Literature Report III

Ni-Catalyzed Regiodivergent and Stereoselective Hydroalkylation of Acyclic Branched Dienes with Unstabilized C(sp^3) Nucleophiles

Reporter: Zi-Qi Hu
Checker: Mu-Wang Chen
Date: 2020-11-23

Mazet, C. *et al*. *J*. *Am*. *Chem*. *Soc*. **2020**, *142*, 16486.

CV of Prof. Clement Mazet

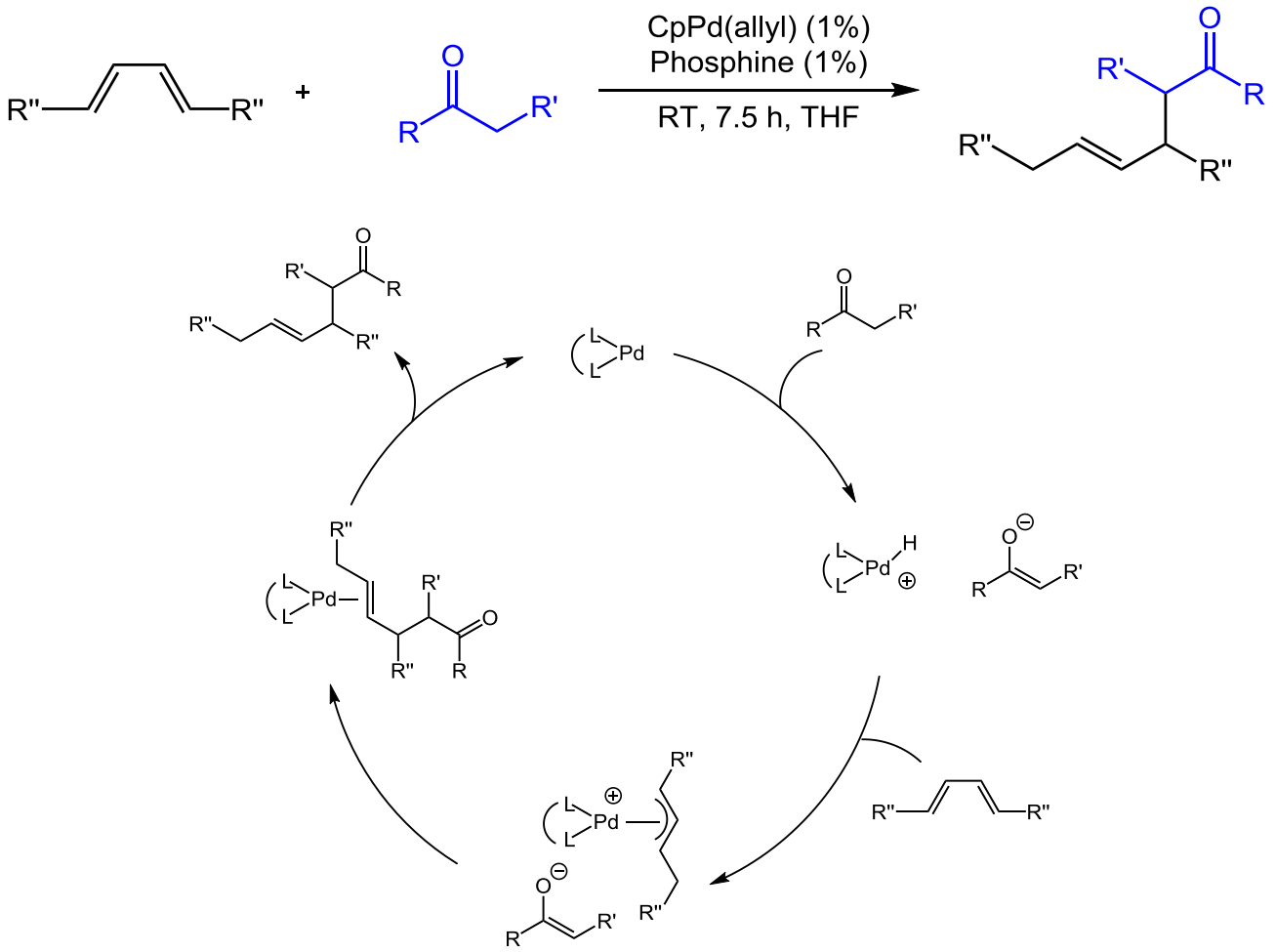
Education:

- **1998-1999** B.S., University of Strasbourg
- **1999-2002** B.A., University of Strasbourg
- **2003-2005** Postdoctoral fellow, University of Basel
- **2006-2007** Postdoctoral fellow, Harvard University
- **2007-2011** Lecturer, University of Geneva
- **2011-2014** Swiss National Foundation Assistant Professor, University of Geneva
- **2014-present** Associate Professor, University of Geneva

Research:

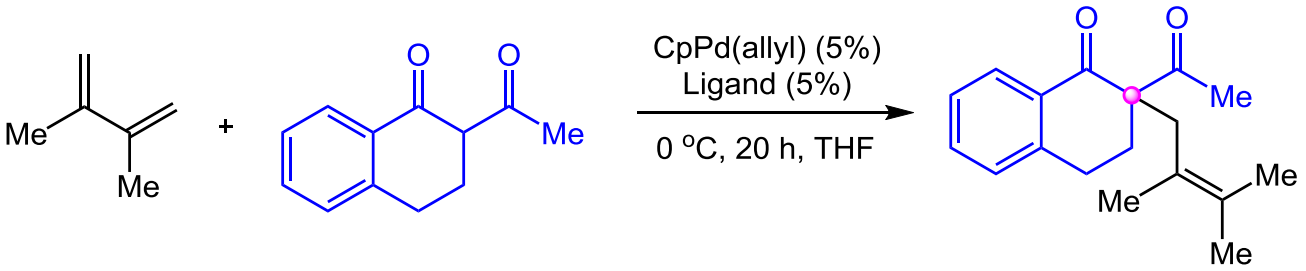
- Isomerizations
- Cross-Couplings
- Ligand and Catalyst Design
- Mechanistic Studies

Introduction

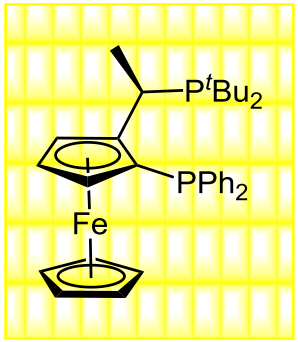


Hartwig, J. F. *et al*. *J. Org. Chem*. **2004**, *69*, 7552.

Introduction

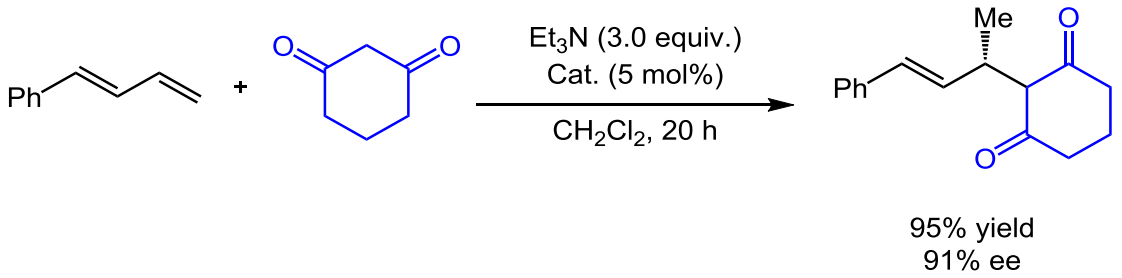


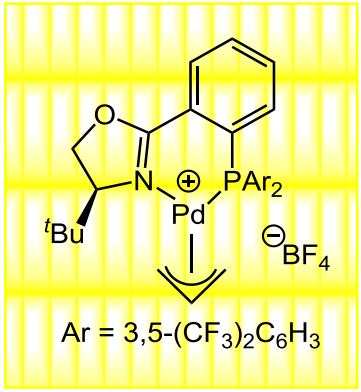
1 example
97% yield
57% ee



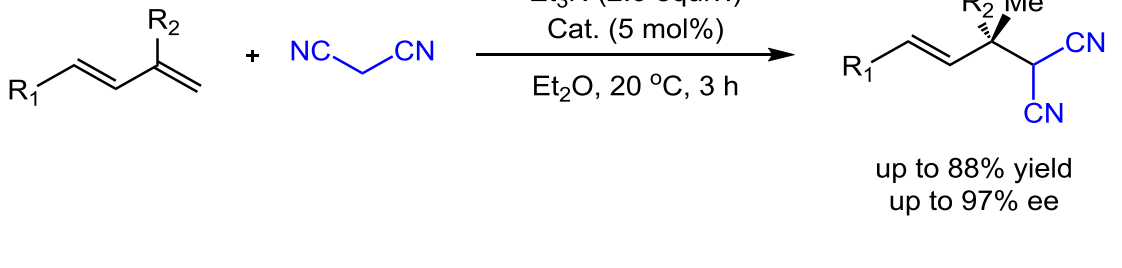
Hartwig, J. F. *et al*. *J. Org. Chem*. **2004**, *69*, 7552.

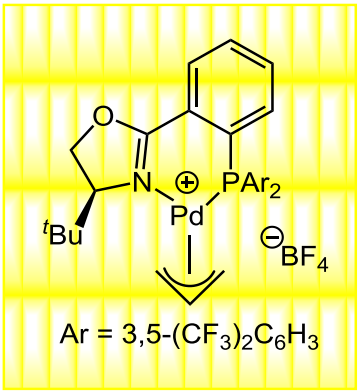
Introduction





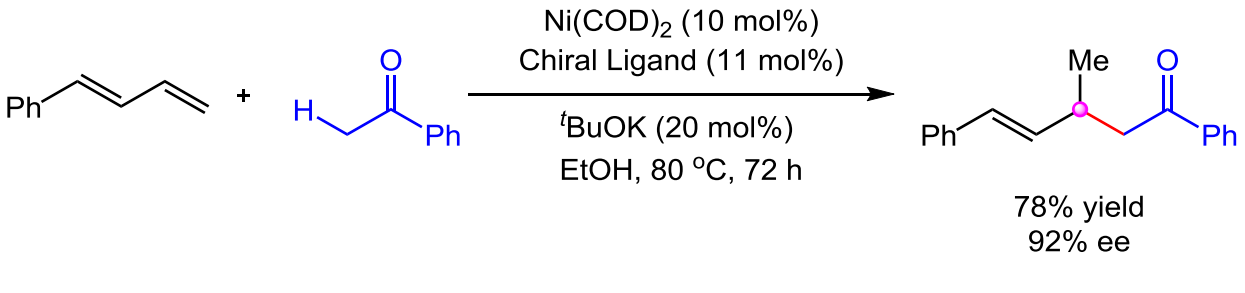
Malcolmson, S. J. *et al*. *J. Am. Chem*. *Soc*. **2018**, *140*, 2761.

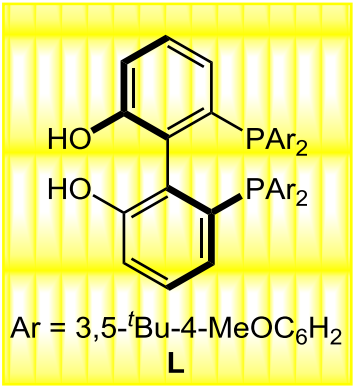


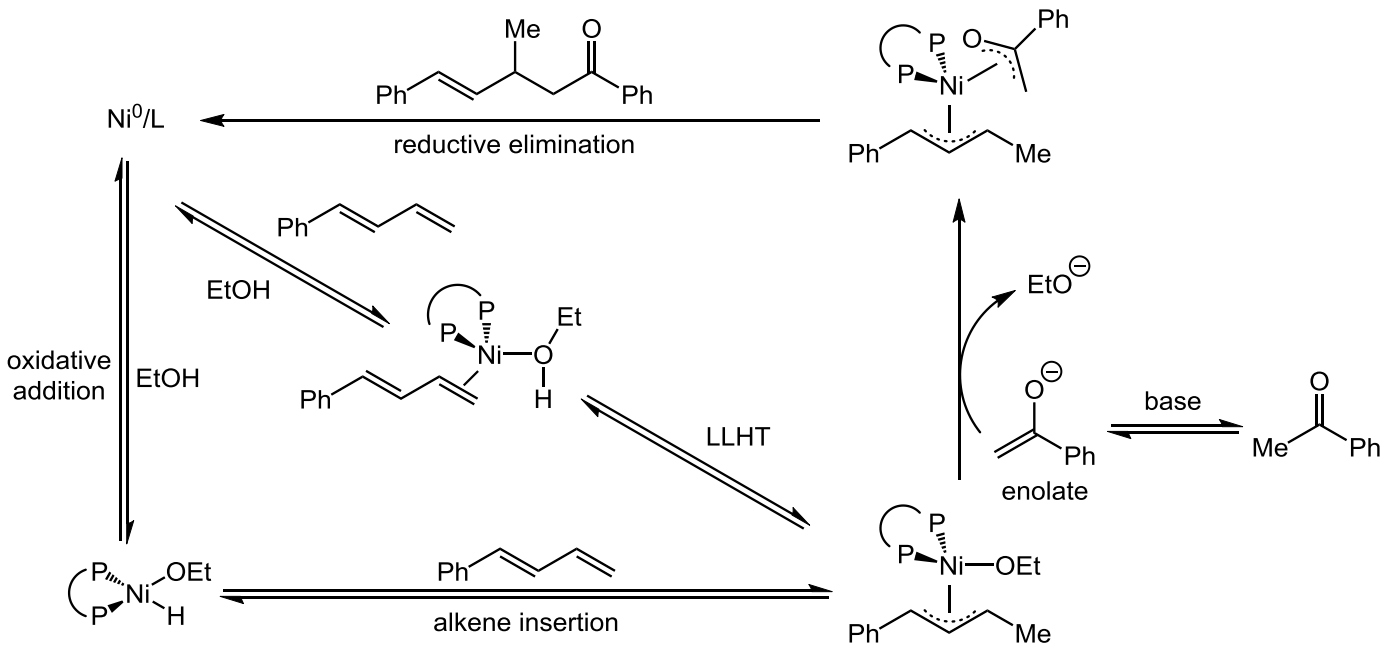


Malcolmson, S. J. *et al*. *Org*. *Lett*. **2020**, *22*, 2032.

Introduction

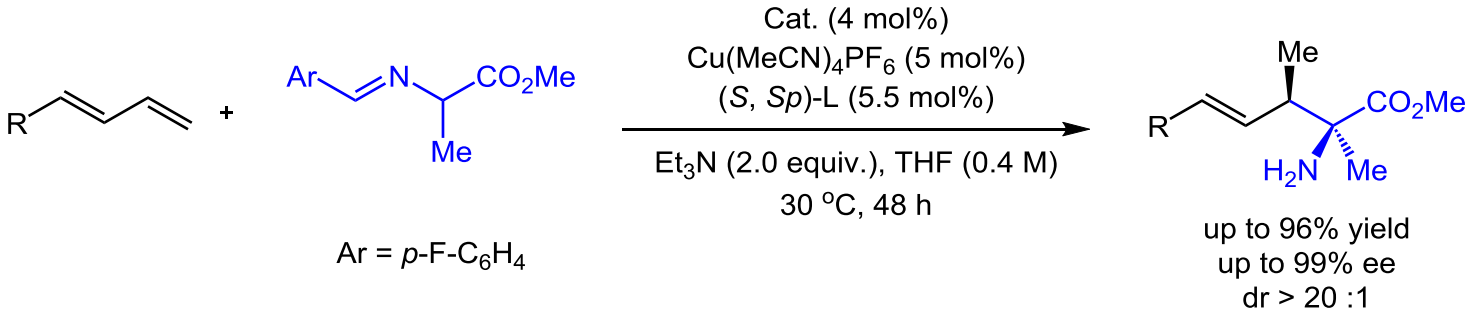


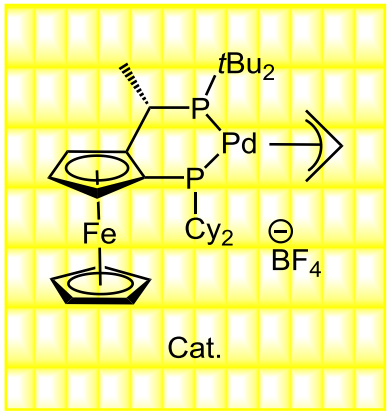


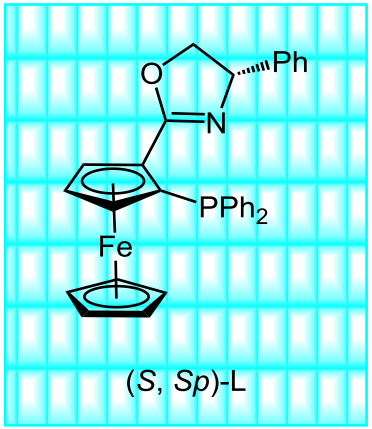


Zhou, Q.-L. *et al*. *J. Am. Chem*. *Soc*. **2018**, *140*, 11627.

Introduction

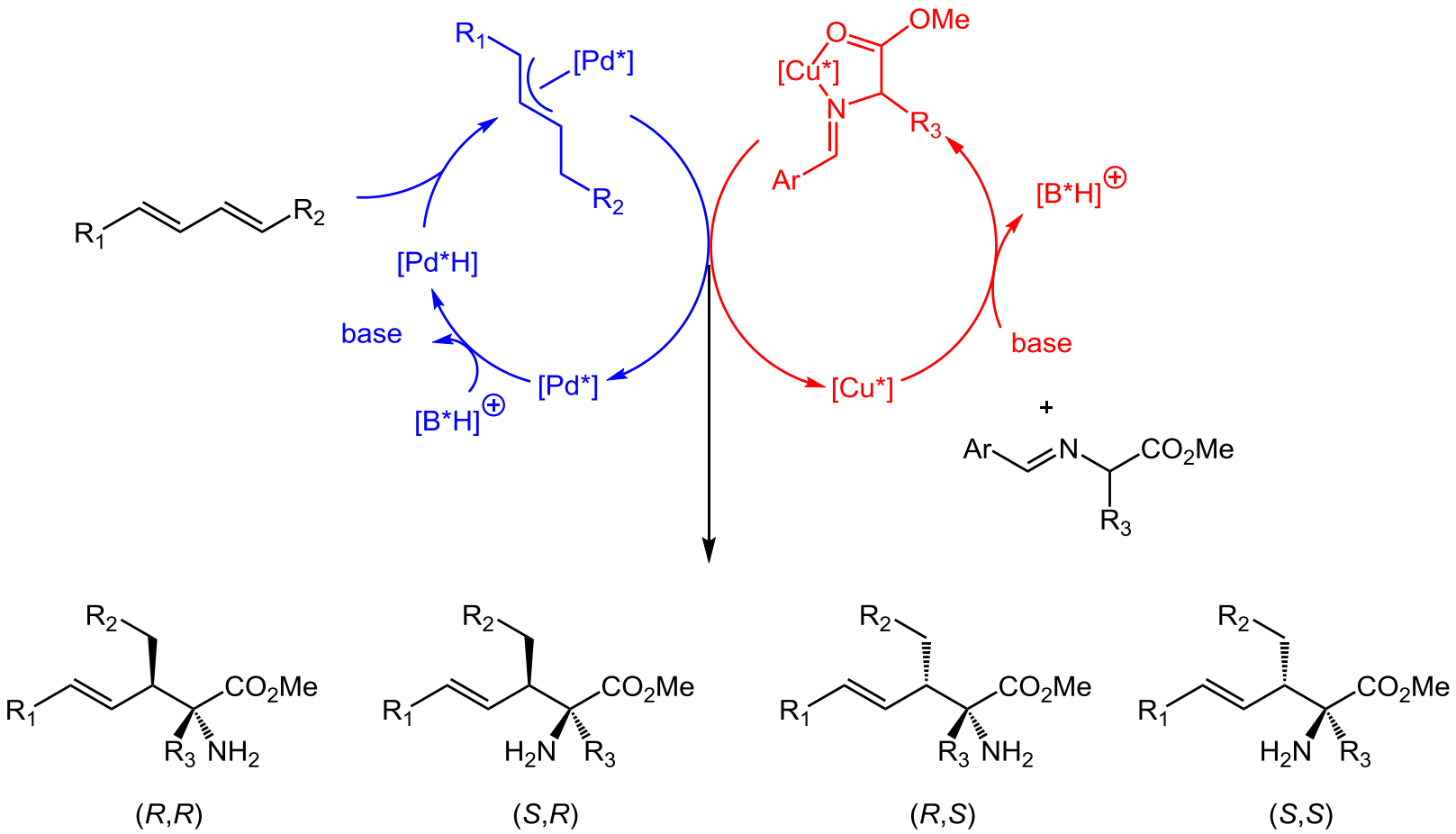






Zi, W. *et al*. *J. Am. Chem. Soc*. **2019**, *141*, 14554.

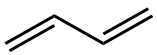
Proposed Mechanism



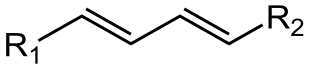
Zi, W. *et al*. *J. Am. Chem*. *Soc*. **2019**, *141*, 14554.

Summary

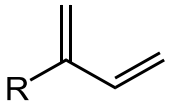
Dienes



terminal diene

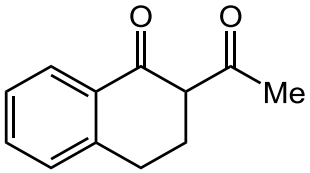


internal diene

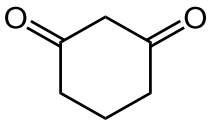


branched diene

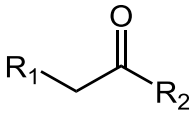
Nu



stabilized Nu



stabilized Nu

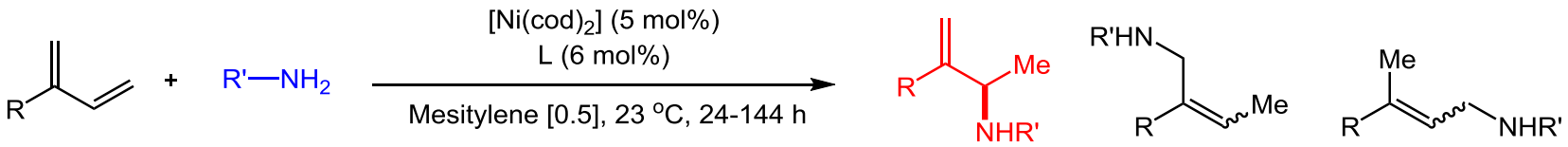


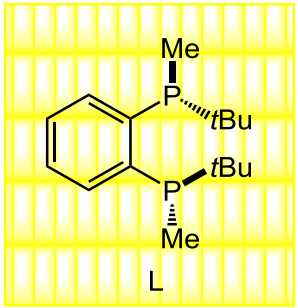
unstabilized Nu

Systems

Pd/L
Ni/L
Pd,Cu/L

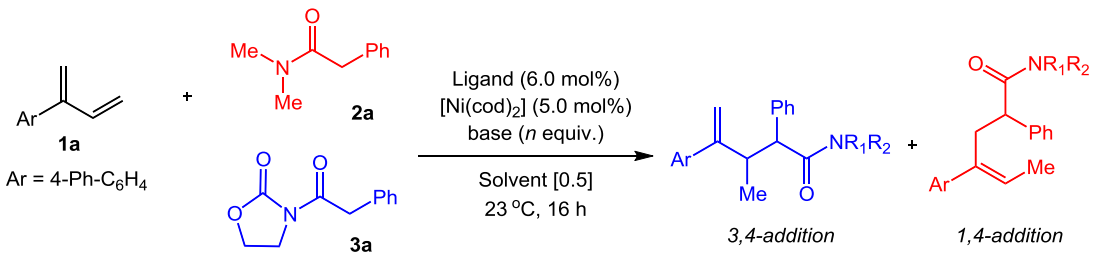
Previous work





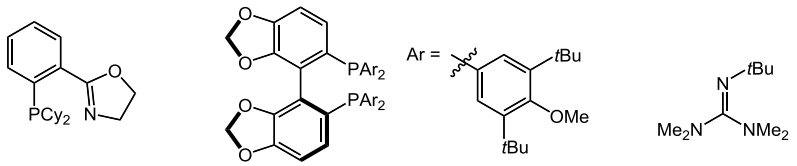
Mazet, C. *et al*. *J*. *Am*. *Chem*. *Soc*. **2019**, *141*, 14814.

Optimization of Reaction Conditions

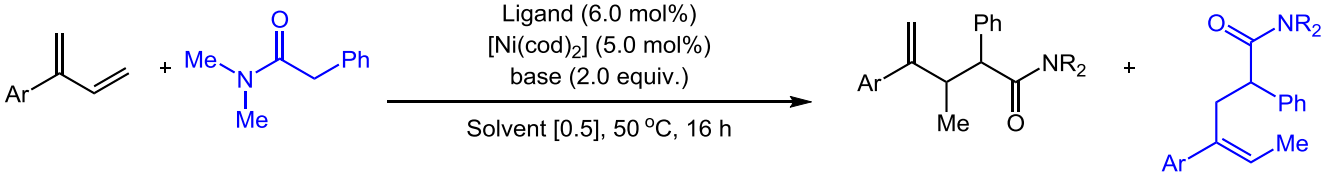


Entry	Nu	L	base (n equiv)	solvent	Conv. (%)[b]	3,4-/1,4-addition[b]
1	**2a**	**L1**	none[c]	mesitylene	<5	-
2[d]	**2a**	**L2**	^{t}BuOK (0.2)	EtOH[e]	<5	-
3[f]	**2a**	**L1**	^{t}BuOK (2.0)	THF	>95	1:19 (*E*/*Z* 2.5:1)
4[f]	**2a**	**L1**	MeOK (0.2)	THF	>95	1:>25 (*E*/*Z* 9:1)
5[g]	**2a**[h]	**L1**	MeOK (0.2)	THF	>95	1:>25 (*E*/*Z* 15:1)
6	**3a**	**L1**	MeOK (0.2)	THF	>95	6.2:1 (*dr* 2.7:1)
7	**3a**	**L1**	BTMG (1.0)	THF	>95	6.5:1 (*dr* 2.8:1)
8	**2a**	**L1**	BTMG (1.0)	THF	<5	-

[a] Reaction condition: **1a** (0.1 mmol), **2a** or **3a** (0.2mmol). [b] Determined by ^{1}H NMR using an internal standard. [c] 1.0 equiv of trifluoroethanol. [d] 100 °C. [e] 0.2 M. [f] 50 °C. [g] 48 h. [h] 1.2 equiv.



Optimization of Reaction Conditions

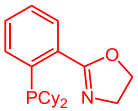


1a
Ar = 4-Ph-C_6H_4

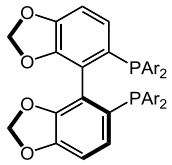
2a
(1.2 equiv.)

4aa
3,4-addition

5
1,4-addition

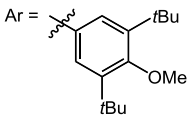


L1
Cy-Phox



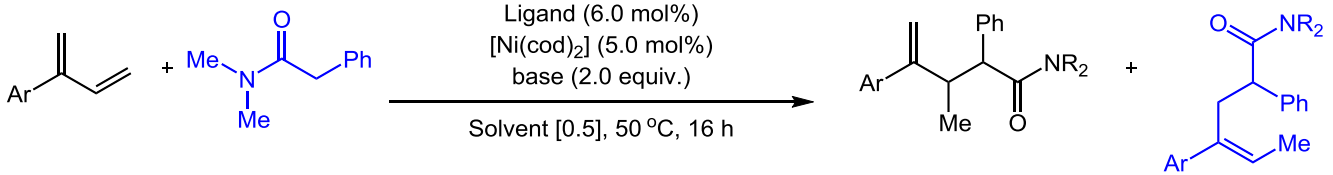
(*S*)-**L2**
DTBM-SegPhos

Entry	Ligand	base	solvent	**1a** Conv. (%)	**4aa** (%)	**5aa** (%)	*E*/*Z* (**5aa**)
1	**L1**	None [b]	mesitylene	>99	5	95	2.5:1
2[c]	**L2**	KO^{t}Bu	EtOH	>99	5	95	2.5:1
3	**L2**	KO^{t}Bu	THF	>99	5	95	2.5:1
4	**L1**	KOMe	THF	>99	0	>95	9:1
5	**L1**	Et_3N	THF	35	0	0	-

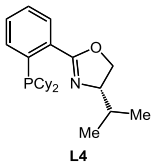


[a] Reaction conditions: all reactions were performed with **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), $Ni(cod)_2$ (0.005 mmol, 5 mol%), Ligand (0.006 mmol, 6 mol%), base (0.20 mmol, n equiv) in THF (2.0 mL, 0.5 M) at 50 °C. Consumption of **1a**, conversions and E/Z ratio were assessed by ^1H NMR. [b] 1.0 equiv. of trifluoroethanol. [c] Using 0.2 equiv. of KO^{t}Bu and EtOH [0.2] at 100 °C. [d] Obtained as a racemic mixture.

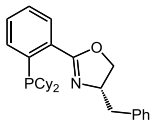
Optimization of Reaction Conditions



1a Ar = 4-Ph-C_6H_4 | **2a** (1.2 equiv.) | **4aa** *3,4-addition* | **5** *1,4-addition*



L4



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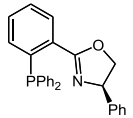
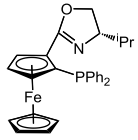


L13

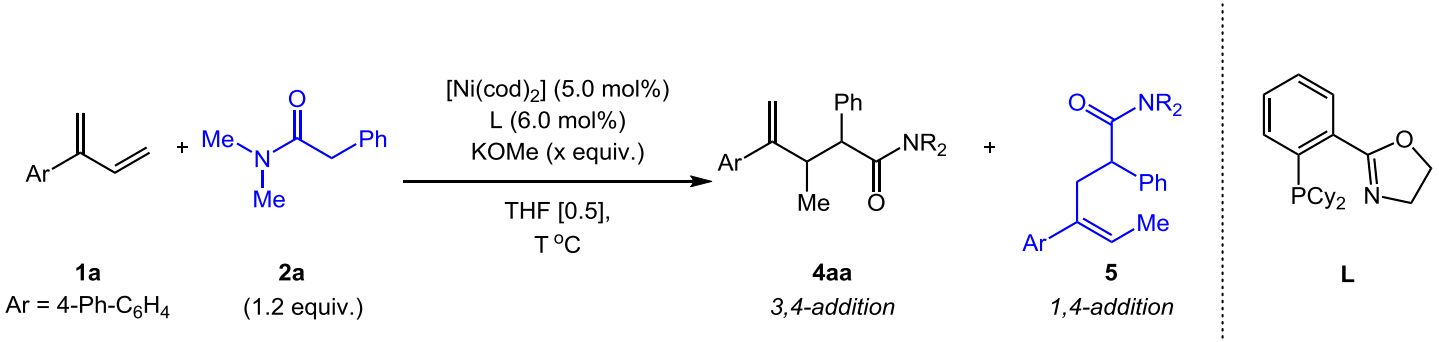


L14

Entry	Ligand	base	solvent	**1a** Conv. (%)	**4aa** (%)	**5aa** (%)	*E*/*Z* (**5aa**)
6	dppe	KOMe	THF	>99	0	>95	9:1
7	dppf	KOMe	THF	>99	<1	>95	8:1
8	Rac-BINAP	KOMe	THF	>99	1	>95	9:1
9[d]	(*S*)-**L4**	KOMe	THF	>99	0	>95	8:1
10[d]	(*S*)-**L5**	KOMe	THF	35	0	>95	8:1
11[d]	(*S*)-**L13**	KOMe	THF	35	0	81	9:1
12[d]	(*S,Sp*)-**L14**	KOMe	THF	35	0	>95	9:1

[a] Reaction conditions: all reactions were performed with **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), $Ni(cod)_2$ (0.005 mmol, 5 mol%), Ligand (0.006 mmol, 6 mol%), base (0.20 mmol, n equiv) in THF (2.0 mL, 0.5 M) at 50 °C. Consumption of **1a**, conversions and E/Z ratio were assessed by ^1H NMR. [b] 1.0 equiv. of trifluoroethanol. [c] Using 0.2 equiv. of KO*t*Bu and EtOH [0.2] at 100 °C. [d] Obtained as a racemic mixture.

Optimization of Reaction Conditions

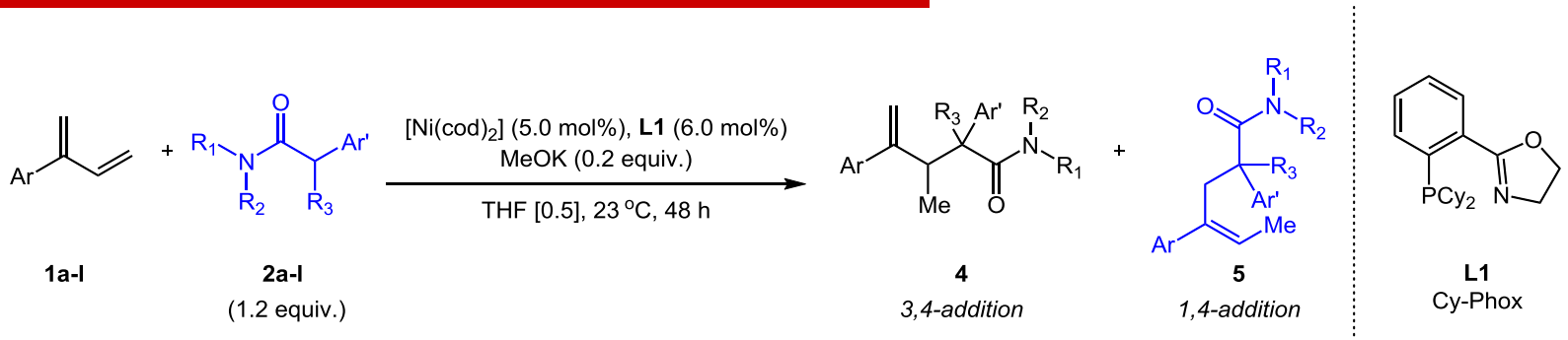


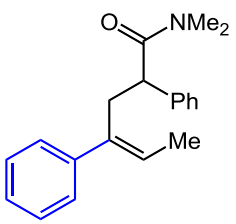
1a Ar = 4-Ph-C_6H_4 | **2a** (1.2 equiv.) | **4aa** *3,4-addition* | **5** *1,4-addition* | **L**

Entry	T (°C)	t (h)	x	**1a** Conv. (%)	**4aa** (%)	**5aa** (%)	*E*/*Z* (**5aa**)
1	50	16	2.0	>99	0	95	9:1
2	23	16	1.0	69	0	66	13:1
3	23	16	0.2	78	0	75	15:1
4	23	48	0.2	96	0	95	15:1
5[c]	23	16	0.2	2	0	0	-

[a] Reaction conditions: all reactions were performed with **1a** (0.10 mmol, 1.0 equiv.), **2a** (0.12 mmol, 1.2 equiv.), $Ni(cod)_2$ (0.005 mmol, 5 mol%), **L1** (0.006 mmol, 6 mol%), KOMe (0.10 x mmol, x equiv) in THF (0.2 mL, 0.5 M) at indicated temperature. Consumption of **1a**, conversions and E/Z ratio were assessed by ^1H NMR. [b] Using 2.0 equiv. of **2a**. [c] Using BTMG as base.

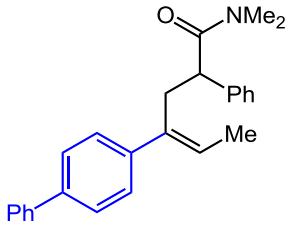
Substrate Scope





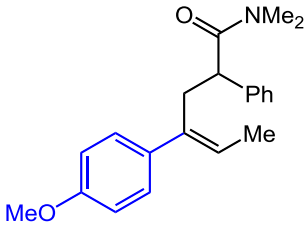
5aa

82% yield
rr>25:1; E/Z 4.7:1



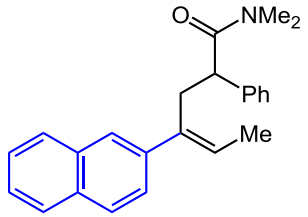
5ba

93% yield
rr>25:1; E/Z 15:1



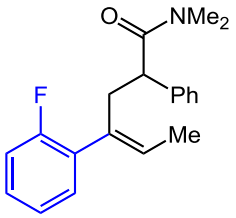
5ca

73% yield
rr>25:1; E/Z 2.8:1



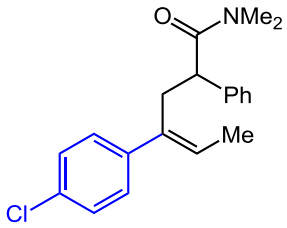
5da

93% yield
rr>25:1; E/Z 11:1



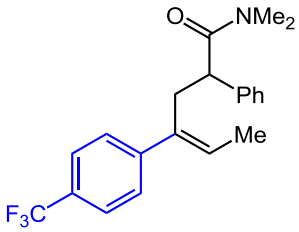
5ea

86% yield
rr>25:1; E/Z 8.2:1



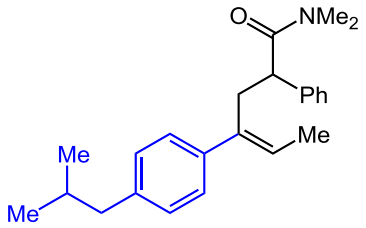
5fa

92% yield
rr>25:1; E/Z 5.5:1



5ga

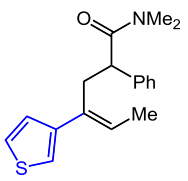
98% yield
rr>25:1; E/Z 5.1:1



5ha

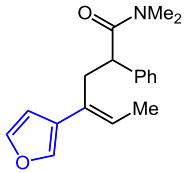
85% yield
rr>25:1; E/Z 3.8:1

Substrate Scope



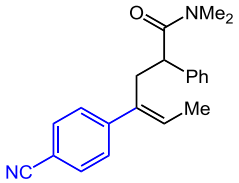
5ia

72% yield
rr>25:1; E/Z 1.7:1



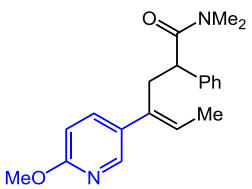
5ja

71% yield
rr>25:1; E/Z 2.8:1



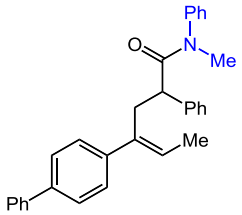
5ka

52% yield
rr>25:1; E/Z 3.2:1



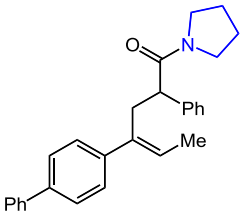
5la

83% yield
rr>25:1; E/Z 3.6:1



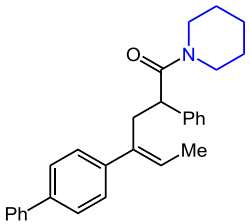
5ab

89% yield
rr>25:1; E/Z 19:1



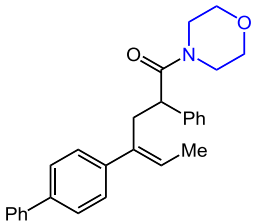
5ac

97% yield
rr>25:1; E/Z 13:1



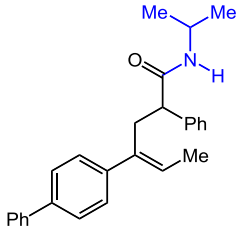
5ad

94% yield
rr>25:1; E/Z 10:1



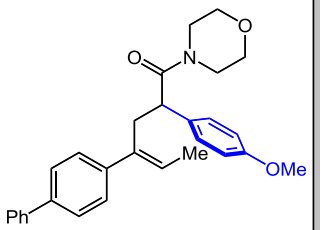
5ae

96% yield
rr>25:1; E/Z 22:1



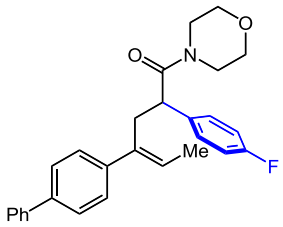
5af

82% yield
rr>25:1; E/Z 10:1



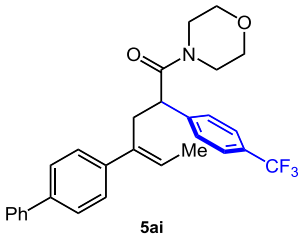
5ag

89% yield
rr>25:1; E/Z 13:1



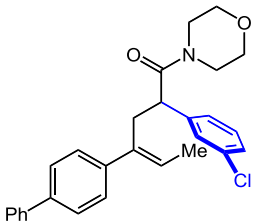
5ah

97% yield
rr>25:1; E/Z 17:1



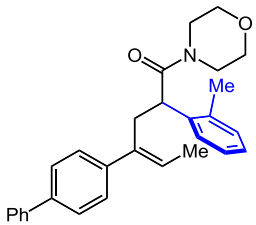
5ai

90% yield
rr>25:1; E/Z 13:1



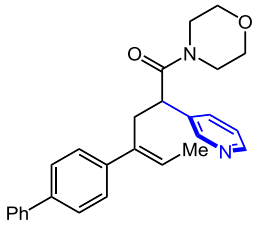
5aj

99% yield
rr>25:1; E/Z 13:1



5ak

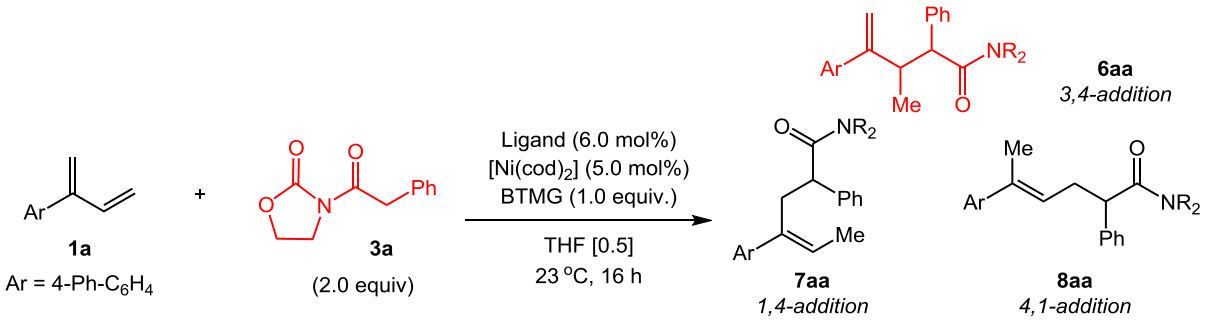
93% yield
rr>25:1; E/Z 21:1

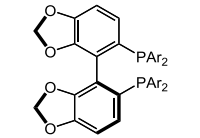


5al

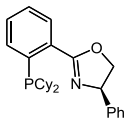
98% yield
rr>25:1; E/Z 13:1

Optimization of Reaction Conditions

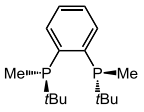




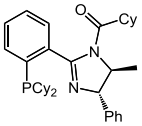
(*S*)-**L2**
Ar = 3,5-(*t*Bu)$_2$-4-OMe-C$_8$H$_2$



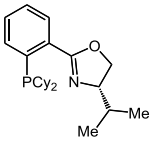
(*R*)-**L6**



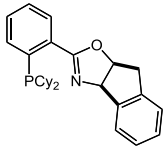
(*R*,*R*)-**L3**



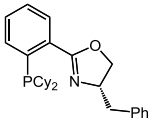
(*R*,*R*)-**L7**



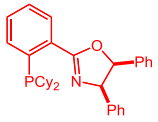
(*S*)-**L4**



(3*R*,8*S*)-**L8**



(*S*)-**L5**

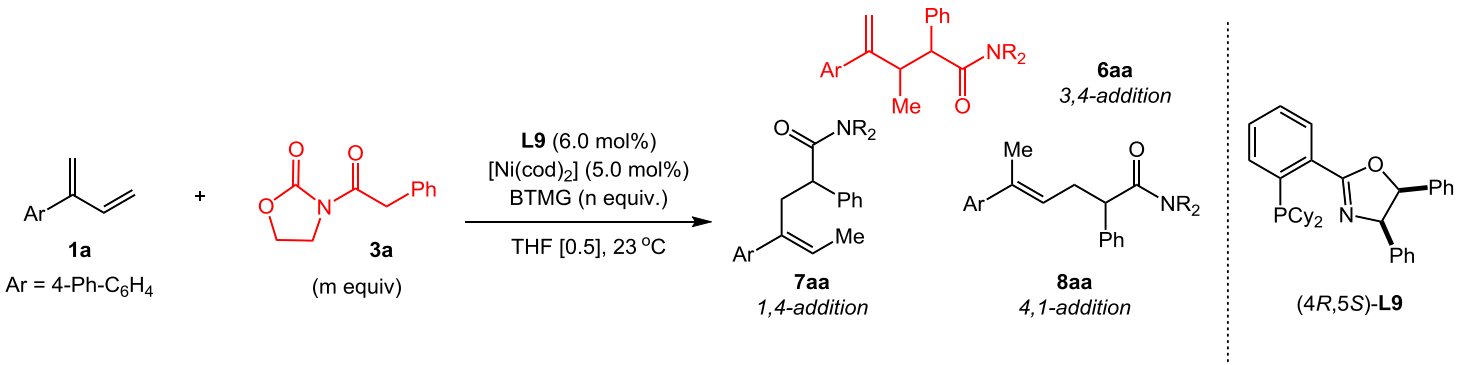


(4*R*,5*S*)-**L9**

Entry[a]	L	Conv. (%)[b]	**6aa:7aa:8aa**[b]	dr$_{\mathbf{6aa}}$[b]	Ee$_{6aa}$(%)[c]
1	**L2**	<5	-	-	-
2	**L3**	>95	3.8:4.2:1	2.8:1	77
3	**L4**	95	7.3:1:1.1	3.3:1	18
4[d]	**L5**	80	16.3:2.8:1	3.3:1	3
5	**L6**	>95	11.3:1:1.9	5.3:1	87
6	**L7**	51	6.1:1:6	5.3:1	70
7	**L8**	59	5.7:1:1.7	2.3:1	-79
8	**L9**	>95	11.1:1:1.9	5.3:1	92
9[e]	**L9**	>95	1.3:1:2.1	7.0:1	92

[a] Reaction condition: **1a** (0.1 mmol), **3a** (0.2mmol). [b] Determined by ^{1}H NMR using an internal standard. [c] Determined by HPLC using a chiral stationary phase. [d] Using MeOK (0.2 equiv) as base. [e] **3a** (1.2 equiv), BTMG (0.2 equiv), 48 h.

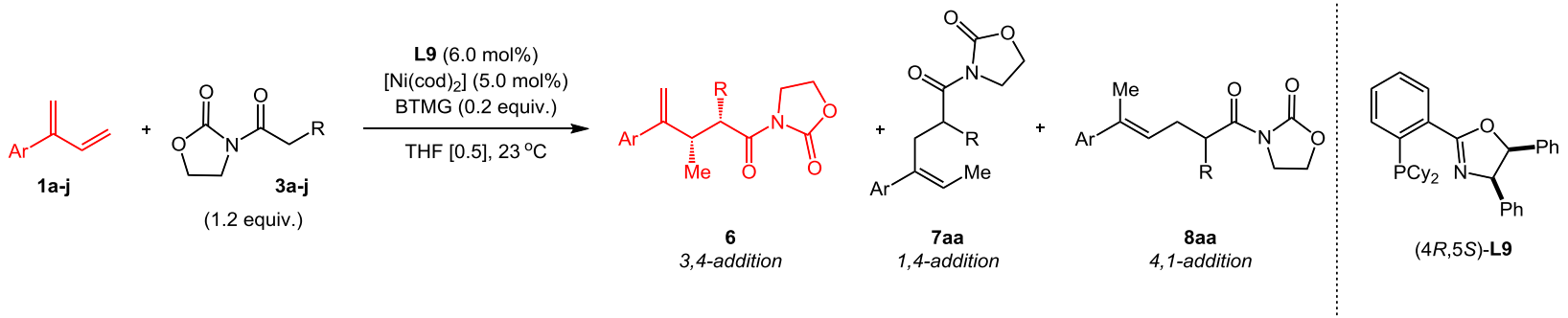
Optimization of Reaction Conditions

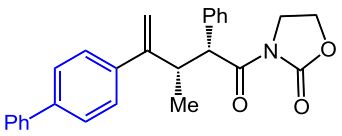


Entry	t (h)	m	n	**1a** Conv. (%)	**6aa** (%)	**7aa** (%)	**8aa** (%)	*dr* (**6aa**)	*ee*(**6aa**)[b] (%)
1	16	2.0	1.0	99	78	7	13	5.3:1	92;80
2	24	1.2	1.0	99	81	6	13	7.0:1	92;79
3	48	1.2	0.2	99	78	6	13	7.0:1	92;79
4[c]	48	2.0	0.2	99	75	8	2	5.3:1	91;80

[a] Reaction conditions: all reactions were performed with **1a** (0.10 mmol, 1.0 equiv.), **3a** (0.1 m mmol, m equiv.), $Ni(cod)_2$ (0.005 mmol, 5 mol%), **L9** (0.006 mmol, 6 mol%), BTMG (0.10 n mmol, n equiv) in THF (2.0 mL, 0.5 M) at room temperature. Consumption of **1a**, conversions of **6aa**, **7aa**, **8aa** and diastereoisomeric ratio were assessed by ^1H NMR. Enantiomeric excess determined by HPLC equipped with chiral columns. [b] Representing the ee of major diastereoisomer and minor diastereoisomer. [c] Using KOMe as base.

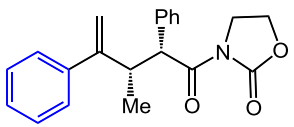
Substrate Scope





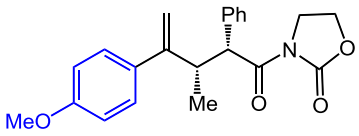
6aa

71% yield, *rr* 4.1:1
92% ee, *dr* 7.0:1



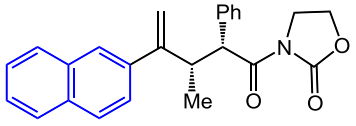
6ba

54% yield, *rr* 2.8:1
94% ee, *dr* 6.0:1



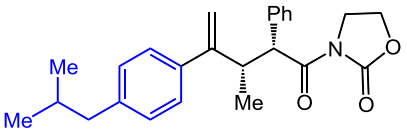
6ca

56% yield, *rr* 2.2:1
91% ee, *dr* 5.3:1



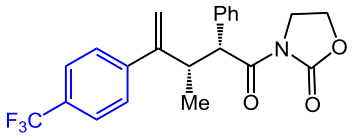
6da

67% yield, *rr* 5.2:1
92% ee, *dr* 11.0:1



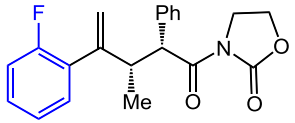
6ea

50% yield, *rr* 1.8:1
94% ee, *dr* 5.7:1



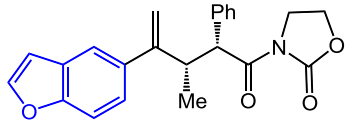
6ga

70% yield, *rr* 6.8:1
87% ee, *dr* 7.7:1



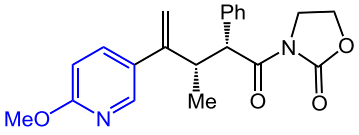
6ha

41% yield, *rr* 2.7:1
90% ee, *dr* 2.5:1



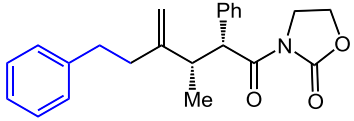
6ja

53% yield, *rr* 2.3:1
88% ee, *dr* 7.0:1



6ia

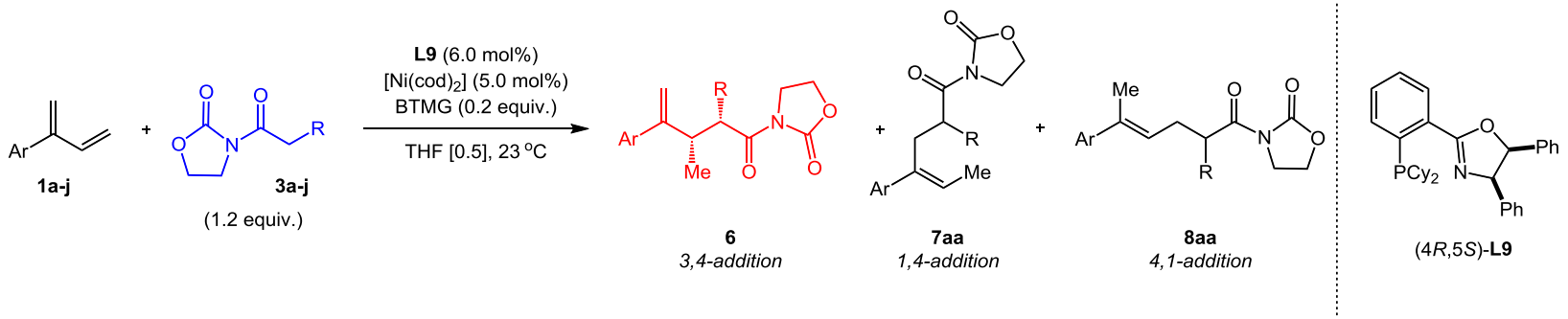
62% yield, *rr* 4.8:1
88% ee, *dr* 5.2:1

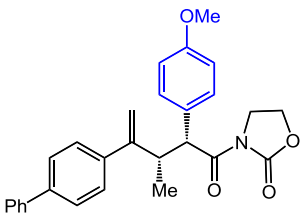


6ma

< 5% conv.

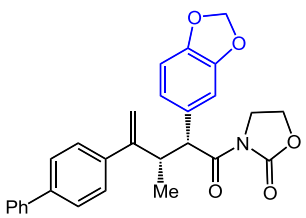
Substrate Scope





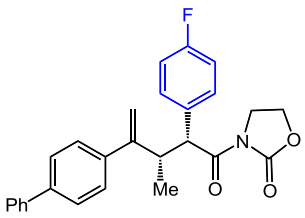
6ab

78% yield, *rr* 10:1
91% ee, *dr* 9.0:1



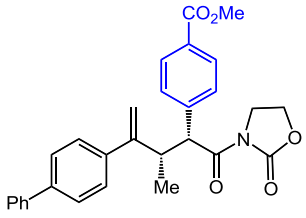
6ac

72% yield, *rr* 9.0:1
89% ee, *dr* 5.7:1



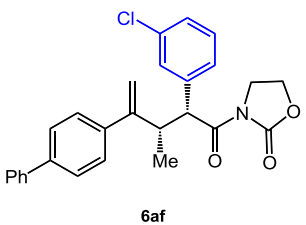
6ad

65% yield, *rr* 3.5:1
88% ee, *dr* 7.0:1



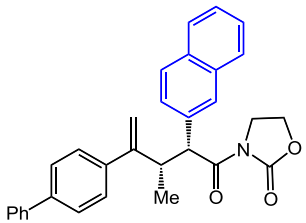
6ae

40% yield, *rr* 1.3:1
67% ee, *dr* 3.0:1



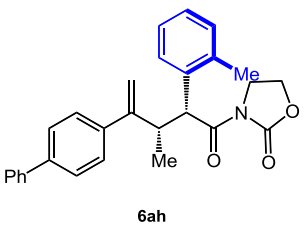
6af

61% yield, *rr* 3.2:1
90% ee, *dr* 5.4:1



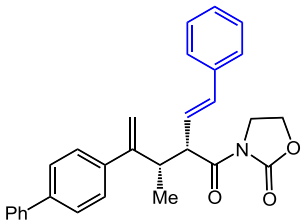
6ag

57% yield, *rr* 3.0:1
91% ee, *dr* 5.8:1



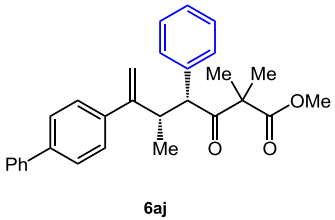
6ah

46% yield, *rr* 2.0:1
94% ee, *dr* 2.6:1



6ai

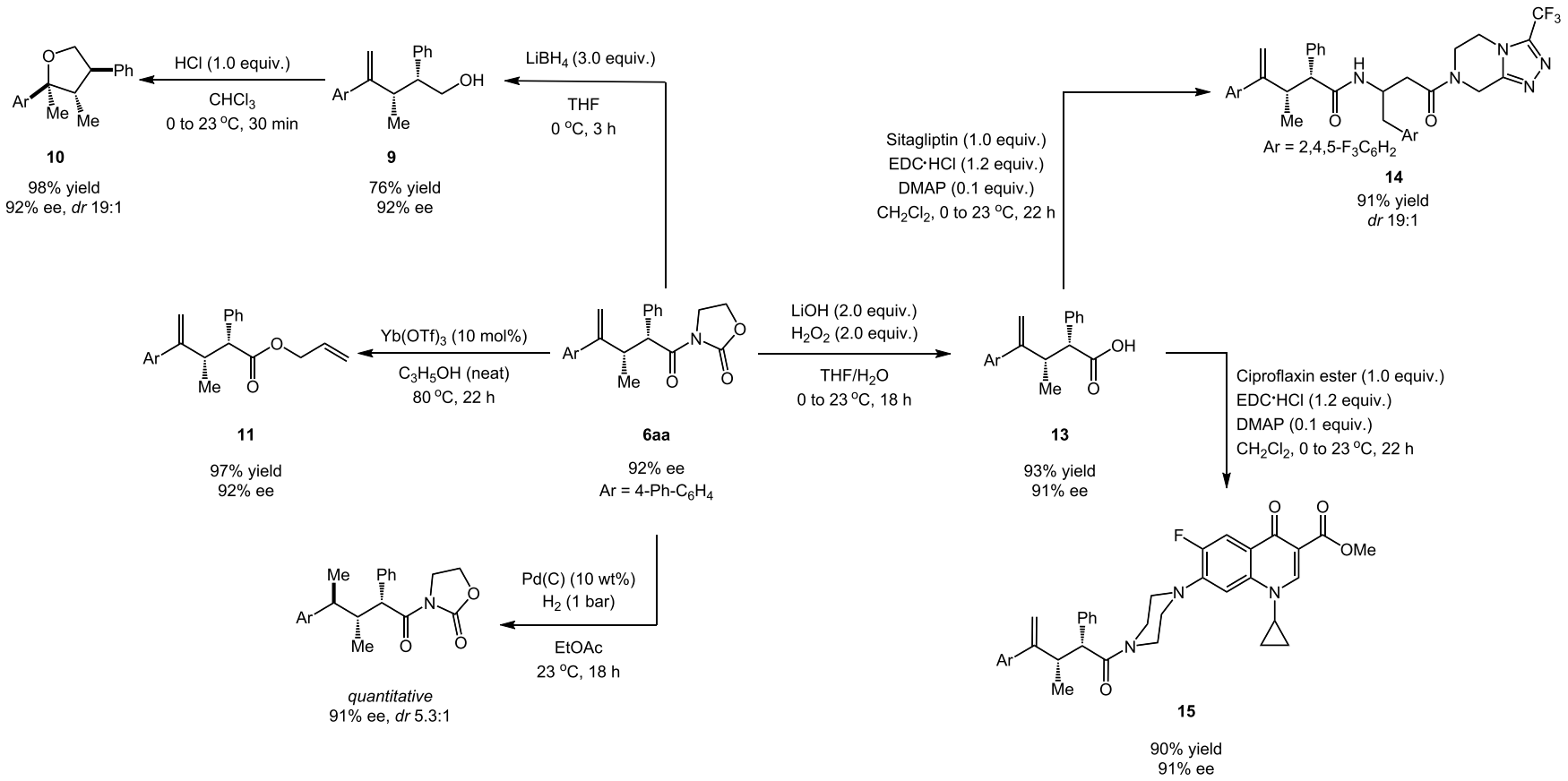
46% yield, *rr* 2.1:1
88% ee, *dr* 3.4:1



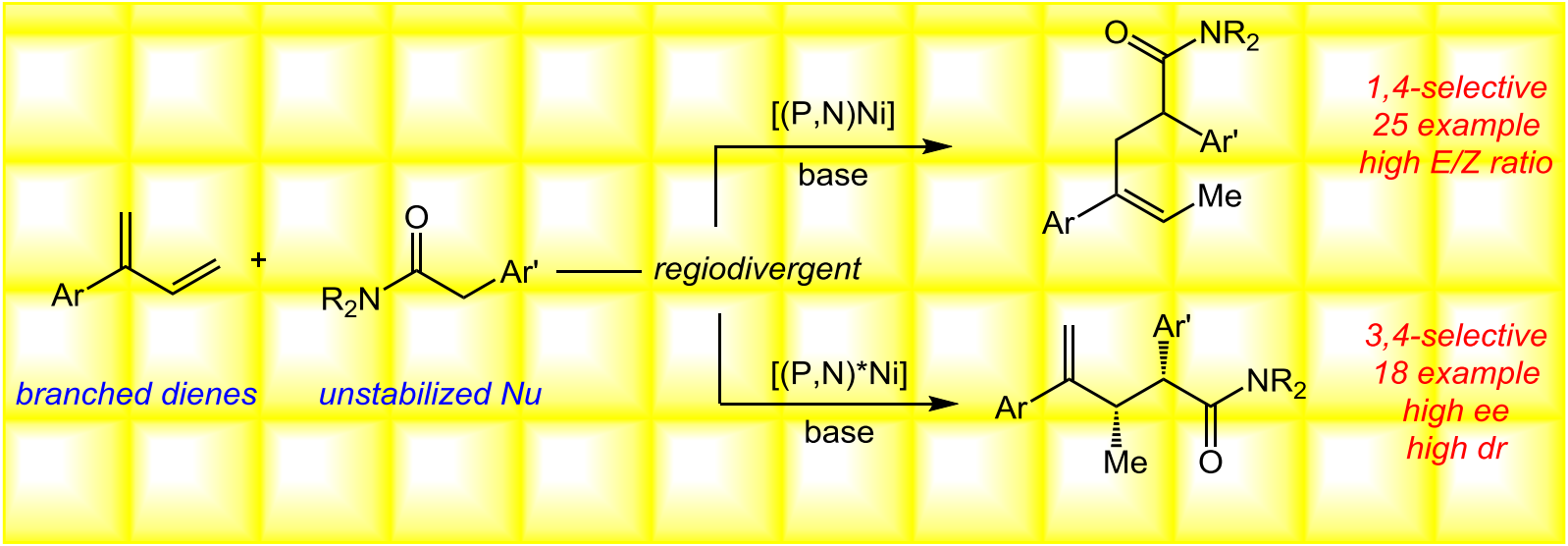
6aj

68% yield, *rr* 2.8:1
41% ee, *dr* 14.0:1

Product Transformation



Summary



Mazet, C. *et al*. *J*. *Am*. *Chem*. *Soc*. **2020**, *142*, 16486.

The First Paragraph

Writing Strategy

通过碳–碳键形成反应构建相邻立体中心的困难

↓

共轭二烯分子间氢烷基化存在的困难

↓

成功开发金属催化二烯氢烷基化的意义

The First Paragraph

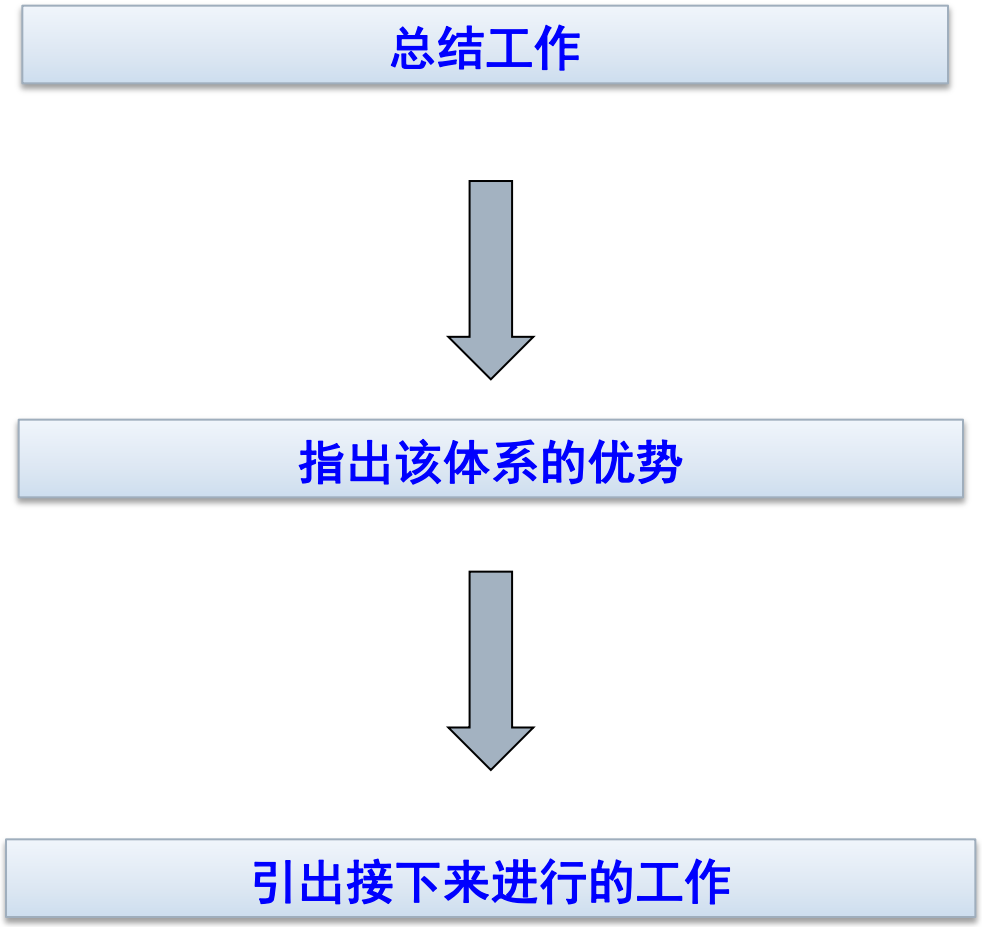
The development of novel methods for the diastereoselective and enantioselective construction of adjacent stereocenters based on C-C bond-forming reaction is a resounding challenge in chemical synthesis. The atom-economical intermolecular hydroalkylation of conjugated dienes has recently emerged as an enabling strategy because it provides access synthetically useful compounds with an allylic stereocenter, compounds that would be difficult to prepare using conventional protocols. The influence of substitution pattern of dienes on reactivity and selectivity and the diversity of insertion modes conceivable for a transition-metal catalyst across the conjugated double bonds pose major difficulties for their selective functionalization.

The First Paragraph

Consequently, in its most demanding version, the successful development of a metal-catalyzed hydroalkylation of dienes requires addressing altogether chemoselectivity, regioselectivity, diastereoselectivity, and-ultimately-enantioselectivity challenges.

The Last Paragraph

Writing Strategy



The Last Paragraph

In addition to stereoselectivity, regioselectivity is often a major challenge in diene hydrofunctionalization reactions. In this article, we have reported two complementary regiodivergent Ni-catalyzed hydroalkylations of branched dienes with unstabilized C(sp^3) nucleophiles. The first system uses an achiral C1-symmetric phosphinooxazoline ligand and simple amides, which once deprotonated in situ, undergo a highly 1,4-selective addition process with excellent stereocontrol of the trisubstituted C=C bond generated. The method displays a broad scope in both the nucleophilic and electrophilic component, enabling the use of sensitive functionalities and heteroaromatic-containing precursors.

The Last Paragraph

Switching to imides as carbon nucleophiles favored formation of 3,4-addition products. The constructions of vicinal tertiary stereocenters was achieved with moderate to high diastereoselectivity and excellent enantioselectivity by means of a novel chiral (P,N) ligand. Notably, a wide range of functional groups were compatible with the mild conditions employed and several postcatalytic derivatizations were conducted to measure the synthetic potential of the method. Studies aiming at understanding the factors that determine reactivity and selectivity for both systems are currently ongoing in our laboratories.

Representative Examples

Reasoing (考虑到.....) that the use of imides in place of amides in the Ni-catalyzed 3,4-hydroalkylation diene may positively influence the stereoselective outcome of the reaction, we directly set out to (着手于) develop an enantioselective variant of this process.

To date (到目前为止), there is only a handful of (少量) reports on the selective intermolecular hydroalkylation of 1,3-dienes..

Although 5aa was not our initial target, the presence of two stereogenic elements and two functional handles in its structure prompted (促使、激励) us to further explore conditions favoring its formation.

Acknowledgement

Thanks
for your attention