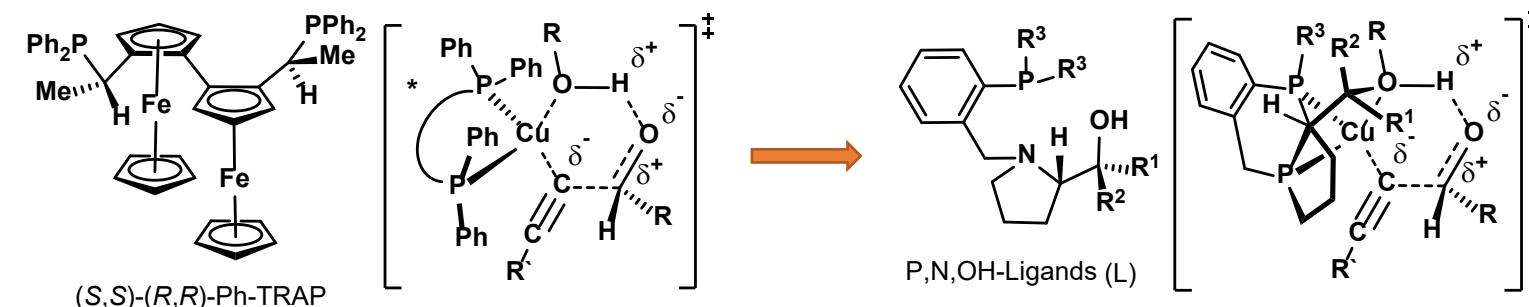
- Sawamura, M. et al. *Org. Lett.* **2007**, *9*, 3901–3904  
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 Sawamura, M. et al. *Chem. - Eur. J.* **2017**, *23*, 8400–8404  
 Sawamura, M. et al. *Chem. Sci.* **2018**, *9*, 3484–3493  
 Sawamura, M. et al. *Org. Lett.* **2019**, *21*, 1717–1721



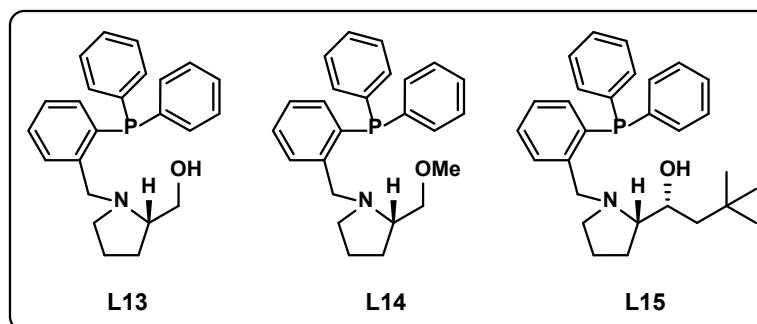
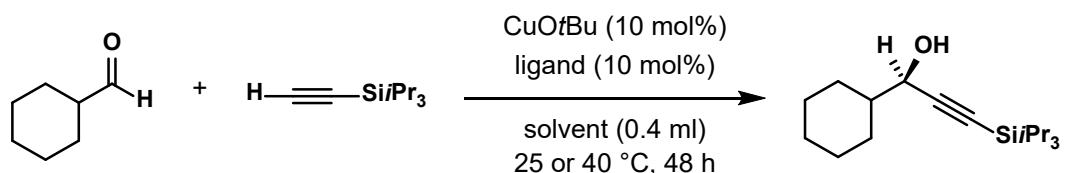
# Prolinol-Derived Ligands—Design & Initial Work



Design of Hydrogen-Bonding-Based Catalysts:



The Effect of Solvents and Chiral Ligands:

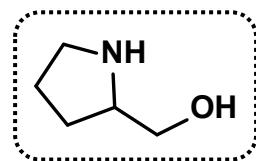


Entry	Ligand	Solvent	T (°C)	Yield (%)	e.r.
1	L13	toluene	40	43	66:34
2		THF	40	32	64:38
3		MeCN	40	18	72:28
4		EtOH	40	70	82:18
5		iPrOH	40	92	83:17
6		tBuOH	40	92	82:18
7	L14	tBuOH	40	0	-
8	L15	iPrOH	40	95	94:6
9	L15	iPrOH	25	99	95:5
10	L15	tBuOH	25	98	96:4

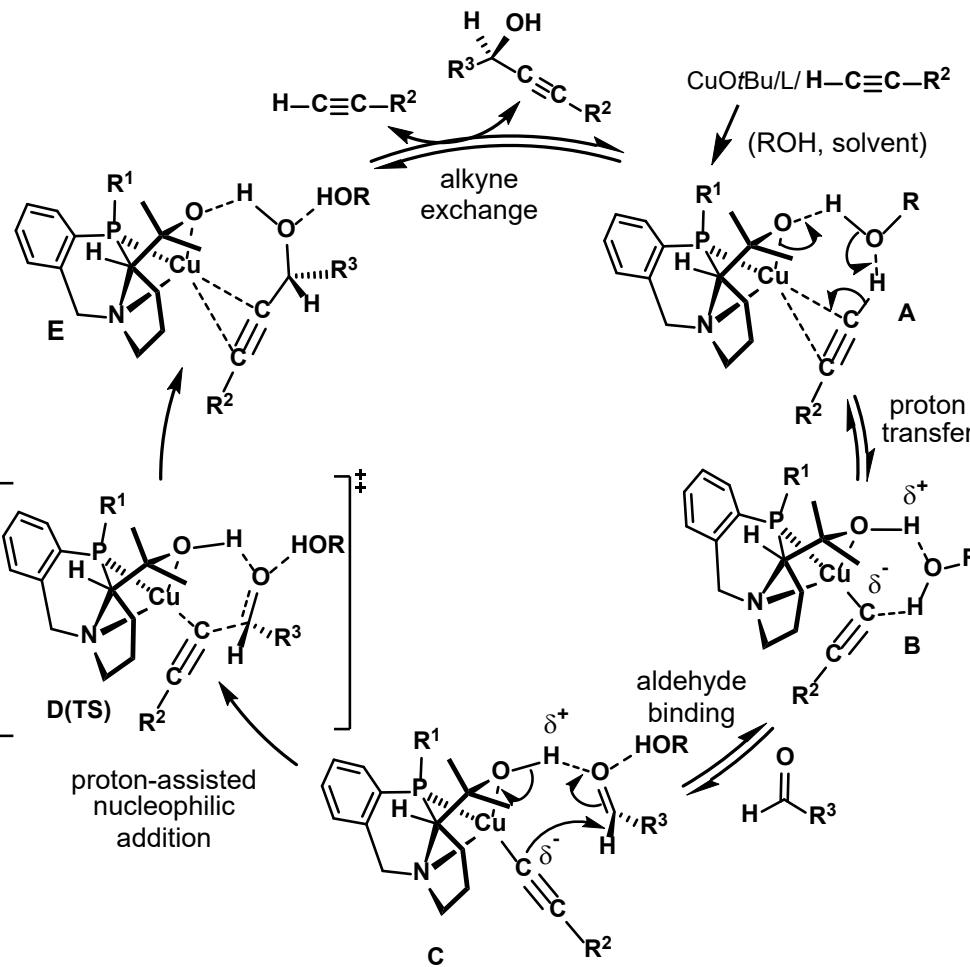
非质子性溶剂

质子性溶剂 (醇)

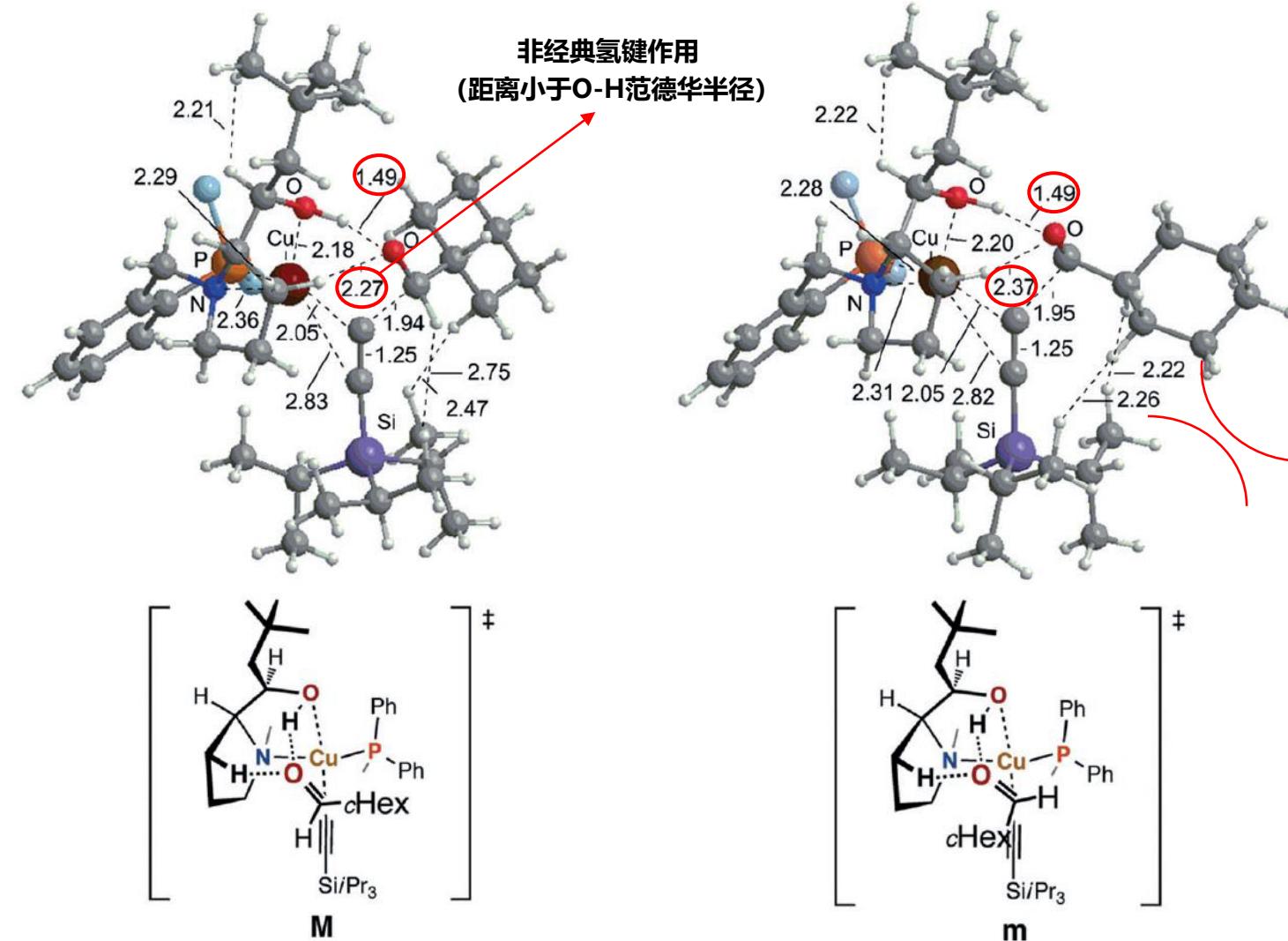
配体影响

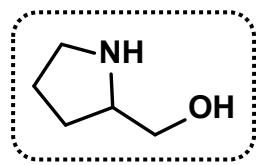


## Proposed Reaction Pathway:

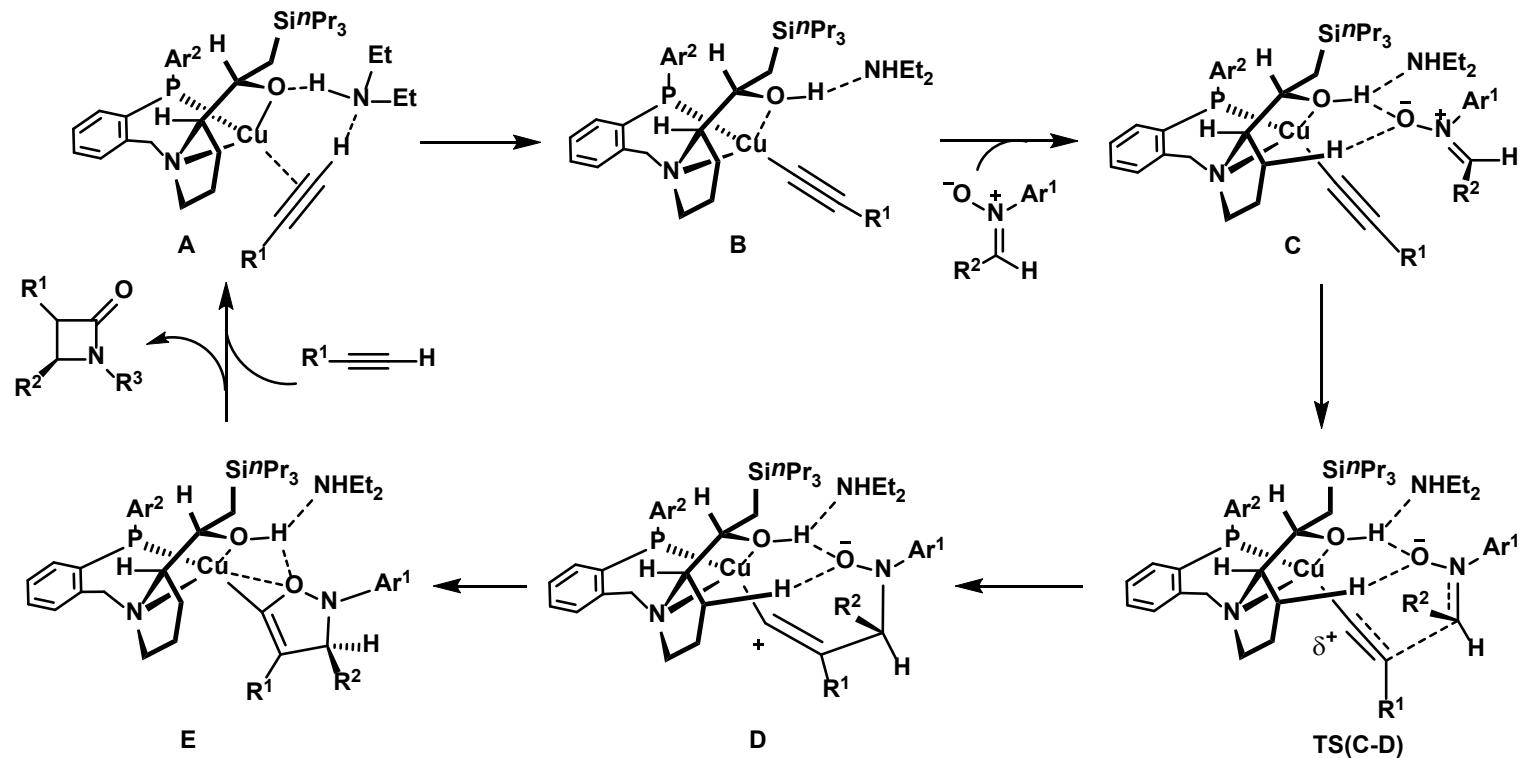
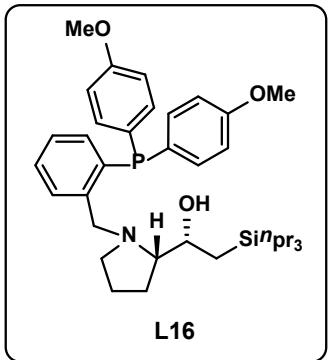
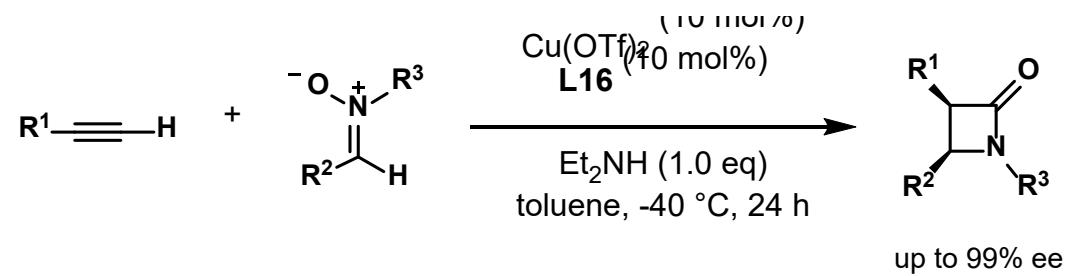


## DFT Calculations:



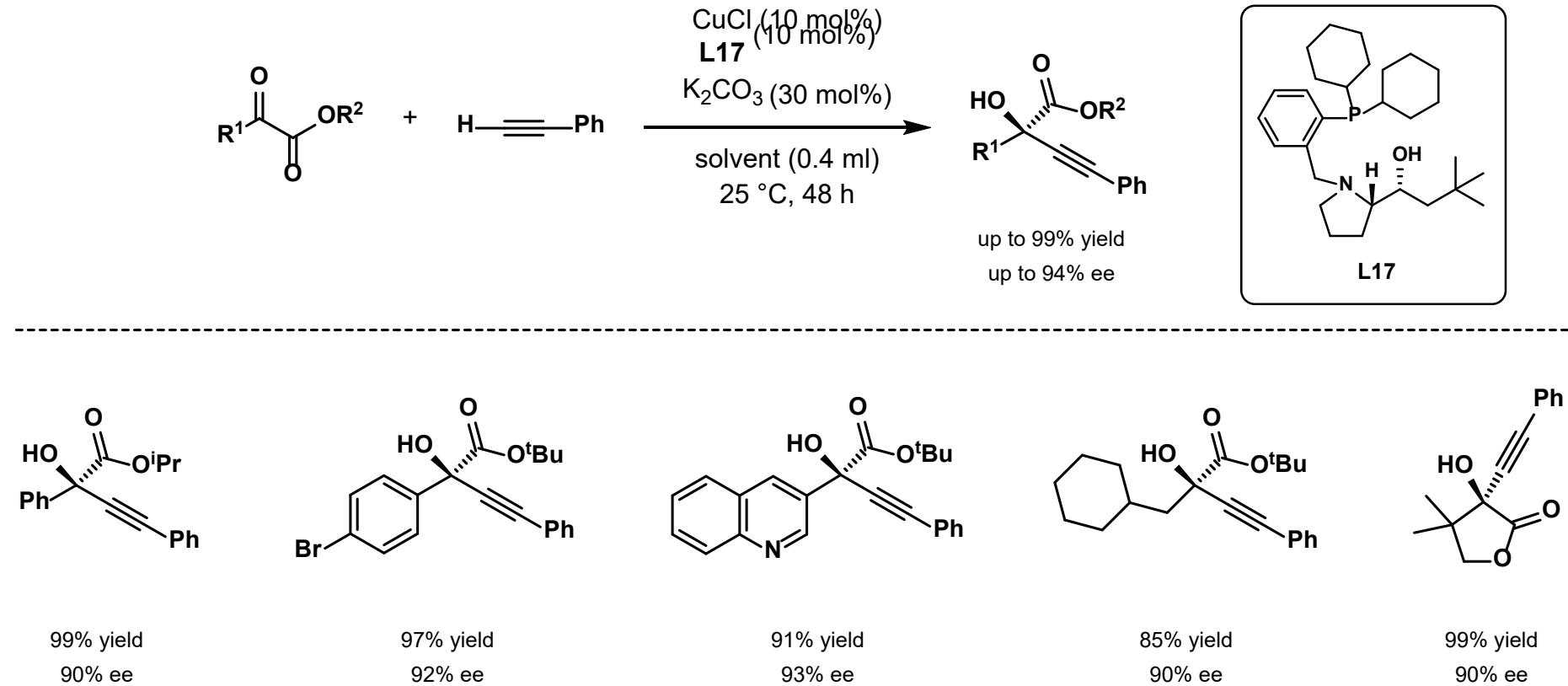
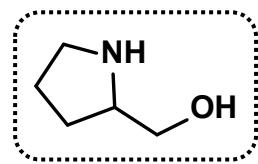


Enantiocontrolled Kinugasa Reaction:



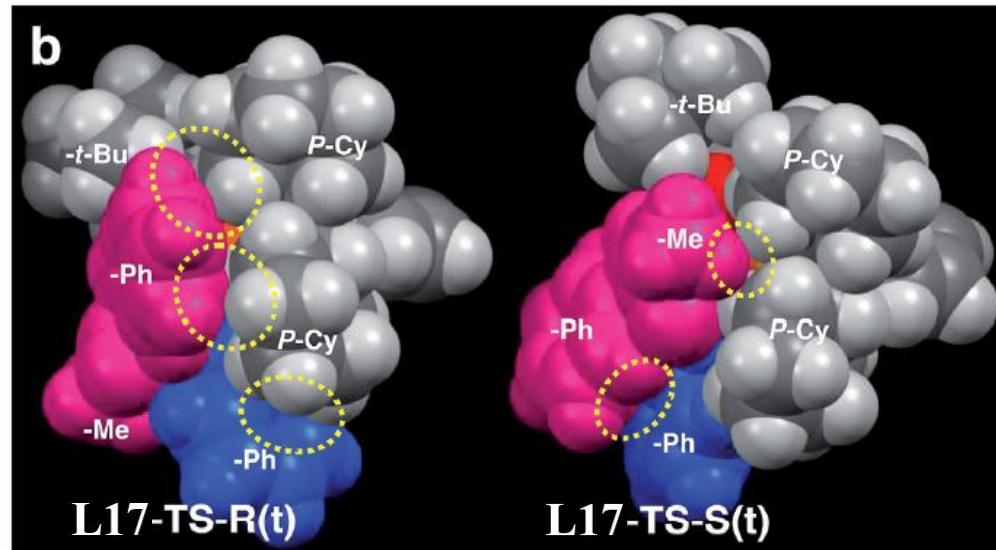
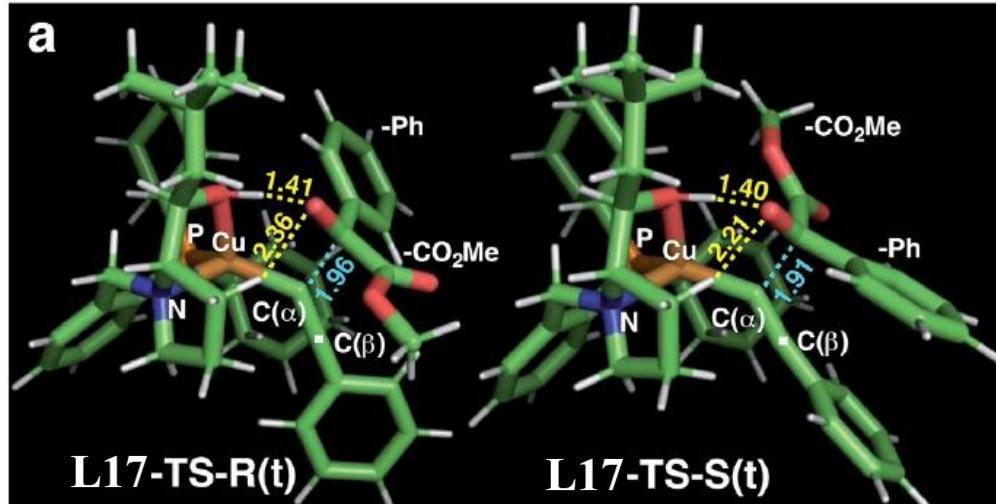
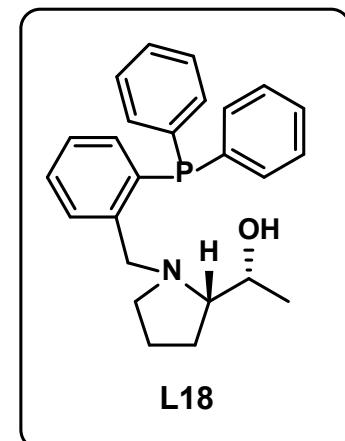
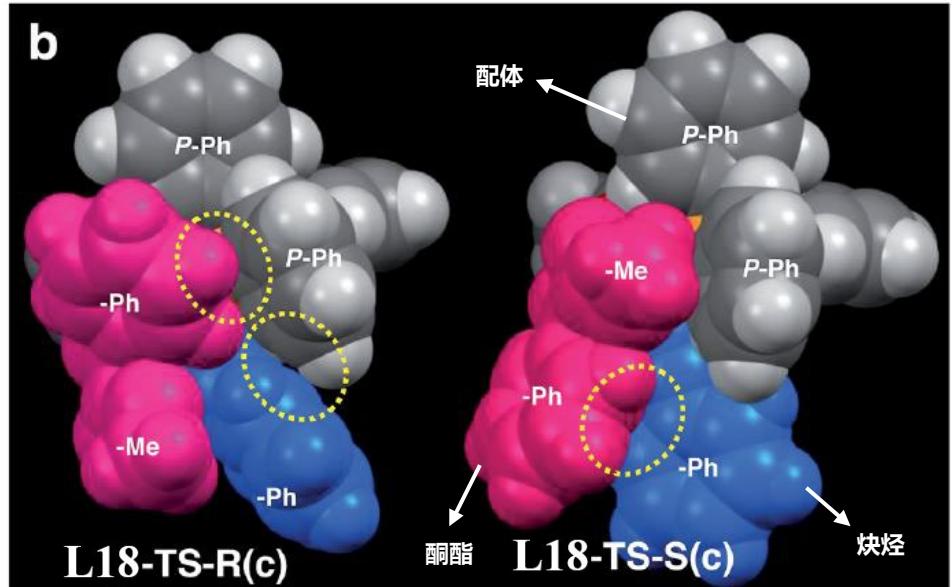
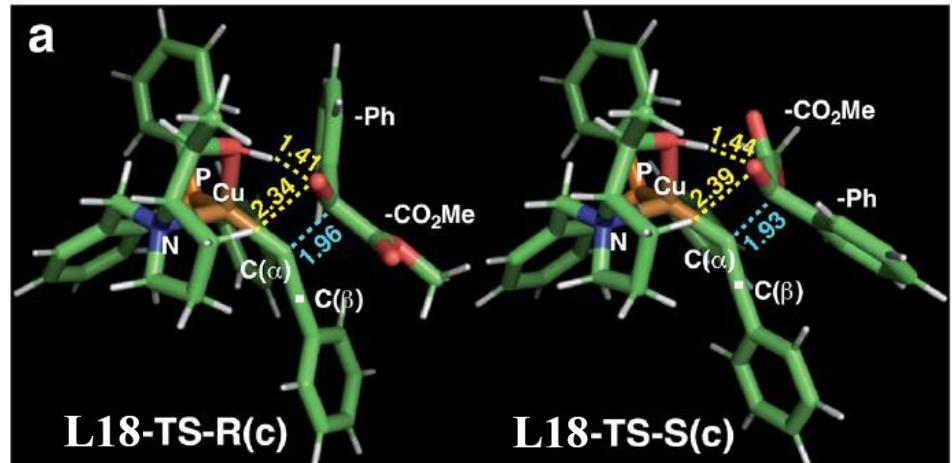
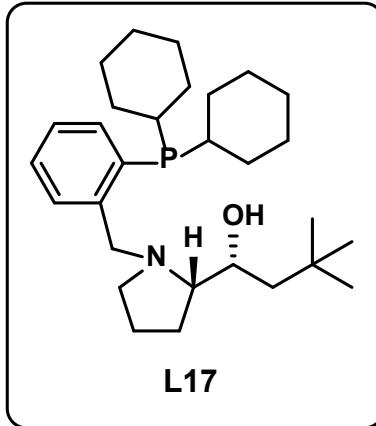
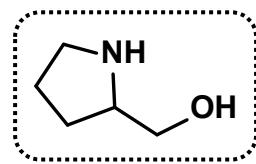


# Prolinol-Derived Ligands—Application





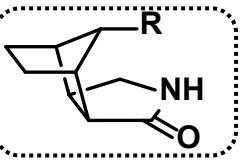
# Prolinol-Derived Ligands—Dispersion Interactions



伦敦色散力 (影响面选择性)

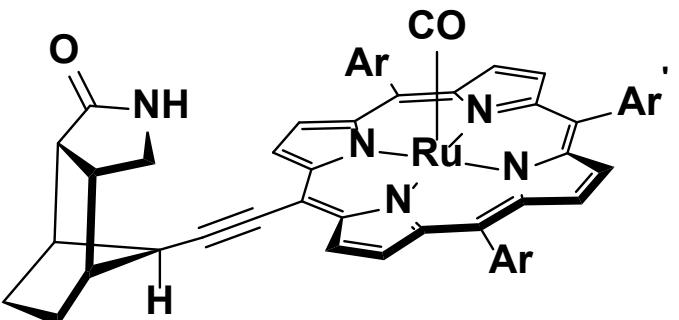


# Chiral Lactam Scaffolds

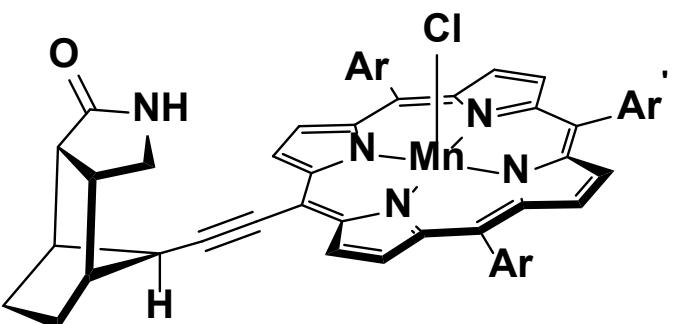


Thorsten Bach

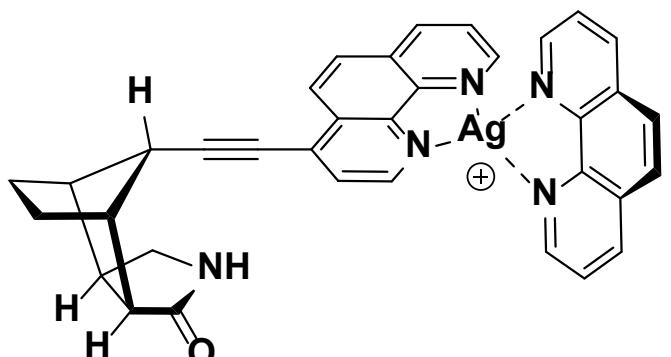
(Technical University of Munich)



Bach, T. et al. (2010)

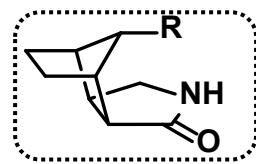


Bach, T. et al. (2018)

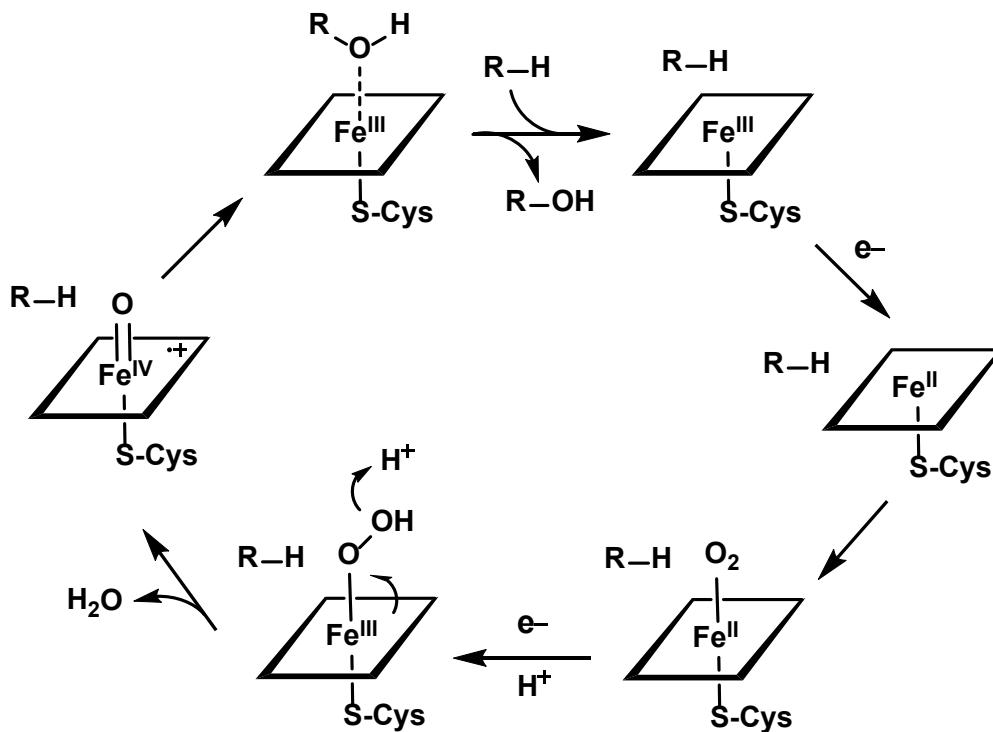
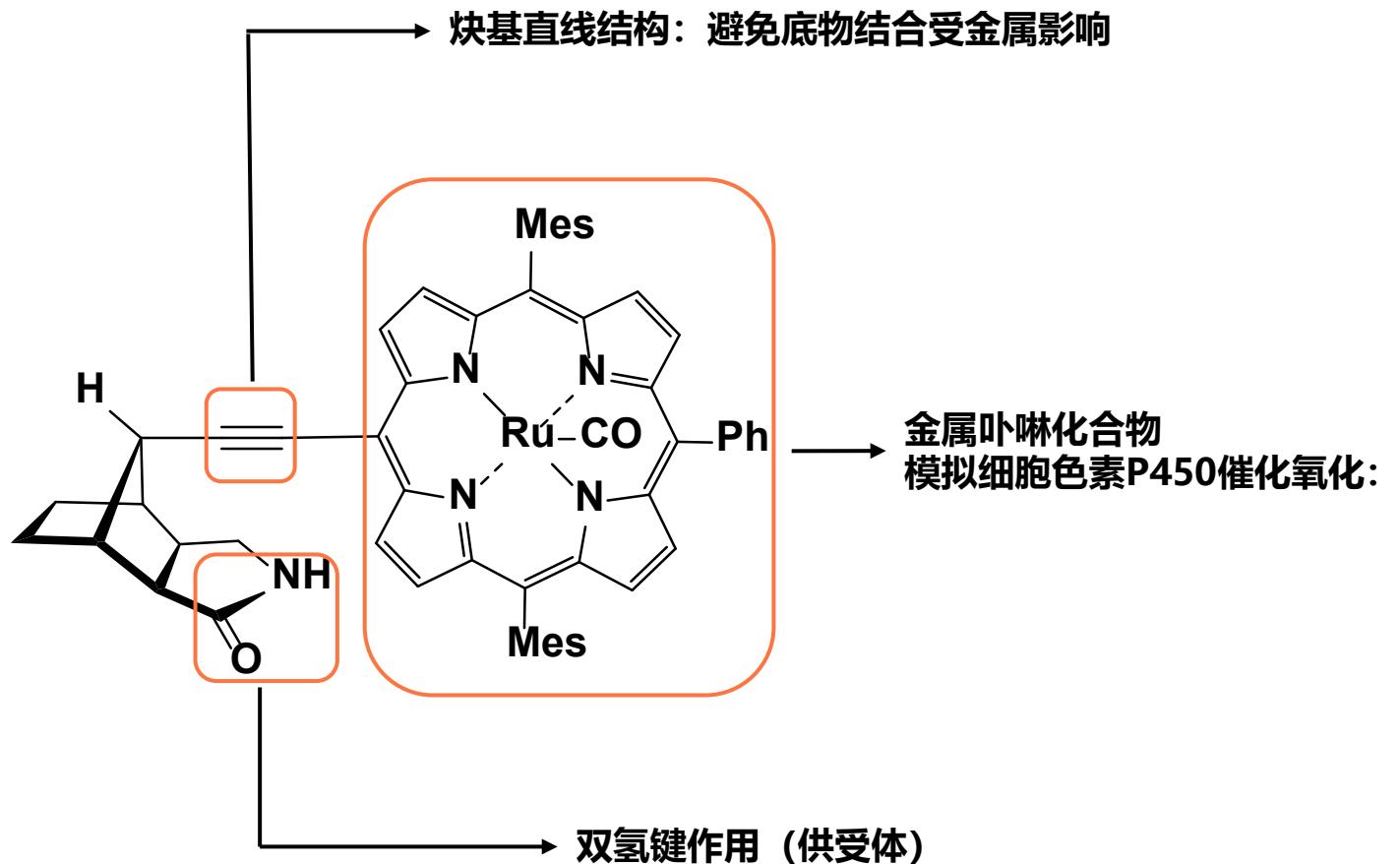


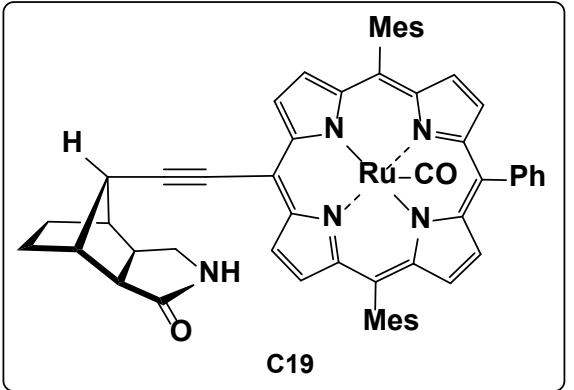
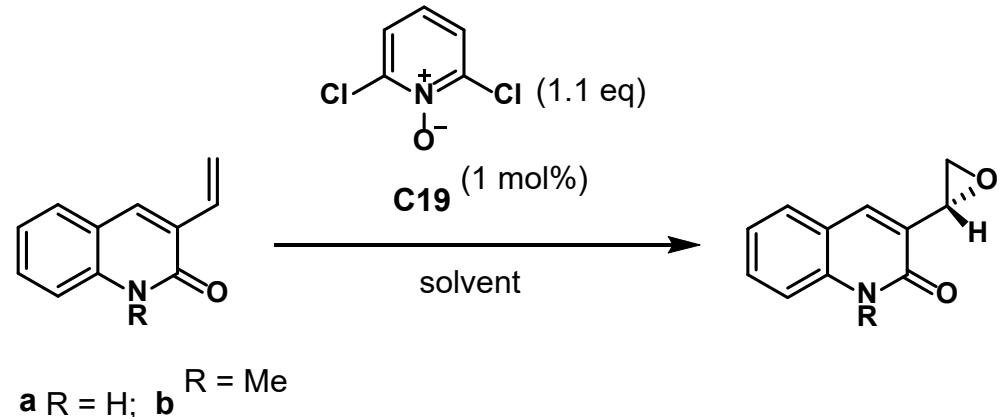
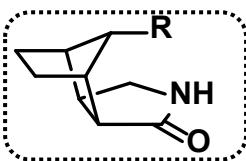
Bach, T. et al. (2020)

- Bach, T. et al. *J. Am. Chem. Soc.* **2010**, *132*, 15911–15913  
Bach, T. et al. *J. Am. Chem. Soc.* **2012**, *134*, 12869–12878  
Bach, T. et al. *Angew. Chem., Int. Ed.* **2014**, *54*, 691–695  
Bach, T. et al. *Angew. Chem., Int. Ed.* **2018**, *57*, 2953–2957  
Bach, T. et al. *J. Am. Chem. Soc.* **2020**, *142*, 7374–7378  
Bach, T. et al. *Angew. Chem., Int. Ed.* **2021**, *60*, 7920–7926



Design of Catalysts:

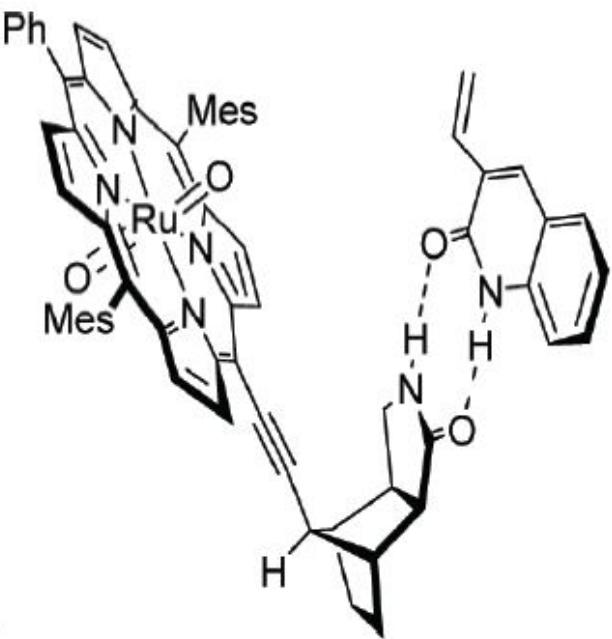




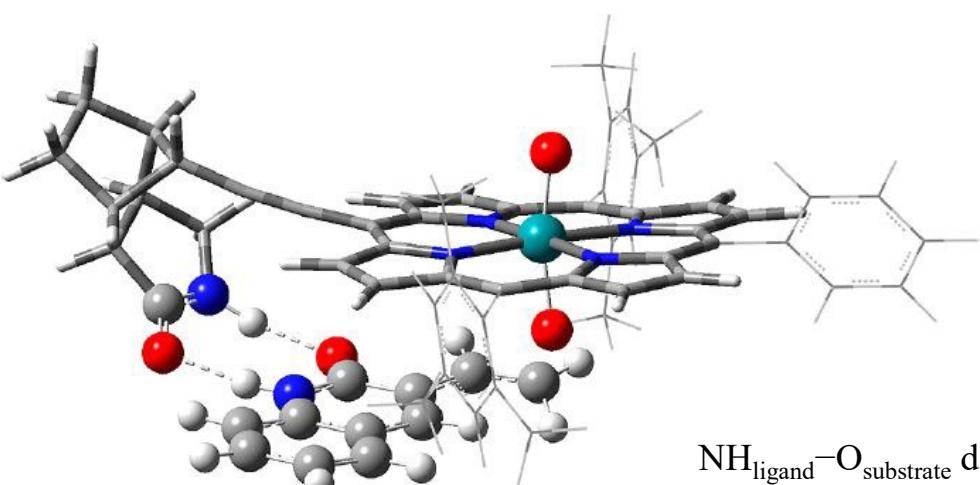
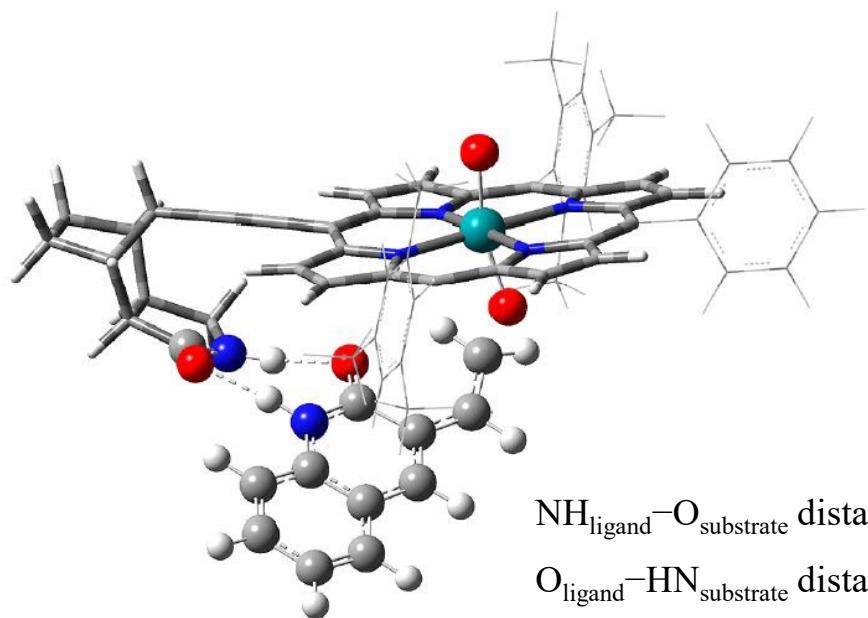
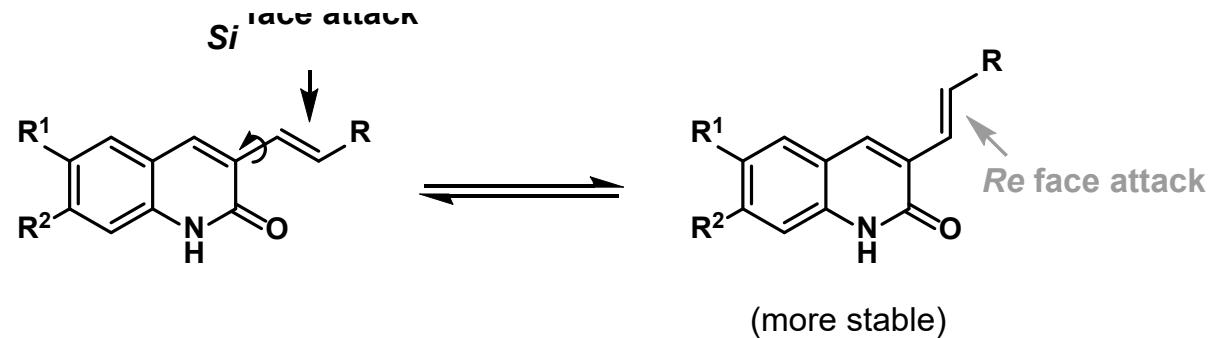
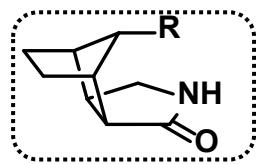
entry	substrate	solvent	T (°C)	product	yield (%)	ee (%)
1	<b>a</b>	benzene	25	<b>2a</b>	71	95
2	<b>b</b>	benzene	25	<b>2b</b>	55	≤ 5
3*	<b>a</b>	benzene	25	<b>2a</b>	68	14

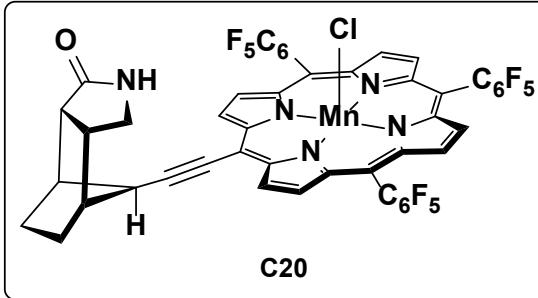
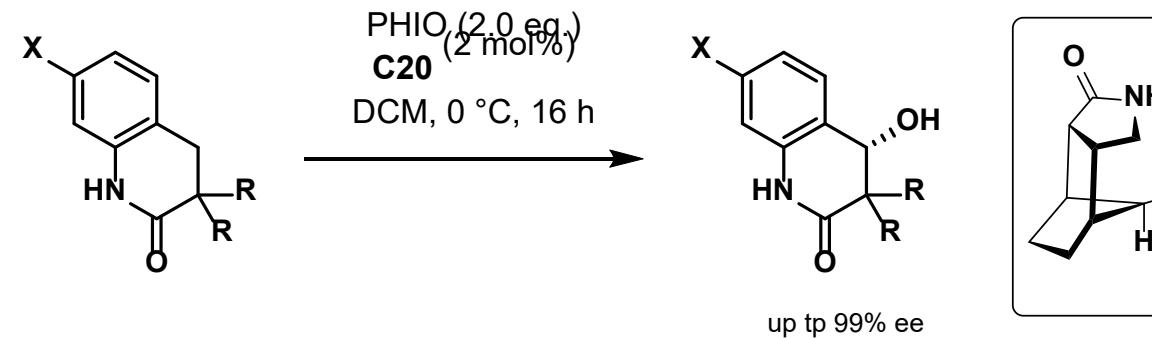
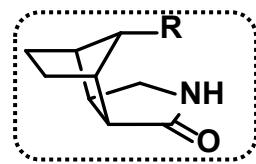
\* 催化剂C19中 N-H 变为 N-Me

Semiempirical Calculation:

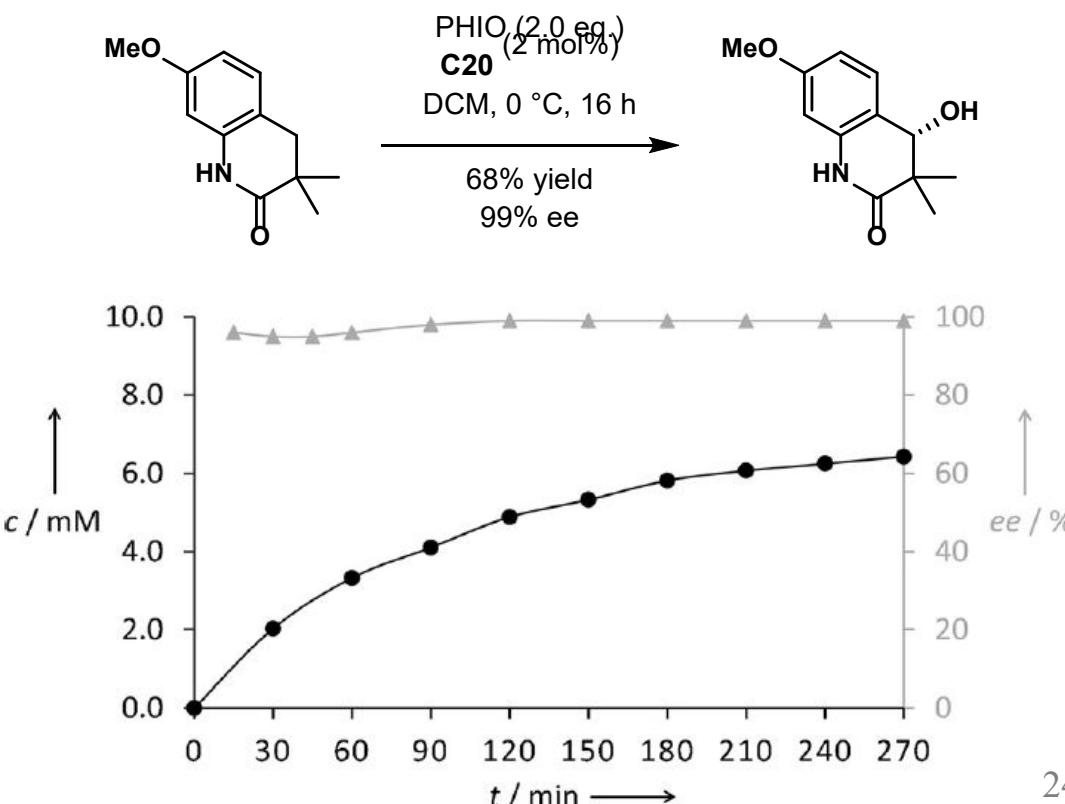
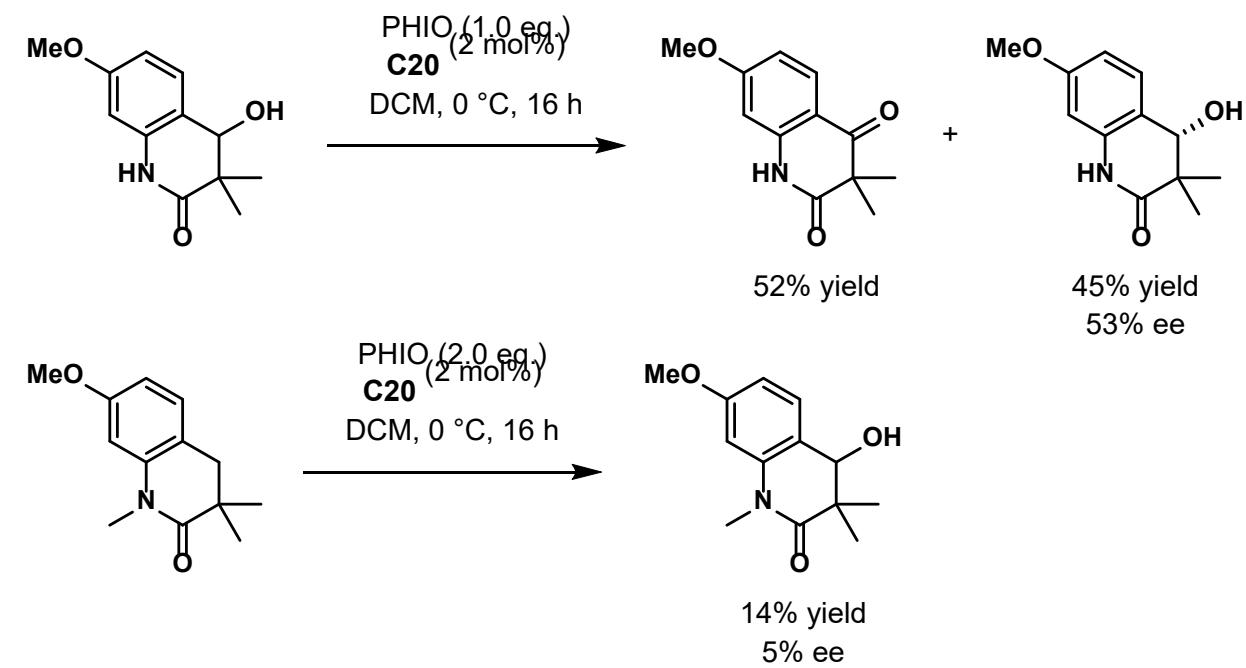


底物-配体间双氢键模型



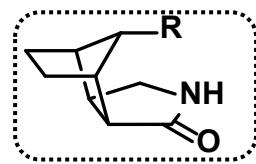


### Control Experiments:

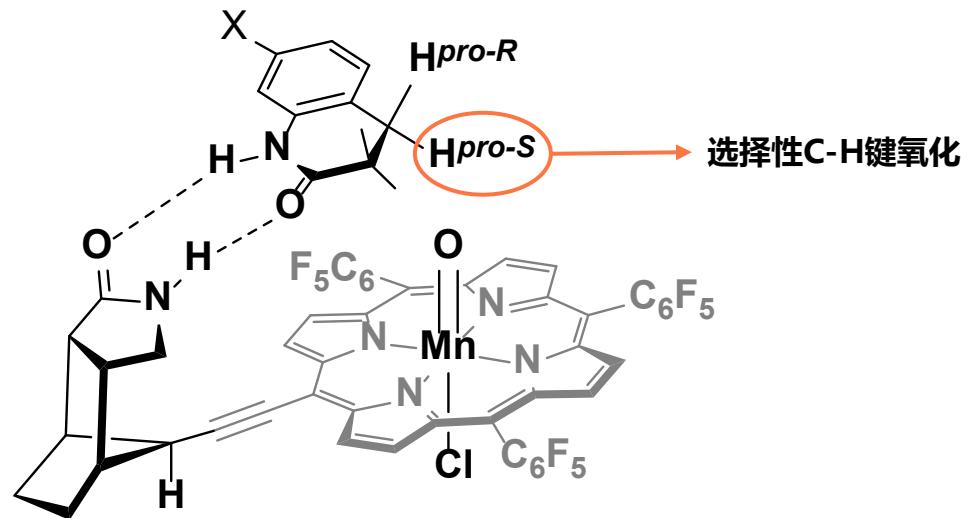




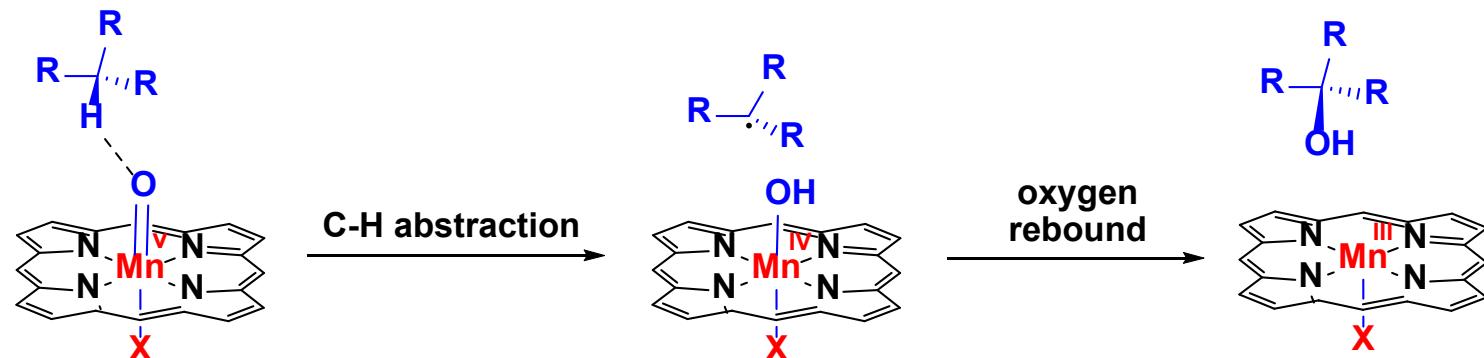
# Chiral Lactam Scaffolds—Oxidation Mechanism

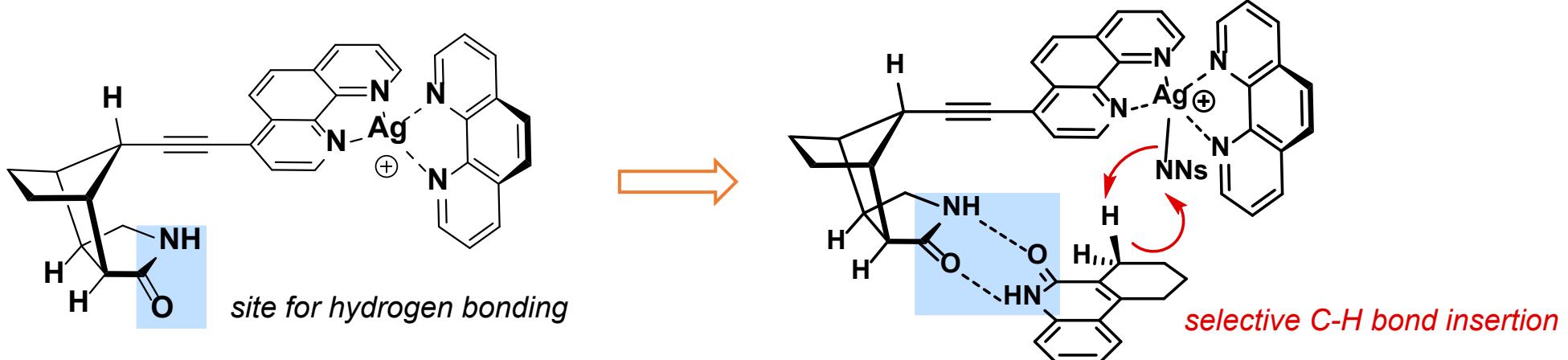
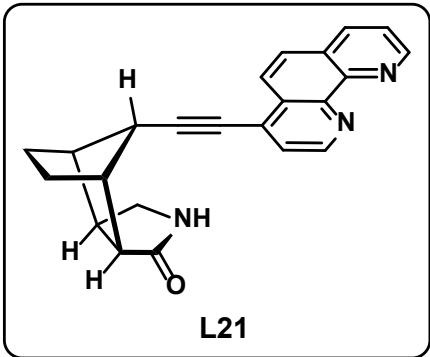
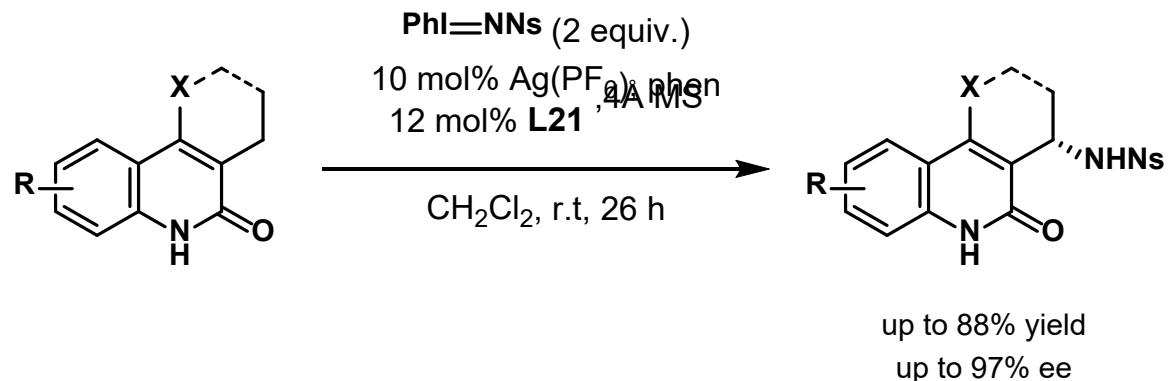
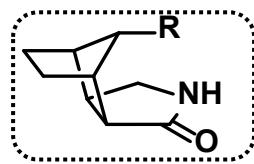


Substrate with Mn Catalyst:



Groves, J. T. et al. (2007):





# PART 3

## Ion-Pairing Interactions



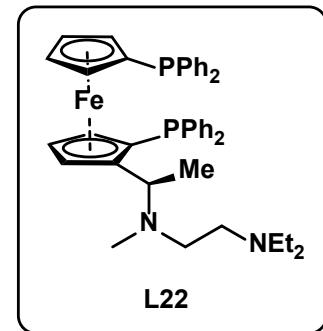
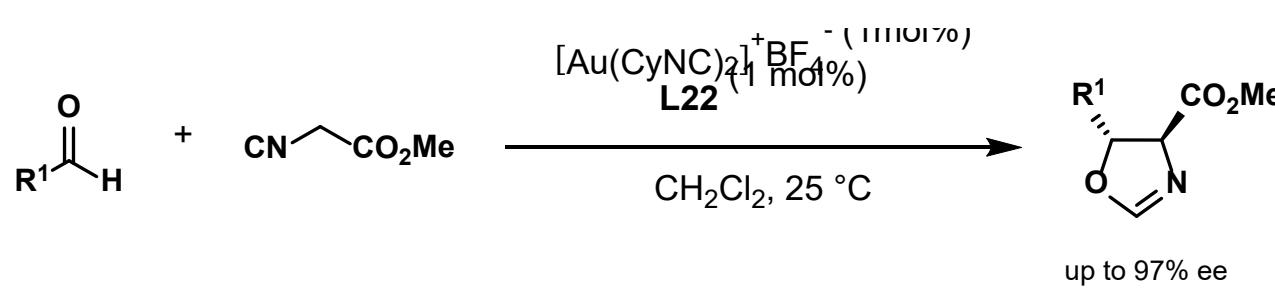
# Ion-Pairing Interactions

Distance dependencies of the representative noncovalent interactions

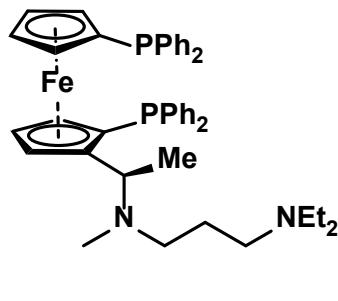
Entry	Noncovalent interaction	Energy dependence on distance
1	Steric repulsion	$\text{R}-\text{CH}_3 \quad \text{H}_3\text{C}-\text{R}$
2	Hydrogen bond	$\text{N}-\text{H} \cdots \text{O}=\text{C}$
3	Ion pair	$\text{R}-\overset{+}{\text{NH}_3} \quad \overset{-}{\text{O}_2\text{C}}-\text{R}$



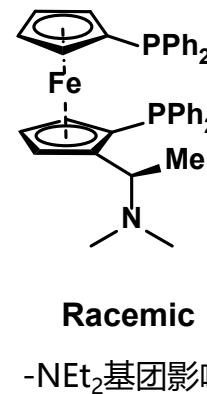
# Ion-Pairing Interactions—Initial Work



Control Experiments:

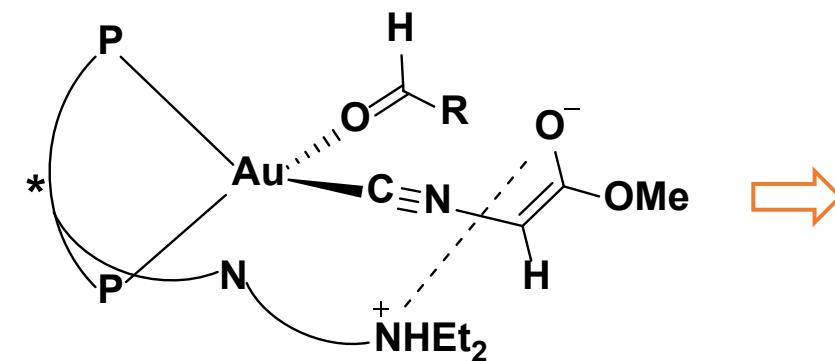


支链长度影响

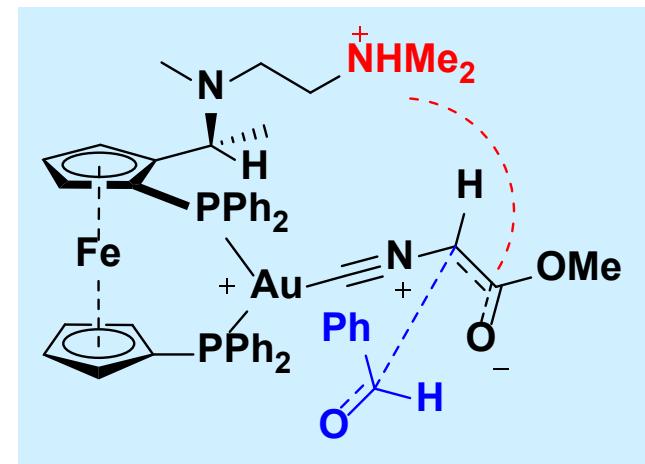


-N<sub>2</sub>Et基团影响

Ion-Pairing Interaction:

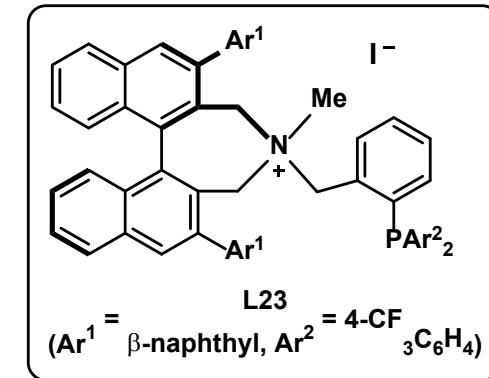
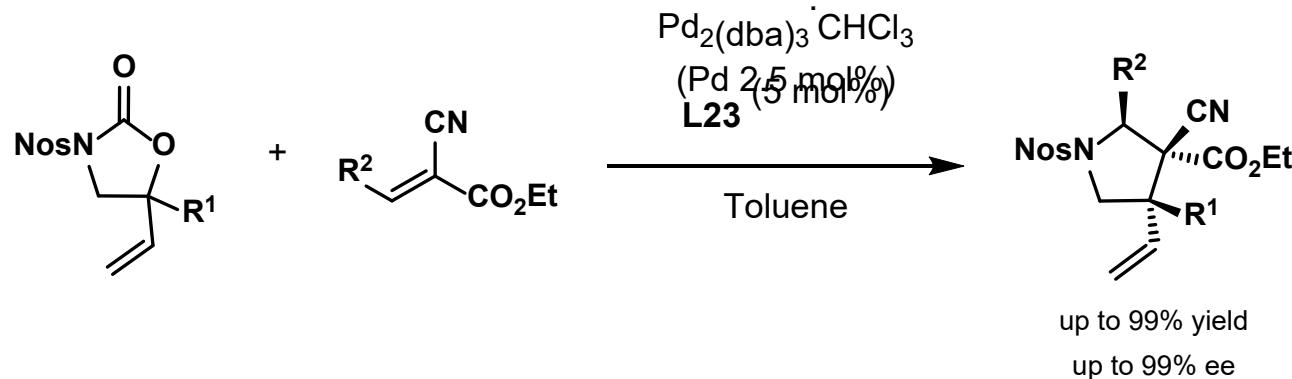


Togni, A. et al. (1990):

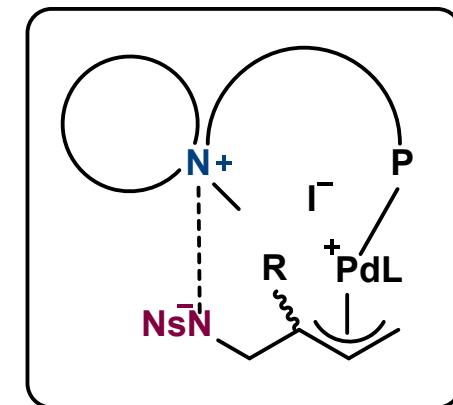
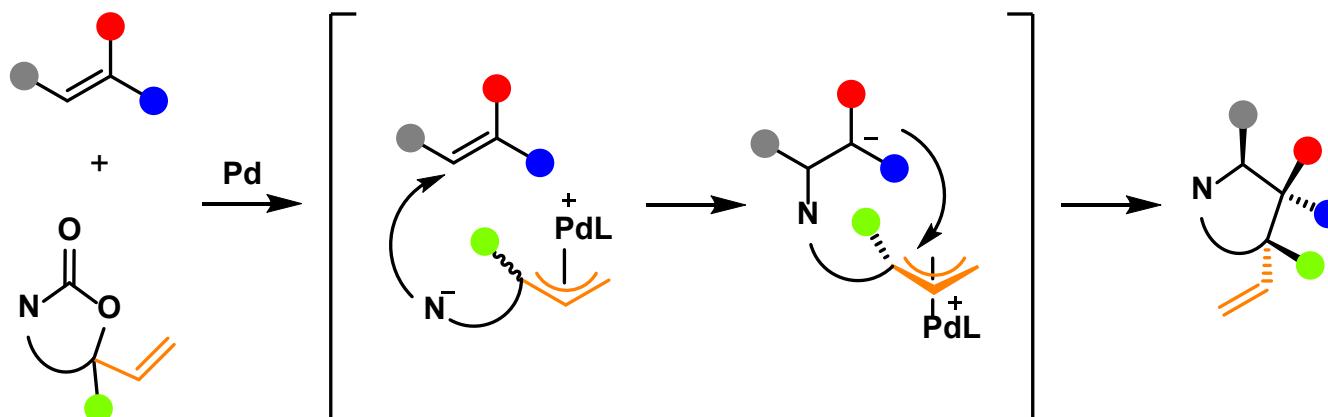




# Ion-Pairing Interactions—Ammonium Derivative Ligand

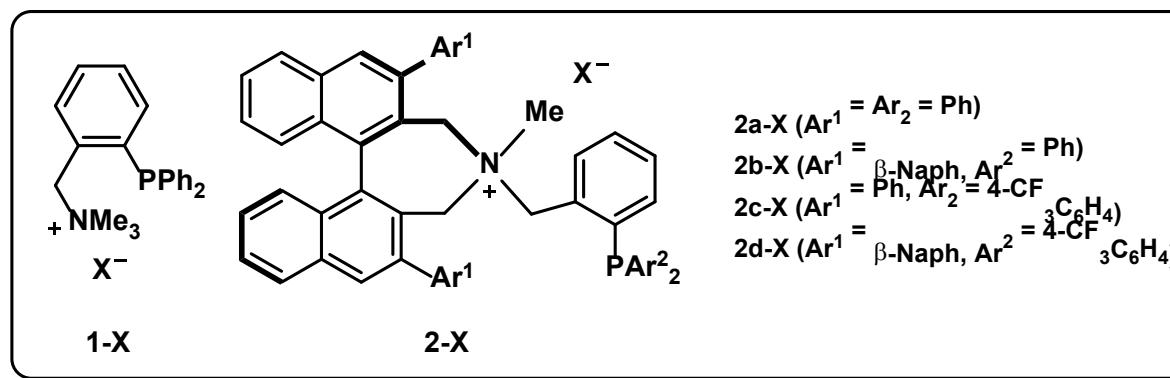
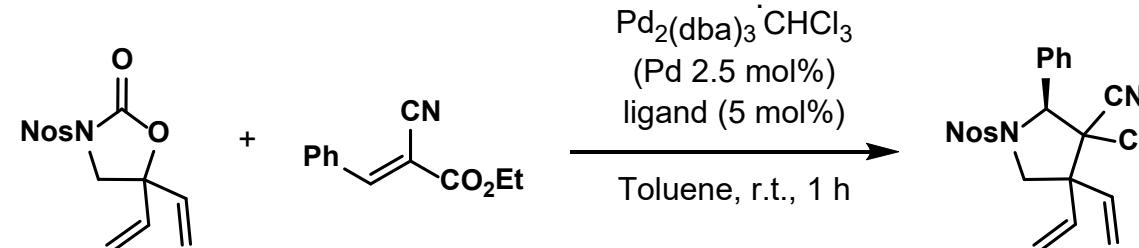


Reaction Process:





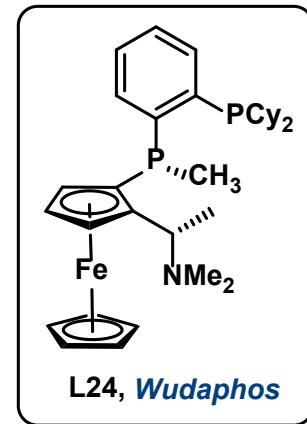
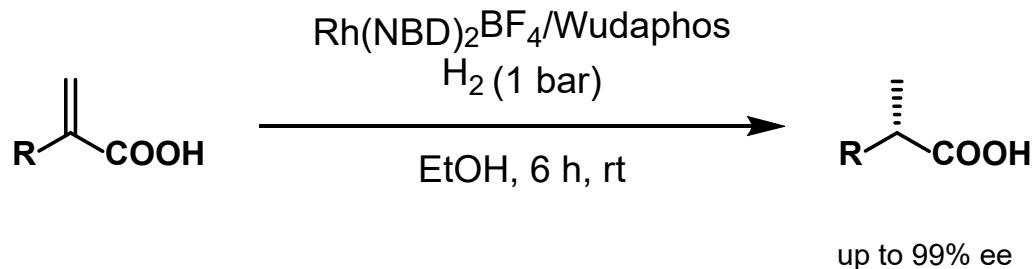
# Ion-Pairing Interactions—Ammonium Derivative Ligand



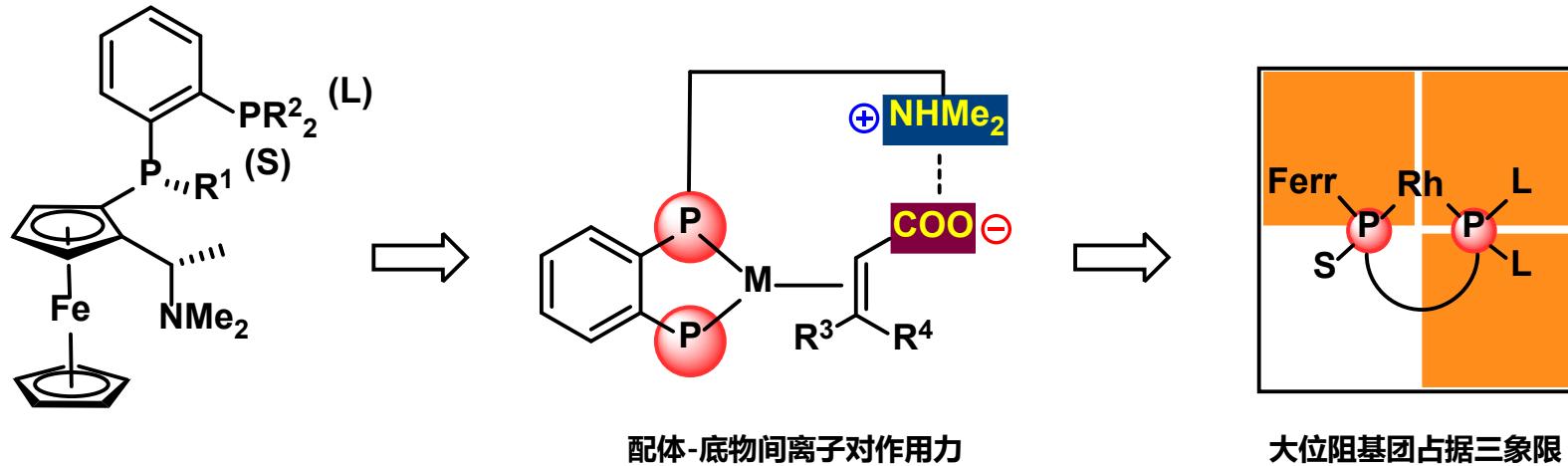
Entry	Ligand	Yield (%)	ee (%)	
1	$\text{PPh}_3$	43	-	→ N·与Pd结合
2	1-Br	99	-	→ X·与Pd结合
3	2a-Br	94	63	
4	2b-Br	99	63	
5	2c-Br	99	57	
6	2d-Br	99	75	
7	2d-Cl	99	72	
8	2d-I (L23)	99	90	



# Ion-Pairing Interactions—Wudaphos



Design of Ligands:

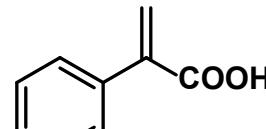




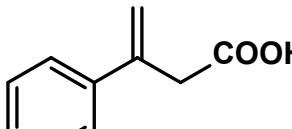
# Ion-Pairing Interactions—Wudaphos

Control Experiments:

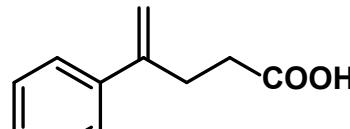
a) *chain length effect*:



> 99% Conv.  
98% ee



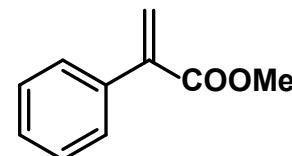
> 99% Conv.  
7% ee



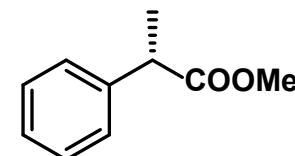
> 99% Conv.  
3% ee

b) *noncovalent ion pair interaction*:

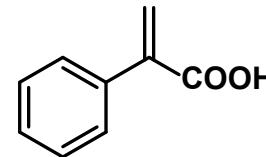
验证离子对作用力  
对反应的影响



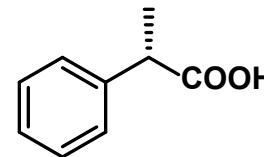
Rh(NBD)<sub>2</sub>BF<sub>4</sub>/Wudaphos  
H<sub>2</sub>(1 bar), 6 h, rt



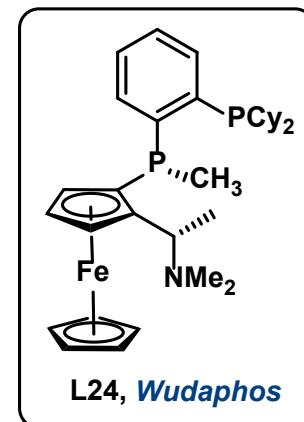
No reaction!



Rh(NBD)<sub>2</sub>BF<sub>4</sub>/Wudaphos  
H<sub>2</sub>(1 bar), 6 h, rt  
Base



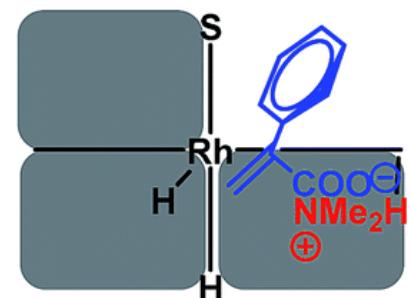
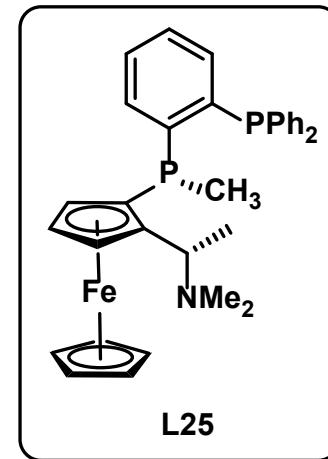
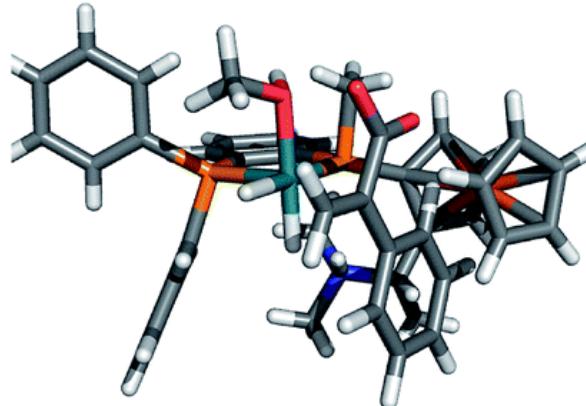
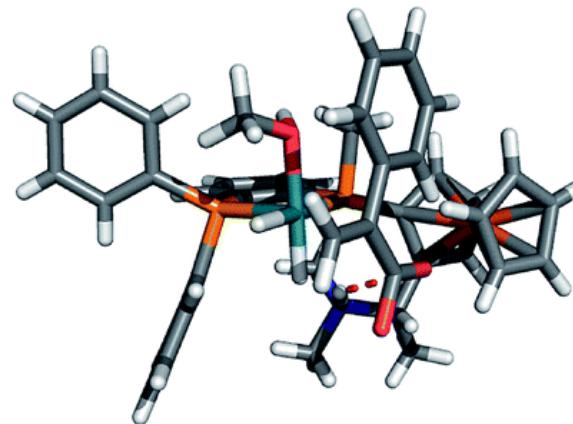
Cs<sub>2</sub>CO<sub>3</sub> (0.5 equiv.): Conv.% > 99, ee% = 79  
NEt<sub>3</sub> (1.0 equiv.): Conv.% = 91, ee% = 0



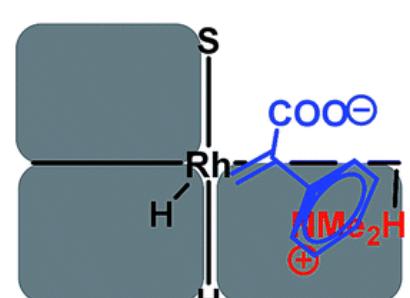
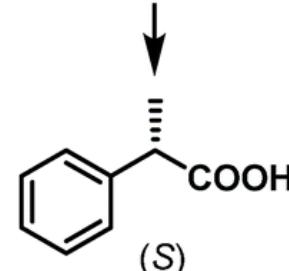


# Ion-Pairing Interactions—Wudaphos

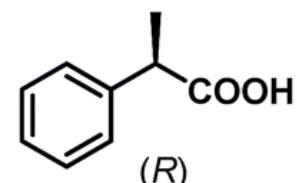
3D Models (L25):



Favored

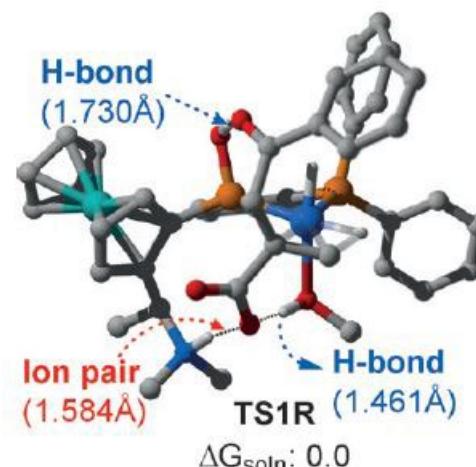
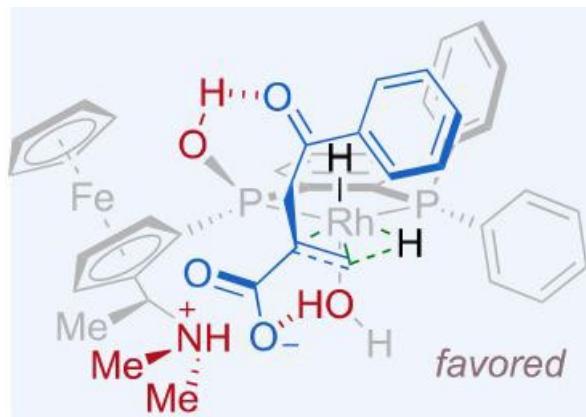
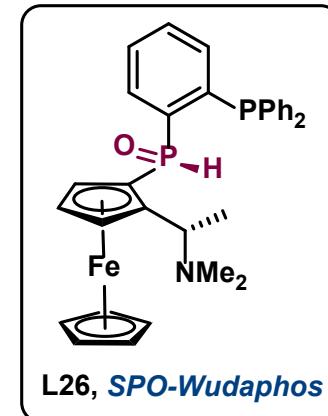
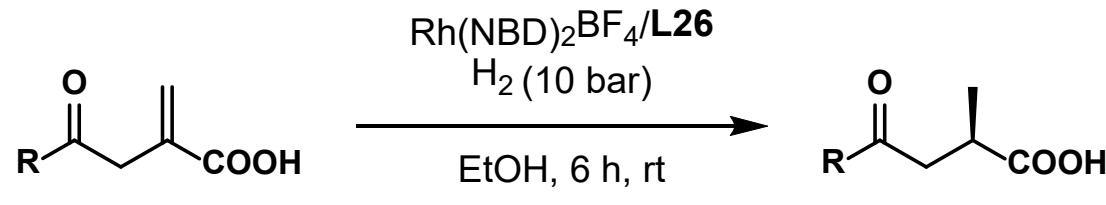


Disfavored

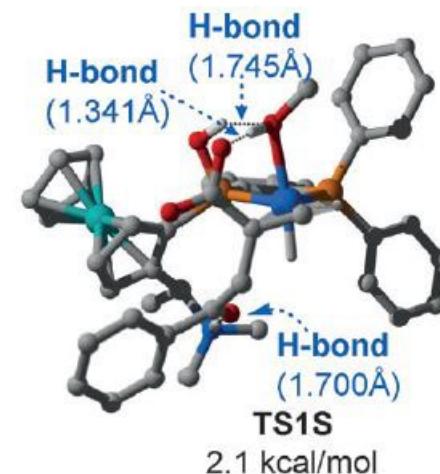




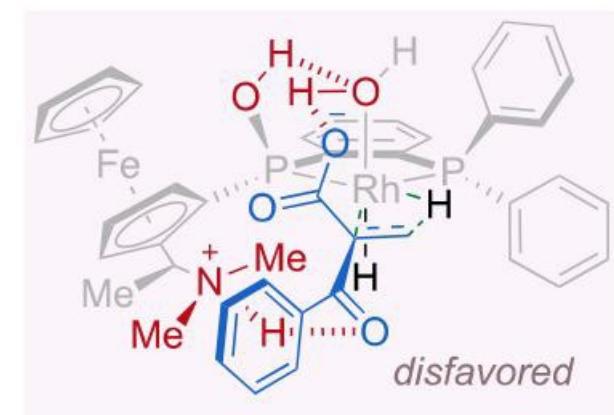
# Ion-Pairing Interactions—Wudaphos



**Ion pair**  
**2 H-bonds**  
**Favored**



**3 H-bonds**  
**(no Ion pair)**  
**Disfavored**

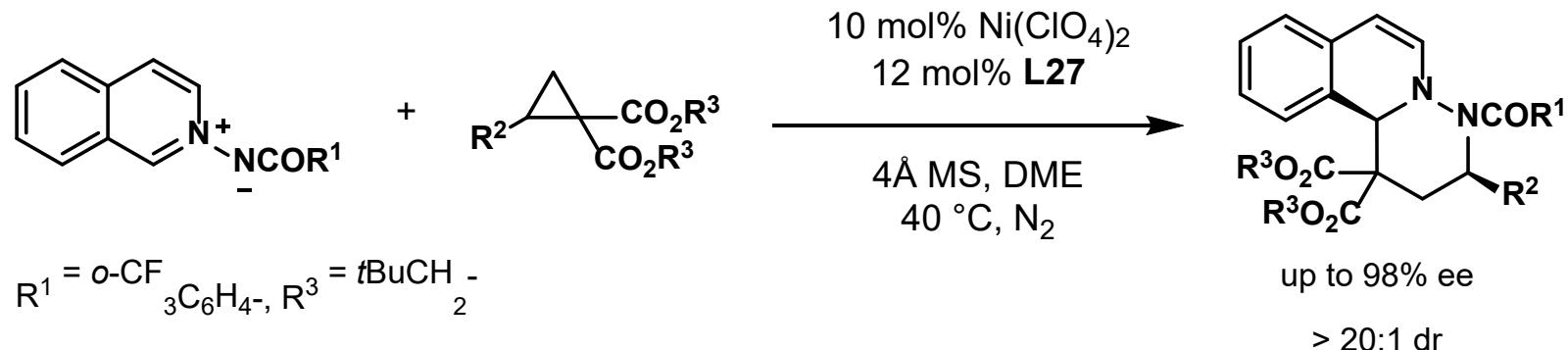


# PART 4

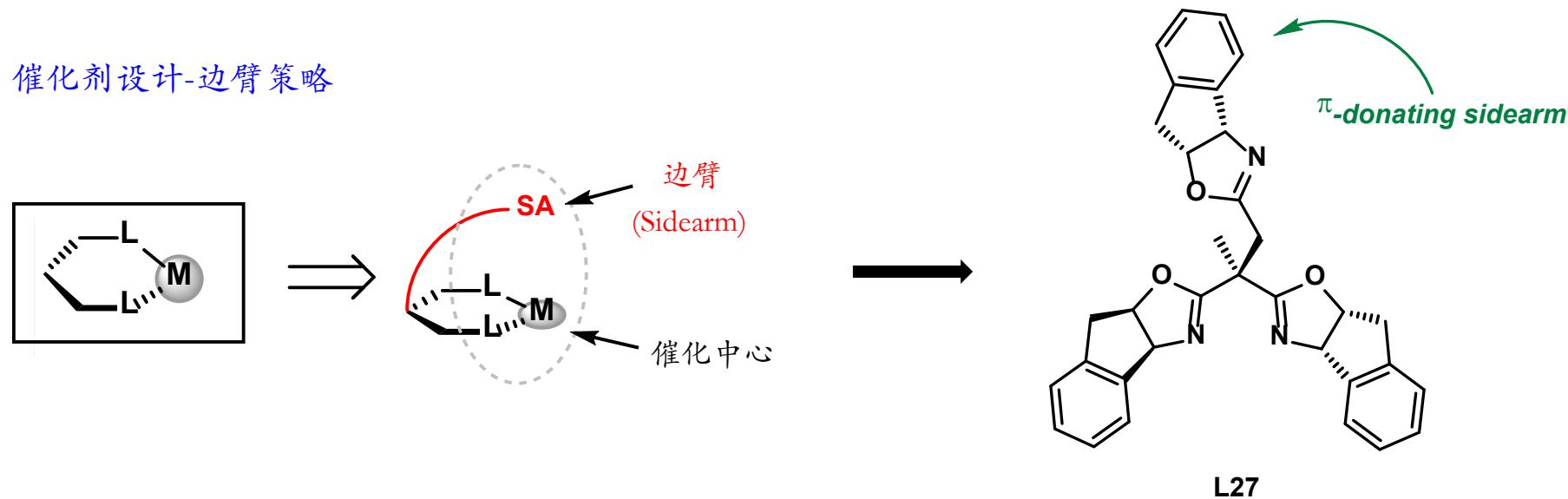
## $\pi-\pi$ Stacking Interactions



## $\pi-\pi$ Stacking Interactions—Sidearm Strategy



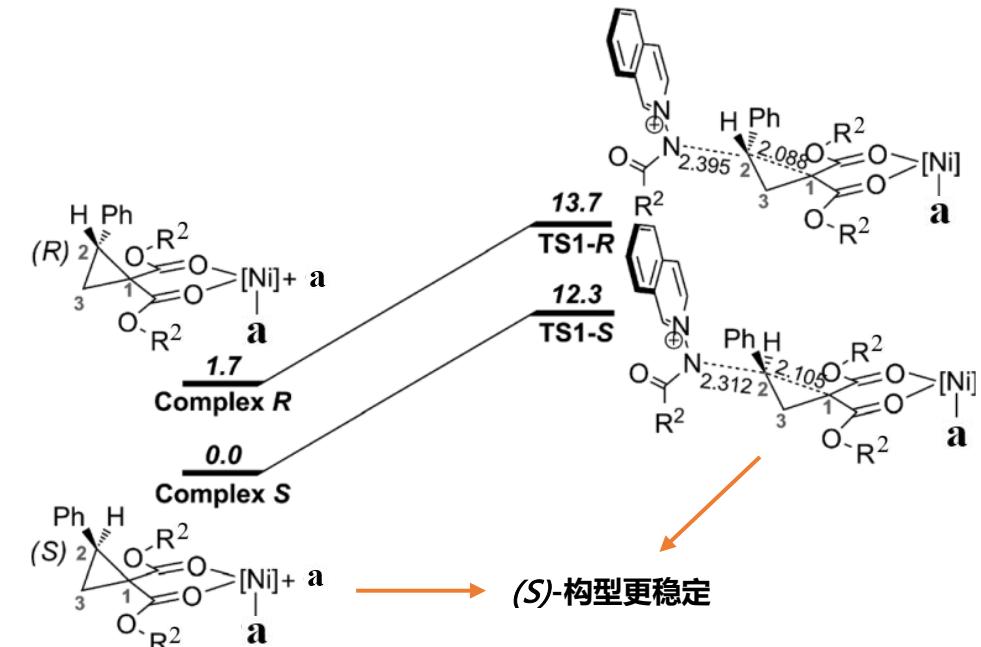
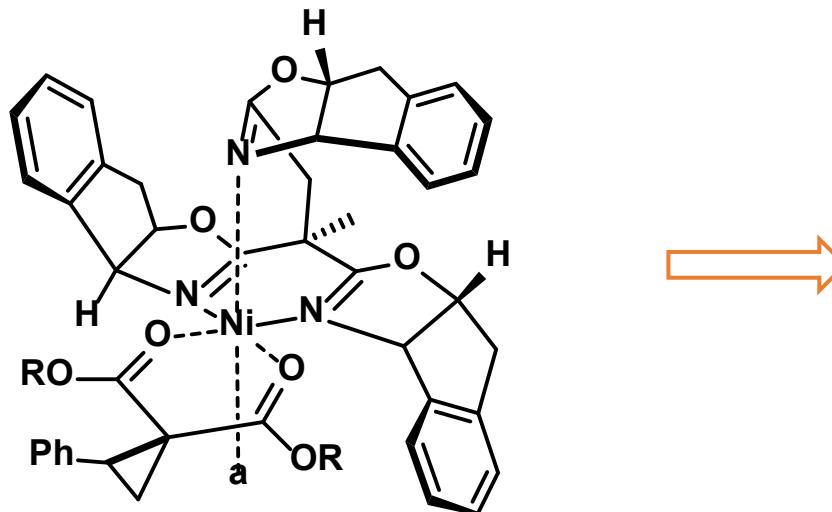
催化剂设计-边臂策略



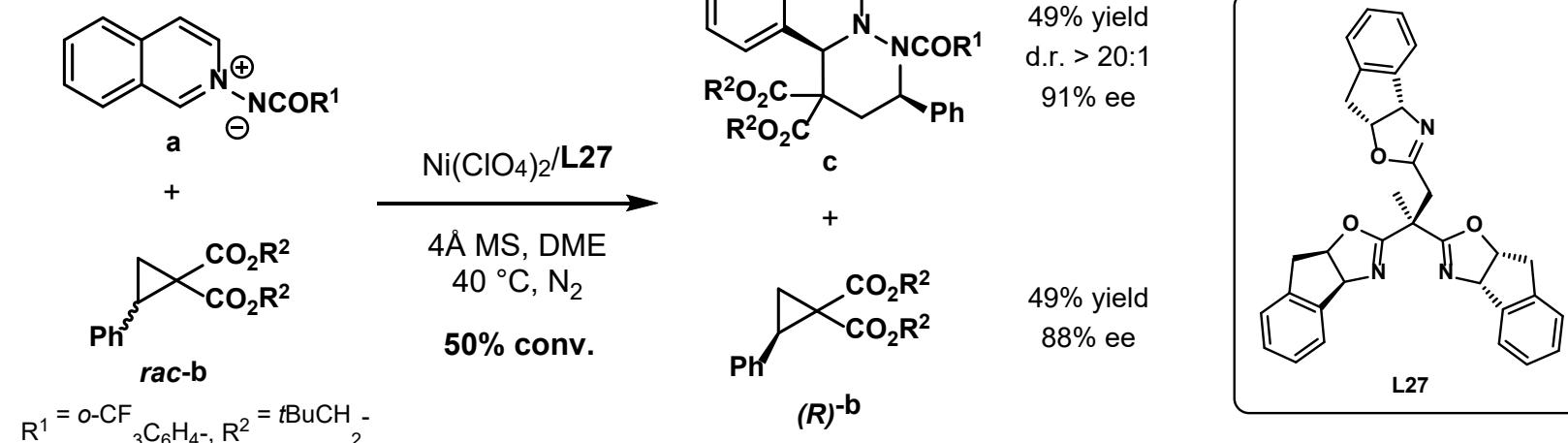


# $\pi-\pi$ Stacking Interactions—Sidearm Strategy

The Coordination Model (DFT):

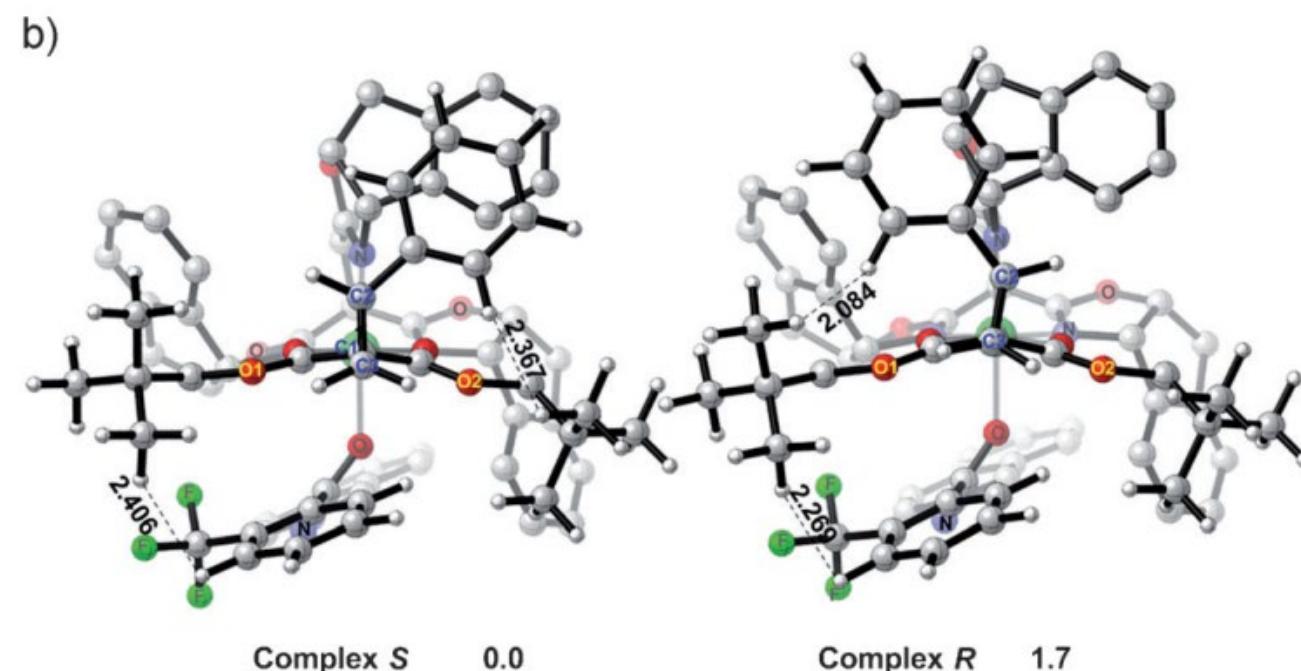
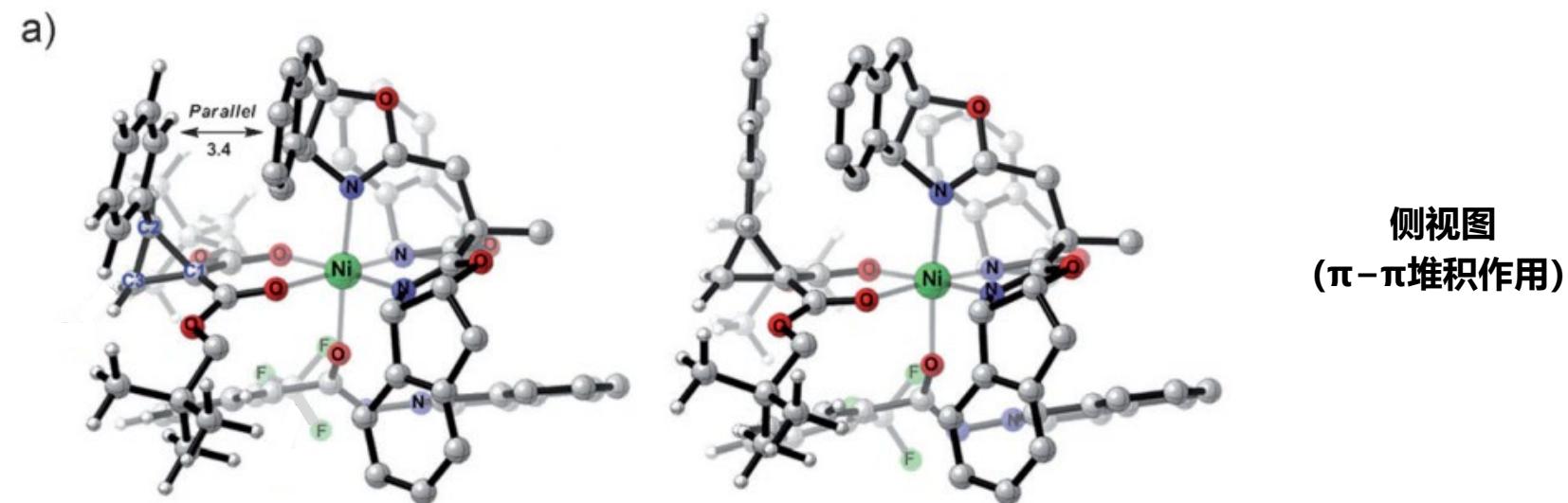
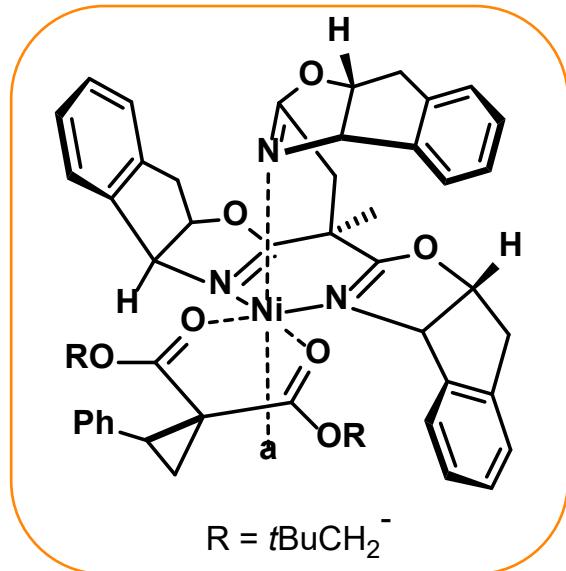


Kinetic Resolution Experiments:





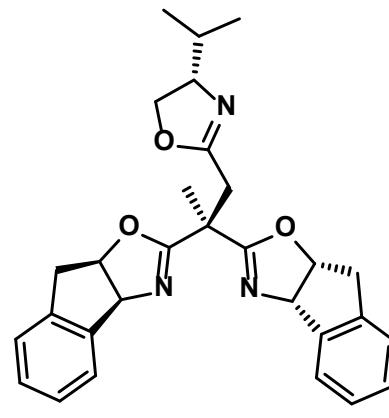
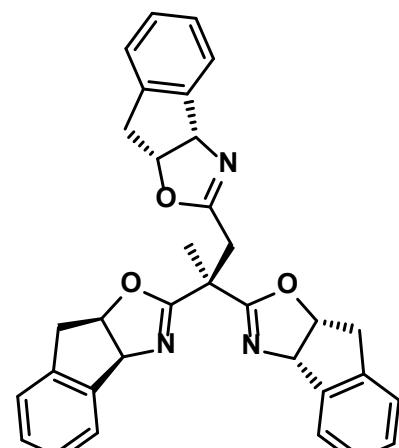
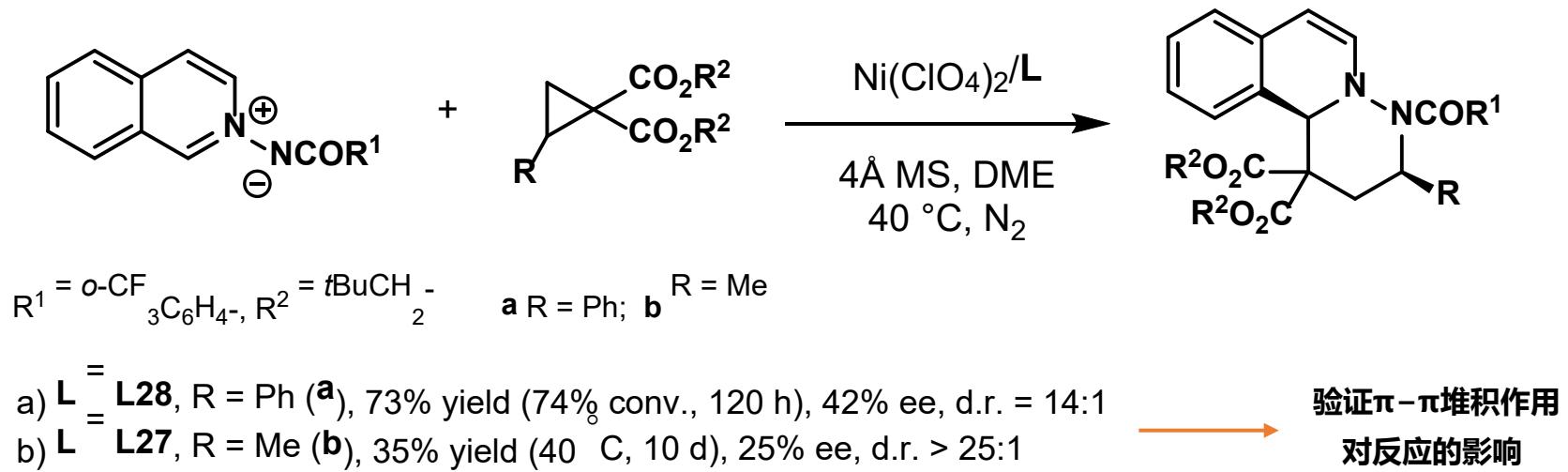
## $\pi$ - $\pi$ Stacking Interactions—Sidearm Strategy





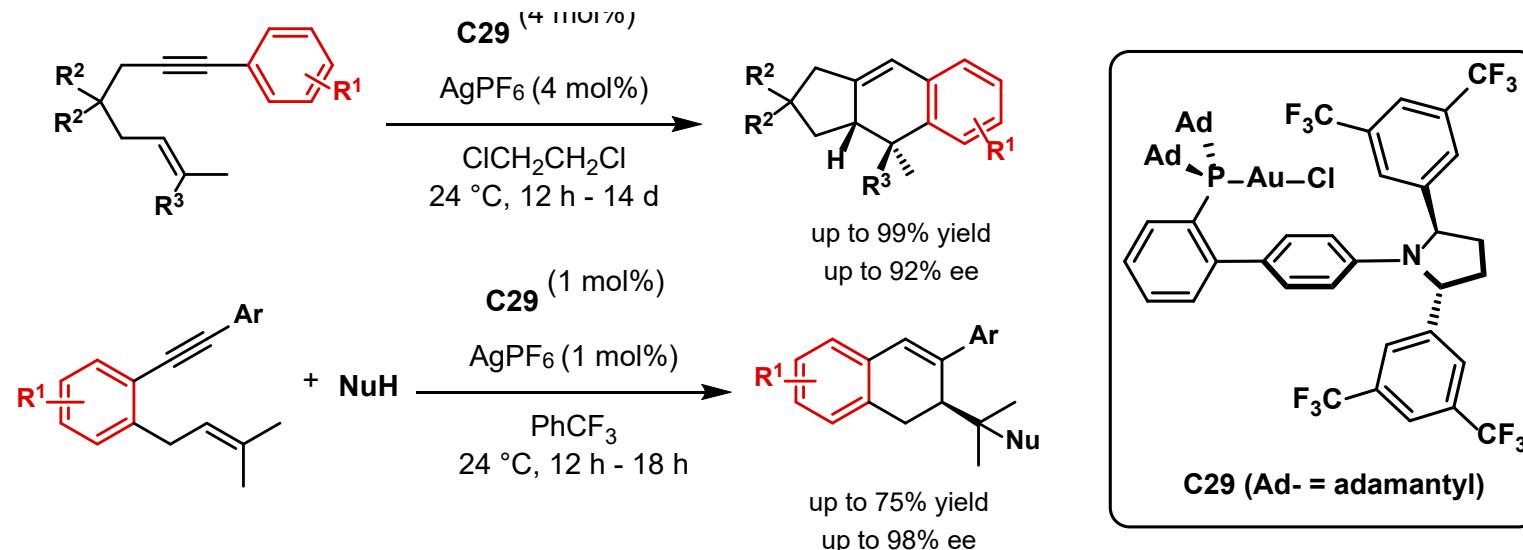
## $\pi$ - $\pi$ Stacking Interactions—Sidearm Strategy

Control Experiments:

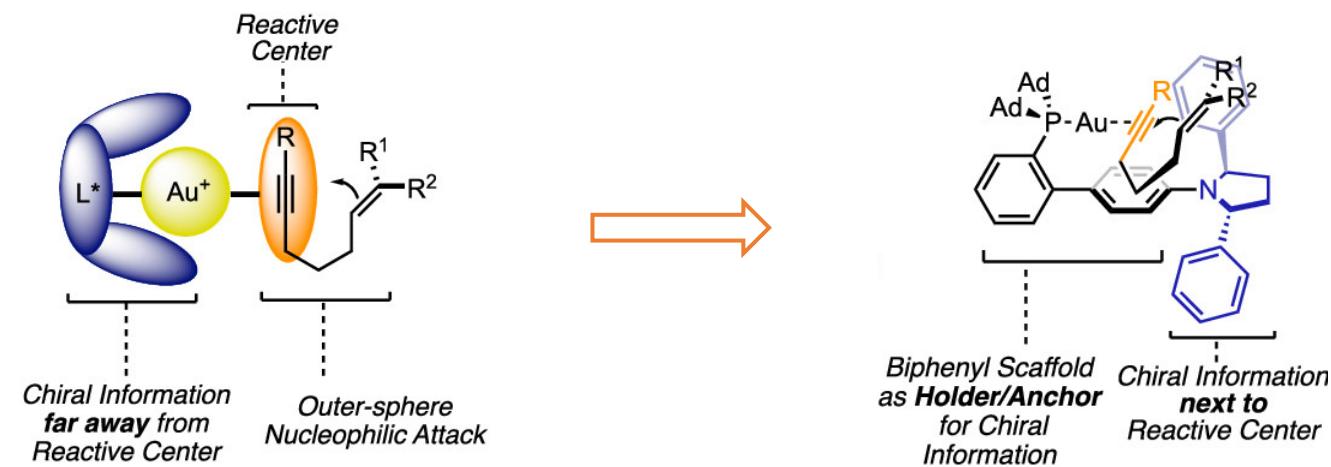




# $\pi$ - $\pi$ Stacking Interactions—Enyne Cyclization

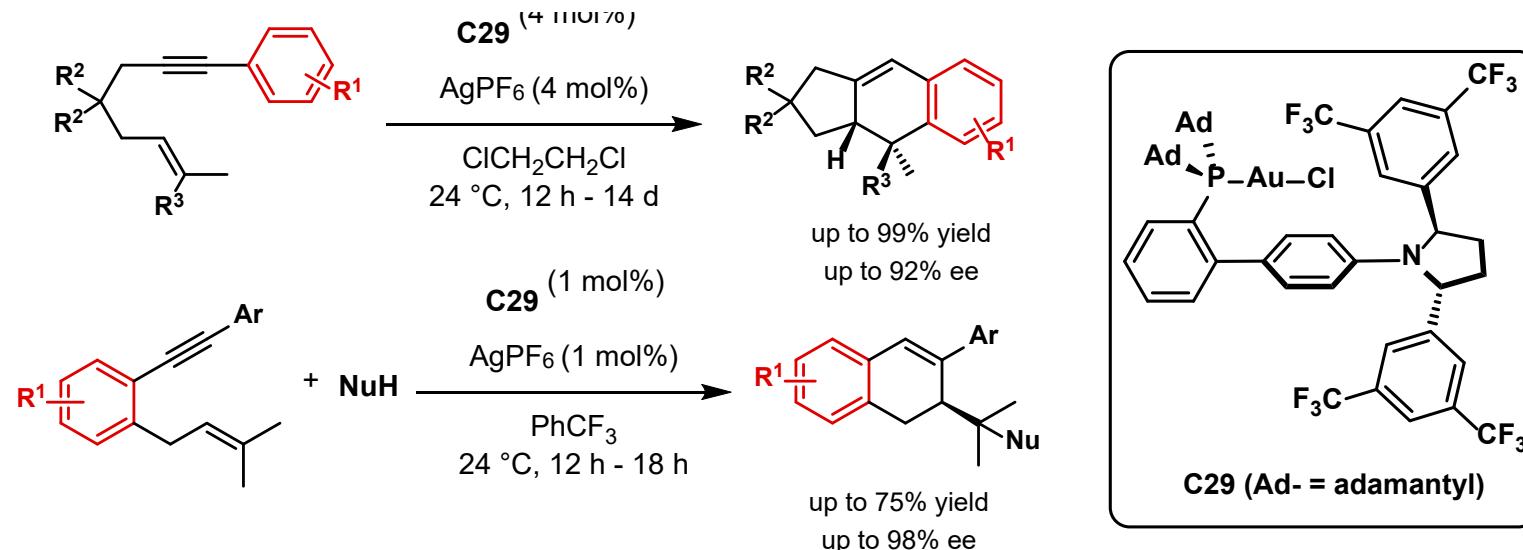


Design of Catalysts:

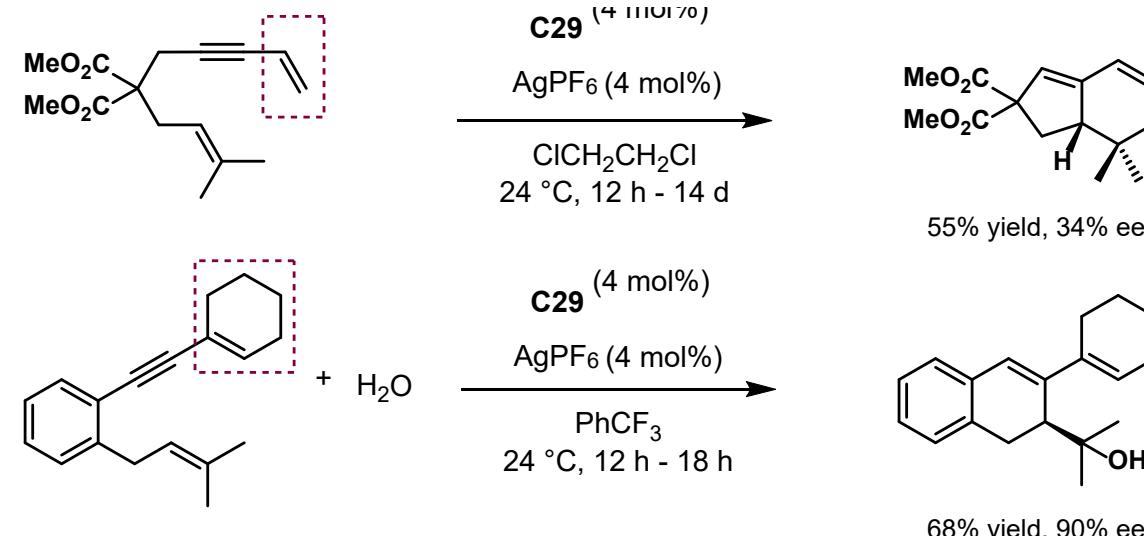




# $\pi$ - $\pi$ Stacking Interactions—Enyne Cyclization



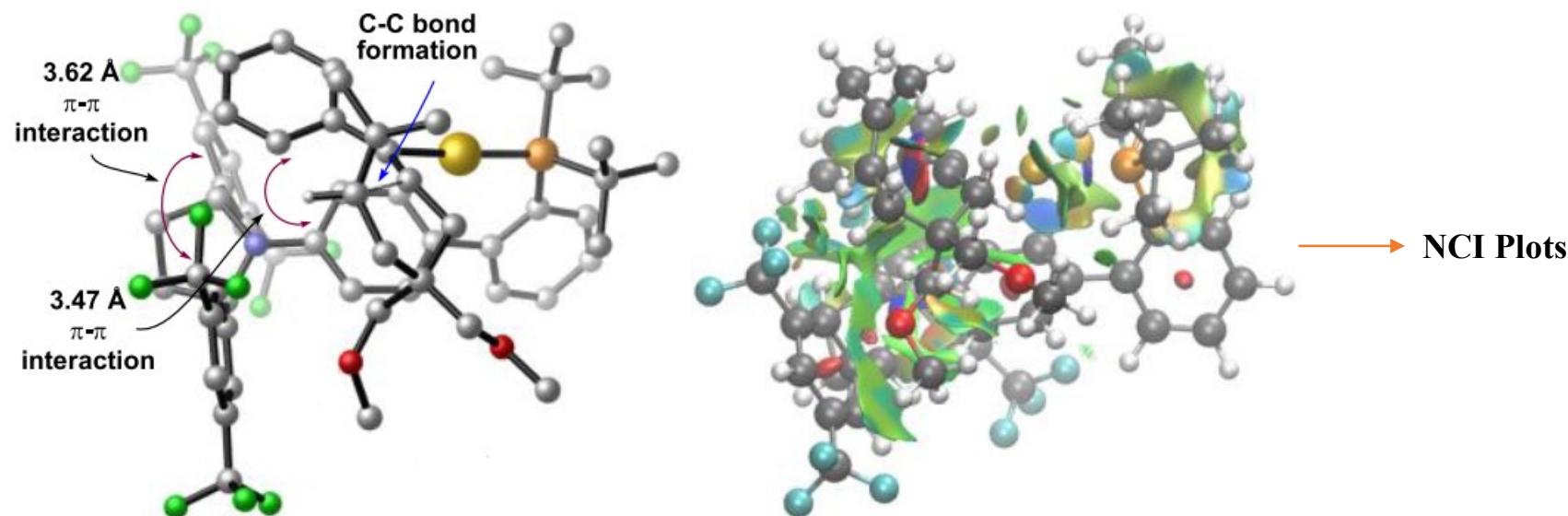
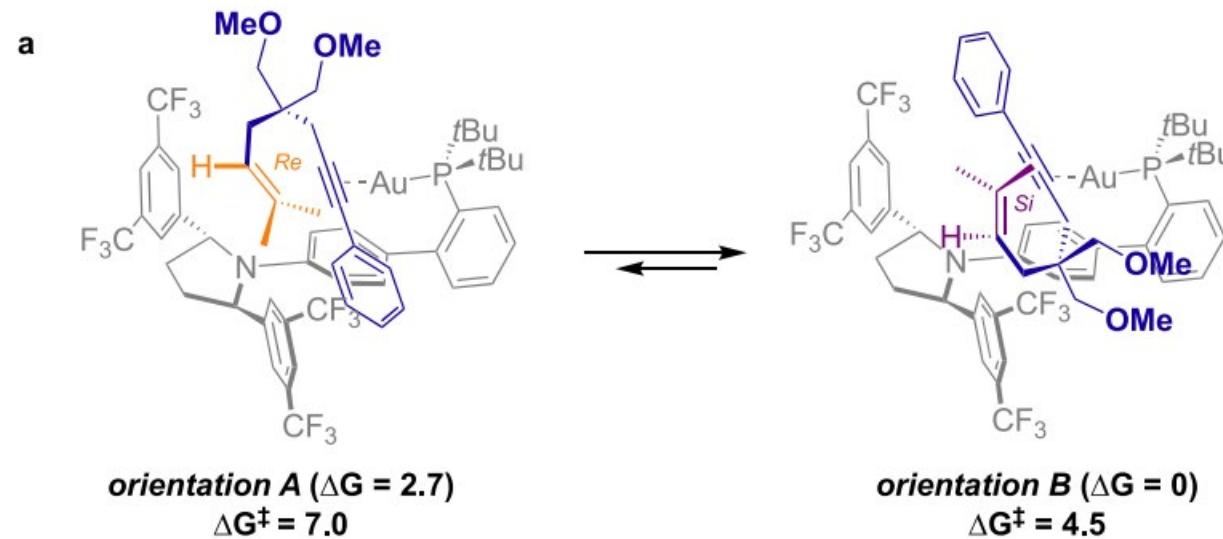
Control Experiments:





# $\pi$ - $\pi$ Stacking Interactions—Enyne Cyclization

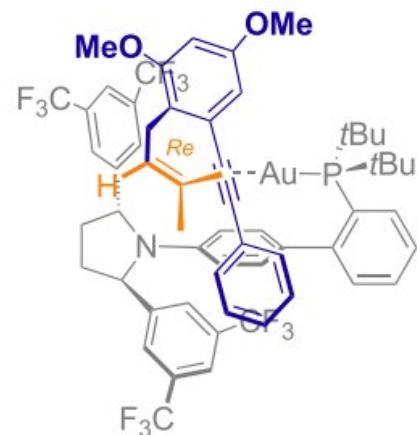
DFT Calculations:



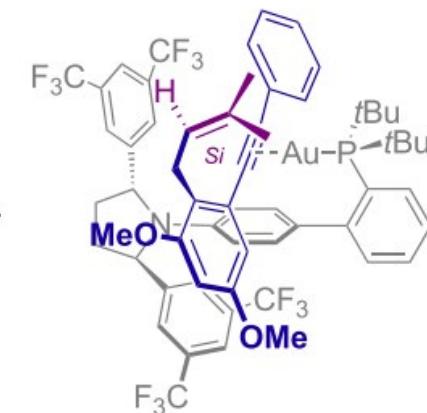
# $\pi-\pi$ Stacking Interactions—Enyne Cyclization

DFT Calculations:

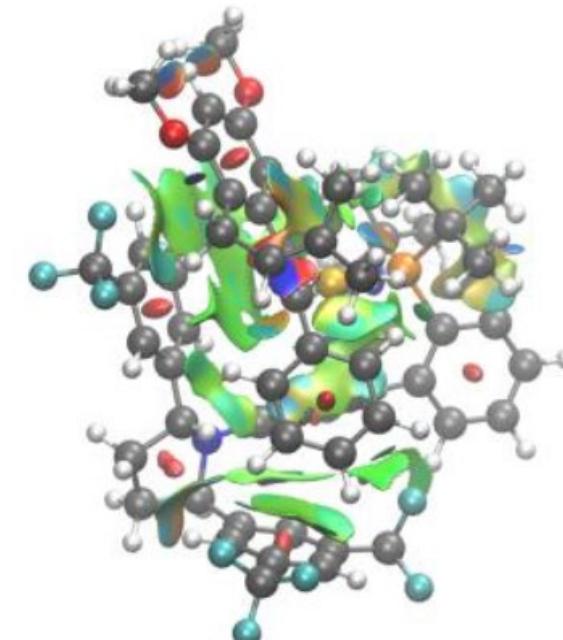
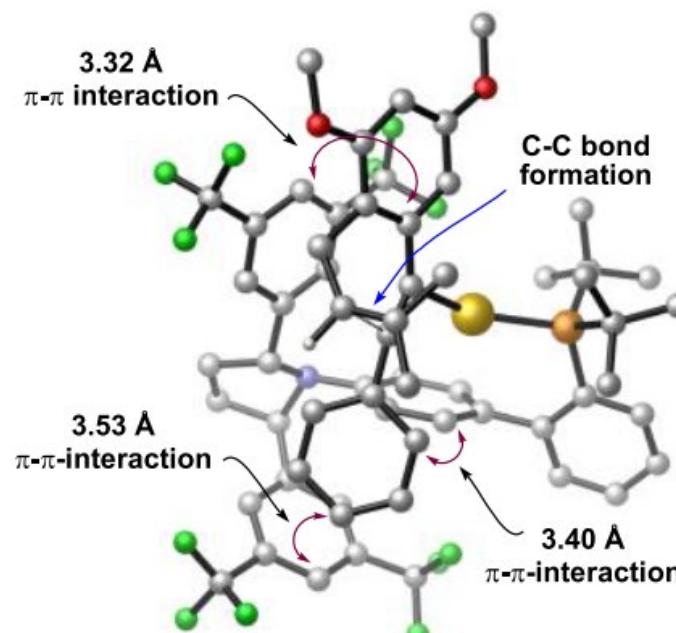
b



**orientation A ( $\Delta G = 0$ )  
 $\Delta G^\ddagger = 4.2$**



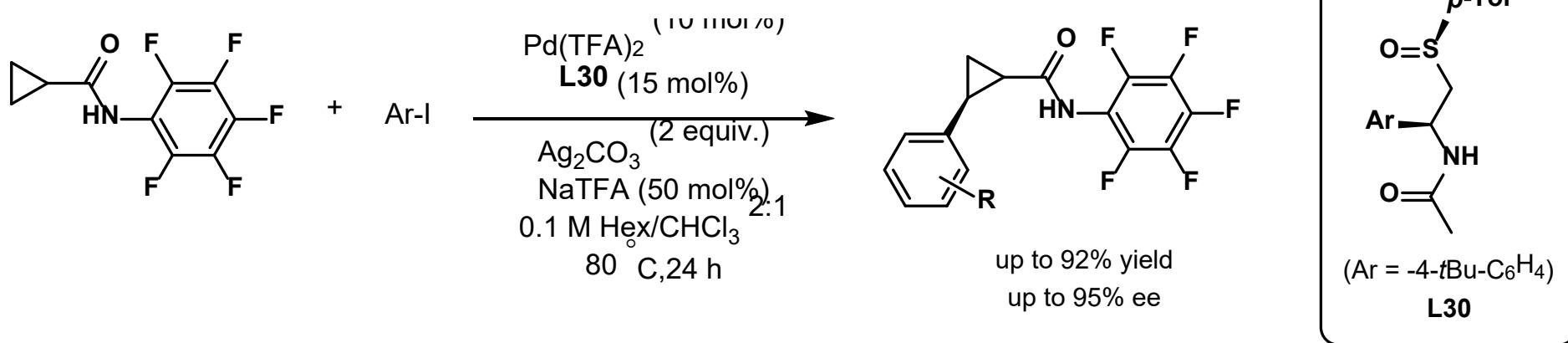
**orientation B ( $\Delta G = 4.4$ )  
 $\Delta G^\ddagger = 6.7$**



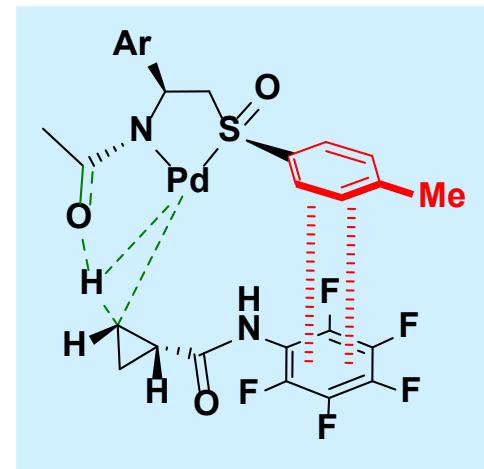
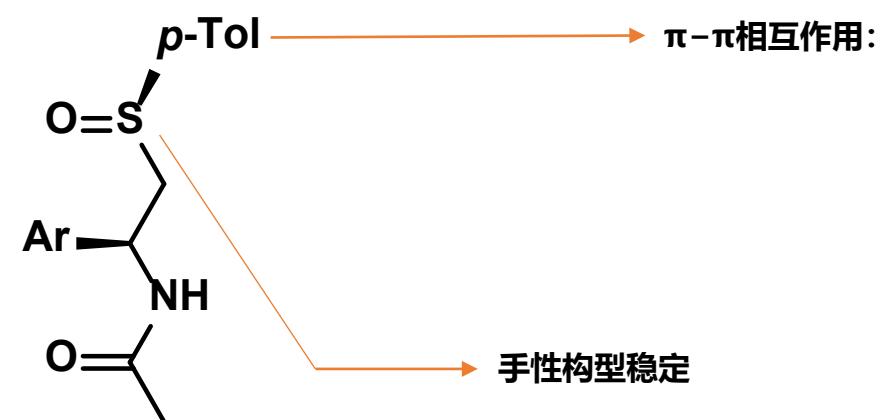
→ NCI Plots



## $\pi-\pi$ Stacking Interactions—Arene-Perfluoroarene



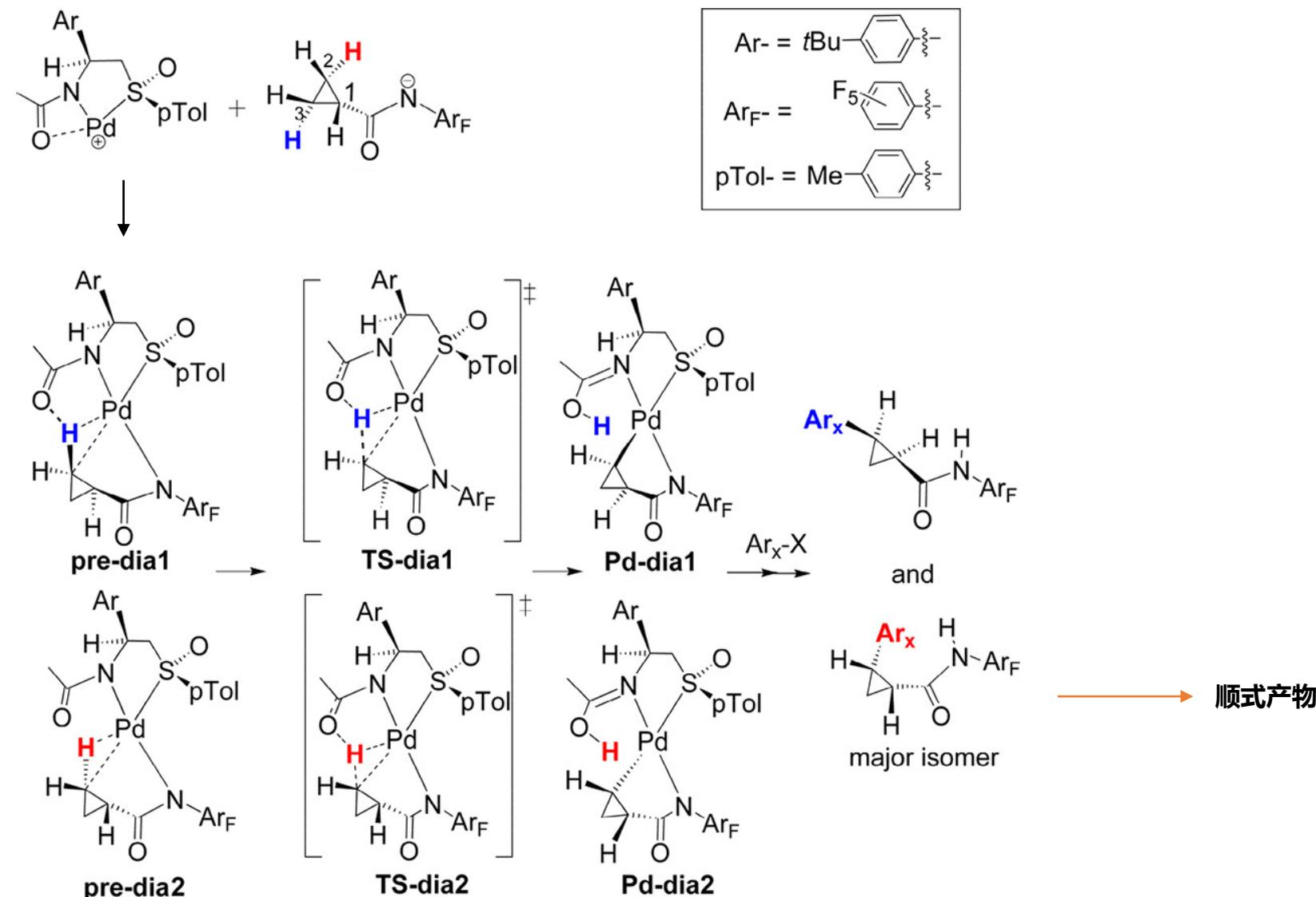
Design of Ligands:





# $\pi$ - $\pi$ Stacking Interactions—Arene-Perfluoroarene

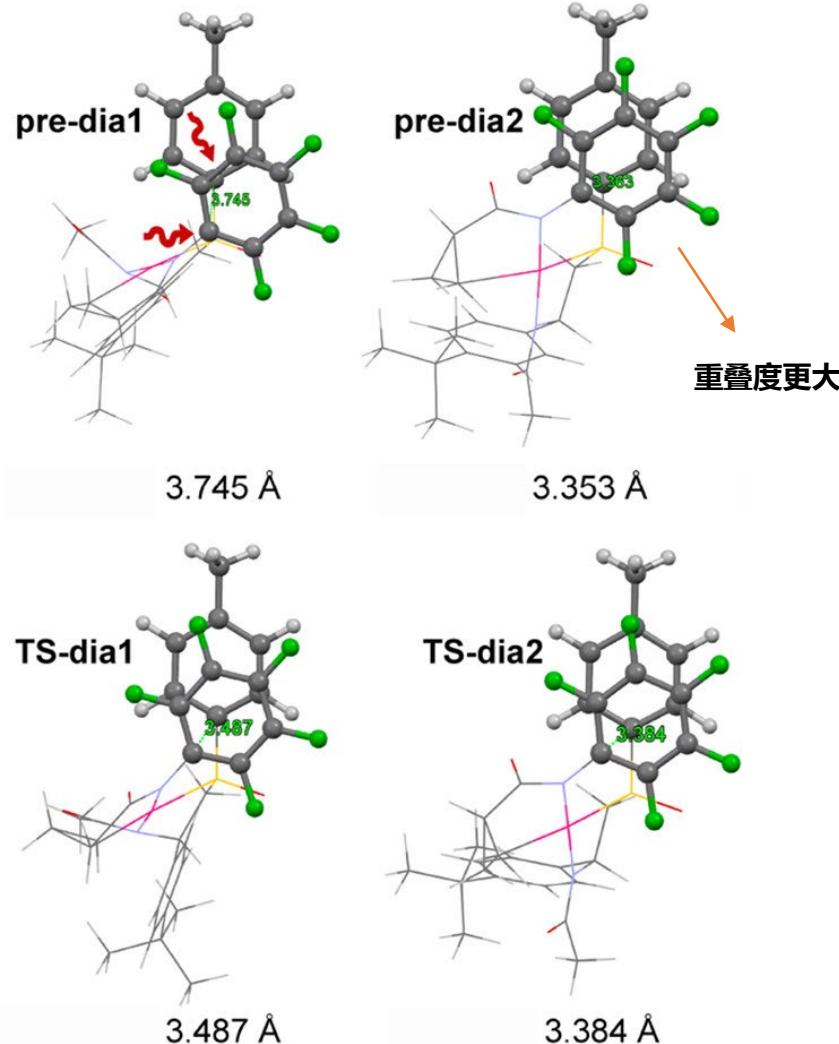
Proposed Mechanism:



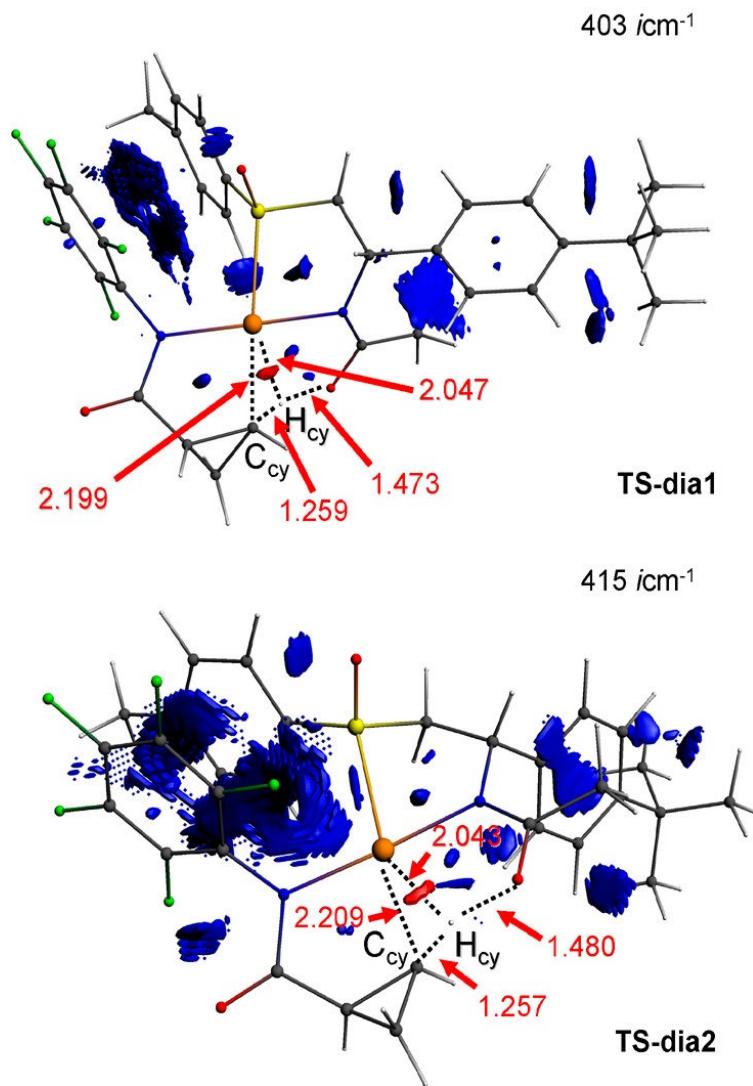


# $\pi$ - $\pi$ Stacking Interactions—Arene-Perfluoroarene

DFT Calculations:

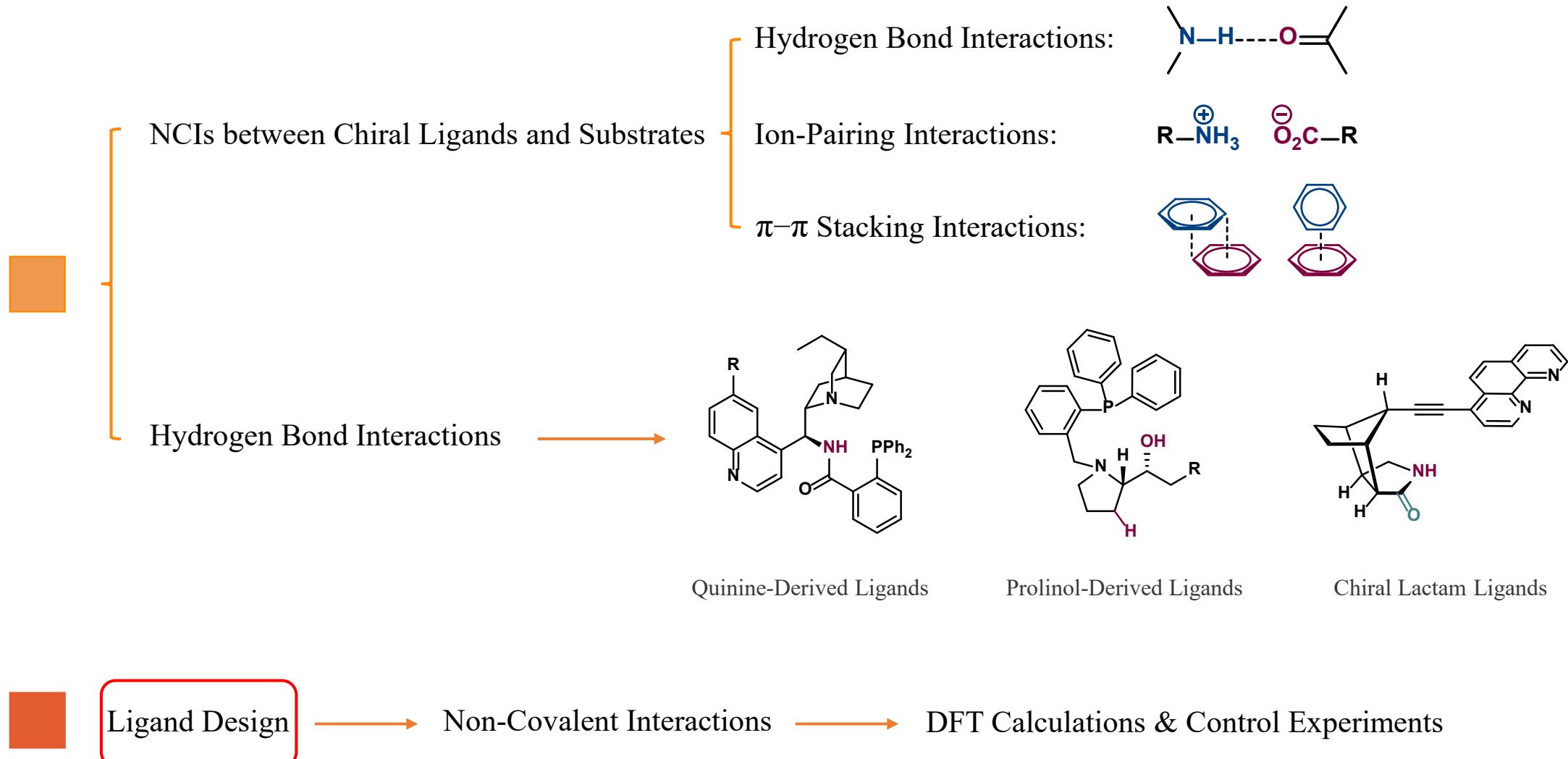


NCI Plots:





# Summary



THANKS

