Literature Report

Diastereoselective and Enantioselective Conjunctive Cross-Coupling Enabled by Boron Ligand Design

Reporter : Hong-Qiang Shen
Checker : Xiang Li
Date : 2018-12-17

Myhill, J. A.; Wilhelmsen, C. A.; Zhang, L.; **Morken, J. P.**
J. Am. Chem. Soc. **2018**, *140*, 15181-15185.

Contents

CV of James P. Morken

Research:

- Developing of new catalytic asymmetric reactions
- Studying their utility in complex molecule synthesis.

Education:

1985-1989 B. S., U C, Santa Barbara.

1989-1990 Associate Research Chemist, ICI Americas.

1990-1995 Ph. D., Boston College (Advisor: A. H. Hoveyda).

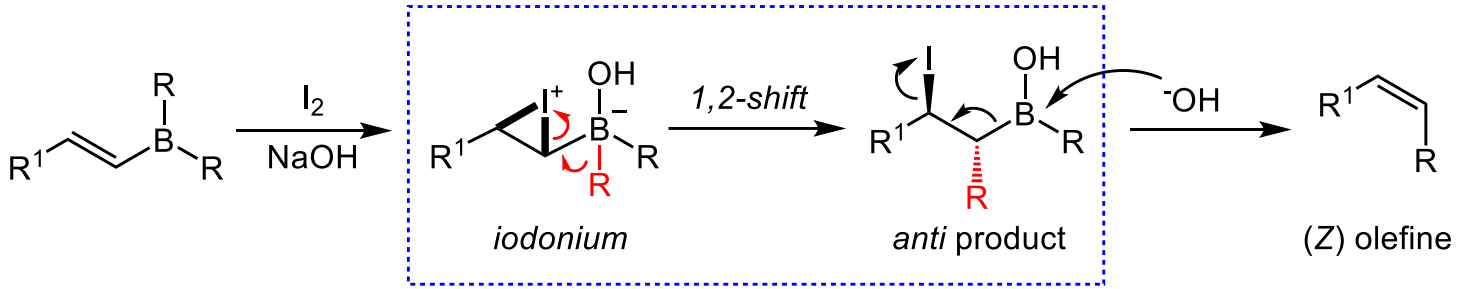
1995-1997 Postdoctoral Fellow, Harvard University (Advisor: S. L. Schreiber).

1997-2002 Assistant Professor of Chemistry, UNC Chapel Hill.

2002-2006 Associate Professor of Chemistry, UNC Chapel Hill.

2006-至今 Professor of Chemistry, Boston College.

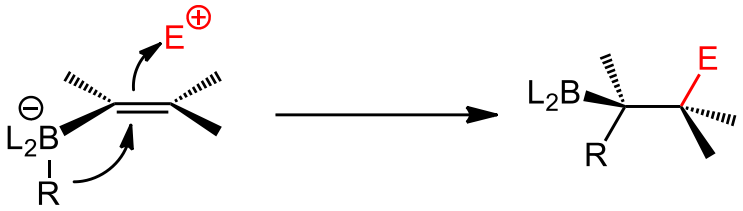
Zweifel Olefination



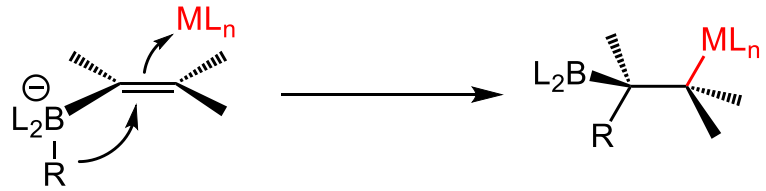
Zweifel, G. *et al. J. Am. Chem. Soc.* **1967**, *89,* 3652.

Introduction

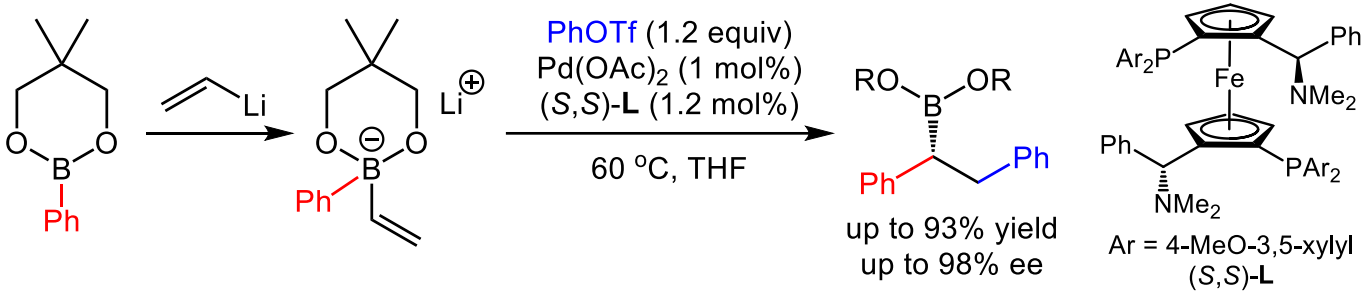
Electrophile-induced 1,2-metallate rearrangement

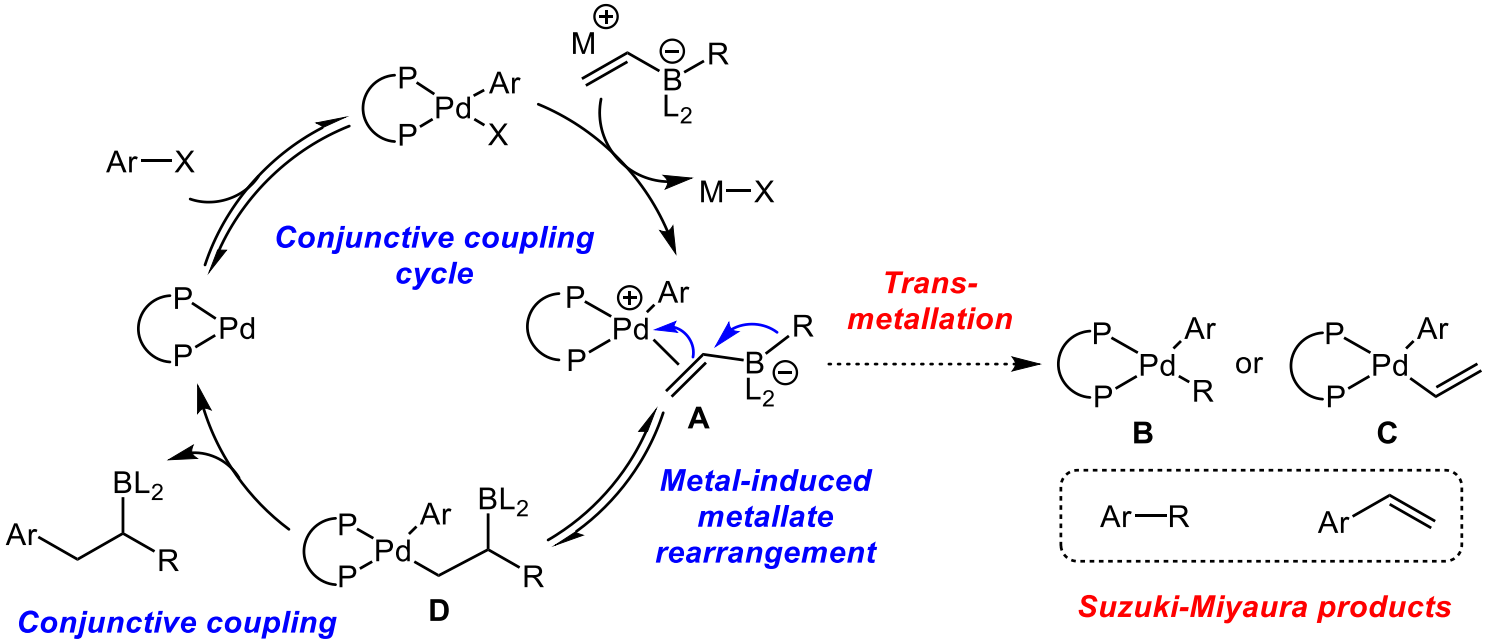


Metal-induced 1,2-metallate rearrangement



Conjunctive Cross-Coupling





Morken, J. P. *et al. Science* **2016**, *351*, 70.

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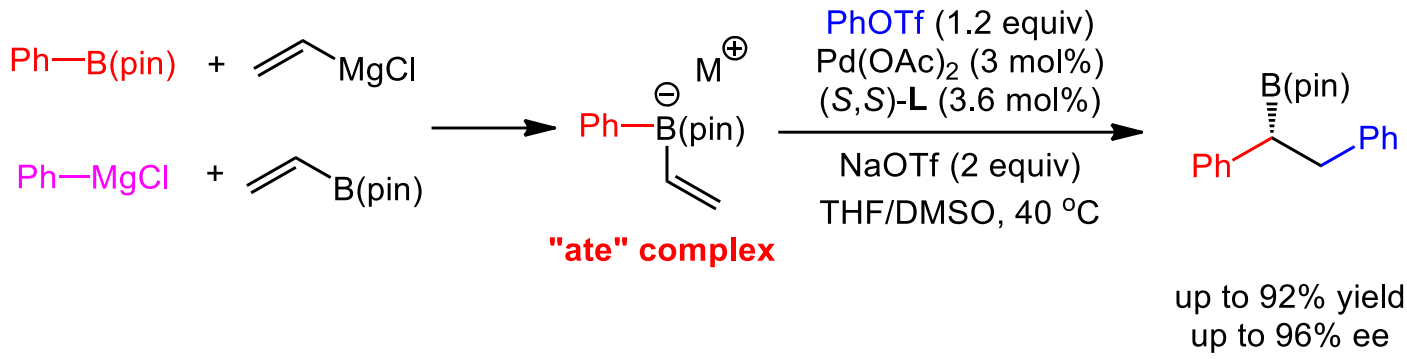
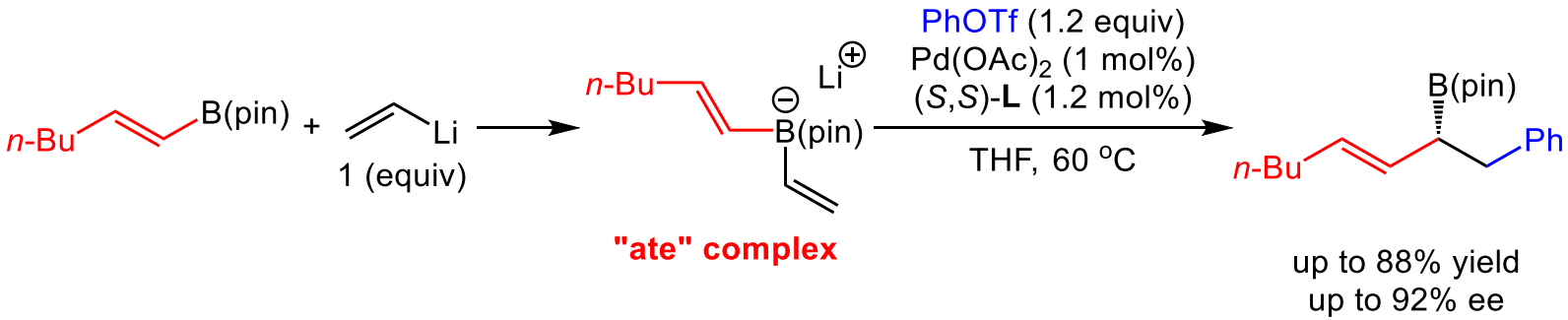


Morken, J. P. *et al. J. Am. Chem. Soc.* **2017**, *139*, 3153.



Morken, J. P. *et al. J. Am. Chem. Soc.* **2017**, *139*, 5027.

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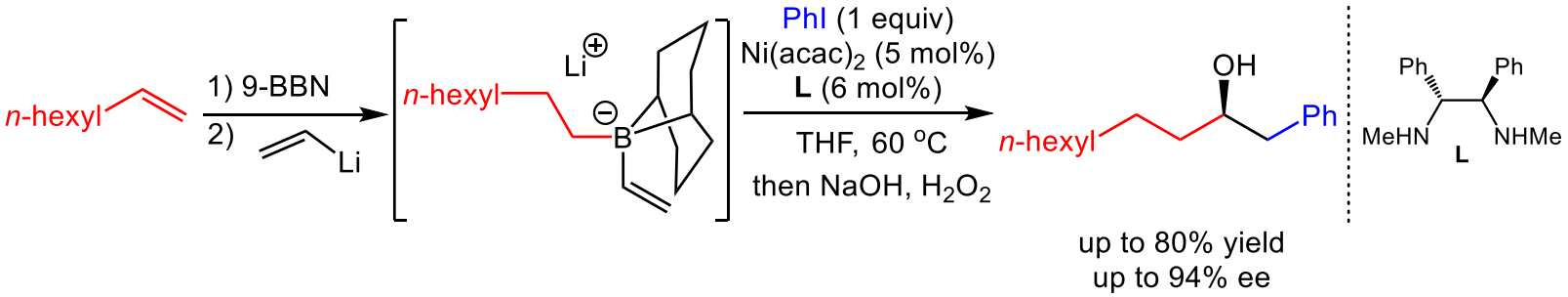
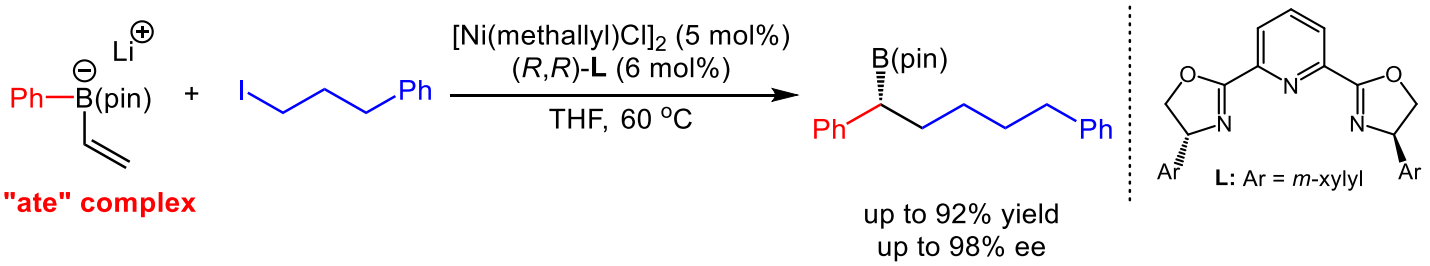


Morken, J. P. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 11870.



Morken, J. P. *et al. J. Am. Chem. Soc.* **2017**, *139*, 17293.

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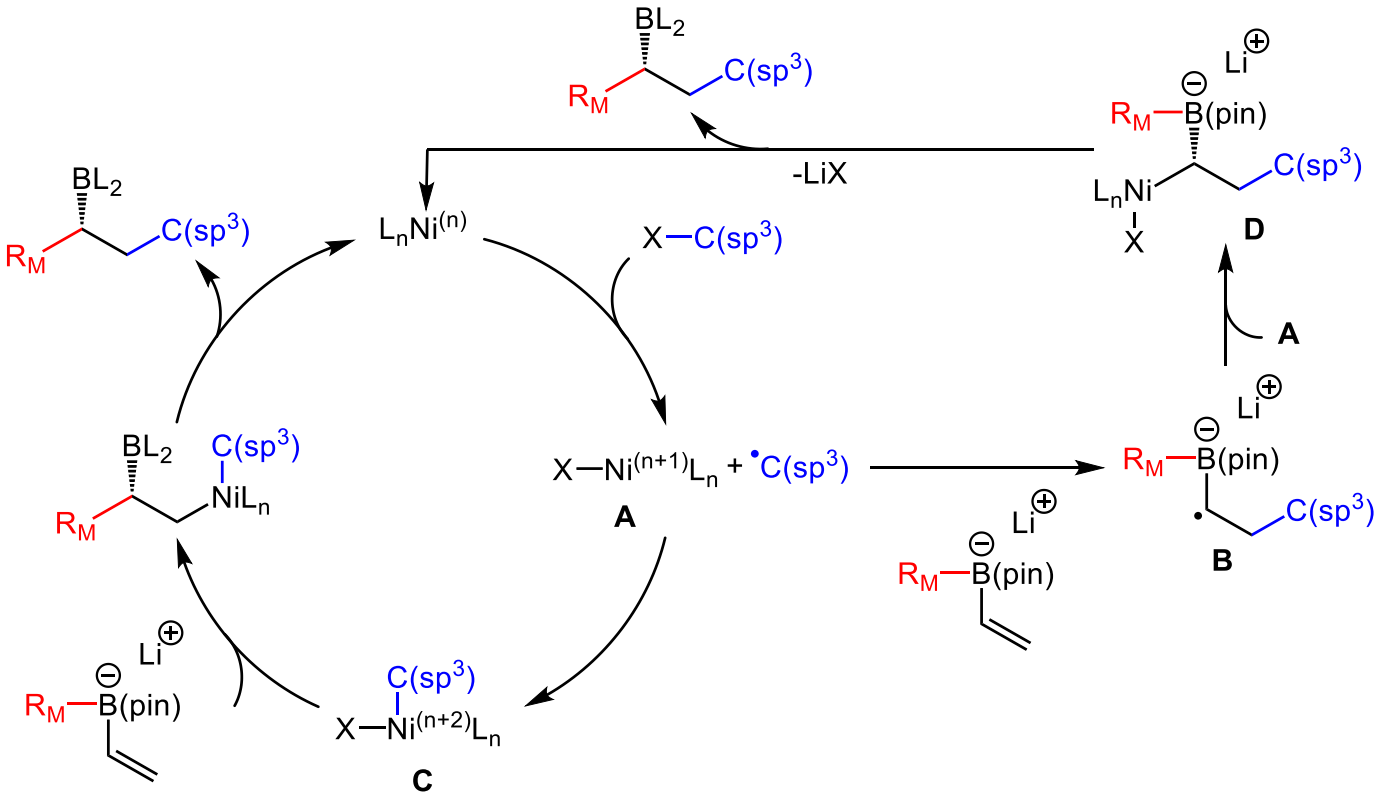

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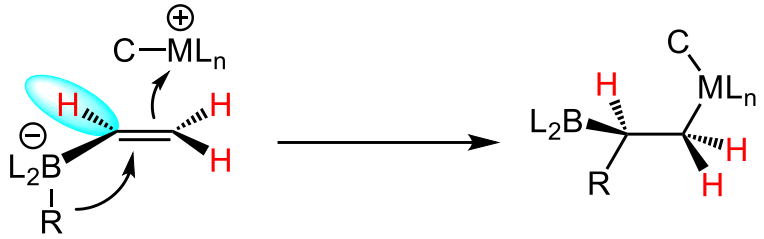
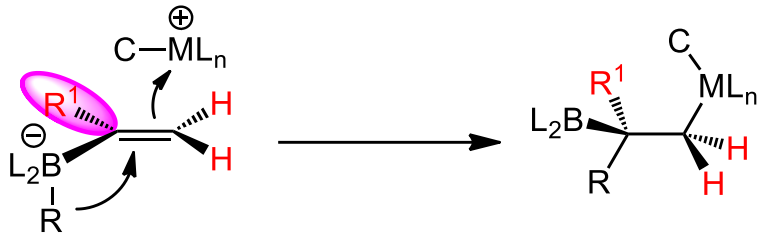
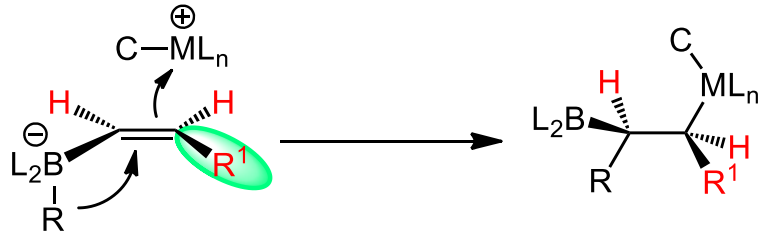
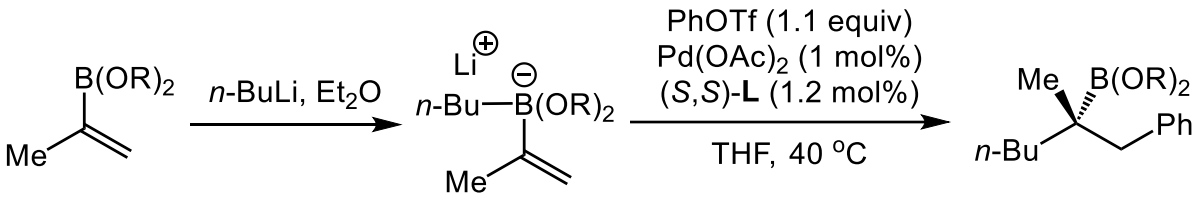
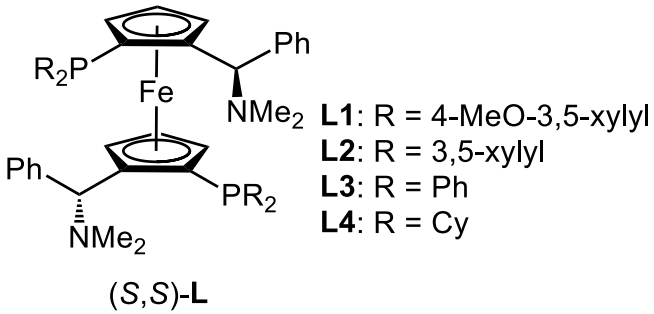






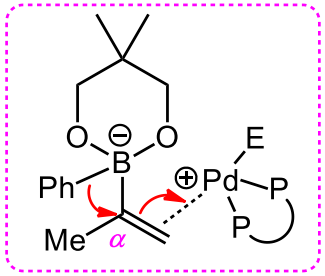
α-Substituted Alkenylboronates



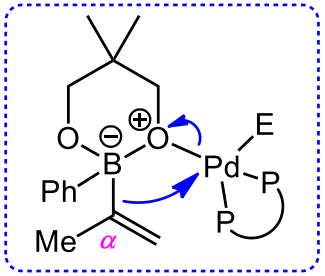


(*S*,*S*)-**L**

L1: R = 4-MeO-3,5-xylyl
L2: R = 3,5-xylyl
L3: R = Ph
L4: R = Cy



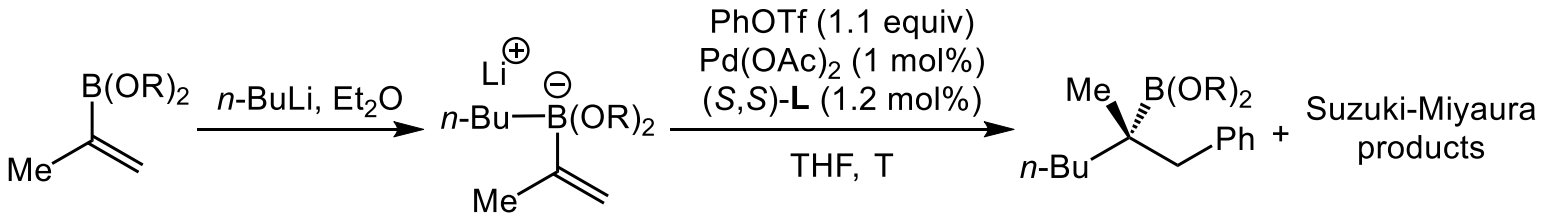
A
Conjunctive coupling



B
Suzuki-Miyaura coupling

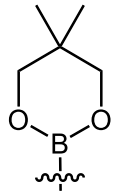
Morken, J. P. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12799.

Optimization of the Reaction Parameters

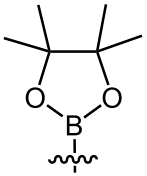


1 **2** **3** **4**

Entry[a]	$B(OR)_2$	Ligand	T °C	**3**:**4**[b]	Yield of **3** (%)[c]	Ee (%)[d]
1	B(neo)	**L1**	60	1:2.9	22	80
2	B(neo)	**L2**	60	1:2.3	23	82
3	B(neo)	**L3**	60	1:3.6	22	nd
4	B(neo)	**L4**	60	1:4.5	18	nd
5	B(pin)	**L1**	60	1:0.11	90	80
6	B(pin)	**L2**	60	1:0.25	83	76
7	B(pin)	**L3**	60	1:0.13	94	72
8	B(pin)	**L4**	60	1:0.20	88	20
9	B(pin)	**L1**	40	1:0.11	91	84
10	B(pin)	**L1**	22	1:0.06	94	88



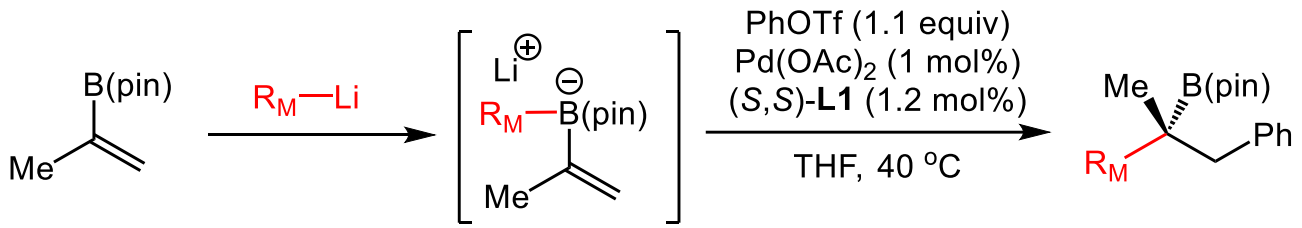
B(neo)
A

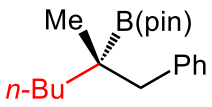


B(pin)
B

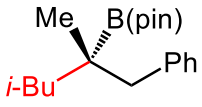
[a] Reaction conditions: **1** (0.20 mmol), *n*-BuLi (0.20 mmol), THF (1.0 mL). [b] Determined by NMR analysis. [c] Isolated yields. [d] Determined by HPLC.

Substrate Scope

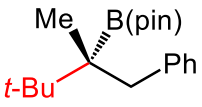




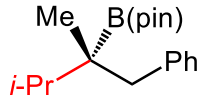
3a: 94% yield, 88% ee[a]



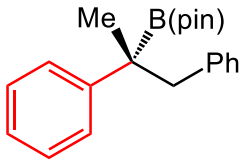
3b: 94% yield, 86% ee



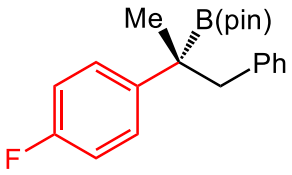
3c: 88% yield, 92% ee



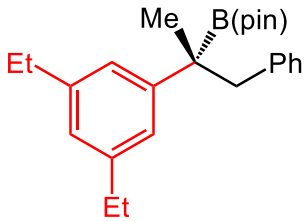
3d: 96% yield, 72% ee



3e: 90% yield, 82% ee



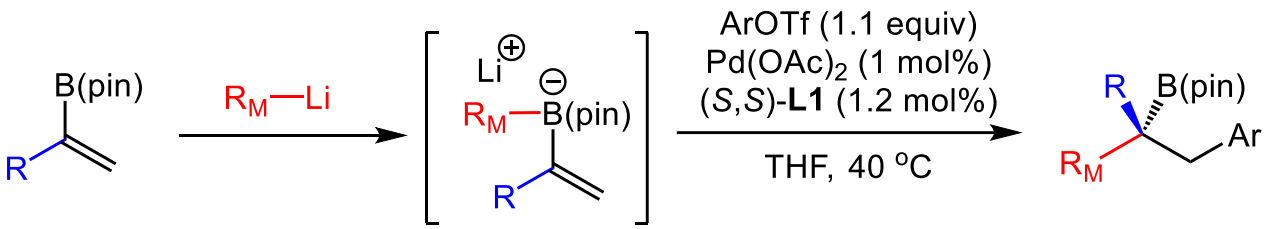
3f: 82% yield, 76% ee

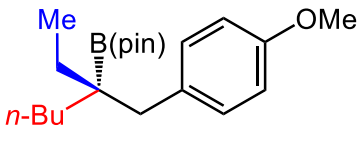


3g: 75% yield, 86% ee

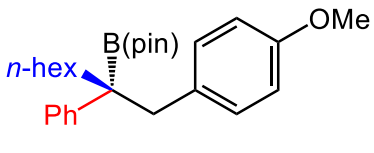
[a] 22 °C

Substrate Scope

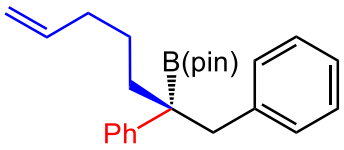




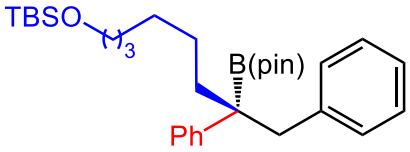
3h: 72% yield, 68% ee



3i: 86% yield, 84% ee

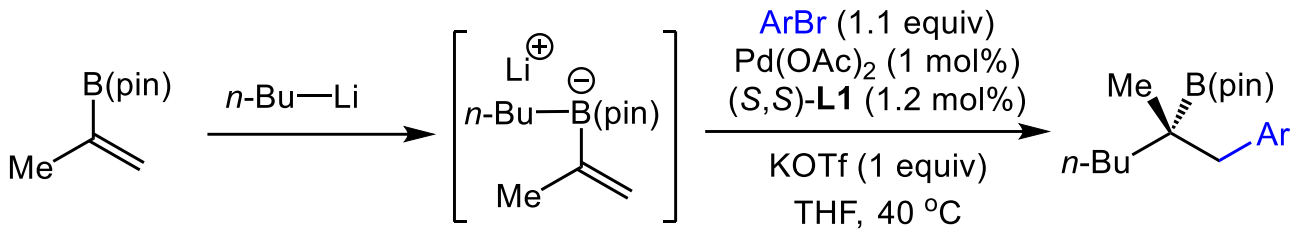


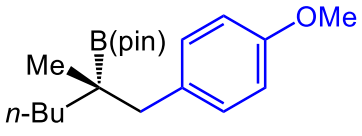
3j: 87% yield, 82% ee



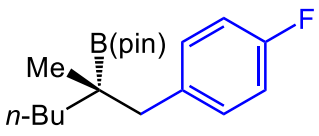
3k: 73% yield, 82% ee

Substrate Scope

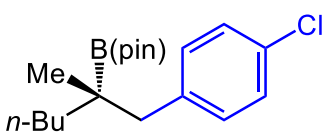




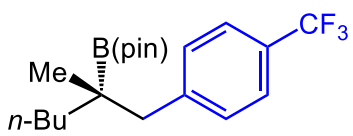
3l: 95% yield, 84% ee



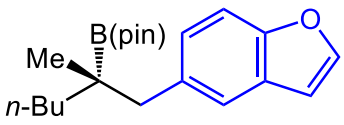
3m: 92% yield, 80% ee



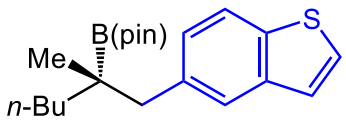
3n: 96% yield, 72% ee



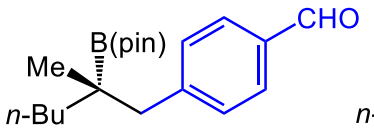
3o: 91% yield, 72% ee



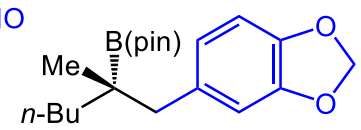
3p: 85% yield, 80% ee



3q: 85% yield, 82% ee



3r: 81% yield, 80% ee



3s: 96% yield, 80% ee

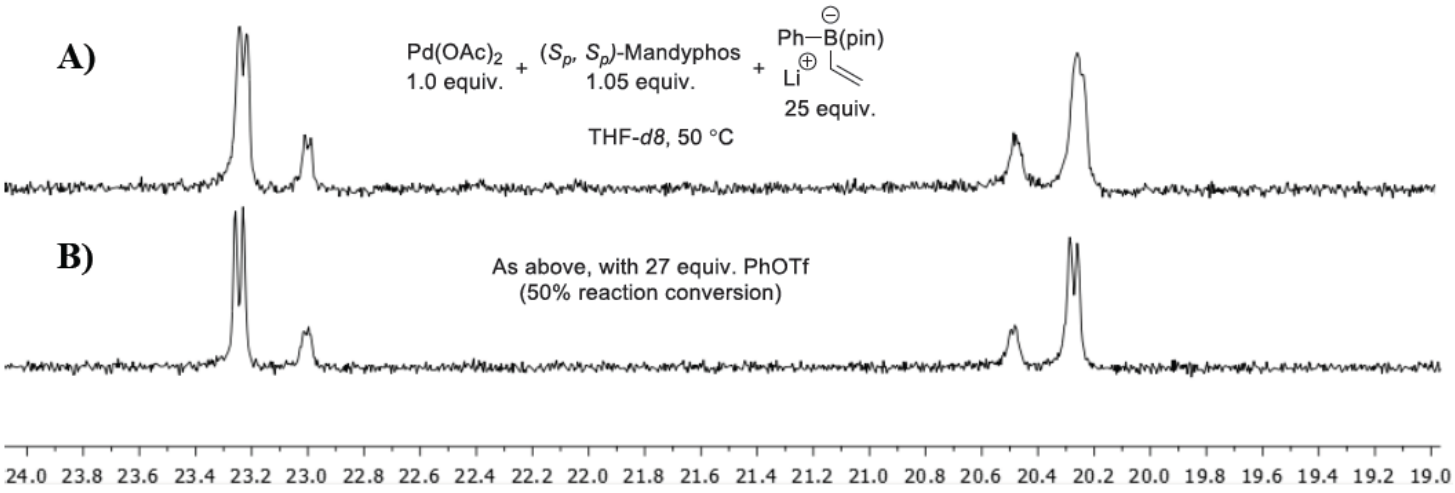
Control Experiments

1) Analysis of the effect of individual reaction components：

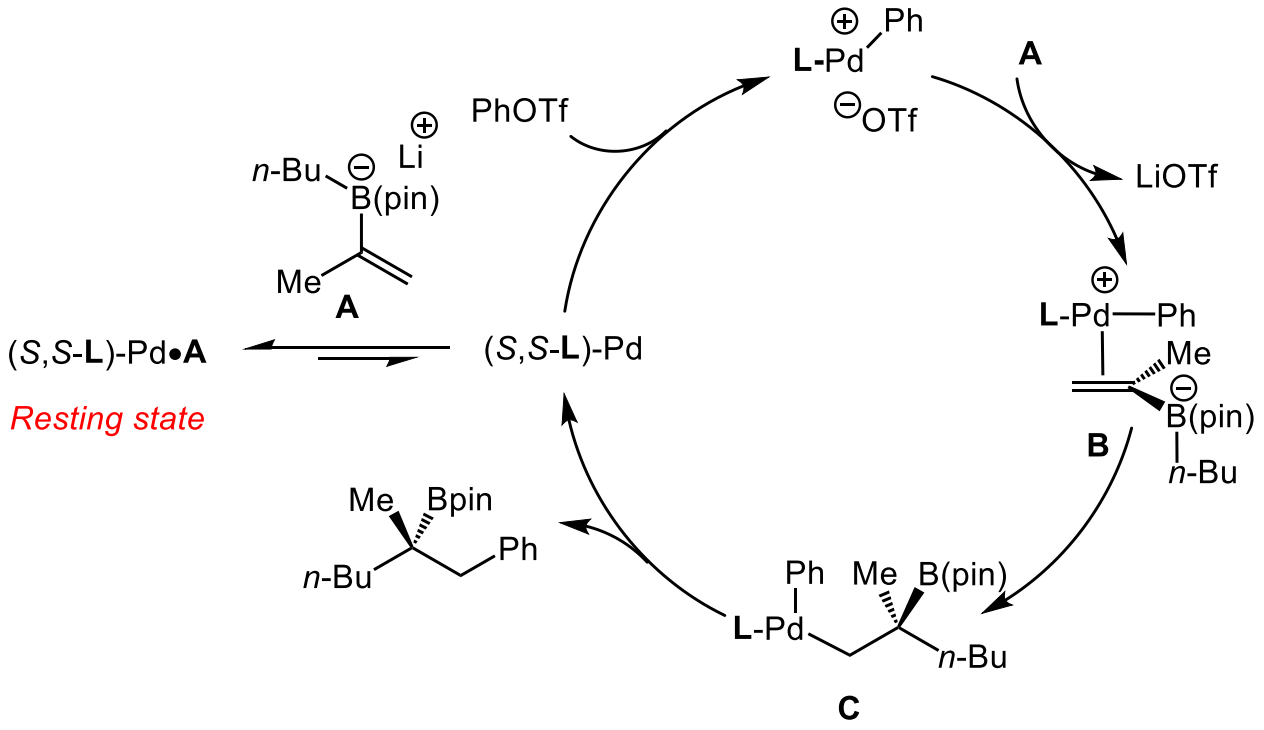
- First-order in catalyst (order = 1.1)
- First-order in electrophile (order = 1.4)
- Inverse order in “ate” complex (order = -0.9)

$$\text{Rate} = k \cdot \frac{[\text{cat}][\text{ArOTf}]}{[\text{'ate' complex}]}$$

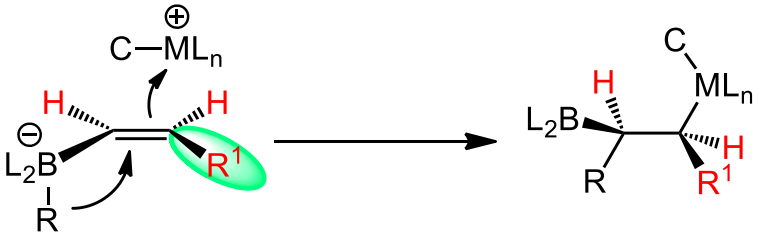
2) ^{31}P NMR spectra:

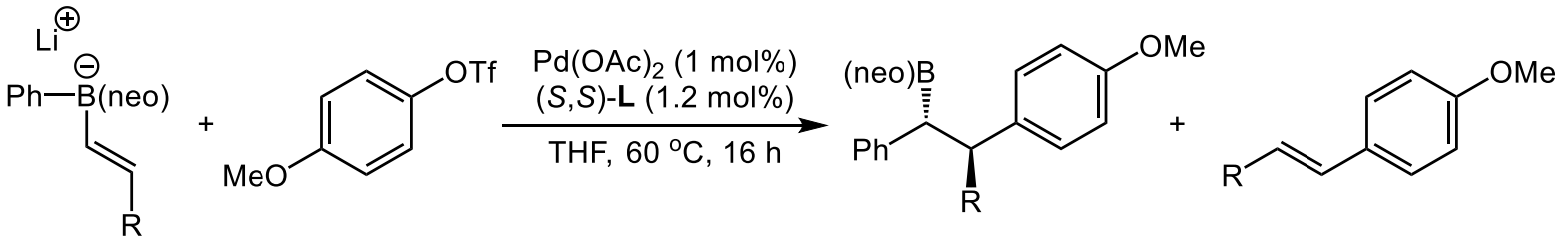


Proposed Mechanism



β-Substituted Alkenylboronates





1a

R = H
R = Ph

2a

3a

R = H: 84% yield, 94% ee
R = Ph: 13% yield, >20:1 d.r., 98% ee

4

R = H: <5% yield
R = Ph: 75% yield

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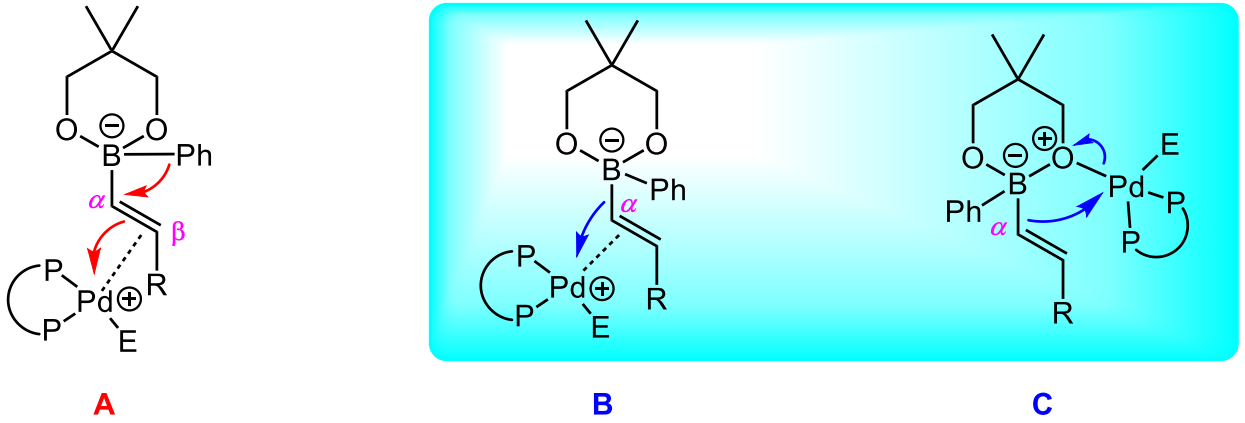
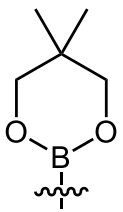
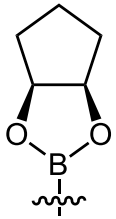
β-Substituted Alkenylboronates



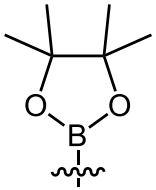
β-Substituted Alkenylboronates



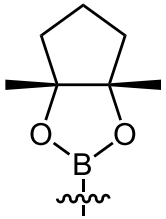
L1



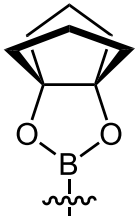
L2



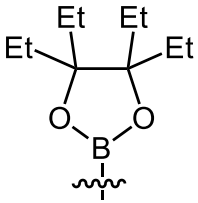
L3



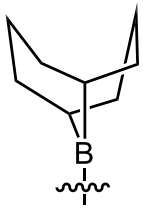
L4



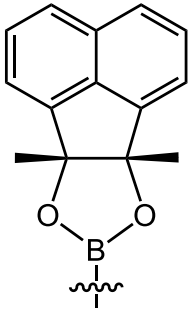
L5



L6

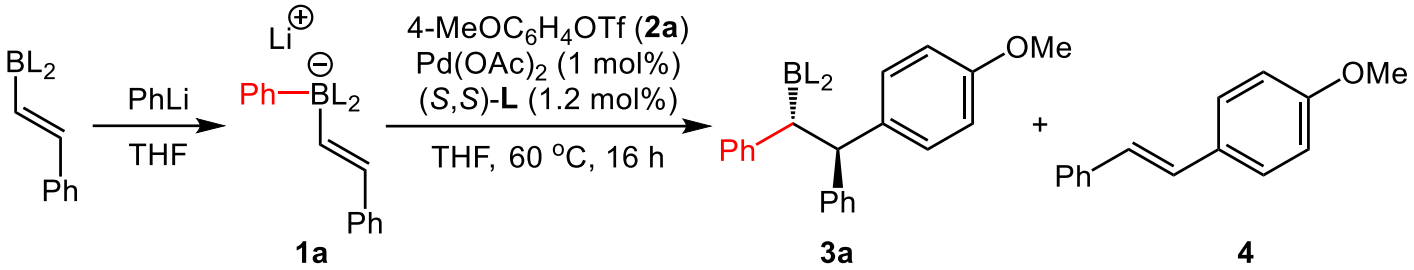


L7



L8
(mac)

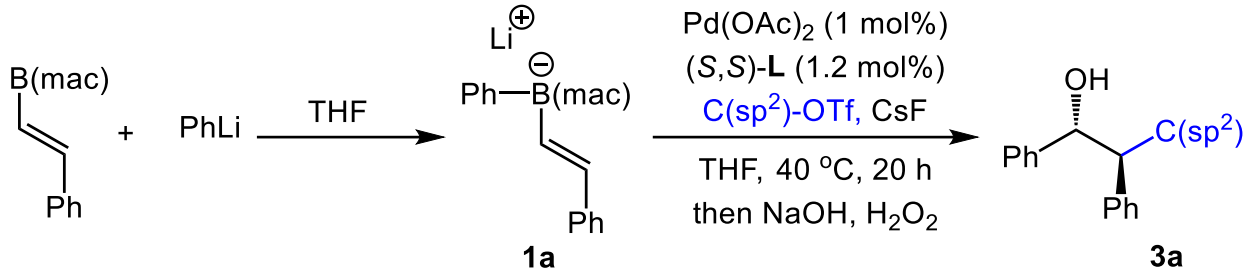
Optimization of the Reaction Parameters

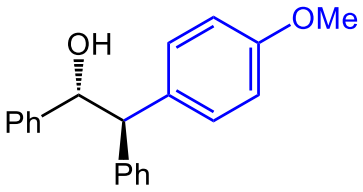


Entry[a]	BL_2	**3a**:**4**[b]	**3** Yield (%)[c]	d.r.[b]	Ee (%)[d]
1	L1	1:5.8	13	>20:1	98
2	L2	1:20	<5	nd	nd
3	L3	1:2	35	>20:1	96
4	L4	1.7:1	56	>20:1	98
5	L5	1:2	30	>20:1	nd
6	L6	1:3	20	>20:1	nd
7	L7	>20:1	92	>20:1	34
8	L8	2.5:1	75	>20:1	98
9[e]	L8	4.2:1	83	>20:1	98

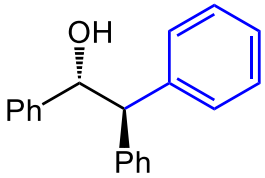
[a] Reaction conditions: **1a** (0.20 mmol), THF (1.0 mL). [b] Determined by NMR analysis. [c] Isolated yields. [d] Determined by HPLC. [e] Reaction at 40 °C and with 1 equiv of CsF.

Substrate Scope

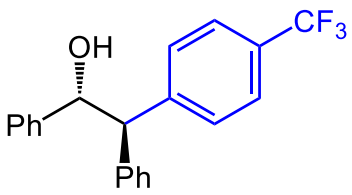




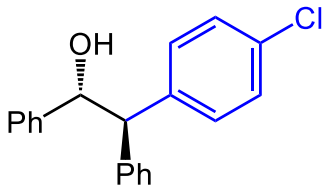
3a: 73% yield, 98% ee



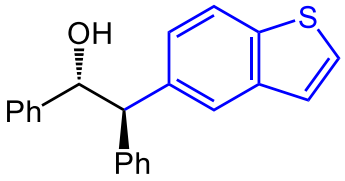
3b: 81% yield, 98% ee



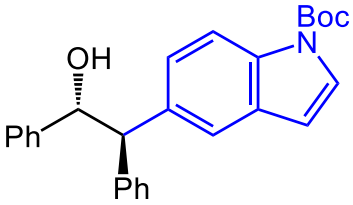
3c: 40% yield, 96% ee



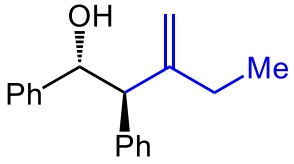
3d: 46% yield, 98% ee



3e: 43% yield, 98% ee

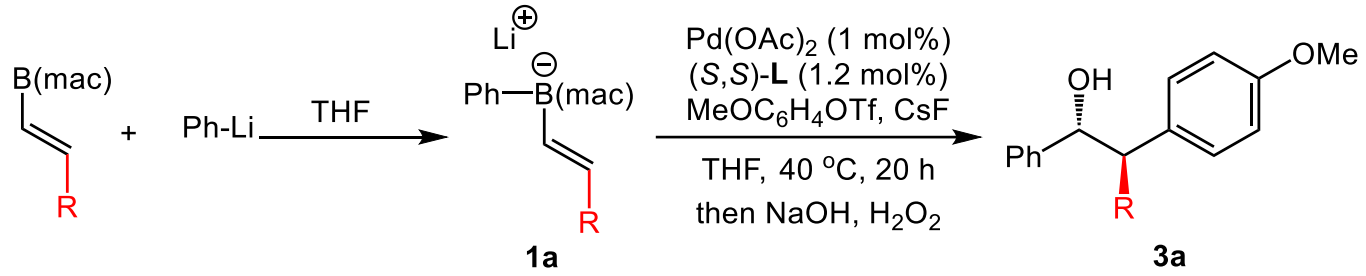


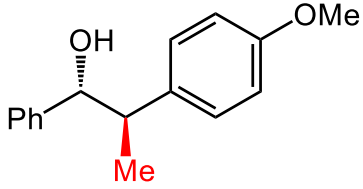
3f: 58% yield, 98% ee



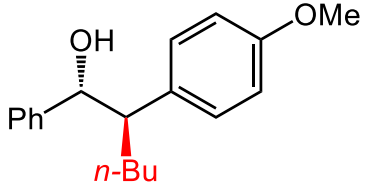
3g: 60% yield, 98% ee

Substrate Scope

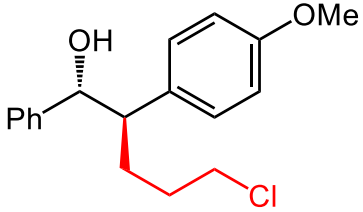




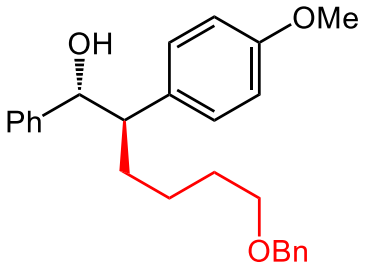
3h: 65% yield, 98% ee



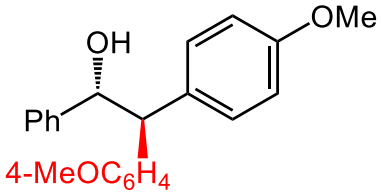
3i: 58% yield, 98% ee



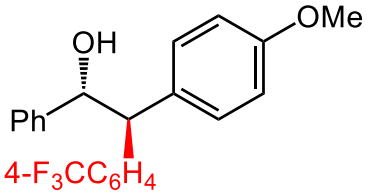
3j: 51% yield, 98% ee



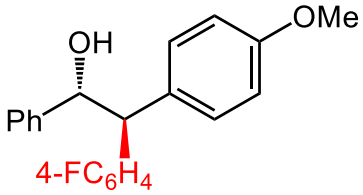
3k: 50% yield, 98% ee



3l: 46% yield, 98% ee

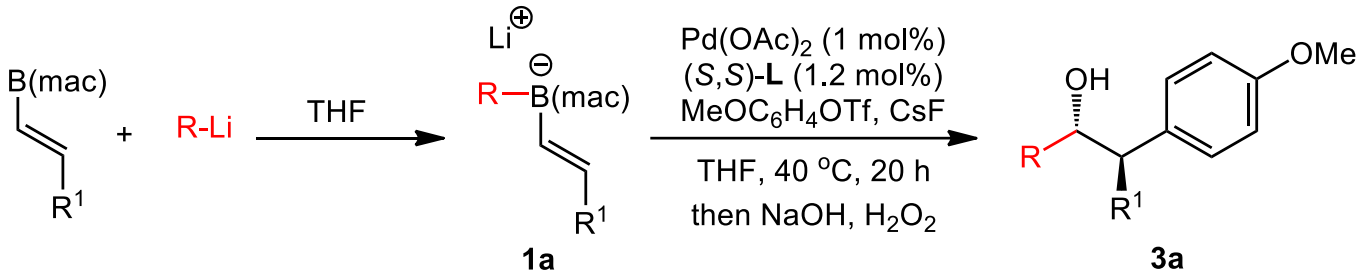


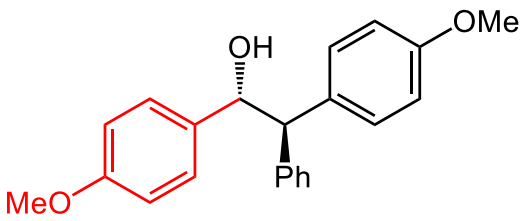
3m: 64% yield, 98% ee



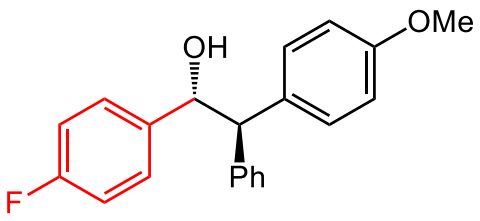
3n: 62% yield, 98% ee

Substrate Scope

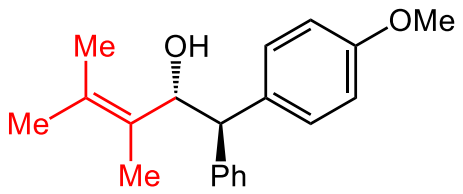




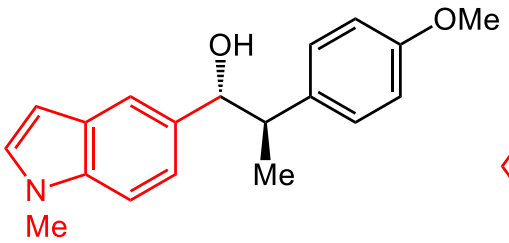
3o: 74% yield, 98% ee



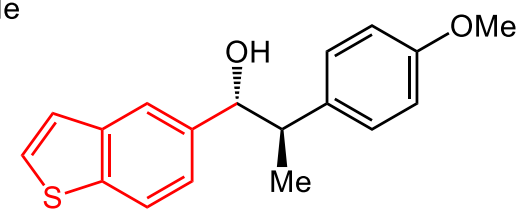
3p: 64% yield, 98% ee



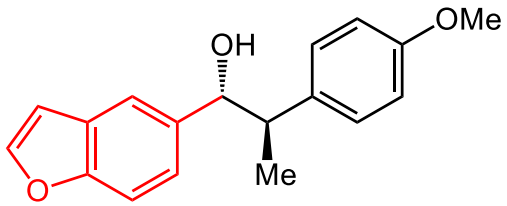
3q: 54% yield, 20% ee



3r: 64% yield, 98% ee

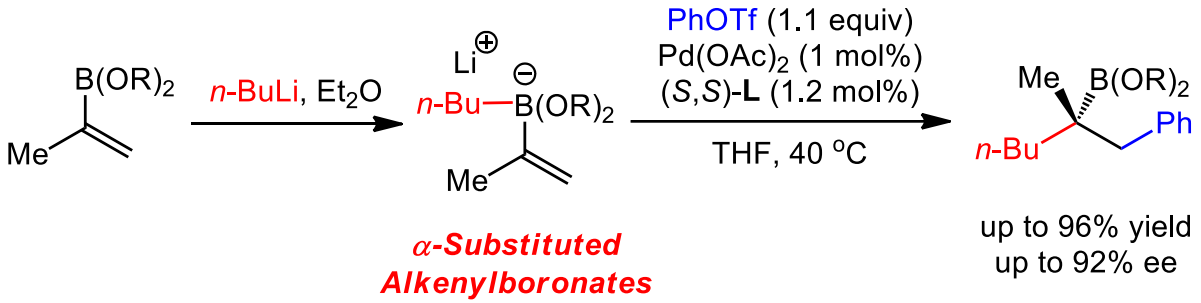


3s: 57% yield, 98% ee

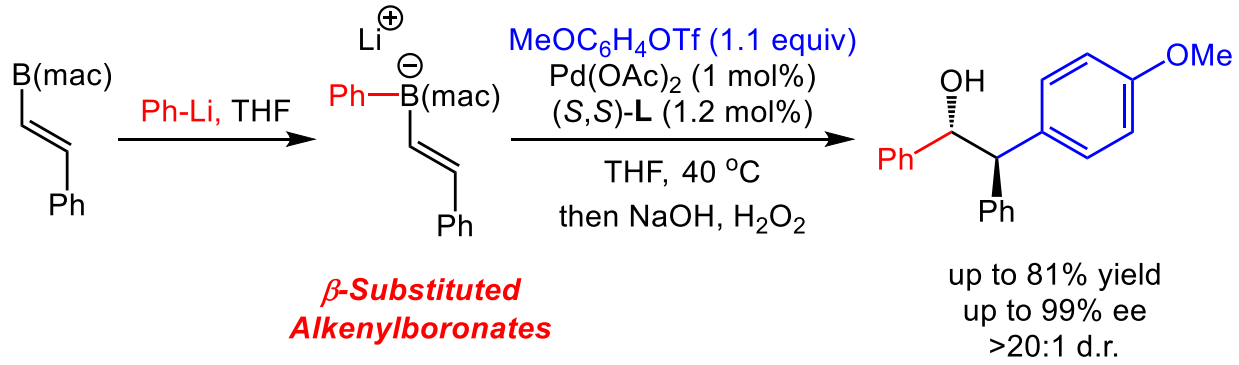


3t: 47% yield, 98% ee

Summary



Morken, J. P. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 12799.



Morken, J. P. *et al. J. Am. Chem. Soc.* **2018**, *140*, 15181.

The First Paragraph

Configurationally defined benzhydryl stereocenters are important structural motifs that appear in a broad array of natural products and therapeutic agents. Accordingly, a variety of catalytic methods have been developed to target their construction. Although recent advances in benzylic cross-coupling have provided important tools to target these features, an added synthetic challenge arises when benzylic stereocenters are sited adjacent to additional stereogenic centers. In these situations, multistep organic synthesis is often required for construction of the stereochemical dyad of interest. Our group has been developing a catalytic conjunctive cross-coupling reaction that converts vinylboron “ate” complexes and electrophiles to enantiomerically enriched secondary or tertiary alkylboronic esters bearing a single stereocenter.

The First Paragraph

To address the problem of benzhydryl construction as outlined above, we questioned whether β-substituted alkenylboronic esters might engage in conjunctive cross-coupling and deliver compounds that bear vicinal stereogenic centers. In this report, we describe the development of this process and provide insight about how the structure of boron ligands can tip the reaction outcome in favor of the conjunctive coupling product or the classic Suzuki−Miyaura product

The Last Paragraph

In summary, we have established a catalytic, diastereo-, and enantioselective conjunctive coupling of β-substituted alkenylboronic esters. This process employs an encumbered diolato ligand to control the reaction of alkenylboron “ate” complexes, tipping the reaction in favor of a metalate shift-based pathway rather than direct transmetalation. Further studies on the mechanistic origin of chemoselectivity with B(mac)-derived “ate” complexes will be reported in due course.