Literature Report 17

Nickel-Catalyzed Enantioselective Reductive Heck Reaction of Olefins Enabled by Chiral NHC Ligands

Reporter: Han Wang
Checker: Yu Yang
Date: 2026.3.30

Liu, M.-Y.; Zhang, K.-X.; Pan, J.-B.; Zhou, Q.-L.; Xiao, L.-J. *Angew. Chem. Int. Ed.* **2026**, *65*, e25600.

CV of Dr. Li-Jun Xiao（肖力军）

Background:

- **2008-2012** M.S., China Pharmaceutical University
- **2012-2017** Ph.D., Nankai University, (Prof. Zhou, Qi-Lin)
- **2018-2021** Postdoc., The Scripps Research Institute
- **2021-present** Tenure-Track, Nankai University

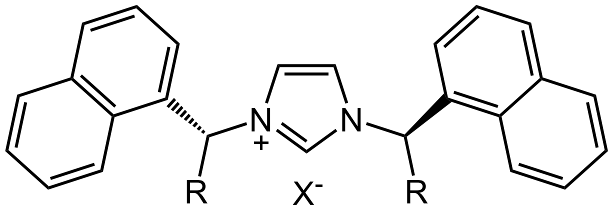
Research:

- ✓ **Organometallic Chemistry**
- ✓ **Transition-Metal Catalysis**
- ✓ **Catalytic Asymmetric Synthesis**

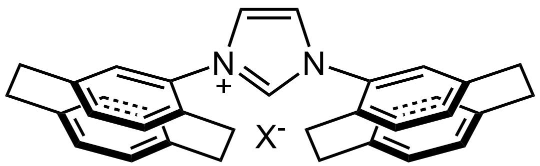
Contents

Introduction

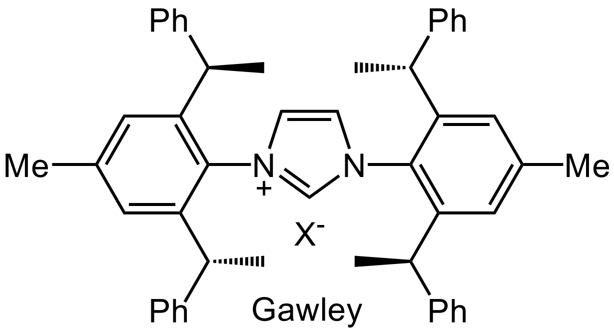
NHCs with sidechain chirality



Hermann/Enders/Kündig

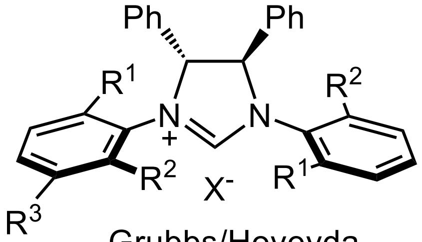


Andrus

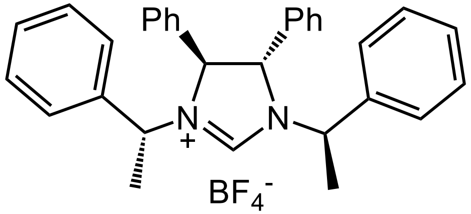


Gawley

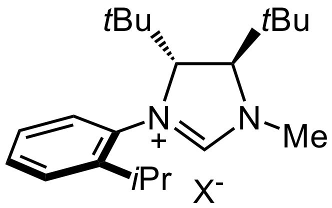
NHCs with backbone chirality



Grubbs/Hoveyda

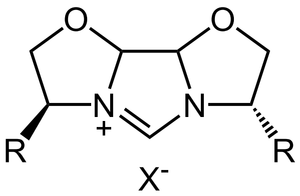


Alexakis

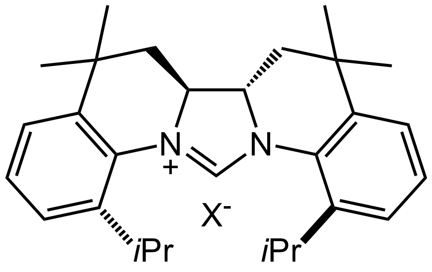


Collins

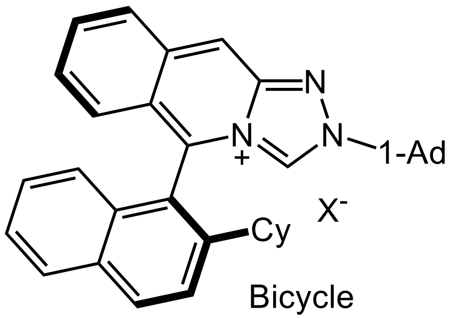
NHCs with chiral multicycle structure



Glorius

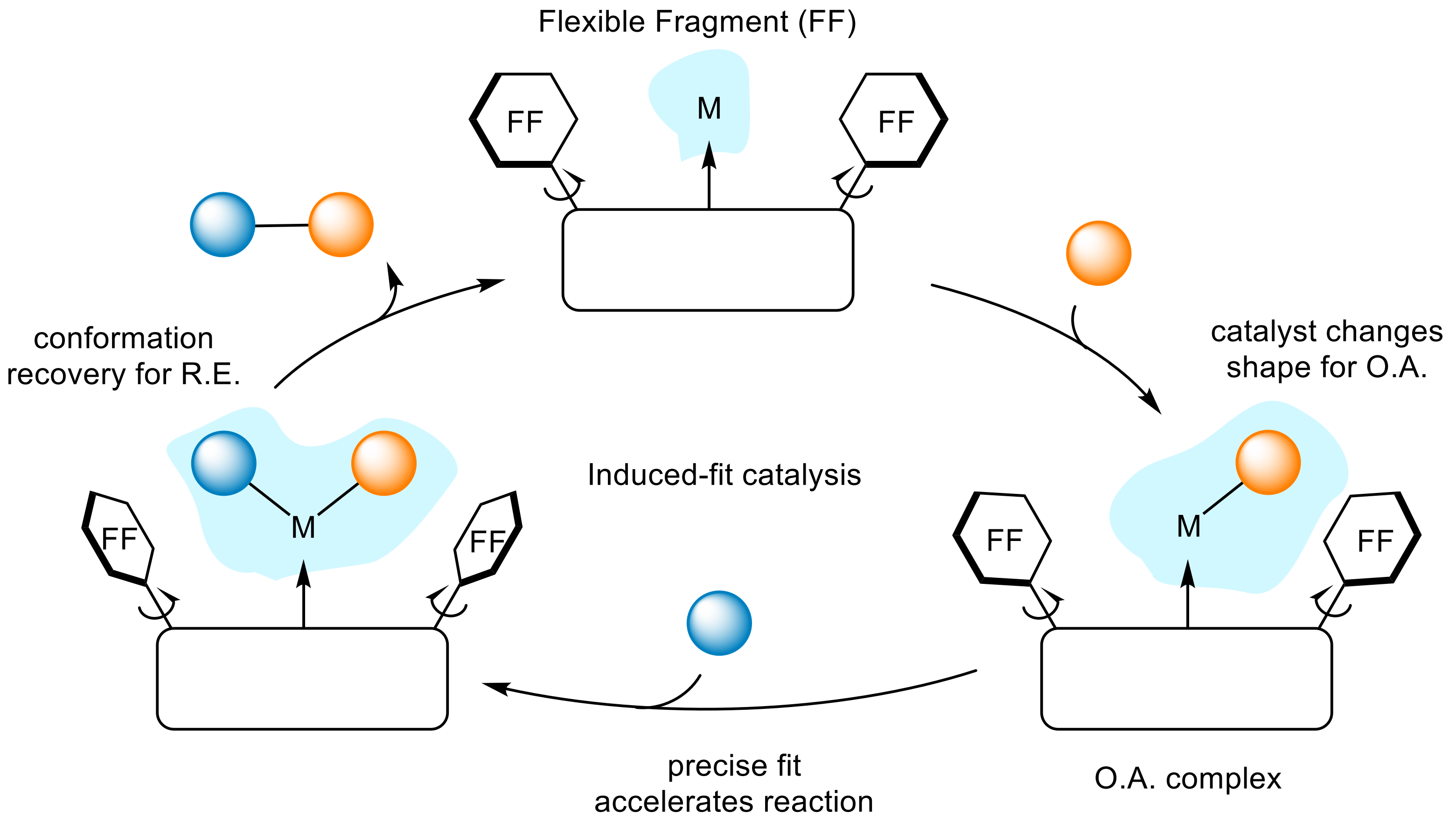


Murakami



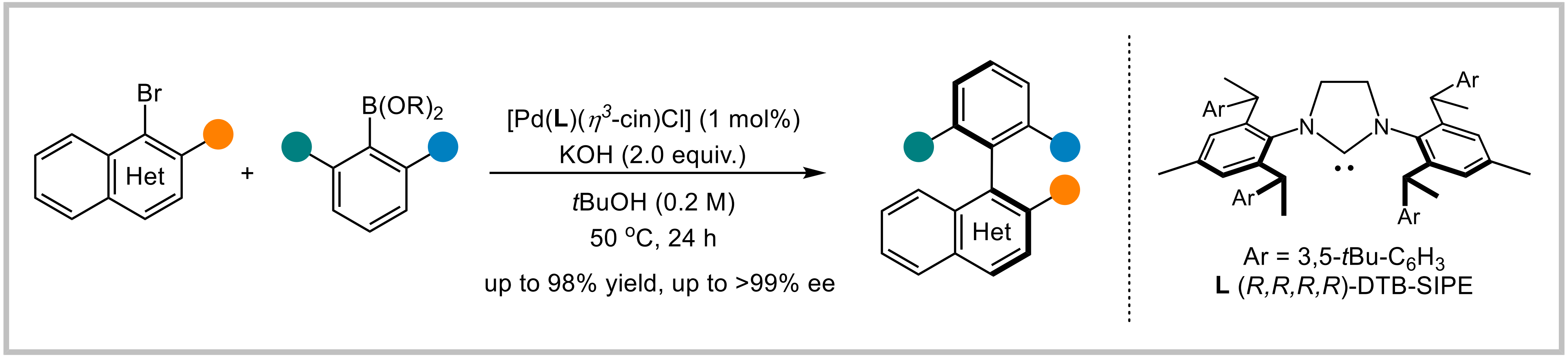
Bicycle

Introduction

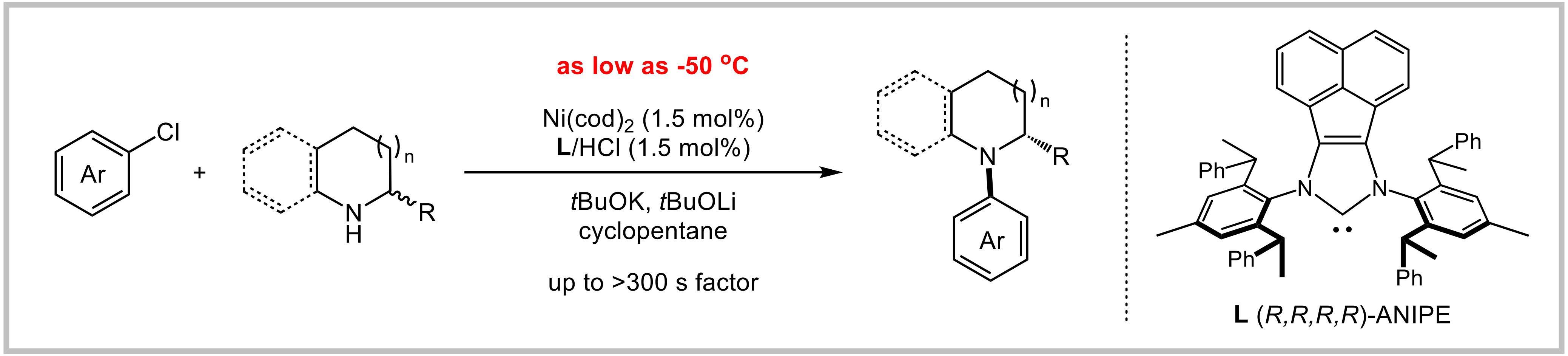


- Cross-Coupling
- Hydrogen-Transfer
- C-H Functionalization
- Nucleophilic Addition
- Functionalization of Alkenes

Cross-Coupling

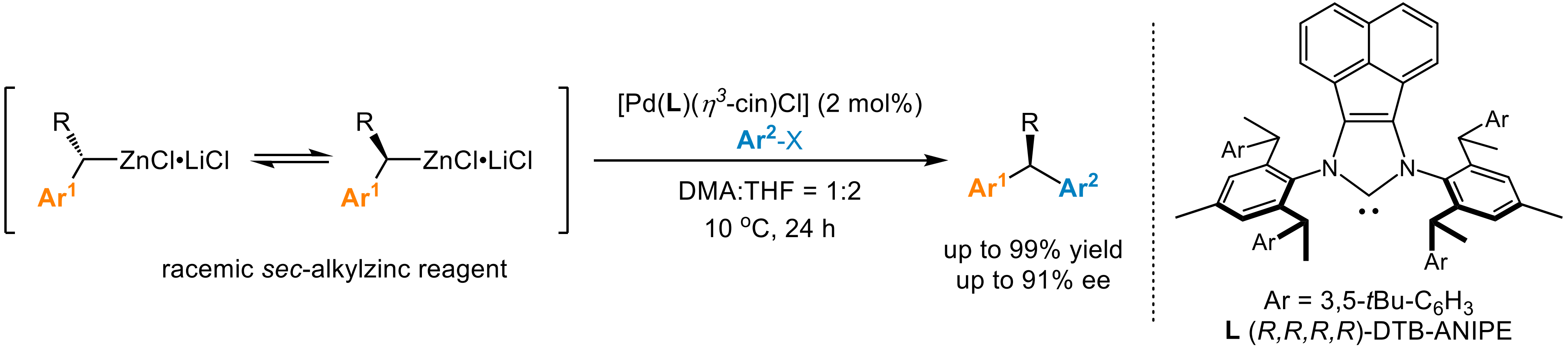


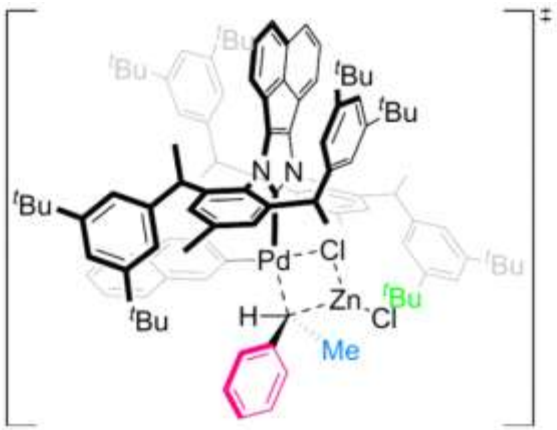
Shen, D.; Xu, Y.; Shi, S.-L. *J. Am. Chem. Soc.* **2019**, *141*, 14938-14945.



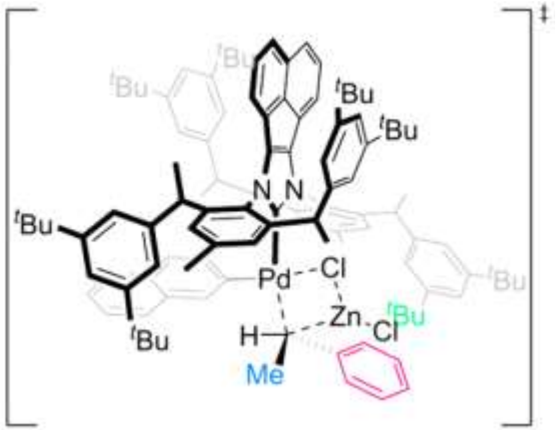
Wang, Z.-C.; Xie, P.-P.; Xu, Y.; Hong, X.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2021**, *60*, 16077-16084.

Cross-Coupling





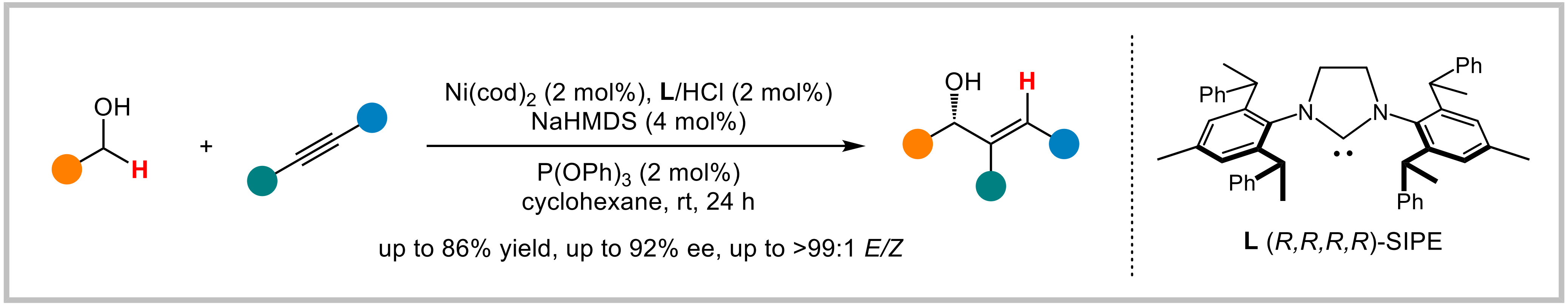
$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol
$\Delta\Delta H^{\ddagger}$ = 0.0 kcal/mol



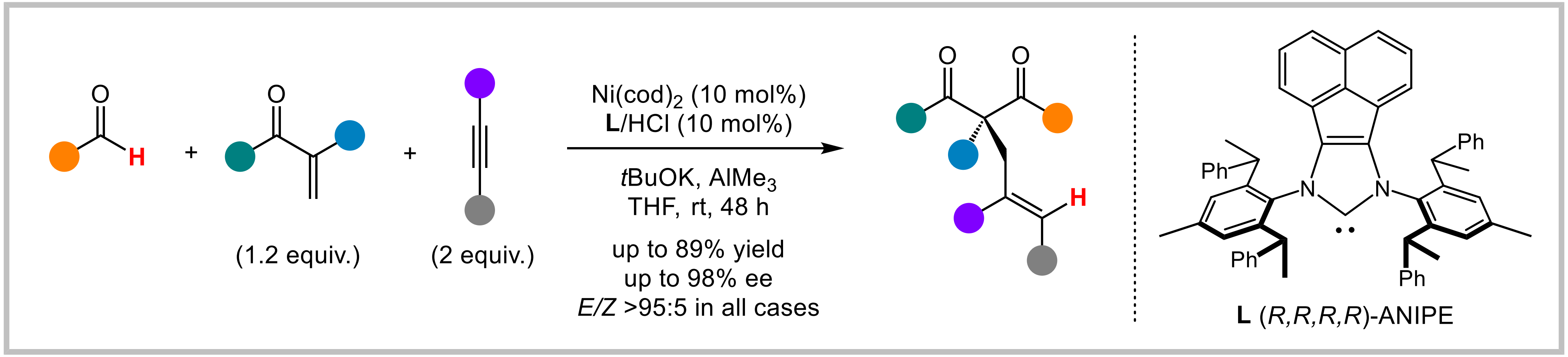
$\Delta\Delta G^{\ddagger}$ = 5.5 kcal/mol
$\Delta\Delta H^{\ddagger}$ = 4.3 kcal/mol

Zhang, J.-W.; Wu, H.; Shen, D.; Wu, R.-K.; Wang, Z.-C.; Hong, X.; Shi, S.-L. *CCS Chem*. **2026**, *8*, 754-763.

Hydrogen Transfer

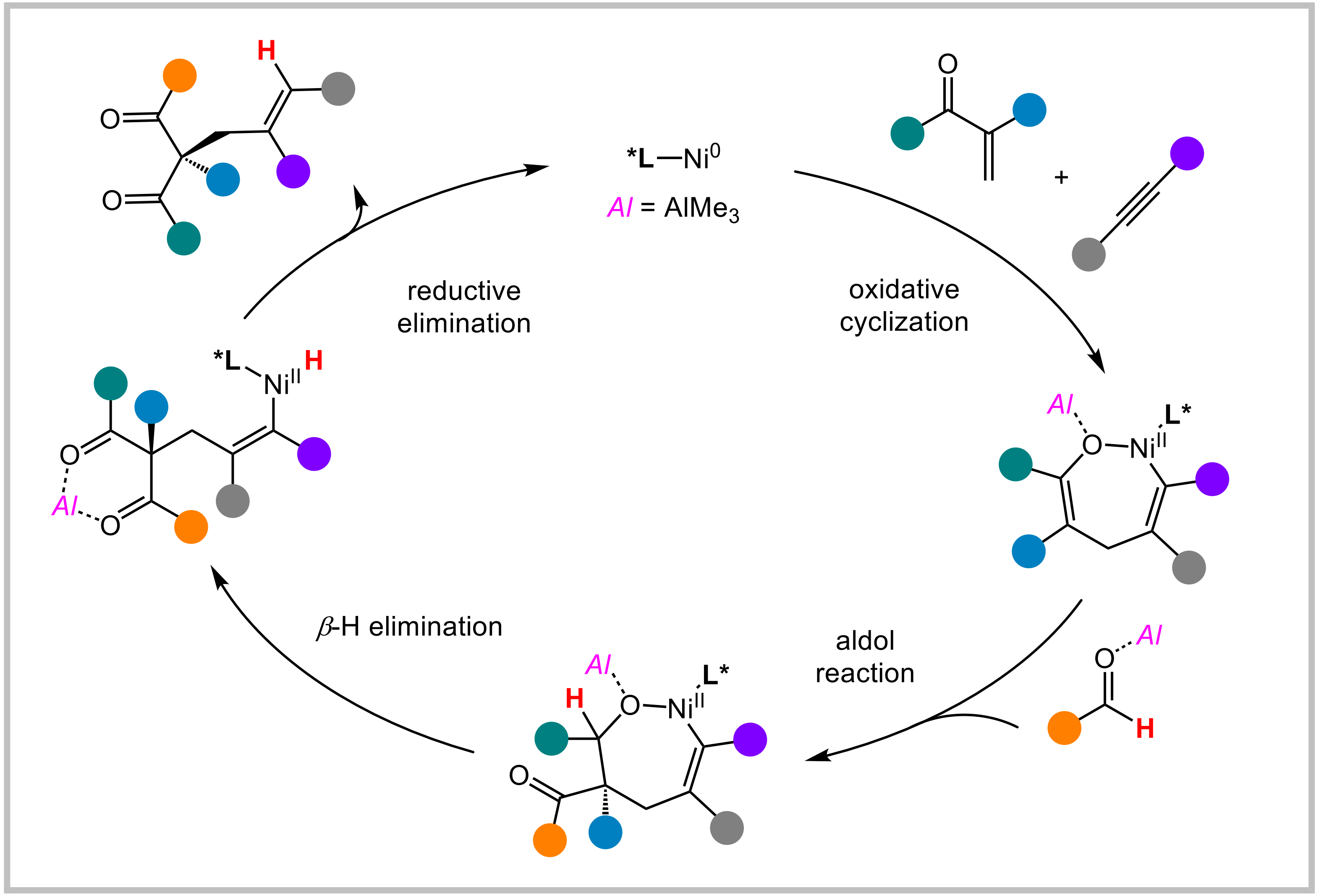


Cai, Y.; Zhang, J, W.; Li, F.; Liu, J.-M.; Shi, S.-L. *ACS Catal.* **2019**, *9*, 1-6.

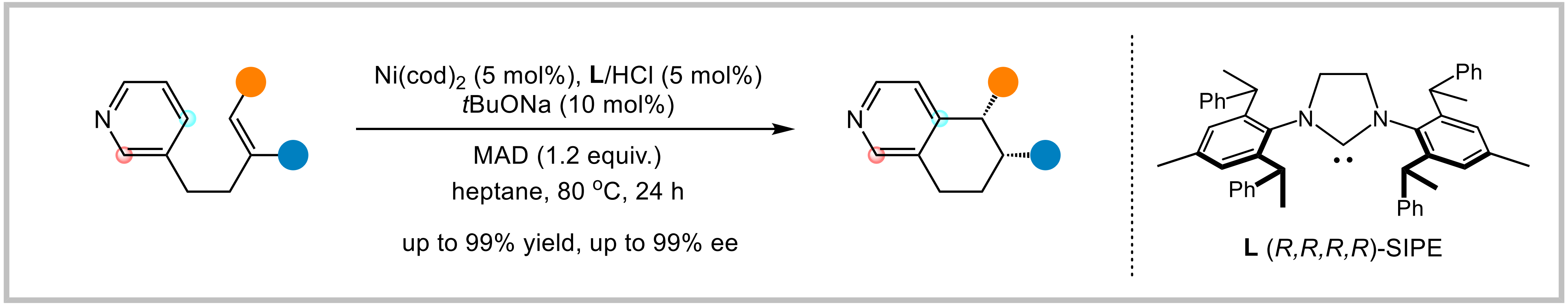


Zhang, W.-B.; Chen, G.; Shi, S.-L. *J. Am. Chem. Soc.* **2022**, *144*, 130-136.

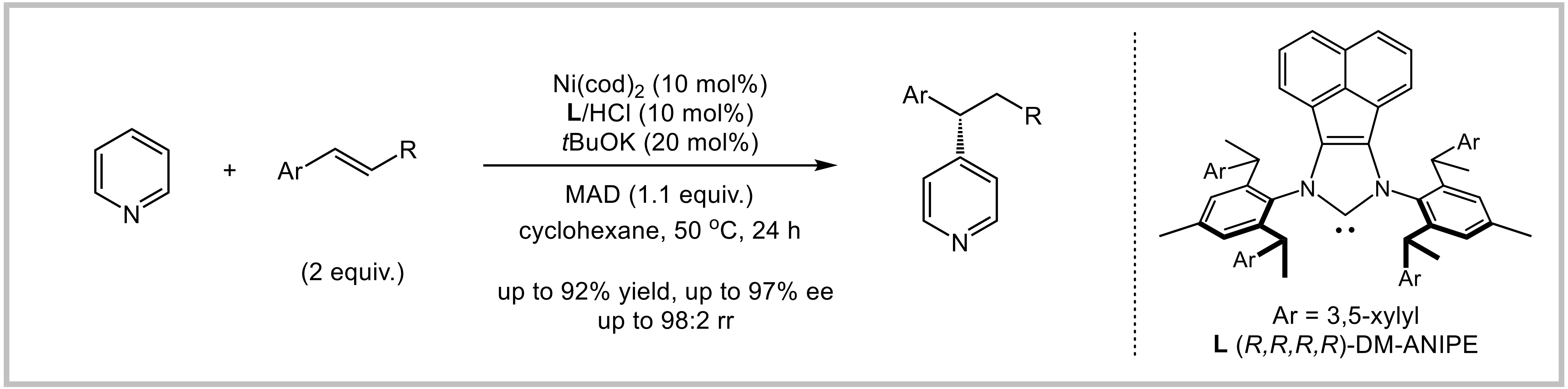
Hydrogen Transfer



C-H Functionalization

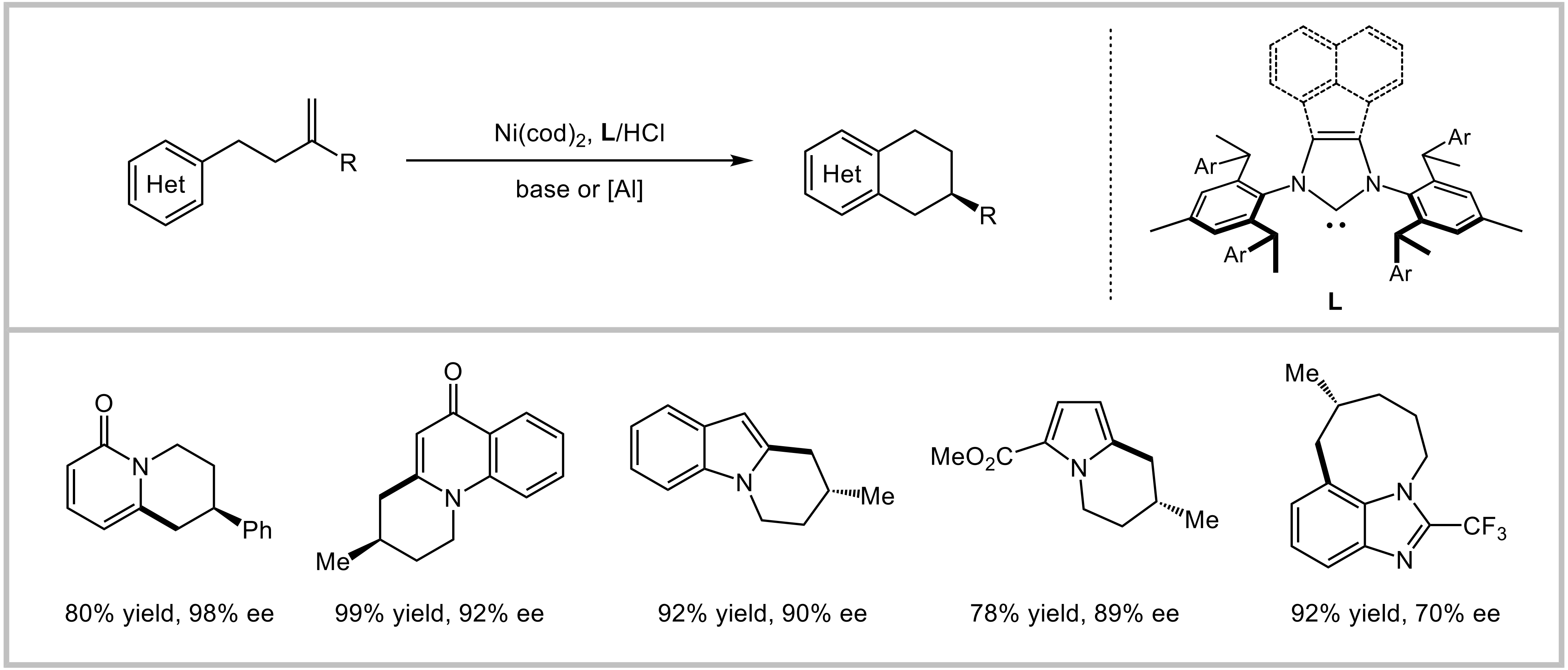


Zhang, W.-B.; Yang, X.-T.; Ma, J.-B.; Su, Z.-M.; Shi, S.-L. *J. Am. Chem. Soc.* **2019**, *141*, 5628-5634.



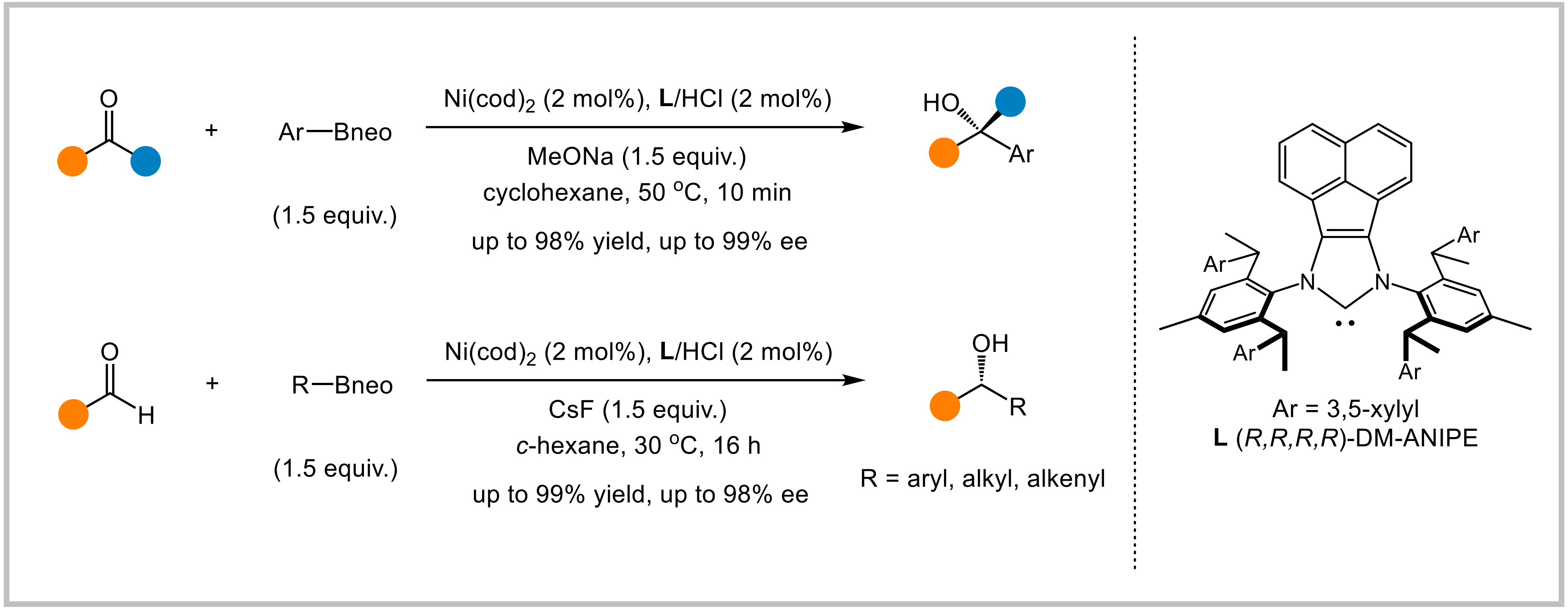
Ma, J.-B.; Zhao, X.; Zhang, D.; Shi, S.-L. *J. Am. Chem. Soc.* **2022**, *144*, 13643-13651.

C-H Functionalization



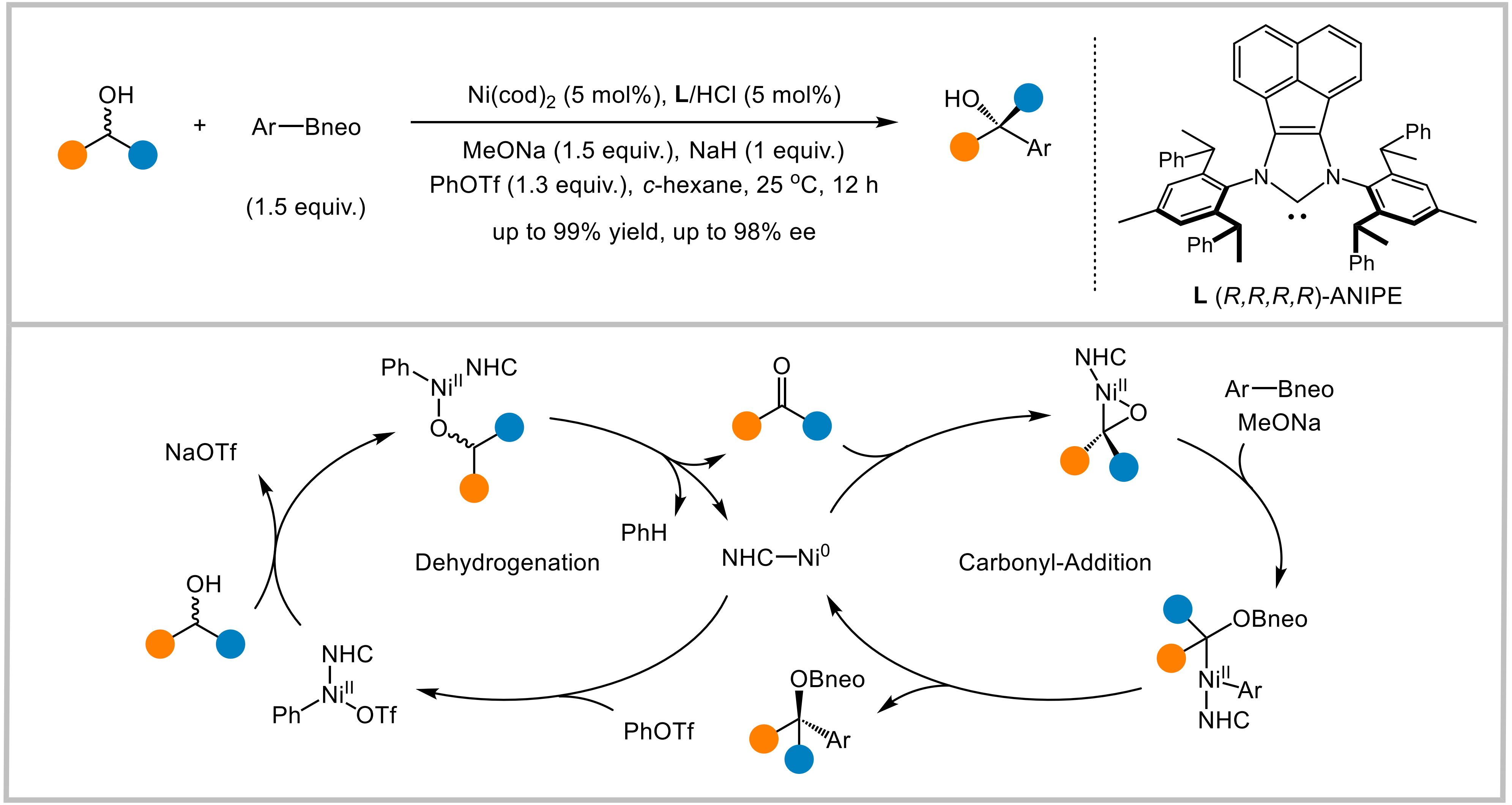
Diesel, J.; Grosheva, D.; Kodama, S.; Cramer, N. A. *Angew. Chem. Int. Ed.* **2019**, *58*, 11044-11048.
Shen, D.; Zhang, W.-B.; Li, Z.; Shi, S.-L.; Xu, Y. *Adv. Synth. Catal.* **2020**, *362*, 1125-1130.
Li, J.-F.; Xu, W.-W.; Wang, R.-H.; Li, Y.; Yin, G.; Ye, M. *Nat. Commun.* **2021**, *12*, 3070.
Zhang, G.; Zhao, C.-Y.; Min, X.-T.; Ji, D.-W.; Hu, Y.-C.; Chen, Q.-A. *Nat. Catal.* **2022**, *5*, 708-715.

Nucleophilic Addition



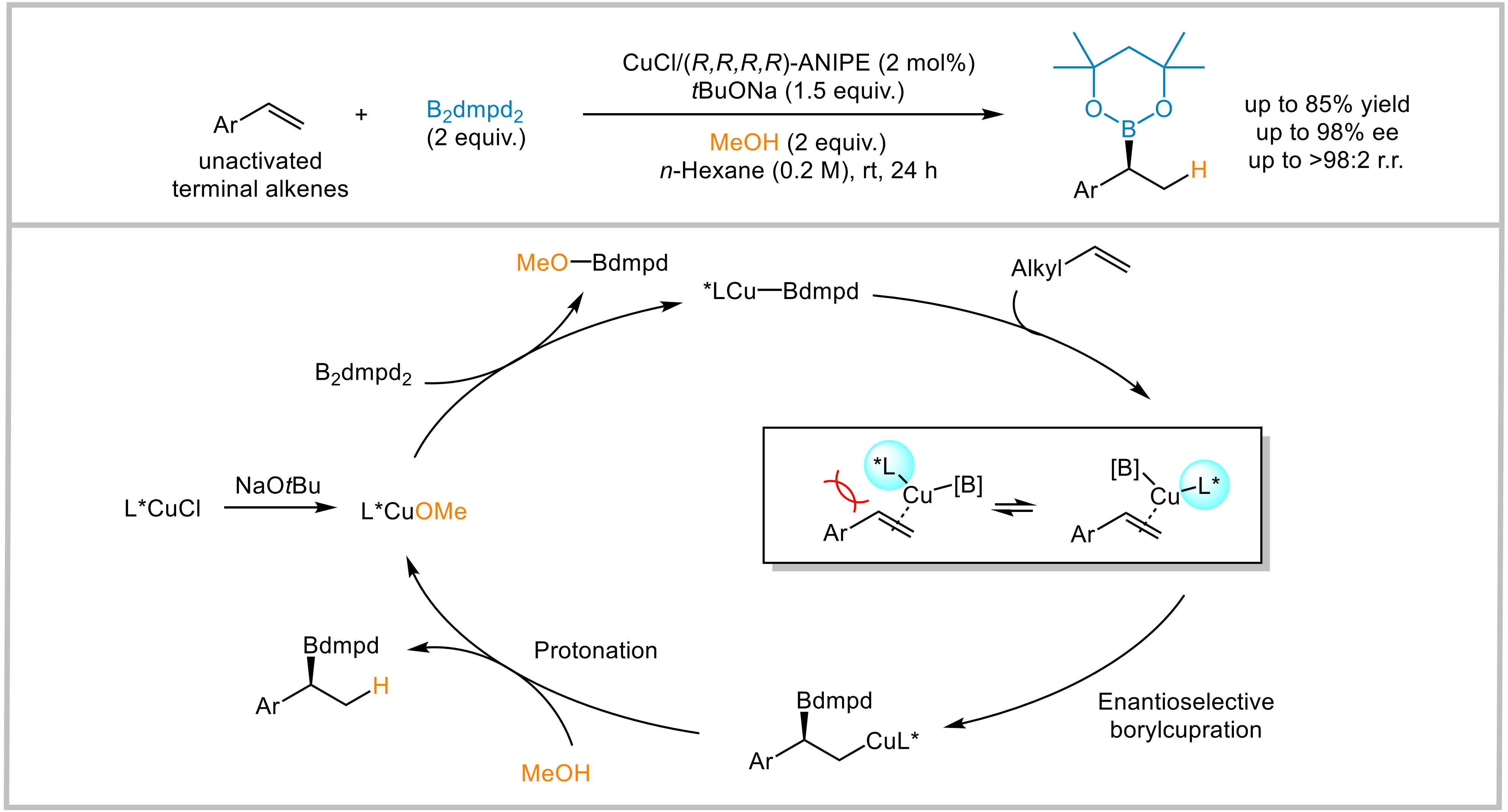
Cai, Y.; Ruan, L.-X.; Rahman, A.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2021**, *60*, 5262-5267.
Wang, Z.-C.; Gao, J.; Cai, Y.; Ye, X.; Shi, S.-L. *CCS Chem.* **2022**, *4*, 1169-1179.
Liu, S.-Y.; Wang, Z.-C.; Shi, S.-L. *Chin. J. Chem.* **2024**, *42*, 2161-2165.

Nucleophilic Addition



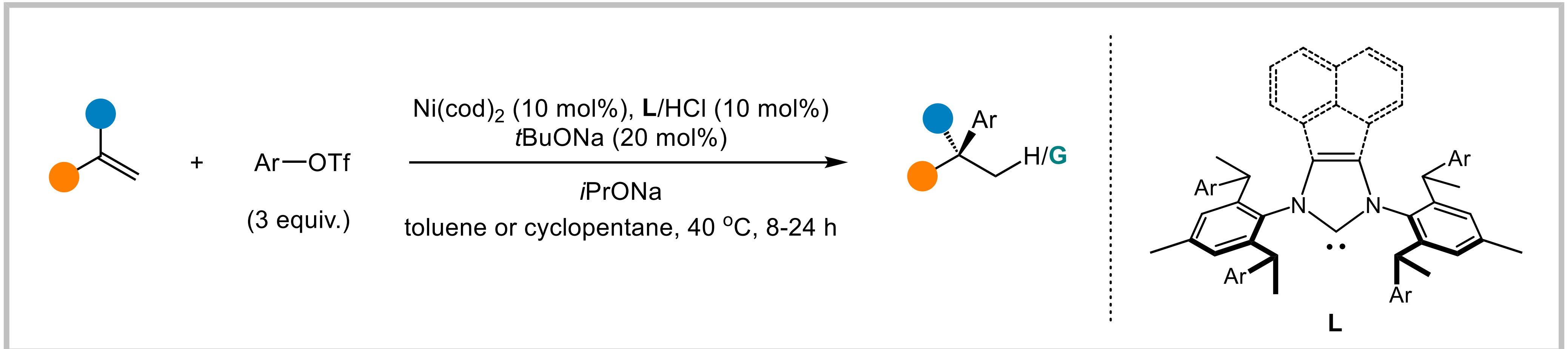
Cai, Y.; Shi, S.-L. *J. Am. Chem. Soc.* **2021**, *143*, 11963-11968.

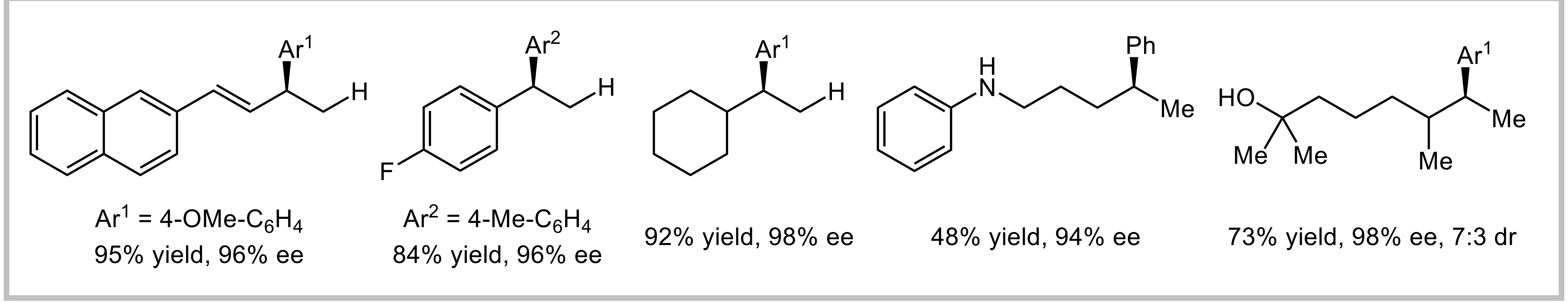
Functionalization of Alkenes



Cai, Y.; Yang, X.-T.; Zhang, S.-Q.; Li, F.; Li, Y.-Q.; Hong, X.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2018**, *57*, 1376-1380.

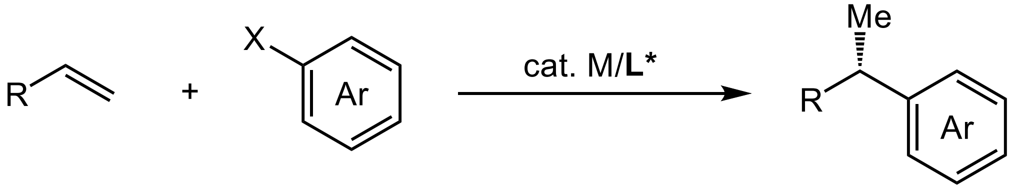
Functionalization of Alkenes





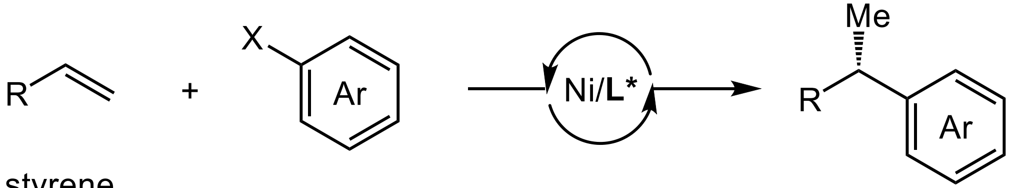
Liu, C.-F.; Wang, Z.-C.; Luo, X.; Lu, J.; Ko, C. H. M.; Shi, S.-L.; Koh, M. J. *Nat. Catal.* **2022**, *5*, 934-942.
Wang, Z.-C.; Luo,X.; Zhang, J.-W.; Liu, C.-F.; Koh, M. J.; Shi, S.-L. *Nat. Catal.* **2023**, *6*, 1087-1097.
Wang, Z.-C.; Zhang, J.-W.; Koh, M. J.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2023**, *62*, e202310203.
Wu, H.-Y.; Koh, M. J.; Wang, Z.-C.; Shi, S.-L. *Angew. Chem. Int. Ed.* **2025**, *64*, e202503126.

Prospect



♦Inertness of C-Br and C-Cl bonds
♦Chemo-, regio- and stereocontrol

X	styrene	1,3-diene	α-olefin
OTf	√	√	√
I	√	–	–
Br	√	–	–
Cl	–	–	–



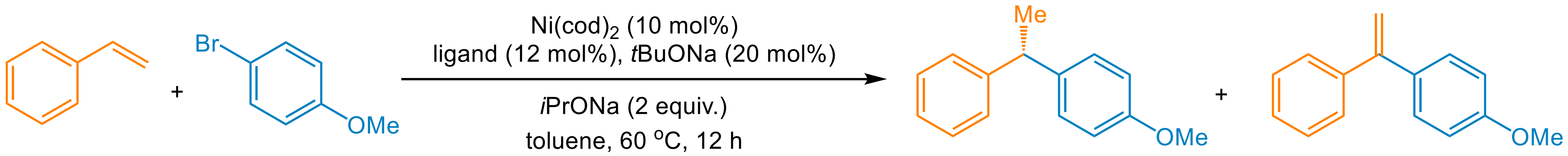
styrene
1,3-diene
α-olefin

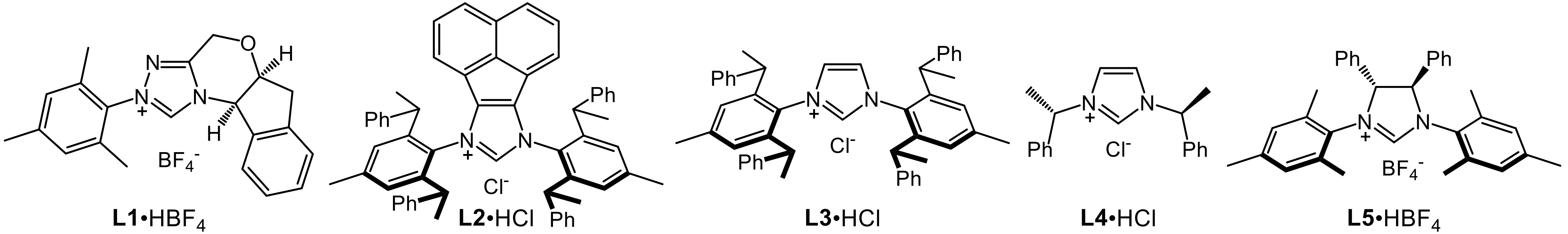
X = Br, Cl

63 examples
up to 94% yield
up to 99% ee

X	styrene	1,3-diene	α-olefin
Br	√	√	√
Cl	√	√	√

Optimization of the Reaction Conditions





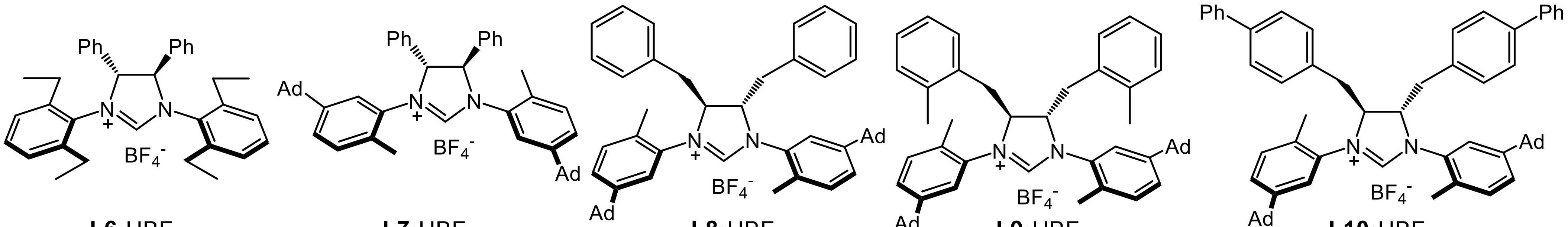
L1•HBF$_4$
16% yield, 60% ee
22% Heck product

L2•HCl
trace
80% Heck product

L3•HCl
16% yield, 0% ee
28% Heck product

L4•HCl
31% yield, 10% ee
22% Heck product

L5•HBF$_4$
21% yield, 40% ee
44% Heck product



L6•HBF$_4$
22% yield, 48% ee
52% Heck product

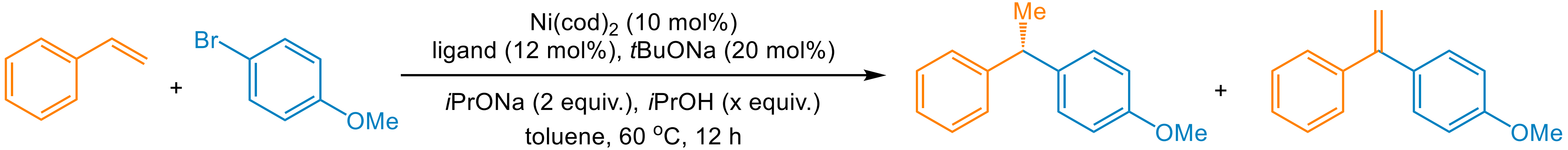
L7•HBF$_4$
43% yield, 92% ee
50% Heck product

L8•HBF$_4$
45% yield, 91% ee
13% Heck product

L9•HBF$_4$
61% yield, 94% ee
36% Heck product

L10•HBF$_4$
70% yield, 97% ee
24% Heck product

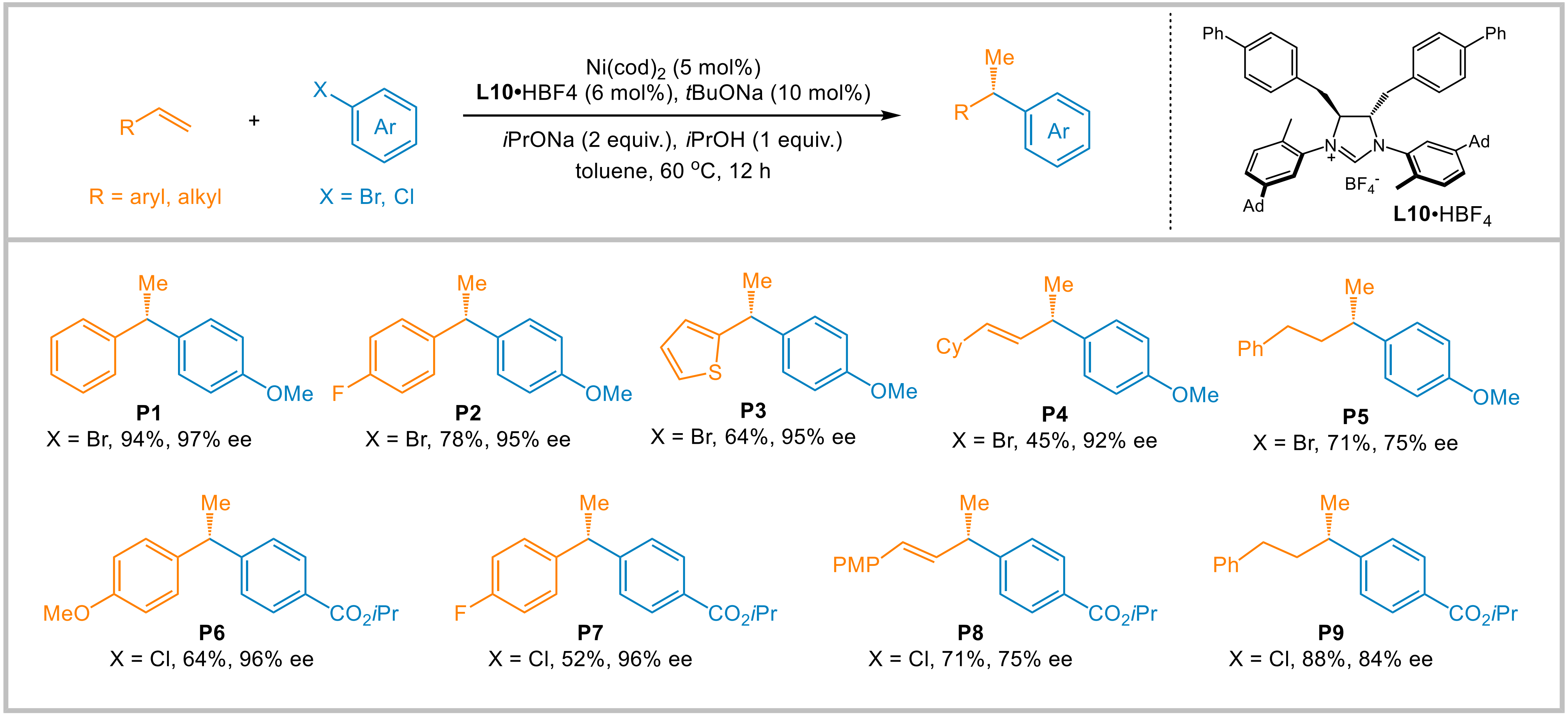
Optimization of the Reaction Conditions



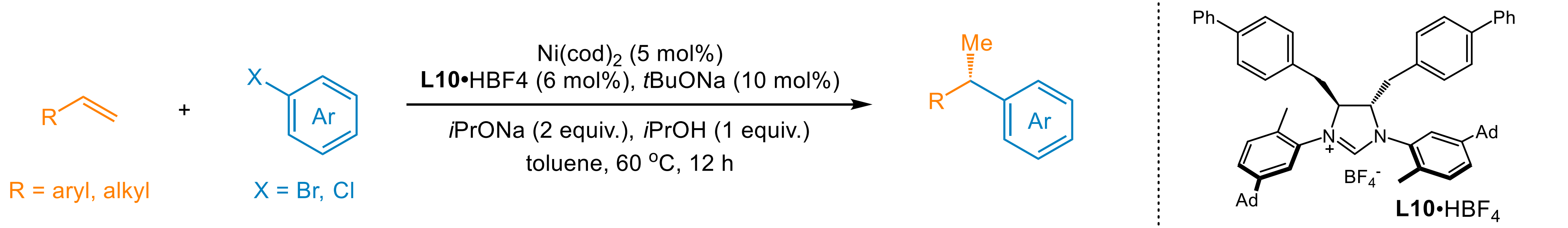
Entry[a]	[Ni]	*i*PrOH (x equiv.)	Yield (%)	Ee (%)	Heck Product (%)
1	10 mol%	0	70	97	24
2	10 mol%	1	92	97	<5
3	10 mol%	2	84	97	<5
4	5 mol%	1	96(94)[b]	97	<5

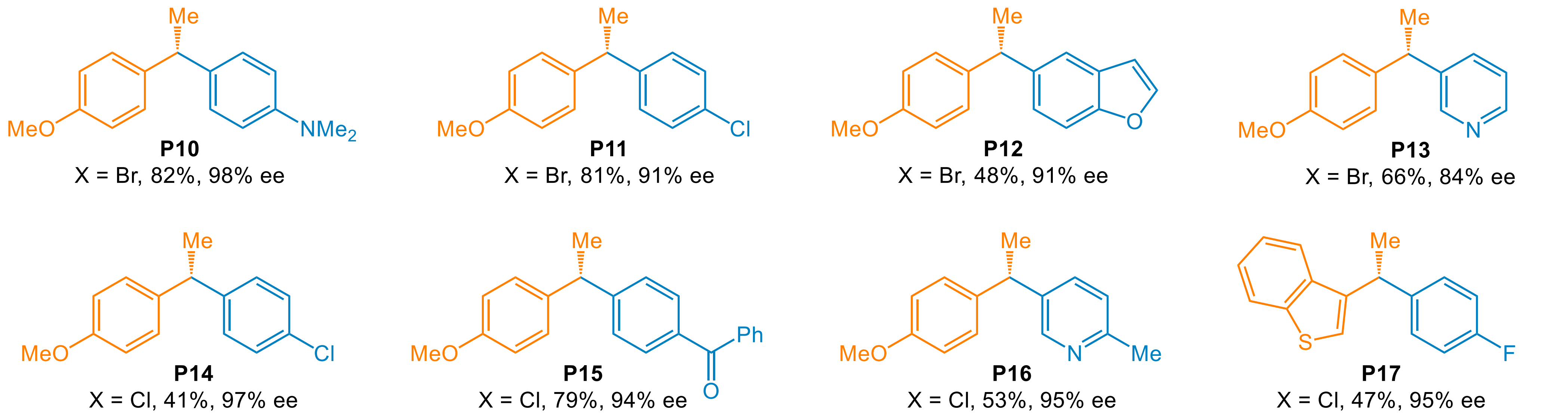
[a] Reaction conditions: $Ni(cod)_2$ (10 mol%), **L10**/HBF_4 (12 mol%), *t*BuONa (20 mol%), *i*PrONa (2.0 equiv), *i*PrOH (x equiv), styrene (0.1 mmol), 1-bromo-4-methoxybenzene (0.2 mmol), toluene (1.0 mL). Yields were determined by ^{1}H NMR analysis using dibromomethane as an internal standard. Enantioselectivity (ee) was determined by chiral HPLC analysis. [b] Isolated yield.

Scope of Olefins



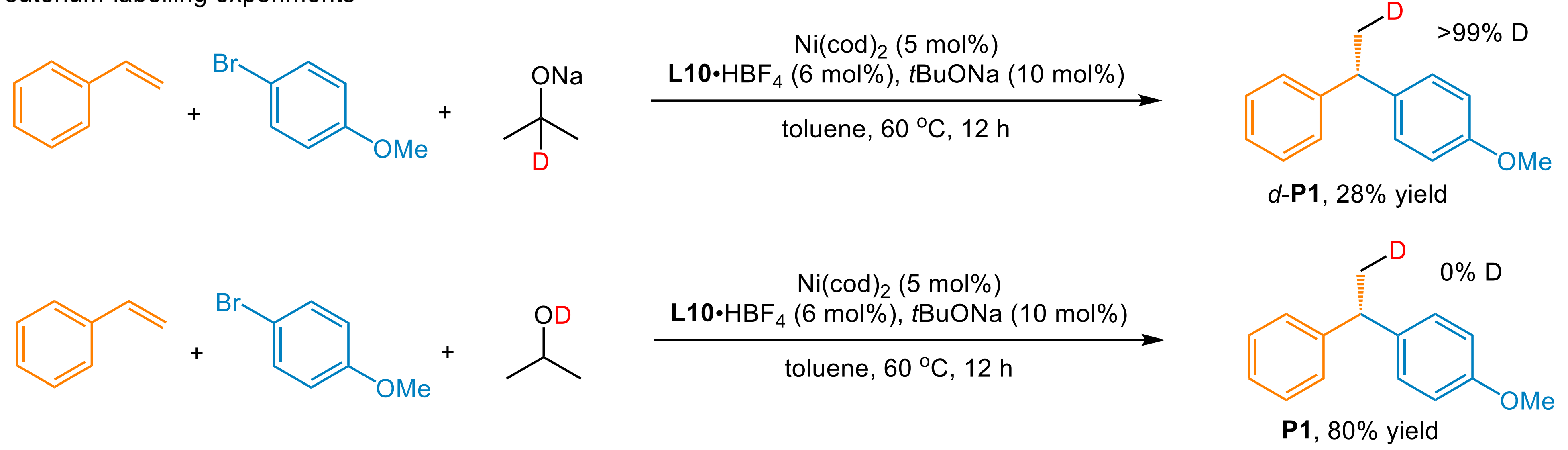
Scope of Aryl Bromides and Chlorides



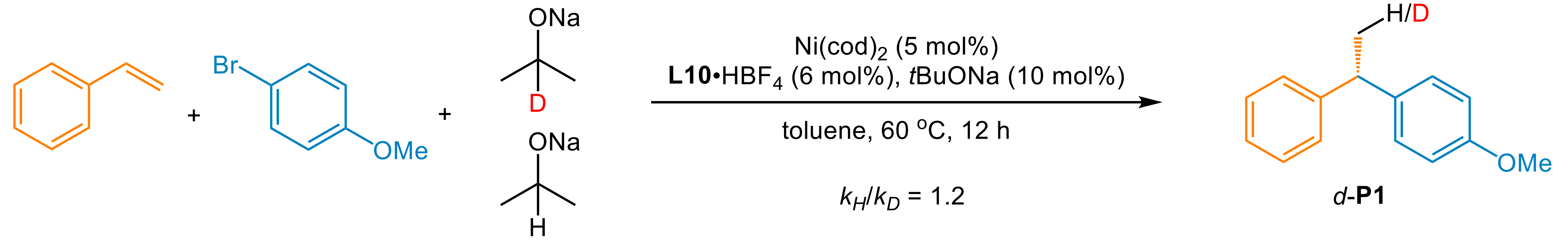


Mechanistic Investigations

Deuterium-labelling experiments

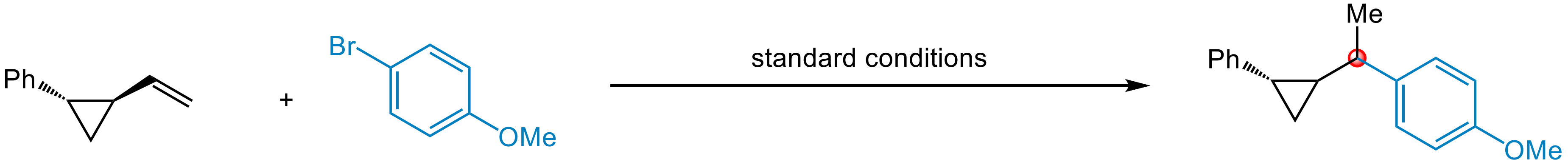


Parallel kinetic isotope effect (KIE) experiment



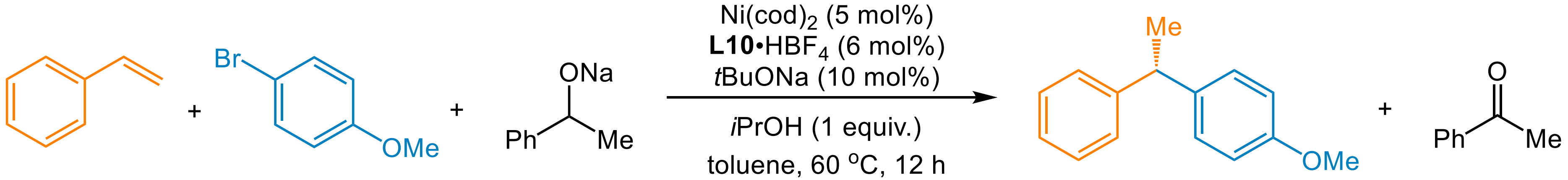
Mechanistic Investigations

Radical clock experiment



P18, 61% yield, 57:43 dr

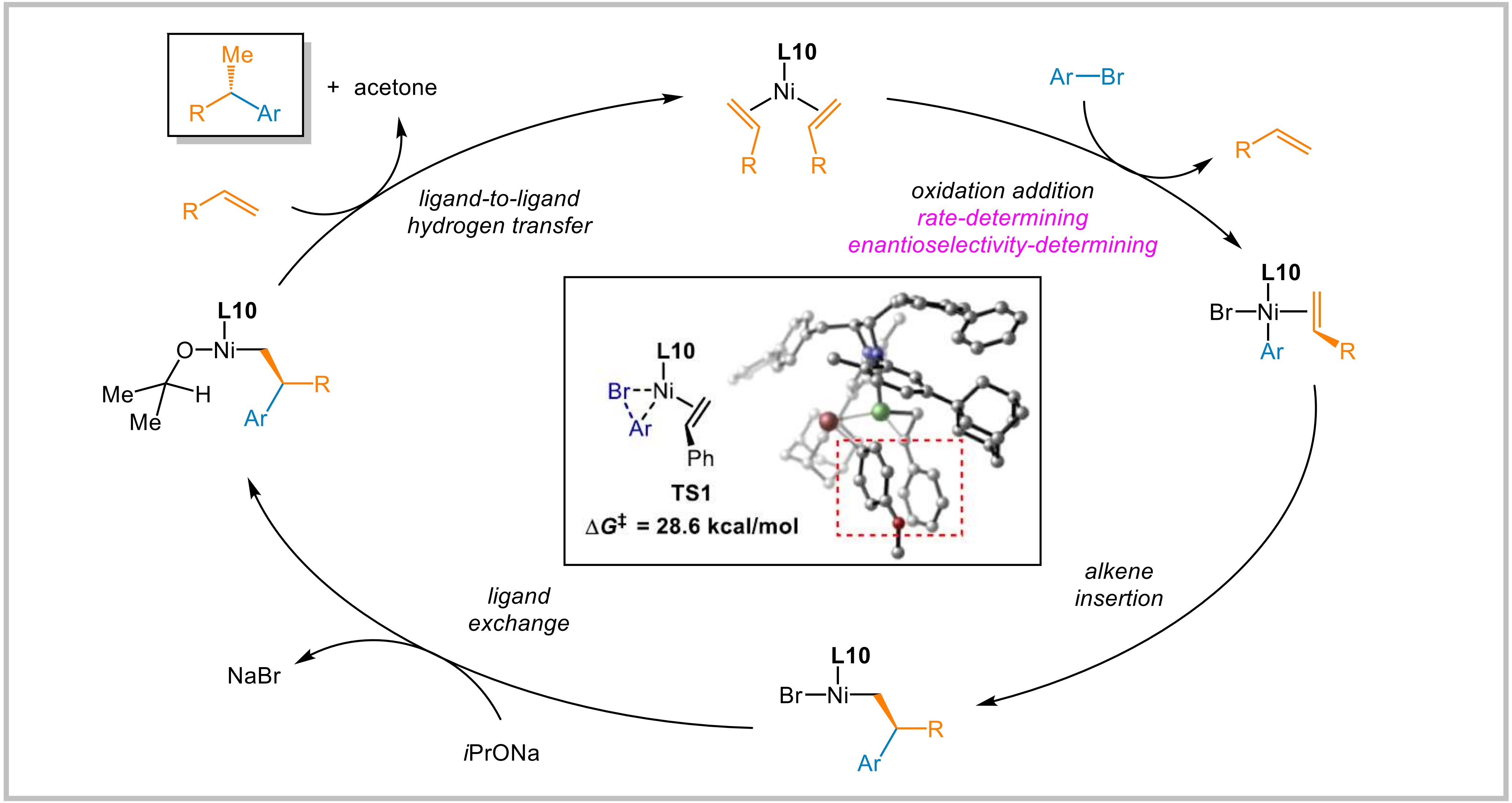
Ketone trapping experiment



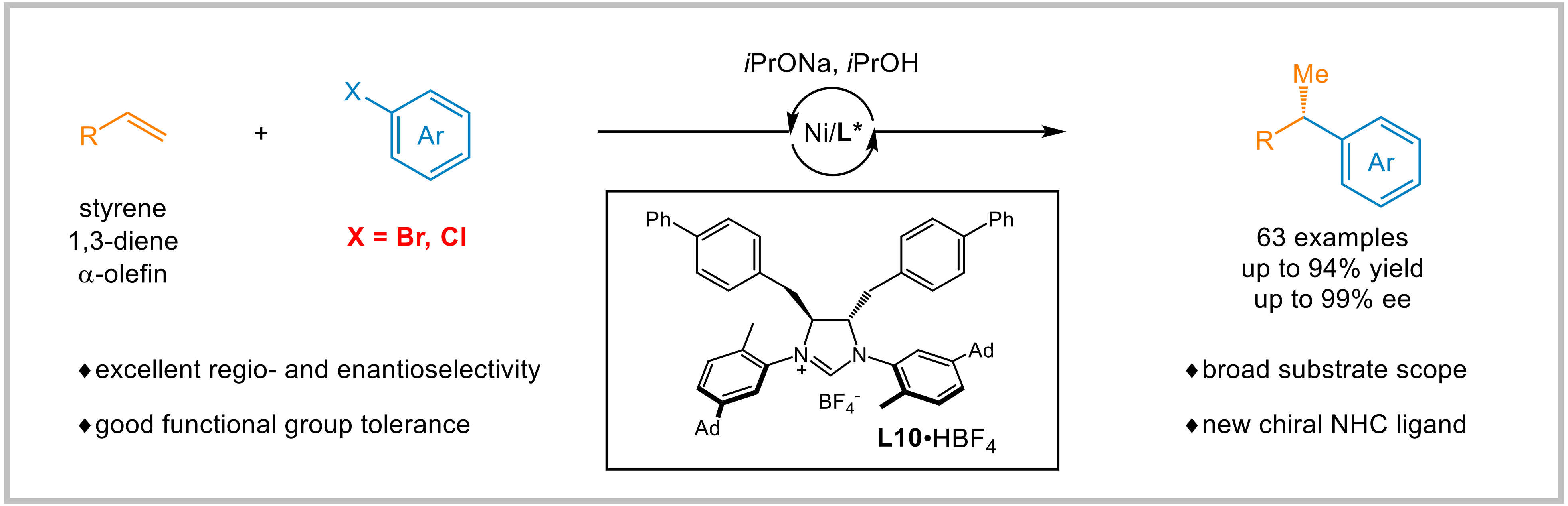
P1 33% yield

25% yield

Proposed Mechanism



Summary



- Ni-catalyzed reductive Heck reaction with bromides and chlorides as coupling partners;
- A novel class of chiral NHC ligands with remote *meta*-substituents was developed;
- OA is the rate- and enantioselectivity-determining step, driven by π-π interactions.

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Writing Strategy

➢The First Paragraph

烯烃氢芳基化的重要性

↓

简述现状提出挑战

↓

还原型 Heck 反应策略

♣ Hydroarylation of alkenes—the formal addition of an aryl group and a hydrogen across a C=C bond—offers a direct and economical route to $C(sp^3)$-$C(sp^3)$ motifs, which are ubiquitous in pharmaceuticals and complex natural products.

♣ The classical Mizoroki-Heck reaction has long been a cornerstone for constructing $C(sp^2)$-$C(sp^2)$ linkages; however, its reductive counterpart, which delivers hydroarylated products by intercepting alkyl-metal intermediates with a hydride, remains comparatively underexploited, despite its powerful retrosynthetic logic.

♣ Reductive Heck reactions, a major type of alkene hydroarylation, enable the construction of alkyl-aryl bonds from simple alkenes rather than preformed alkyl electrophiles or organometallic.

Writing Strategy

➢The Last Paragraph

总结核心成果

↓

强调研究意义和重要性

↓

未来展望

- ♣ In summary, we have developed a highly enantioselective, nickel-catalyzed reductive Heck reaction of a broad range of olefins—including styrenes, 1,3-dienes, and aliphatic alkenes—with both aryl bromides and aryl chlorides as coupling partners, enabled by flexible, electron-rich, chiral NHC ligands.
- ♣ This method streamlines access to valuable chiral benzylmethyl frameworks from abundant feedstocks, thereby expanding the scope of enantioselective cross-coupling of olefins and high-lighting the versatility of tailored saturated NHC ligand design for carbon–halide bond activation and enantioselectivity control.
- ♣ The flexibility and electronrich nature of these ligands suggest broad applicability and offer new solutions to longstanding challenges in the field.

Representative Examples

- Experimental studies and DFT calculations **elucidated** the origins of stereo induction and structure-reactivity relationships. (v. 阐明)

- Hydroarylation of alkenes-the formal addition of an aryl group and a hydrogen across a C=C bond-offers a direct and economical route to C(sp^3)-C(sp^3) motifs, which are **ubiquitous** in pharmaceuticals and complex natural products. (adj. 普遍存在的)

- Here, differences in the electronic nature of the aryl olefin substituents generally exerted **negligible** effects on both yield and enantioselectivity. (adj. 可忽略不计的)