Palladium-Catalyzed Asymmetric Benzylic Alkylation Reactions

Reporter: Hong-Qiang Shen
Checker: Cong Liu
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Masahiro Miura
Osaka University

Masahiro Miura *et al.*
Angew. Chem. Int. Ed. **2016**, *55*, 6973.

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Introduction

Prof. Masahiro Miura

Education:

1978 B. A. Osaka University Faculty of Engineering

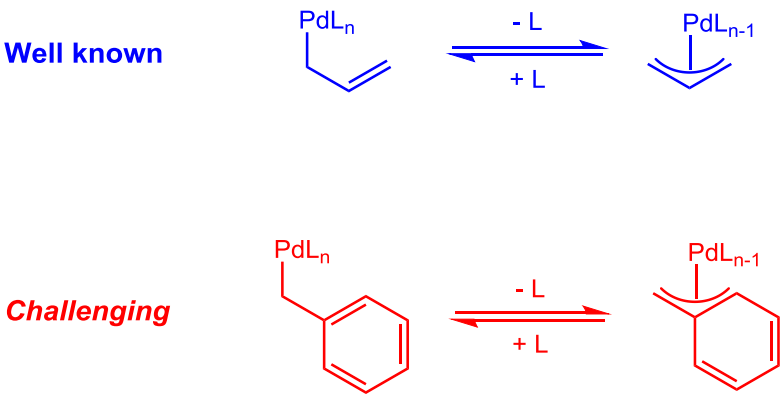
1983 Ph. D. Osaka University Graduate School

1990-1991 Humboldt Fellow with Prof. K. Griesbaum, Karlsruhe University

1998-2005 Associate Professor, Osaka University (Japan)

2005- Professor, Osaka University (Japan)

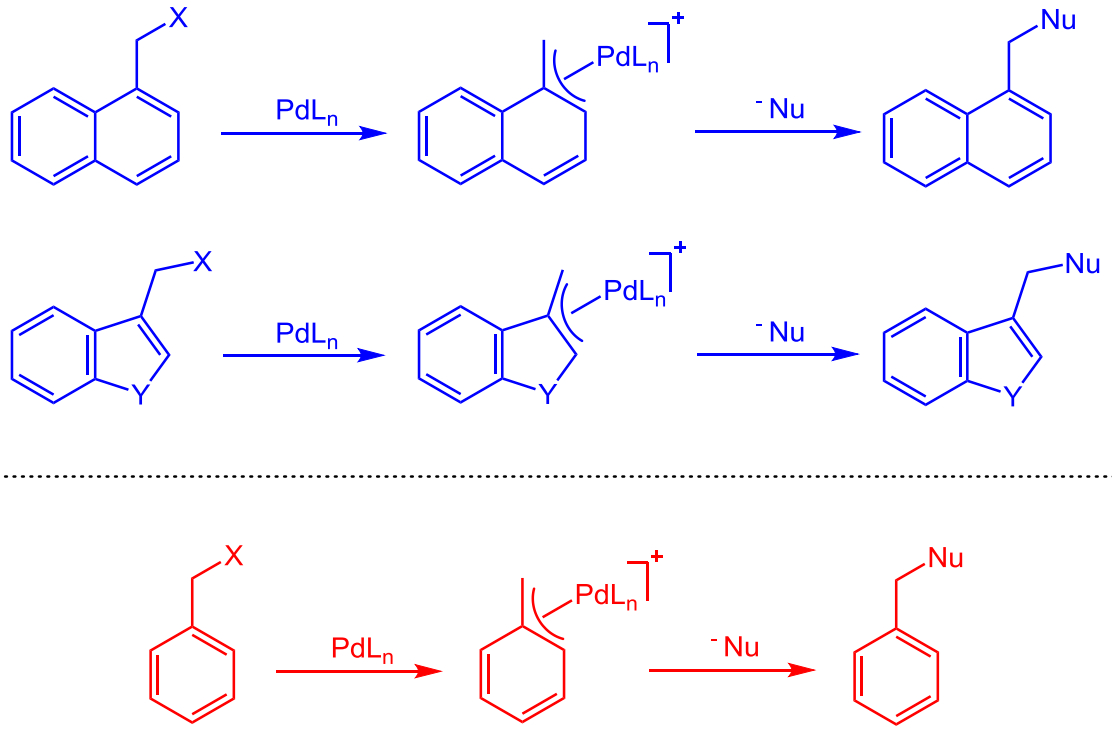
Introduction



➢ Ionization of the electrophile can be challenging since the π-benzyl intermediate is ***dearomatized.***

Trost, B. M. *et al. Angew. Chem. Int. Ed*. **2014**, *53*, 2826.

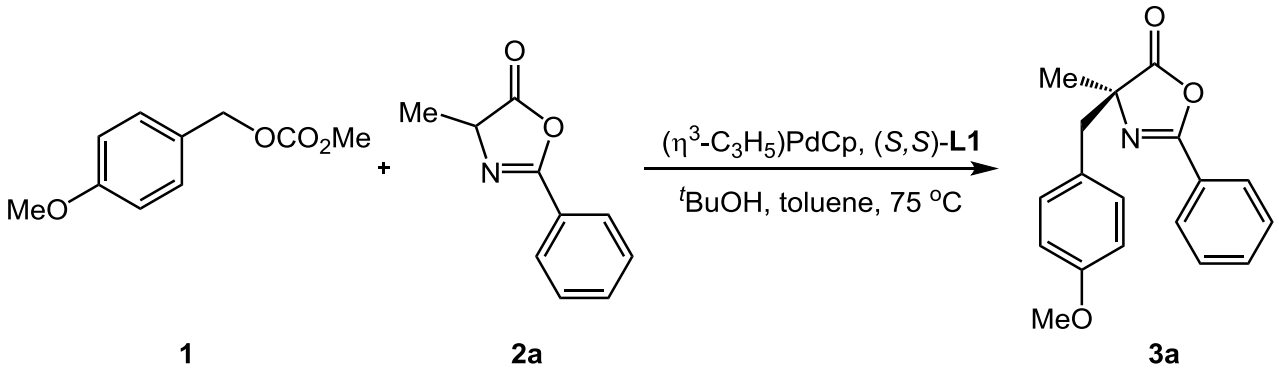
Introduction



➢ As for Electrophiles containing a ***naphthalene*** or ***heteroaromatic*** moiety, the barrier to ionization and dearomatization is lower.

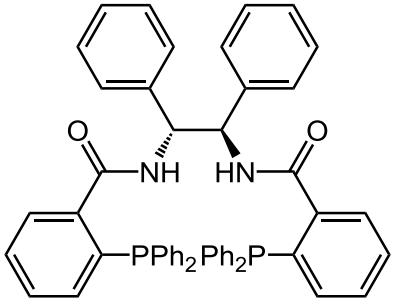
Trost, B. M. *et al. J. Am. Chem. Soc*. **2012**, *134*, 5778.

Initial Experiment



1 **2a** **3a**

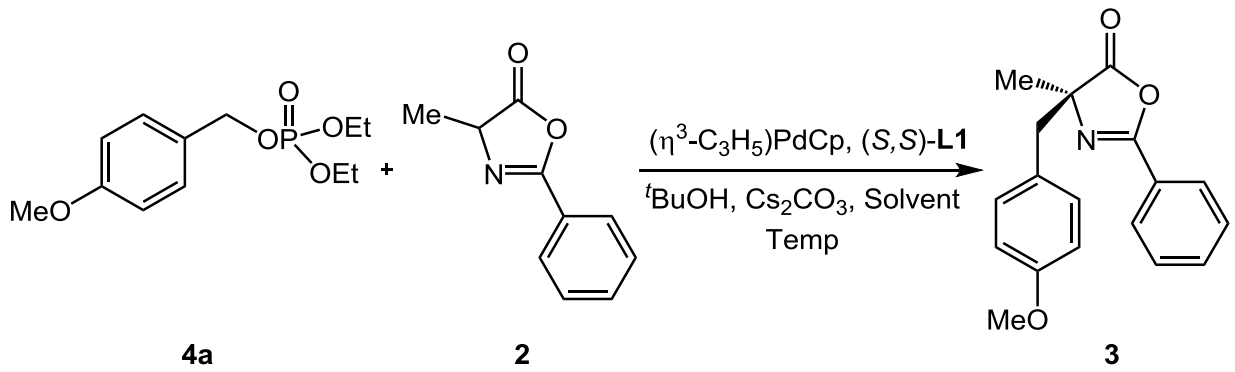
25% yield, 89% ee



(*S,S*)-**L1**

Trost, B. M. *et al. J. Am. Chem. Soc*. **2012**, *134*, 5778.

Optimization Experiments

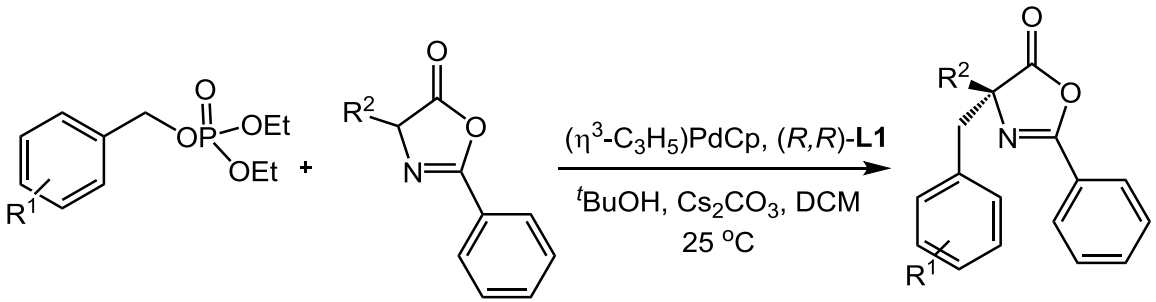


4a **2** **3**

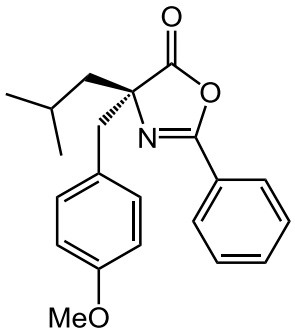
Entry	Cs_2CO_3 (equiv)	Solvent	T (°C)	Yield (%)[a]	Ee (%)[b]
1	0	Toluene	75	10	78
2	0.1	Toluene	75	25	91
3	0.1	DCM	25	23	97
4	0.5	DCM	25	63	97
5[c]	0.6	DCM	25	90	96
6[d]	0.6	DCM	25	17	88

Reaction conditions: **4a** (0.2 mmol), **2** (1.0 equiv), (η^3-C_3H_5)PdCp (5.0 mol%), **L1** (6.0 mol%), ^{t}BuOH (5.0 equiv), 20 h. [a] Isolated yield. [b] Determined by chiral HPLC. [c] **2** (1.5 equiv). [d] Reaction run without ^{t}BuOH.

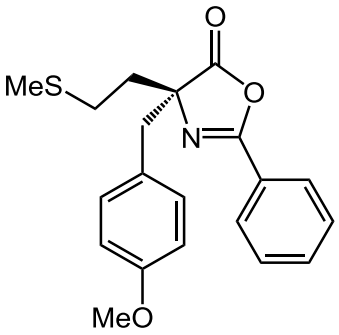
Electron-Rich Phosphates



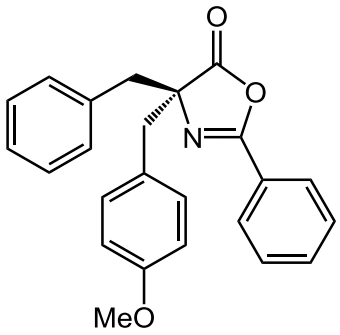
4a-f **2a-d** **3a-i**



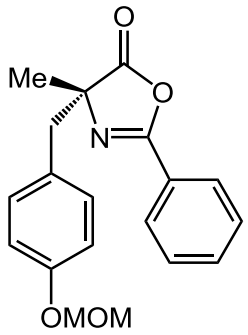
3b 65% yield, 88% ee



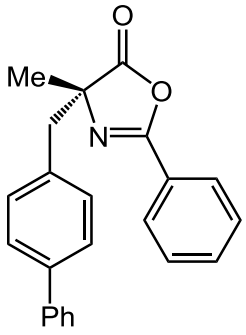
3c 86% yield, 92% ee



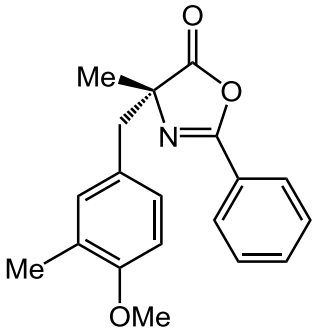
3d 78% yield, 82% ee



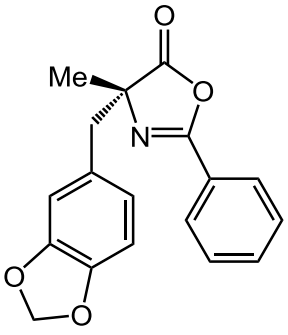
3e 94% yield, 96% ee



3f 92% yield, 91% ee

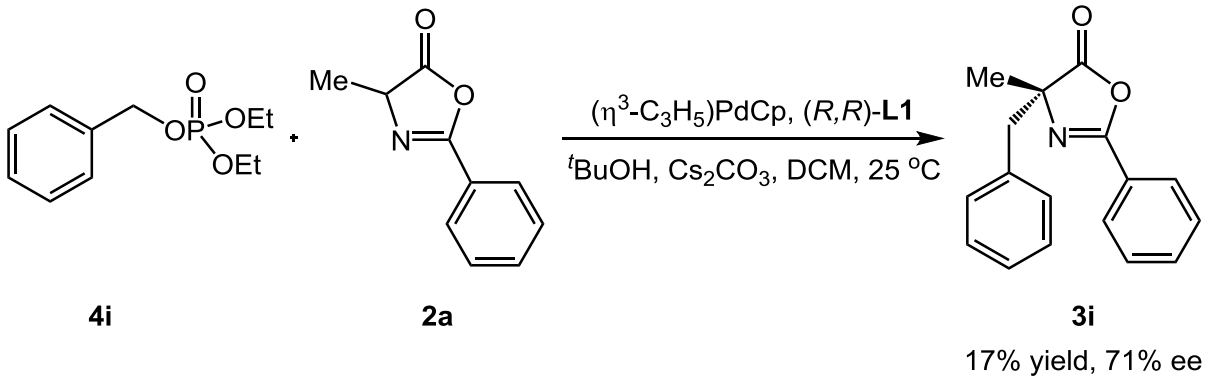


3g 99% yield, 94% ee



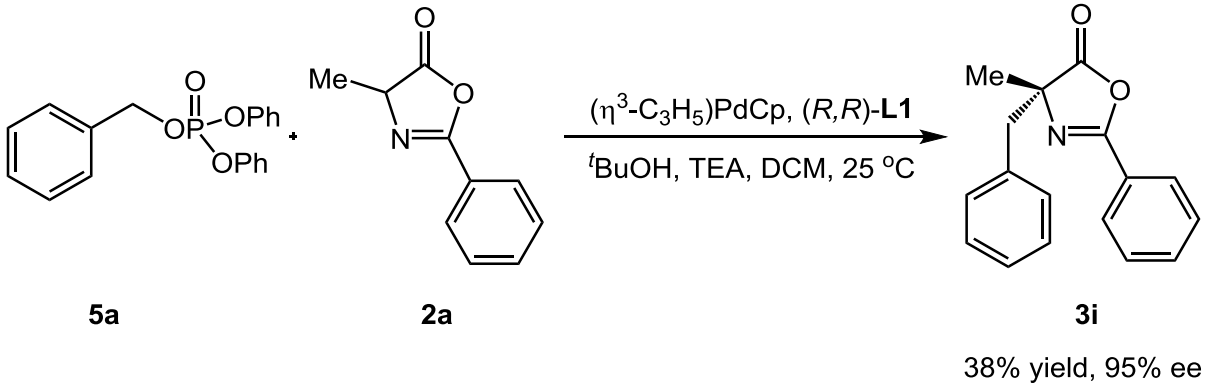
3h 83% yield, 90% ee

Optimization of Electron-Neutral Phosphates



4i **2a** **3i**

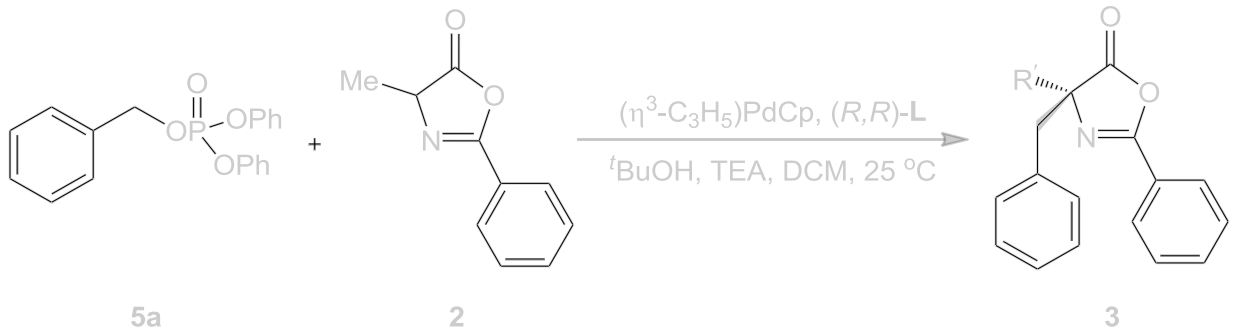
17% yield, 71% ee



5a **2a** **3i**

38% yield, 95% ee

Optimization of Electron-Neutral Phosphates

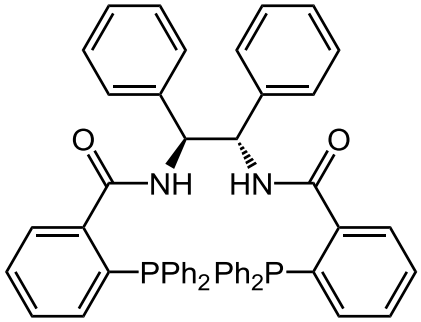


5a 2 3

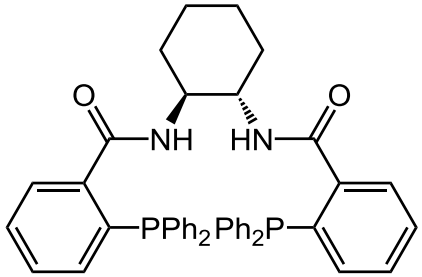
Entry	L	Solvent	T (°C)	Yield (%)[a]	Ee (%)[b]
1	L1	DCM	25	55	-94[c]
2	L2	DCM	25	53	-54[c]
3	L3	DCM	25	47	83
4	L4	DCM	25	28	59

Reaction conditions: **5a** (0.2 mmol), **2** (1.5 equiv), (η^3-C_3H_5)PdCp (5.0 mol%),**L** (6.0 mol%), TEA (1.2 equiv), ^{t}BuOH (5.0 equiv), 16 h. [a] Isolated yield. [b] Determined by chiral HPLC. [c] Reaction run with (*S,S*)-**L**.

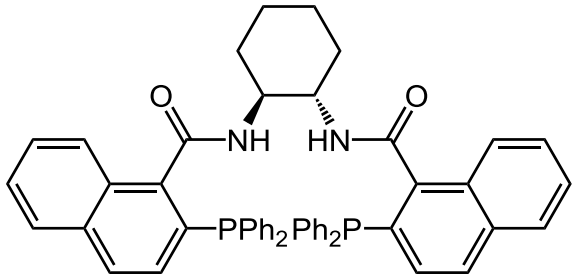
Optimization of Electron-Neutral Phosphates



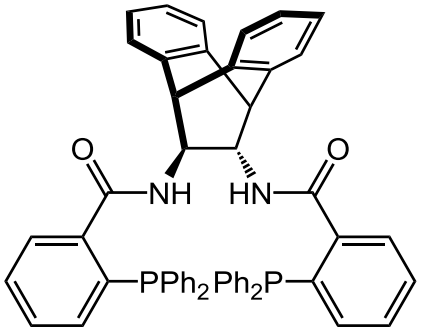
L1



L2

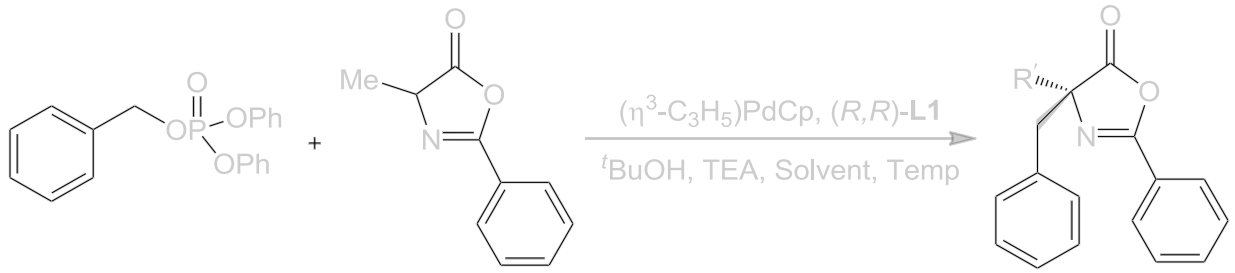


L3



L4

Optimization of Electron-Neutral Phosphates

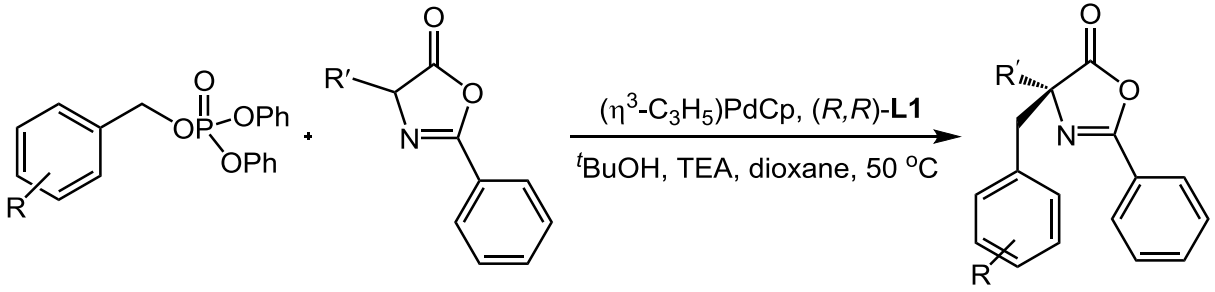


5a 2 3

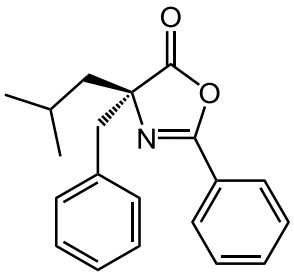
Entry	Solvent	T (°C)	Yield (%)[a]	Ee (%)[b]
1	DCM	25	55	-94[e]
2	Toluene	25	40	96
3	DME	25	23	96
4	THF	25	42	95
5	Dioxane	25	57	96
6	Dioxane	50	77	93
7[c]	Dioxane	50	83	93
8[c,d]	Dioxane	50	34	93

Reaction conditions: **5a** (0.2 mmol), **2** (1.5 equiv), (η^3-C_3H_5)PdCp (5.0 mol%),**L** (6.0 mol%), TEA (1.2 equiv), ^{t}BuOH (5.0 equiv), Solvent (0.5 mL),16 h. [a] Isolated yield. [b] Determined by HPLC. [c] Solvent (0.3 mL), [d] Reaction run without ^{t}BuOH, [e] Reaction run with (*S,S*)-**L1** .

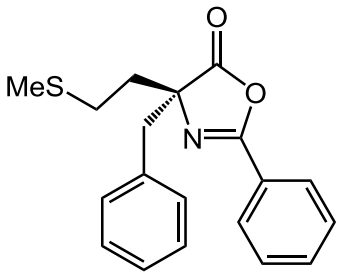
Electron-Neutral Phosphates



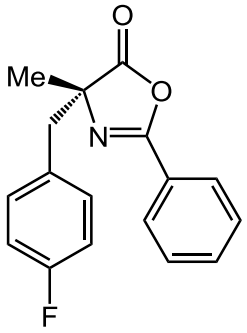
5a-f **2a-c** **3j-p**



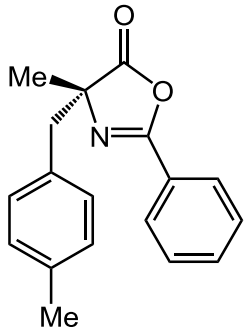
3j 88% yield, 93% ee



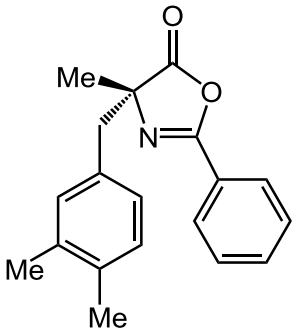
3k 80% yield, 85% ee



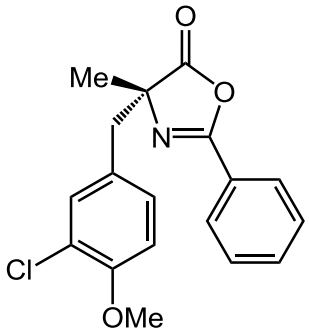
3l 74% yield, 94% ee



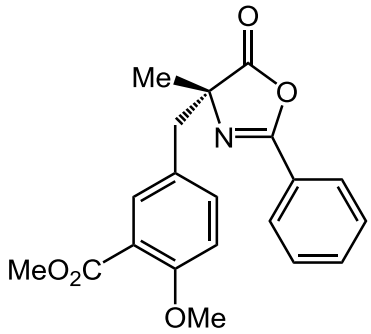
3m 91% yield, 95% ee



3n 87% yield, 93% ee

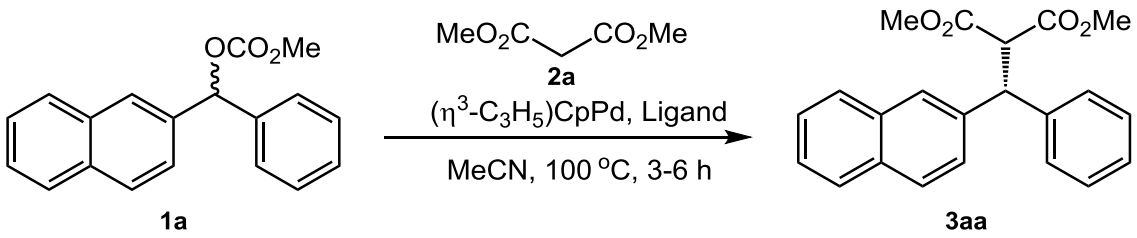


3o 82% yield, 84% ee



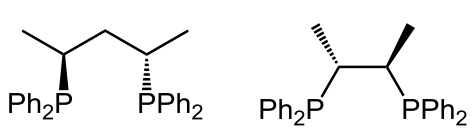
3p 79% yield, 78% ee

Ligand Screening



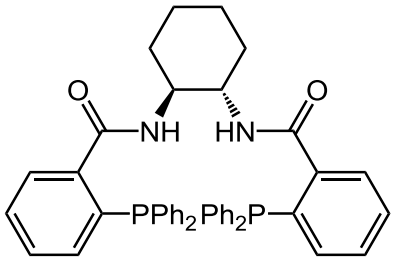
1a

3aa

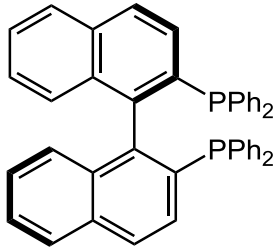


(*S,S*)-BDPP
89%, 26% ee

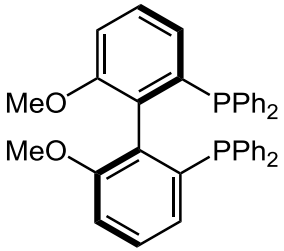
(*R,R*)-Chiraphos
9%, n.d.



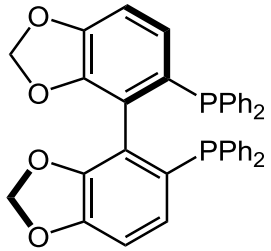
(*R,R*)-DPPBA
0%, n.d.



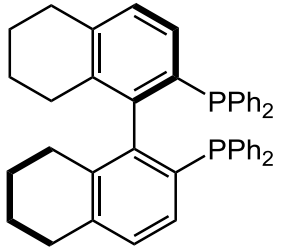
(*R*)-BINAP
94%, 54% ee



(*R*)-MeO-BIPHEP
90%, 50% ee



(*R*)-SEGPHOS
61%, 64% ee



(*R*)-H_8-BINAP
40%, 64% ee

Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), MeCN (3.0 mL), (η^3-C_3H_5)CpPd (2.5 mol%), Ligand (2.5 mol%), 100 °C, 3-6 h. n.d. = not determined.

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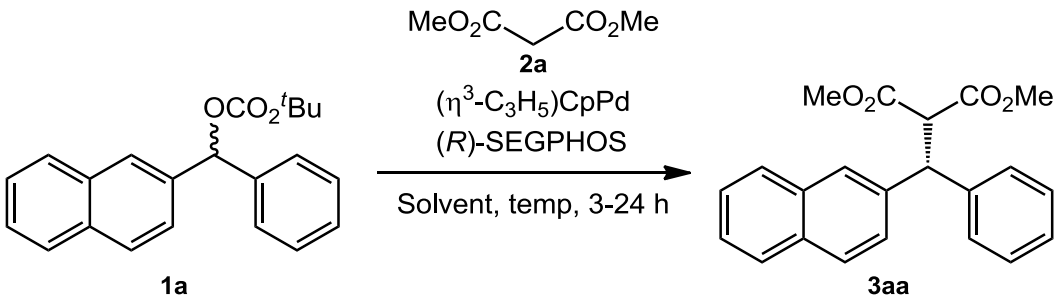
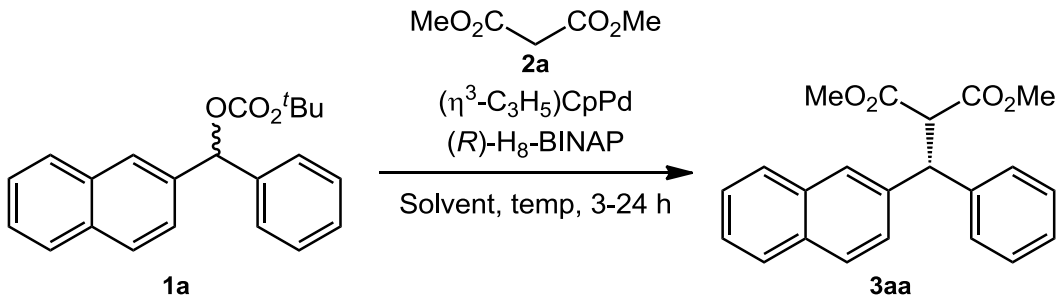
Optimization Experiments



Entry	Solvent	Temp (°C)	Yield[a] (%)	Ee[b] (%)
1	MeCN	80	52	74
2	DMSO	80	31	74
3	MeCN	60	(4)	n.d.
4	DMSO	60	(9)	n.d.
5[c]	MeCN	60	91	40
6[c]	DMSO	60	95	88

Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), (η^3-C_3H_5)PdCp (2.5 mol%), Ligand (2.5 mol%), Solvent (3.0 mL), 3-24 h. [a] Isolated yields are shown, yields estimated by GC are in parenthese. [b] Determined by chiral HPLC, n.d. = not determined. [c] (η^3-C_3H_5)PdCp (5.0 mol%), Ligand (5.0 mol%).

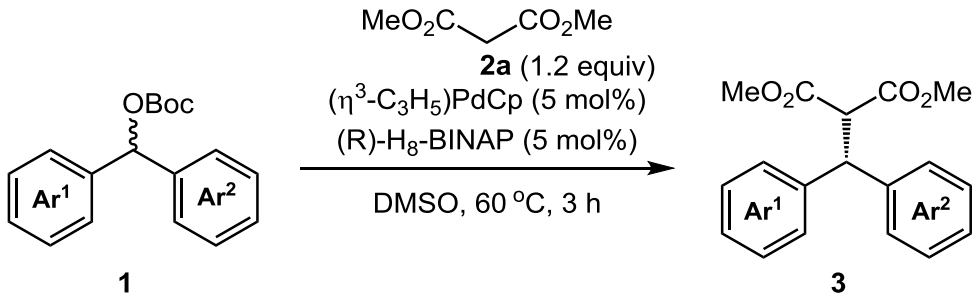
Optimization Experiments

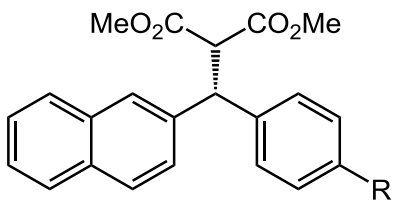


Entry	Solvent	Temp (°C)	Yield[a] (%)	Ee[b] (%)
1	MeCN	80	76	70
2	DMSO	80	98	84
3	MeCN	60	(13)	n.d.
4	DMSO	60	19	n.d.
5[c]	MeCN	60	89	80
6[c]	DMSO	60	97	90

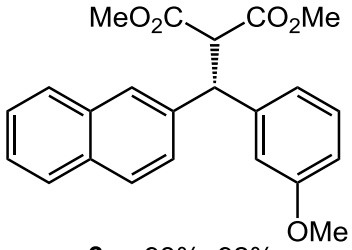
Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), (η^3-C_3H_5)PdCp (2.5 mol%), Ligand (2.5 mol%), Solvent (3.0 mL), 3-24 h. [a] Isolated yields are shown, yields estimated by GC are in parenthese. [b] Determined by chiral HPLC, n.d. = not determined. [c] (η^3-C_3H_5)PdCp (5.0 mol%), Ligand (5.0 mol%).

Substrate Scope

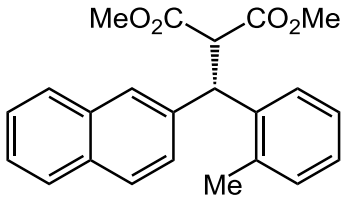




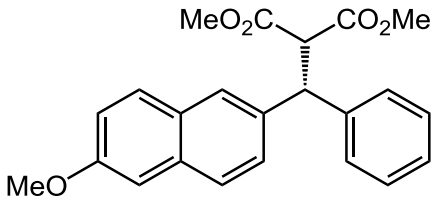
R = H: **3aa** 97 %, 90% ee.
R = OMe: **3ba** 99%, 86% ee.
R = CF_3: **3ca** 93%, 84% ee.
R = Cl: **3da** 86%, 82% ee.



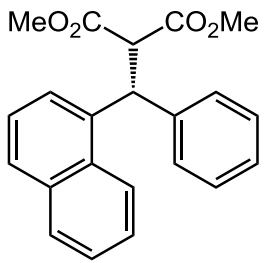
3ea 93%, 92% ee



3fa 68%, 90% ee
80 °C, 12 h

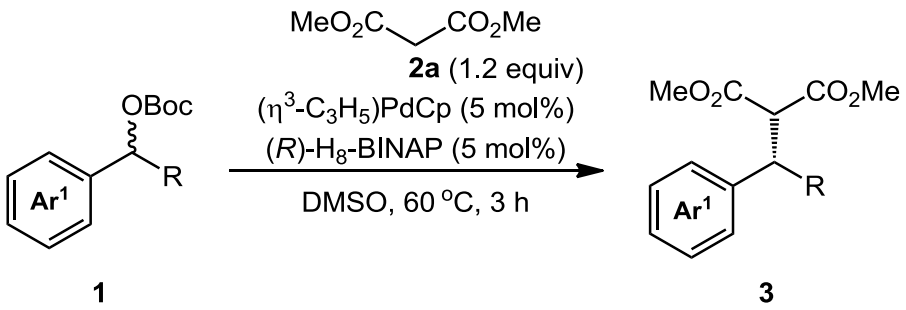


3ga 93%, 88% ee

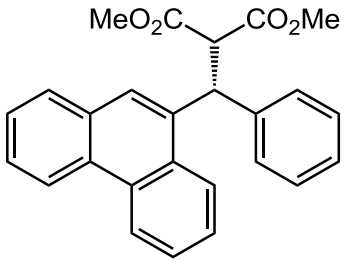


3ha 48%, 80% ee, **24h**

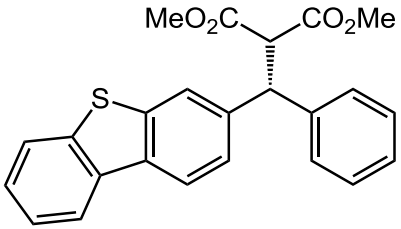
Substrate Scope



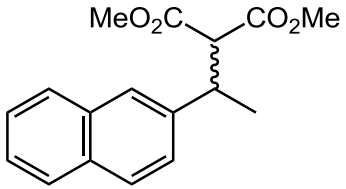
1 **3**



3ia 99%, 96% ee

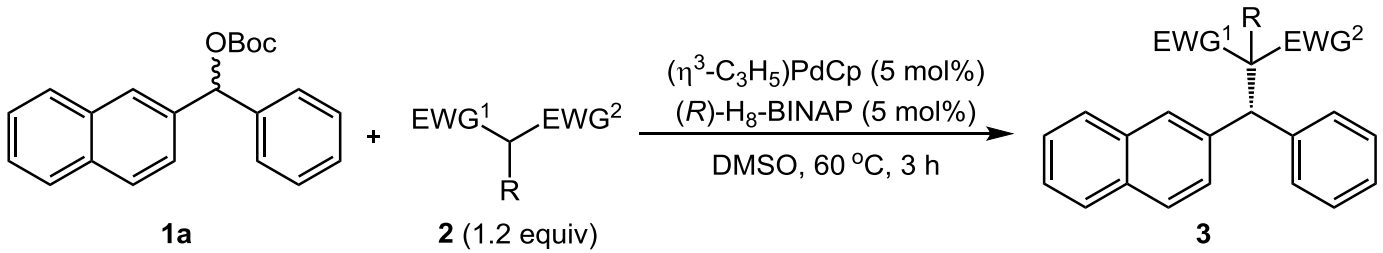


3ja 69%, 68% ee
(10 mol% catalyst)



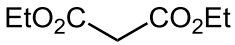
3ka 90%, 0% ee

Substrate Scope

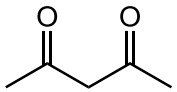


1a + **2** (1.2 equiv) → **3**

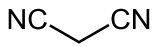
Representative active methylene compounds



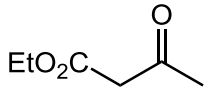
87%, 90% ee



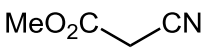
71%, 86% ee



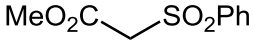
79%, 88% ee



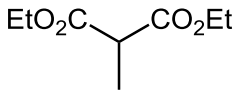
76%, 82% ee, 1:1 dr



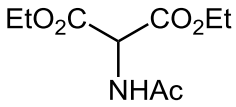
88%, 88% ee, 1:1 dr



61%, 88% ee, 1:1 dr

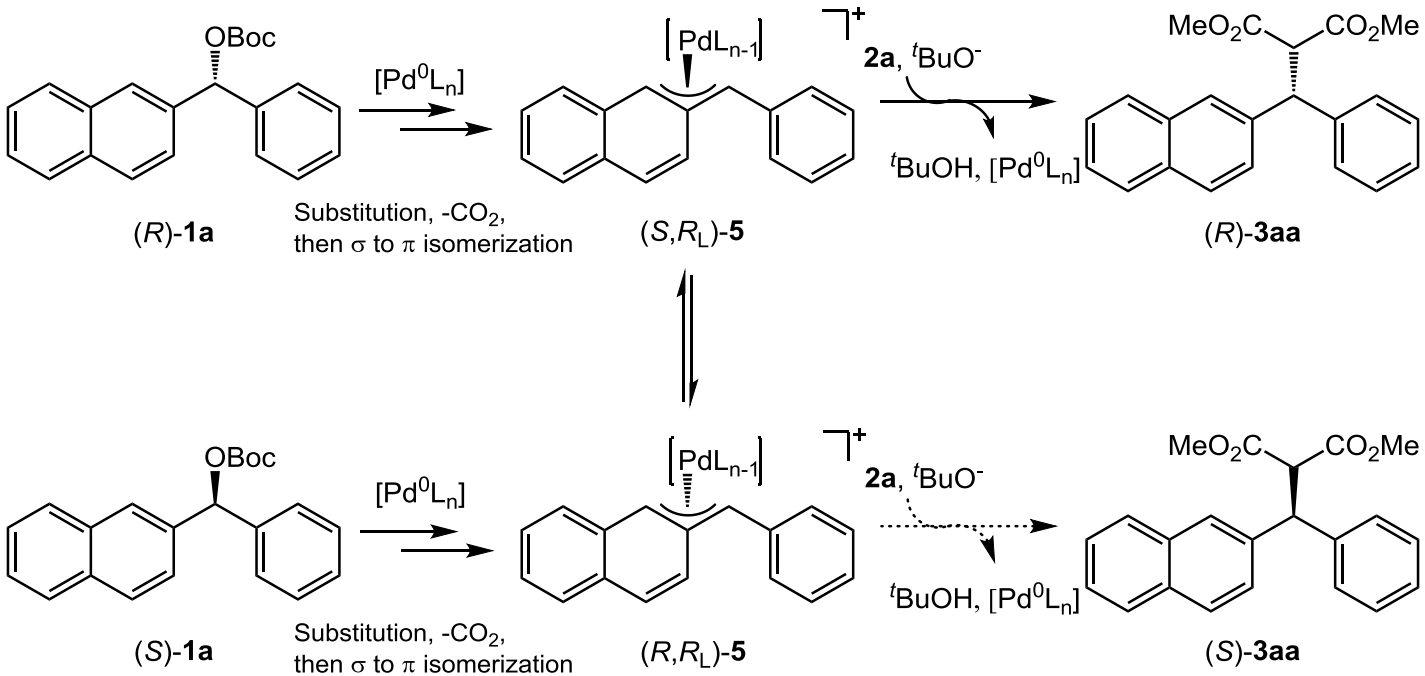


70%, 78% ee

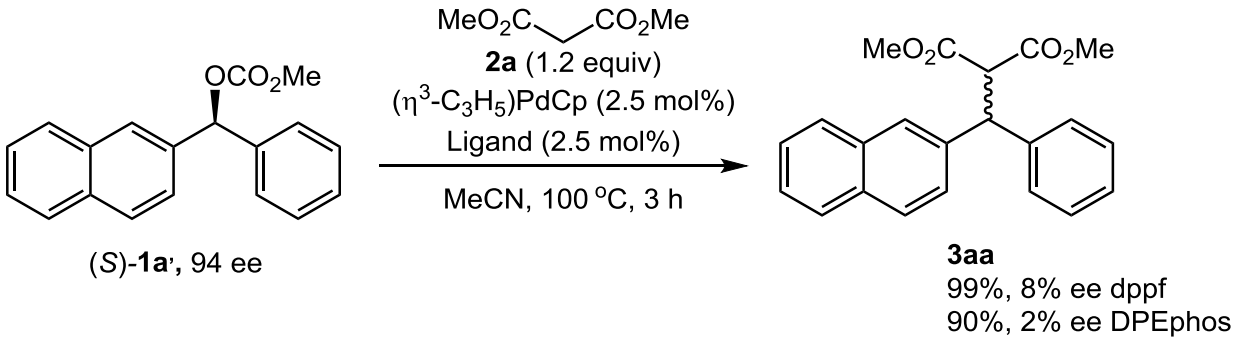


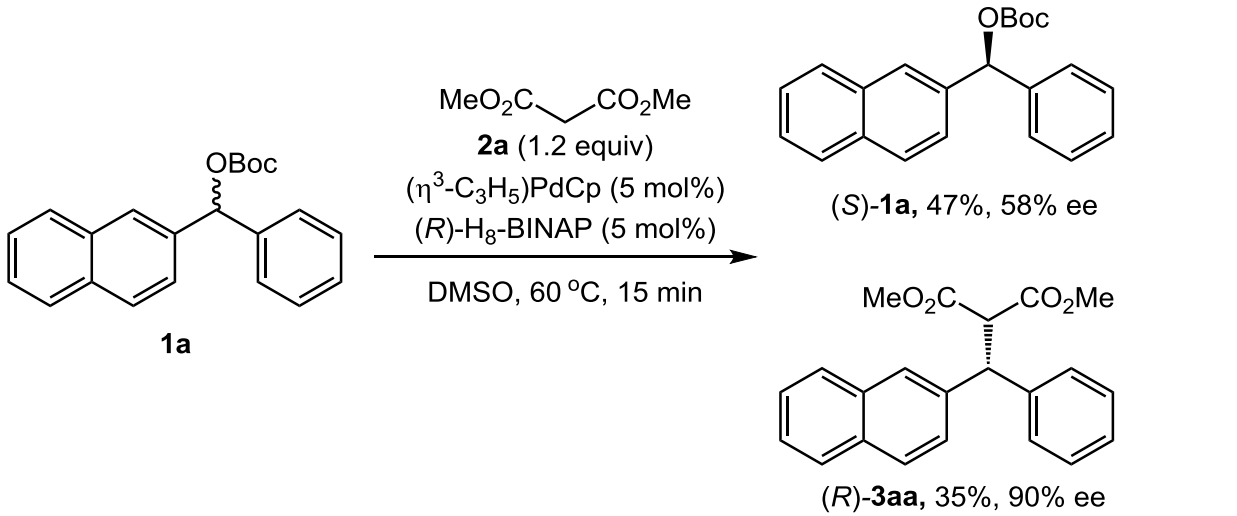
83%, 86% ee

Plausible Mechanism



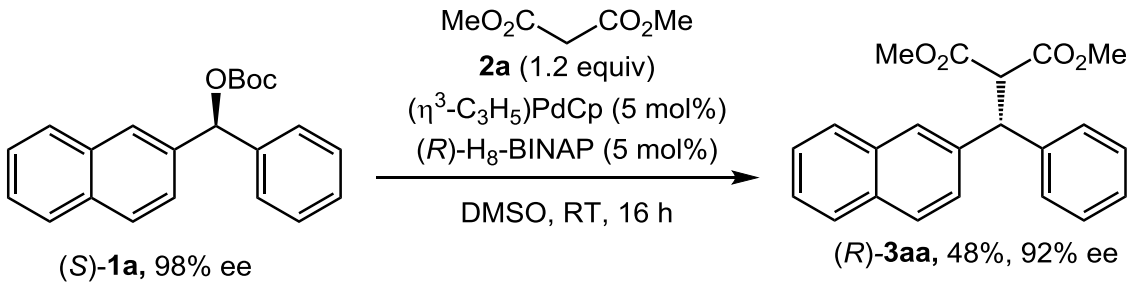
Control Experiments





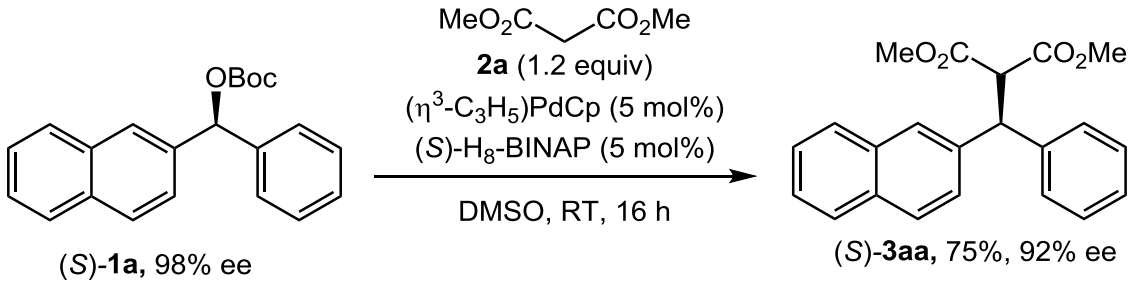
- The racemization proceeds smoothly, and no enantiospecific reaction occurs.
- The substrate-dependent partial kinetic resolution occurs in the substitution step.
- Stereochemistry is controlled by the catalyst in the final C-C forming event.

Control Experiments



(*S*)-**1a,** 98% ee

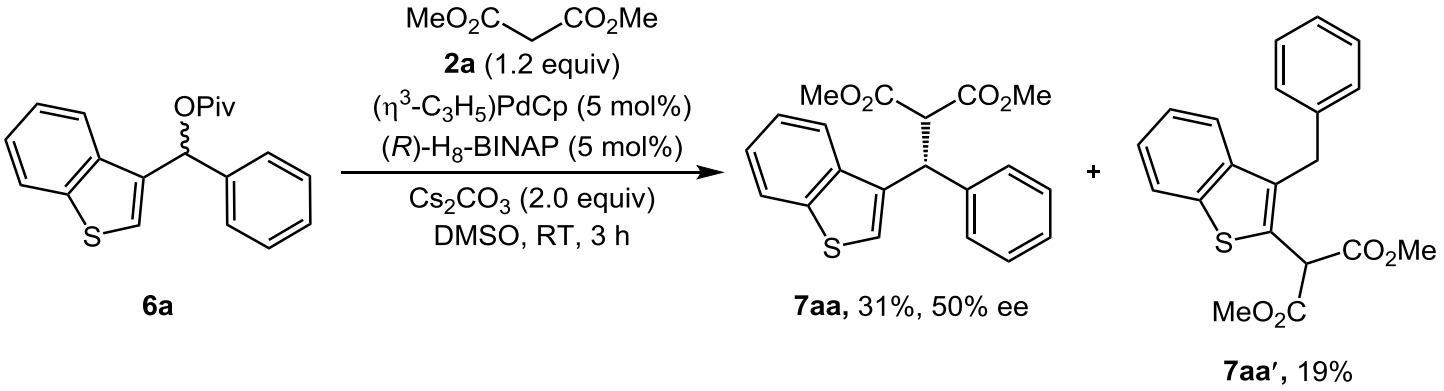
(*R*)-**3aa,** 48%, 92% ee



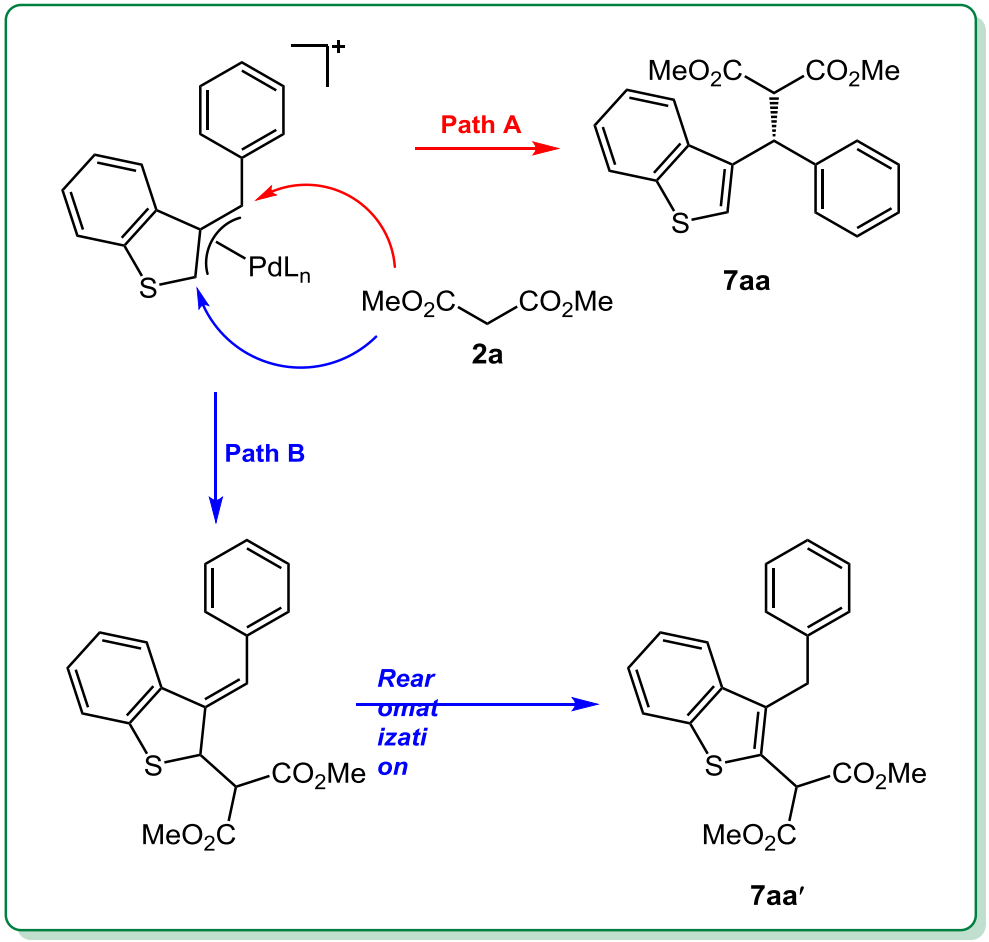
(*S*)-**1a,** 98% ee

(*S*)-**3aa,** 75%, 92% ee

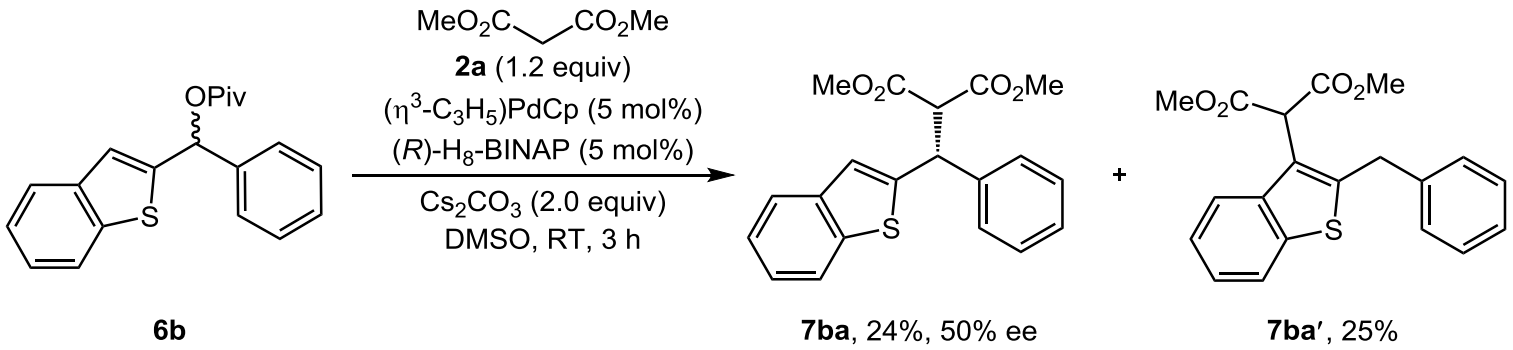
Naphthalene limitation



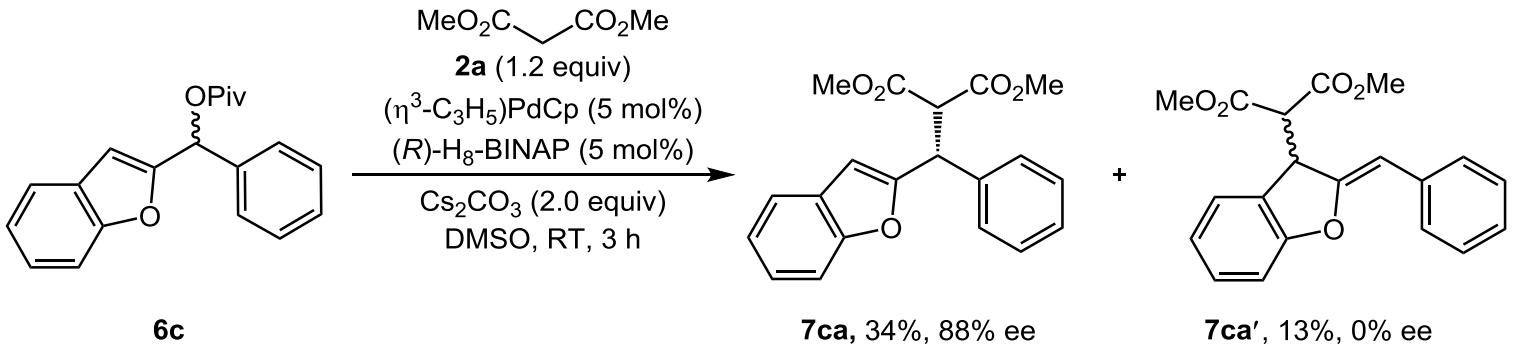
Naphthalene limitation



Naphthalene limitation



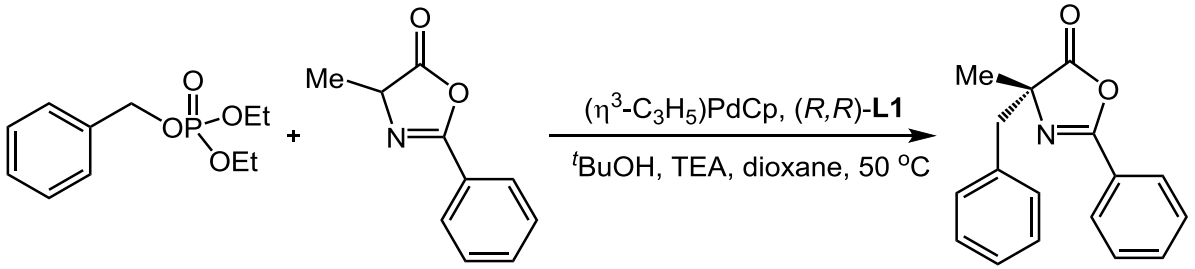
6b **7ba**, 24%, 50% ee **7ba′**, 25%



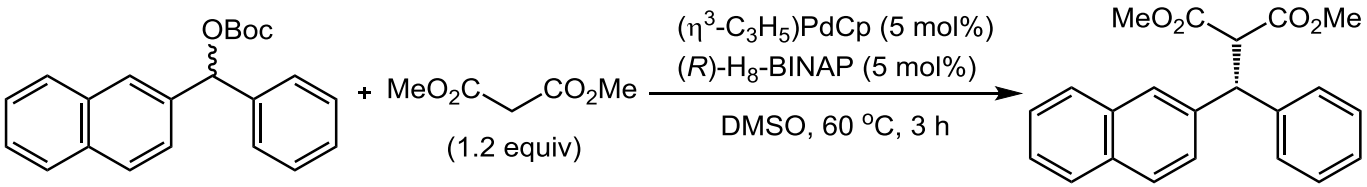
6c **7ca,** 34%, 88% ee **7ca′**, 13%, 0% ee

Summary

Trost's Work: Achiral primary benzylic carbonates or phosphates



Miura's Work: Racemic secondary benzyl electrophiles



Palladium-catalyzed cross-coupling reactions are one of the most powerful and reliable synthetic tools for the construction of versatile carbon frameworks in modern organic chemistry. Among them, the asymmetric allylic alkylation with allylic electrophiles via π-allylpalladium intermediates (Tsuji-Trost reaction) has been extensively studied and applied to the synthesis of various complex natural products and bioactive molecules. In contrast, the asymmetric benzylic alkylation with benzylic electrophiles via π-benzylpalladium intermediates has been less developed despite its isoelectronic character to the π-allylpalladium. Although related asymmetric palladium catalysis with prochiral nucleophiles and achiral primary benzylic carbonates or phosphates were recently reported by Trost and Czabaniuk, a dynamic kinetic asymmetric transformation (DYKAT) with racemic secondary benzyl electrophiles still remains largely elusive.

In conclusion, we have developed a Pd/(*R*)-H_8-BINAP catalyzed asymmetric benzylic alkylation of active methylene compounds with racemic diarylmethyl carbonates and pivalates. To the best of our knowledge, this is the first successful example of the dynamic kinetic asymmetric transformation (DYKAT) of secondary benzylic electrophiles via π-benzylpalladium intermediates. The present results provide an enantioconvergent approach to optically active benzylic alkylation products from racemic benzyl alcohol derivatives and prompt further development of related asymmetric catalysis based on the DYKAT process of secondary benzyl electrophiles. Expansion of the scope of nucleophiles and overcoming the “naphthalene limitation” are currently underway in our laboratory.