

# Zhu shaolin Group

Synthetic Organic Chemistry and Catalysis

Ni-H Catalysis

Yuzhong Gao

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# Shaolin Zhu



## Education

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2015.09-至今: 南京大学 化学与生物医药创新研究院 双聘PI

2015.09-至今: 南京大学 化学系 教授

2013.02-2015.08: 麻省理工学院 化学系 博士后(导师:Stephen L. Buchwald院士)

2010.12-2013.01: 普林斯顿大学 化学系 博士后(导师:David W. C. MacMillan院士)

2010.08-2010.11: 研究助理 中科院上海有机所 (导师:马大为院士)

2005.08-2010.07: 博士 中科院上海有机化学研究所 (导师:马大为院士)

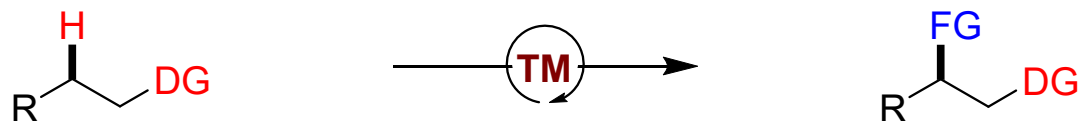
## Research

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有机合成, 不对称催化, 化学生物学

# Alternative Strategy for Formal Remote C(sp<sup>3</sup>)-H functionalization

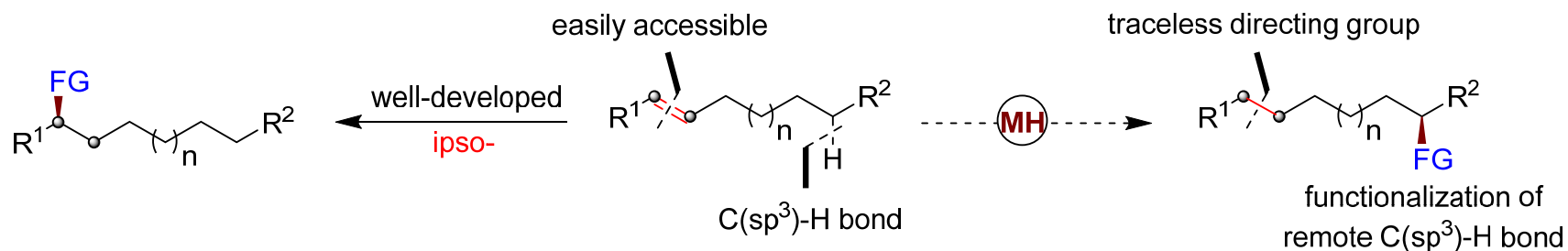
## ◆ Traditional C(sp<sup>3</sup>)-H functionalization



### Limitations:

- ◆ Polar directing group required
- ◆ install/remove directing group
- ◆ functionalization at nearby
- ◆ High temperature

## ◆ Alternative approach: C=C as a traceless directing group for remote C(sp<sup>3</sup>)-H functionalization?



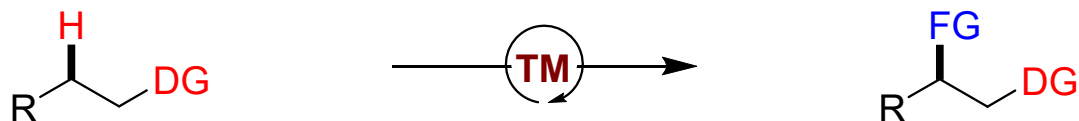
### Selected reviews of remote functionalization:

Marek, I. *Nat Chem.* **2016**, 8, 209.

Martin, R. & Marek, I. *ACS Cent. Sci.* **2018**, 4, 153.

# Alternative Strategy for Formal Remote C(sp<sup>3</sup>)-H functionalization

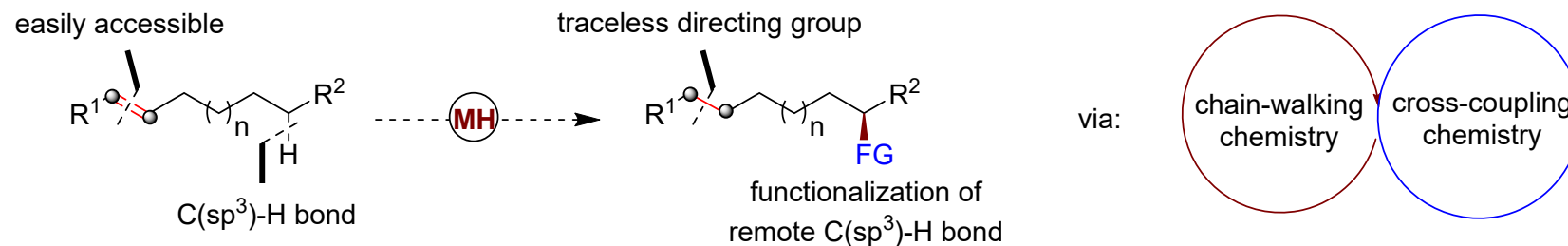
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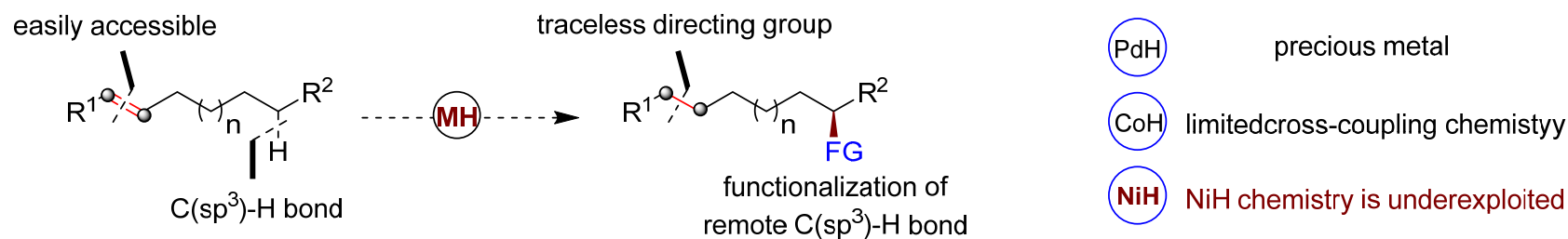
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# Alternative Strategy for Formal Remote C(sp<sup>3</sup>)-H functionalization

## ◆ Traditional C(sp<sup>3</sup>)-H functionalization

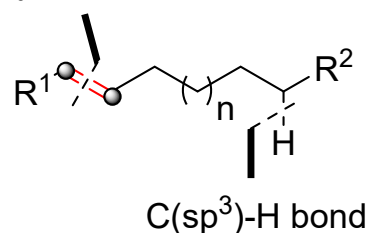


### Limitations:

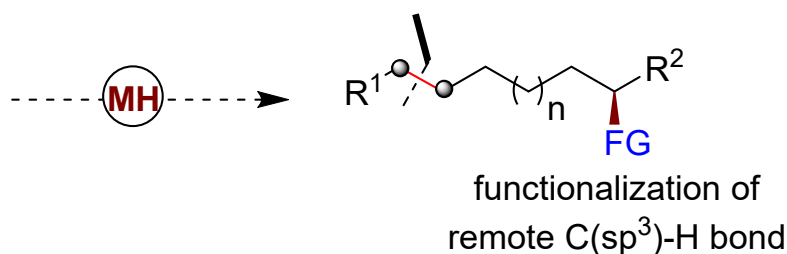
- ◆ Polar directing group required
- ◆ install/remove directing group
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- ◆ High temperature

## ◆ Alternative approach: C=C as a traceless directing group for remote C(sp<sup>3</sup>)-H functionalization?

easily accessible



traceless directing group



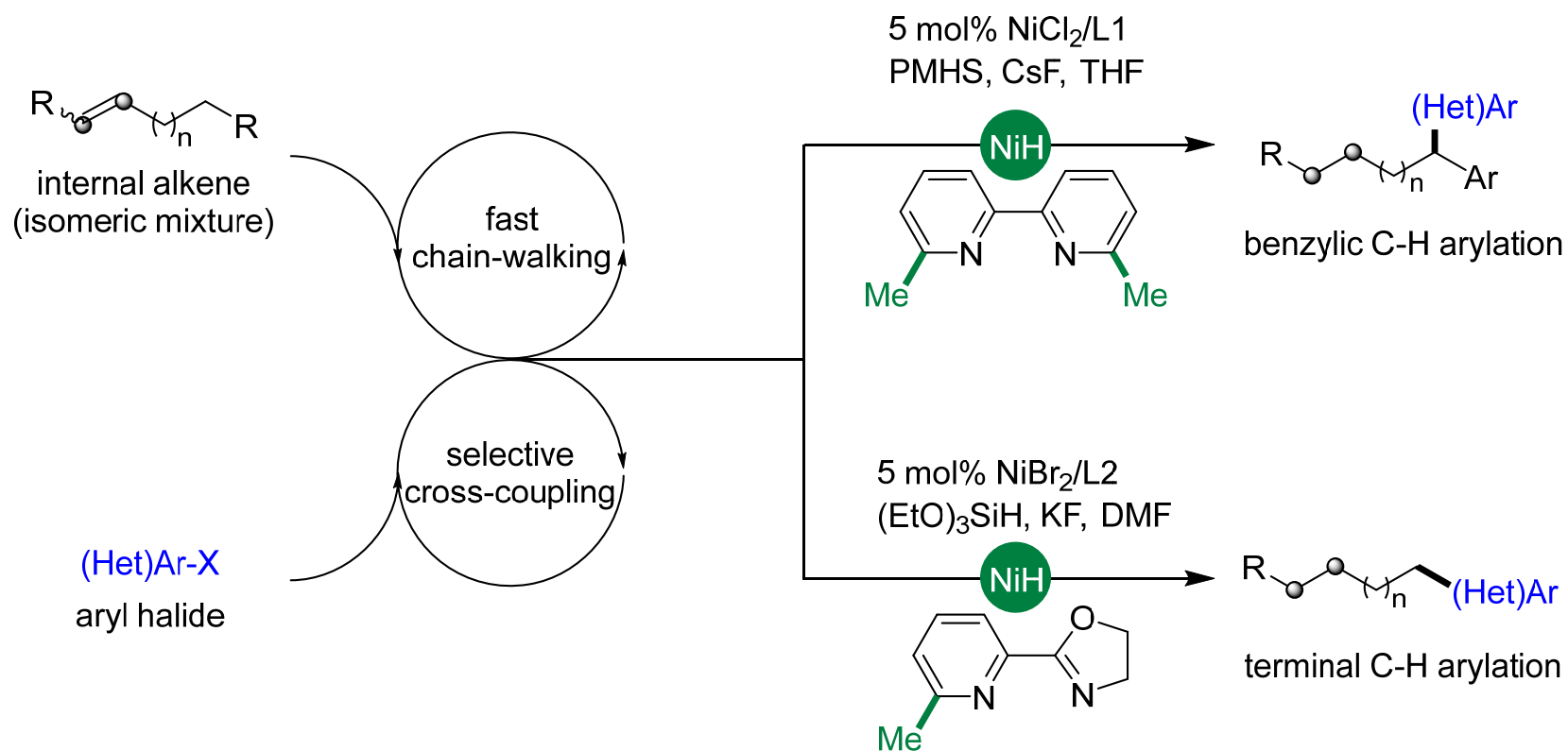
### Highlights

- ◆ avoid organometallic reagents
- ◆ diverse functionalization
- ◆ regio- & enantioselective
- ◆ regioconvergent/regiodivergent
- ◆ mild conditions

Zhu, S. *Acc. Chem. Res.* **2022**, *55*, 3519.

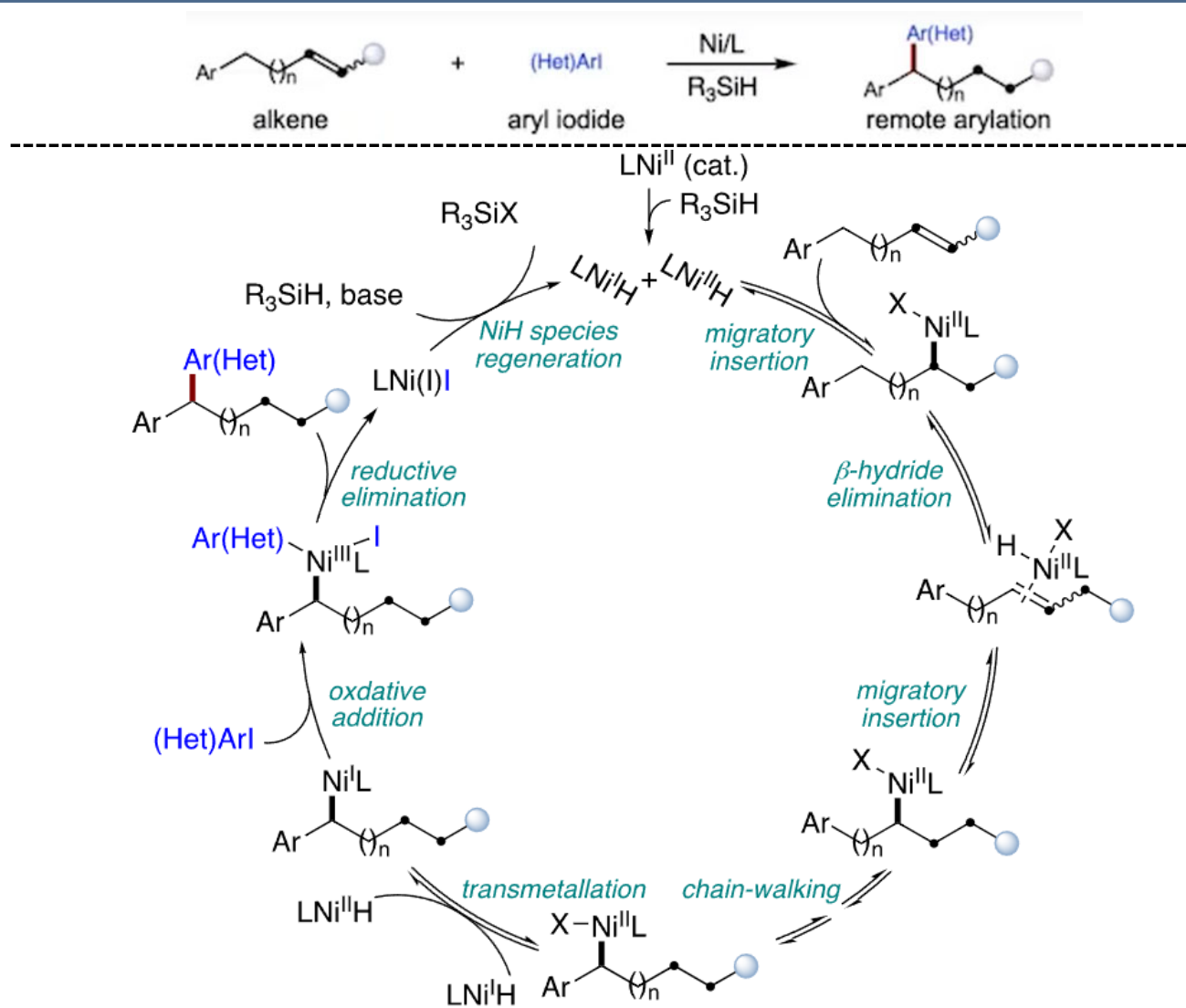
# NiH-Catalyzed Regiodivergent Remote Hydroarylation of Olefins

## ◆ Switchable regioselectivity: ligand controlled



*J. Am. Chem. Soc.* **2017**, 139, 1061.

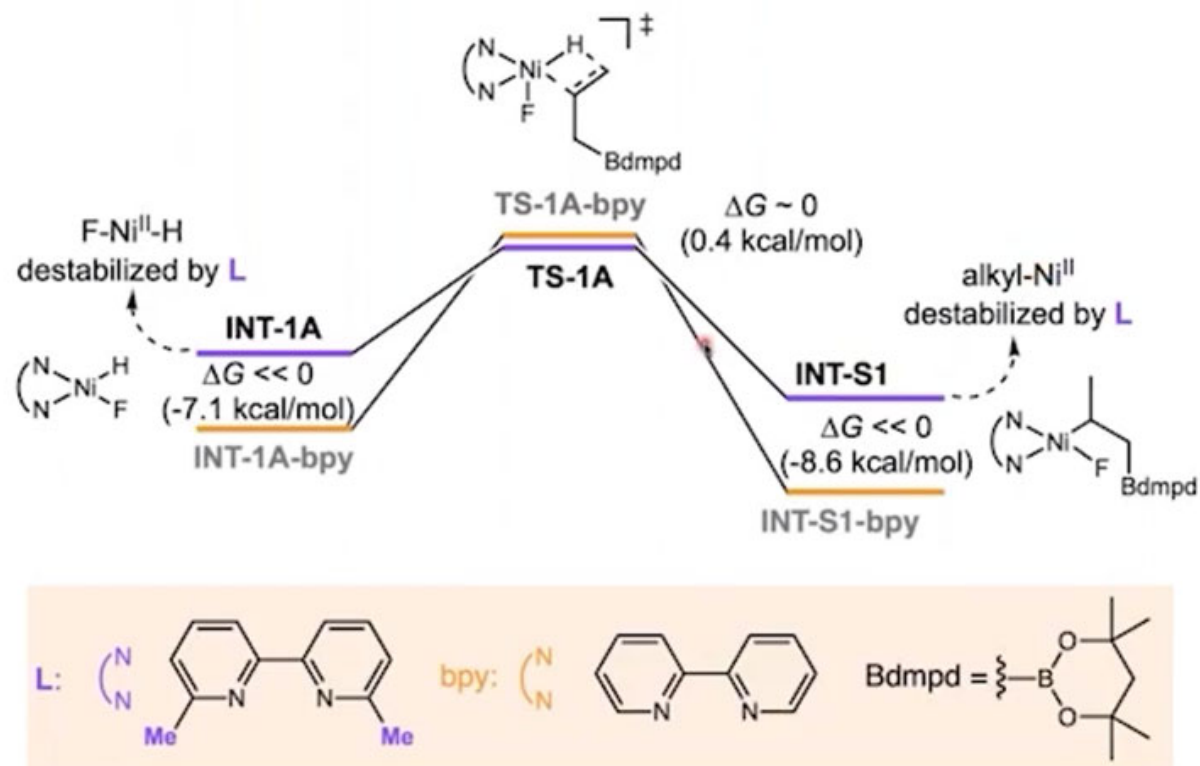
# Remote Hydroarylation: Proposed Catalytic Cycle





# DFT

## ◆ Thermodynamics: ligand effect in chain-walking process

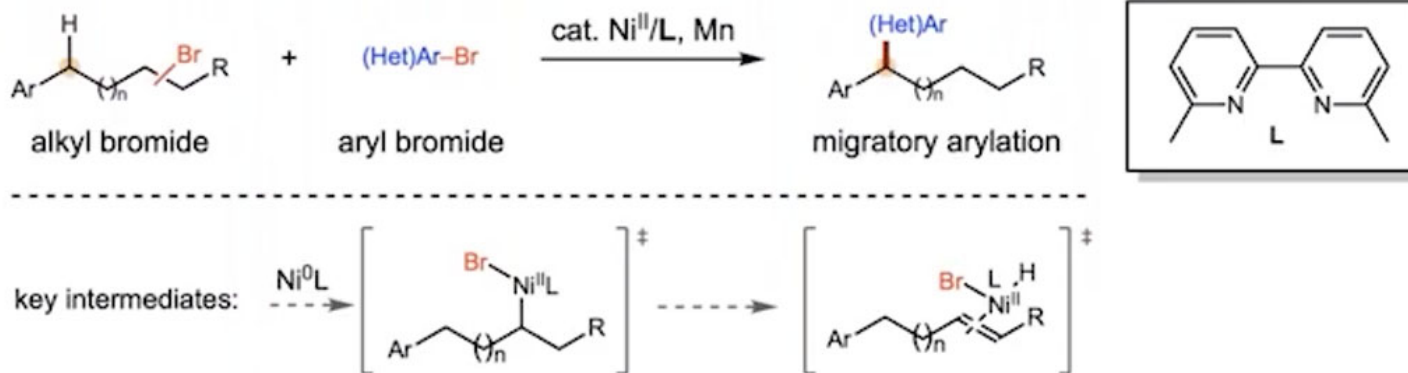


Conclusion: L could increase the chain-walking reactivity

*Chem.* **2021**, *7*, 3173.

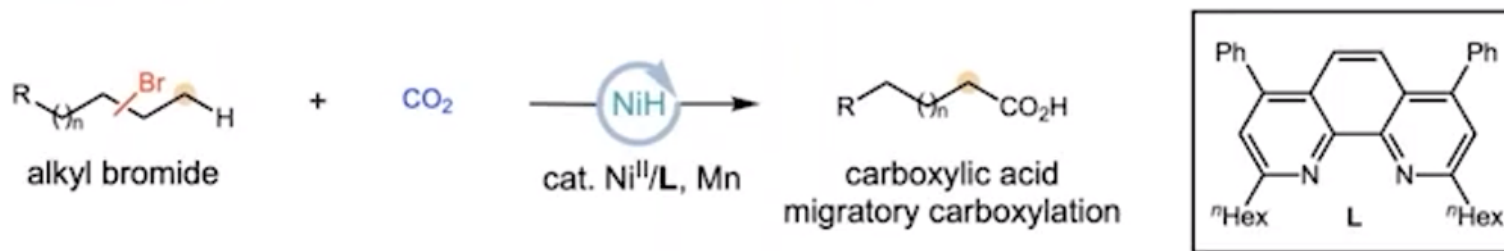
# Remote Hydroarylation of Alkenes: $n\text{PrBr/Mn}$ as Hydride Source

## ◆ Migratory reductive cross-coupling of alkyl bromides with aryl bromides



*J. Am. Chem. Soc.* **2017**, 139, 13929.

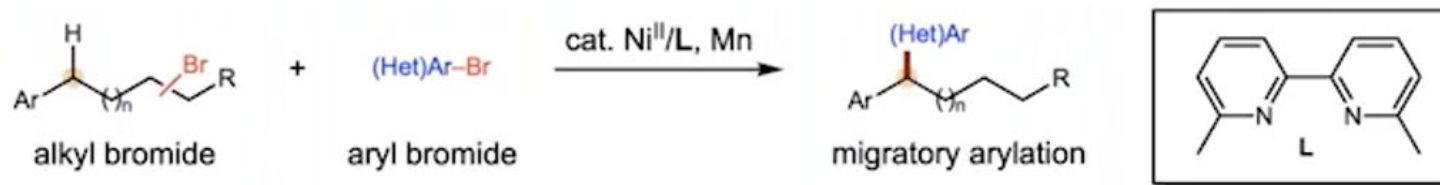
## ◆ Martin's work



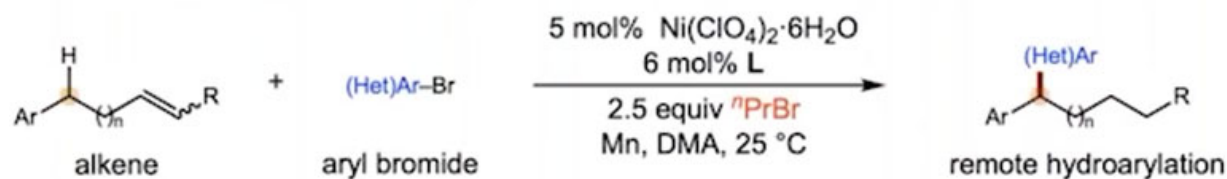
Martin, R. et al. *Nature* **2017**, 139, 13929.

## Remote Hydroarylation of Alkenes: <sup>n</sup>PrBr/Mn as Hydride Source

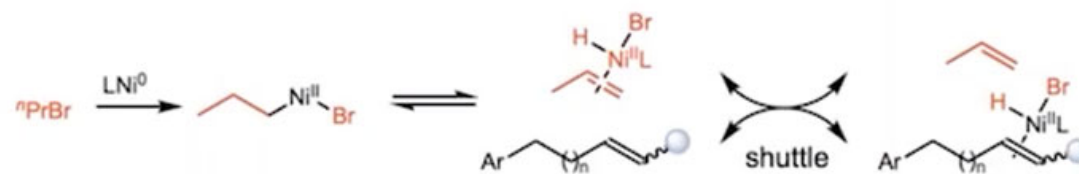
- ◆ Migratory reductive cross-coupling of alkyl bromides with aryl bromides



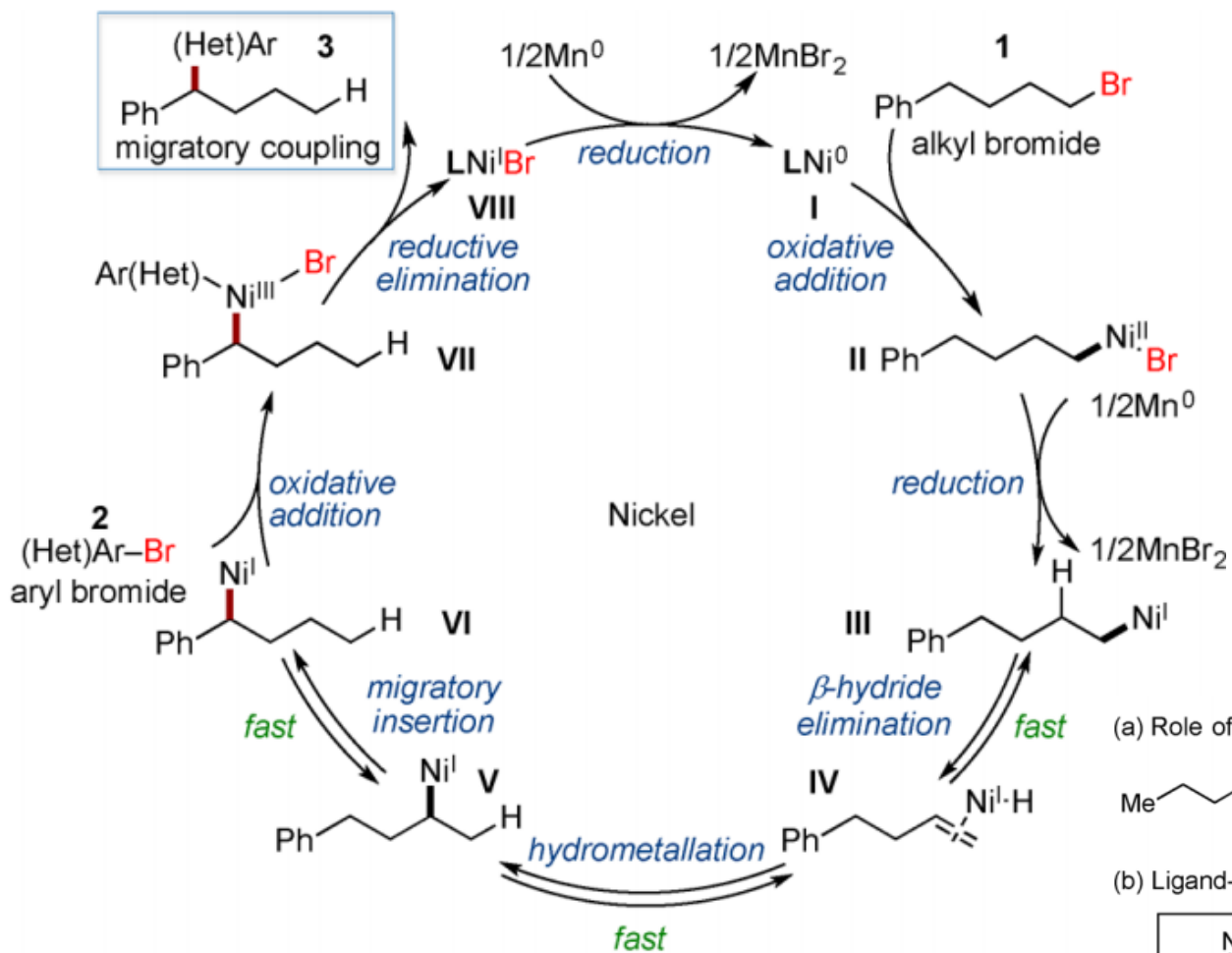
- ◆ Alternative approach: provides hydride source in the present of  $\text{Mn}^0$



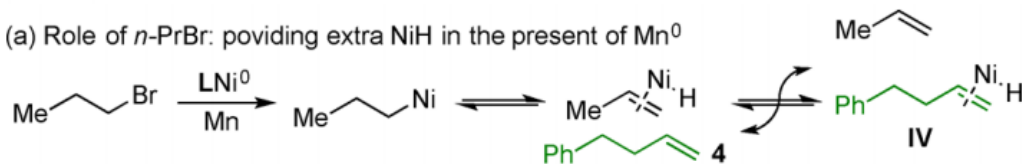
Role of <sup>n</sup>PrBr: provides hydride source in the present of  $\text{Mn}^0$



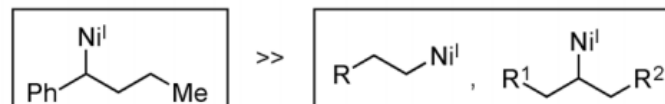
*J. Am. Chem. Soc.* **2017**, 139, 13929.



(a) Role of *n*-PrBr: providing extra NiH in the present of Mn<sup>0</sup>



(b) Ligand-controlled arylation reactivity: benzylnickel(I)  $\gg$  other alkyl nickel(I)

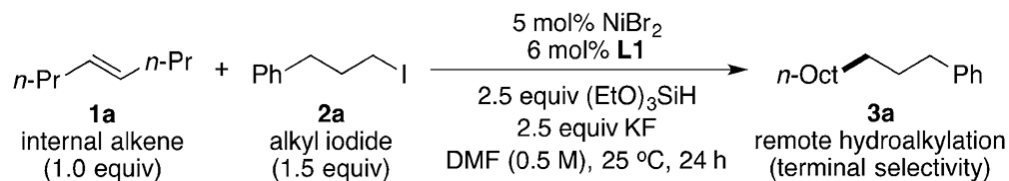


正丙基溴提供额外的NiH物种

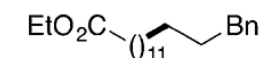
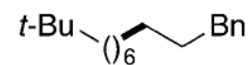
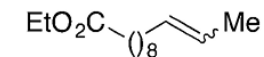
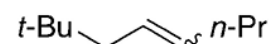
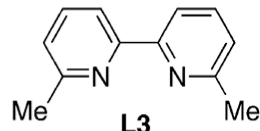
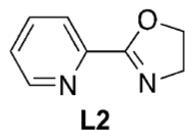
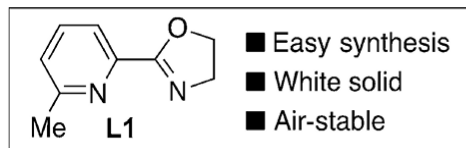
## **Diverse remote hydroarylation**

# 1.1、烯烃末端的C(sp<sup>3</sup>)-H烷基化

**Table 1:** Variation of reaction parameters.



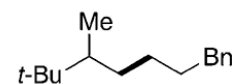
Entry	Variation from the standard conditions	Yield [%] <sup>[a]</sup>	rr <sup>[b]</sup>
1	–	91 (82)	82:1
2	NiCl <sub>2</sub> instead of NiBr <sub>2</sub>	79	29:1
3	(EtO) <sub>2</sub> MeSiH instead of (EtO) <sub>3</sub> SiH	82	23:1
4	PMHS instead of (EtO) <sub>3</sub> SiH	10	8:1
5	CsF instead of KF	0	–
6	THF instead of DMF	trace	–
7	<b>L2</b> instead of <b>L1</b>	13	1:2
8	<b>L3</b> instead of <b>L1</b>	0	–
9 <sup>[c]</sup>	1-bromo-3-phenylpropane instead of <b>2a</b>	82	32:1
10 <sup>[d]</sup>	1-chloro-3-phenylpropane instead of <b>2a</b>	0	–



**3f** 70% yield, 66:1 rr

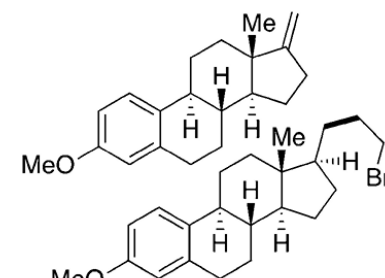
**3l** 43% yield, >99:1 rr

1,1-disubstituted alkene



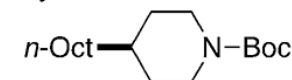
**3t** R = *i*-Pr, 56% yield, >99:1 rr

**3u** R = *t*-Bu, 68% yield, >99:1 rr



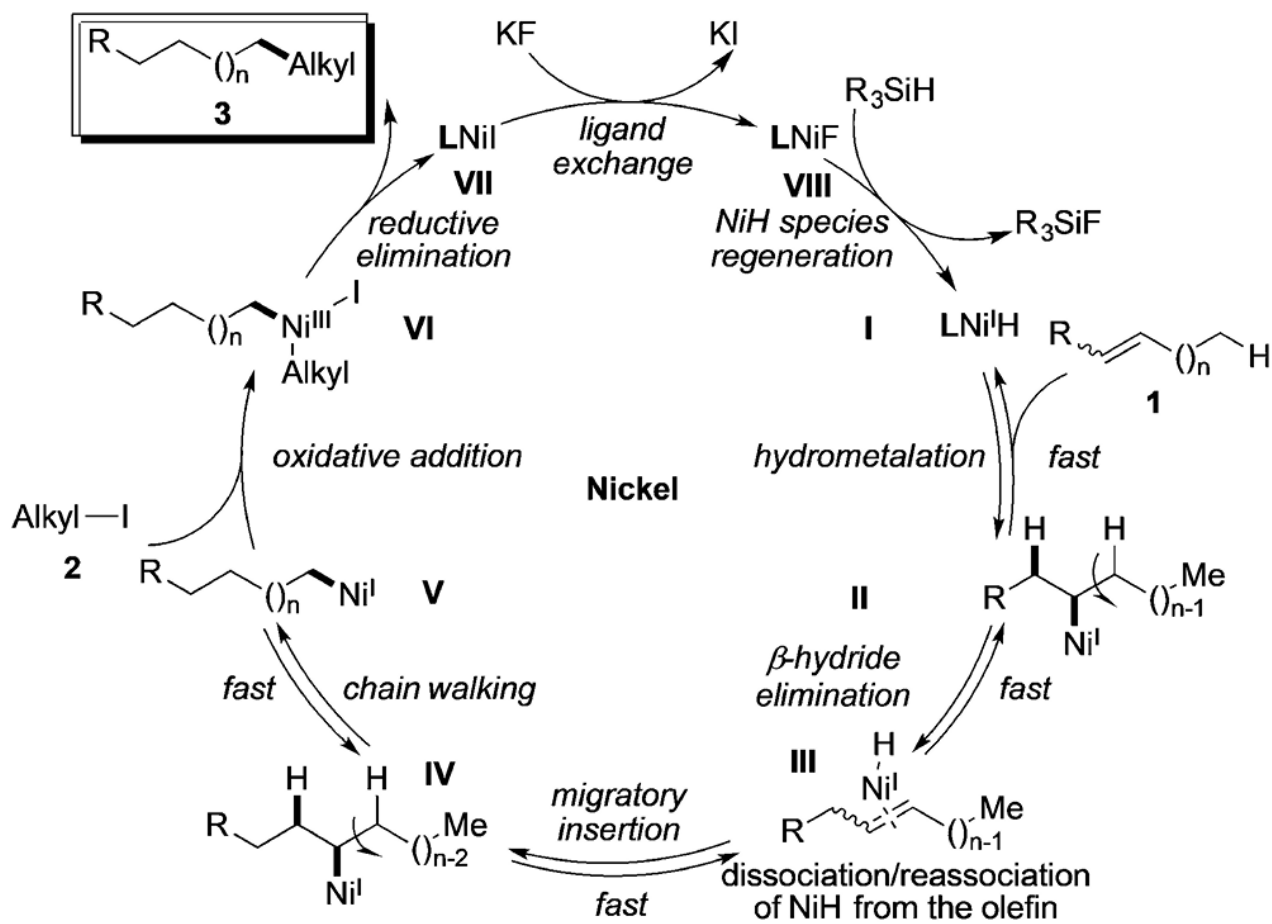
**3v'** 87% yield, 9:1 dr, >95:5 rr

2° alkyl iodides



**4x** 64% yield, 52:1 rr

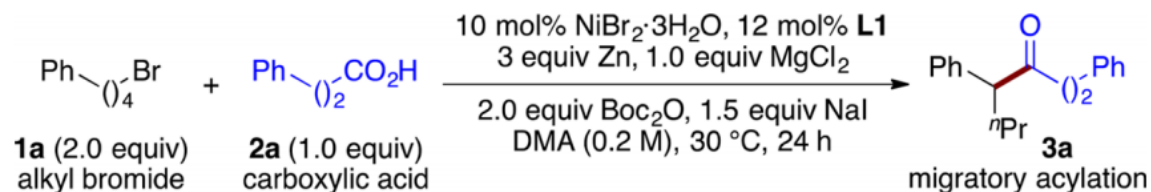
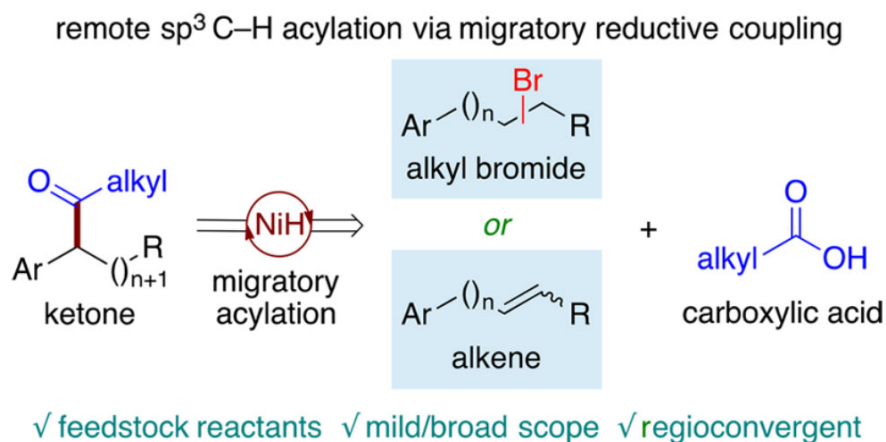
*Angew. Chem. Int. Ed.* **2018**, *57*, 4058.



Ni(I) hydride species disengages during the chain walking process:



## 1.2、卤代烷或烯烃与羧酸的迁移还原酰化反应



Entry	Deviation from standard conditions	Yield of <b>3a</b> (%) <sup>a</sup>	rr <sup>b</sup>
1	none	84 (70)	>99:1
2	NiBr <sub>2</sub> , instead of NiBr <sub>2</sub> ·3H <sub>2</sub> O	67	>99:1
3	NiI <sub>2</sub> , instead of NiBr <sub>2</sub> ·3H <sub>2</sub> O	58	>99:1
4 <sup>c</sup>	Ni(cod) <sub>2</sub> , instead of NiBr <sub>2</sub> ·3H <sub>2</sub> O	<b>3A</b> 63 (53)	97:3
5 <sup>c</sup>	bpy, instead of <b>L1</b>	<b>3A</b> 67	>99:1
6	Mn, instead of Zn	32	>99:1
7	THF, instead of DMA	14	>99:1
8	w/o NaI	34	>99:1
9 <sup>d</sup>	alkyl iodide, instead of <b>1a</b>	61	>99:1
10 <sup>e</sup>	alkyl chloride, instead of <b>1a</b>	none	–
11	w/o MgCl <sub>2</sub>	3	ND
12	w/o Boc <sub>2</sub> O	trace	ND

**L1**

**3A**

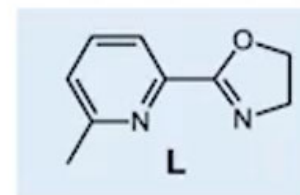
ipso-acylation

NaI的作用是使烷基溴原位生成活性更强的烷基碘化物

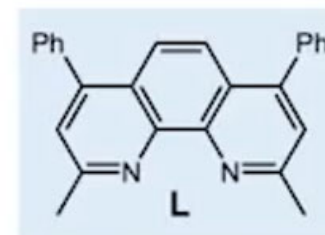
母体联吡啶配体取代L1只导致3A产物生成



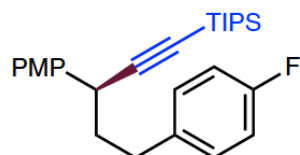
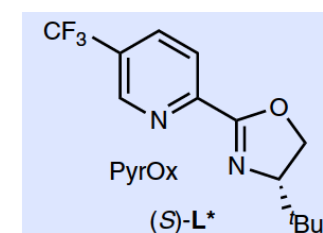
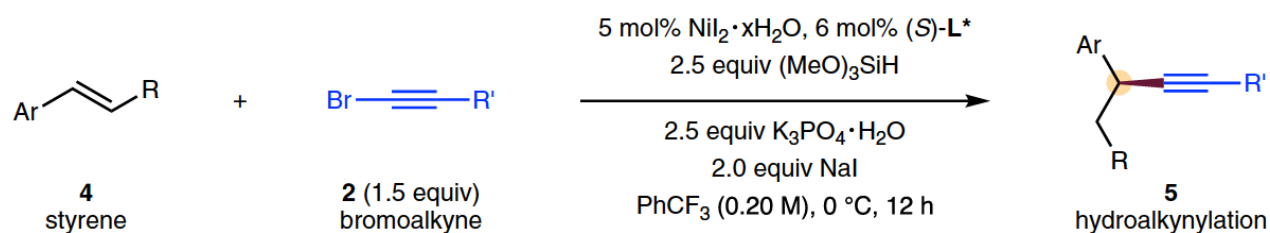
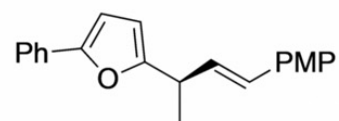
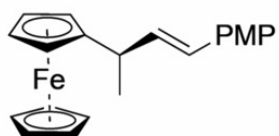
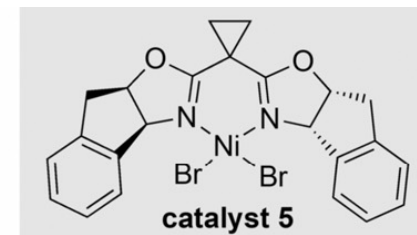
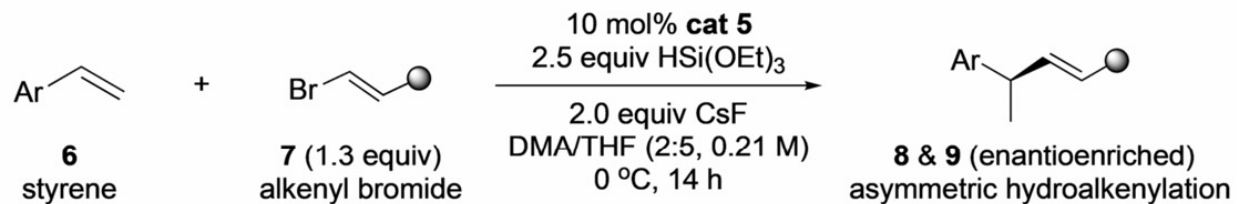
## 1.3、烯烃与烯基溴、炔基溴的还原交叉偶联



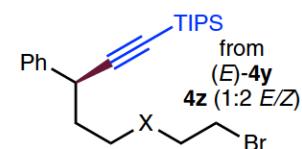
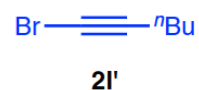
*Angew. Chem. Int. Ed.* **2021**, 60, 4060–4064



*Nat. Commun.* **2021**, 12, 3792.

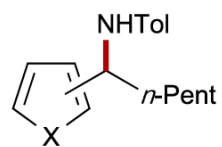
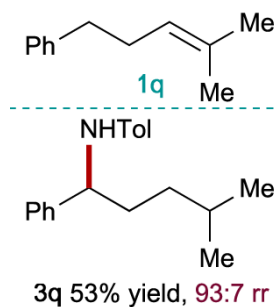
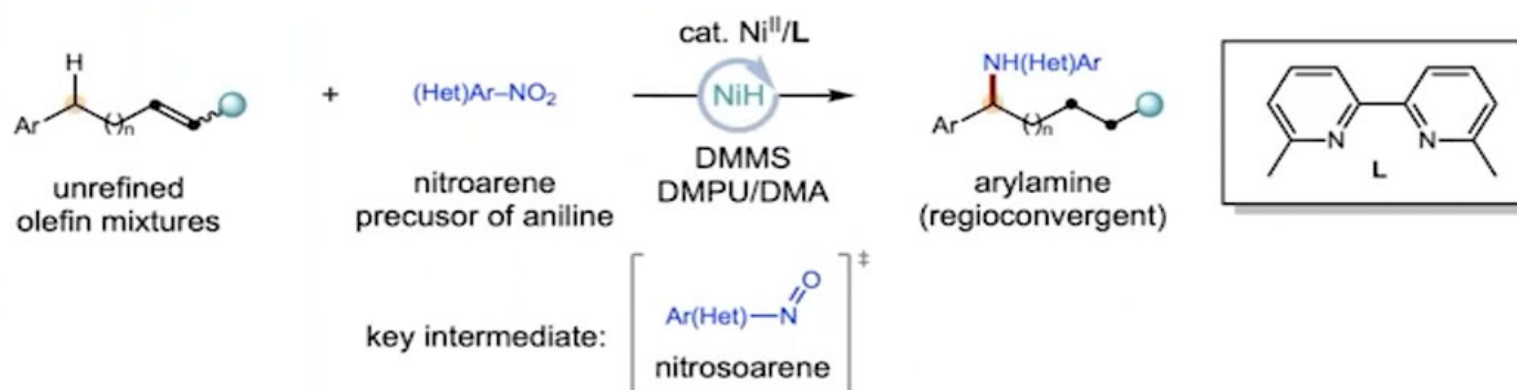


unsuccessful substrates

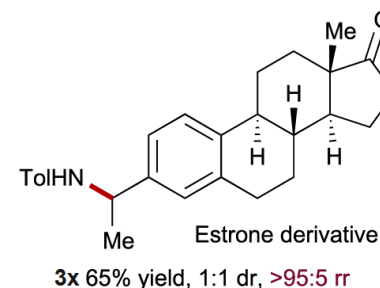


**5y** X = O, 81% yield, 88% ee  
**5z** X =  $\text{CH}_2$ , 62% yield, 94% ee

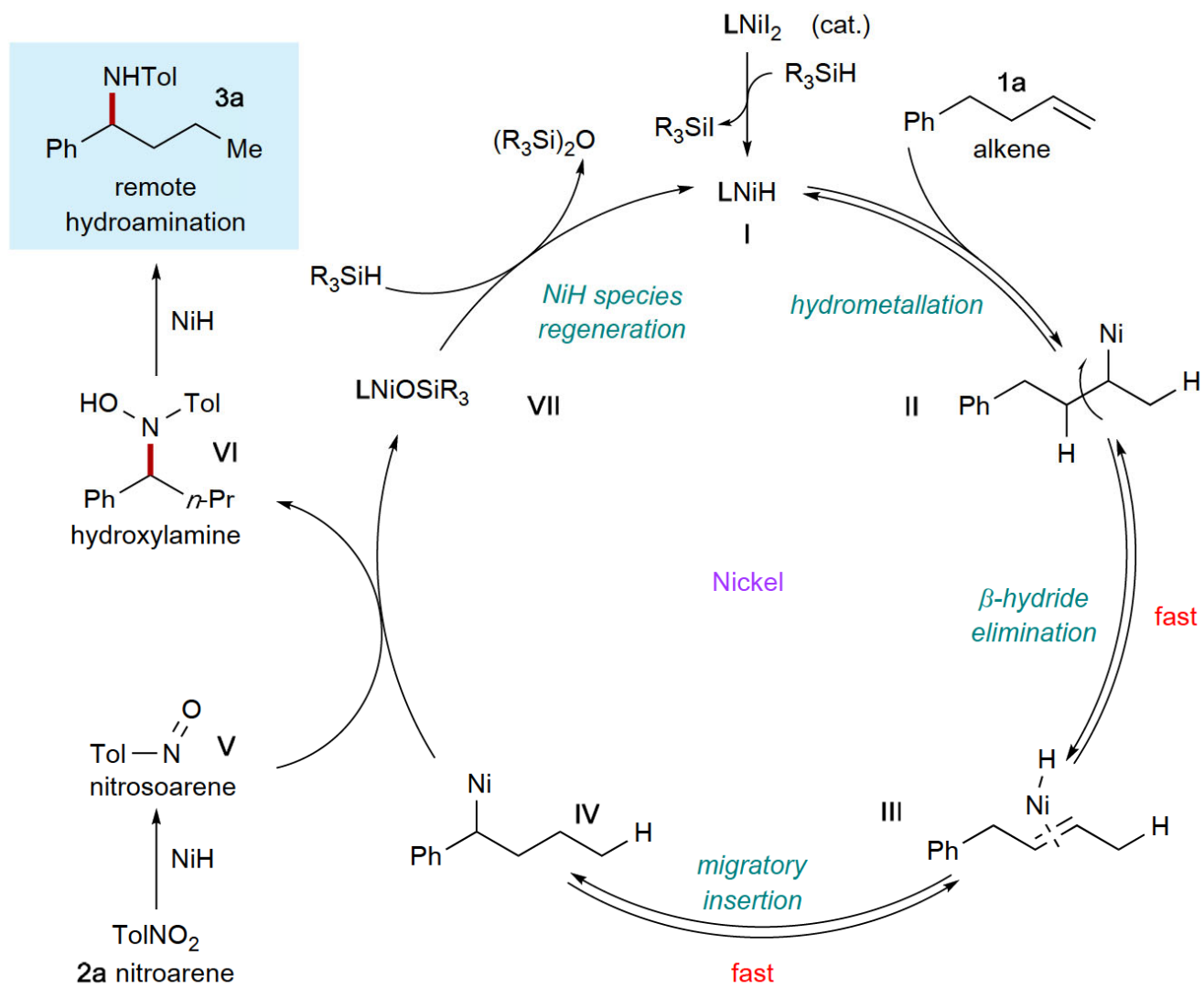
# 1.4、烯烃与硝基芳烃的远端sp<sup>3</sup> C-H胺化反应



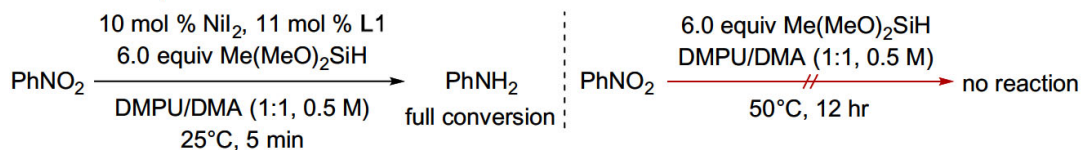
**3h** 2-Furan, 63% yield, >99:1 rr  
**3i** 3-Thiophene, 72% yield, >99:1 rr



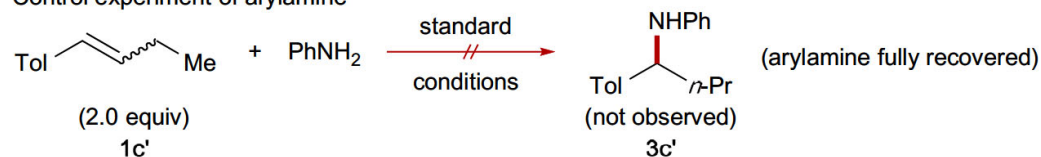
*Chem* **2018**, *4*, 1645



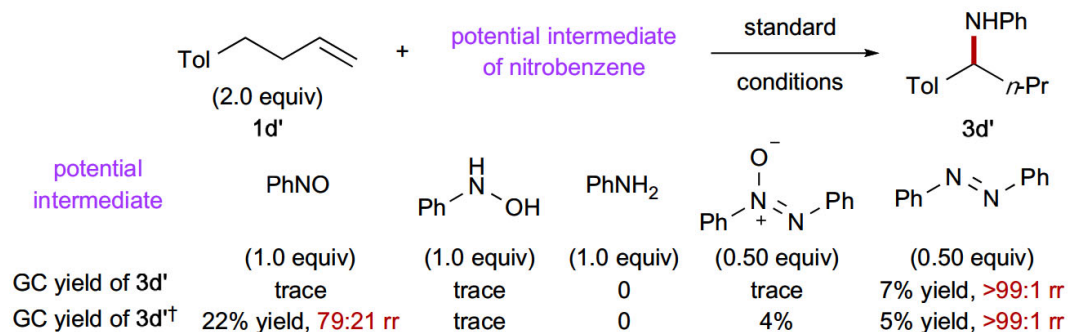
**A** Control experiments of nitroarene



**B** Control experiment of arylamine

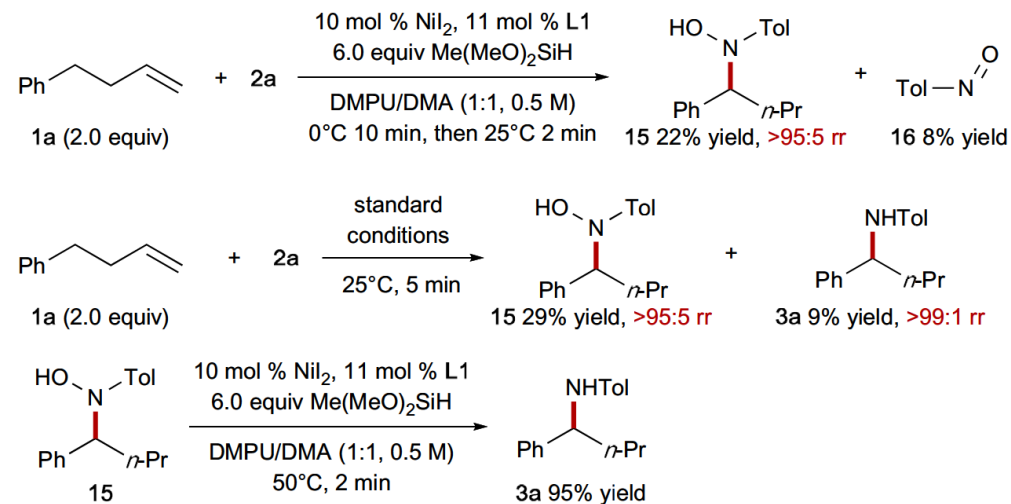


**C** Control experiments with potential intermediates



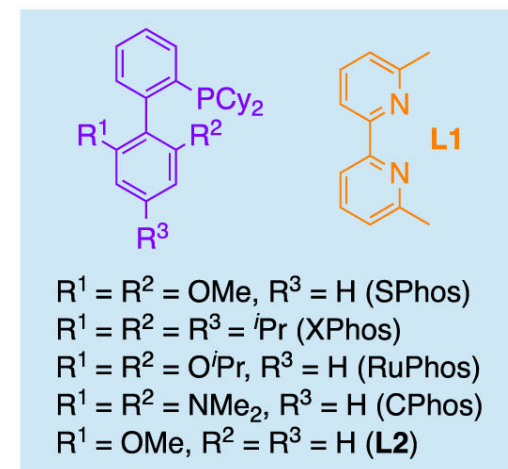
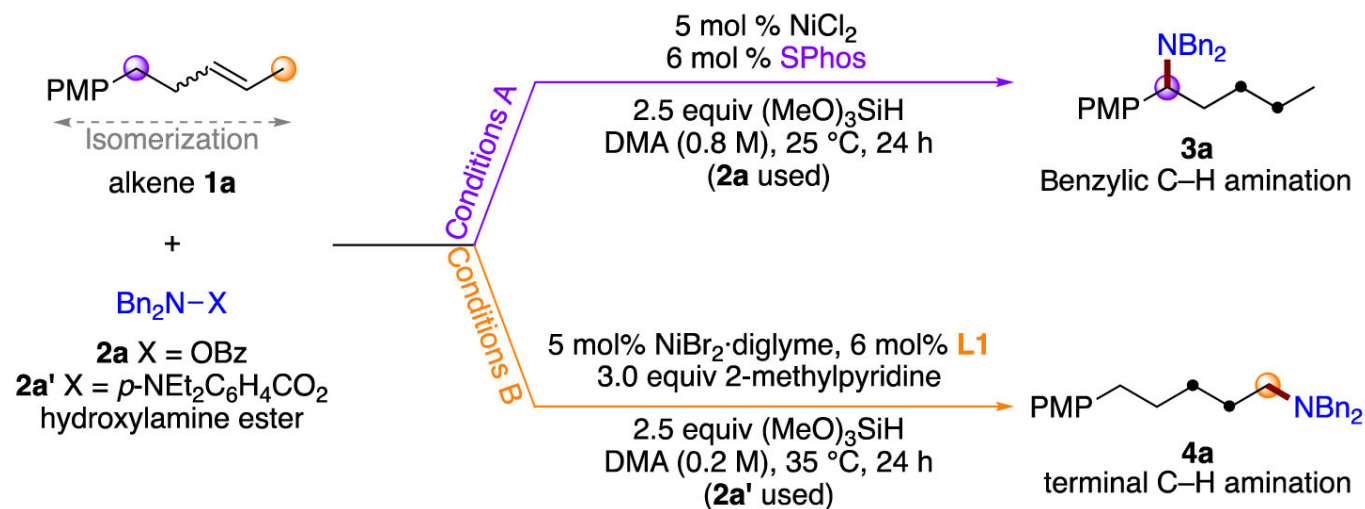
<sup>†</sup>These intermediates were added slowly at 25°C over 1 hr, then the reaction mixture was stirred at 50°C for another 1 hr.

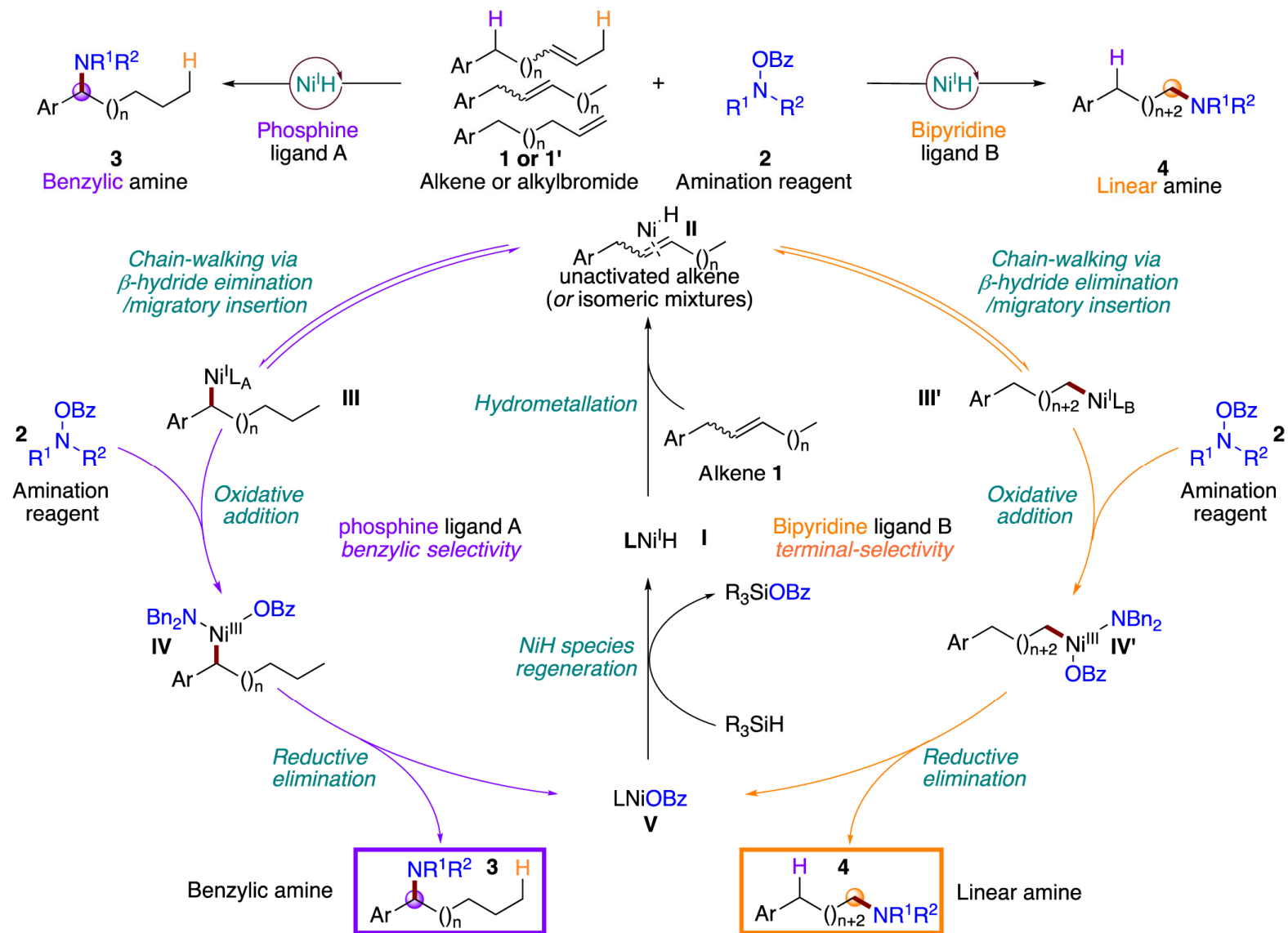
**D** Monitoring the reaction progress



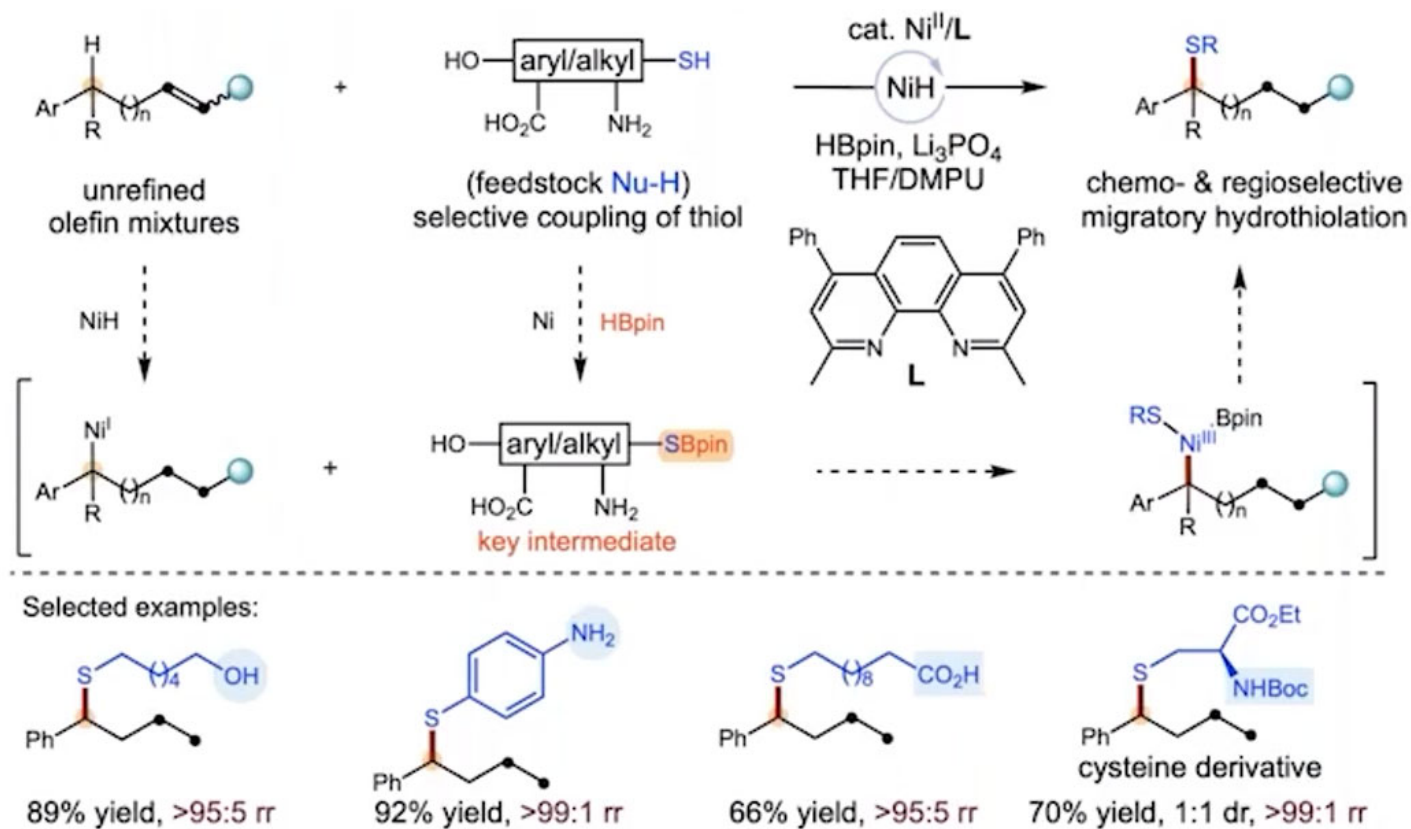
标准条件下从羟胺定量得到最终产物

# 1.5、烯烃的sp<sup>3</sup>C-H迁移胺化反应





# 1.6、烯烃和炔与硫醇的选择性迁移氢硫醇化反应

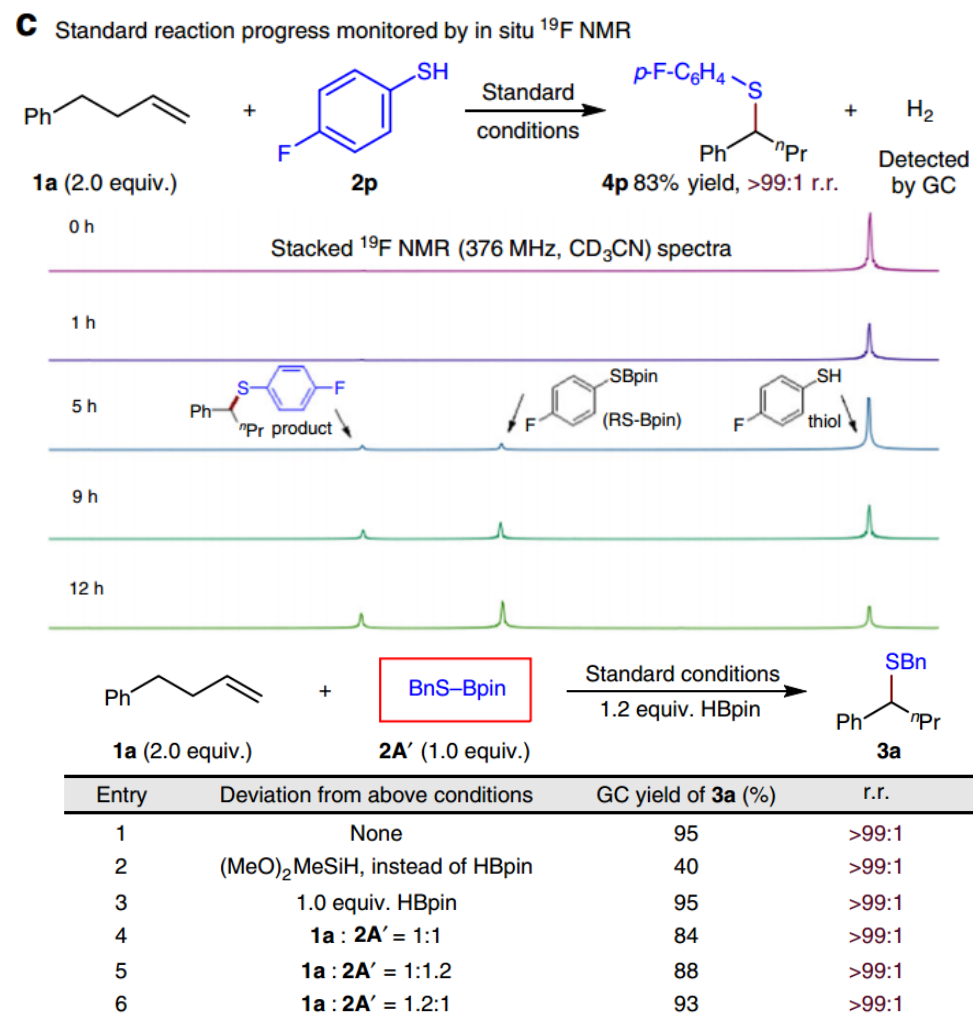
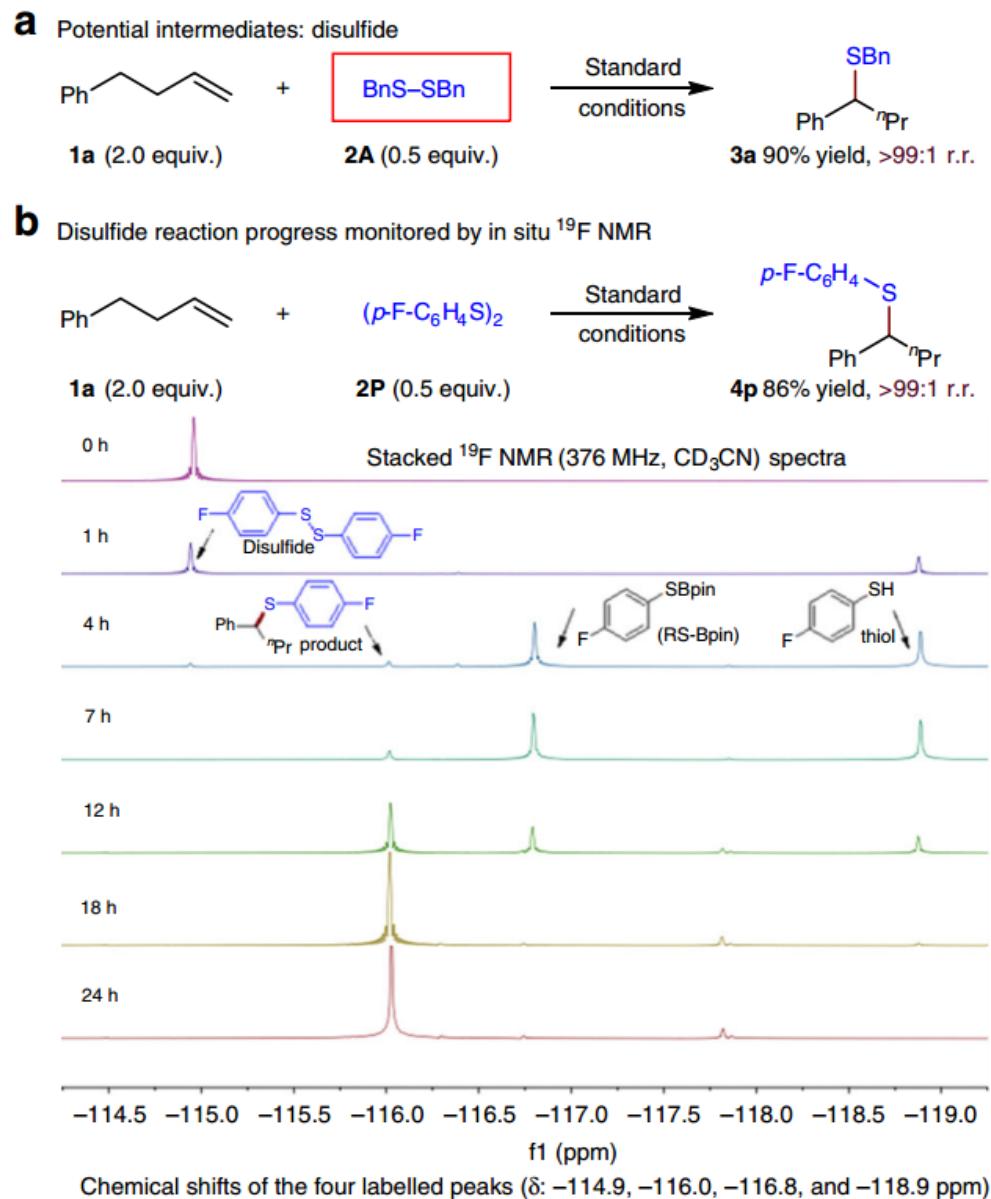


(a) 硫基在一系列潜在的活性官能团(如酰胺、酸、醇和胺)存在下具有高的化学选择性

(b) 在多个位点之间具有优异的区域选择性, 包括苄基位置、醚的 $\alpha$ 位置或烯烃链的末端位置;

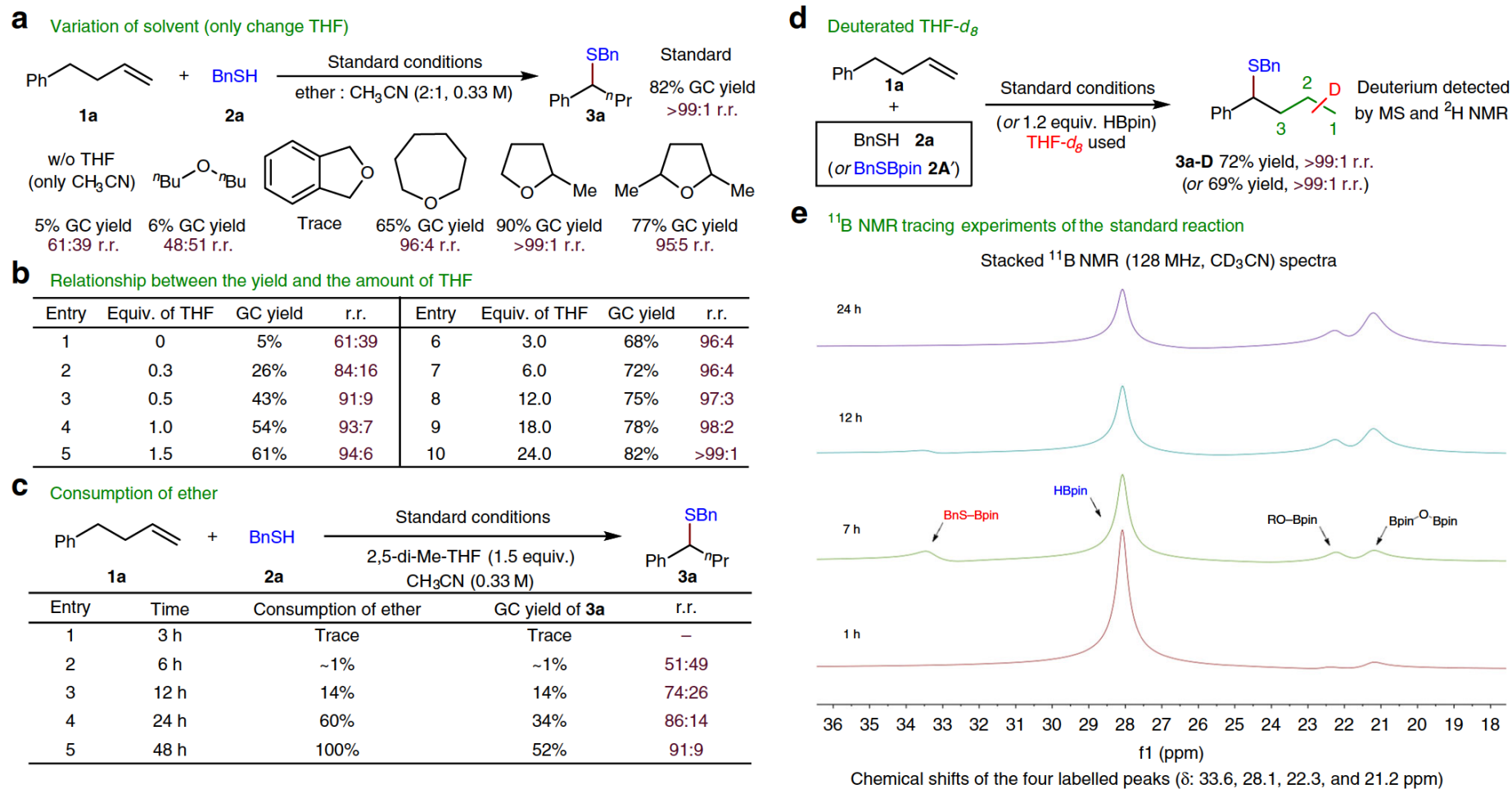
(c) 原料硫醇作为硫代试剂, 这样的工艺避免了制备亲电性硫代试剂。





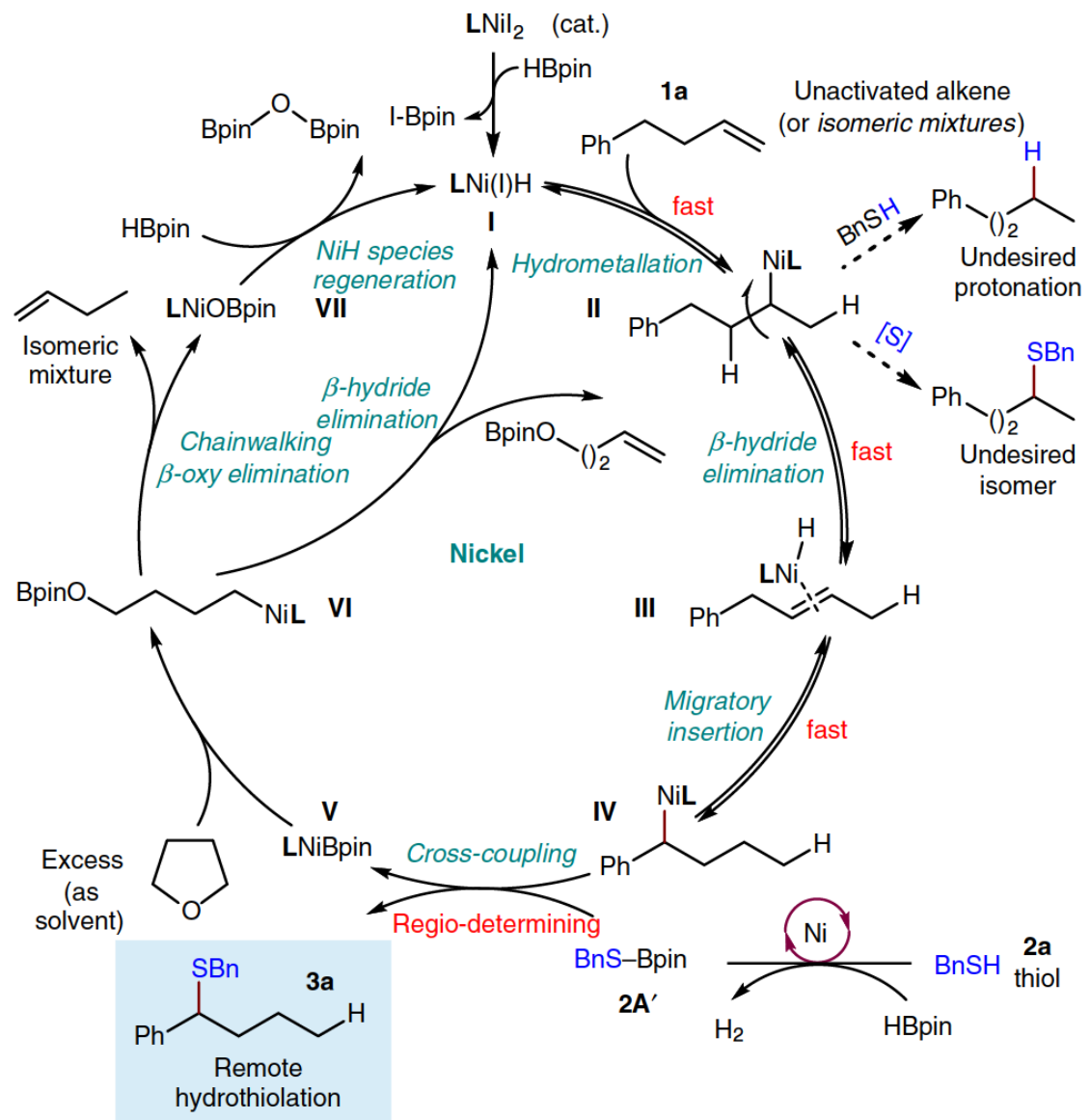
**Fig. 7** Optimized reaction conditions using RS-Bpin as the thiolation reagent. 0.20 mmol Scale, average of two experiments

GC分析也观察到该标准反应中有 $\text{H}_2$ 生成



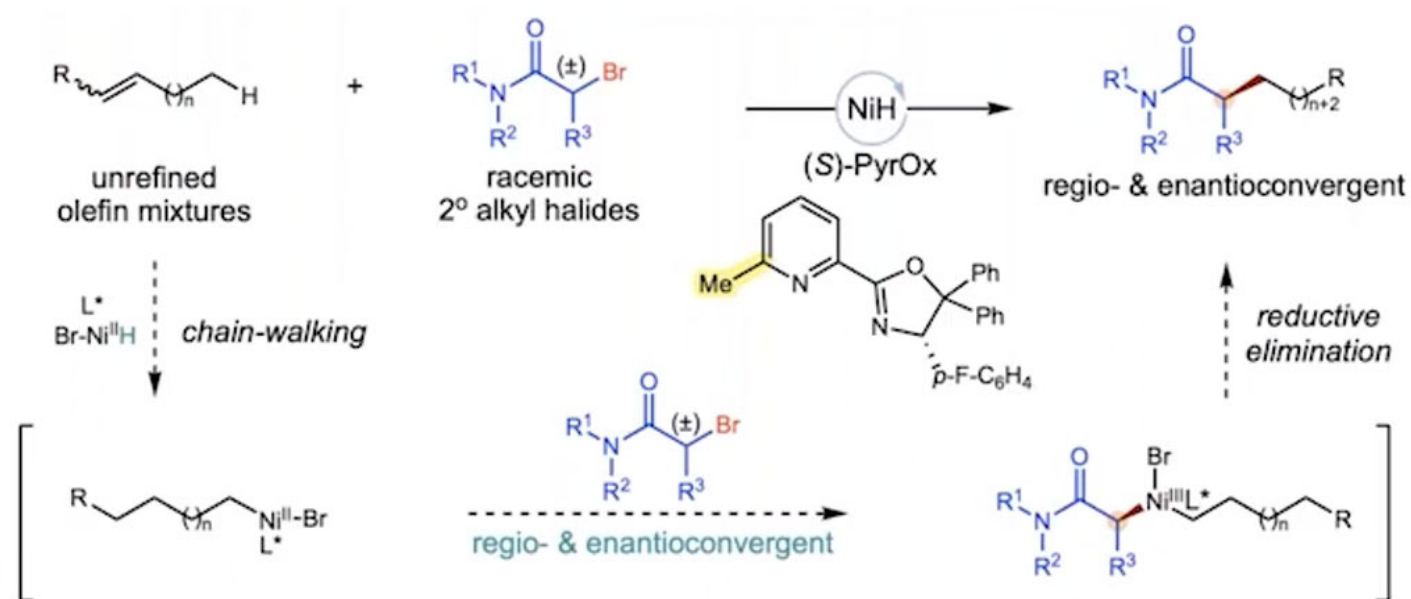
**Fig. 8** Role of solvent tetrahydrofuran (THF). **a** Variation of solvent (only change THF). **b** Relationship between the yield and the amount of THF. **c** Consumption of ether. **d** Deuterated THF-*d*<sub>8</sub>. **e** Reaction progress monitored by in situ Boron-11 NMR (<sup>11</sup>B NMR) (128 MHz, CD<sub>3</sub>CN) of the standard reaction

少量的NiD参与链行走过程，并且少量的NiD应该来自氘代THF-d8

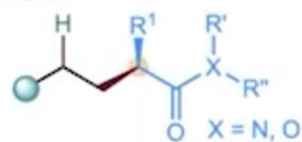


# Asymmetric remote hydroarylation

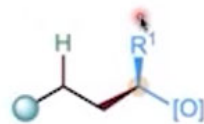
## 2.1、烯烃与 $\alpha$ -溴代酰胺的末端不对称烷基化



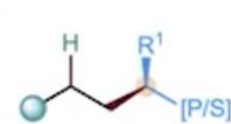
Similar work:



Fu, G. C. *Nature* **2018**, 563, 379.  
Shang, M. *JACS* **2022**, 144, 1130.

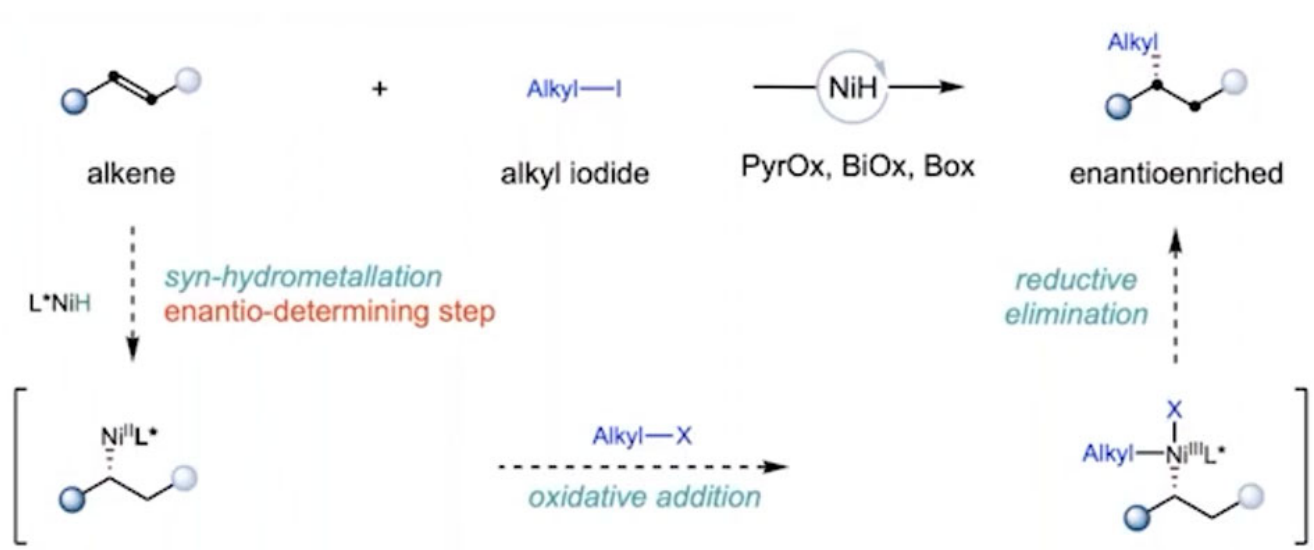


Fu, G. C. *JACS* **2020**, 142, 5870.

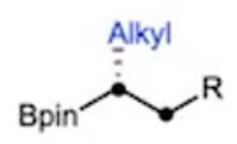


Fu, Y.; & Lu, X. *JACS* **2020**, 142, 214.

*Angew. Chem. Int. Ed.* **2019**, 58, 1754–1758

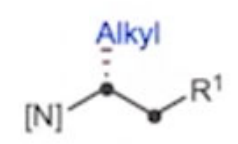


Selected examples:



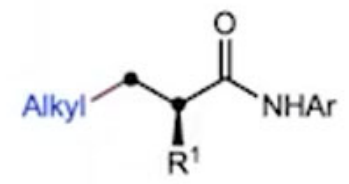
Hu, X.

*Nat. Chem.* **2021**, 13, 270.



Fu, Y. & Lu, X.; Hu, X.; Shu, W.

*Nat. Commun.* **2021**, 12, 1313.  
*J. Am. Chem. Soc.* **2021**, 143, 1959.  
*Nat. Commun.* **2021**, 12, 2771.

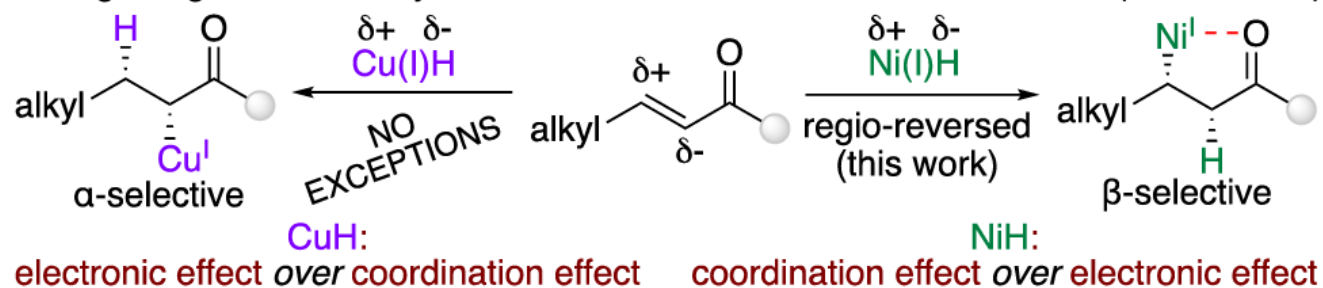


Shu, W.

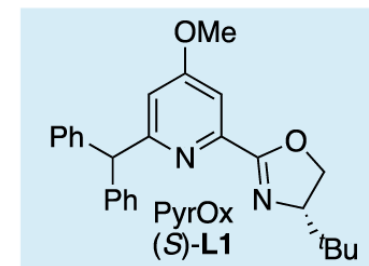
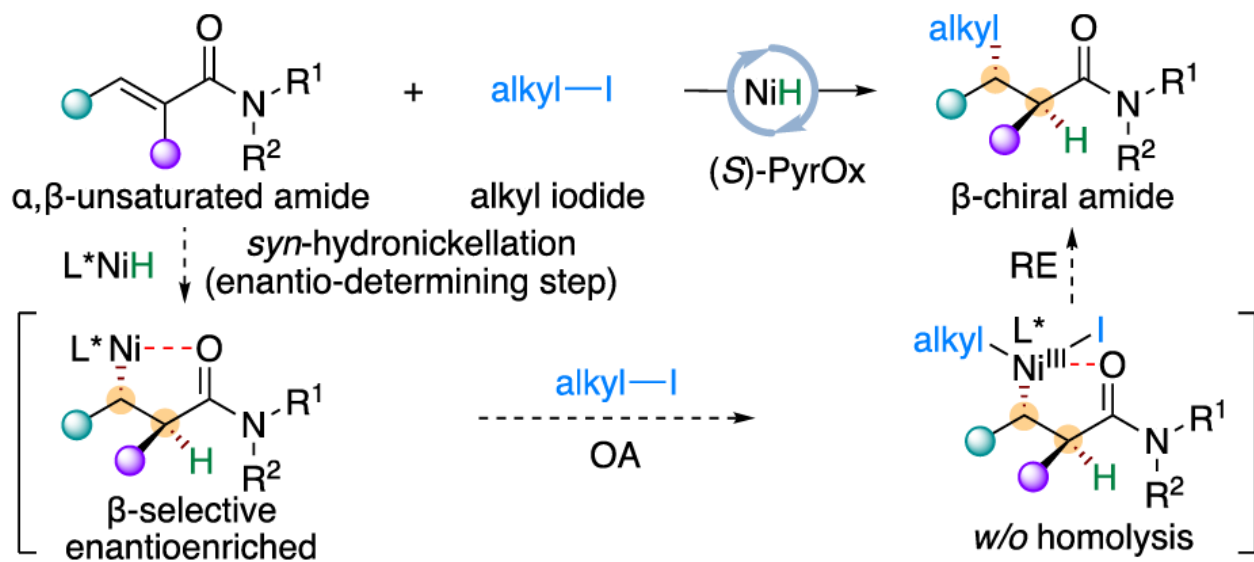
*Angew. Chem. Int. Ed.*  
**2021**, 60, 1599.

## 2.2、 $\alpha$ , $\beta$ -不饱和酰胺的不对称烷基化

Design: regio-reversed hydrometallation of electron-deficient alkenes (CuH vs NiH)

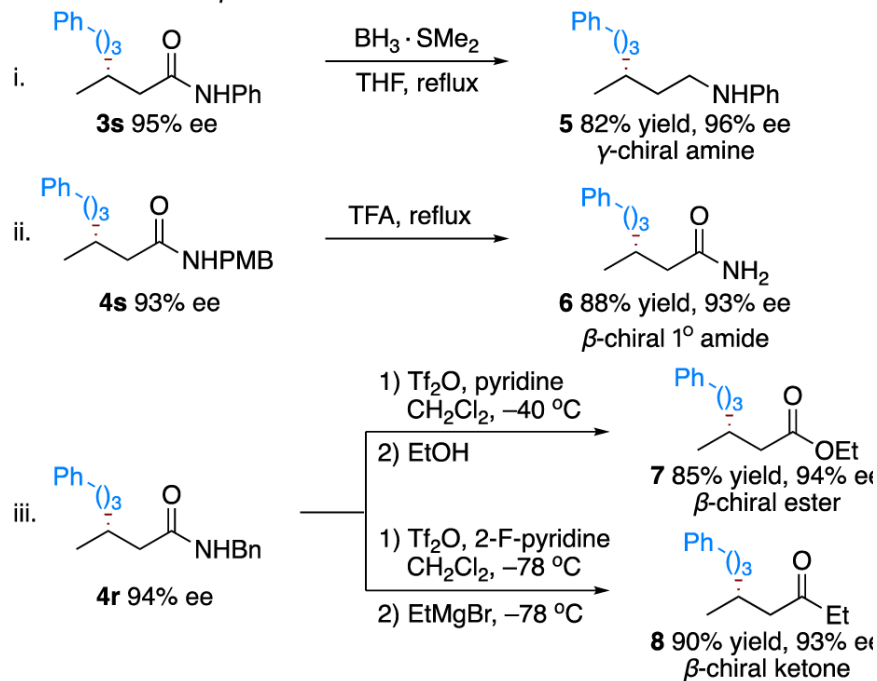


This work: regio-reversed asymmetric hydroalkylation of  $\alpha,\beta$ -unsaturated amides

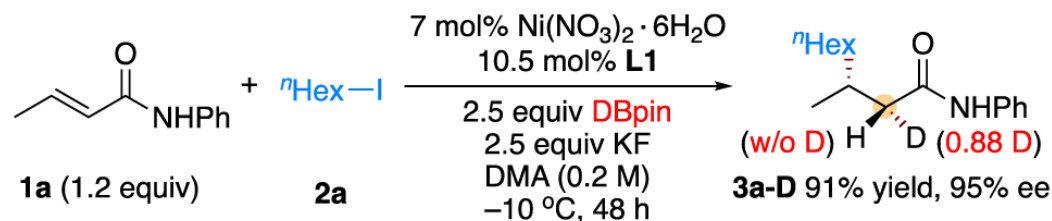


ACS Catal. 2021, 11, 8766–8773

b) Transformations of  $\beta$ -chiral amides

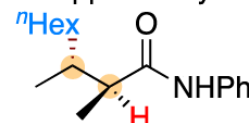


c) Isotopic labelling experiment

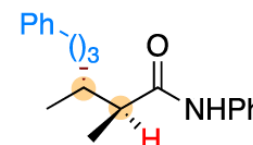


■ *syn*-hydronicellation is proposed to be the *enantio-determining step*

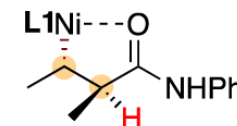
also supported by



81% yield, >20:1 dr, 86% ee

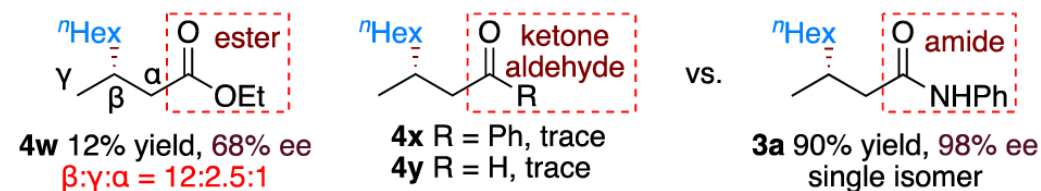


91% yield, >20:1 dr, 84% ee



proposed via amide-directed *syn*-hydronicellation

d) Poor results of  $\alpha,\beta$ -unsaturated carbonyl substrates with a weak directing group



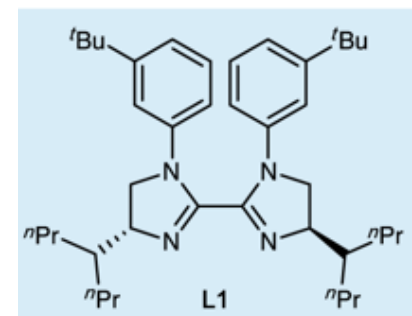
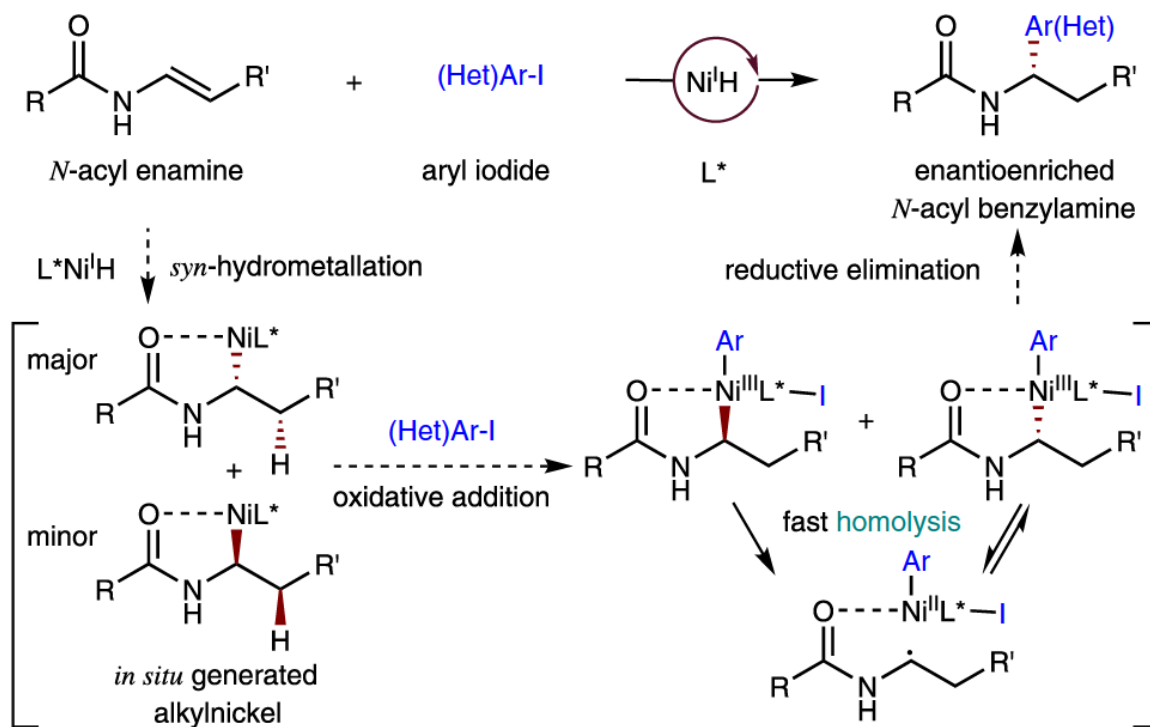
NiH插入是对映体决定步骤

酰胺导向基团起到重要作用



## 2.3、N-酰基烯胺的不对称芳基

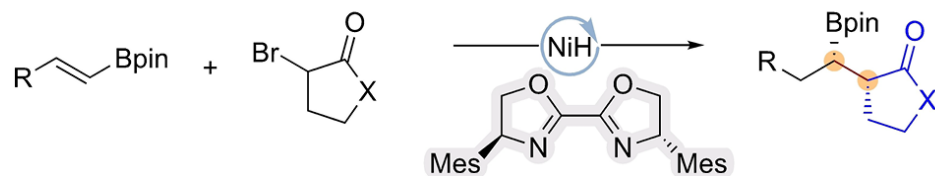
ii This work: NiH-catalysed enantioselective hydroarylation of *N*-acyl enamines



*Nat. Commun.* **2021**, 12, 638.

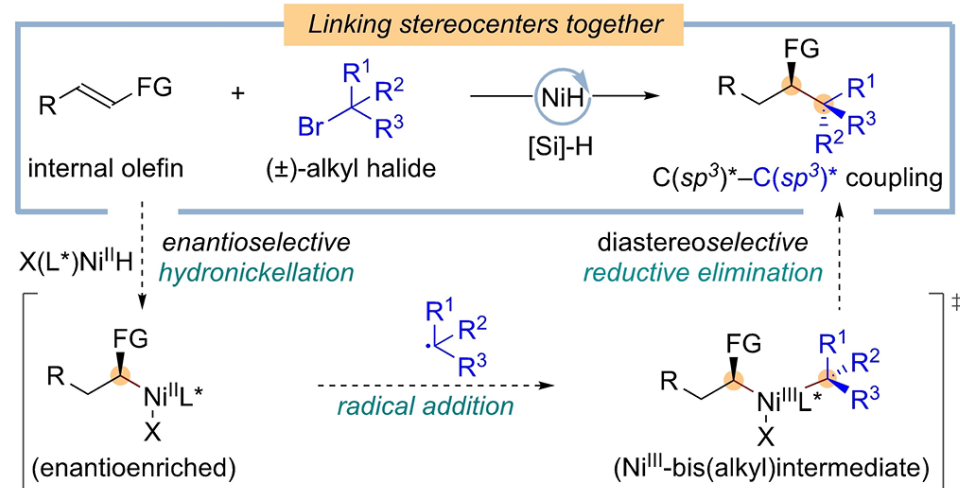
## 2.4、烯酰胺或烯氨基甲酸酯与外消旋 $\alpha$ -溴酰胺的加氢烷基化

A recent elegant example from Hu and coworkers (ref 9a)

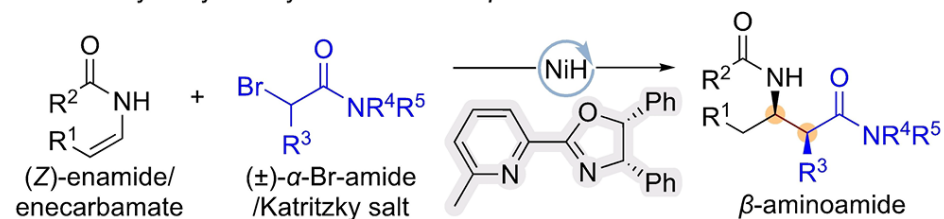


Hu, X. Et al. *Nat. Catal.* **2022**, 5, 1180.

C. Concept: NiH catalysis enables enantio- and diastereoselective hydroalkylation

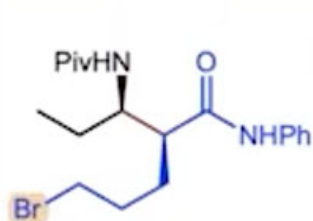


D. Demo: asym. hydroalkylation to access  $\beta$ -aminoamides w vicinal stereocenters

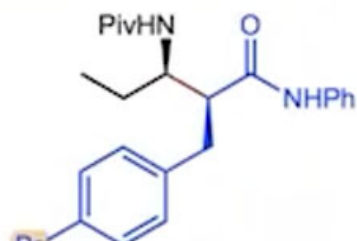


[linking stereocenters together: **1** ligand, **2** vicinal stereocenters, **3-D** structure]  
 [divergent synthesis of high-value  $\beta$ -amino amides] [excellent rr, dr & ee]

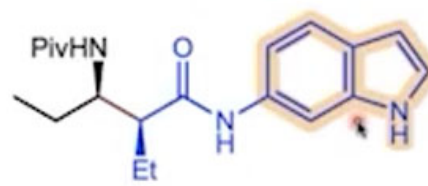
*Angew. Chem. Int. Ed.* **2023**, 62, e202311094



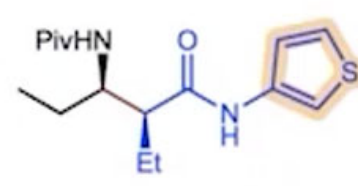
68% yield  
96:4 dr, 99% ee



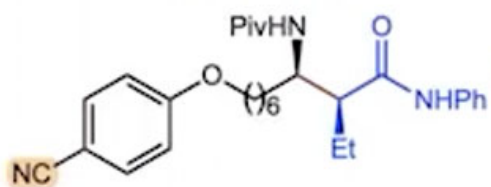
61% yield  
98:2 dr, 99% ee



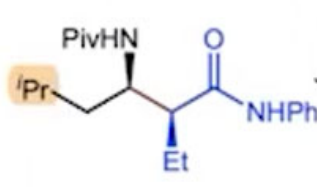
73% yield  
96:4 dr, 98% ee



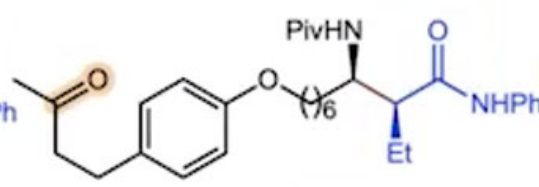
68% yield  
98:2 dr, 98% ee



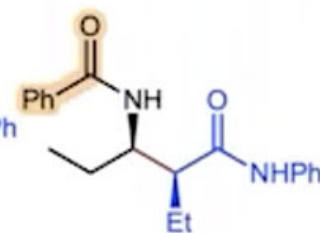
73% yield  
>20:1 dr, 93% ee



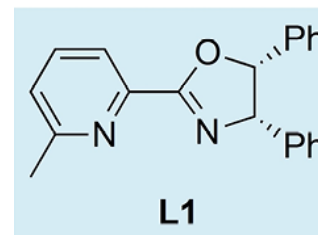
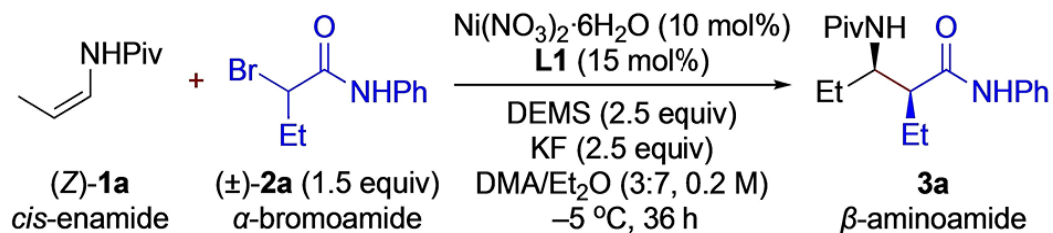
66% yield  
96:4 dr, 97% ee



76% yield  
>20:1 dr, 96% ee



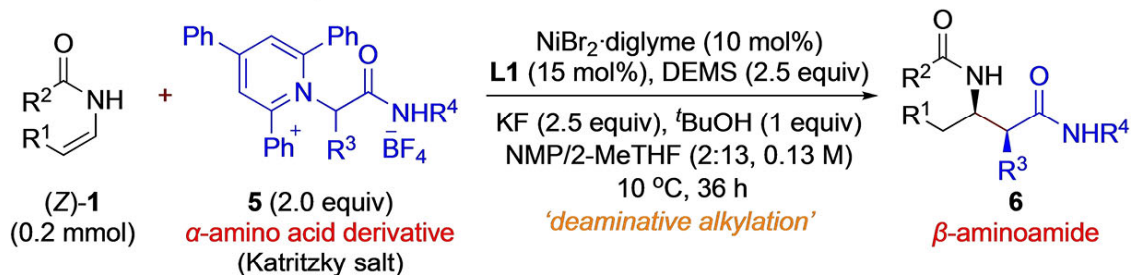
70% yield  
>20:1 dr, 93% ee



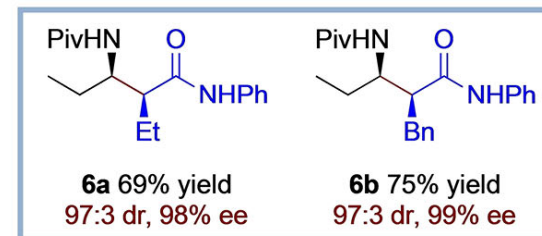
Entry	Variation	Yield [%] <sup>[a]</sup>	rr <sup>[b]</sup>	dr <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	None	75 (73)	99:1	98:2	97
15	(E)- <b>1a</b> used	20	61:39	92:8	98
18	$\alpha$ -chloroamide ( <b>2a-Cl</b> ) used	trace	–	–	–

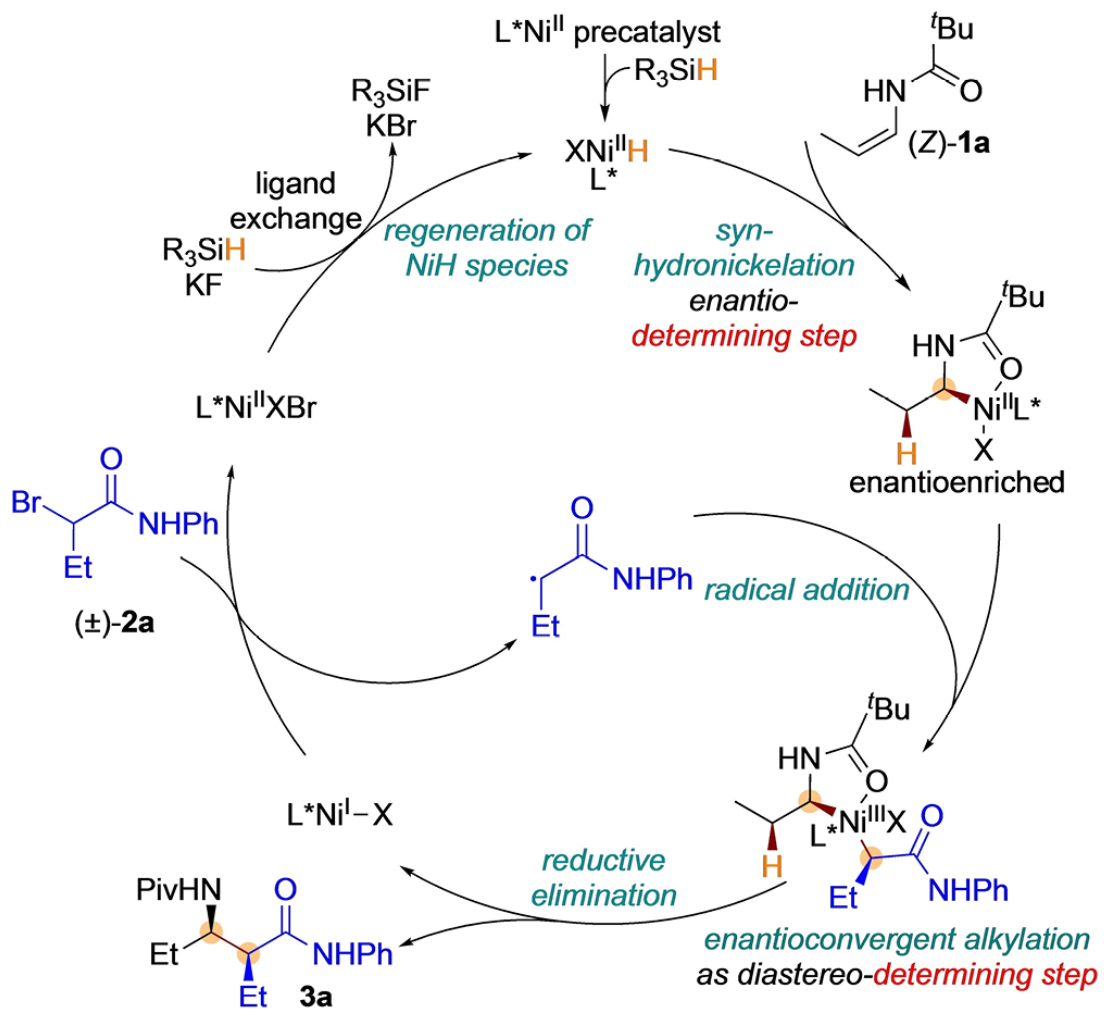
当使用反应性较低的反式烯胺时，对反应性和区域选择性都有负面影响，导致 $\alpha$ -溴酰胺的还原性脱溴。

#### A. From $\alpha$ -aminoamides to $\beta$ -aminoamides

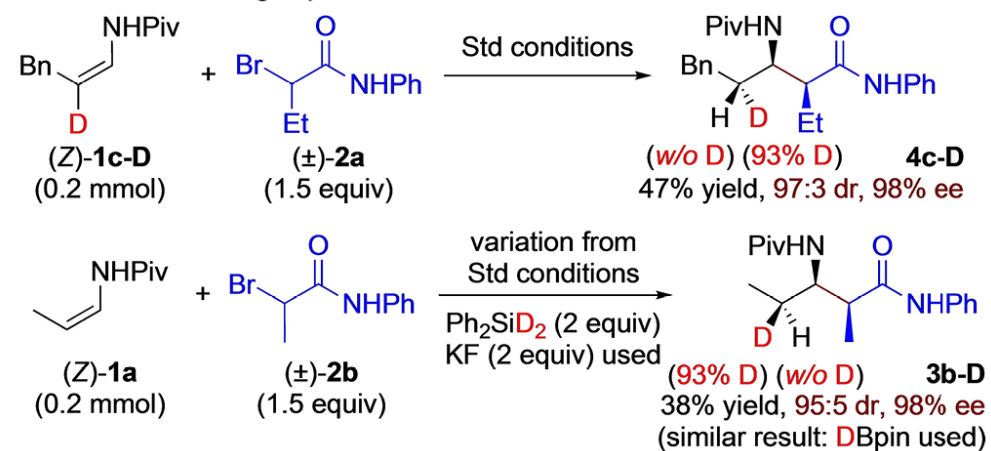


Demo:



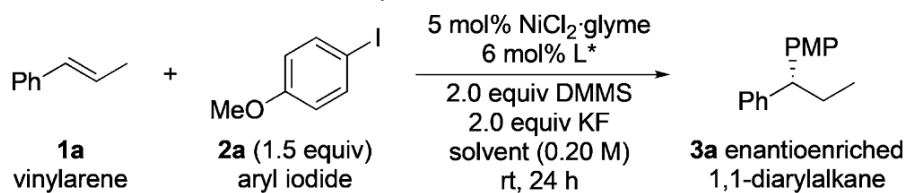


A. Deuterium-labeling experiment

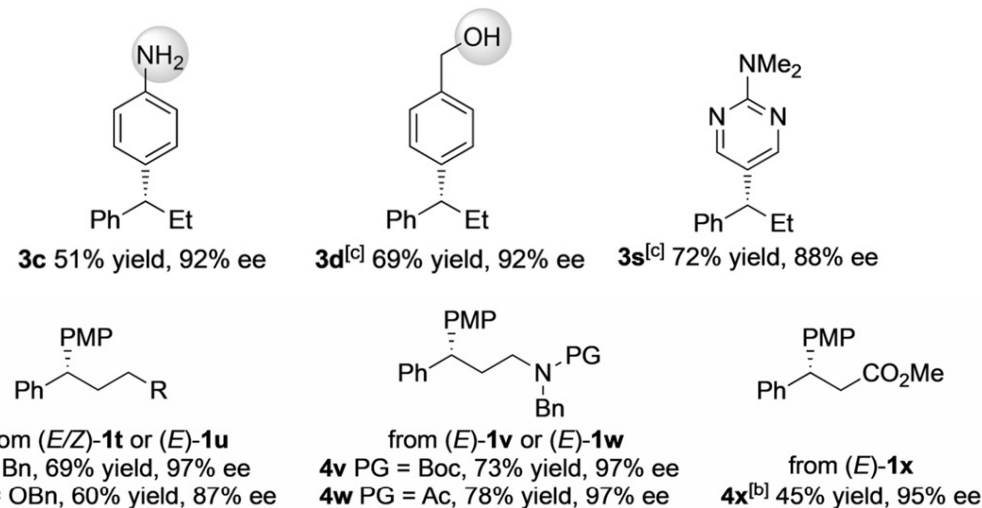
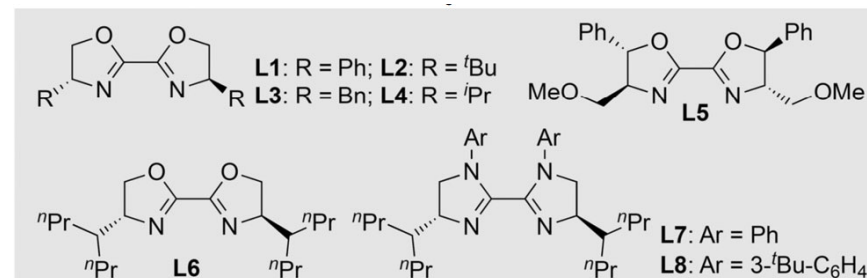


## 2.5、乙烯基芳烃的不对称C(sp<sup>3</sup>)-H芳基化

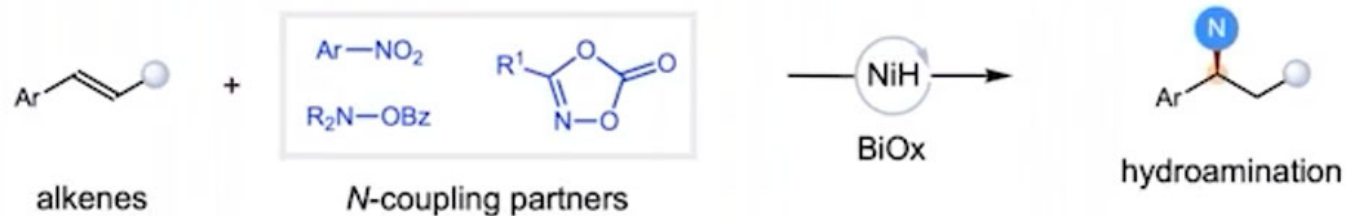
**Table 1:** Variation of reaction parameters.



Entry	Conditions	Ligand	Solvent	Yield [%] <sup>[a]</sup>	ee [%] <sup>[b]</sup>
1	as shown	<b>L1</b>	DMPU	9	3
2	as shown	<b>L2</b>	DMPU	18	16
3	as shown	<b>L3</b>	DMPU	33	64
4	as shown	<b>L4</b>	DMPU	6	52
5	as shown	<b>L5</b>	DMPU	27	-66
6	as shown	<b>L6</b>	DMPU	18	80
7	as shown	<b>L7</b>	DMPU	54	89
8	as shown	<b>L8</b>	DMPU	50	93
9	as shown	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	85	94
10 <sup>[c]</sup>	as shown	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	98 (89)	94
11 <sup>[c]</sup>	<i>cis</i> -styrene	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	95 (85)	94
12 <sup>[c]</sup>	4-Br-anisole	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	10	94
13 <sup>[c]</sup>	NiCl <sub>2</sub> ·6H <sub>2</sub> O	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	83	94
14 <sup>[c]</sup>	CsF	<b>L8</b>	DMPU/PhCF <sub>3</sub> (1:2)	28	92
15 <sup>[c]</sup>	as shown	<b>L8</b>	PhCF <sub>3</sub>	< 5	-

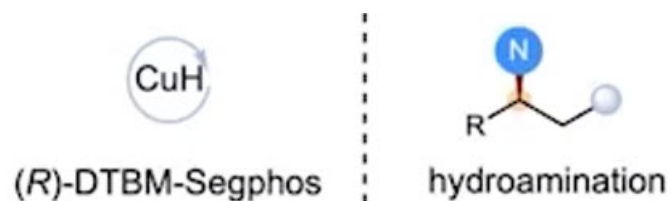


## 2.6、手性苯胺的合成



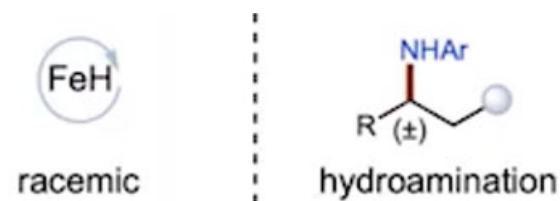
*Angew. Chem. Int. Ed.* **2021**, 60, 23584.

### ◆ Previous work: hydroamination of alkenes

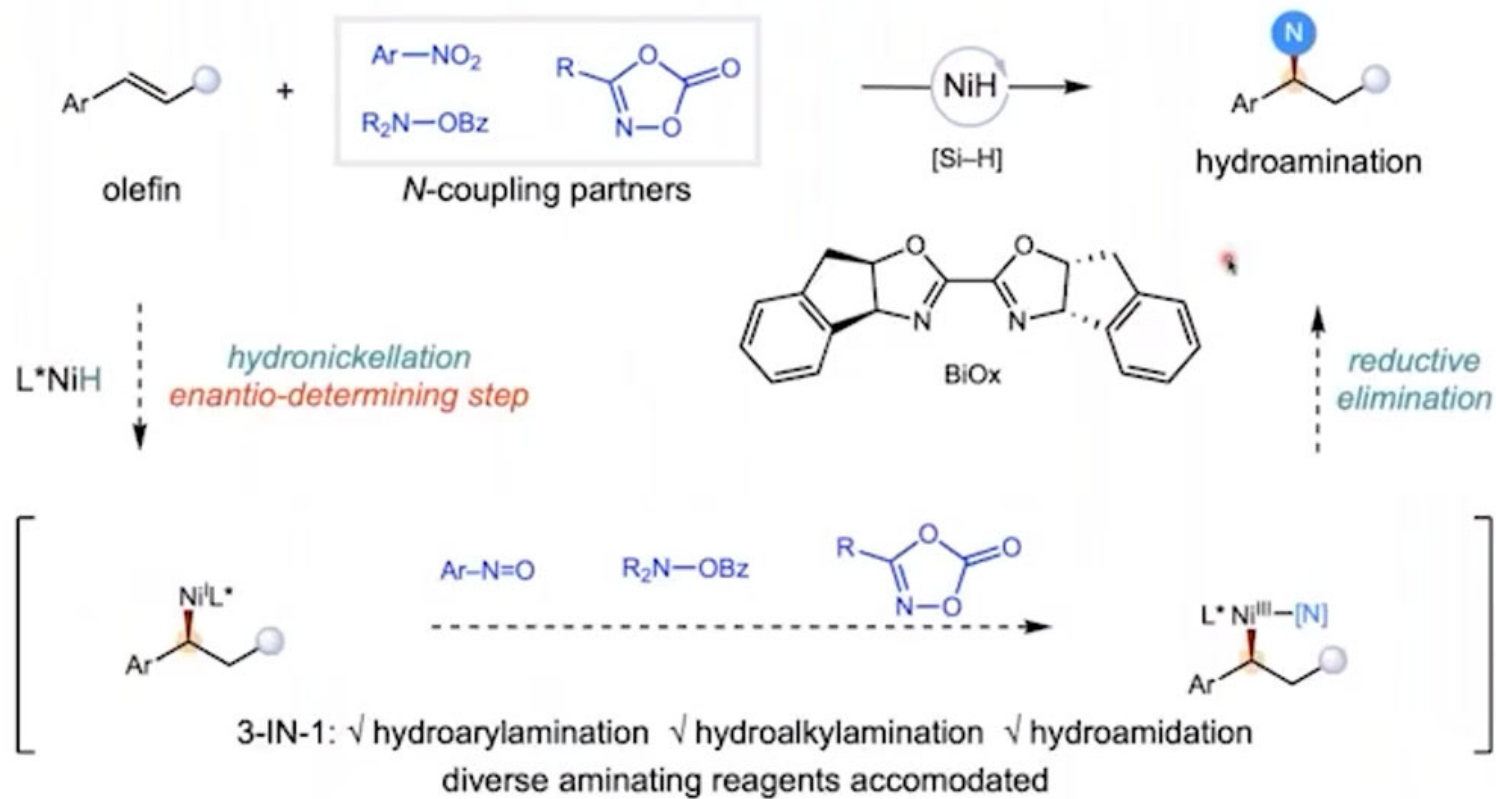


**Buchwald, S. L. *J. Am. Chem. Soc.* 2013, 135, 13746.**

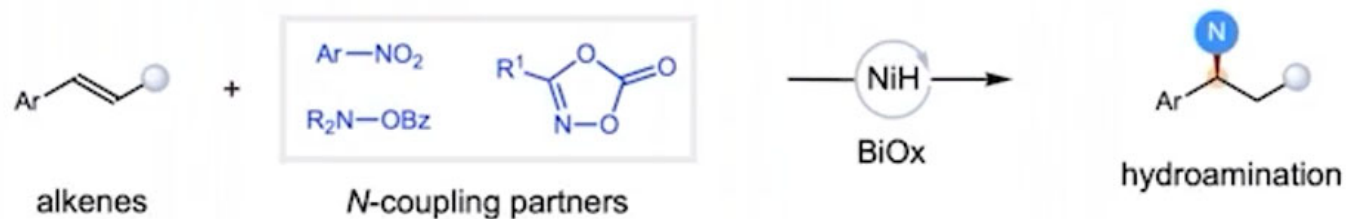
**Miura & Hirano, *Angew. Chem. Int. Ed.* 2013, 52, 10830.**



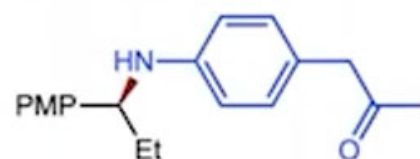
**Baran, P. S. *Science* 2015, 348, 886.**



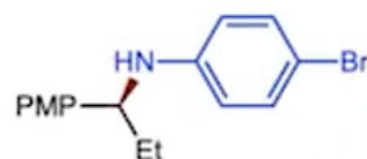




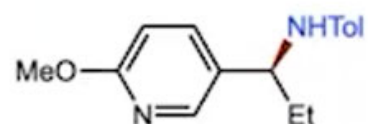
#### Arylamines



64% yield, 92% ee

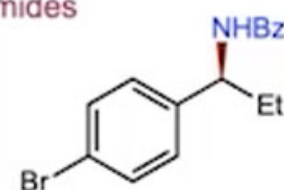


52% yield, 90% ee



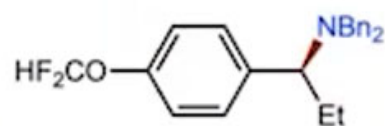
63% yield, 80% ee

#### Amides

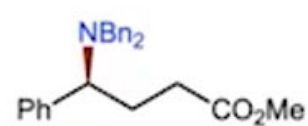


67% yield, 88% ee

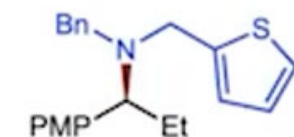
#### Alkylamines



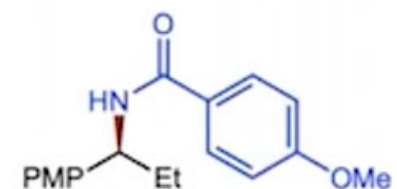
73% yield, 87% ee



70% yield, 90% ee

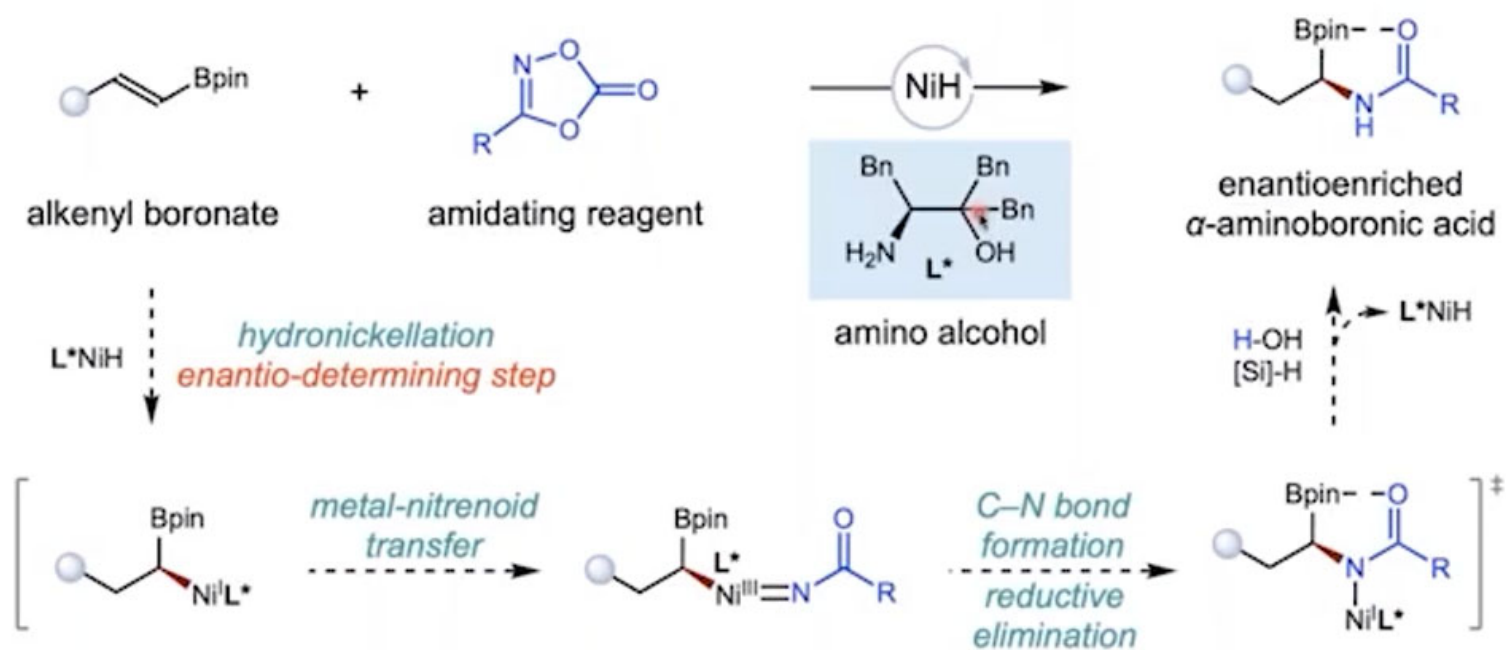


87% yield, 91% ee



70% yield, 89% ee

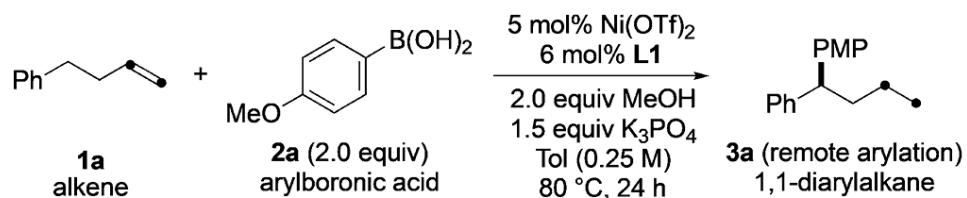
## 2.7、含硼烯烃的胺化



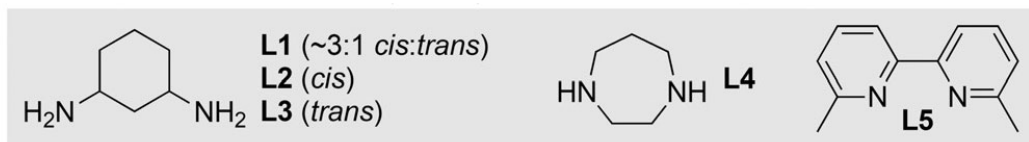
*Nat. Commun.* **2022**, 13, 5630.

## 2.8、烯烃与芳基硼的接力迁移芳基化反应

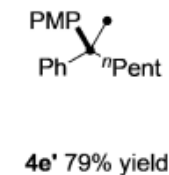
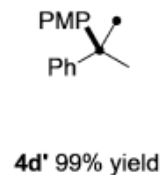
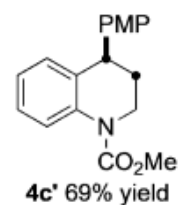
**Table 1:** Variation of reaction parameters.

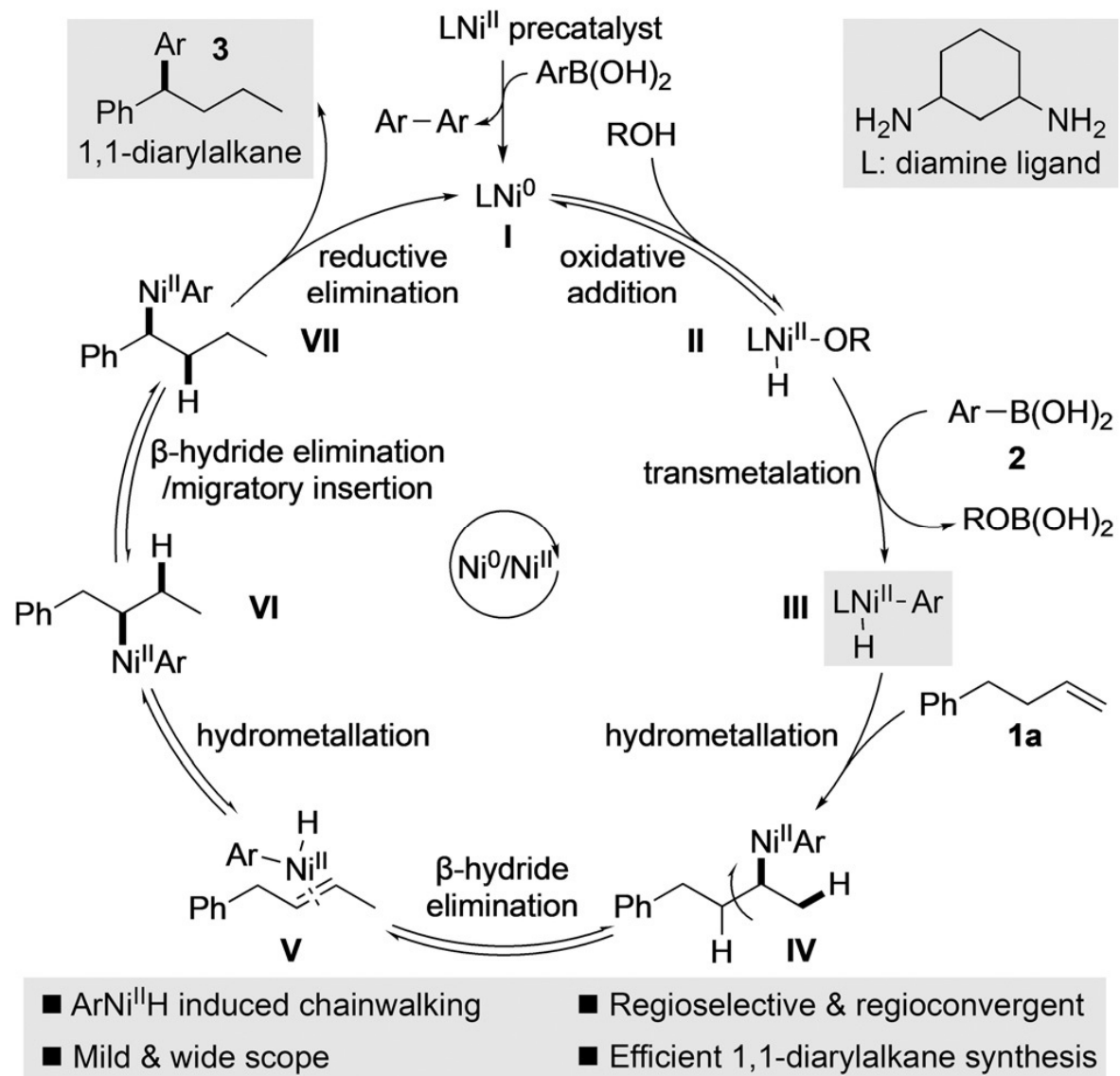


Entry	Variation from standard conditions	Yield [%] <sup>[a]</sup>	rr <sup>[b]</sup>
1	none	99 (84)	> 99:1
2	Ni(cod) <sub>2</sub> instead of Ni(OTf) <sub>2</sub>	91	> 99:1
3	<b>L2</b> instead of <b>L1</b>	99	> 99:1
4	<b>L3</b> instead of <b>L1</b>	71	89:11
5	<b>L4</b> instead of <b>L1</b>	57	> 99:1
6	P <sup>t</sup> Bu <sub>3</sub> or <b>L5</b> instead of <b>L1</b>	NR	–
7	no MeOH	8	> 99:1
8	EtOH instead of MeOH	83	> 99:1
9	THF instead of Tol	76	> 99:1
10	MeOH as solvent	NR	–
11	CsF instead of K <sub>3</sub> PO <sub>4</sub>	77	> 99:1
12	1.5 equiv <b>2a</b>	78	> 99:1
13	70 °C	85	> 99:1



### 甲醇作为氢源





# Ligand Relay Catalysis

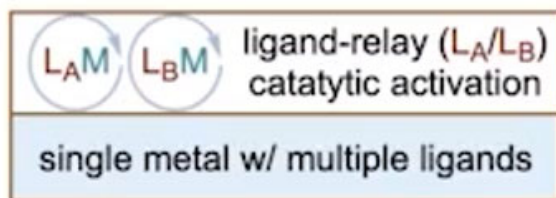
# Ligand Relay Catalysis

## ◆ Challenge in NiH-catalyzed enantioselective remote hydrofunctionalization



Hard to design a single chiral  $L^*$  to efficiently promote both *chain-walking* & *asymmetric coupling*

## ◆ Ligand relay catalysis: A solution to simplify the ligand design



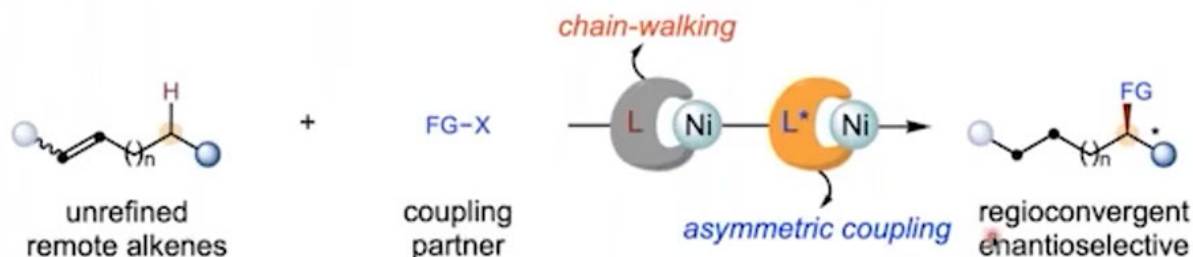
# Ligand Relay Catalysis

## ◆ Challenge in NiH-catalyzed enantioselective remote hydrofunctionalization



Hard to design a single chiral  $\text{L}^*$  to efficiently promote both *chain-walking* & *asymmetric coupling*

## ◆ Ligand relay catalysis: A solution to simplify the ligand design



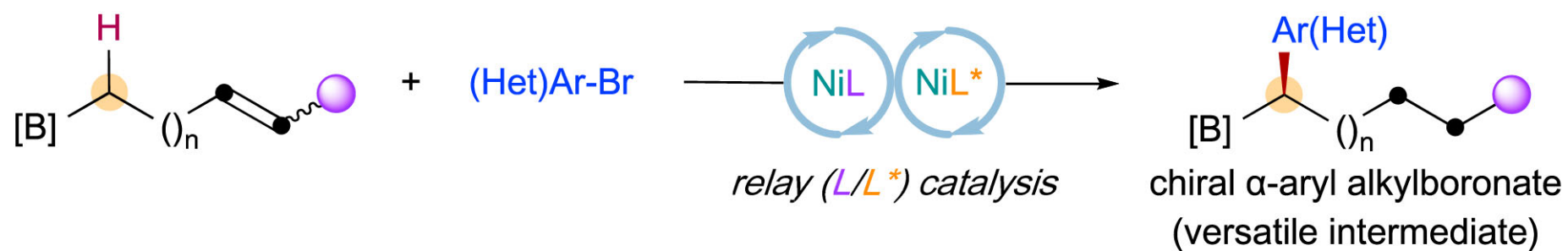
### Requirement:

- orthogonal and complementary
- easily undergo ligand exchange w/ Ni

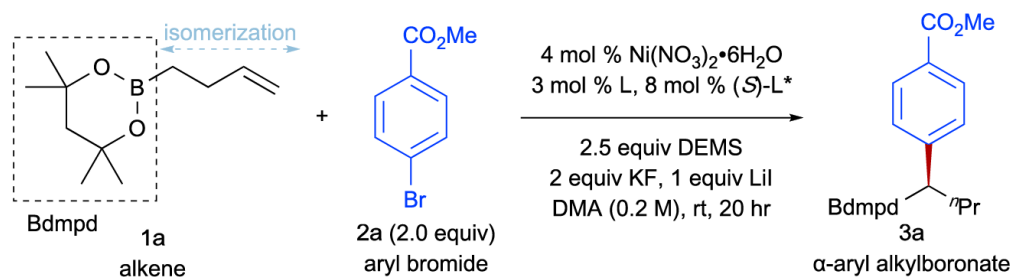
### Advantages:

- simplify ligand design
- enhance whole efficiency

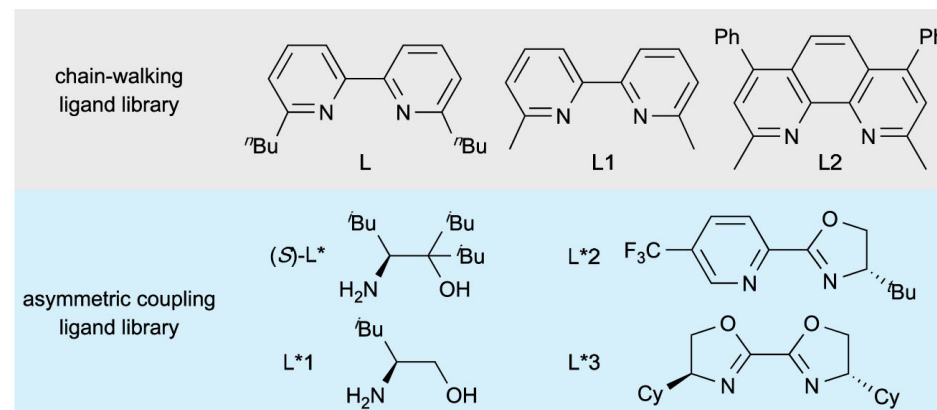
### 3.1、含硼烯炔远端不对称芳基化（双配体协同催化）







entry	deviation from standard conditions	yield of 3a (%)	rr	ee (%)
1	none	77 (70)	>99:1	93
2	NiBr <sub>2</sub> ·dme instead of Ni(NO <sub>3</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	67	>99:1	89
3 <sup>a</sup>	w/o L	10	48:52	93
4 <sup>a</sup>	w/o ( <i>S</i> )-L*	31	96:4	0
5	( <i>S</i> )-L* reduced to 4 mol%	74	>99:1	93
6	( <i>S</i> )-L* reduced to 1 mol%	63 (52) <sup>b</sup>	>99:1	91
7	L1 instead of L	70	>99:1	91
8	L2 instead of L	23	>99:1	28
9	L*1 instead of ( <i>S</i> )-L*	36	>99:1	10
10	L*2 instead of ( <i>S</i> )-L*	49	94:6	75
11	L*3 instead of ( <i>S</i> )-L*	36	>99:1	34
12	PMHS instead of DEMS	64	>99:1	89
13	w/o KF (base)	0	–	–
14	w/o Lil (additive)	60	>99:1	93
15	THF instead of DMA	22	>99:1	83
16	Arl instead of ArBr	72	>99:1	92
17	Bpin instead of Bdpmpd	78 (71)	>99:1	90

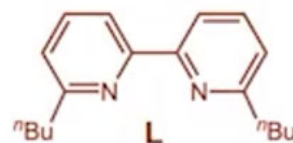




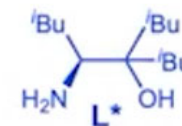
entry	deviation from standard conditions	yield (%)	rr	ee (%)
1	none	77 (70)	>99:1	93
2	w/o L	10	48:52	93
3	L* reduced to 1 mol%	63 (52)	>99:1	91

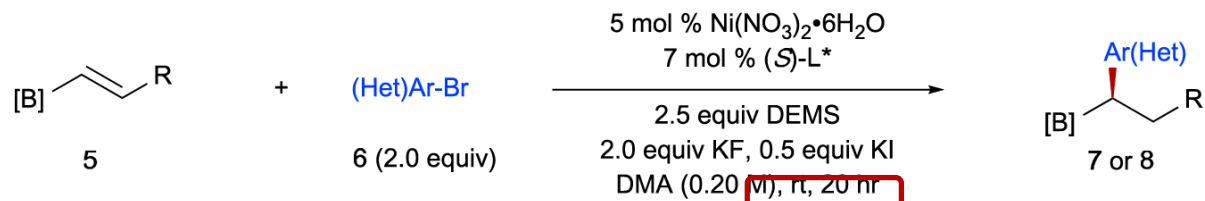


chain-walking  
ligand library

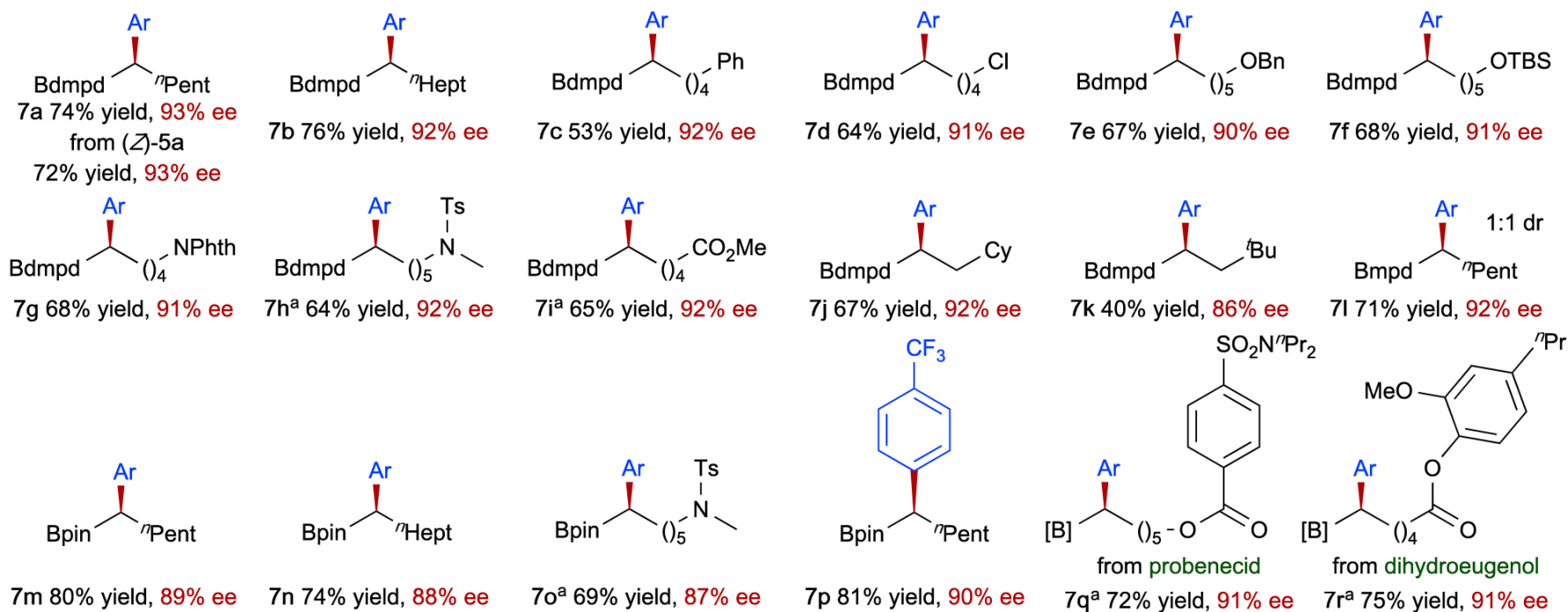


asymmetric coupling  
ligand library

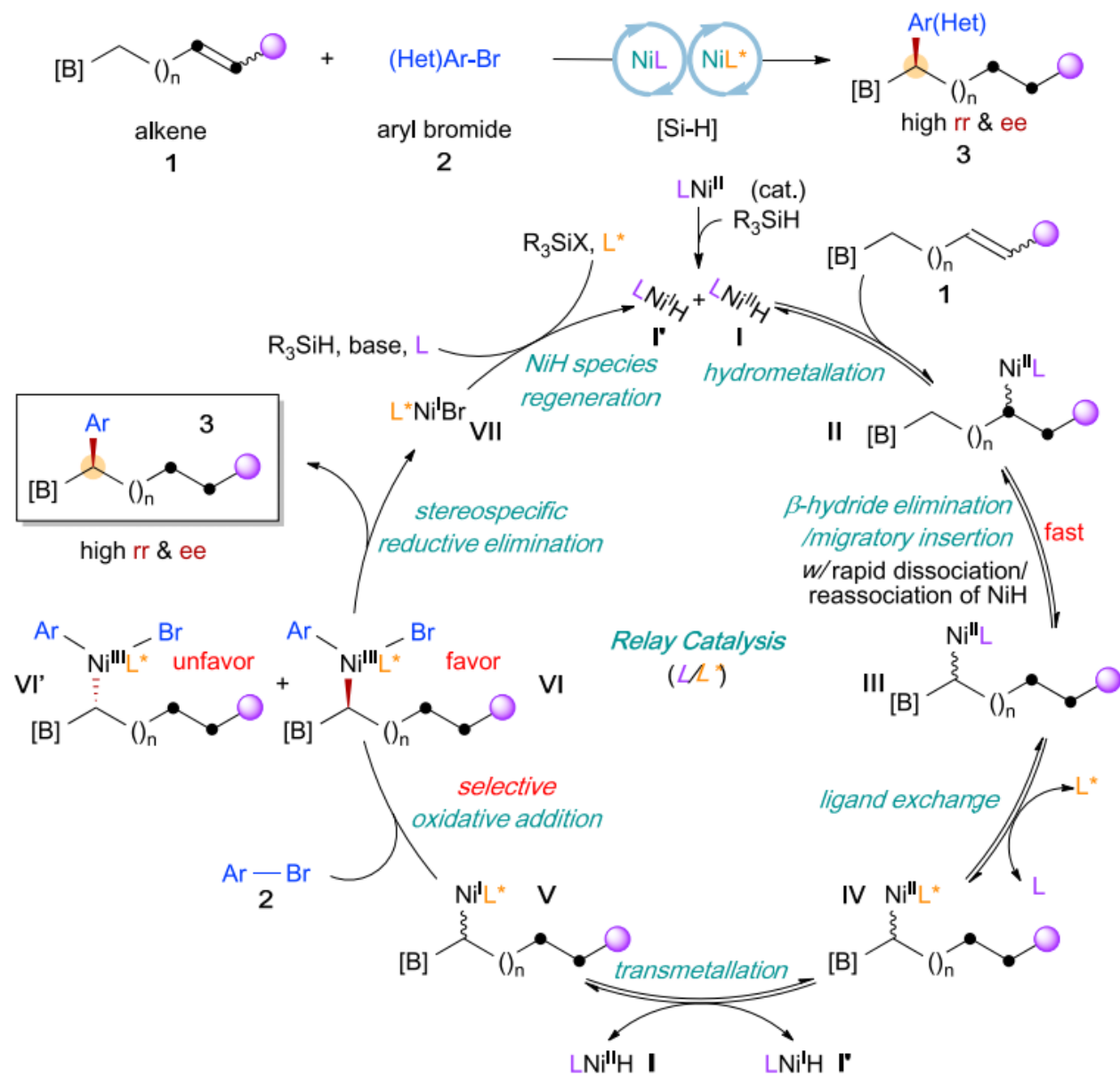


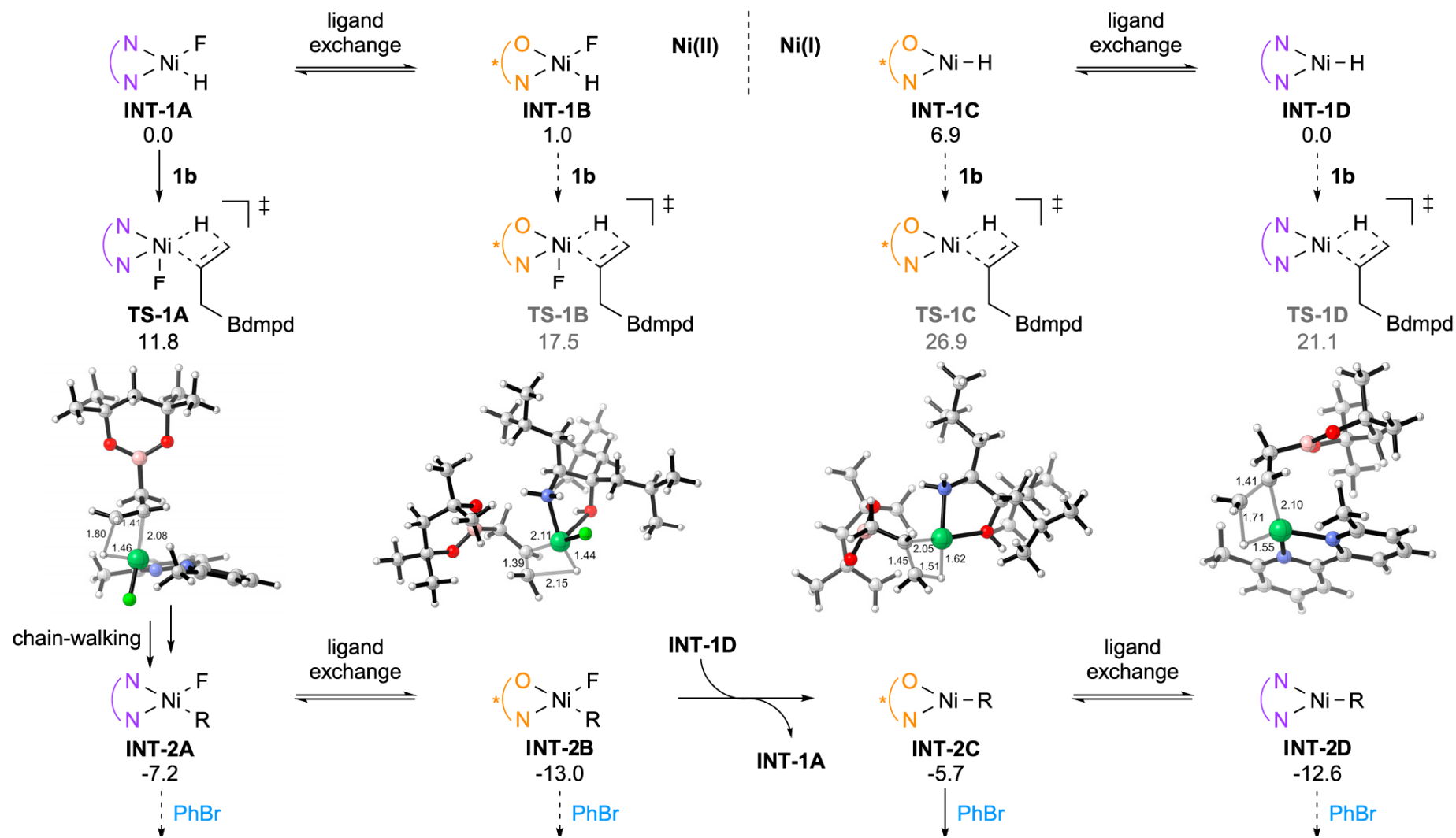


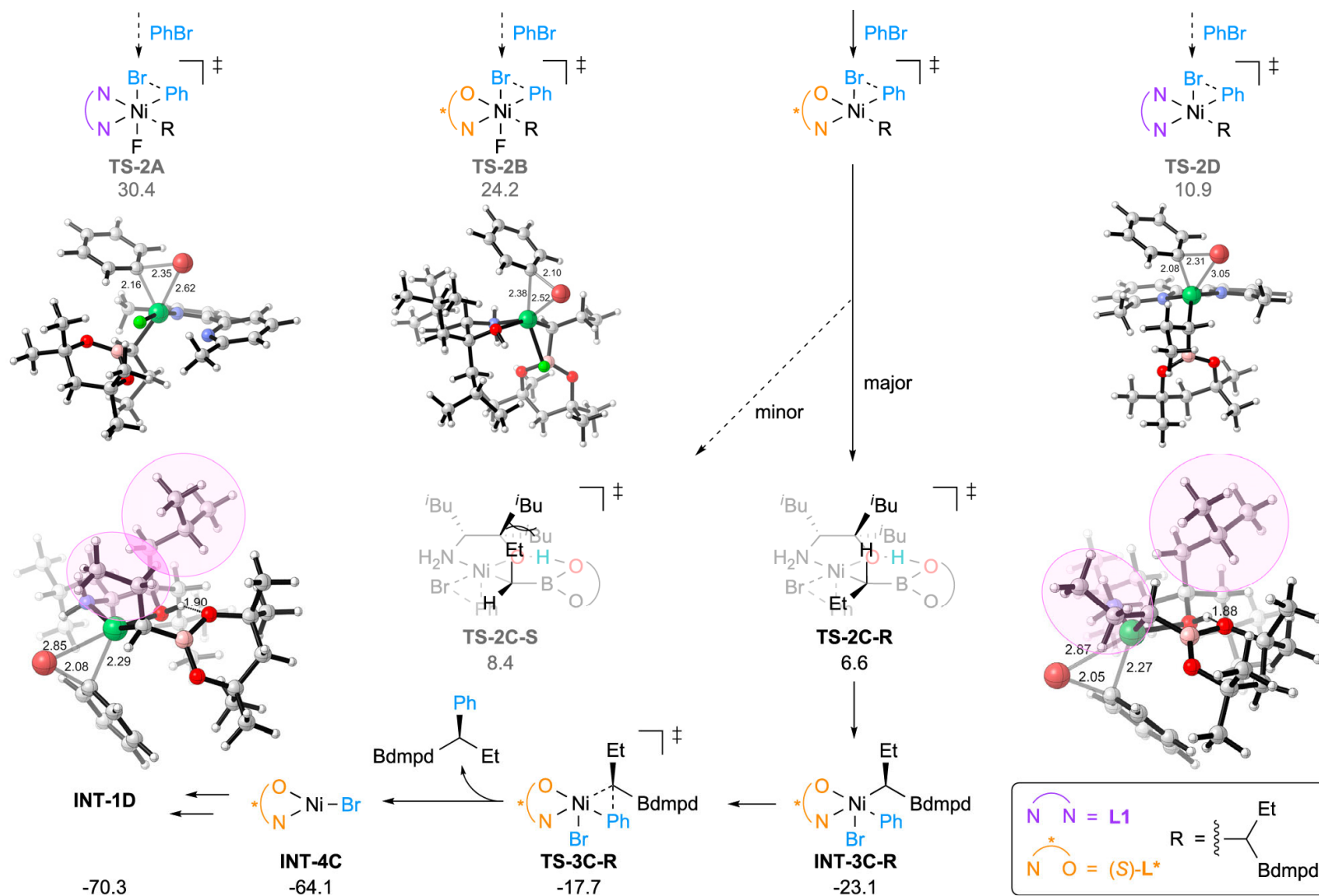
**A** scope of alkenyl boronates (2a used)

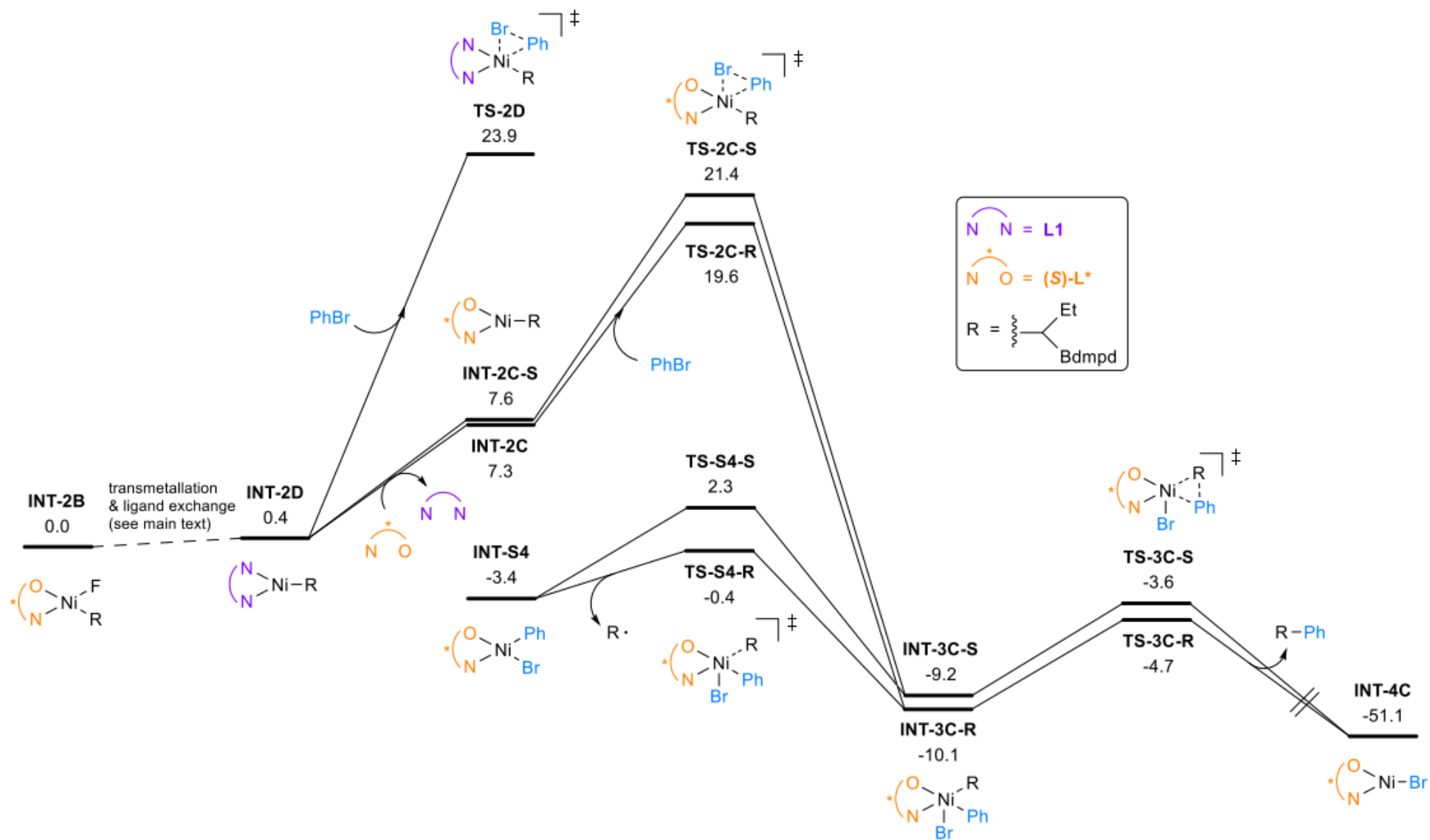


该反应可以扩展到烯基硼酸酯本身，仅需单手性氨基醇配体



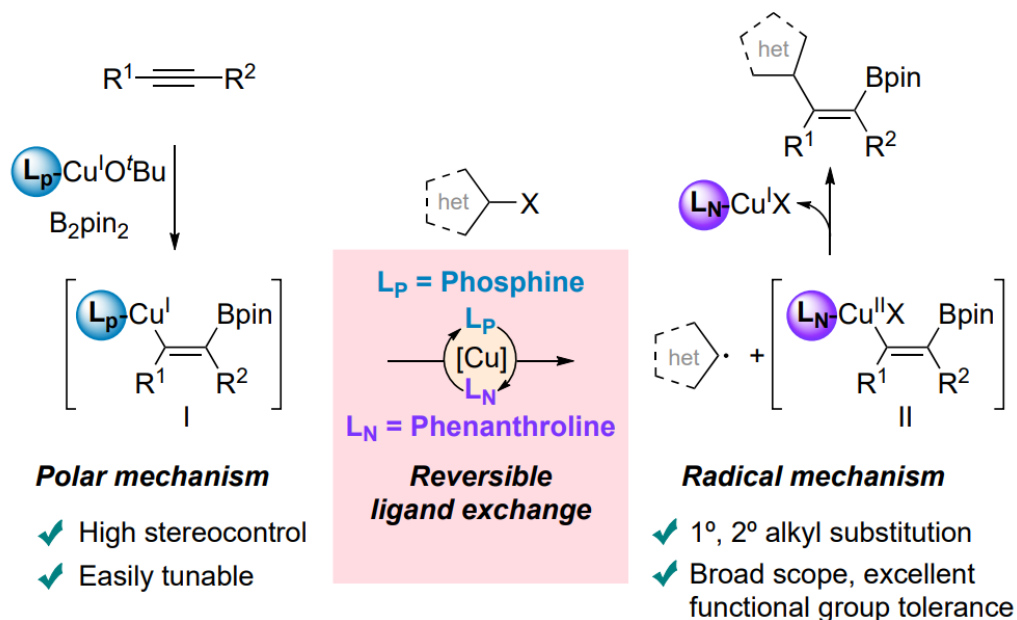






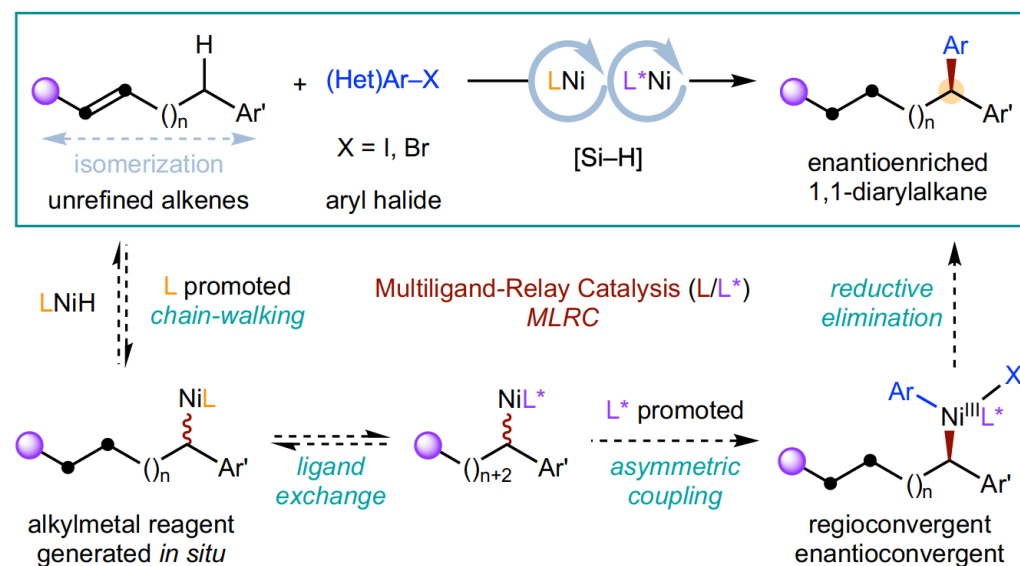
## 3.2、配体接力：烯烃远端的C(sp<sup>3</sup>)-H不对称芳基化

Pablo Mauleón



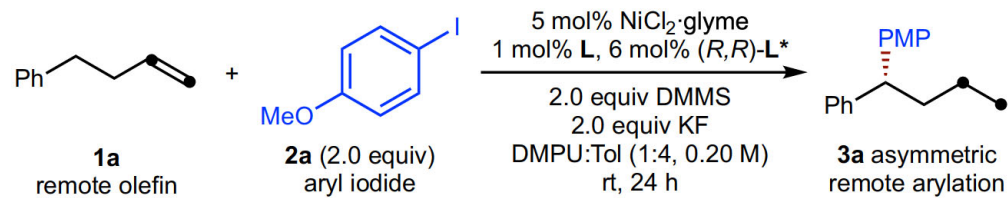
Zhu

c MLRC ( $L/L^*$ ): Asymmetric remote hydroarylation to access chiral 1,1-diaryllalkanes

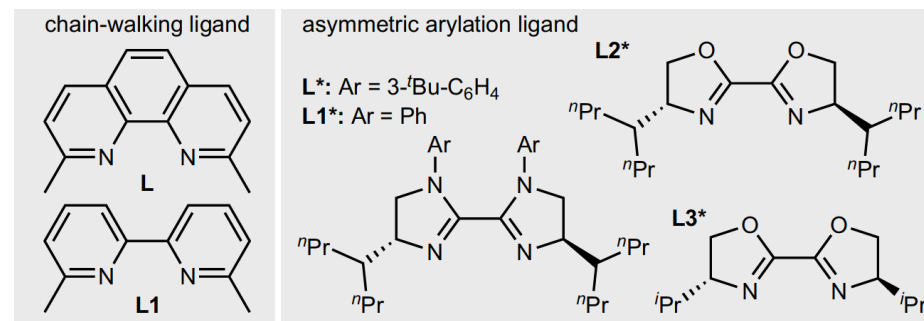


多配体与金属的动态交换可用于顺序促进  
铜催化的中继反应中的不同步骤



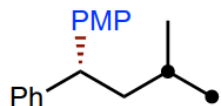


entry	deviation from standard conditions	yield of <b>3a</b> (%) <sup>*</sup>	rr <sup>†</sup>	ee <sup>‡</sup>
1	none	90 (84)	99:1	95
2	w/o <b>L</b>	52	68:32	95
3	w/o (R,R)- <b>L</b> <sup>*</sup>	4	–	–
4	w/o (R,R)- <b>L</b> <sup>*</sup> , 6 mol% <b>L</b> used	77	99:1	–
5	0.4 mol% <b>L</b> , 6 mol% (R,R)- <b>L</b> <sup>*</sup>	86	97:3	96
6	3 mol% <b>L</b> , 3 mol% <b>L</b> <sup>*</sup>	77	>99:1	78
7	<b>L1</b> instead of <b>L</b>	76	97:3	94
8	<b>L1</b> <sup>*</sup> instead of <b>L</b> <sup>*</sup>	91	99:1	91
9	<b>L2</b> <sup>*</sup> instead of <b>L</b> <sup>*</sup>	70	96:4	80
10	<b>L3</b> <sup>*</sup> instead of <b>L</b> <sup>*</sup>	46	94:6	55
11	NiI <sub>2</sub> instead NiCl <sub>2</sub> ·glyme	80	99:1	94
12	PMHS instead DMMS	70	98:2	95
13	K <sub>3</sub> PO <sub>4</sub> ·H <sub>2</sub> O instead KF	79	99:1	93
14	DMPU only	42	96:4	92
15	toluene only	<5	–	–
16	ArBr instead ArI	74	99:1	95

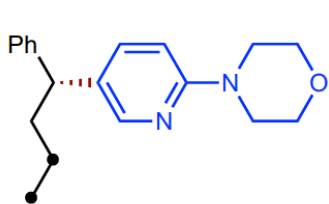


将链行走配体的负载量降低至0.4摩尔%对整体性能几乎没有影响(条目5)。

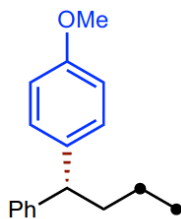
但增加链行走配体负载和减少芳基化配体负载导致产率和对映选择性的适度降低(条目6)



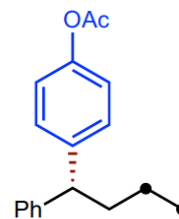
**4n** 41% yield, >99:1 rr, 94% ee



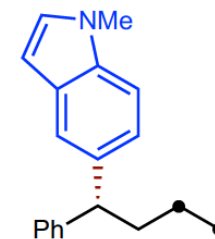
**3t**  
61% yield, 97:3 rr, 95% ee  
47% yield, 97:3 rr, 95% ee\*



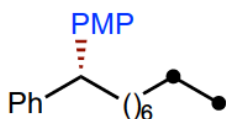
**3a**  
84% yield, 99:1 rr, 95% ee  
67% yield, >99:1 rr, 95% ee\*



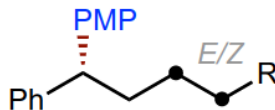
**3b**  
90% yield, 99:1 rr, 90% ee  
74% yield, 99:1 rr, 90% ee\*



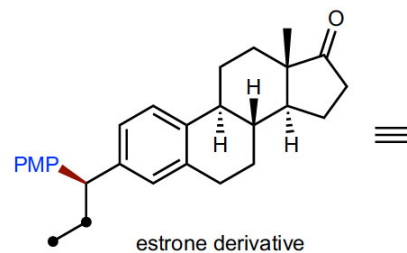
**3r†**  
60% yield, 98:2 rr, 95% ee



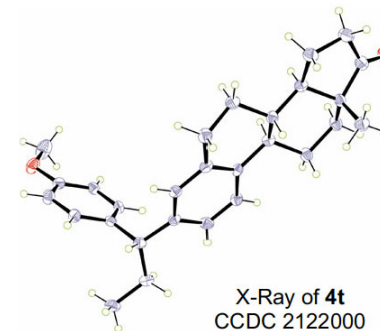
**4m** 38% yield, 96:4 rr, 96% ee  
(57% yield, 99:1 rr, 93% ee)\*



**4u** R = Me, 80% yield, >99:1 rr, 95% ee  
**4v** R = <sup>n</sup>Pent, 58% yield, >99:1 rr, 95% ee



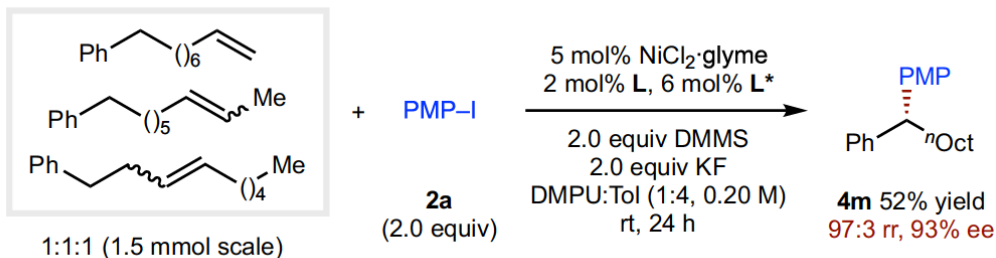
**4t†** 82% yield, >99:1 rr, >20:1 dr



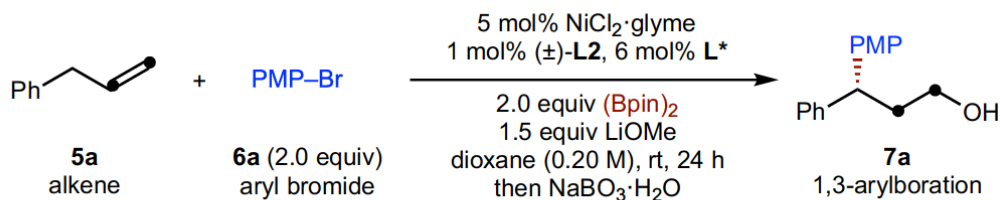
增加链行走配体的负载  
对于长链烯烃底物有益

E/Z构型的烯烃都兼容体系

a Regioconvergent, enantioselective, and bench-top set up experiment

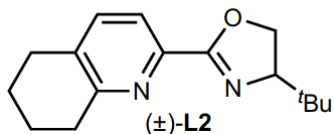


b Application of multiligand-relay catalysis (MLRC) in 1,3-arylboration reaction

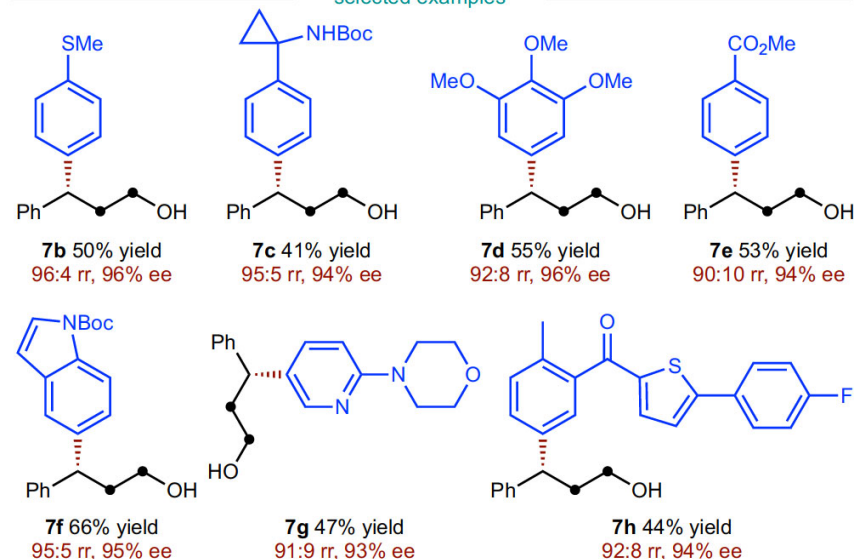


Entry	Variation from standard conditions	Yield (%) <sup>*</sup>	rr <sup>†</sup>	ee (%) <sup>‡</sup>
1	none	65 (61)	95:5	95
2	6 mol% L* only	44	48:52	95
3	6 mol% (R)- or (S)-L2 only	54	95:5	<3
4	(R)- or (S)-L2 instead of (±)-L2	66	95:5	95

\*Yields determined by GC using *n*-dodecane as the internal standard, the yield in parentheses is the isolated yield. <sup>†</sup>rr determined by GC and GC-MS analysis. <sup>‡</sup>Enantioselectivities determined by chiral HPLC analysis.



selected examples



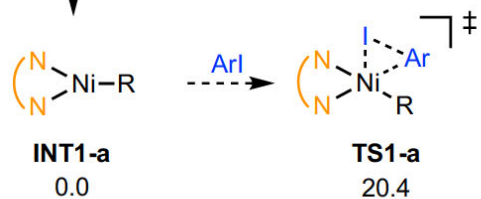
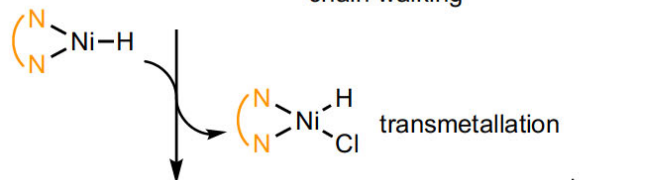
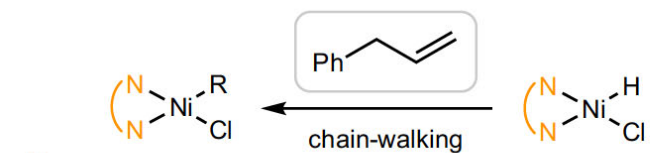
B) This work: Ni-catalyzed asymmetric alkynylboration of vinylarenes



Features: ■ regio- & enantiocontrol ■ mild & reliable ■ valuable synthons

ACS Catal. 2023, 13, 3841–3846

当前的多配体催化也可以应用于烯烃的迁移双官能化



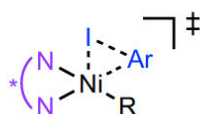
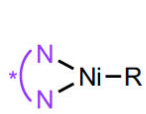
INT1-a  
0.0

TS1-a  
20.4

ligand exchange

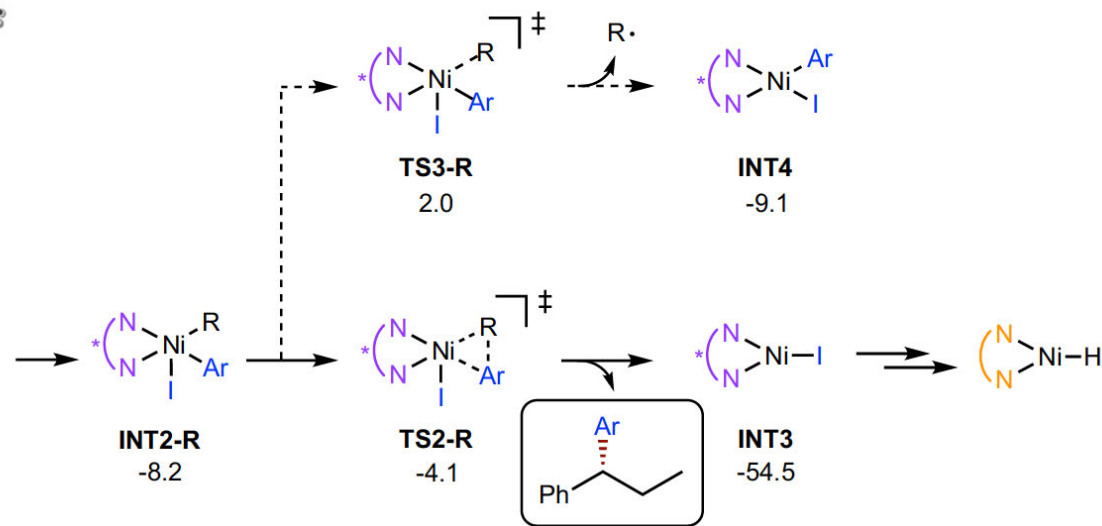
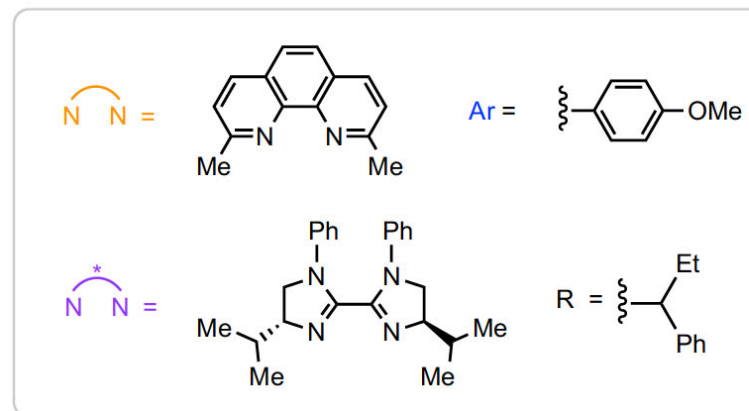
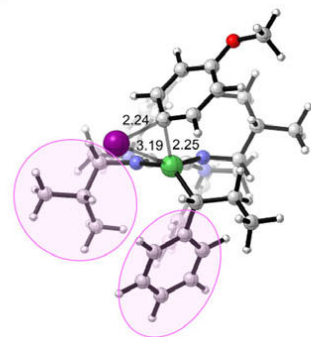
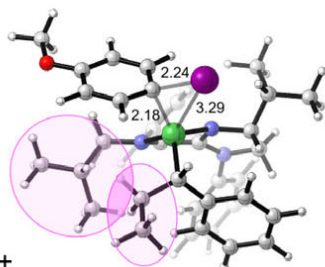
INT1-S  
6.7

TS1-S  
18.0



INT1-R  
5.3

TS1-R  
16.2



TS3-R  
2.0

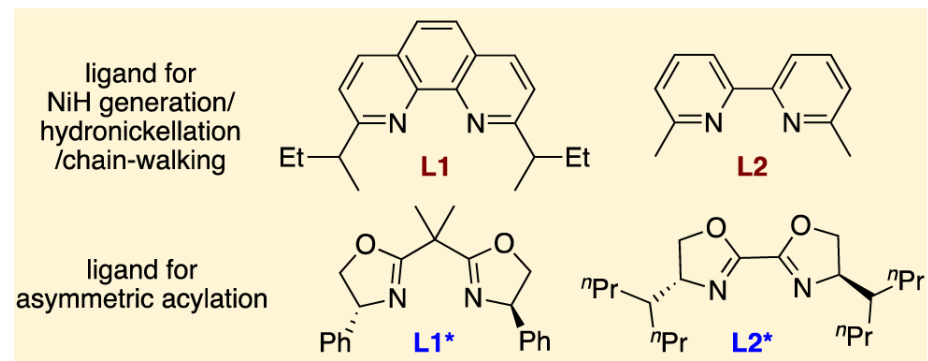
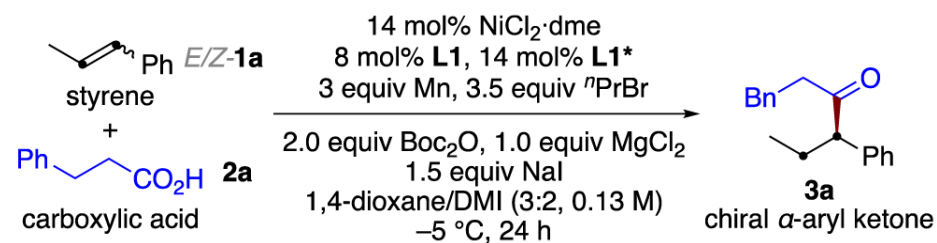
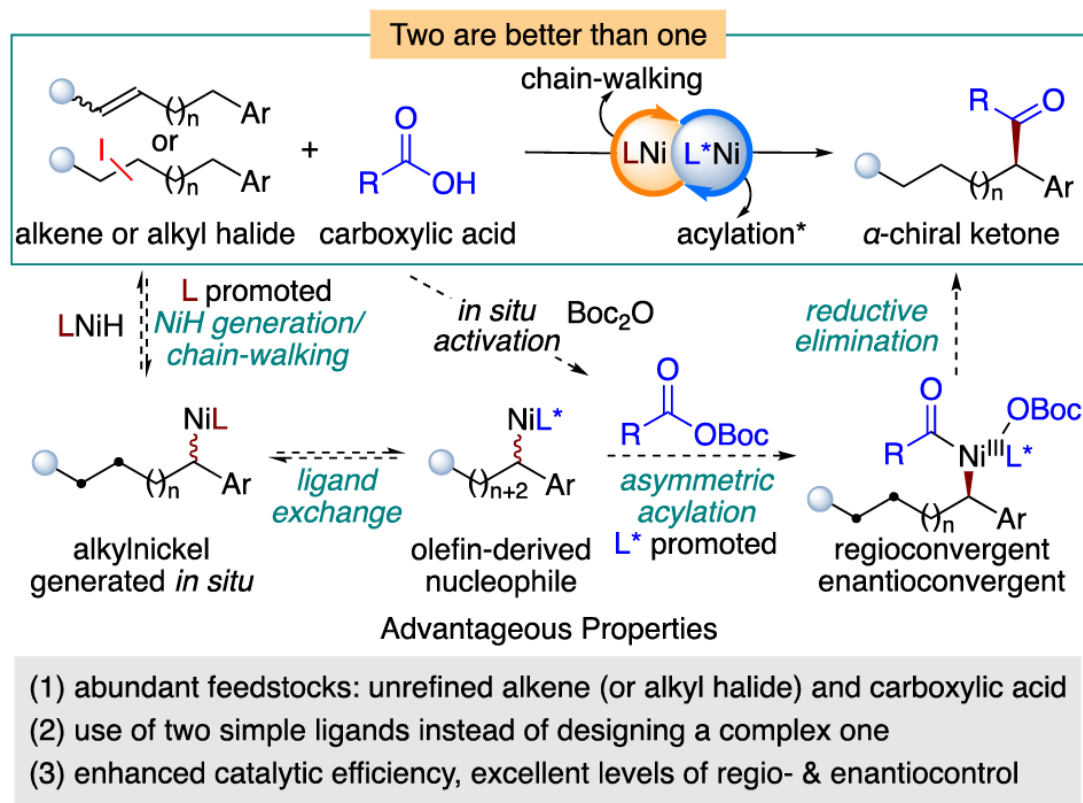
INT4  
-9.1

INT2-R  
-8.2

TS2-R  
-4.1

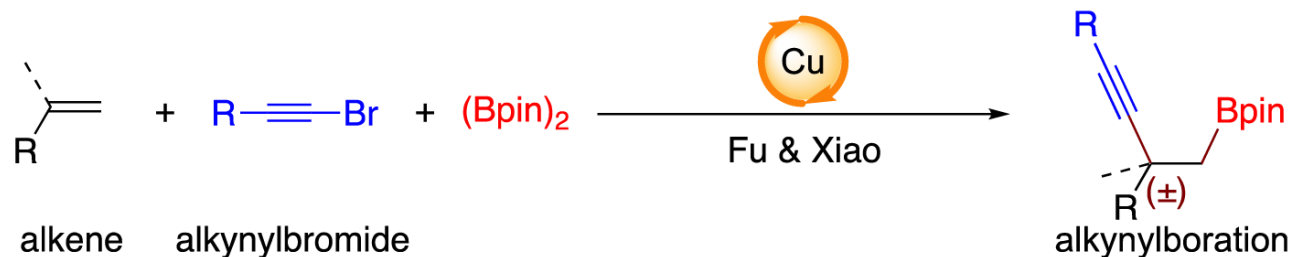
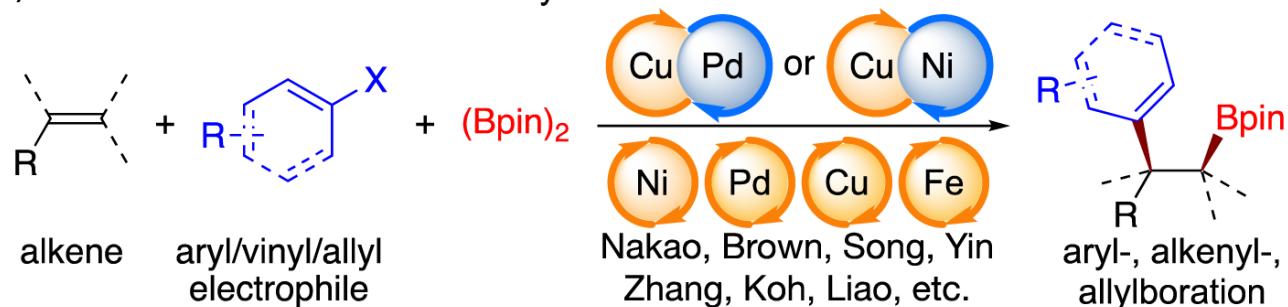
INT3  
-54.5

### 3.3、配体接力:烯烃或卤代烃的不对称迁移还原酰化

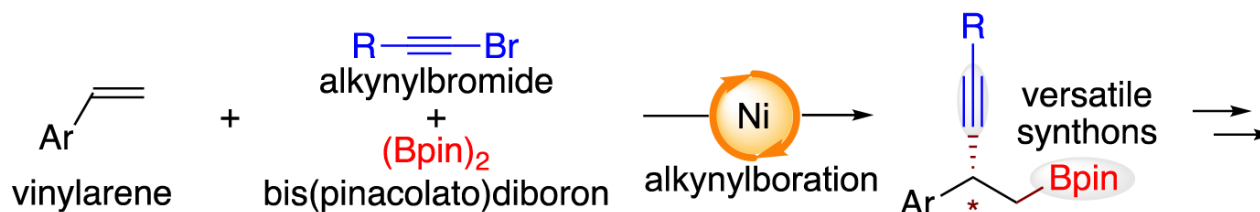


### 3.4、双官能化：乙烯基芳烃的不对称1, 2-炔基硼化反应

A) Prior work: transition-metal catalyzed carboboration of alkenes

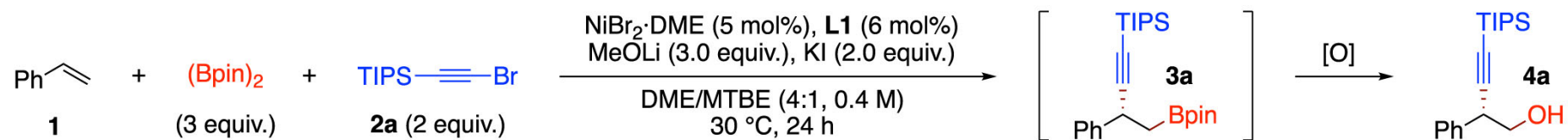


B) This work: Ni-catalyzed asymmetric alkynylboration of vinylarenes

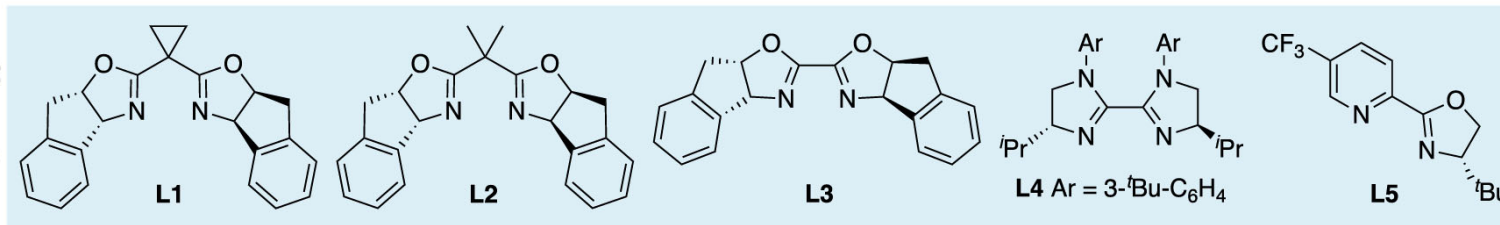
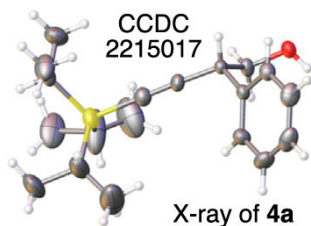


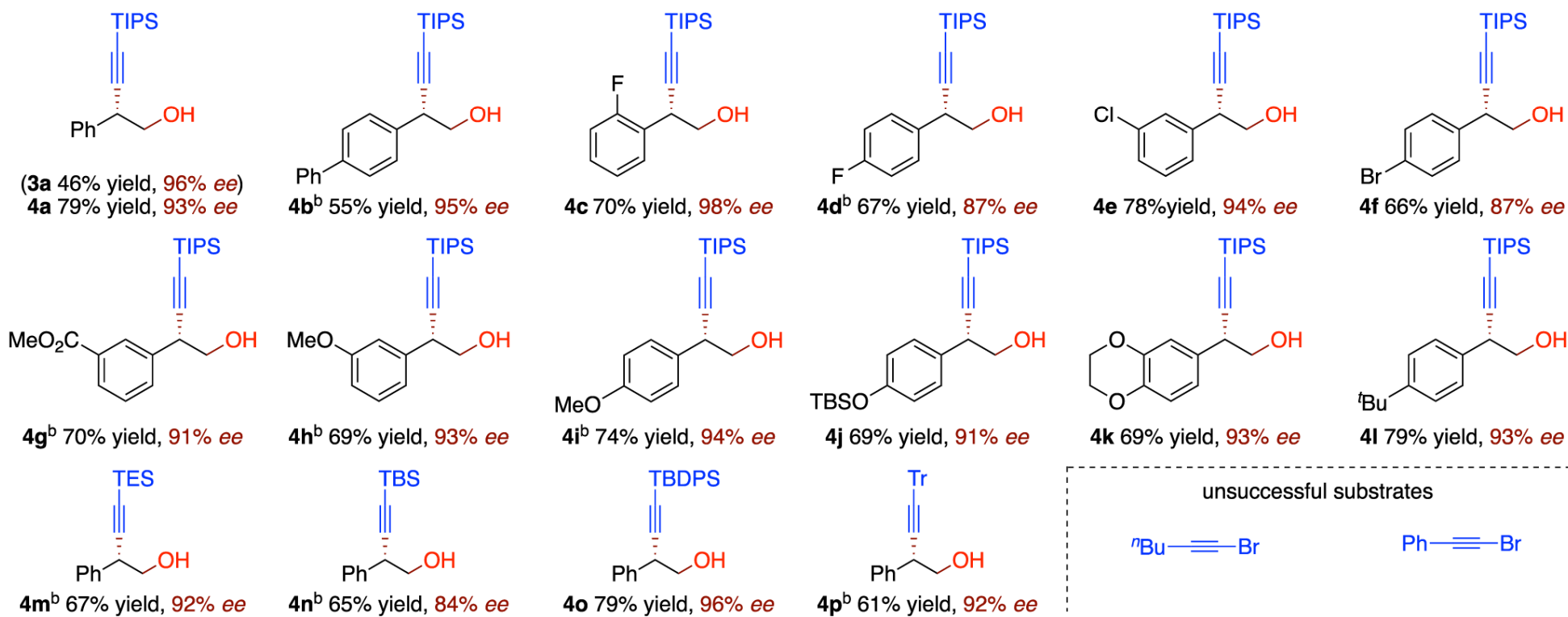
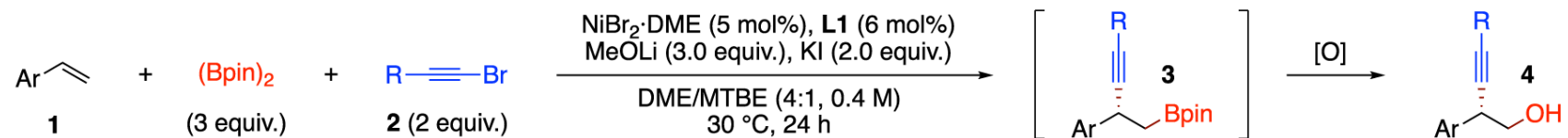
**Features:** ■ regio- & enantiocontrol ■ mild & reliable ■ valuable synthons

*ACS Catal.* **2023**, 13, 3841–3846



Entry	Variation from standard conditions	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	None	82 (79)	93
2	$\text{NiCl}_2 \cdot \text{DME}$ used	70	93
3	$\text{Ni}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ used	70	96
4	<b>L2</b> instead of <b>L1</b>	21	68
5	<b>L3</b> instead of <b>L1</b>	19	50
6	<b>L4</b> instead of <b>L1</b>	47	67
7	<b>L5</b> instead of <b>L1</b>	23	77
8	KF instead of MeOLi	3	nd
9	w/o KI	37	79
10	DME only	85	87
11	MTBE only	13	nd
12	<i>t</i> -BuOH as solvent	69	84
13	at 10 °C	37	96

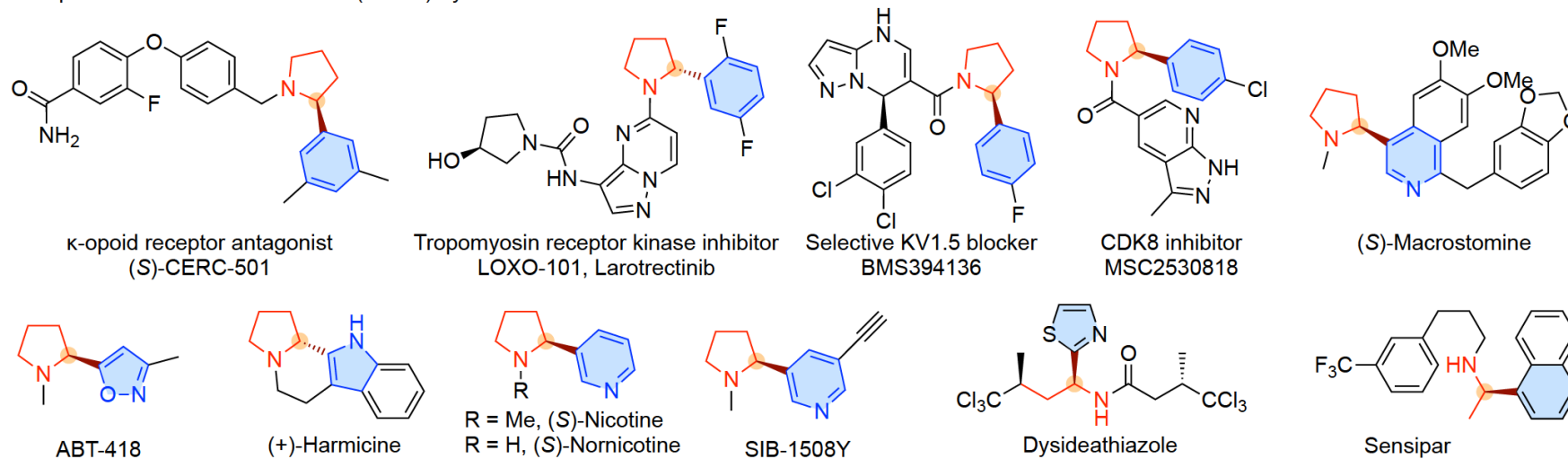




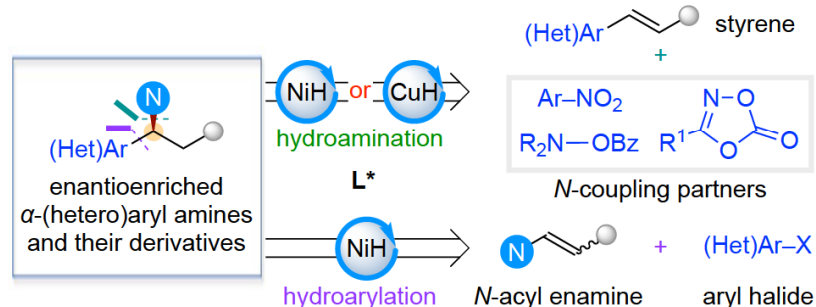


# 3.5、配体接力：含烯环胺或无环胺的不对称芳基化

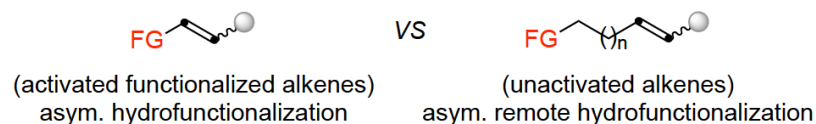
## A. Representative bioactive chiral $\alpha$ -(hetero)aryl-substituted amines



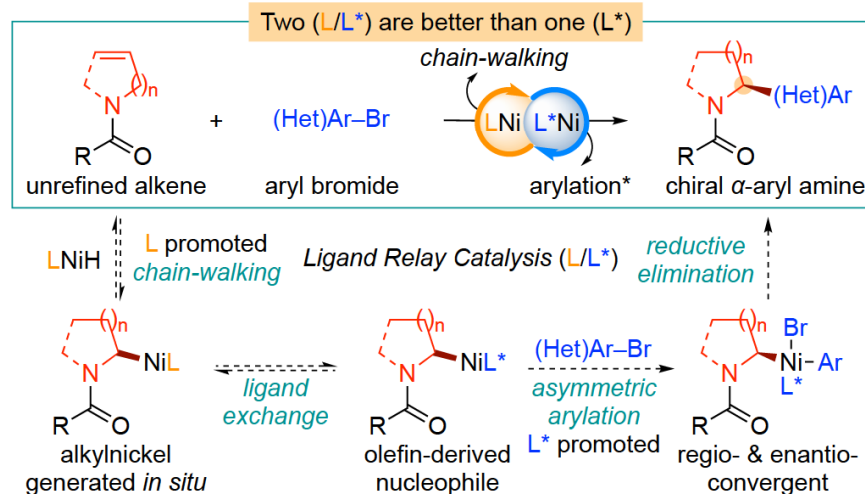
## B. Two known hydrofunctionalization strategies for their synthesis

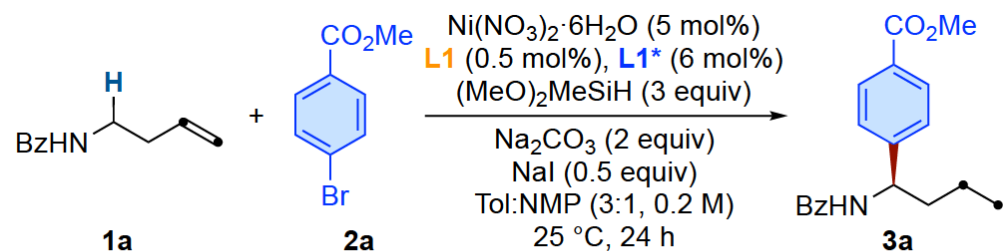


Q: Could unactivated remote alkenes be used?

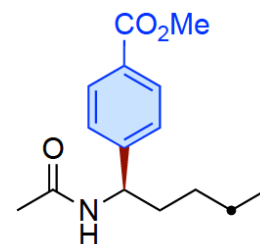


## C. This work: ligand relay catalysis enables asymmetric remote hydroarylation

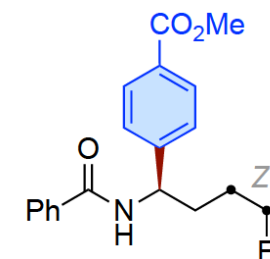




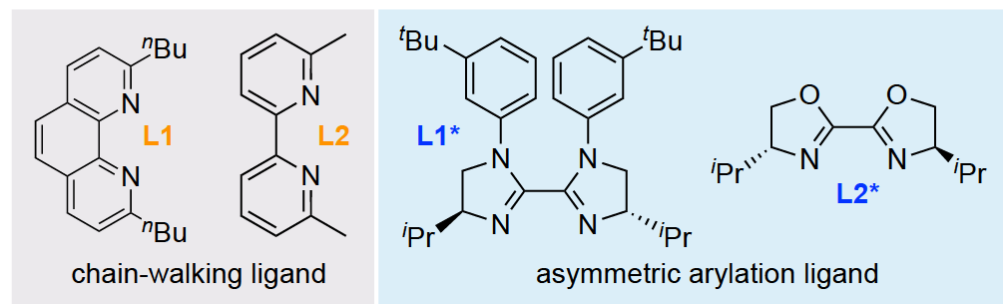
Entry	Variation	Yield [%] <sup>[a]</sup>	rr <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	none	73 (72)	97:3	92
2	w/o <b>L1</b>	0	–	–
3	w/o <b>L1*</b>	0	–	–
4	<b>L1</b> reduced to 0.3 mol%	69	92:8	96
5	<b>L2</b> instead of <b>L1</b>	12	>99:1	89
6	<b>L2*</b> instead of <b>L1*</b>	13	>99:1	–36
7	NiBr <sub>2</sub> ·DME used	69	>99:1	86
8	(EtO) <sub>2</sub> MeSiH used	69	97:3	92
9	K <sub>2</sub> CO <sub>3</sub> instead of Na <sub>2</sub> CO <sub>3</sub>	70	>99:1	60
10	w/o NaI	14	60:40	95
11	Tol only	0	–	–
12	NMP only	19	>99:1	87
13	ArI instead of ArBr	59	94:6	92

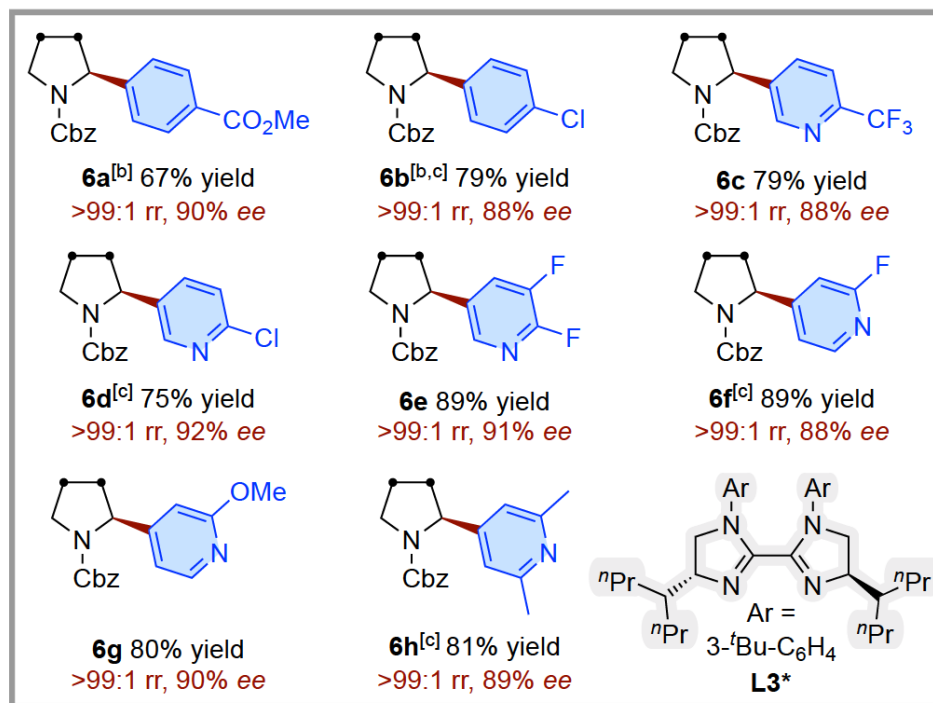
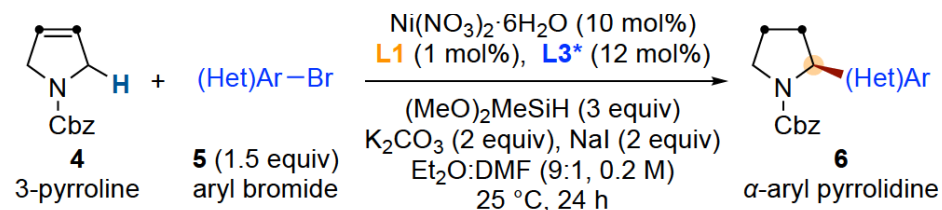


**3s** 50% yield  
>99:1 rr, 92% ee

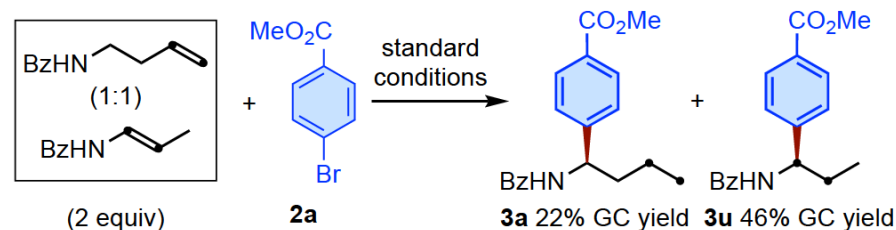


**3t** 51% yield  
>99:1 rr, 91% ee

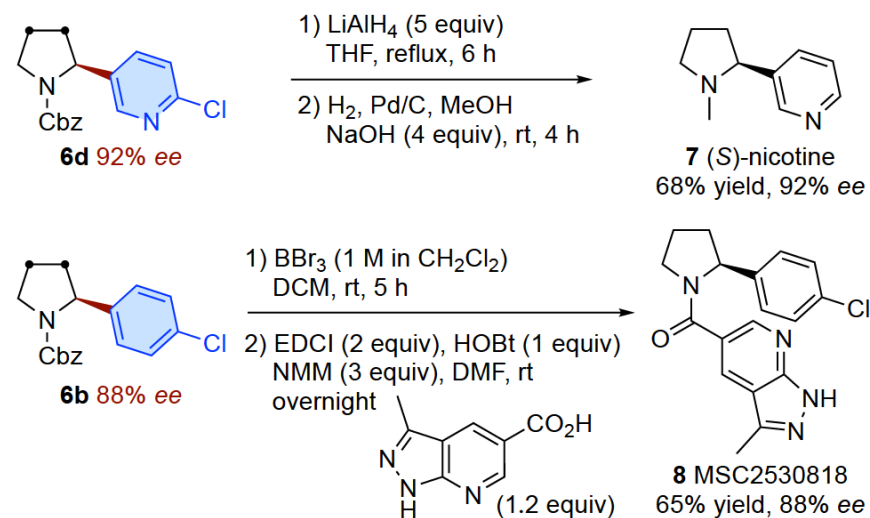




**A. Competition experiment: remote alkene vs *ipso*-alkene**



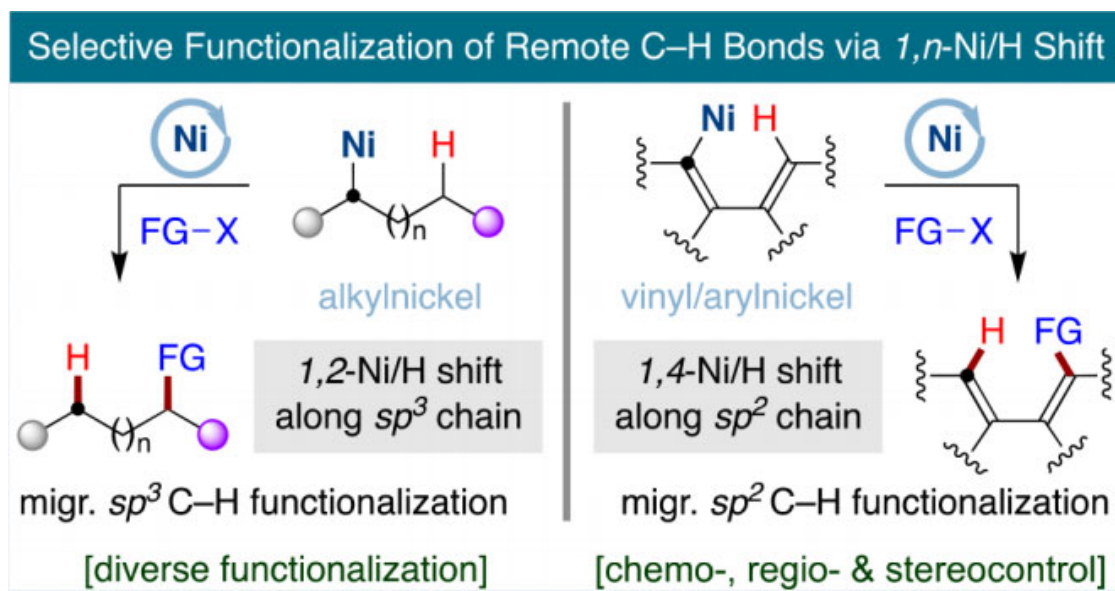
**B. Practical synthesis of (S)-nicotine and a CDK8 inhibitor**



Competition experiment and synthetic application.

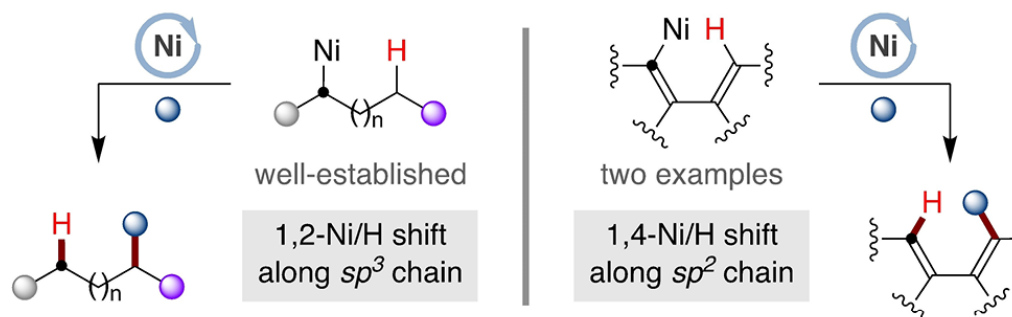
不仅限于含烯烃的无环胺，也适用于许多商业上可用的N-氨基甲酸酯保护的杂环烯烃底物

# 1,4 Ni-H迁移



# 4.1、芳基-乙烯基1,4-镍迁移/还原偶联

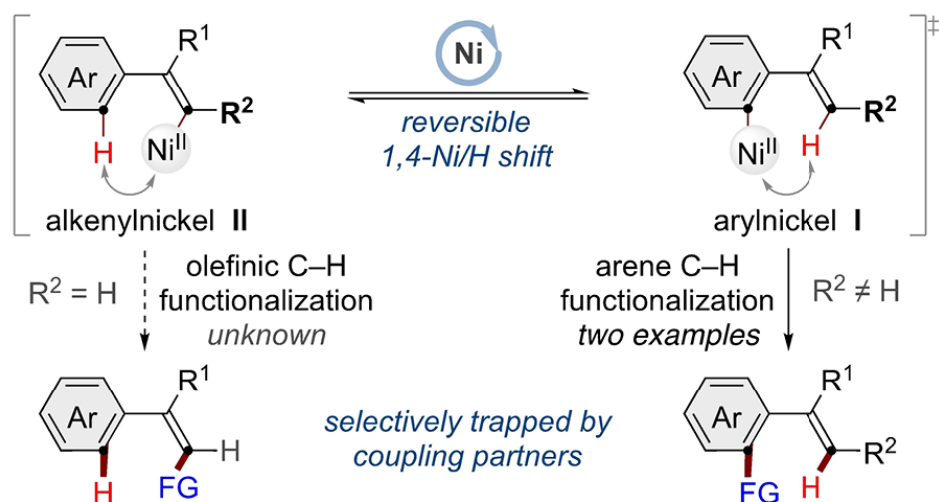
## A. Migratory cross-coupling: an alternative strategy for C–H functionalization



使用镍迁移来实现远端C( $sp^2$ )

H键的功能化的报道较少

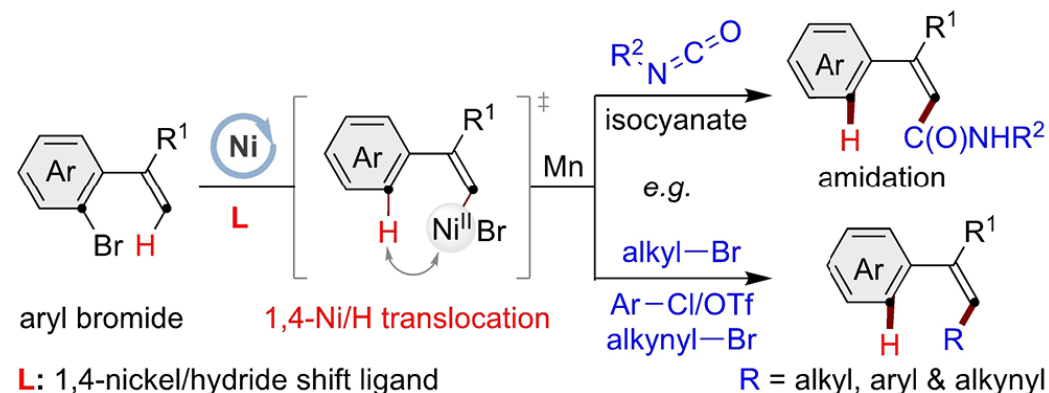
## B. Design: $sp^2$ C–H functionalization via 1,4-Ni migration/reductive coupling



This work  
■ amidation  
■ alkylation, arylation, alkylation

Prior work  
■ carboxylation (Martin)  
■ alkylation (collaborated w/ Martin)

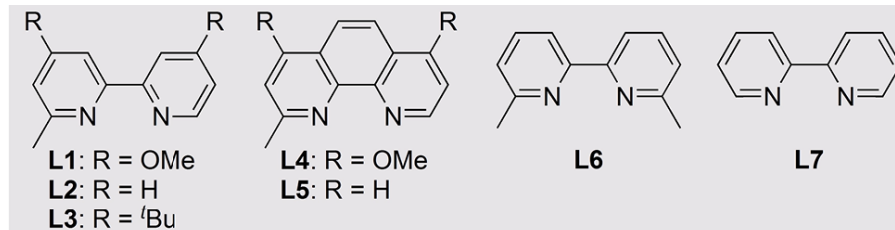
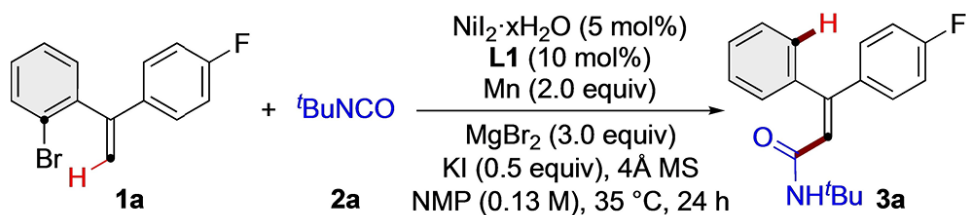
## C. This work: alkenyl $sp^2$ C–H functionalization via aryl-to-vinyl 1,4-Ni/H shift



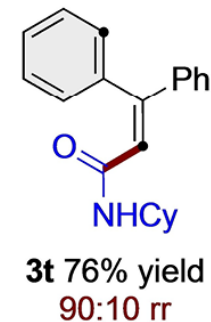
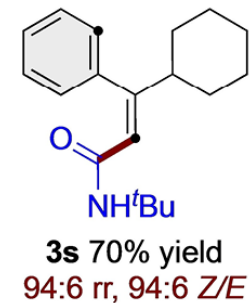
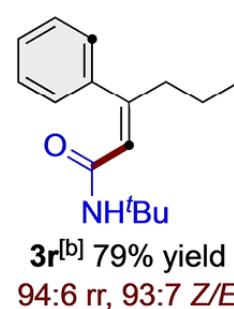
L: 1,4-nickel/hydride shift ligand

[aryl-to-vinyl 1,4-Ni/H shift] [diverse functionalization] [general, mild & reliable]  
[migr.  $sp^2$  C–H functionalization] [excellent chemo-, regio- & *E/Z*-selectivity]

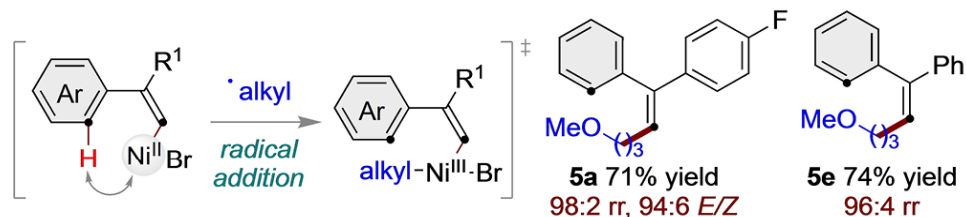
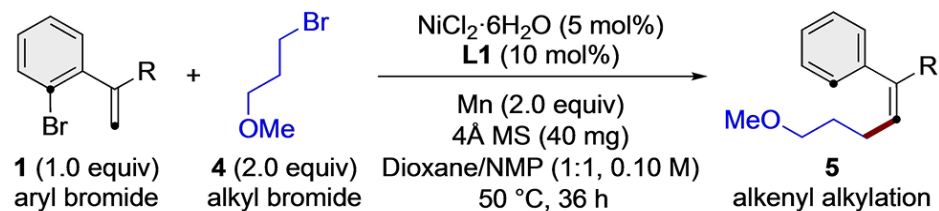
烯基镍中间体空间要求较低



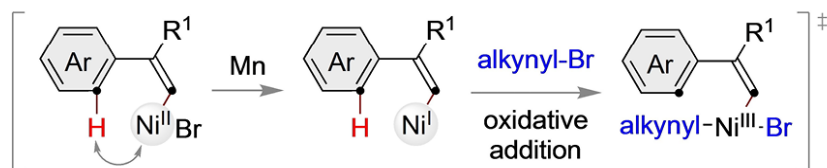
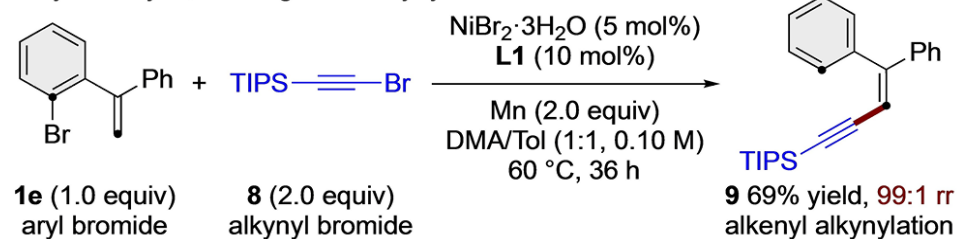
Entry	Variation	Yield [%] <sup>[a]</sup>	rr <sup>[b]</sup>	E/Z <sup>[c]</sup>
1	none	89 (84)	96:4	96:4
2	<b>L2</b> instead of <b>L1</b>	66	92:8	98:2
3	<b>L3</b> instead of <b>L1</b>	77	90:10	98:2
4	<b>L4</b> instead of <b>L1</b>	83	98:2	98:2
5	<b>L5</b> instead of <b>L1</b>	71	90:10	94:6
6	<b>L6</b> or <b>L7</b> instead of <b>L1</b>	trace	–	–
7	Ni(COD) <sub>2</sub> used	84	95:5	93:7
8	NiCl <sub>2</sub> -DME used	87	95:5	93:7
9	Zn instead of Mn	75	84:16	98:2
10	w/o $\text{MgBr}_2$	67	90:10	94:6
11	$\text{MgI}_2$ instead of $\text{MgBr}_2$	76	98:2	90:10
12	w/o KI	86	96:4	96:4
13	w/o 4Å MS	92	96:4	95:5
14	DMA instead of NMP	81	93:7	95:5
15	0 °C instead of 35 °C	48	56:44	98:2
16	50 °C instead of 35 °C	78	98:2	92:8
17	5 mmol-scale	(80)	97:3	96:4



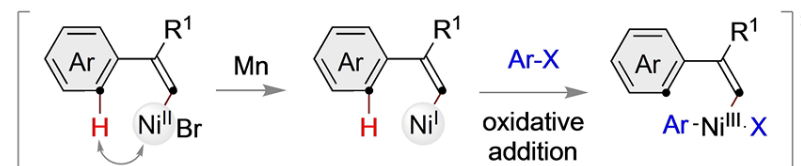
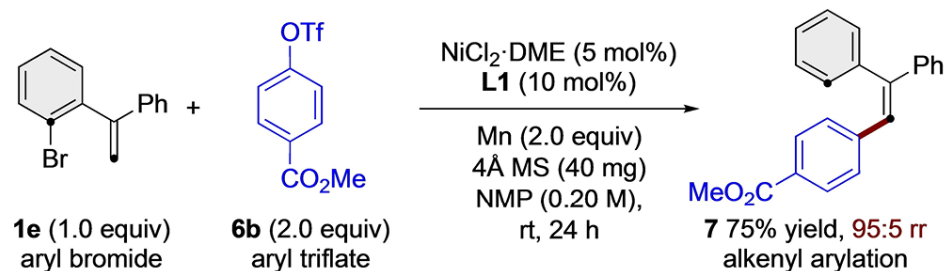
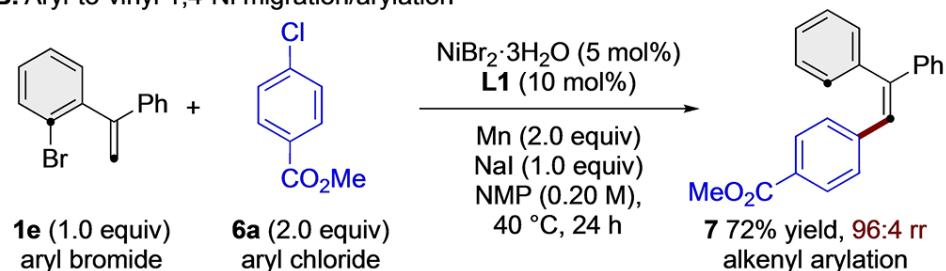
**A. Aryl-to-vinyl 1,4-Ni migration/alkylation**



**C. Aryl-to-vinyl 1,4-Ni migration/alkynylation**

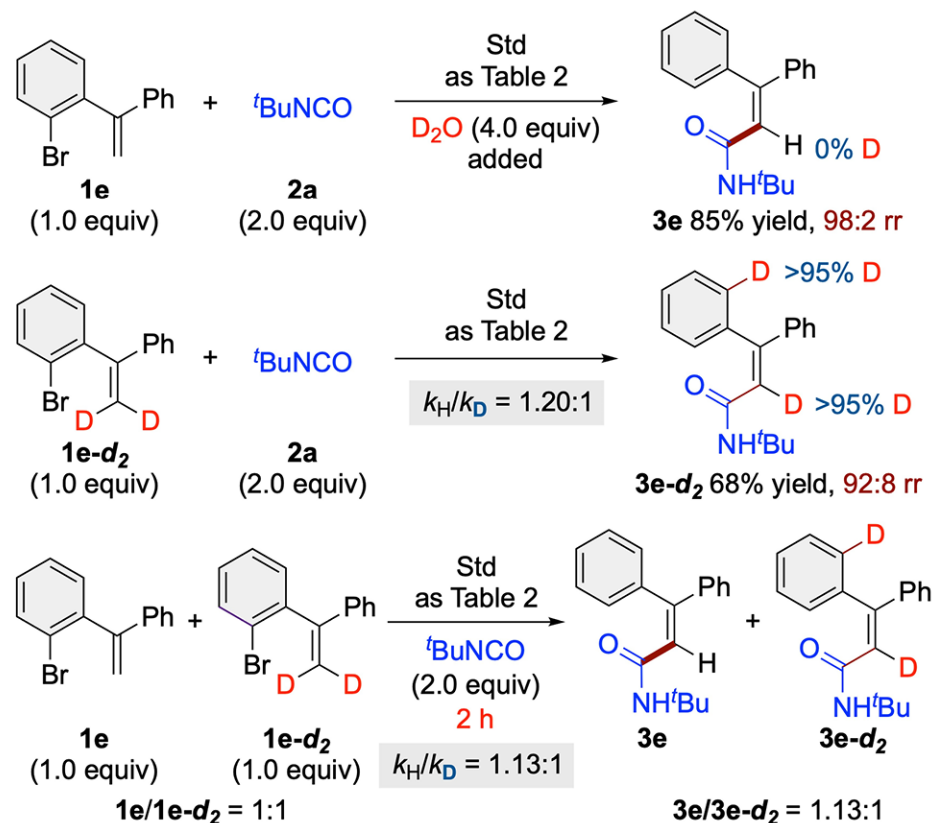


**B. Aryl-to-vinyl 1,4-Ni migration/arylation**



烷基溴、炔基溴、芳基氯等都是合适的偶联伙伴

### A. Isotope-labelling experiments

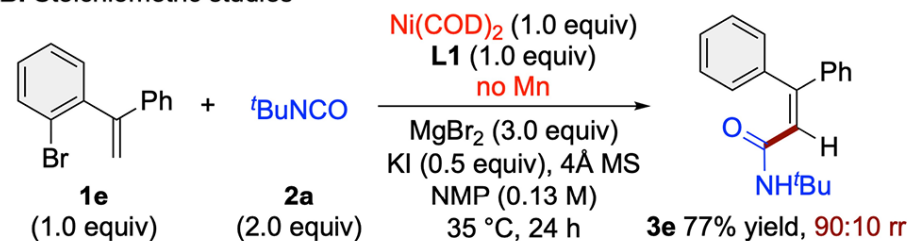


■ intramolecular 1,4-Ni/H shift

■ 1,4-Ni/H shift might not be involved in the rate-limiting step

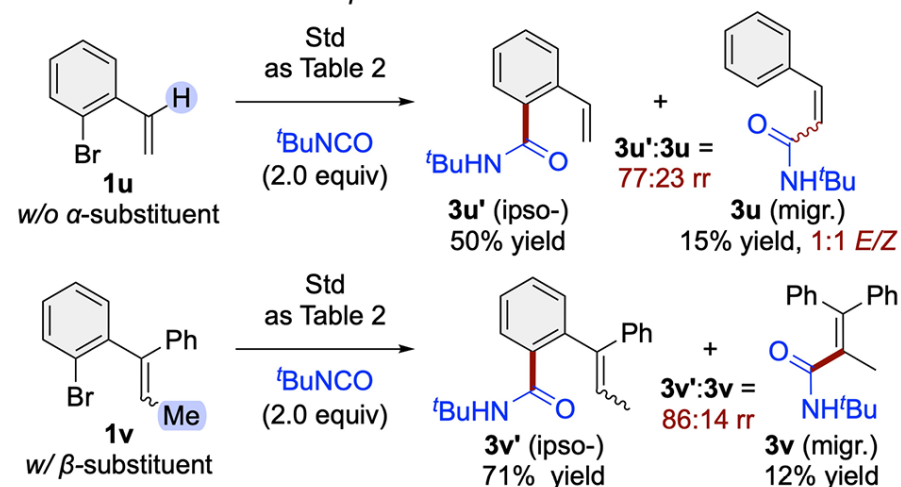
反应中间体与反应介质之间不存在H - D交换

### B. Stoichiometric studies



■ 1,4-Ni/H shift may be triggered by *in situ* generated arylnickel(II) species

### C. Effects of $\alpha$ -substituent and $\beta$ -substituent



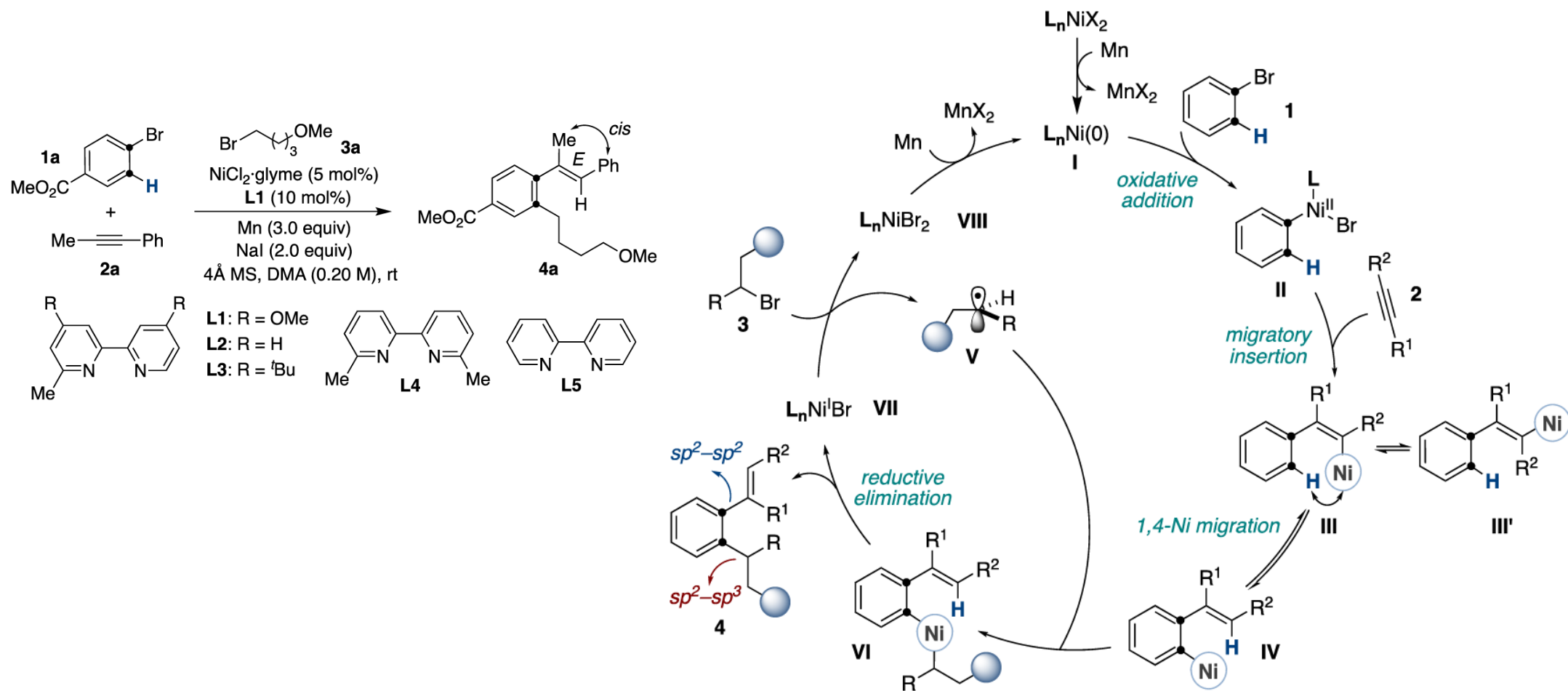
■  $\alpha$ -substituent: may promote 1,4-Ni/H shift

■  $\beta$ -substituent: decreases the ratio of alkenyl functionalization product

原位生成的Ni<sup>II</sup>中间体引发1,4-Ni/H迁移



## 4.2、1,4-NiH迁移：芳基溴化物与炔烃和烷基溴化物的同位/邻位双官能化



*J. Am. Chem. Soc.* **2021**, 143, 20064–20070

Thanks for watching!