Asymmetric Functionalization of racemic Secondary Phosphine Oxides or *H*-Phosphinates

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Supervisor： **Prof. Shengming Ma**

Prof. Hui Qian

Date： **2024.4.26**

Content

Background

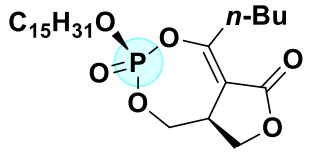
Asymmetric functionalization of racemic secondary phosphine oxides or *H*-phosphinates

- **Asymmetric functionalization via kinetic resolution (KR)**
- **Asymmetric functionalization via dynamic kinetic asymmetric transformation (DYKAT)**

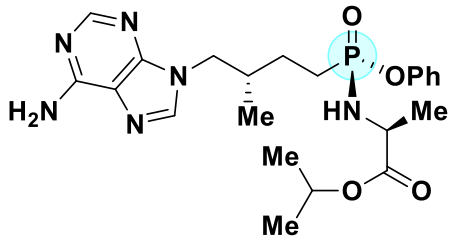
Summary and Outlook

Background

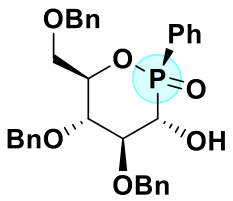
Biologically relevant molecules containing a P(V)=O stereocenter



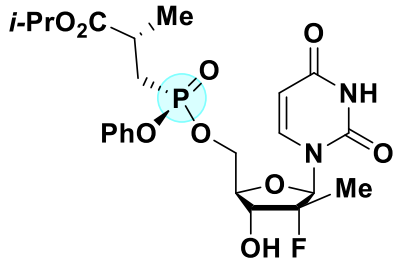
Salinipostin A



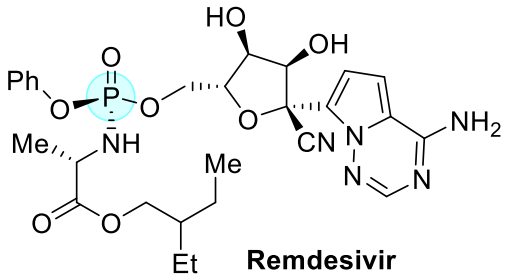
Tenofovir alafenamide



Phostine

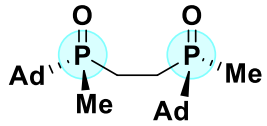


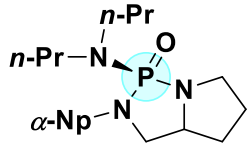
Sofosbuvir

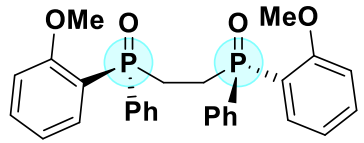


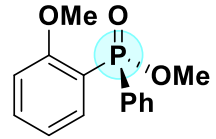
Remdesivir

P-chiral phosphine oxides act as ligand or catalyst

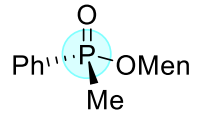




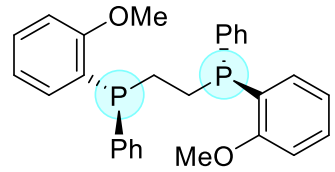




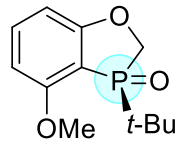
Preparation of *P*-chiral bis- or mono-phosphorus ligand from P(V)=O



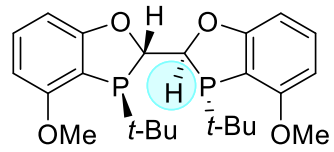
(*R*)-1



(*R,R*)-DIPAMP



(*S*)-1



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

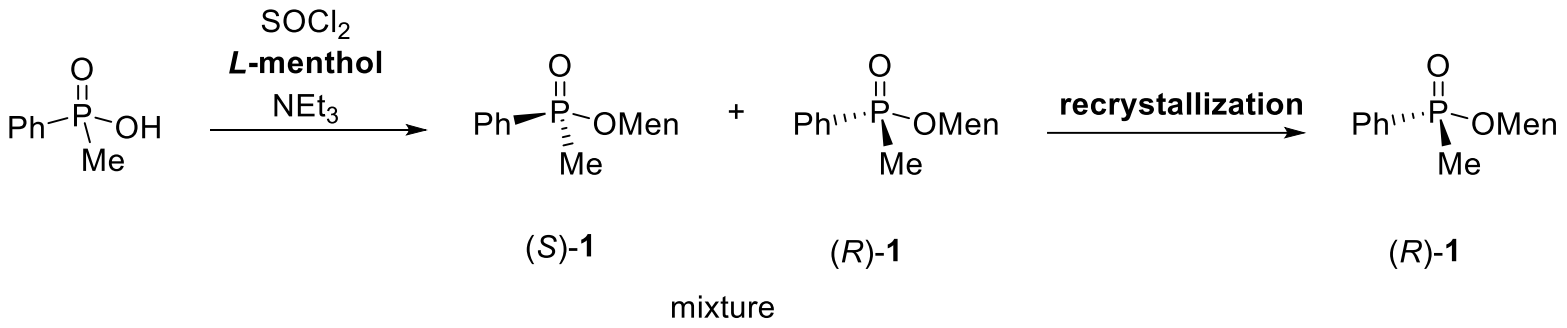
a) Zhou, J. et al. *Acta Chim. Sinica* **2020**, *78*, 193–216. b) Knowles, W.-S. et al. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952. c) Tang, W.-J. et al. *Org. Process Res. Dev.* **2013**, *17*, 1061–1065.

Background

Traditional synthetic method

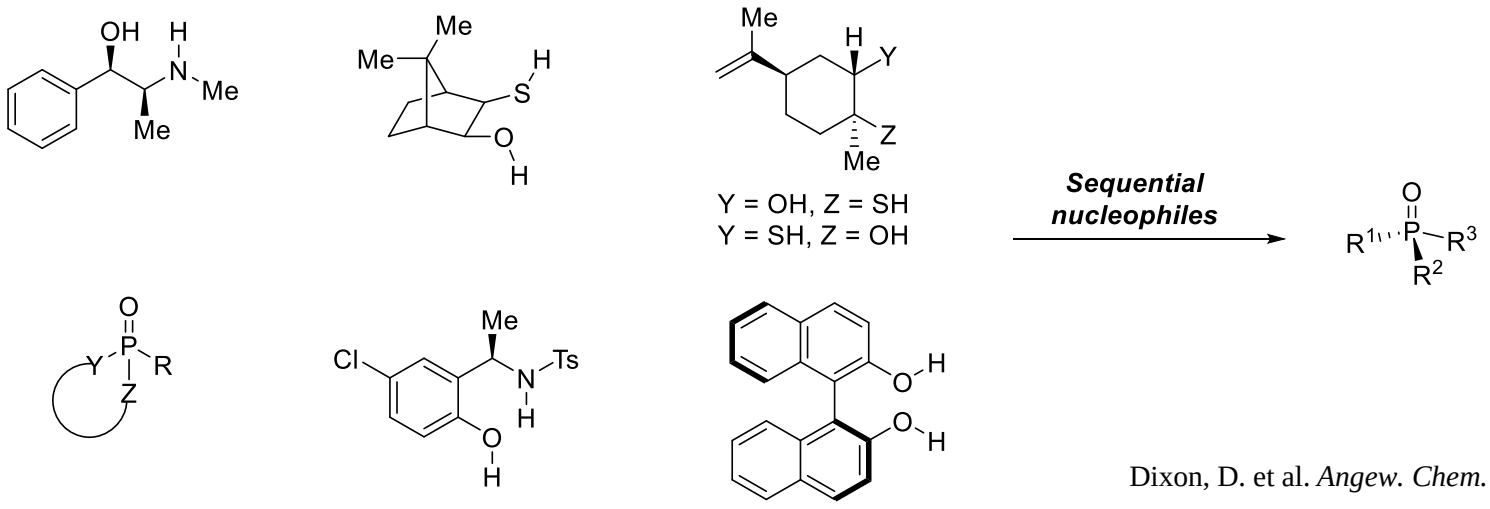
Stoichiometric Chiral reagents

Resolution



Knowles, W.-S. et al. *J. Am. Chem. Soc.* **1977**, *99*, 5946−5952.

Chiral auxiliary



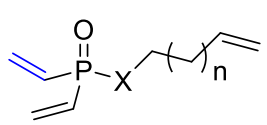
Dixon, D. et al. *Angew. Chem. Int. Ed.* **2024**, e202400673.

Background

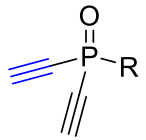
Asymmetric catalysis

Specific substrates

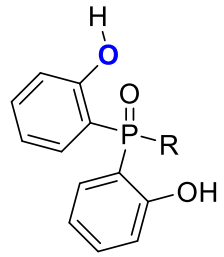
Enantioselective desymmetrization



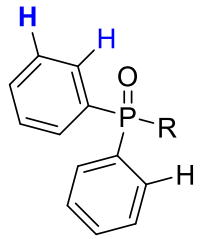
RCM



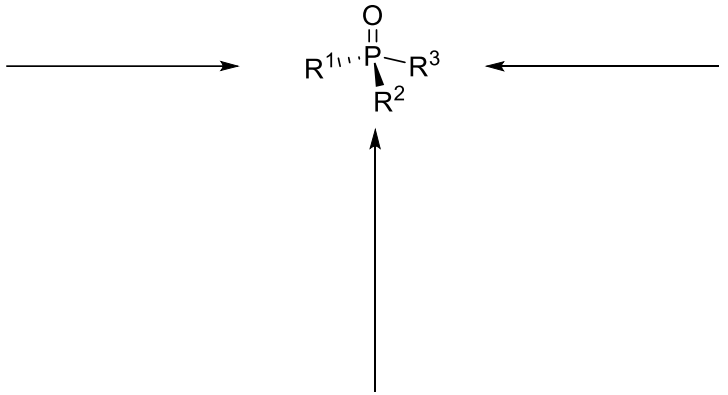
CuAAC



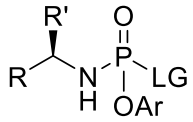
NHC or Lewis Base

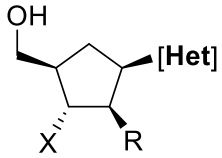


C-H activation



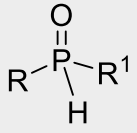
Diastereoselective coupling



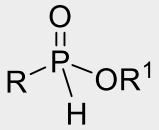


Baran. P,* et al. *ACS Cent. Sci.* **2021**, *7*, 1473–1485.

Direct asymmetric functionalization of racemic SPOs or H-phosphinates



SPOs
Sceondary Phosphine Oxides



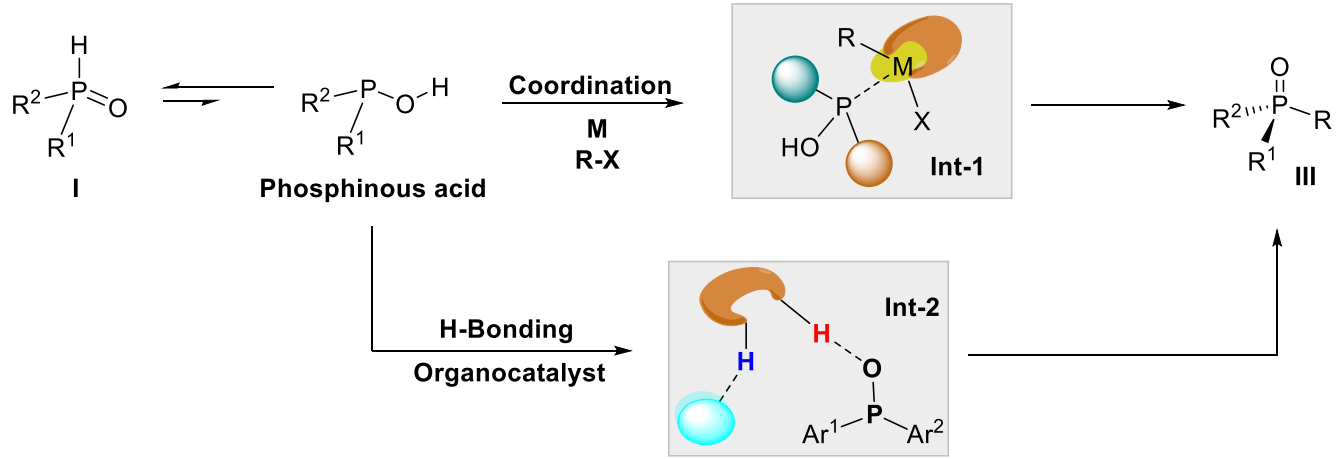
H-phosphinates

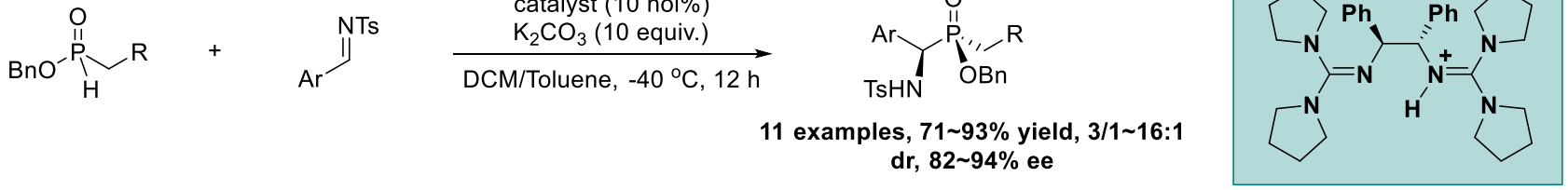
- **Bench stable**
- **Odorlessness and low toxicity**
- **Availability**

Zhou, J. et al. *Acta Chim. Sinica* **2020**, *78*, 193–216.

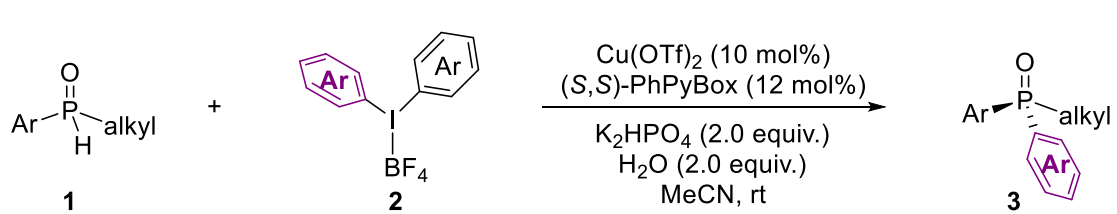
Background

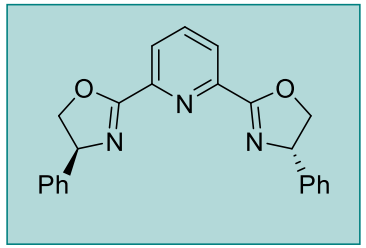
Asymmetric functionalization





Tan, C. et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 7387–7390.





Gaunt, M. et al. *J. Am. Chem. Soc.* **2016**, *138*, 13183−13186.

Content

Background

Asymmetric functionalization of racemic secondary phosphine oxides or *H*-phosphinates

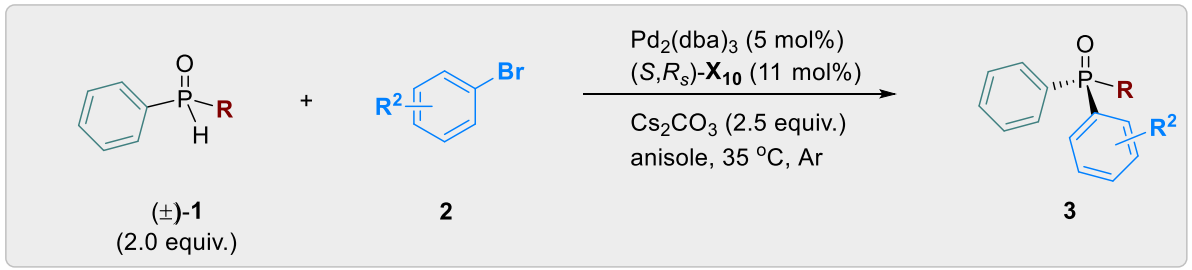
- **Asymmetric functionalization via kinetic resolution (KR)**
- **Asymmetric functionalization via dynamic kinetic asymmetric transformation (DYKAT)**

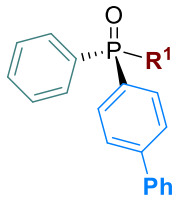
Summary and Outlook

Coupling reaction via kinetic resolution (KR)

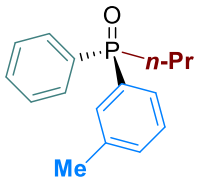
Palladium catalysis

Scope

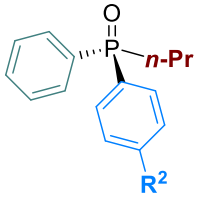




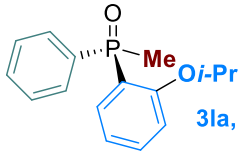
R = Et	3aa	69% yield, 91% ee
R = *n*-Pr	3ba	81% yield, 91% ee
R = *i*-Pr	3ca	64% yield, 93% ee
R = *n*-Bu	3da	47% yield, 93% ee
R = *t*-Bu	3ea	58% yield, 81% ee



3ga, 95% yield, 96% ee

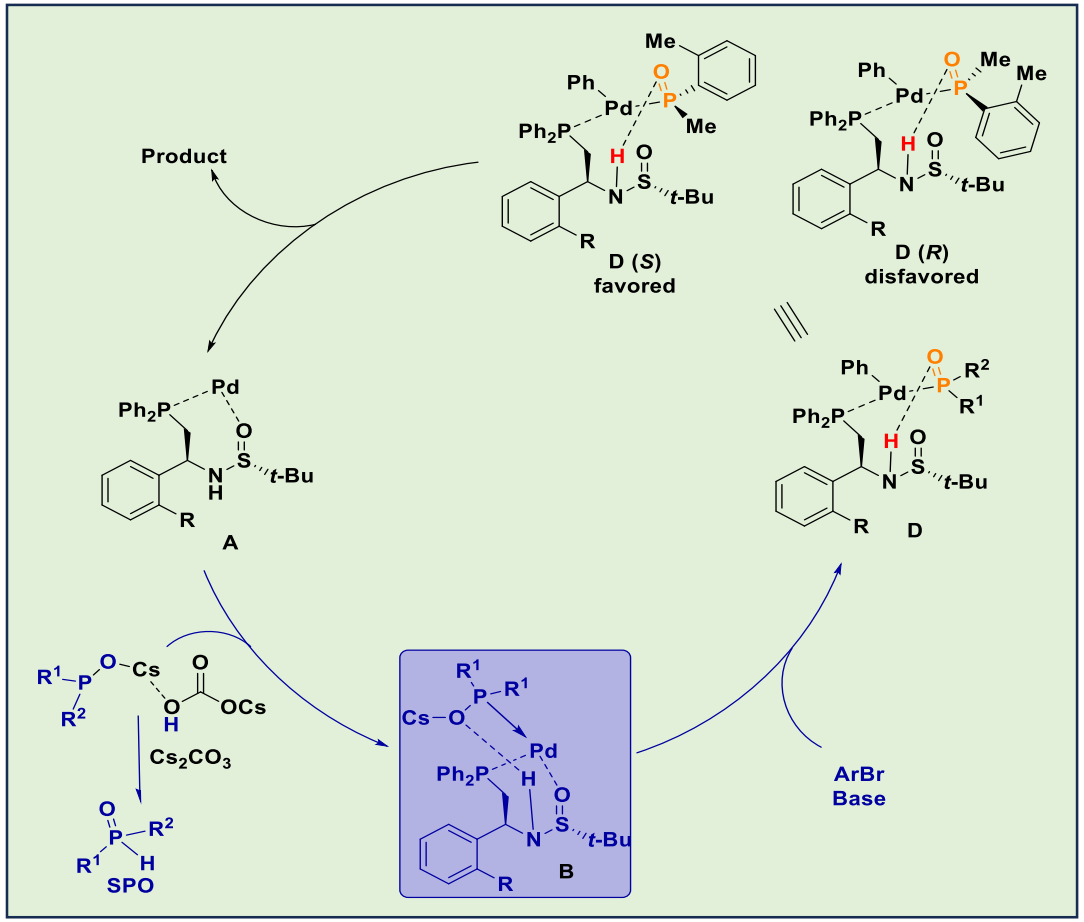


R^2 = OPh	3ha	55% yield, 93% ee
R^2 = NHBoc	3ia	59% yield, 93% ee
R^2 = *t*-Bu	3ja	65% yield, 91% ee
R^2 = Cl	3ka	59% yield, 93% ee



3la, 92% yield, 91% ee

Mechanism

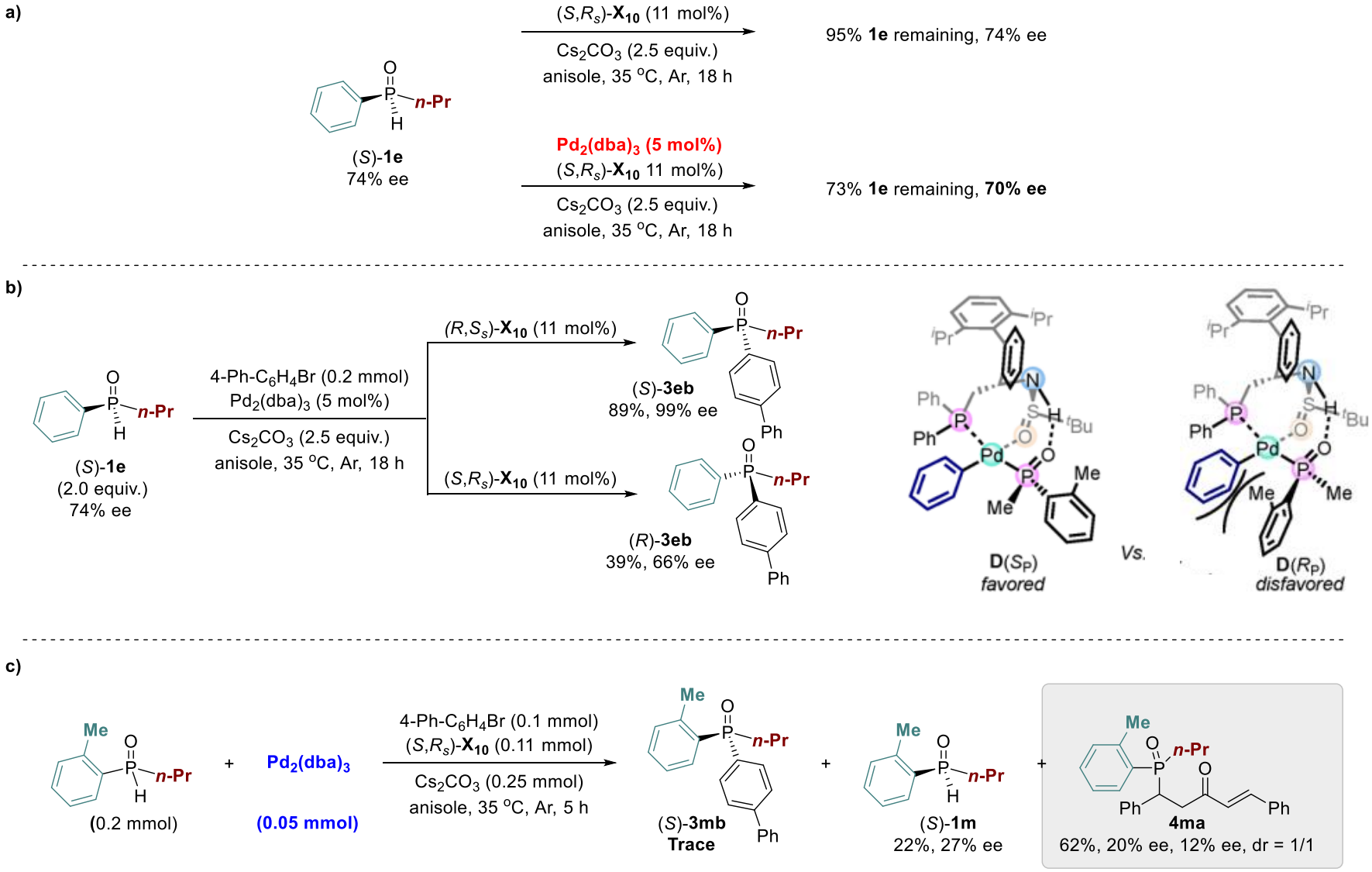


a) Zhang, J.-L. et al. *J. Am. Chem. Soc.* **2019**, *141*, 20556−20564.

Coupling reaction via kinetic resolution (KR)

Palladium catalysis

Mechanistic experiments

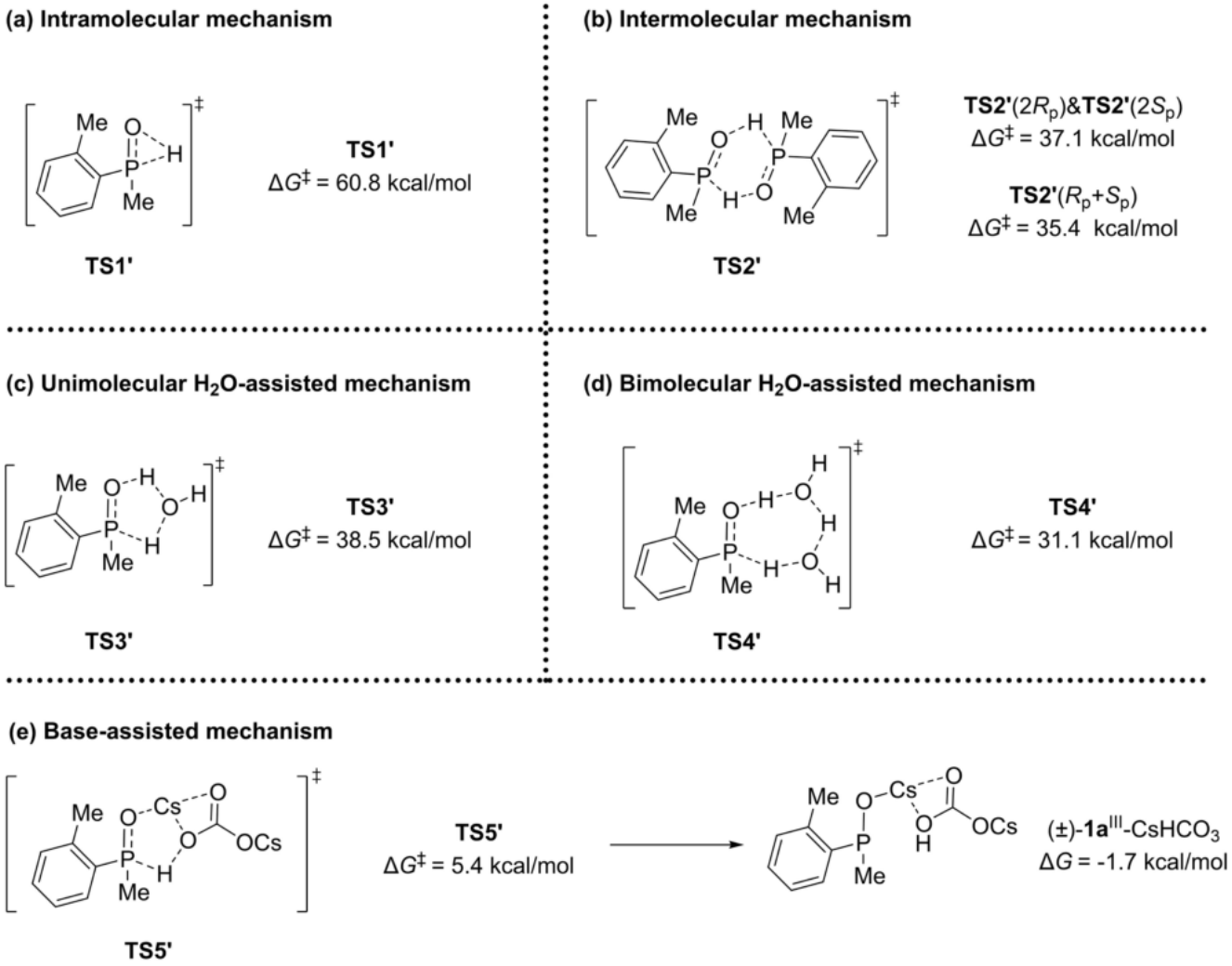


a) Zhang, J.-L. et al. *J. Am. Chem. Soc.* **2019**, *141*, 20556−20564.

Coupling reaction via kinetic resolution (KR)

Palladium catalysis

Exploration of the tautomerization mechanisms of SPOs



Scheme 2. Non-transition-metal-catalyzed tautomerization mechanisms.

Zhang, J.-L. et al. *Eur. J. Org. Chem*. **2023**, *26*, e202300804.

Coupling reaction via kinetic resolution (KR)

Palladium catalysis

DFT computations on the asymmetric arylation

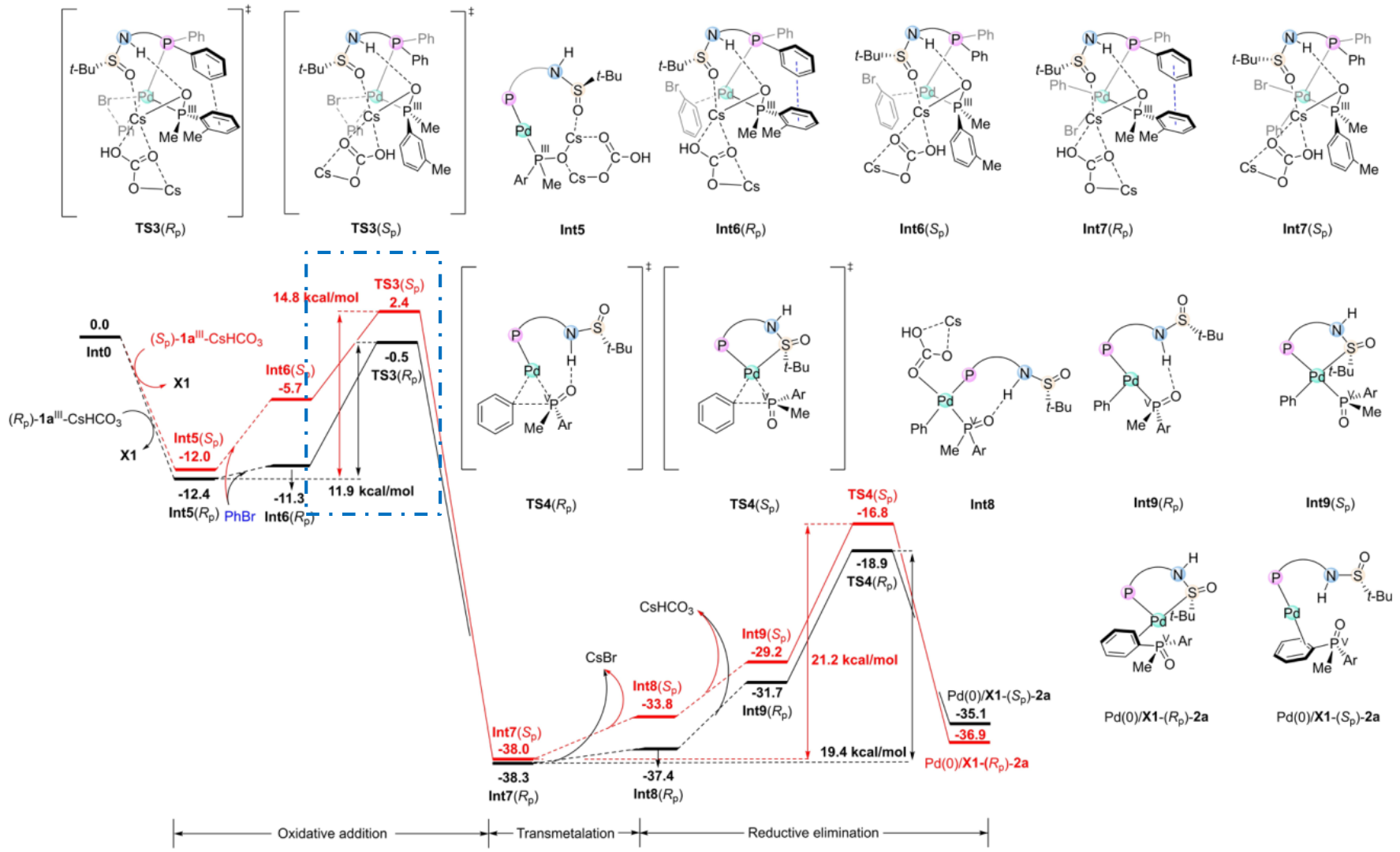


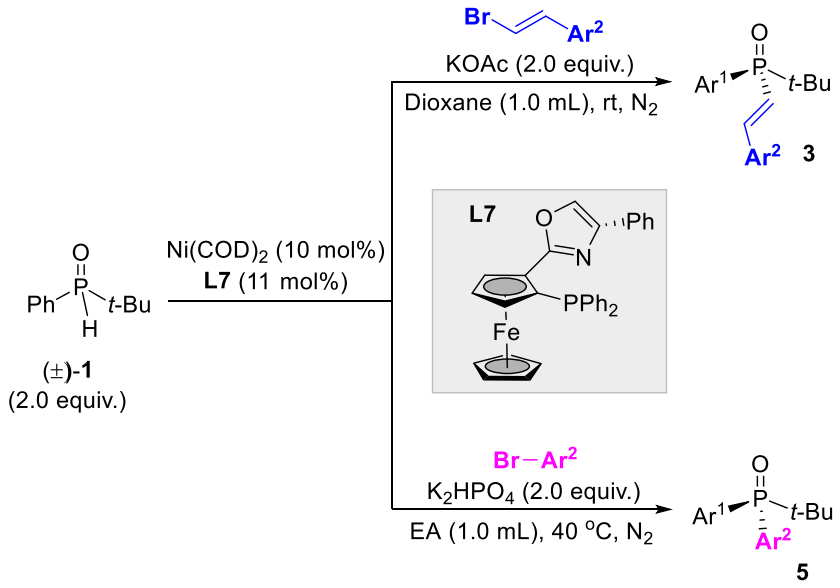
Figure 2. DFT Studies on arylation. Ar = *o*-methylphenyl. Gibbs free energies are in kcal/mol.

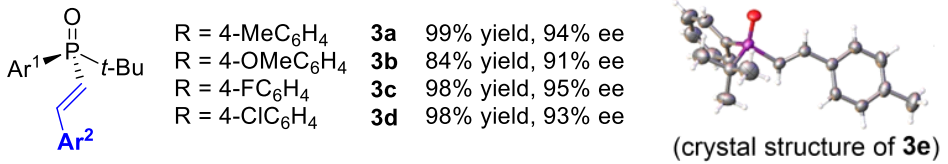
Zhang, J.-L. et al. *Eur. J. Org. Chem.* **2023**, *26*, e202300804.

Coupling reaction via kinetic resolution (KR)

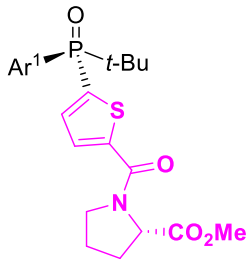
Nickel catalysis

Scope

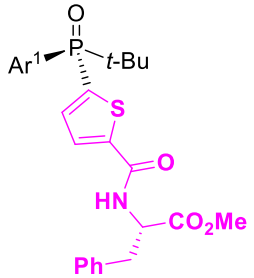




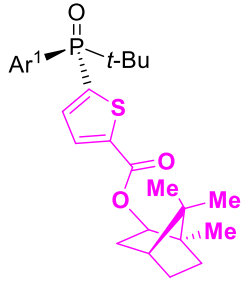
(crystal structure of **3e**)



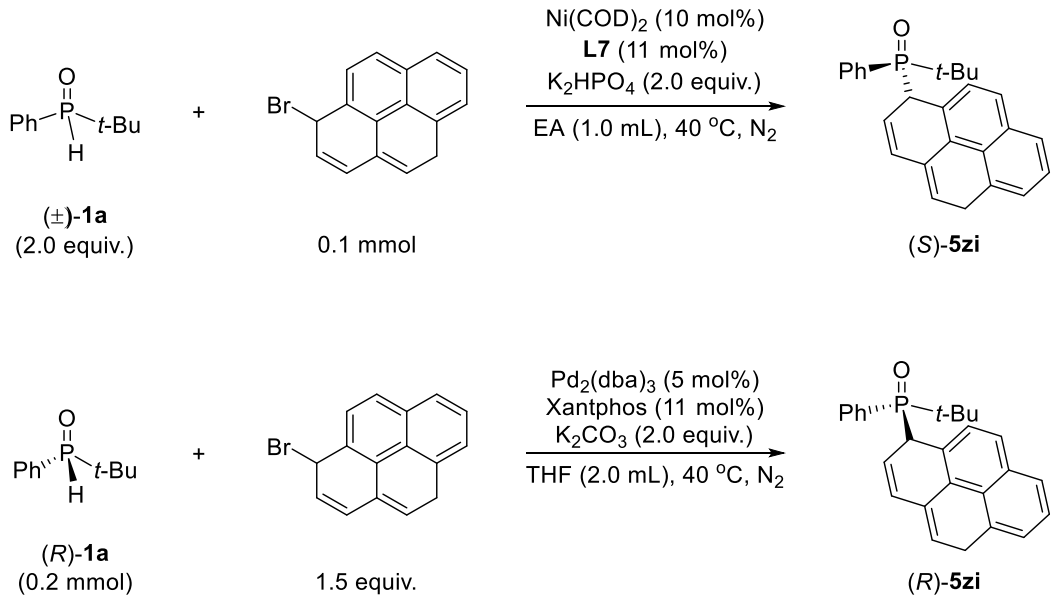
72% yield, 97:3 dr
(from ***L*-Pro**)

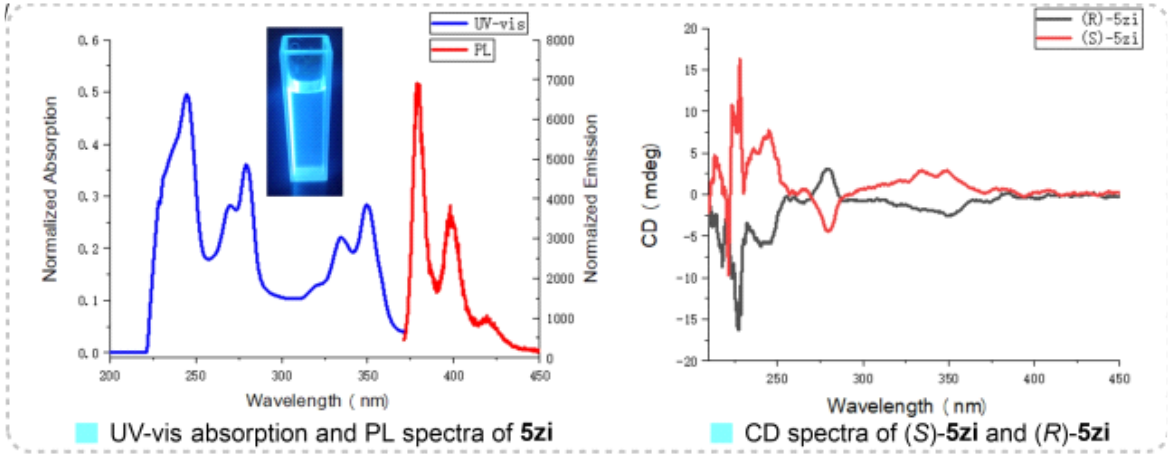


43% yield, 99:1 dr
(from ***L*-Phe**)



88% yield, 98:2 dr
(from **(-)-borneol**)



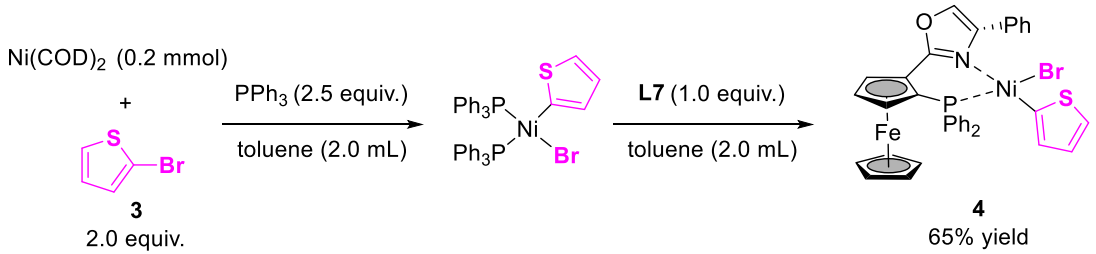


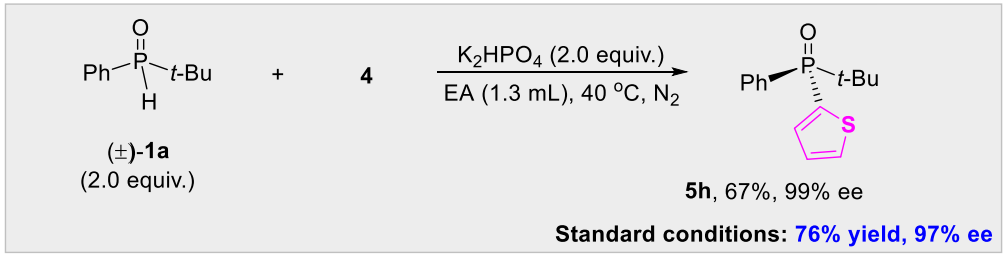
Duan, W.-L. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300011.

Coupling reaction via kinetic resolution (KR)

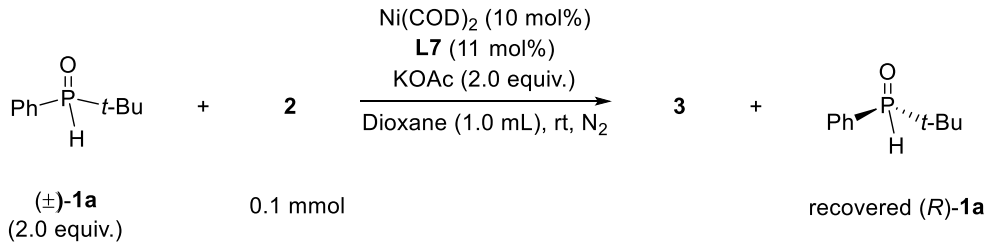
Nickel catalysis

Studies on active intermediate



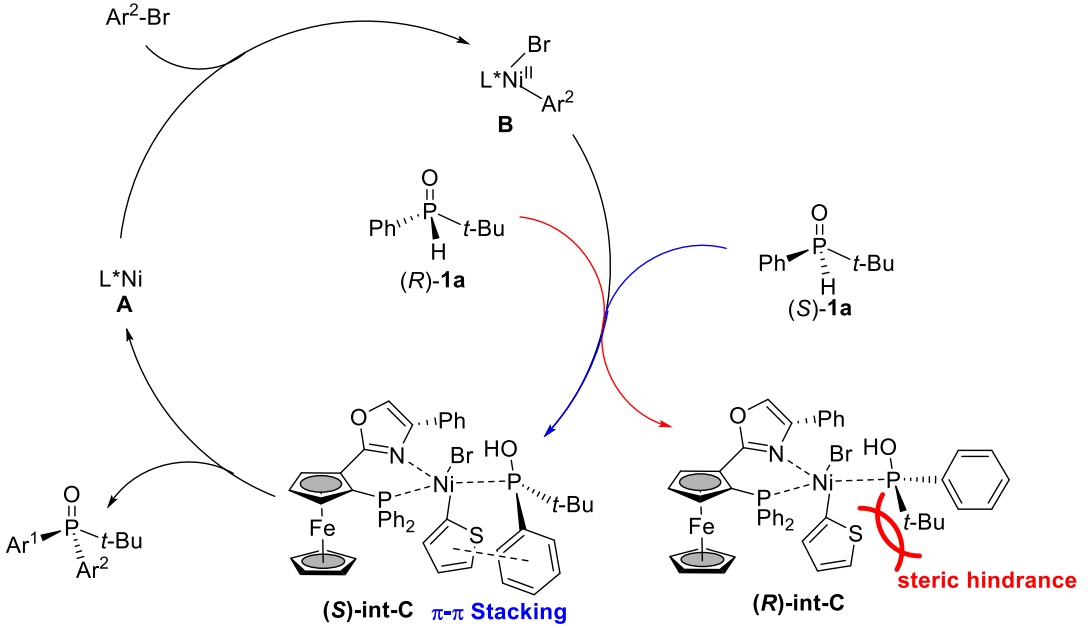


Studies on recovered starting materials



2		Product 3	recovered (*R*)-1a	*S*
R = 4-Me	**3e**	99%, 94% ee	99%, 95% ee	145.7
R = 4-Cl	**3h**	98%, 93% ee	77%, 90% ee	94.5
R = 4-F	**3g**	98%, 95% ee	94%, 88% ee	122.5
R = 3-F	**3k**	90%, 88% ee	55%, 99% ee	80.1
R = 2-F	**3m**	99%, 85% ee	81%, 99% ee	60.6

Proposed mechanism

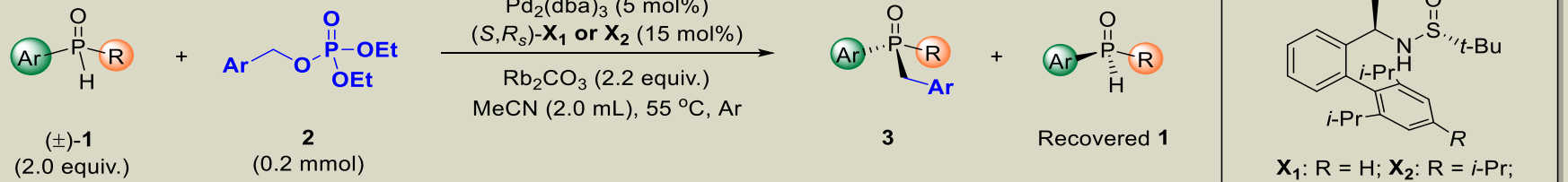


Duan, W.-L. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202300011.

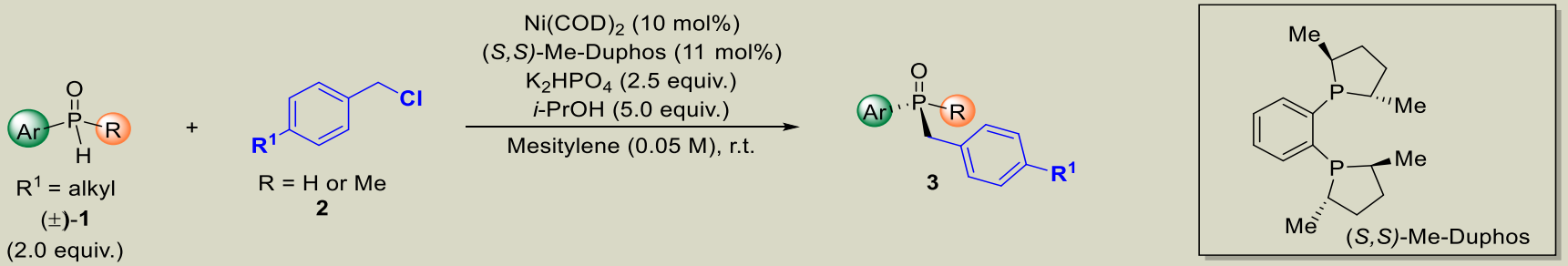
Coupling reaction via kinetic resolution (KR)

Palladium or Nickel catalysis

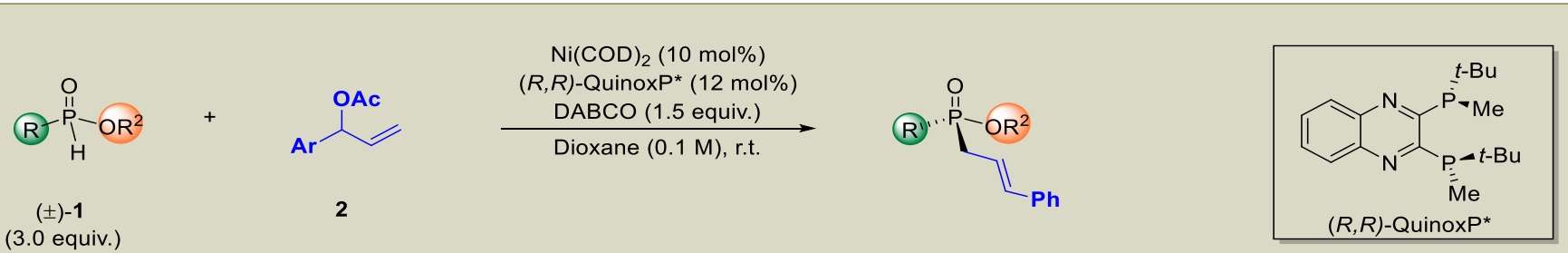
Similar examples



Zhang, J.-L. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 27247 –27252.



Zhang, Q.-W. et al. *Org. Lett.* **2022**, *24*, 1258−1262.

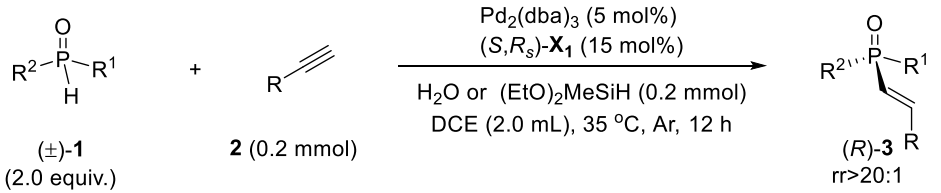


Zhang, Q.-W. et al. *Org. Lett.* **2021**, *23*, 8683−8687.

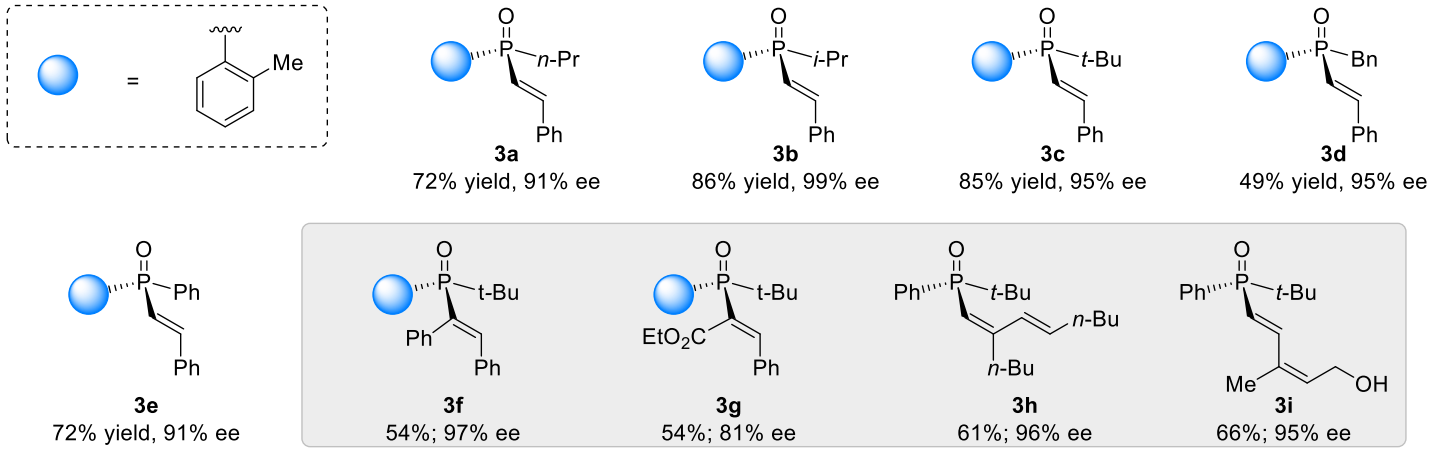
Insertion reaction via kinetic resolution (KR)

Palladium catalysis

anti-Markovnikov products

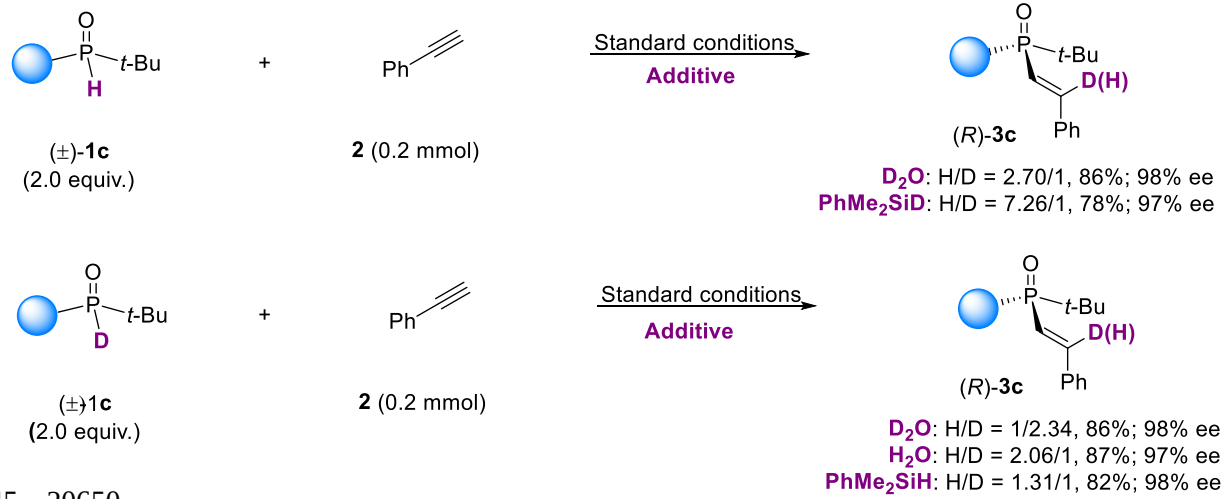


Scope



Mechanistic studies

Deuterium-incorporation experiments

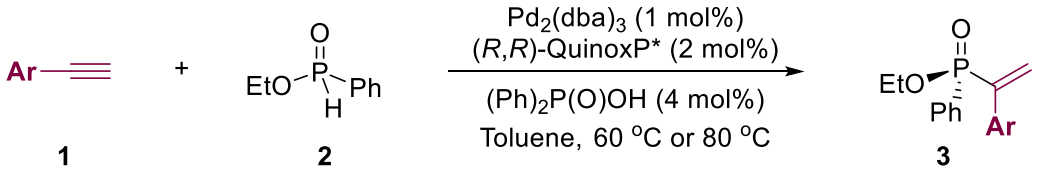


Zhang, J.-L. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 20645 – 20650.

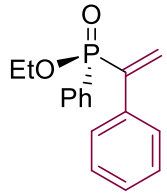
Insertion reaction via kinetic resolution (KR)

Palladium catalysis

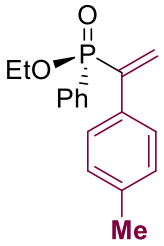
Markovnikov products



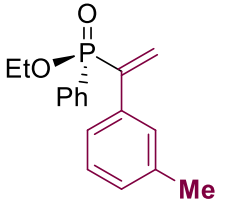
1 2 3



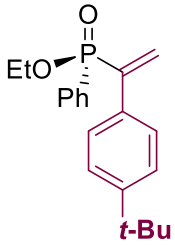
3a
70% yield, 83% ee
60% yield, 84% ee[a]



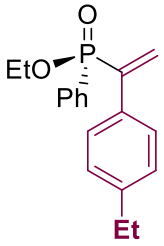
3b
70% yield, 82% ee



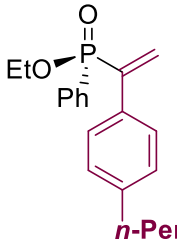
3c
70% yield, 81% ee



3d
84% yield, 81% ee

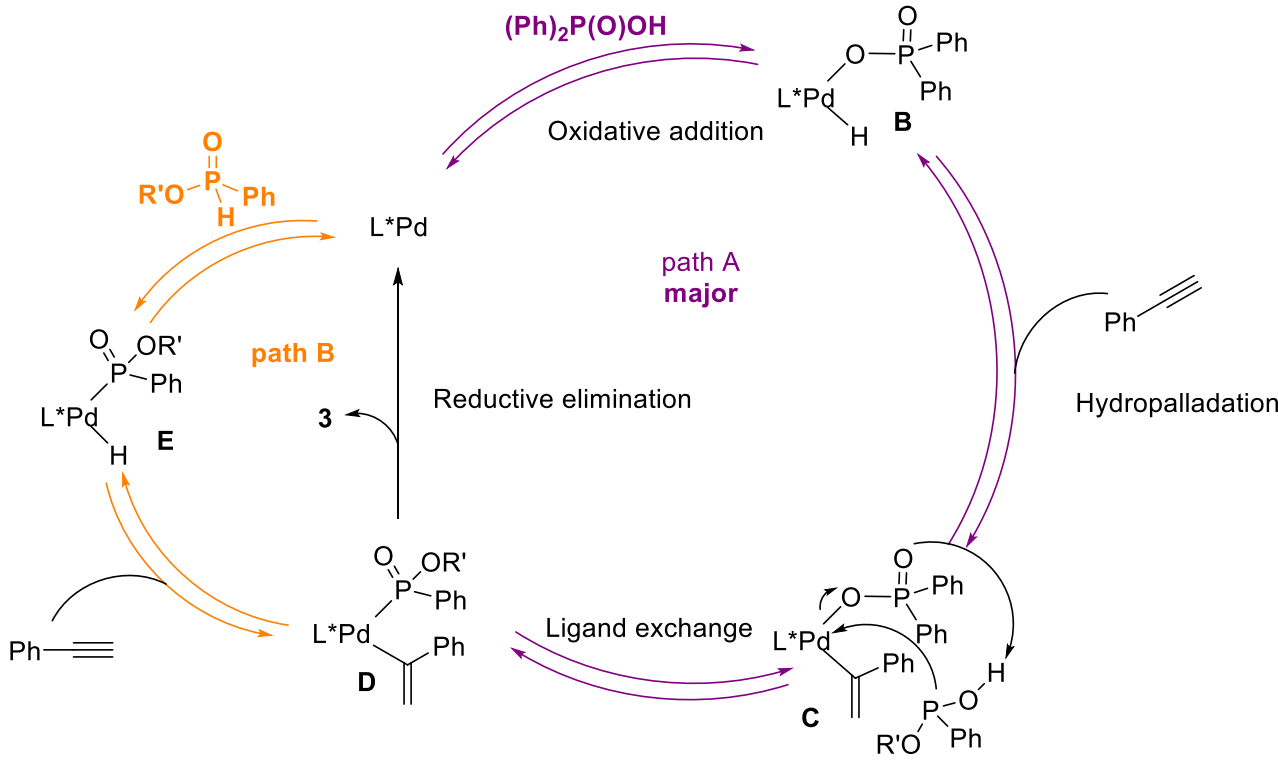


3e
72% yield, 83% ee



3f
54% yield, 82% ee

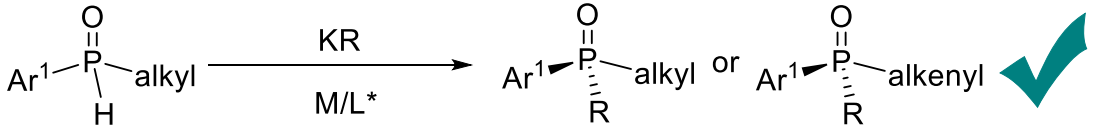
[a] Without phosphoric acid

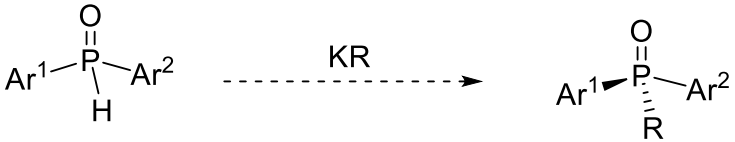


Wang, J. et al. *Chem. Sci*, **2020**, *11*, 7451–7455.

Michael addition reaction via kinetic resolution (KR)

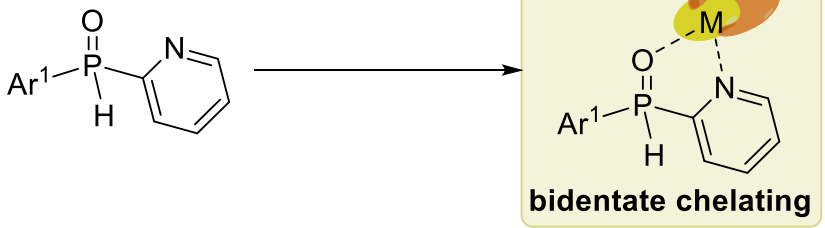
Co catalysis

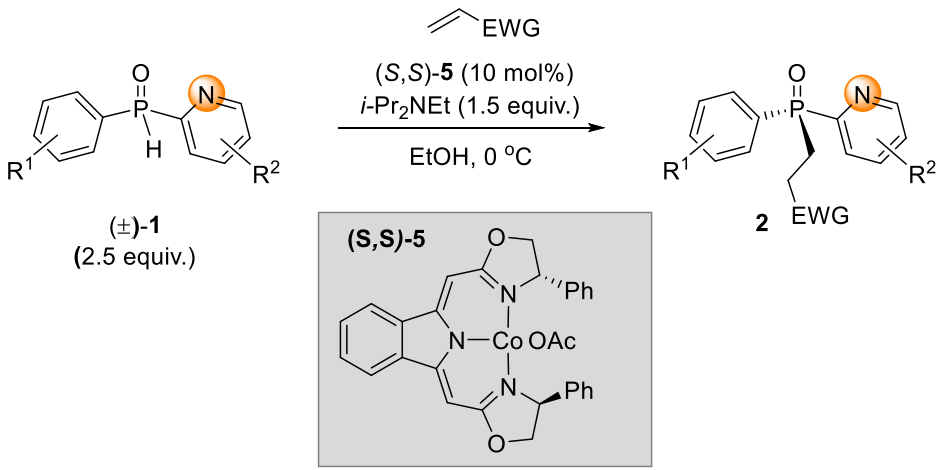




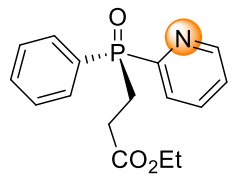
Challenge: substitution group with similar size

Design

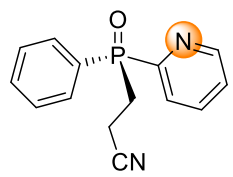




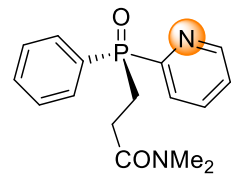
Scope



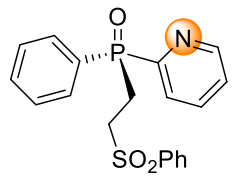
(*R*)-**2a**
98% yield, 96% ee



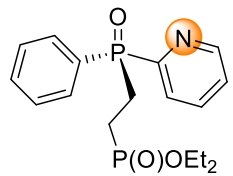
(*R*)-**2b**
84% yield, 92% ee



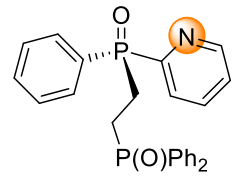
(*R*)-**2c**
99% yield, 90% ee



(*R*)-**2d**
85% yield, 94% ee



(*R*)-**2e**
82% yield, 86% ee

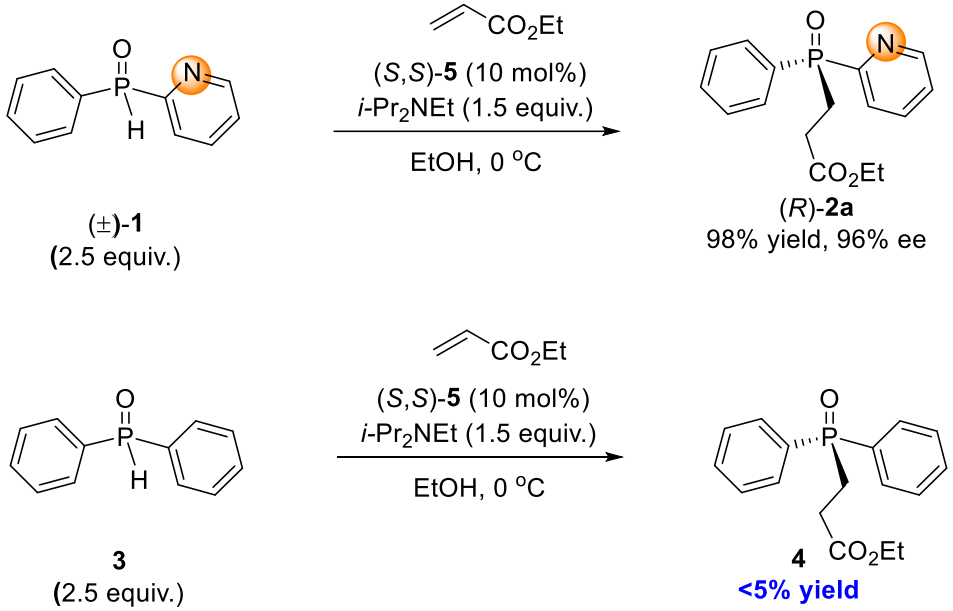


(*R*)-**2d**
68% yield, 94% ee

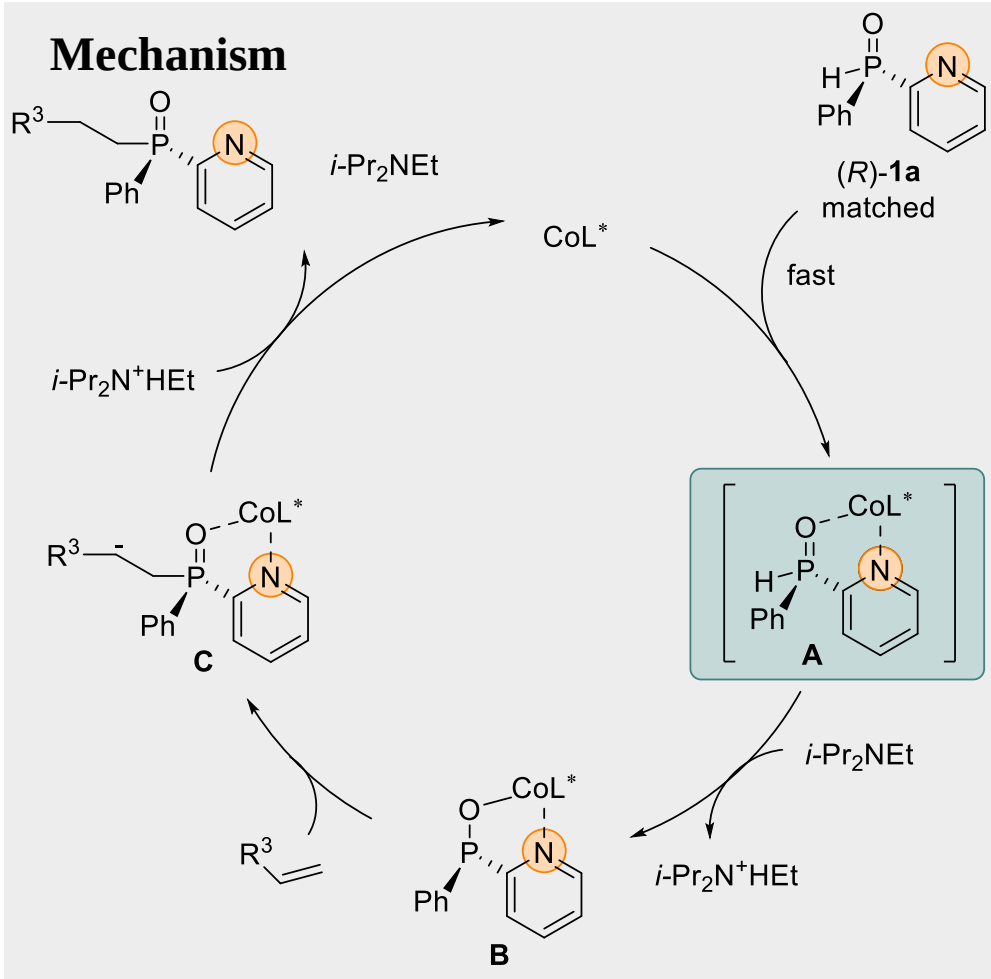
Michael addition reaction via kinetic resolution (KR)

Co catalysis

Compared experiments



Mechanism

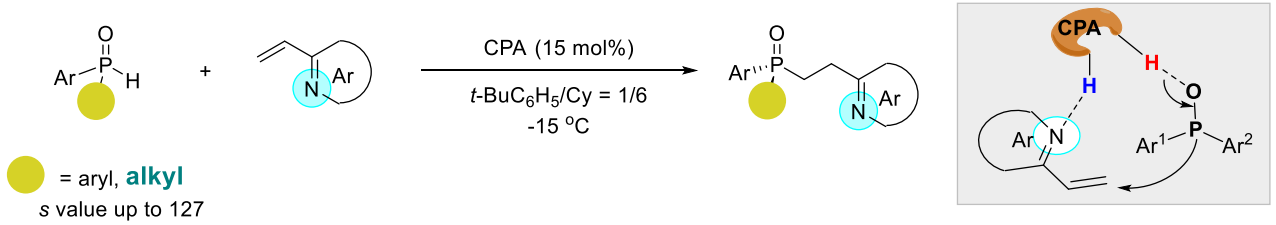


Duan, W.-L. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 27241 –27246.

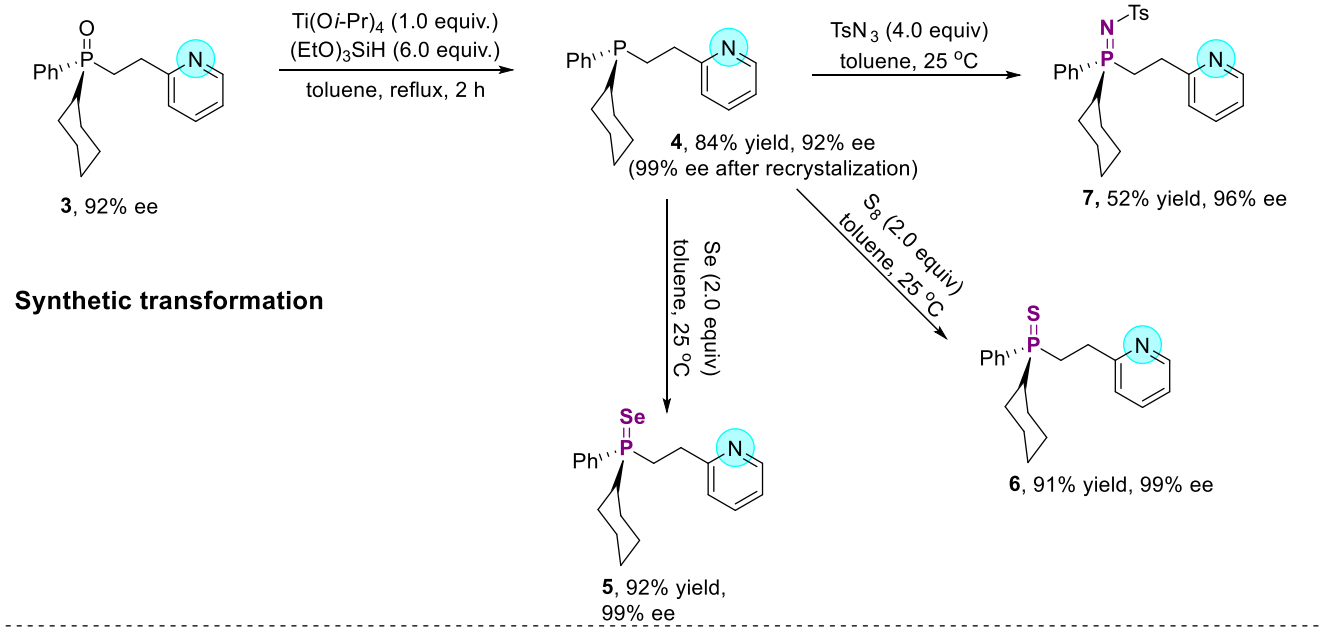
Michael addition reaction via kinetic resolution (KR)

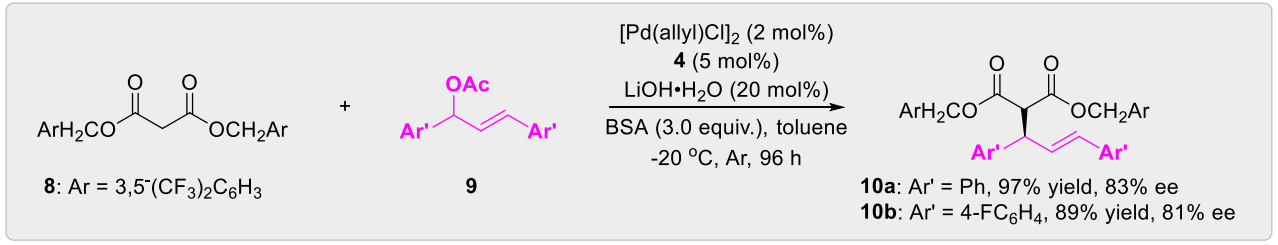
CPA catalysis

Hydrogen-Bond



Application



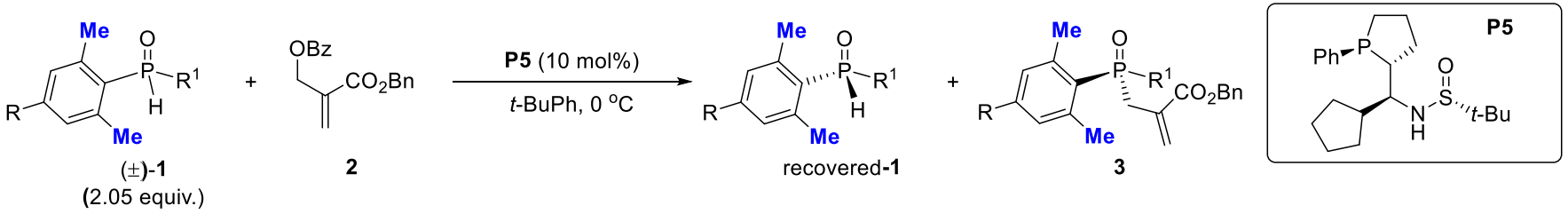


Jiang, Z.-Y. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216605.

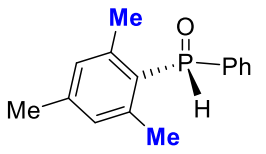
Michael addition reaction via kinetic resolution (KR)

Sulfinamide catalysis

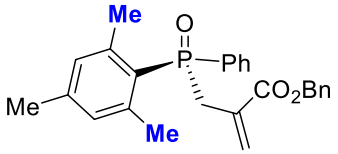
Steric hindrance



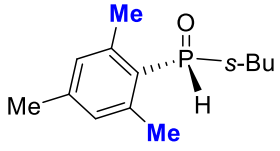
Scope



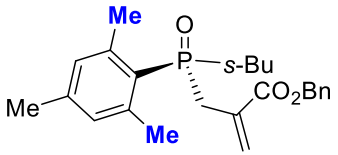
(*R*)-**1a**, 40%, 89% ee
s = 57



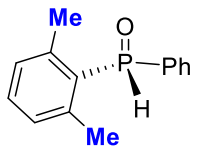
3aa, 41%, 90% ee



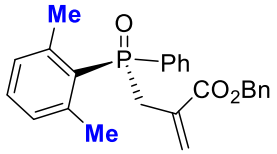
(*R*)-1**d**, 27% ee
s = 18.7



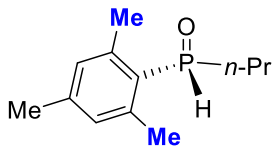
3da, 69%, 87% ee



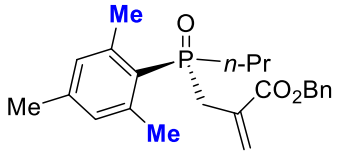
(*R*)-**1b**, 38%, 85% ee
s = 53



3ba, 39%, 90% ee

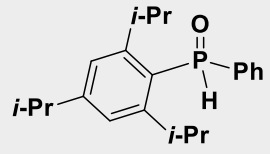


(*R*)-**1c**, 25% ee
s = 12.9

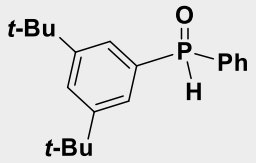


3ca, 62%, 82% ee

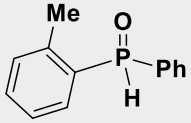
Failed examples



Trace

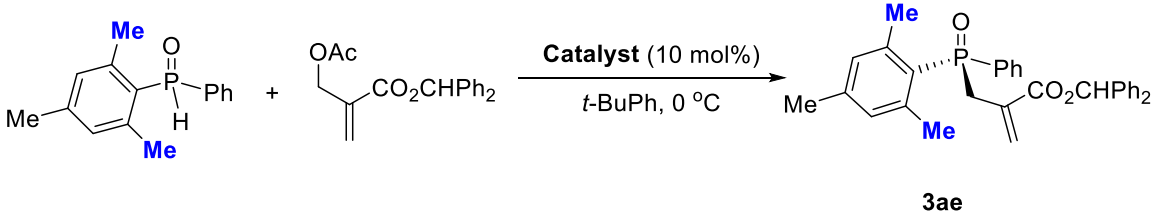


1: 10% ee
3: 10% ee

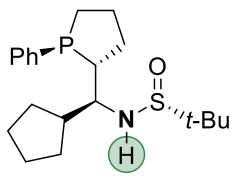


1: 39% ee
3: 66% ee

Compared experiments

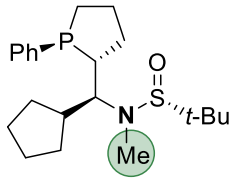


3ae



P5

3ae, 39%, 92% ee
***s* = 72**

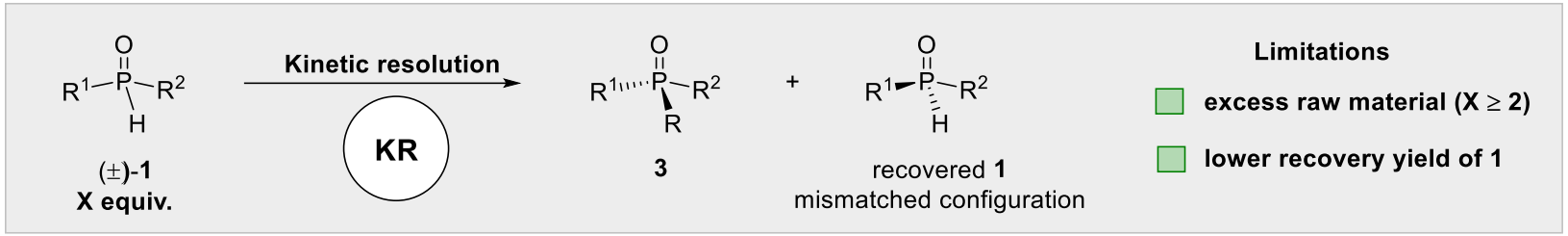


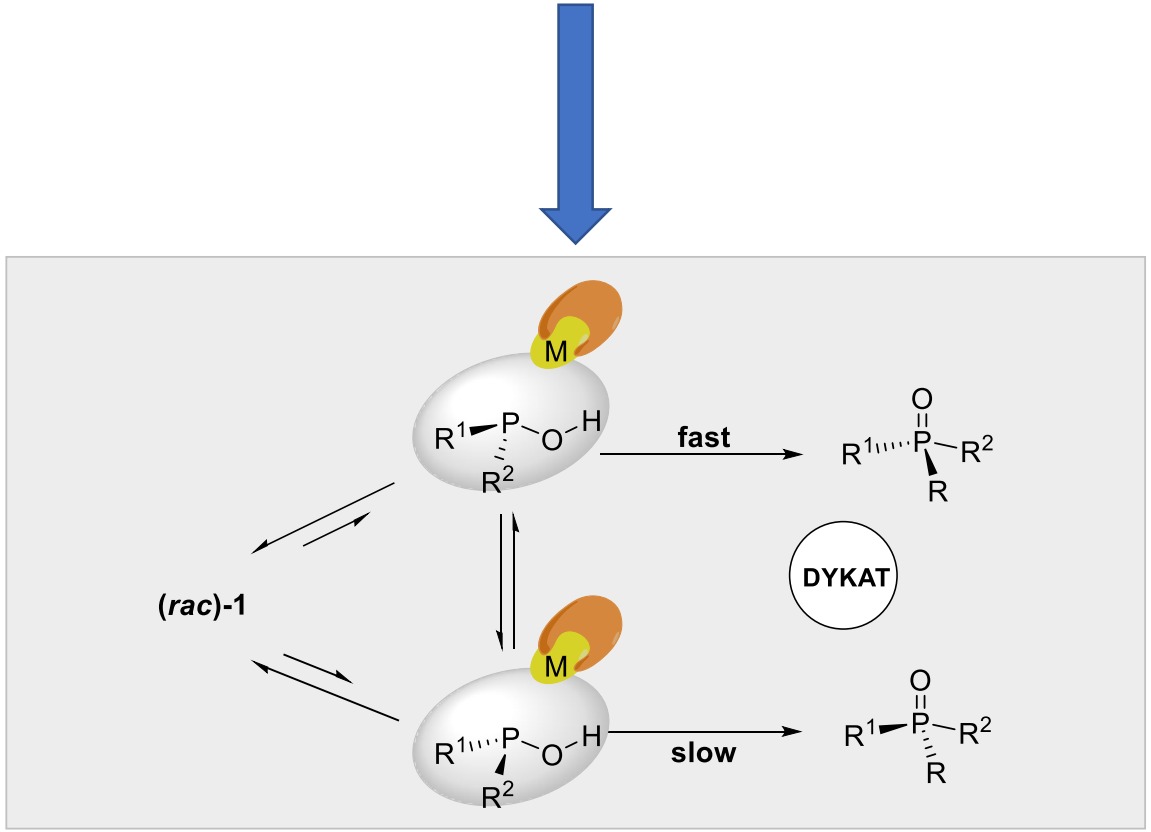
***N*-Me-P5**

3ae, 16%, 24% ee
***s* = 2**

Zhang, J.-L. et al. *Chem. Sci*. **2020**, *11*, 9983–9988.

Asymmetric functionalization via KR





Content

Background

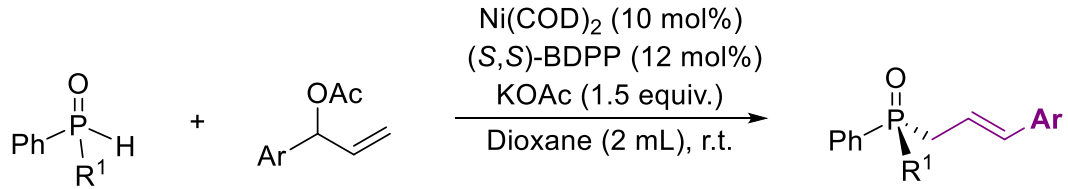
Asymmetric functionalization of racemic secondary phosphine oxides or *H*-phosphinates

- Asymmetric functionalization via kinetic resolution (KR)
- **Asymmetric functionalization via dynamic kinetic asymmetric transformation (DYKAT)**

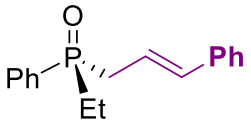
Summary and Outlook

Coupling reaction via DYKAT

Nickel catalysis

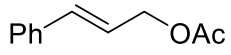


(±)-**1** + **2** (1.2 equiv.) → **3**



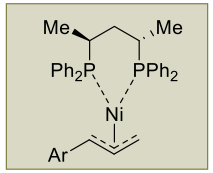
3b

LG	Yield	ee of 3b
OAc	96% yield	94% ee
OBz	96% yield	94% ee
OBoc	22% yield	94% ee
p-OMeOBz	95% yield	94% ee

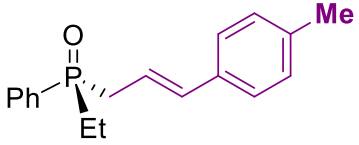


2a'

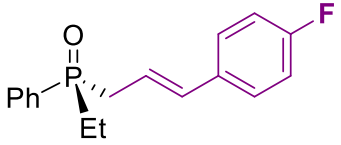
3b, 95% yield, 94% ee



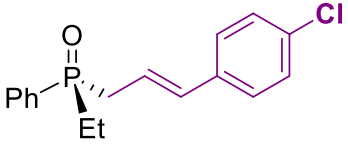
proposed intermediate



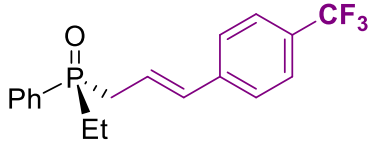
3c
77% yield, 94% ee



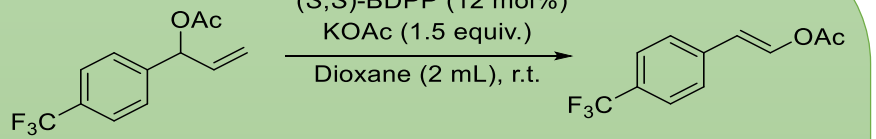
3d
88% yield, 92% ee



3e
84% yield, 92% ee



3e
74% yield, 92% ee



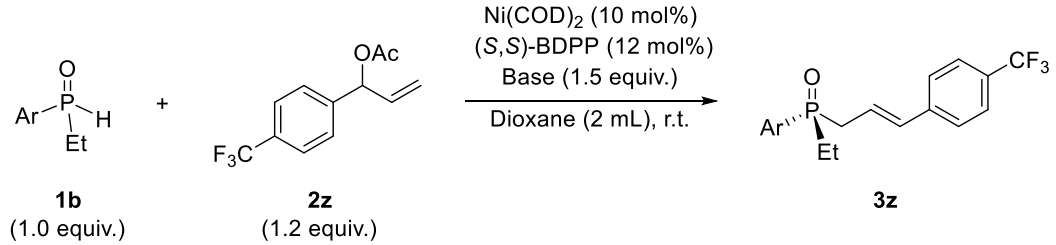
2z → **2zz**

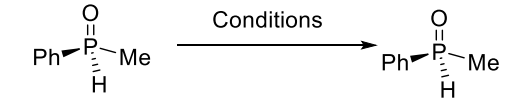
Time/h	Ratio of **2z/2zz**
0	100:0
1	3.76:1
2	3.17:1
3	2.57:1
4	2.70:1
5	2.33:1
6	2.33:1
7	2.03:1
14	1.44:1
20	1.08:1

Zhang, Q.-W. et al. *J. Am. Chem. Soc.* **2019**, *141*, 16584−16589.

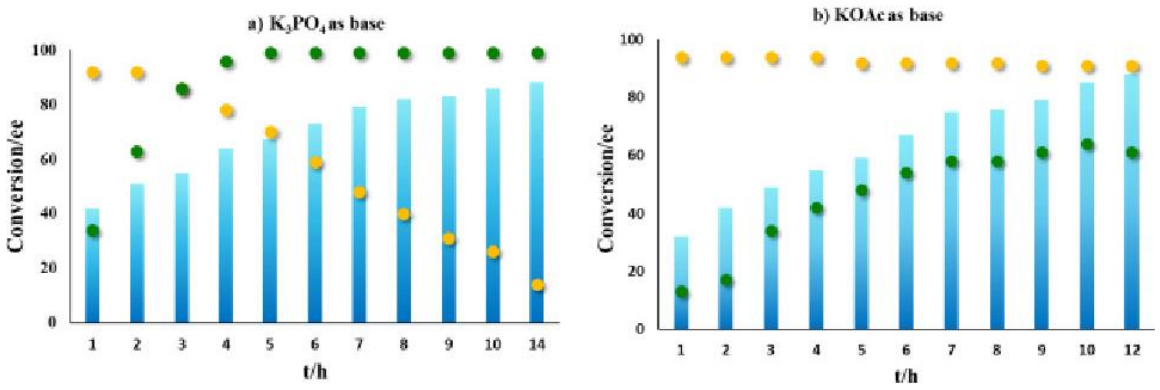
Coupling reaction via DYKAT

Nickel catalysis

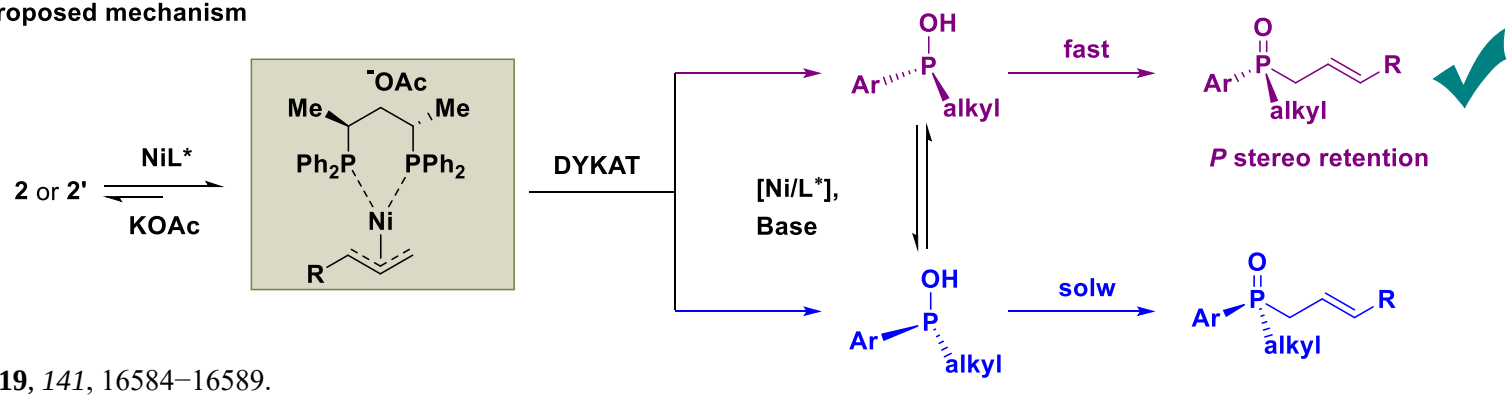




Entry	Conditions	Initial ee%	recovered ee%
1	none	91	91
2	1.5 equiv. KOAc	91	91
3	1.5 equiv. HOAc	91	91
4	1.5 equiv. K_3PO_4	91	91
5	$Ni(COD)_2$, (*S*,*S*)-BDPP, K_3PO_4	91	91
6	$Ni(COD)_2$, (*S*,*S*)-BDPP, KOAc	91	88
7	$NiBr_2$, (*S*,*S*)-BDPP, K_3PO_4	91	85
8	$NiBr_2$, (*S*,*S*)-BDPP, KOAc	91	34



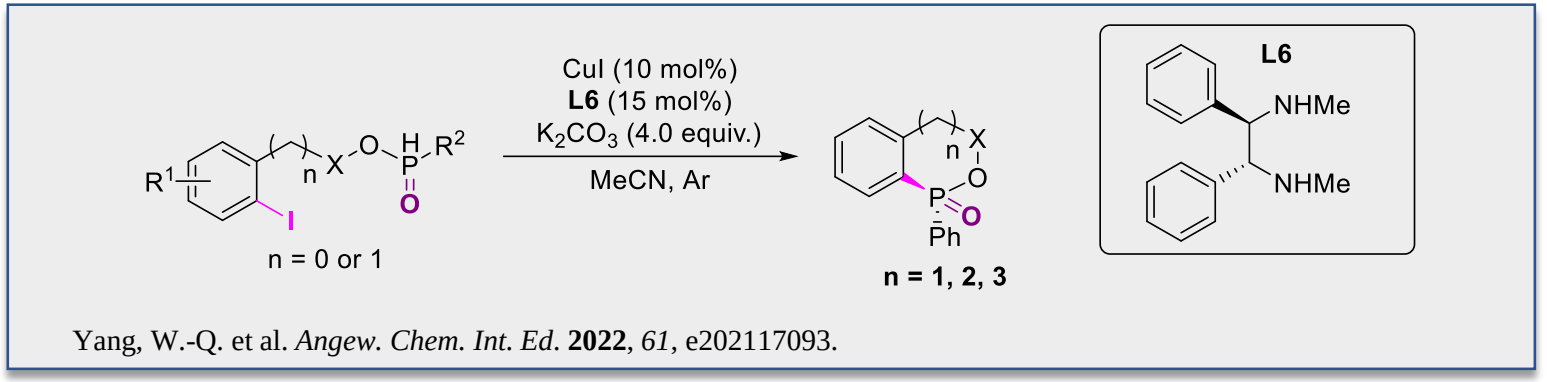
Proposed mechanism



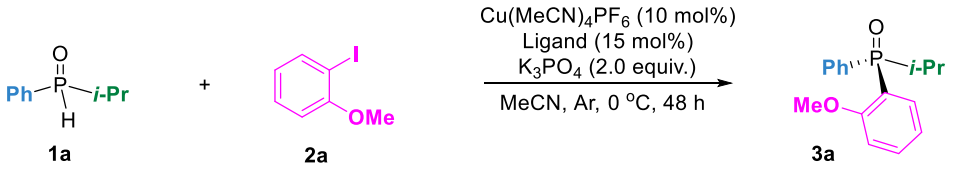
Zhang, Q.-W. et al. *J. Am. Chem. Soc.* **2019**, *141*, 16584−16589.

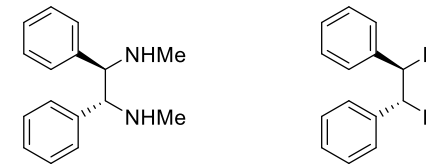
Coupling reaction via DYKAT

Cooper catalysis



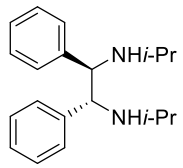
Yang, W.-Q. et al. *Angew. Chem. Int. Ed.* **2022**, *61*, e202117093.



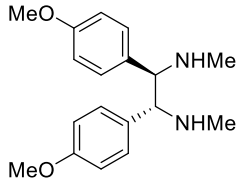


L1
40% yield, 86% ee

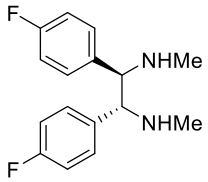
L2
-



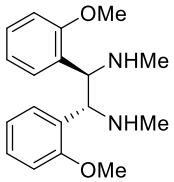
L3
-



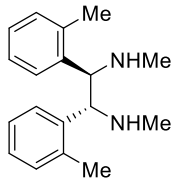
L4
35% yield, 86% ee



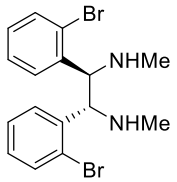
L5
46% yield, 87% ee



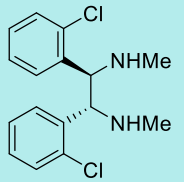
L6
22% yield, 77% ee



L7
11% yield, 84% ee



L8
46% yield, 89% ee



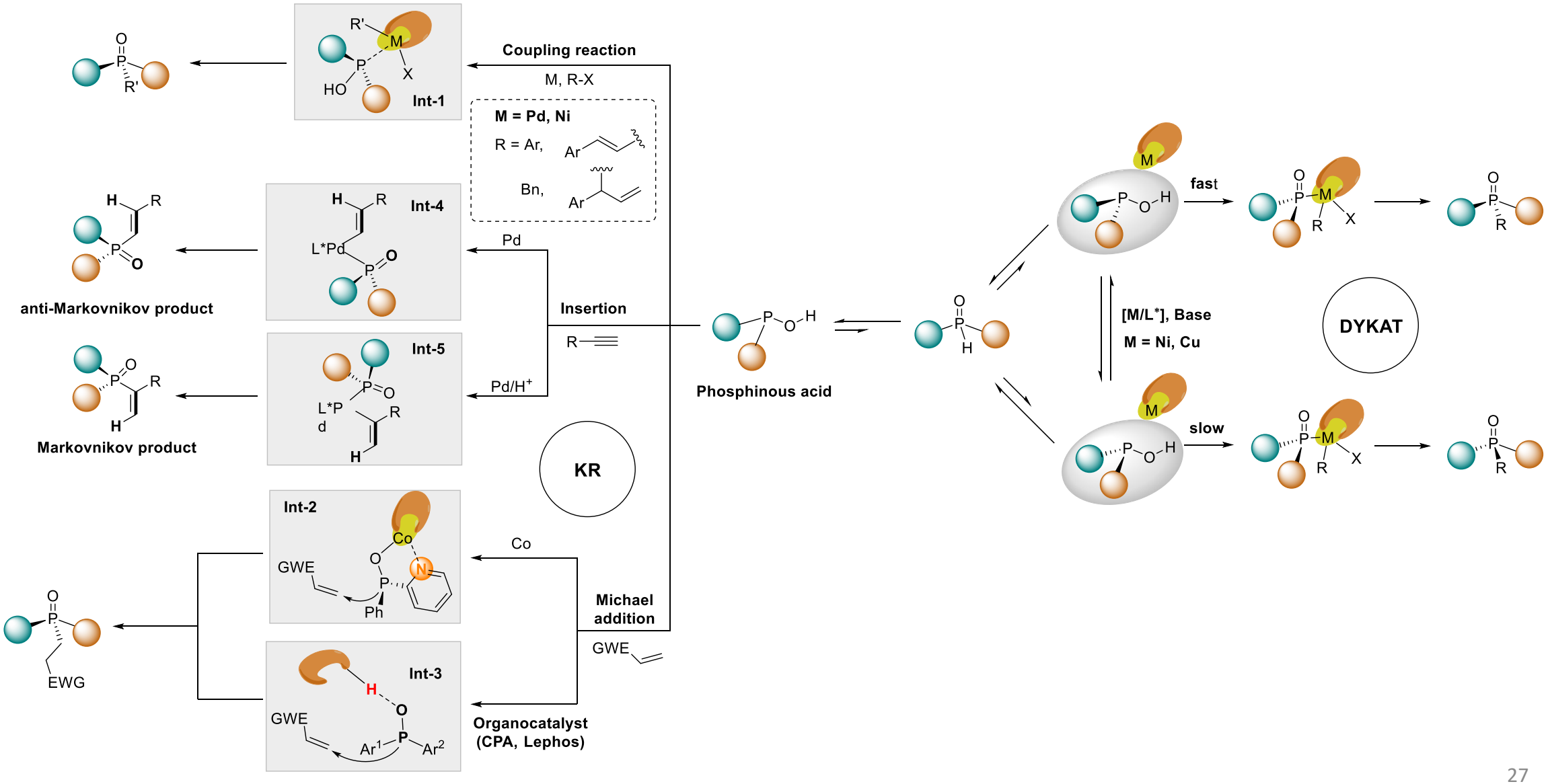
L9
50% yield, 90% ee
79% yield, 90% ee [a]

[a] Reaction was conducted with Cs_2CO_3 for 72 h.

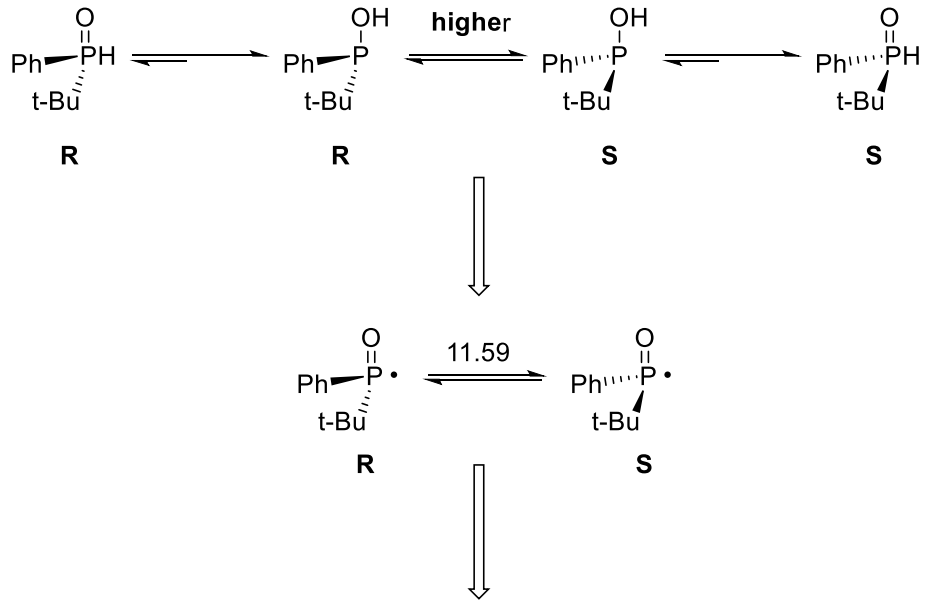
Su, B. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202301628.

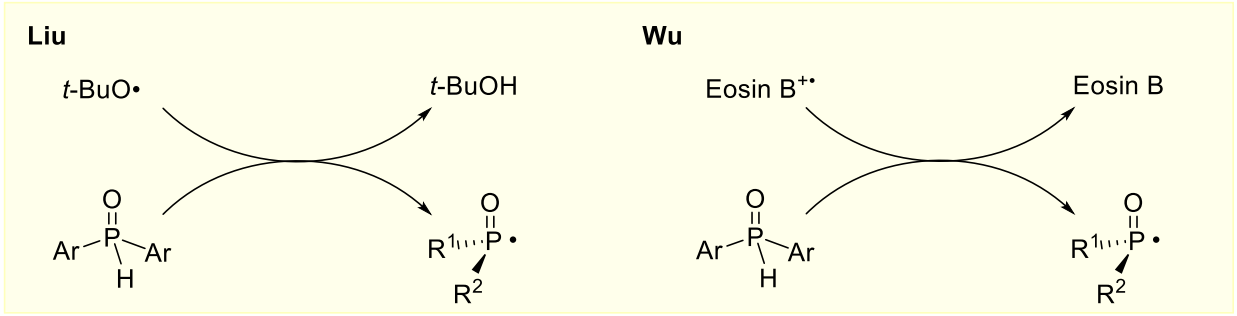
Content

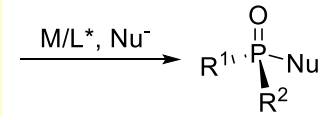
Summary


Int-1
Coupling reaction
M, R-X
M = Pd, Ni
R = Ar,
Bn,
Int-4
Pd
anti-Markovnikov product
Int-5
Insertion
Pd/H+
Markovnikov product
KR
Phosphinous acid
[M/L*], Base
M = Ni, Cu
DYKAT
fast
slow
Int-2
Co
Michael addition
GWE
EWG
Int-3
Organocatalyst (CPA, Lephos)

Outlook-Dynamic Kinetic Resolution (DKR)

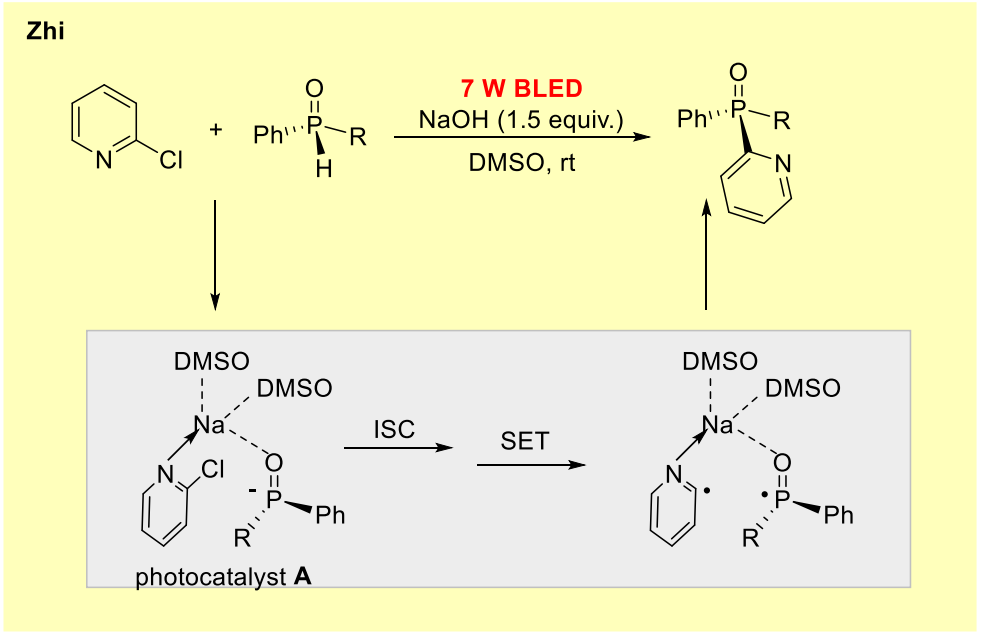


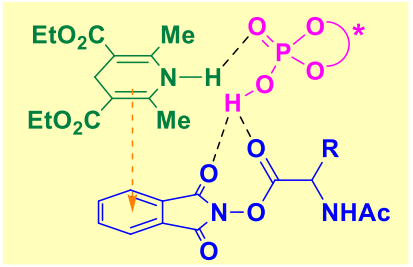




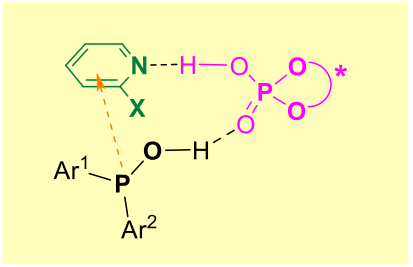
Wu, L. et al. *Org. Lett*. **2016**, *18*, 452−455.
Liu, G.-S. et al. *Org. Lett.* **2019**, *21*, 5015−5020.

Outlook-Photocatalysis





EDA complex activated by CPA

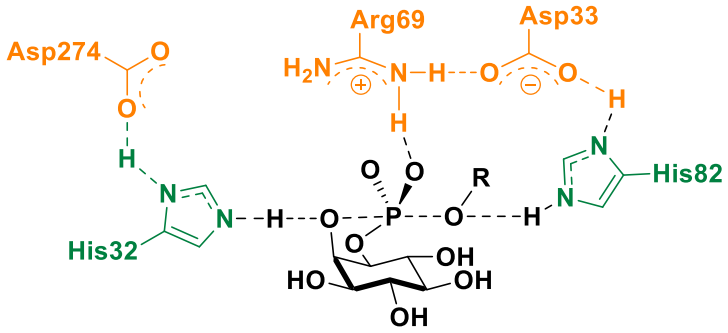


EDA complex activated by CPA

Che, C. et al. *Chem. Sci*. **2022**, *13*, 6519–6524.
Lu, G. et al. *ACS Catal*. **2022**, *12*, 13065−13074.
Jiang, Z. et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216605.

Outlook-New organocatalyst

Construct C-O bond in Enzymes



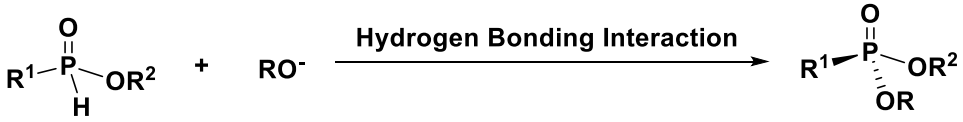
Enzymes lower the barrier to phosphorus bond formation through:

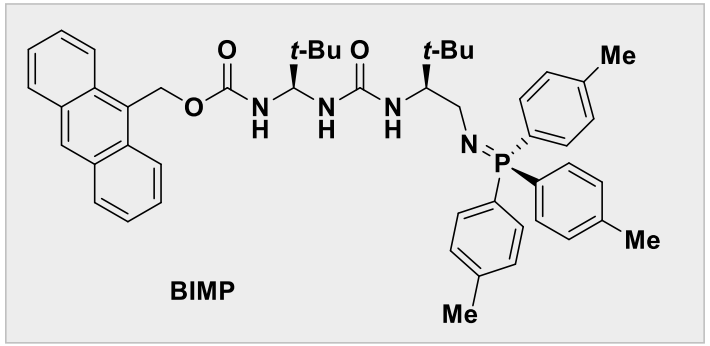
Nucleophile Activation

Leaving Group Activation

Transition State Stabilization

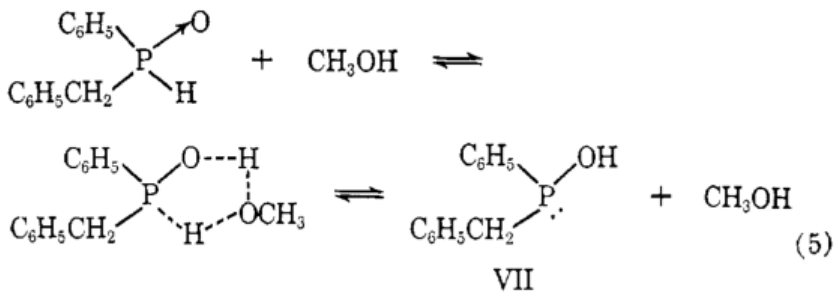
Construct C-O bond by using organocatalyst

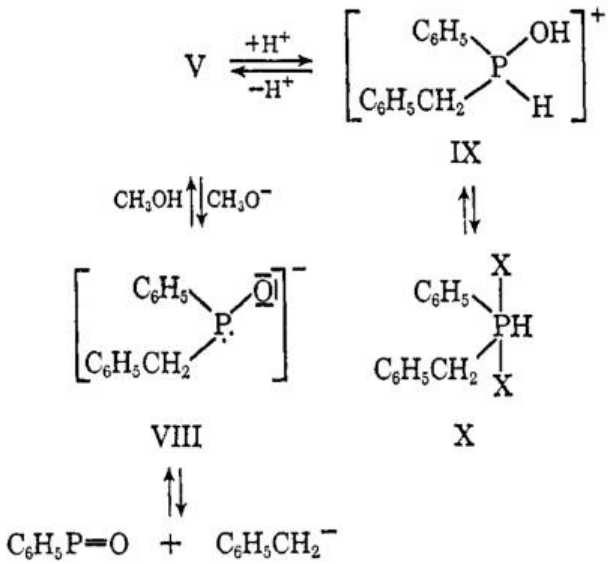




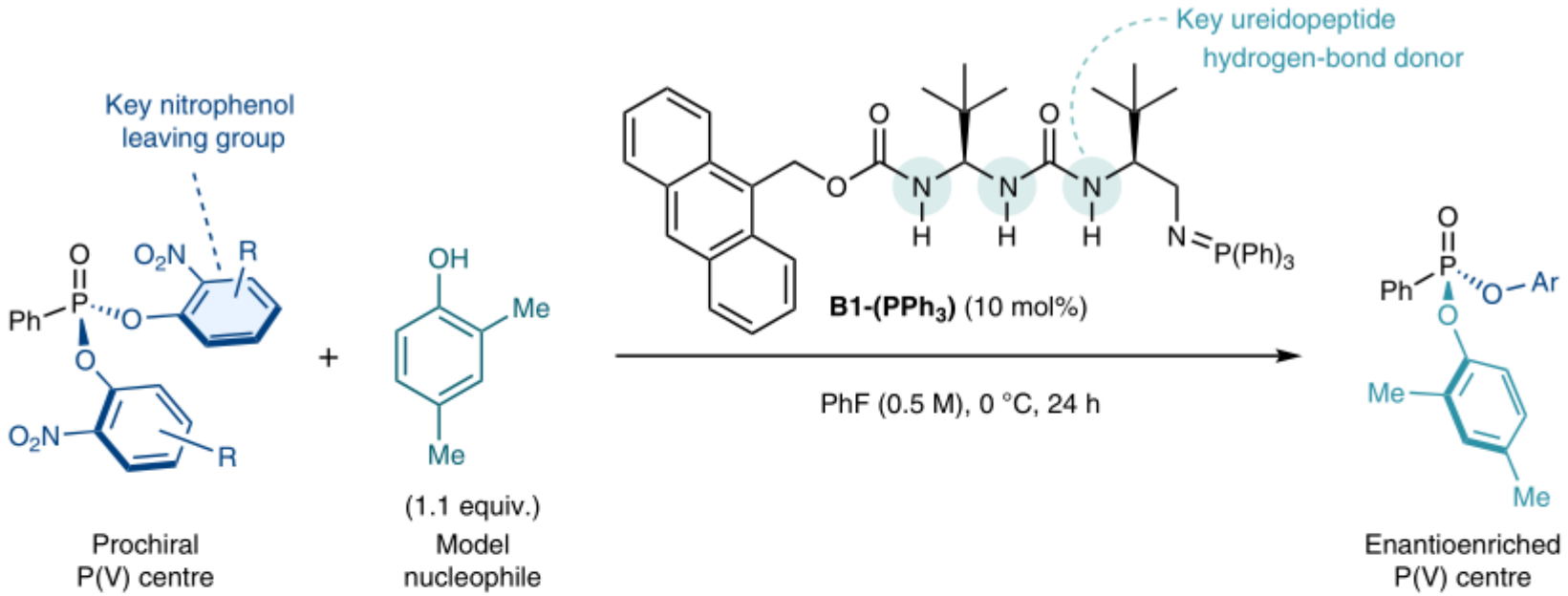
DiRocco. D.-A. et al. *Science* **2017**, *356*, 426–430.
Dixon. D. et al. *Nat. Chem.* **2023**, *15*, 714–721.

Thank you!





J. Am. Chem. Soc. 1968, 90, 3459−3465.



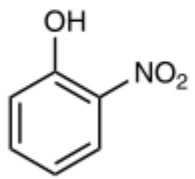
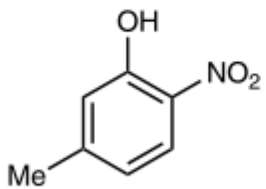
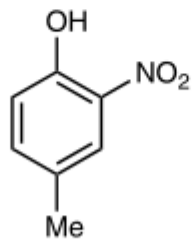
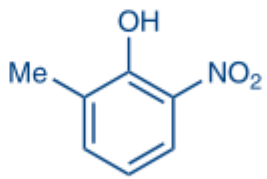
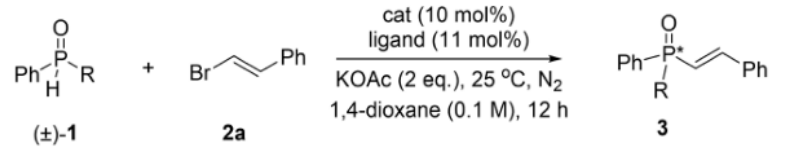
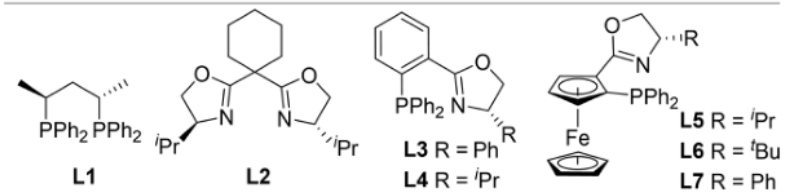
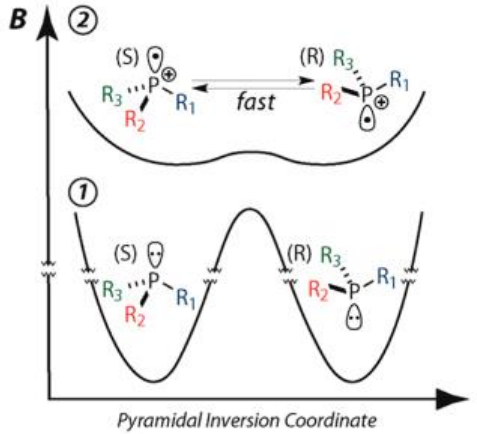
Ar—OH				Optimal conditions
				BIMP (15 mol%) r.t. (0.25 M) $P(p\text{-tol})_3$ instead of PPh_3
LG1; 41% yield 87% e.e.	**LG2;** 34% yield 67% e.e.	**LG3;** 61% yield 89% e.e.	**LG4;** 10% yield 94% e.e.	**1**; 84% yield 91% e.e. ArOH = **LG4**

Table 1: Optimization of reaction conditions.[a]

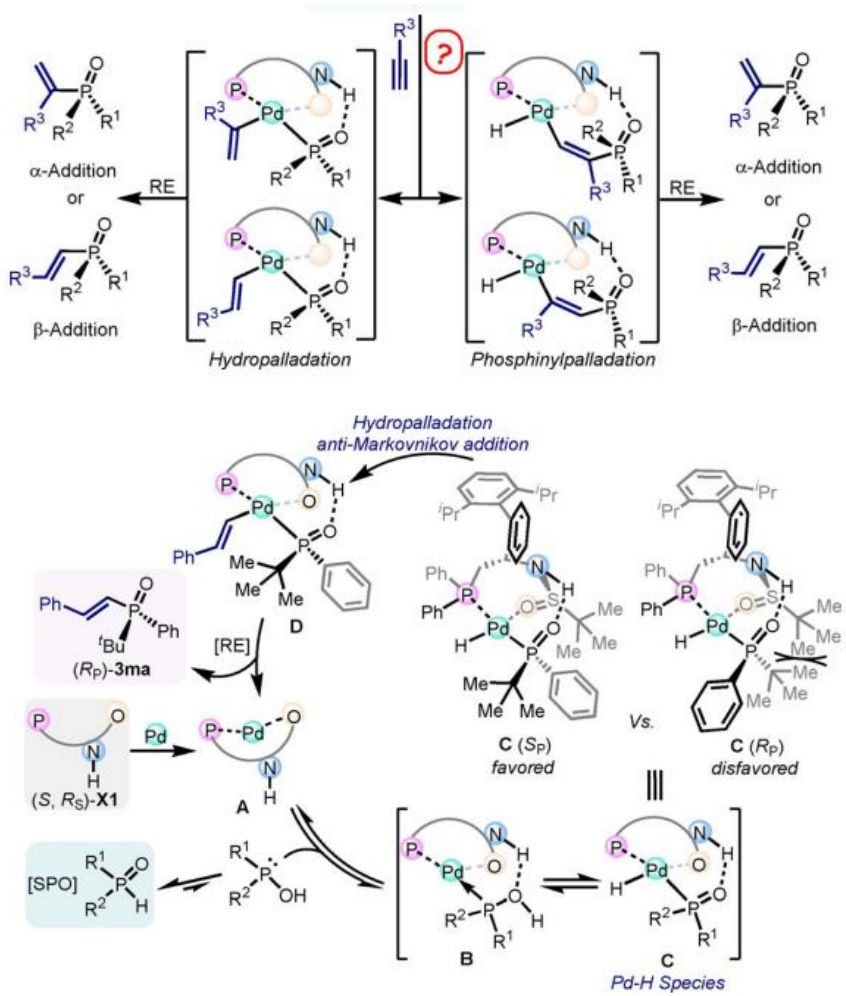




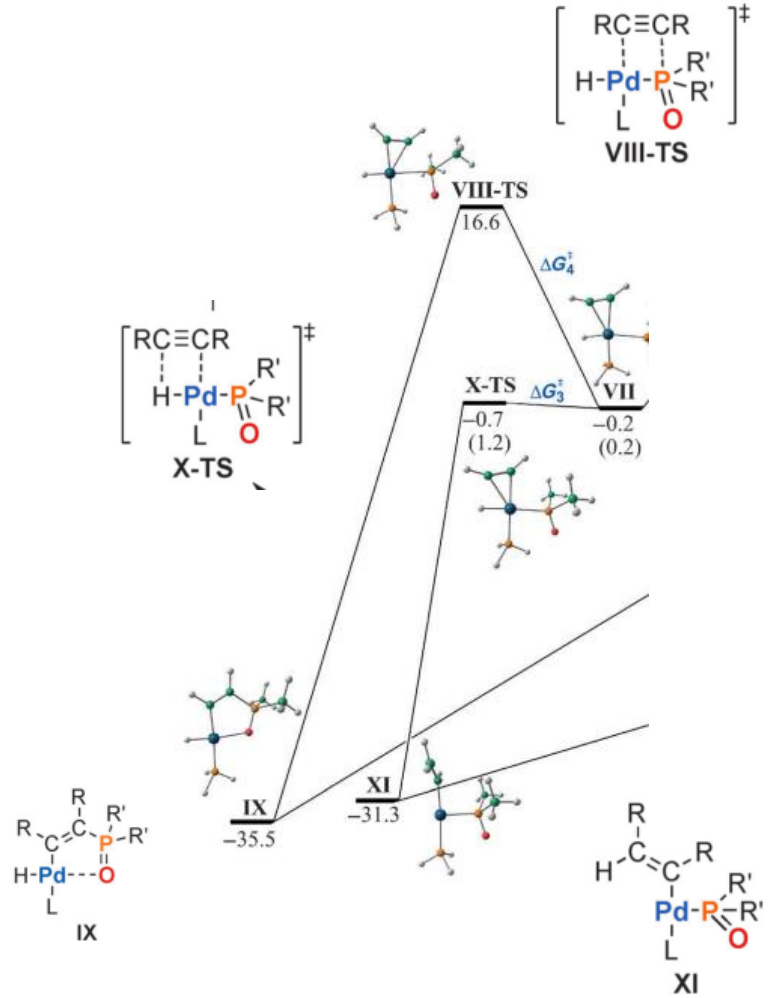
entry	cat	ligand	R	product	yield (%)[b][c]	ee (%)[d]
1	$Ni(cod)_2$	**L1**	^{t}Bu	**3a**	21	9
2	$Ni(cod)_2$	**L2**	^{t}Bu	**3a**	13	8
3	$Ni(cod)_2$	**L3**	^{t}Bu	**3a**	82	78
4	$Ni(cod)_2$	**L4**	^{t}Bu	**3a**	50	89
5	$Ni(cod)_2$	**L5**	^{t}Bu	**3a**	76	86
6	$Ni(cod)_2$	**L6**	^{t}Bu	**3a**	41	94
7	$Ni(cod)_2$	**L7**	^{t}Bu	**3a**	96	95
8	$Pd_2(dba)_3$	**L7**	^{t}Bu	**3a**	95	57
9	$Ni(cod)_2$	**L7**	^{i}Pr	**3b**	41	50
10	$Ni(cod)_2$	**L7**	Et	**3c**	40	44
11	$Ni(cod)_2$	**L7**	Mes	**3d**	13	50

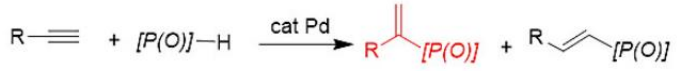


J. Am. Chem. Soc. 2013, 135, 9354–9357



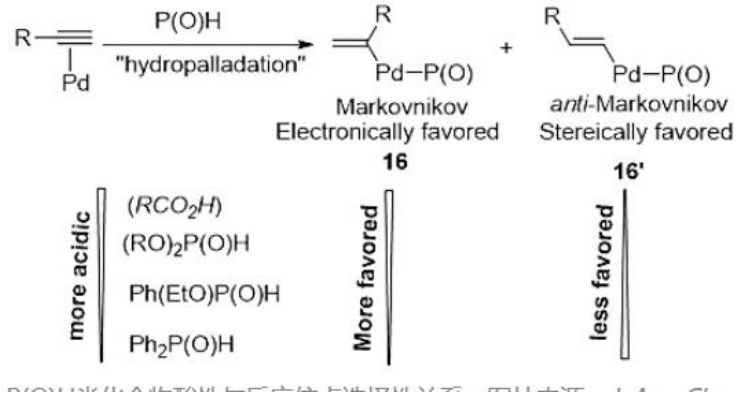
Scheme 4. Proposed mechanism.

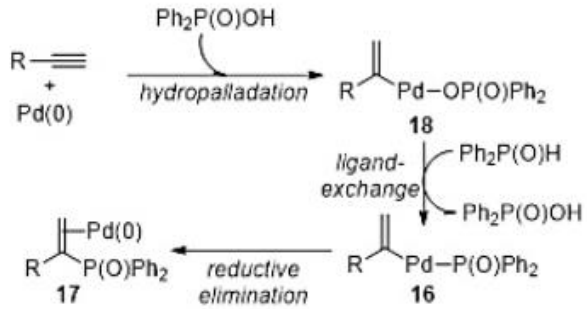




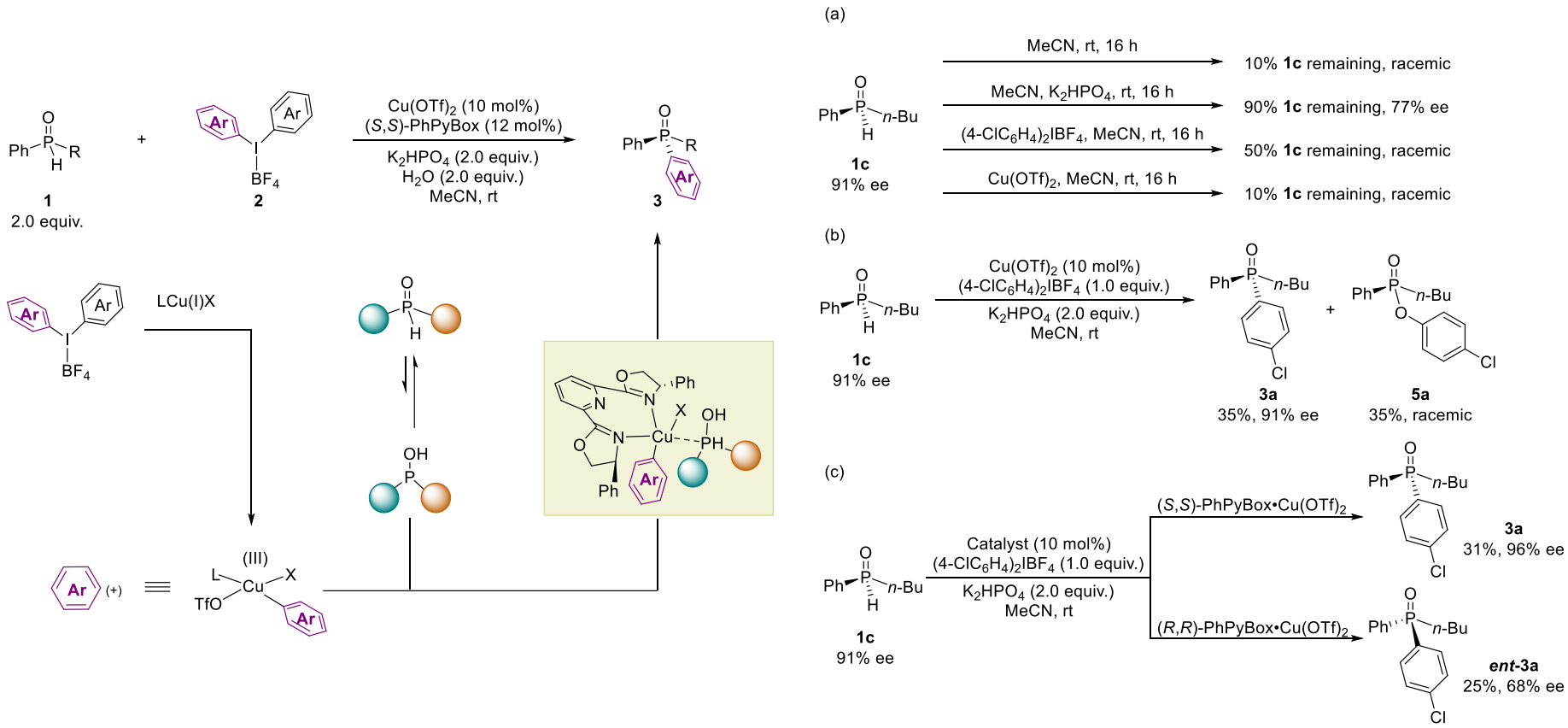
1 2 3 3'

P(O)-H compound	catalyst	major adduct
$(RO)_2P(O)H$	Pd(0)	3
H-phosphonate	$Pd(0)/Ph_2P(O)OH$	3
(RO)(R')P(O)H	Pd(0)	3'
H-phosphinate	$Pd(0)/Ph_2P(O)OH$	3
$R_2P(O)H$	Pd(0)	3'
H-phosphine oxide	$Pd(0)/Ph_2P(O)OH$	3



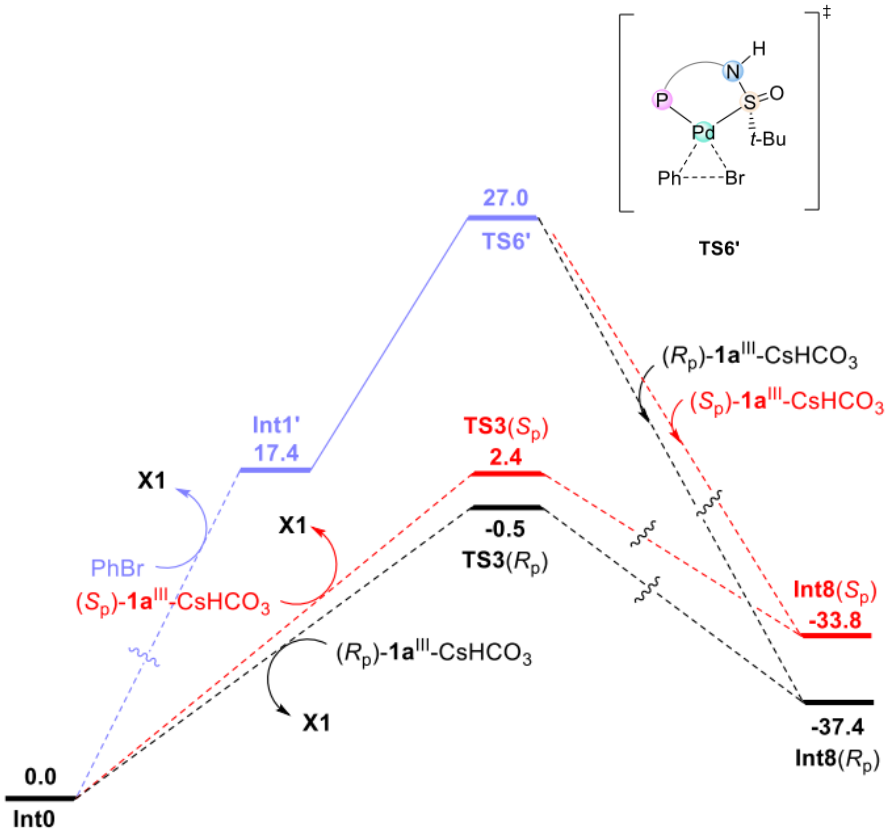


Introduction



Gaunt, M.* et al. *J. Am. Chem. Soc.* **2016**, *138*, 13183−13186.

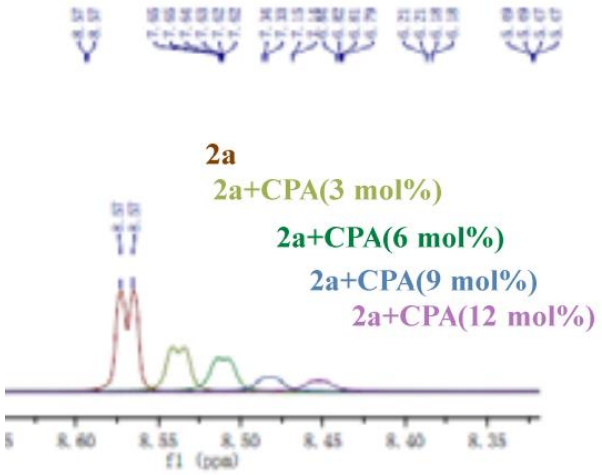
Kinetic resolution

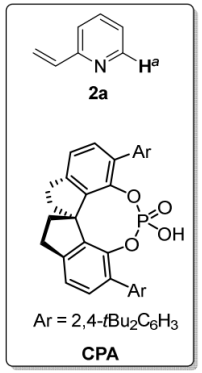


Zhang, J.* et al. *Eur. J. Org. Chem*. **2023**, *26*, e202300804.

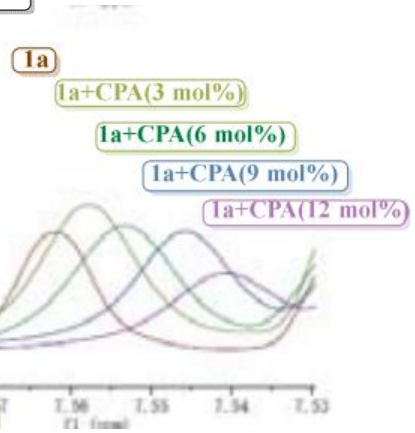
Kinetic resolution

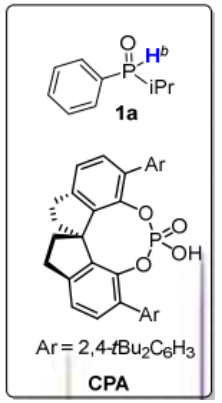
NMR titration experiment





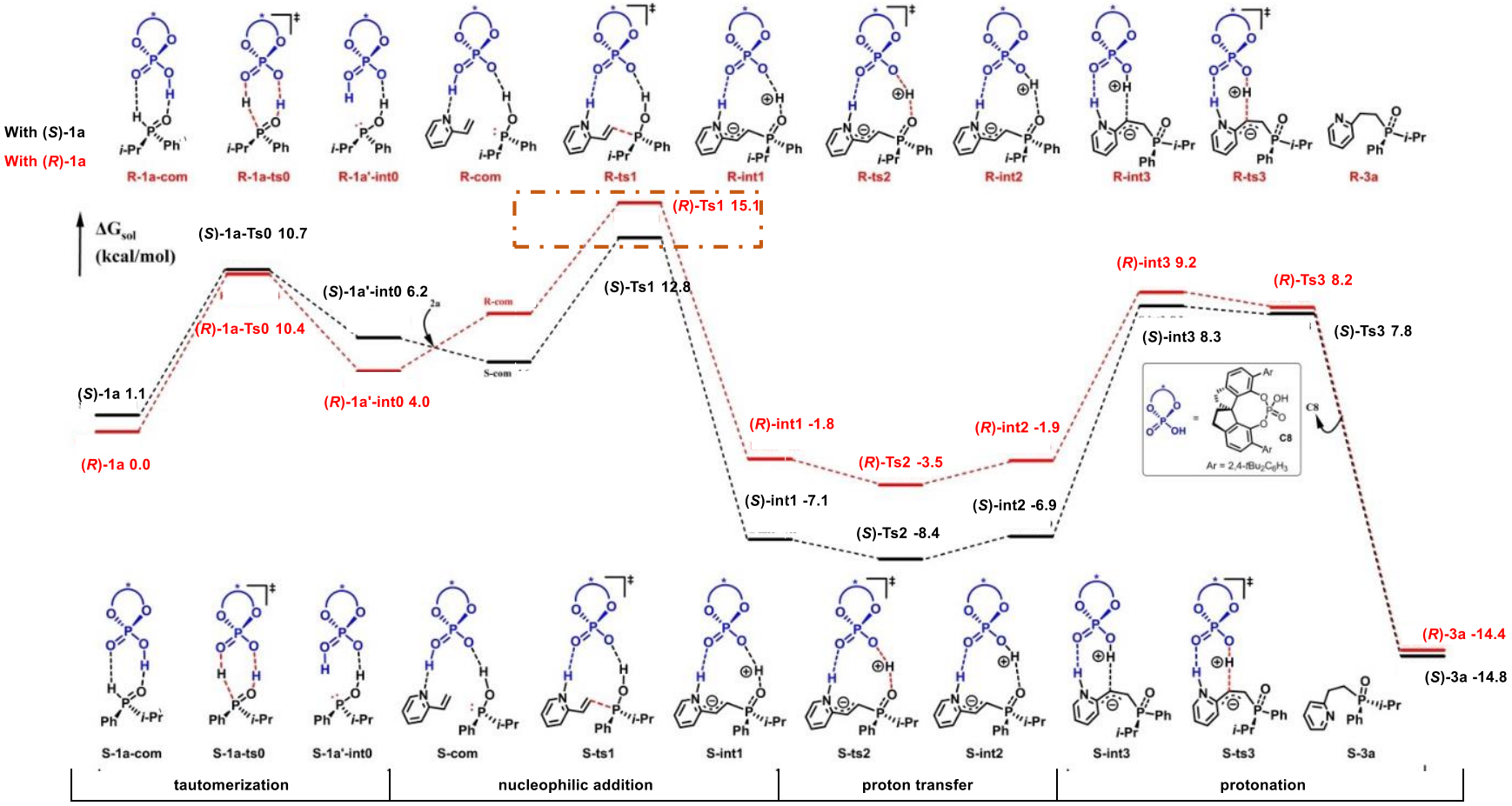
Hydrogen-bonding interaction





Jiang, Z.* et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216605.

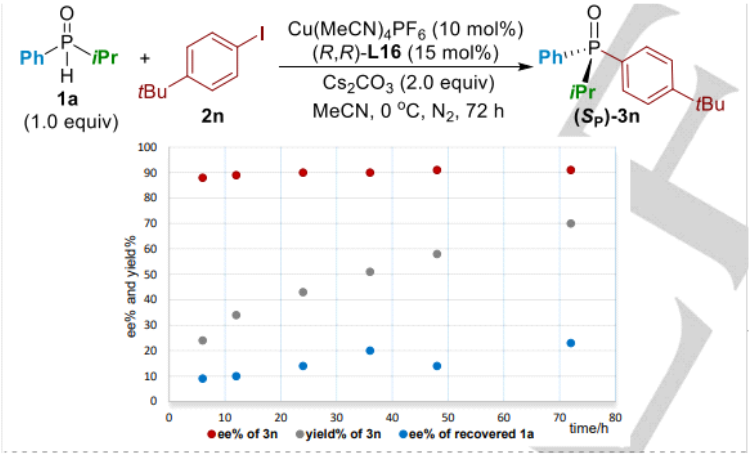
Kinetic resolution



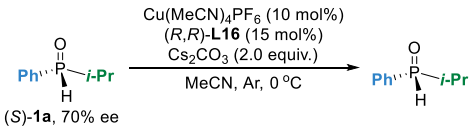
Jiang, Z.* et al. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216605.

Dynamic kinetic asymmetric transforamation

a) reaction profiles regarding yield and ee of pdt. and ee of recovered SM

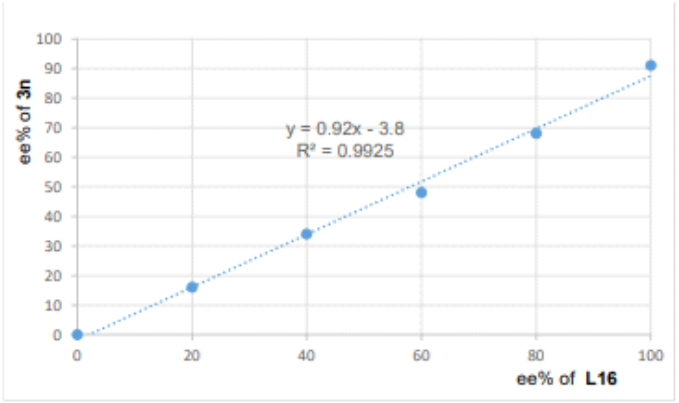


b) racemization study of the SPO

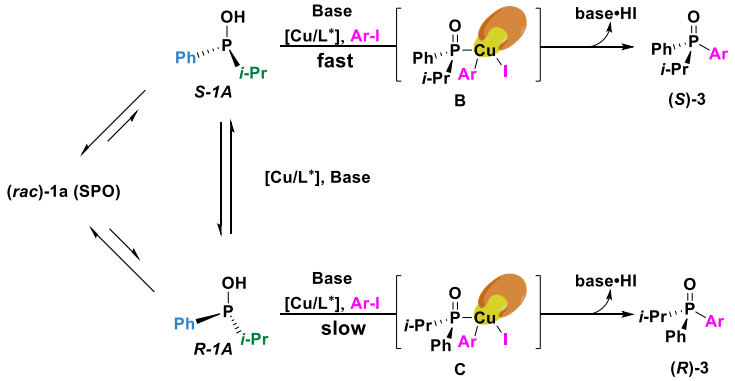


Entry	Conditions	Recovered yield%	Recovered ee%
1	none, 2 h	40	0
2	w/o [Cu/L*], 12 h	90	70
3	w/o Cs_2CO_3, 12 h	38	68

c) Nonlinear effect study on the asymmetric Cu-catalyzed P-C coupling



d) Proposed reaction mechanism



Su, B.* et al. *Angew. Chem. Int. Ed*. **2023**, *62*, e202301628.