

# Literature Report 4

## Ni-catalyzed asymmetric allylation of secondary phosphine oxides

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Reporter: Xiang Li

Checker: Zi-Biao Zhao

Date: 2019-11-11

Zhang, Q.-W. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 16584.

Kalnmals, C. A. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 14098.

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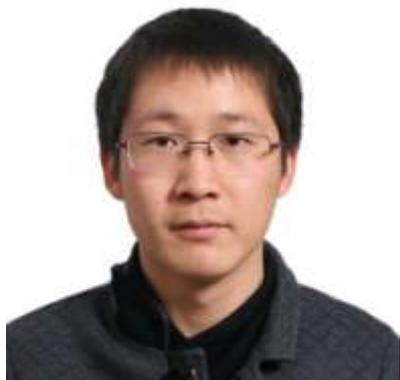
**4**

**Summary**

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# CV of Prof. Qing-Wei Zhang

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## Education:

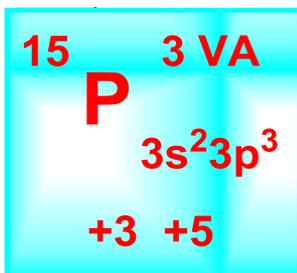
- ❑ **2003-2007** B.A., Lanzhou University
- ❑ **2007-2012** Ph.D., Lanzhou University
- ❑ **2012-2015** Postdoc, Tsinghua University
- ❑ **2015-2018** Postdoc, University of California, Berkeley
- ❑ **2018-Present** Professor, USTC

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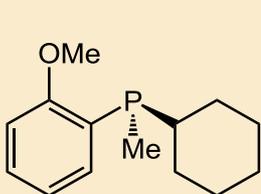
## Research:

- ❑ Transition-metal-catalysis asymmetric synthesis
- ❑ Chiral phosphine, silicon chemistry
- ❑ Mechanism research

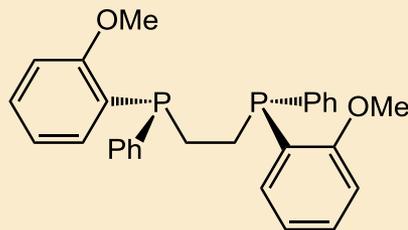
# Introduction



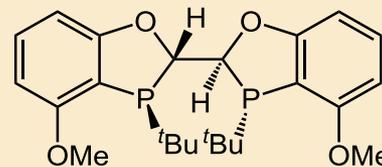
- Transition metal catalysis
- Organocatalysis



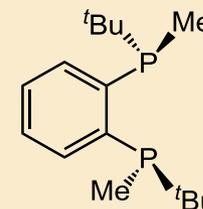
**(R)-CAMP**



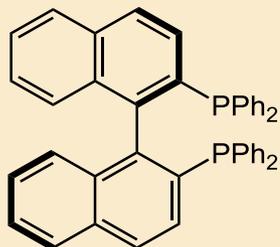
**(R,R)-DiPAMP**



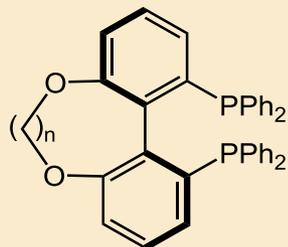
**(S,S,S,S)-MeO-BIBOP**



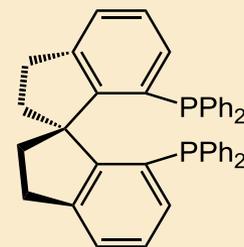
**(R,R)-BenzP\***



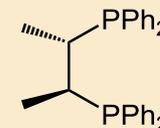
**(R)-BINAP**



**(S)-C<sub>n</sub>-TunaPhos**  
n = 1-6



**(S)-SPD**

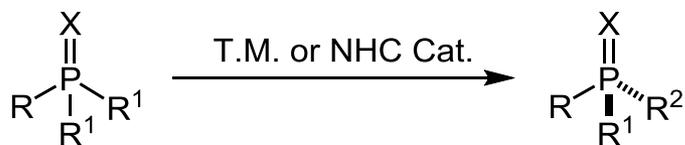


**(S,S)-CHIRAPHOS**

# Introduction

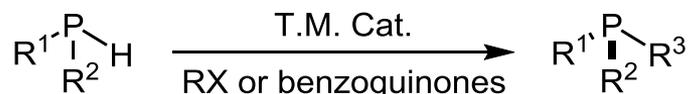
## Catalytic asymmetric synthesis of *P*-stereogenic phosphines

a) Inter/intra molecular **desymmetric** reactions



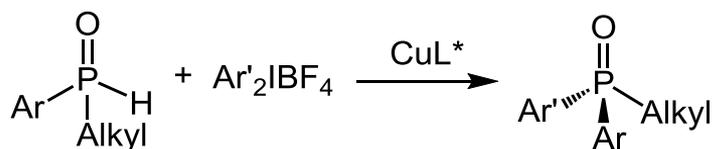
· 1,4-addition · [2+2+2] · C-H activation

b) **DKR** of secondary phosphines



· alkylation · arylation · 1,6-addition

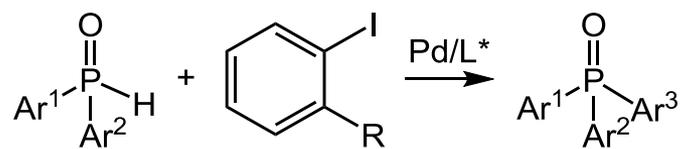
c) **Arylation** of secondary phosphines oxides



2 equiv

excellent ee

d) **KR** of secondary phosphines oxides

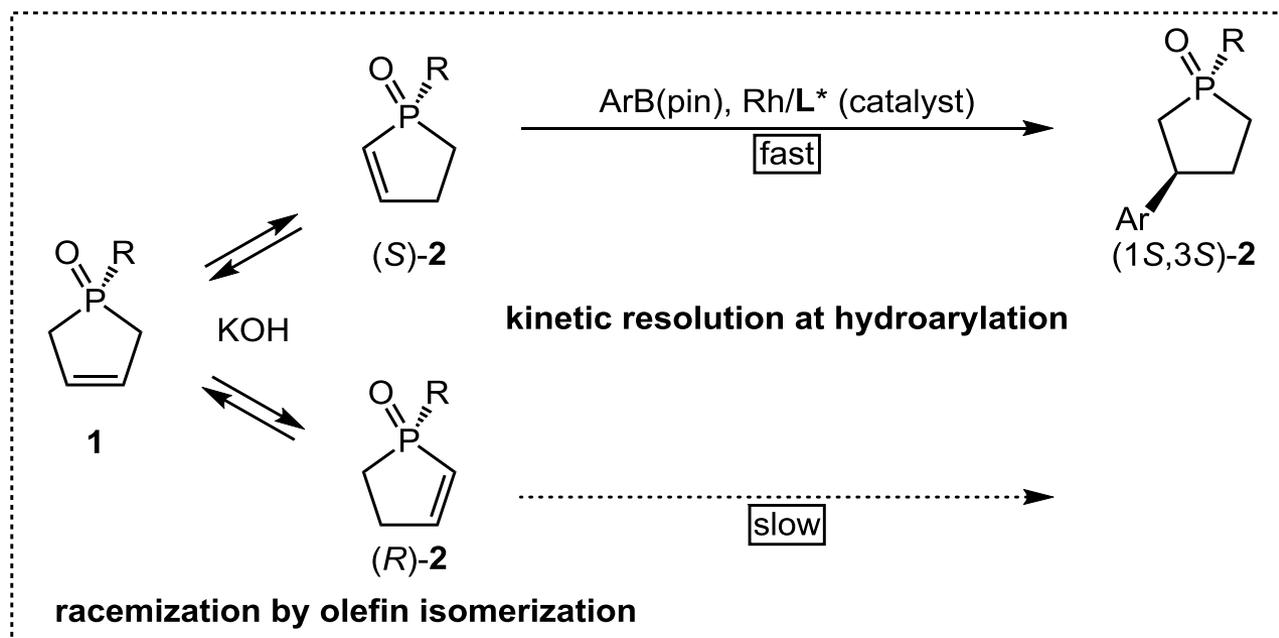
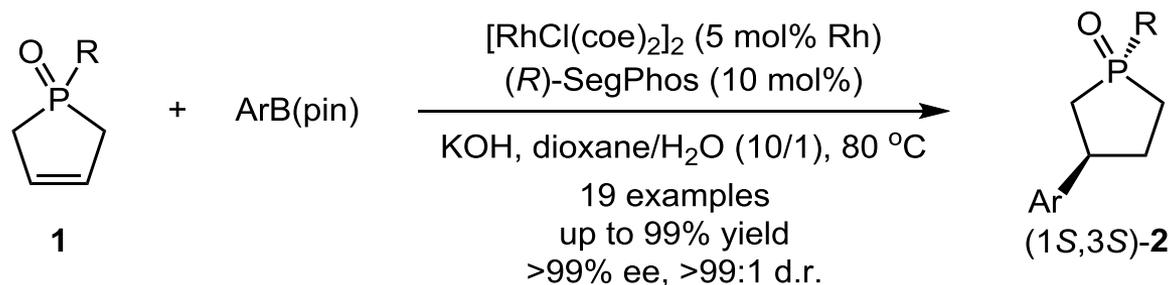


2 equiv

R = *t*BuCONH- moderate to high ee

# Inter/intra molecular **desymmetric** reactions

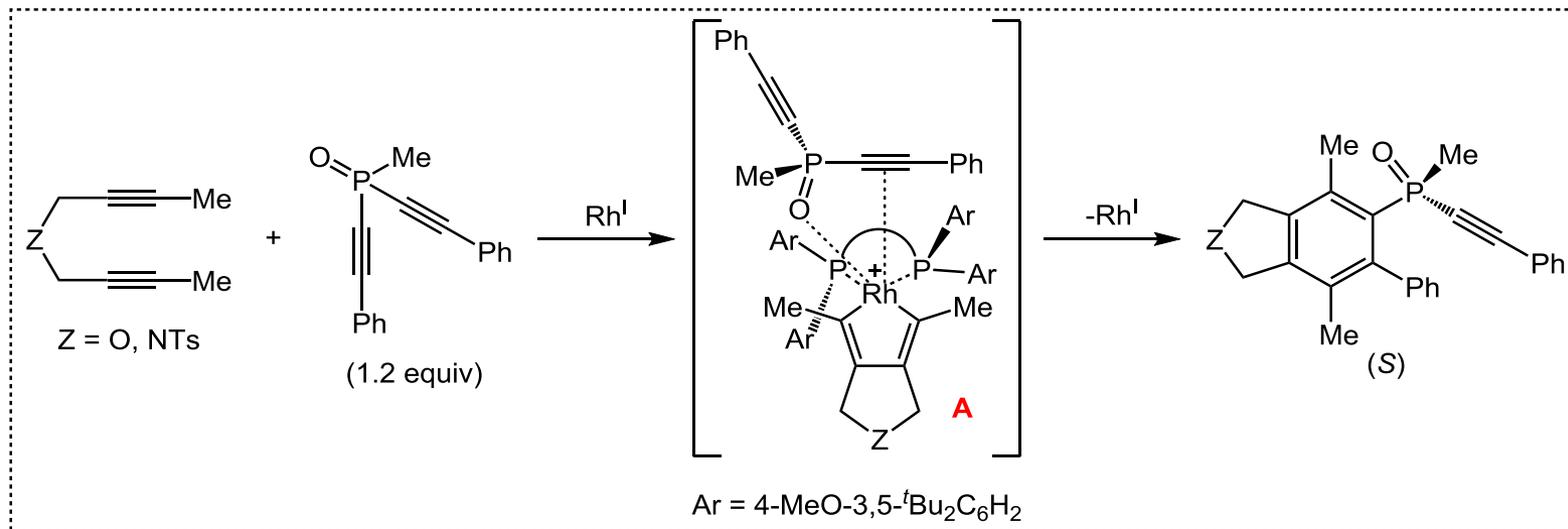
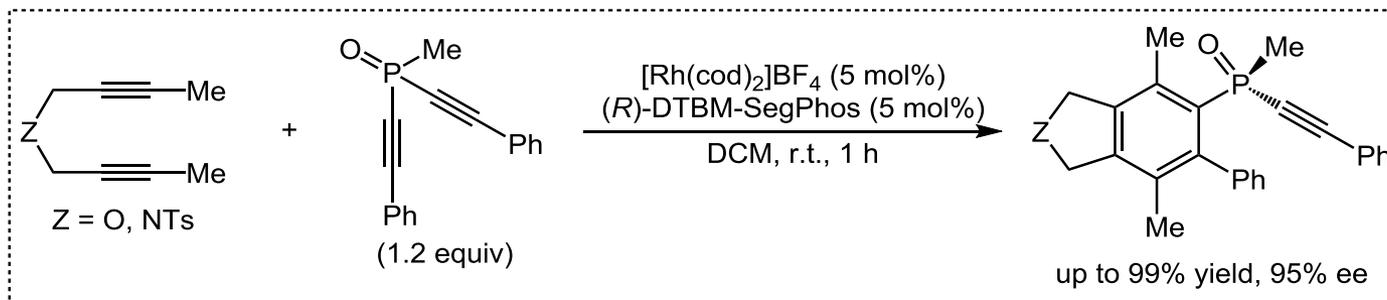
## 1,4- addition



Hayashi, T. *et al.* *J. Am. Chem. Soc.* **2017**, *139*, 8122.

# Inter/intra molecular **desymmetric** reactions

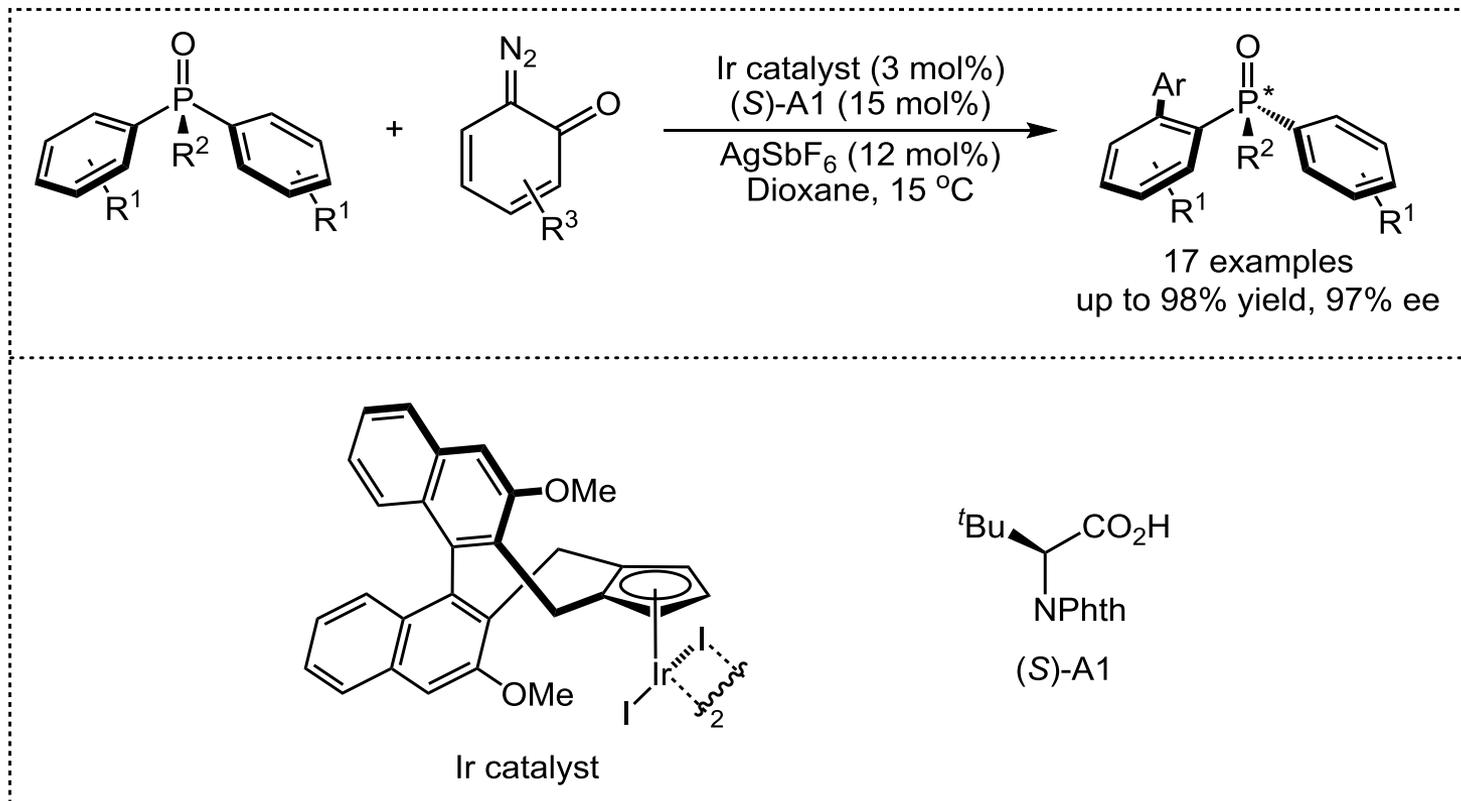
**[2+2+2]**



Tanaka, K. *et al.* *Angew. Chem. Int. Ed.* **2008**, *47*, 3410.

# Inter/intra molecular **desymmetric** reactions

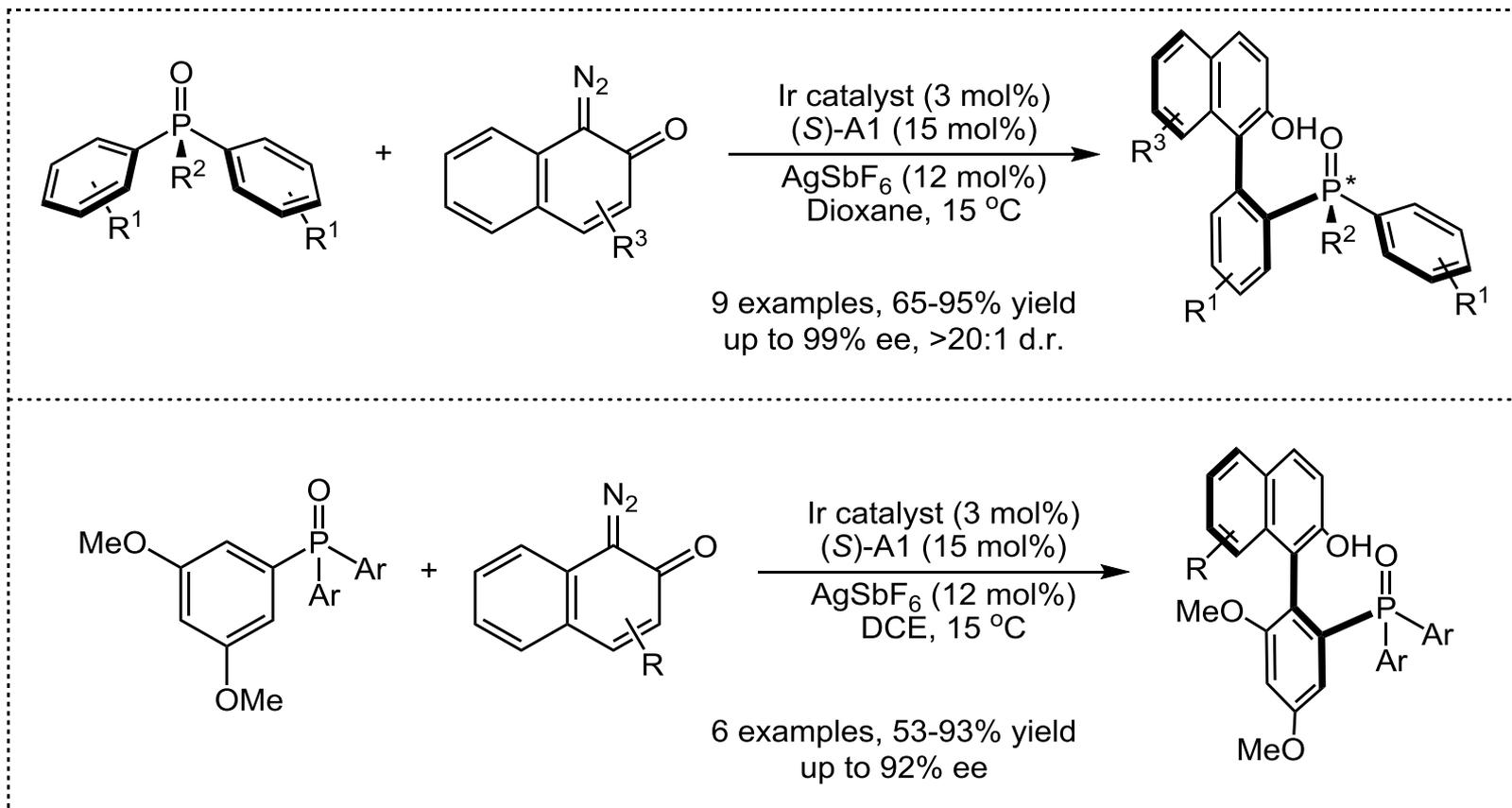
## C-H activation



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12901.

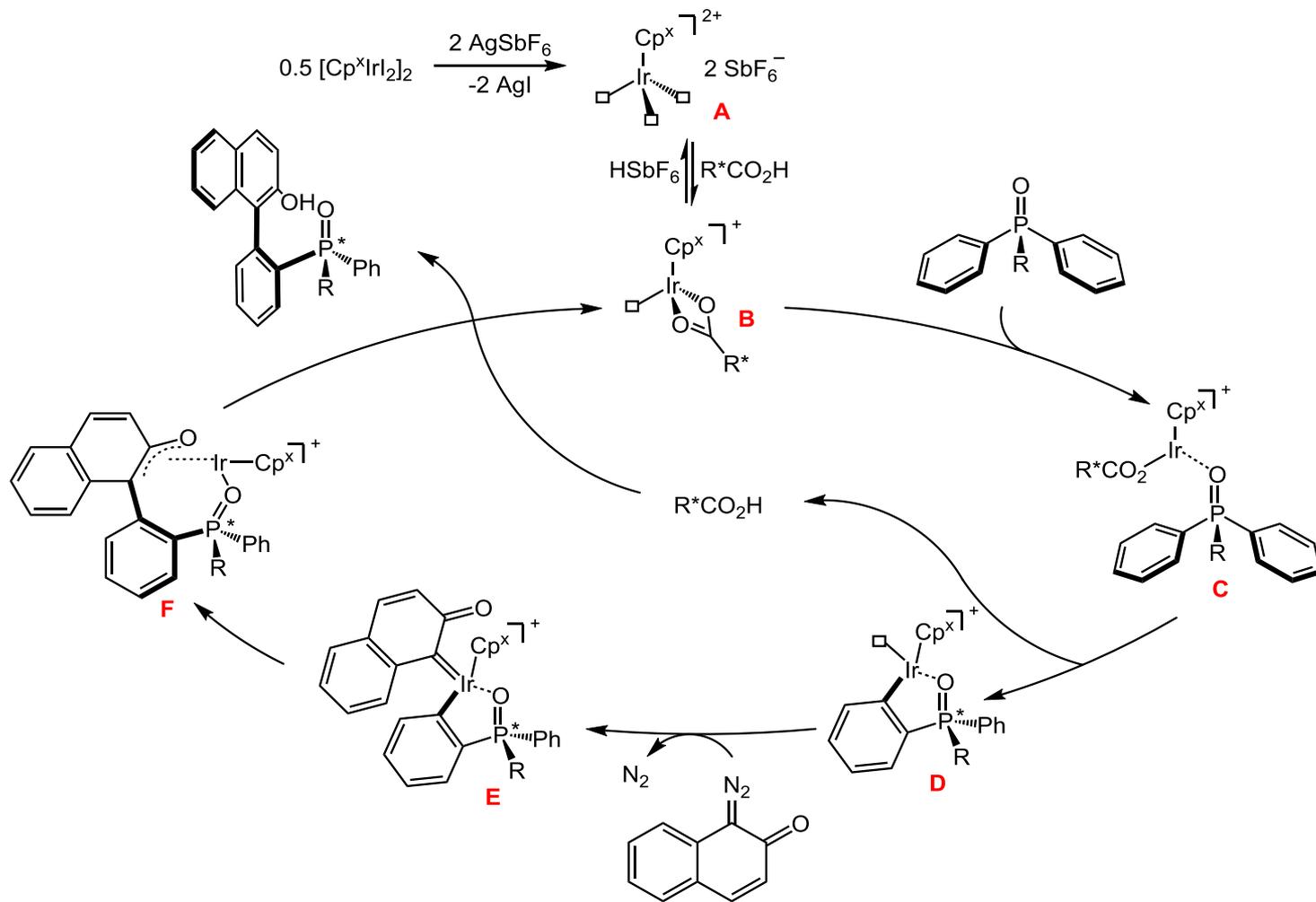
# Inter/intra molecular **desymmetric** reactions

## C-H activation



Cramer, N. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12901.

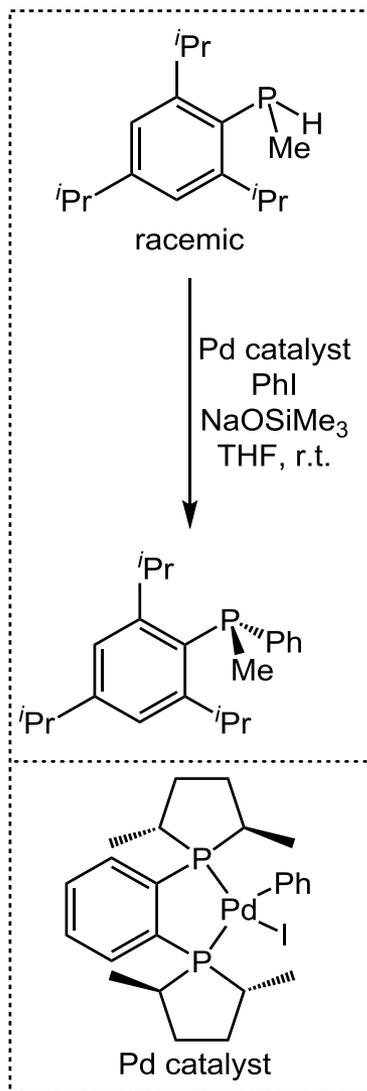
# Inter/intra molecular **desymmetric** reactions



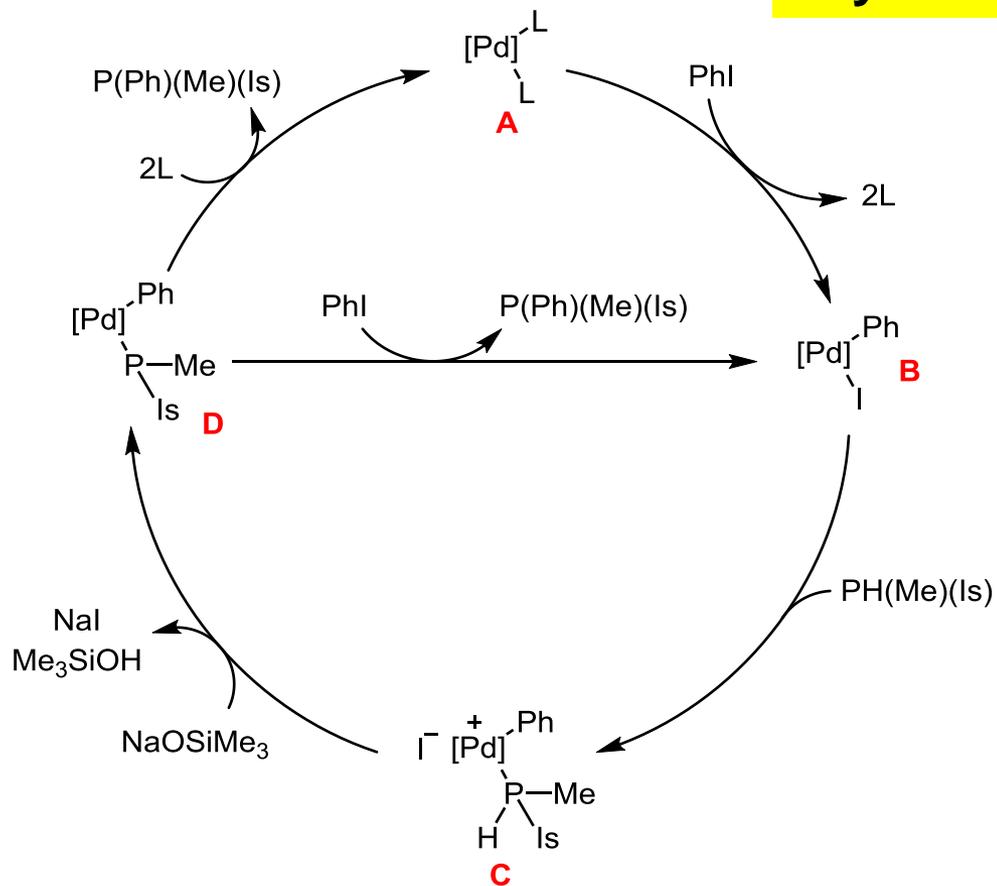
Cramer, N. *et al.* *Angew. Chem. Int. Ed.* **2018**, *57*, 12091.



# DKR of secondary phosphines



## Arylation

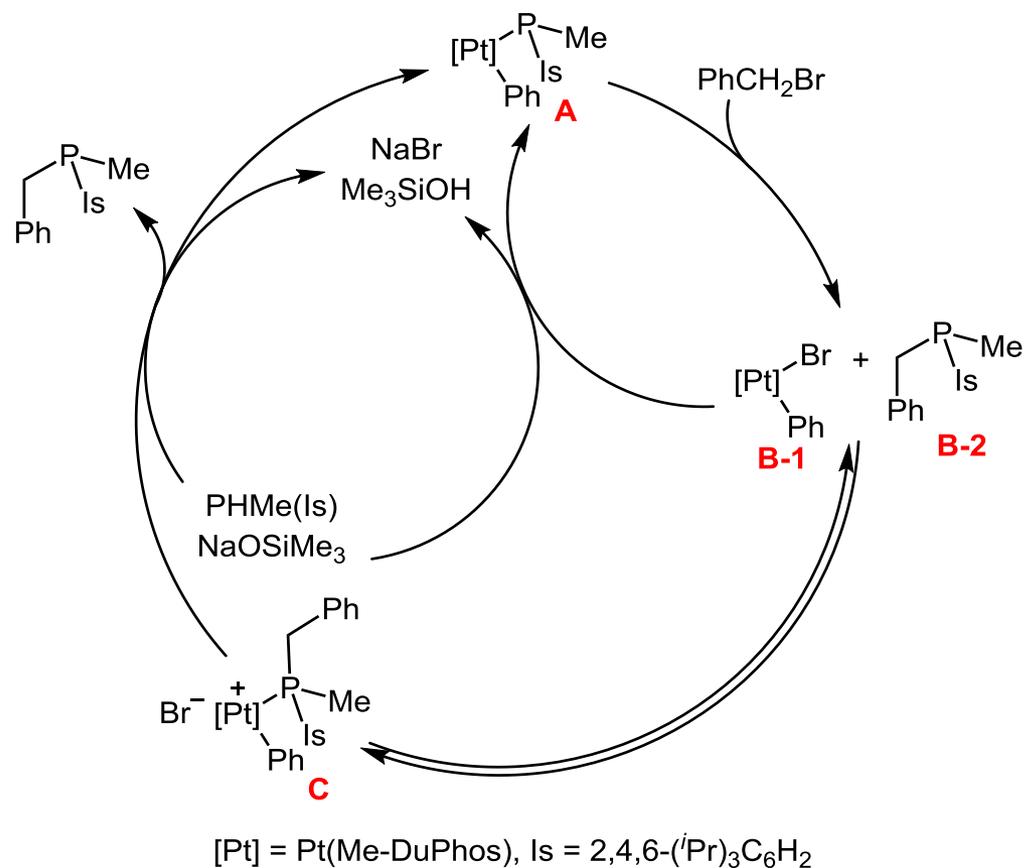
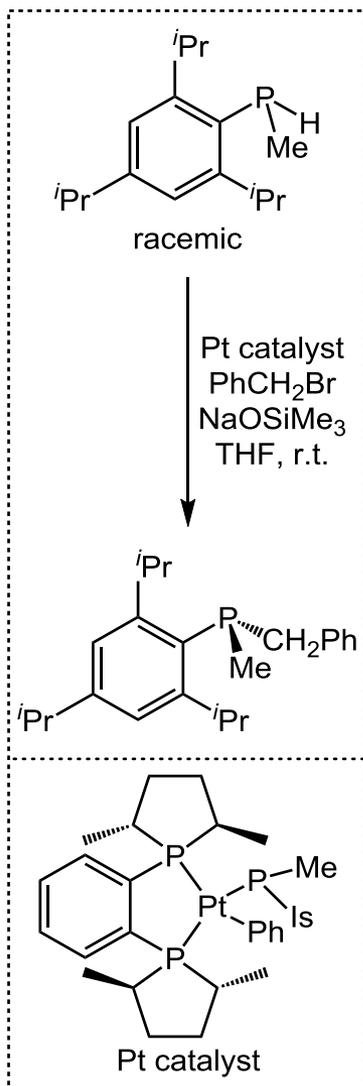


[Pd] = Pd((*R,R*)-Me-DuPhos), Is = 2,4,6-(*i*-Pr)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, L = PH(Me)(Is)

Glueck, D. S. *et al. J. Am. Chem. Soc.* **2002**, *124*, 13356.

# DKR of secondary phosphines

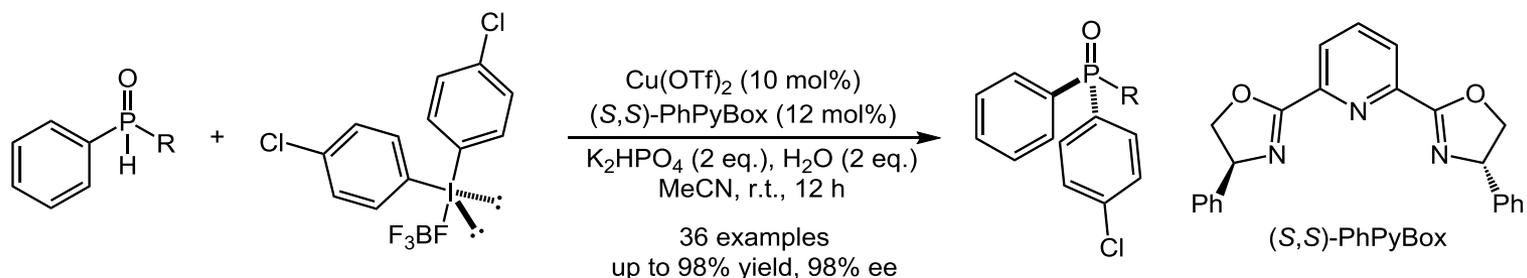
## Alkylation



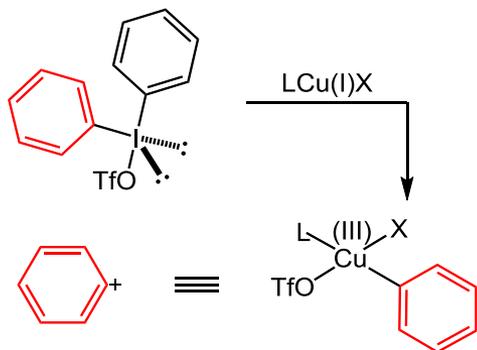
Glueck, D. S. *et al.* *J. Am. Chem. Soc.* **2006**, 128, 2788.



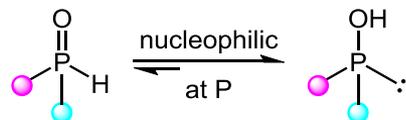
# Arylation of secondary phosphines oxides



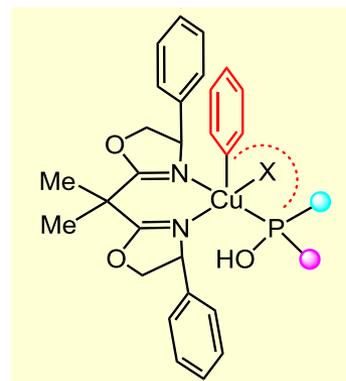
## a) Activation of diaryliodonium salts with copper catalysts



## (b) 2'-Phosphine oxide (SPO) to phosphinous acid tautomerization

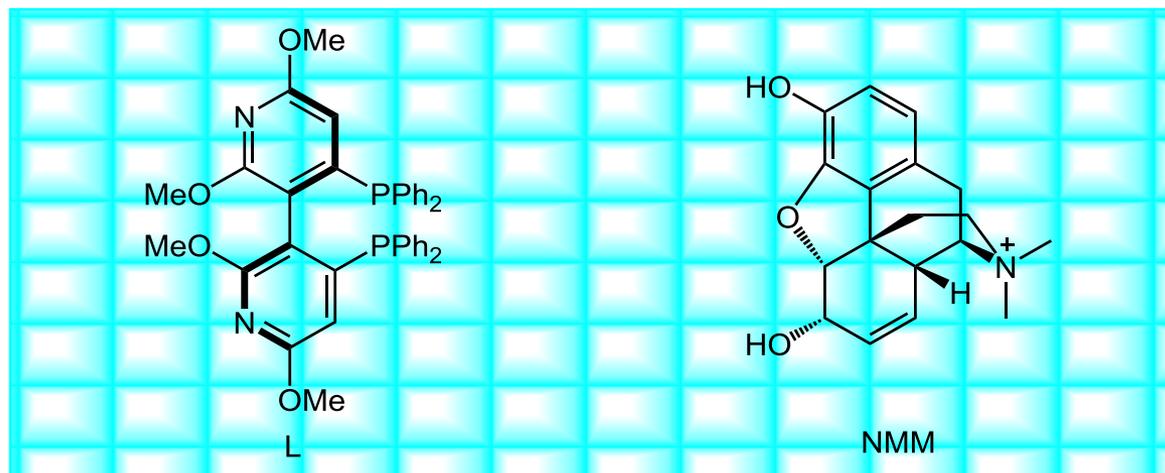
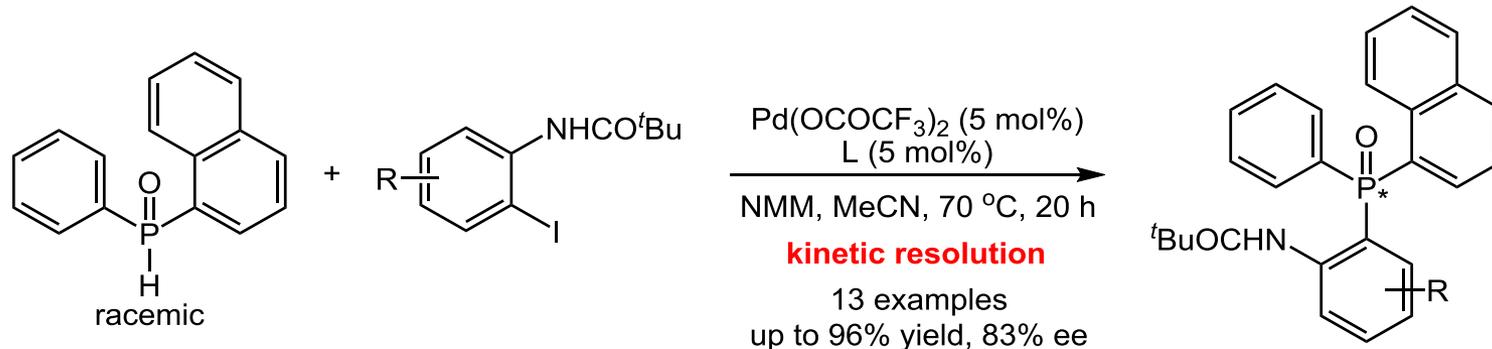


## (c) Enantioselective arylation of SPOs



Gaunt, M. J. *et al.* *J. Am. Chem. Soc.* **2016**, *138*, 13183.

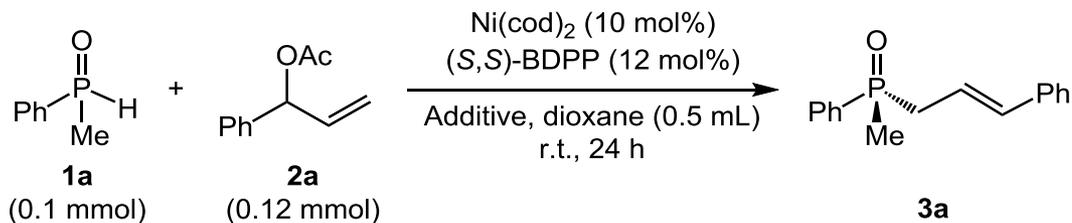
# KR of secondary phosphines oxides



Cai, Q. *et al. Tetrahedron Lett.* **2016**, 57, 5308.

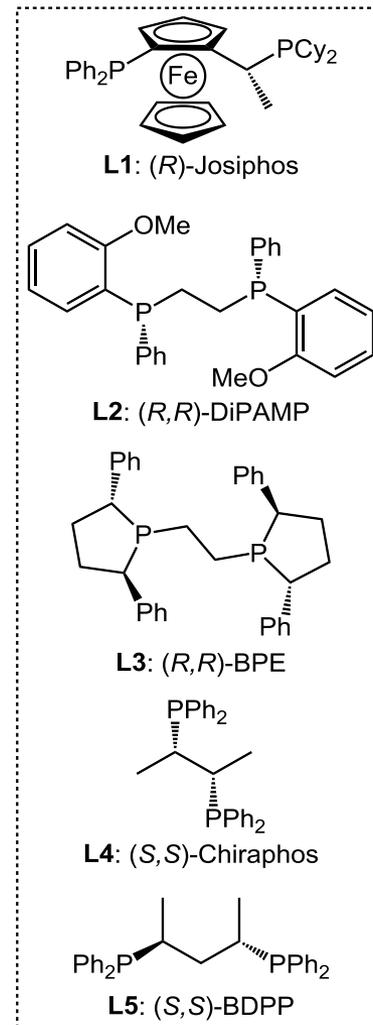


# Optimization of reaction conditions<sup>a</sup>

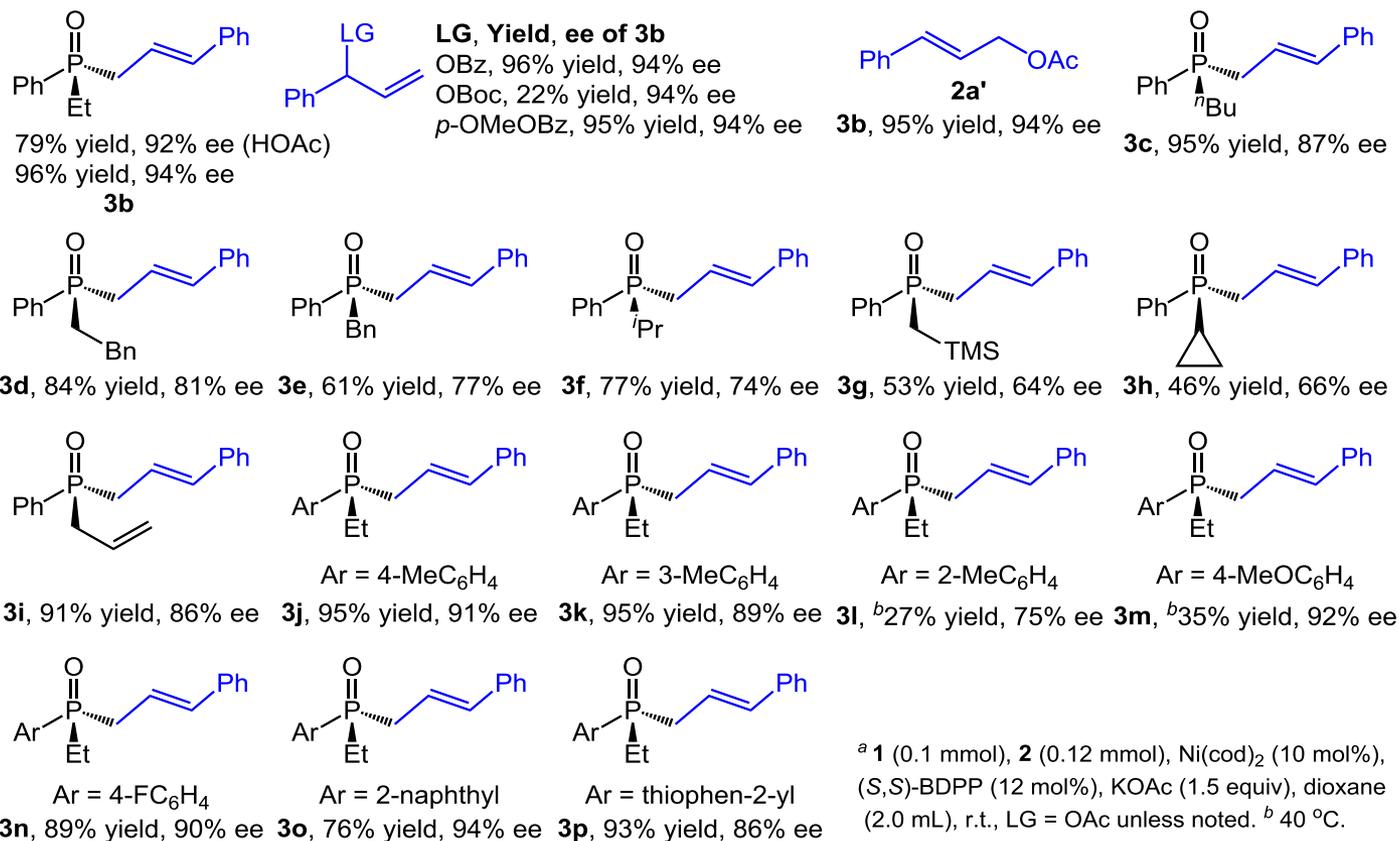
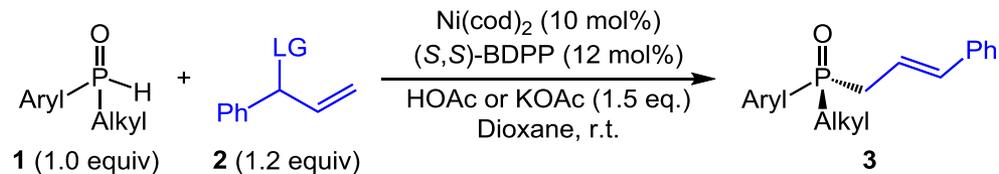


Entry	L	Additive	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	L1	K <sub>3</sub> PO <sub>4</sub>	15	<5
2	L2	K <sub>3</sub> PO <sub>4</sub>	18	17
3	L3	K <sub>3</sub> PO <sub>4</sub>	18	30
4	L4	K <sub>3</sub> PO <sub>4</sub>	30	53
5	L5	K <sub>3</sub> PO <sub>4</sub>	>95	6
6 <sup>d</sup>	L5	K <sub>3</sub> PO <sub>4</sub>	51 (42)	87 (80)
7	L5	DBU	>95	45
8	L5	DABCO	>95	57
9	L5	KOAc	>95	71
10 <sup>e,f</sup>	L5	KOAc	>95	82
11 <sup>e,g</sup>	L5	KOAc	>95, 96 <sup>h</sup>	89

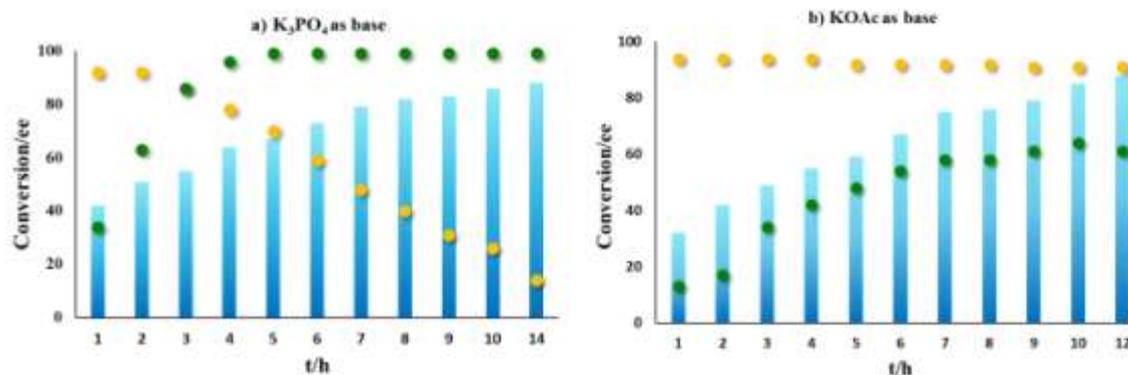
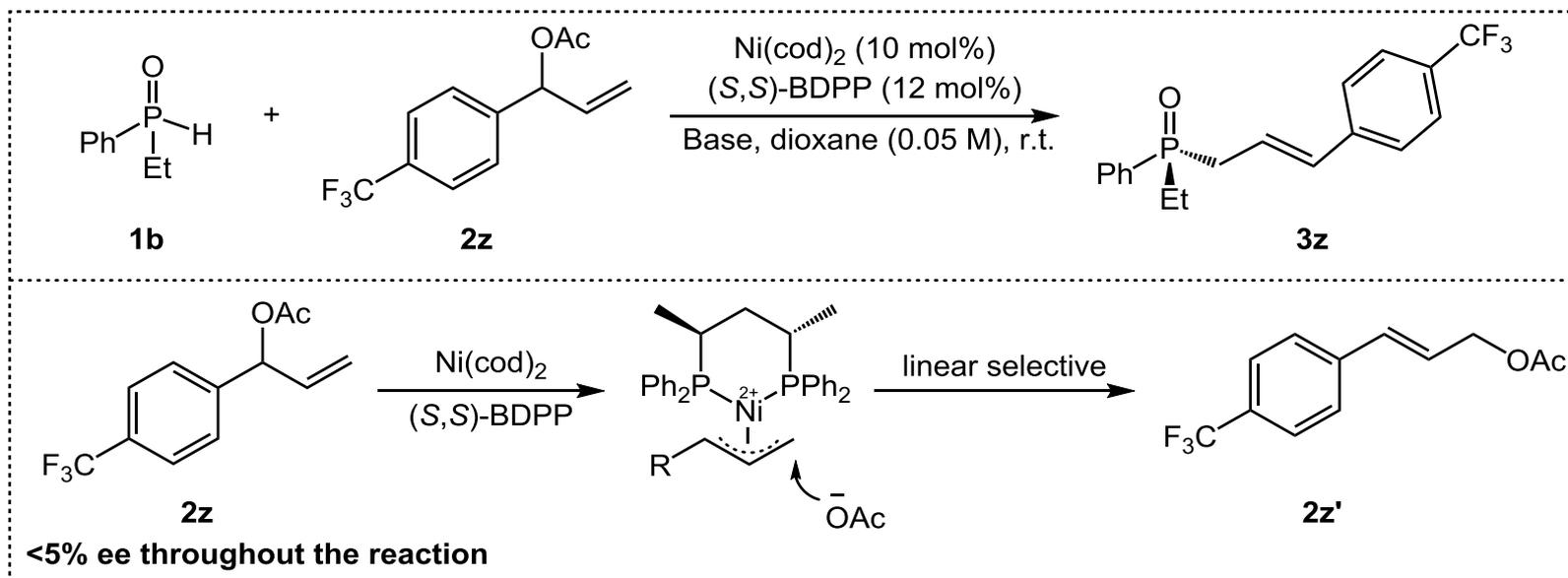
<sup>a</sup> Ni(cod)<sub>2</sub>, (S,S)-BDPP in dioxane was stirred for 10 min, followed by the addition of **1a**, **2a**, and additive (1.5 equiv). <sup>b</sup> NMR yield with PO(OMe)<sub>3</sub> as internal standard; yield of remaining **1a** is shown in parentheses. <sup>c</sup> Determined by chiral HPLC analysis; ee of remaining **1a** is shown in parentheses. <sup>d</sup> 2 h. <sup>e</sup> 2 mL dioxane. <sup>f</sup> 48 h. <sup>g</sup> 72 h. <sup>h</sup> Isolated yield.



# Scope of phosphine oxides

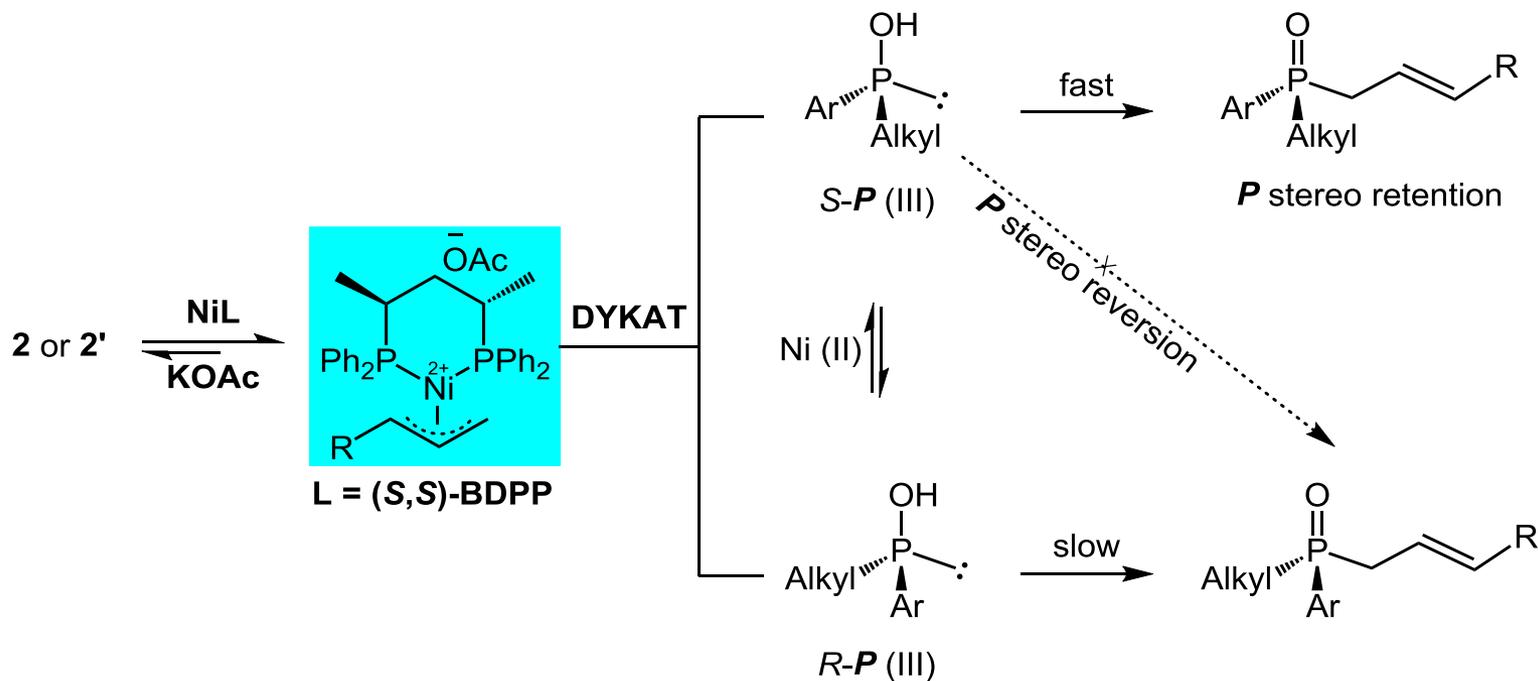


# Mechanistic study



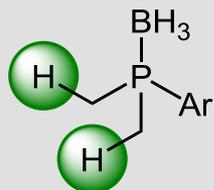
**Figure 1.** Mechanistic study. Green dots, ee of remaining **1b**; yellow dots, ee of **3z**; blue columns, conversion of **1b**.

# Proposed reaction mechanism in terms of DYKAT

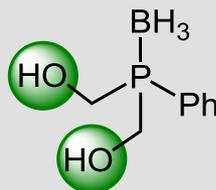


# Pd-catalyzed asymmetric allylic alkylation of phosphinic acids

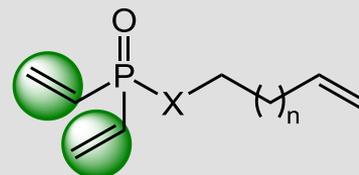
## a) Previously desymmetrized *P*-chiral molecules



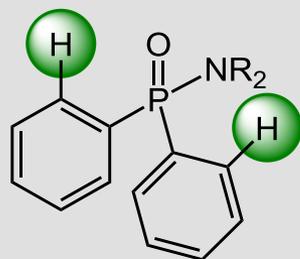
enantioselective  
deprotonation



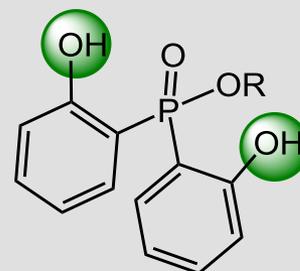
enzymatic  
acylation



asymmetric ring-closing  
metathesis

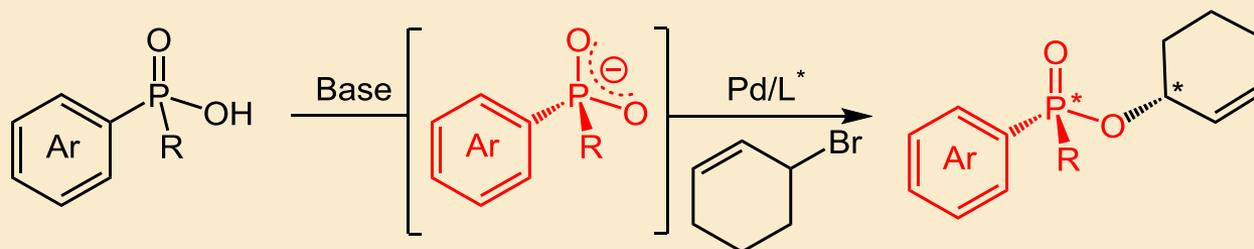


desymmetric C-H activation

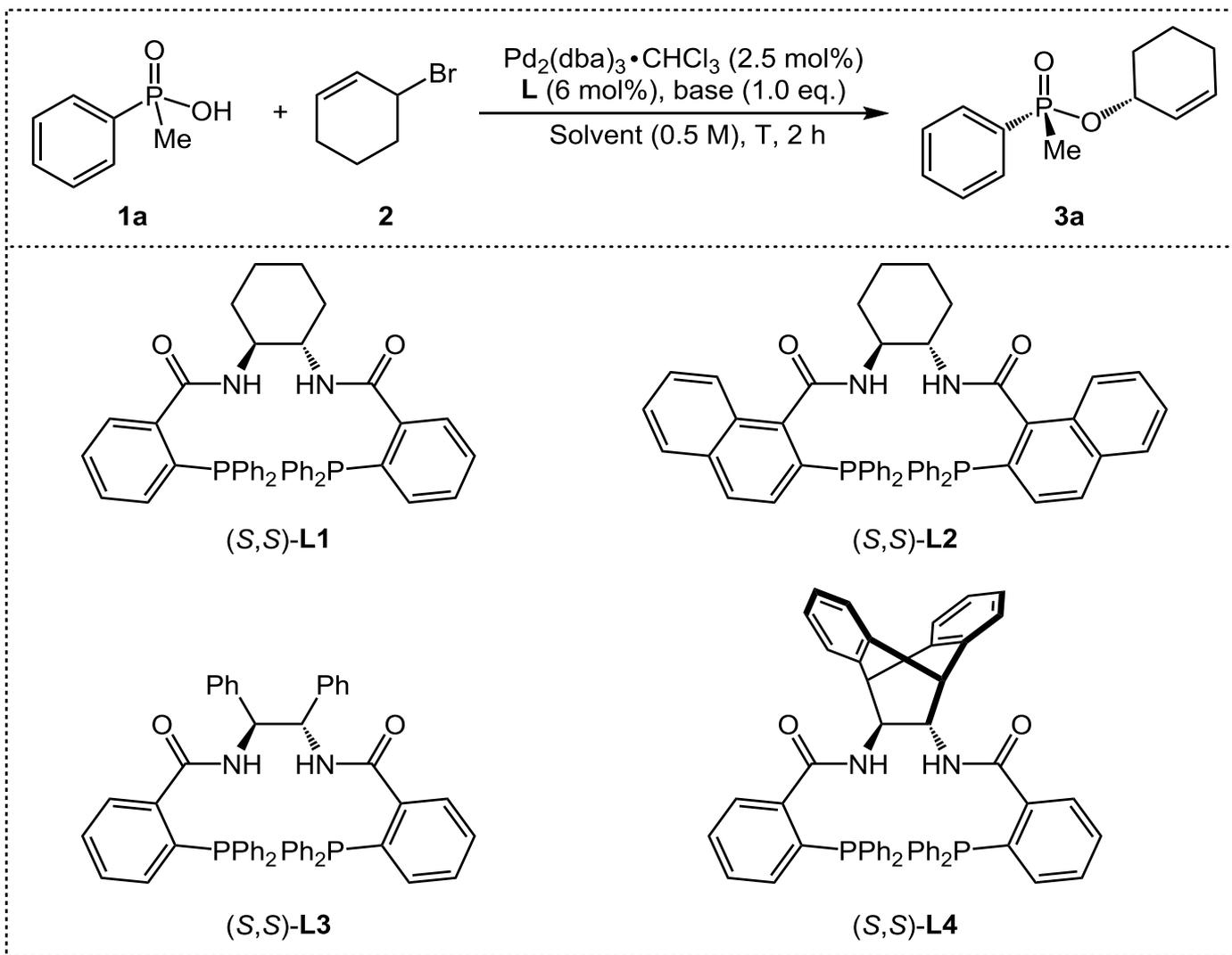


NHC-catalyzed acylation

## b) This work:



# Pd-catalyzed asymmetric allylic alkylation of phosphinic acids



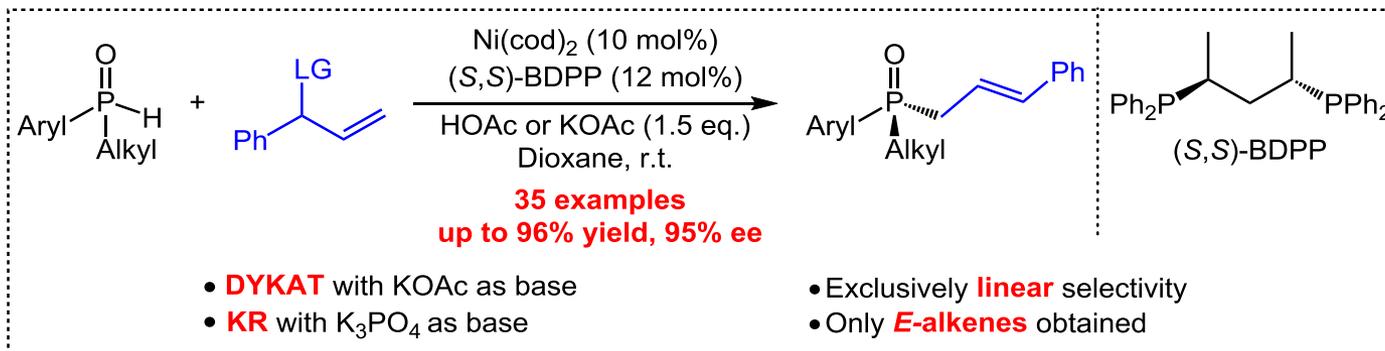
## Optimization of reaction conditions<sup>a</sup>

Entry	L	Solvent	Base	T	Yield (%)	D.r.	Ee (%)
1	L1	THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	83	1:1	96/93
2	L2	THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	97	2:1	80
3	L3	THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	70	1:1	91/92
4	L4	THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	70	6:1	97
5	L4	2-Me-THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	77	5:1	94
6	L4	Dioxane	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	89	5:1	95
7	L4	DME	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	77	4:1	91
8	L4	DCE	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	86	4:1	95
9	L4	Toluene	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	92	4:1	94
10	L4	THF	Li <sub>2</sub> CO <sub>3</sub>	r.t.		no reaction	
11	L4	THF	K <sub>2</sub> CO <sub>3</sub>	r.t.	67	4:1	-
12	L4	THF	NEt <sub>3</sub>	r.t.	77	5:1	90
13	L4	THF	Cs <sub>2</sub> CO <sub>3</sub>	0 °C	76	5.5:1	93
14	L4	THF	Cs <sub>2</sub> CO <sub>3</sub>	40 °C	79	4.5:1	93
15 <sup>b</sup>	L4	THF	Cs <sub>2</sub> CO <sub>3</sub>	r.t.	96	7:1	97

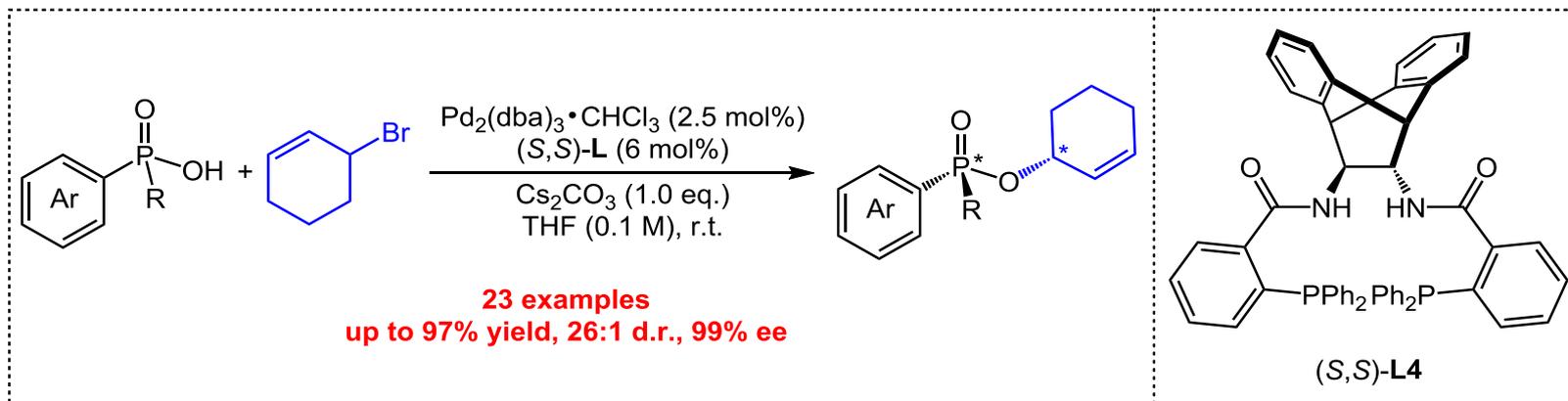
<sup>a</sup> All reactions performed on 0.1 mmol scale. Yields are isolated yields; d.r. determined by crude <sup>31</sup>P NMR, and ee determined by chiral HPLC. In diastereoselective cases, only the ee of the major diastereomer is reported. <sup>b</sup> Reaction concentration of 0.1 M, based on phosphinic acid.



# Summary



Zhang, Q.-W. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 16584.



Kalnals, C. A. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 14098.

## The first paragraph

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Enantioenriched *P*-stereogenic phosphines have served as important chiral ligands for transition metals as well as organocatalysts. However, they are less studied compared to their counterparts that have chiral carbon backbones, in part due to their less availability and synthetic challenges. Traditional methods to synthesize *P*-stereogenic phosphines require the use of stoichiometric amounts of chiral reagents; such as methods include resolution, auxiliary-induced diastereoselective substitution, and enantioselective deprotonation/derivatization reactions. Ephedrine-based strategies are also considered as reliable and robust methods for the preparation of *P*-stereogenic phosphines.

## The last paragraph

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In summary, we have achieved the first example of nickel-catalyzed dynamic kinetic asymmetric transformation (DYKAT) allylation of SPO. A series of *P*-stereogenic tertiary phosphine oxides were synthesized from both racemic allylic esters and secondary phosphine oxides (SPO). The kinetic and racemization study revealed the origin of the DYKAT reaction which relies on the Ni(II) catalyzed racemization of the SPO when KOAc was used as an additive. The finding of this research will expand the applications of SPO in the synthesis of *P*-stereogenic phosphines.

# Acknowledgement

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***Thanks  
for your attention***