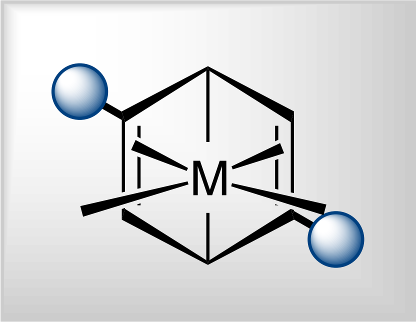
Chiral Olefins as Ligands for Asymmetric Catalysis



Hui-Wen Shih

Group Meeting

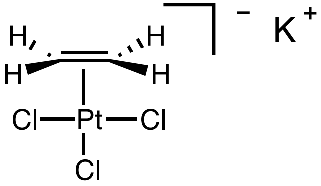
April 20, 2011

Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

Defieber, C.; Grutzmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

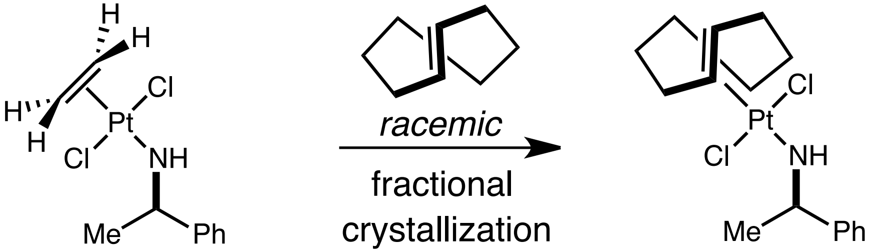
A Brief History

- 1827: Zeise reports first metal-olefin complex



Zeise's salt

- 1962: Cope prepares the first chiral olefin

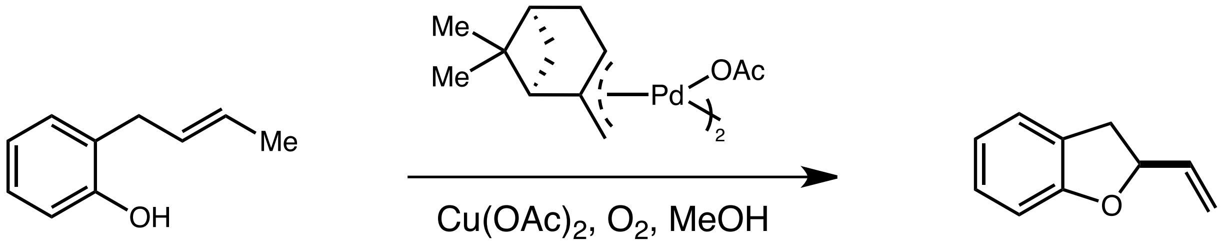


Zeise, W. C. *Poggendorffs Ann. Phys.* **1827**, *9*, 632.

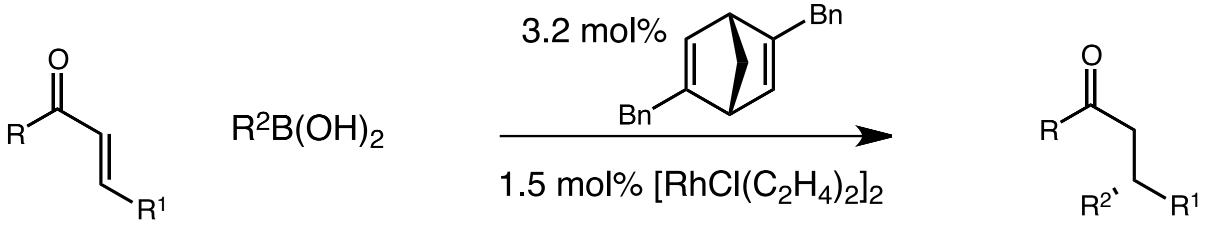
Cope, A. C.; Howell, C. F.; Knowles, A. *J. Am. Chem. Soc.* **1962**, *84,* 3191.

A Brief History

- 1981: Hosokawa and Murahashi develop catalytic asymmetric reaction with chiral allyl ligand



- 2003: Field begins to accelerate with Hayashi's report of chiral diene ligands in rhodium catalysis

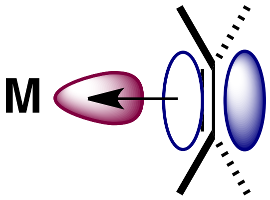


Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

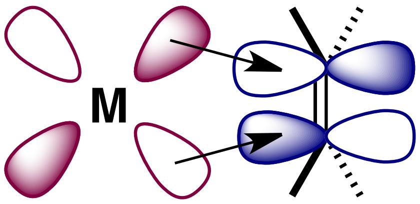
Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11509.

Metal-Olefin Binding

■ Dewar–Chatt–Duncanson model



σ donation



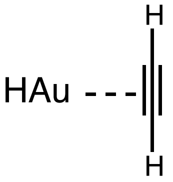
π back-donation

Metal-olefin bond strength is determined by π back-bonding

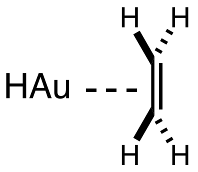
Back-donation increases with metal principle quantum number

■ Comparison of ligand binding energies, ΔE_{int}

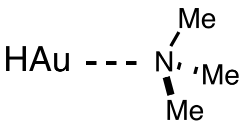
$$\mathrm{HAu{-}L} \xrightarrow{-\Delta E_{\mathrm{int}}} \mathrm{HAu^{*}} \qquad \mathrm{L^{*}}$$



26.6



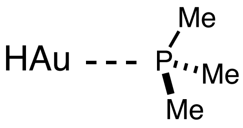
27.6



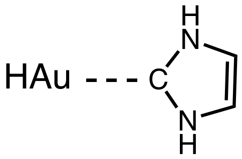
29.9

HAu - - - C≡O

34.2



43.8



52.7

Defieber, C.; Grutzmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

Metal-Olefin Binding

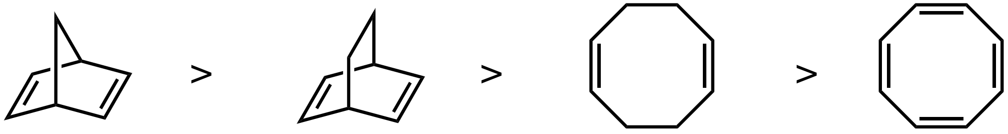
- Olefins have large preparation energies for binding

$$X_nM{-}L \xrightarrow{-\Delta E_{int}} X_nM \qquad L^* \xrightarrow{\Delta E_{prep}} L^*$$

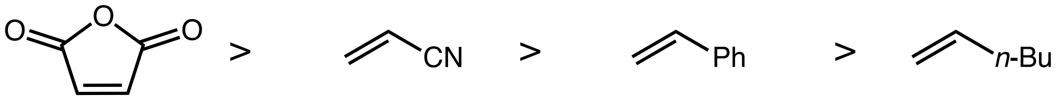
$$\Delta E_{prep} \begin{cases} \text{double bond elongation} \\ sp^2 \text{ to } sp^3 \text{ rehybridization} \end{cases}$$

- Factors that affect binding strength

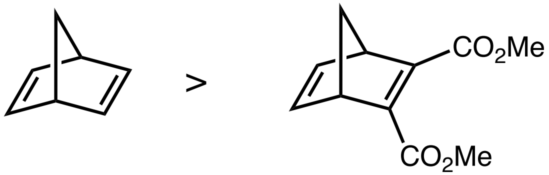
strain release
entropy



substituent electronics



sterics

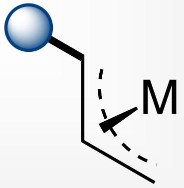


Hartley, F. R. *Chem. Rev.* **1973**, *73*, 163.

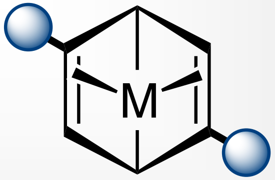
Tolman, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 2780.

Defieber, C.; Grutzmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

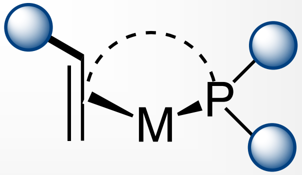
Classes of Chiral Olefins



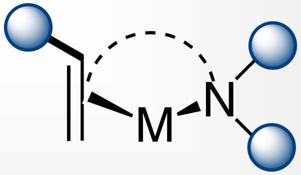
π-allyl



diene

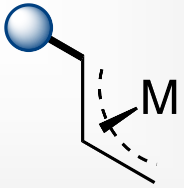


phosphane-olefin



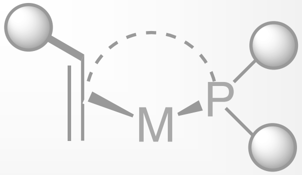
amine-olefin

Classes of Chiral Olefins

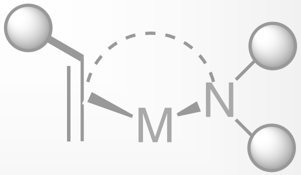


π-allyl

diene



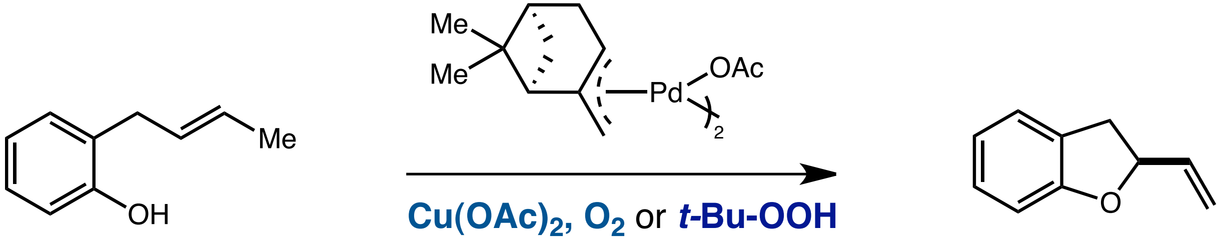
phosphane-olefin



amine-olefin

Chiral Allyl Ligands

- 1981: First catalytic asymmetric reaction (Hosokawa and Murahashi, Osaka University)

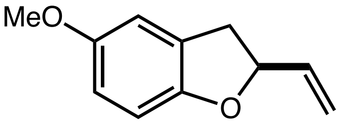


$Cu(OAc)_2$, O_2 or ***t*-Bu-OOH**

MeOH

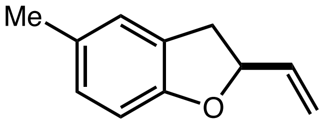
64% Y, 18% ee

43% Y, 17% ee



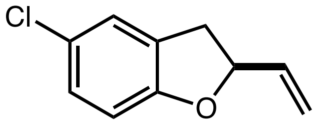
37% Y, 26% ee

16% Y, 22% ee



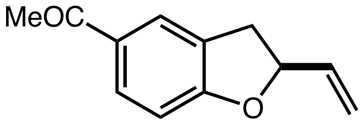
63% Y, 21% ee

28% Y, 18% ee



65% Y, 6% ee

47% Y, 5% ee



71% Y, 1% ee

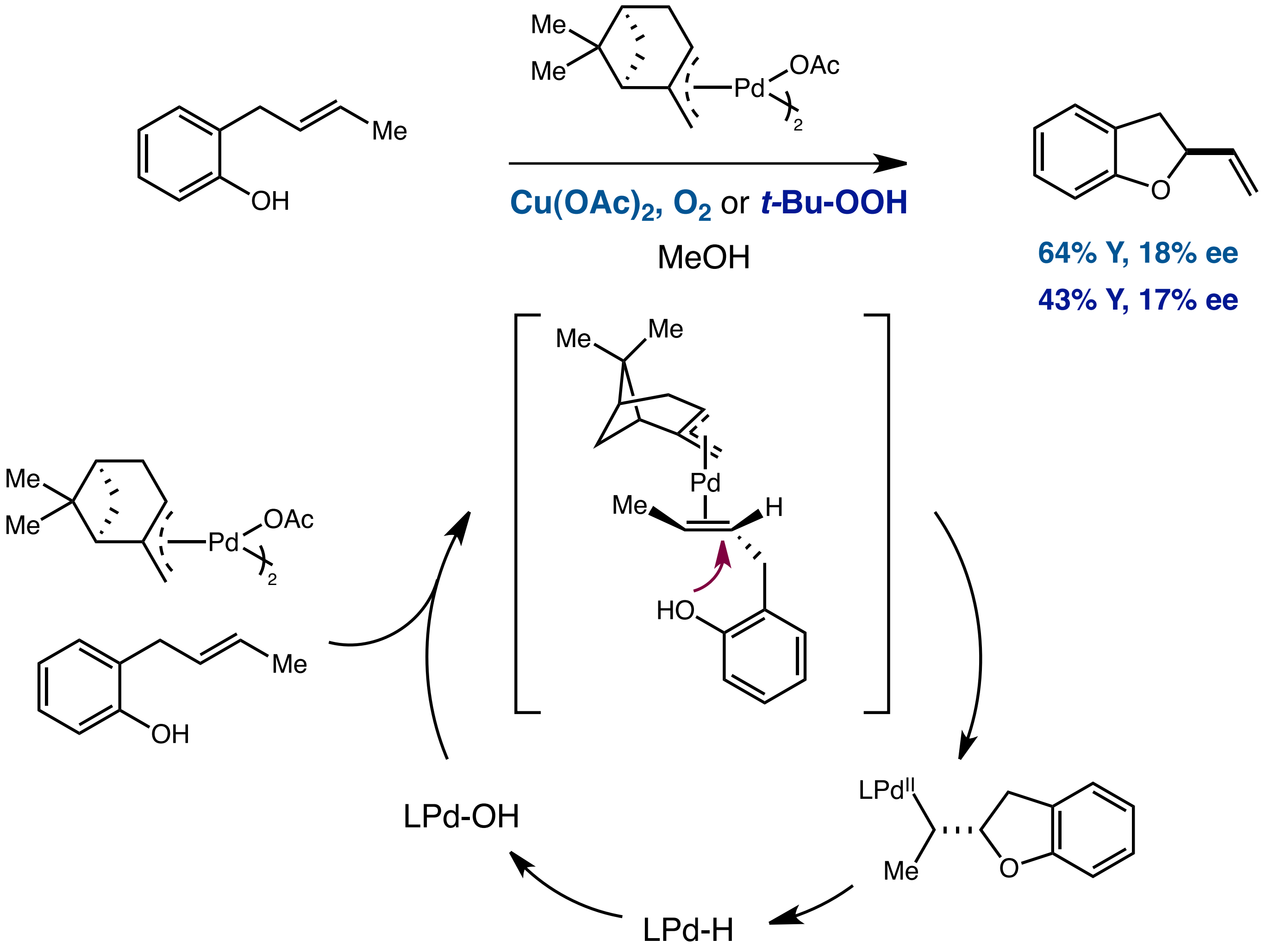
38% Y, 0.1% ee

Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

Chiral Allyl Ligands

- 1981: First catalytic asymmetric reaction (Hosokawa and Murahashi, Osaka University)



$Cu(OAc)_2$, O_2 or ***t*-Bu-OOH**

MeOH

64% Y, 18% ee

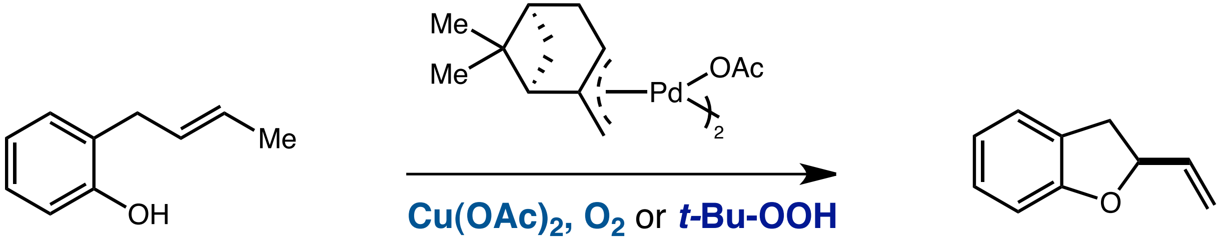
43% Y, 17% ee

Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

Chiral Allyl Ligands

- 1981: First catalytic asymmetric reaction (Hosokawa and Murahashi, Osaka University)

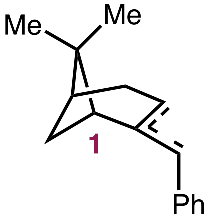


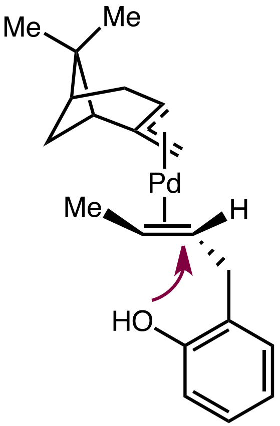
Cu(OAc)$_2$, O$_2$ or ***t*-Bu-OOH**

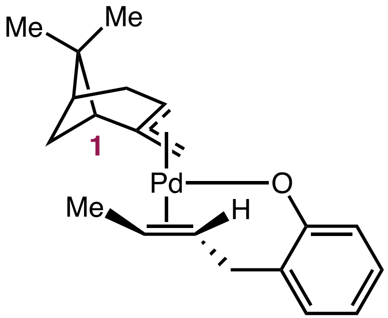
MeOH

64% Y, 18% ee

43% Y, 17% ee







Modified catalyst
Phenyl blocks space under C-1
no enantioselectivity

Me sits in space under C-1 bridgehead
olefin is trans to ligand
attack occurs from back face

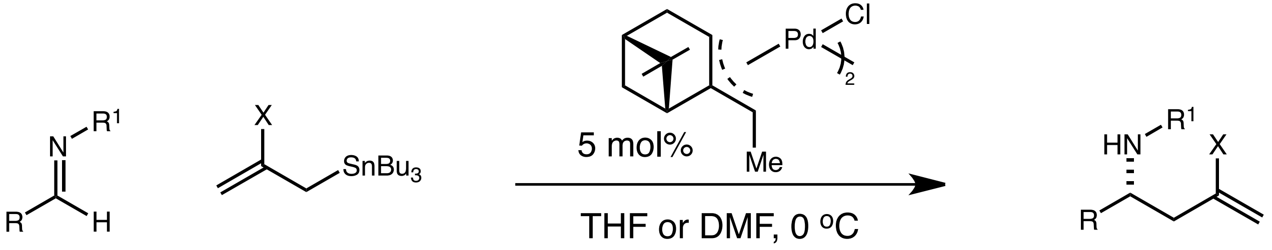
Phenoxy coordination
generates opposite enantiomer

Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

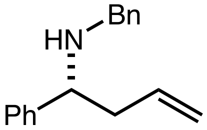
Chiral Allyl Ligands

- Yamamoto: Pd-allyl complexes for enantioselective allylation

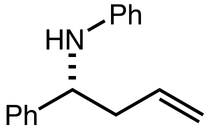


5 mol%

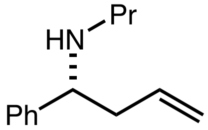
THF or DMF, 0 °C



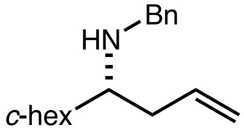
62% Y, 81% ee



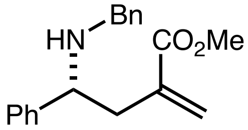
74% Y, 0% ee



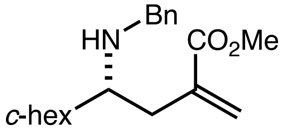
62% Y, 70% ee



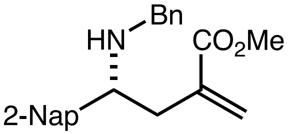
64% Y, 40% ee



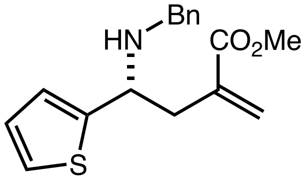
81% Y, 82% ee



63% Y, 60% ee



69% Y, 88% ee



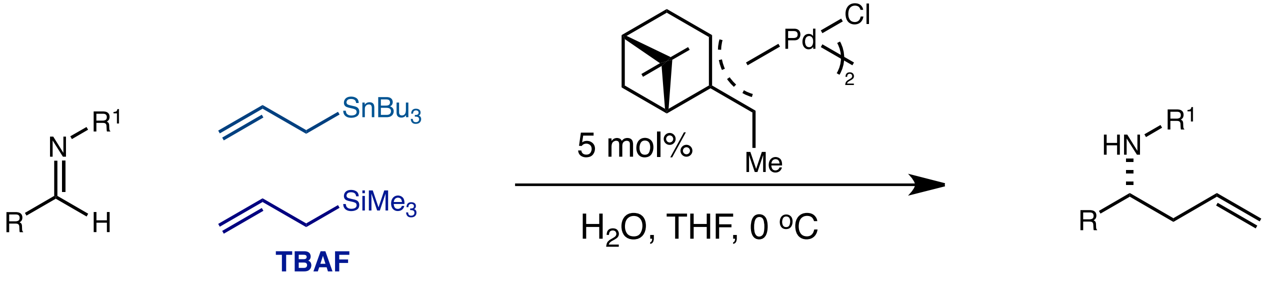
77% Y, 69% ee

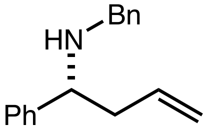
Fernandes, R. A.; Yamamoto. Y. *J. Org. Chem.* **2004**, *69*, 3562.

Nakamura, H.; Nakamura, K.; Yamamoto., Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.

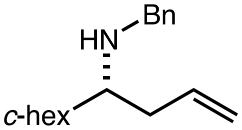
Chiral Allyl Ligands

- Yamamoto: Pd-allyl complexes for enantioselective allylation

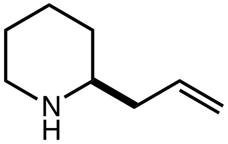




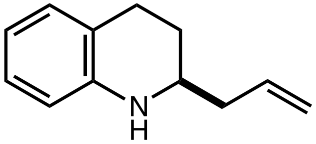
86% Y, 85% ee



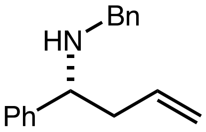
84% Y, 50% ee



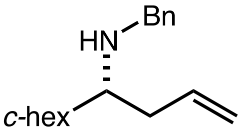
63% Y, 18% ee



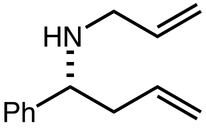
77% Y, 7% ee



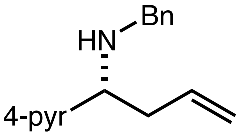
86% Y, 91% ee



86% Y, 52% ee



83% Y, 84% ee



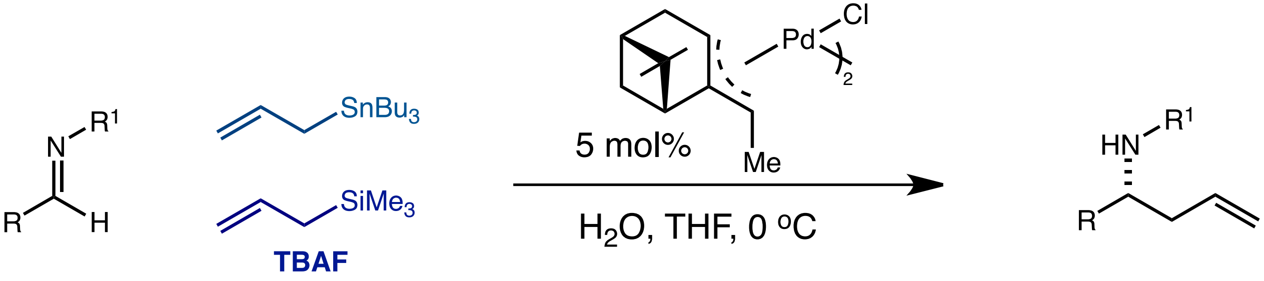
98% Y, 67% ee

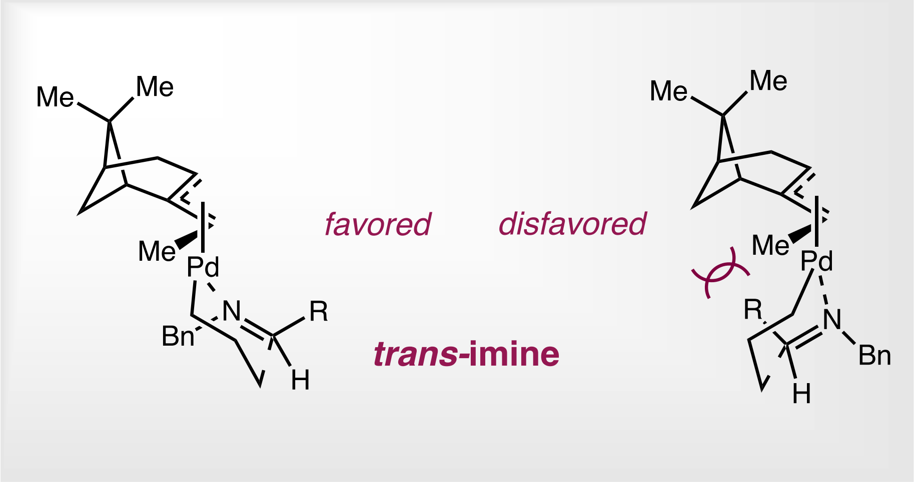
Fernandes, R. A.; Yamamoto. Y. *J. Am. Chem. Soc.* **2004**, *69*, 735.

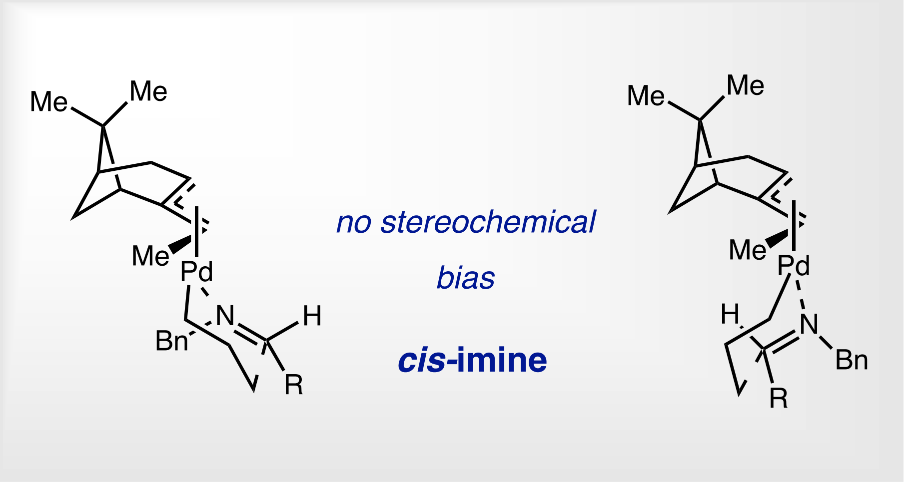
Fernandes, R. A.; Yamamoto., Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.

Chiral Allyl Ligands

- Yamamoto: Pd-allyl complexes for enantioselective allylation

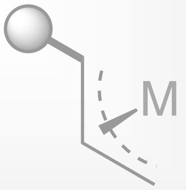




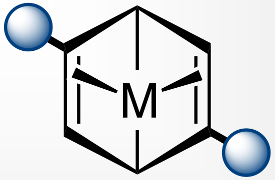


Fernandes, R. A.; Yamamoto., Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.

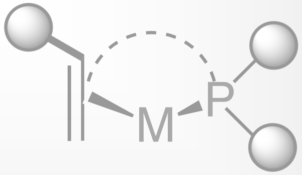
Classes of Chiral Olefins



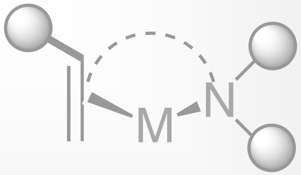
π-allyl



diene



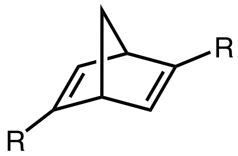
phosphane-olefin



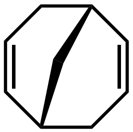
amine-olefin

Chiral Diene Ligands

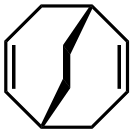
■ Classes of Chiral Diene Ligands



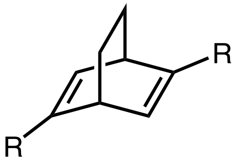
nbd
Hayashi



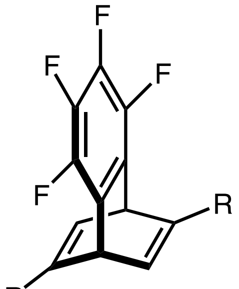
bnd
Hayashi



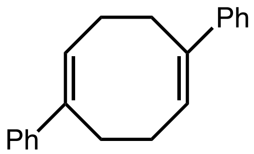
bdd
Hayashi



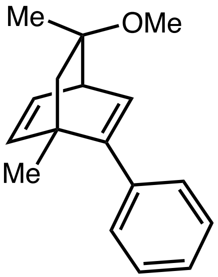
bod
Hayashi



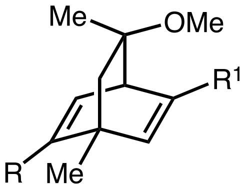
tfb
Hayashi



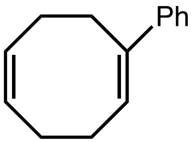
cod
Hayashi



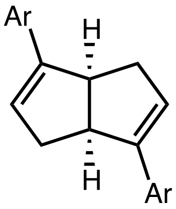
Carreira



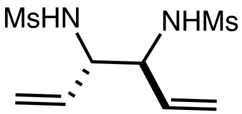
Carreira



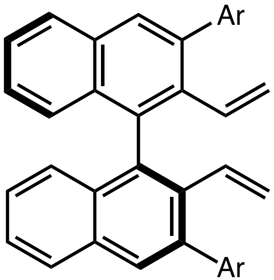
cod
Grützmacher



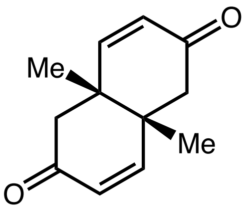
tetrahydropentalenes
Xu, Lin, Laschat



Du



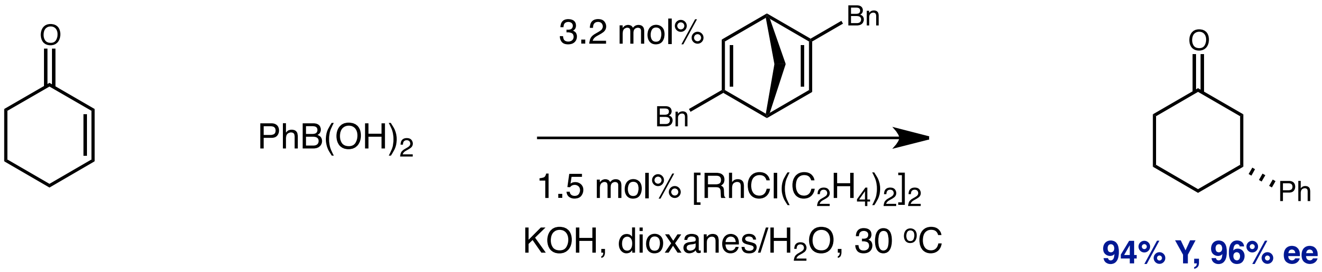
Du



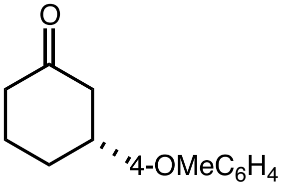
Trauner

Rhodium-Catalyzed 1,4-Additions

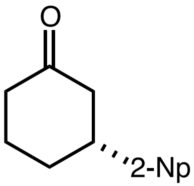
- Hayashi's Seminal Publication



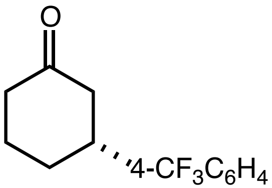
94% Y, 96% ee



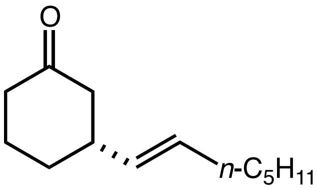
89% Y, 95% ee



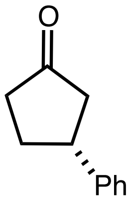
96% Y, 96% ee



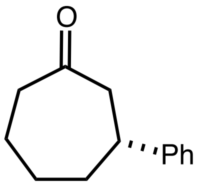
90% Y, 99% ee



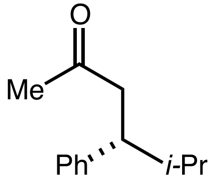
73% Y, 88% ee



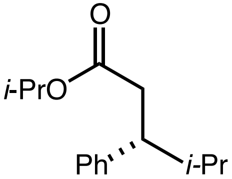
88% Y, 88% ee



81% Y, 90% ee



81% Y, 97% ee

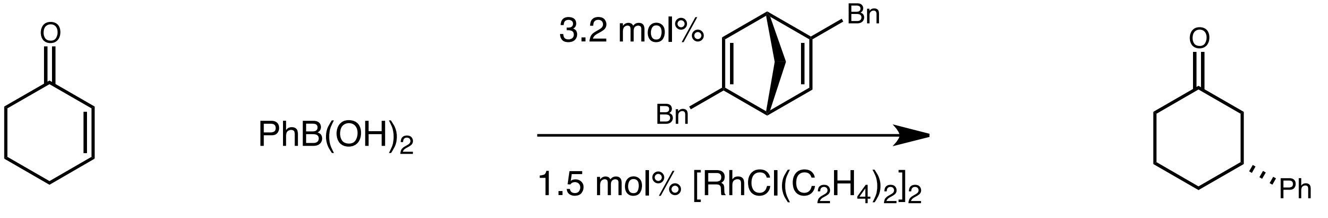


73% Y, 92% ee

Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

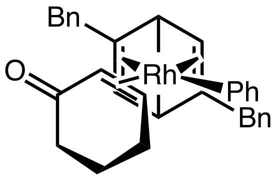
Rhodium-Catalyzed 1,4-Additions

Hiyashi's Seminal Publication

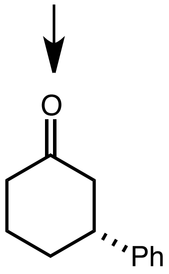


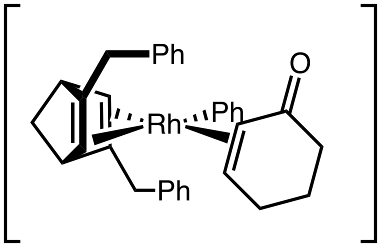
94% Y, 96% ee

Norbornadiene ligands are C_2-symmetric



favored

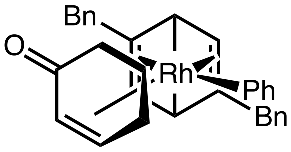




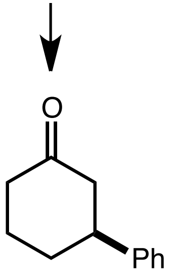
higher catalytic activity

better reactivity

compared to phosphine ligands



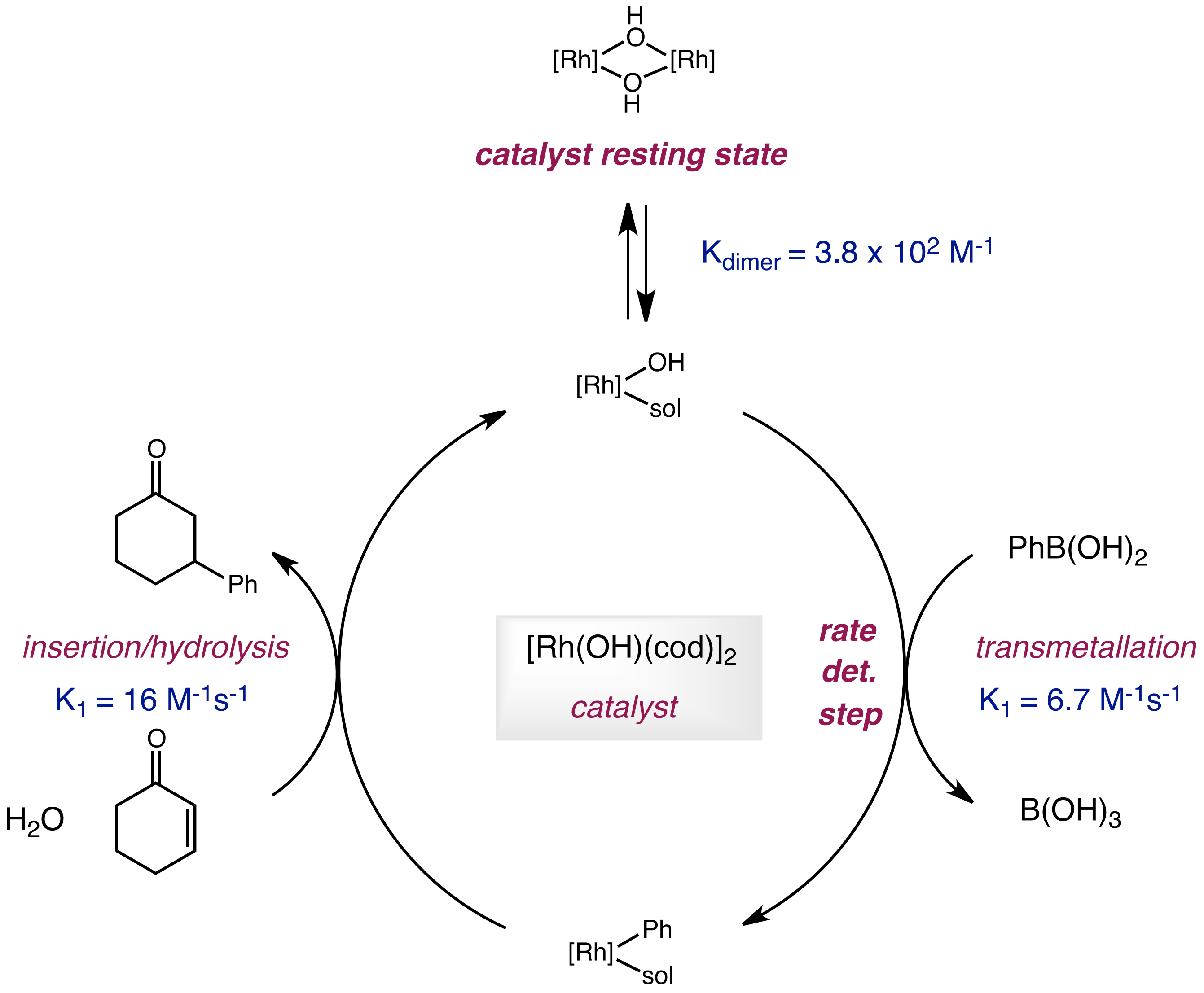
disfavored



Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

Rhodium-Catalyzed 1,4-Additions

- Catalytic cycle



catalyst resting state

$K_{dimer} = 3.8 \times 10^2\ M^{-1}$

[Rh(OH)(cod)]$_2$

catalyst

rate det. step

insertion/hydrolysis

$K_1 = 16\ M^{-1}s^{-1}$

H_2O

transmetallation

$K_1 = 6.7\ M^{-1}s^{-1}$

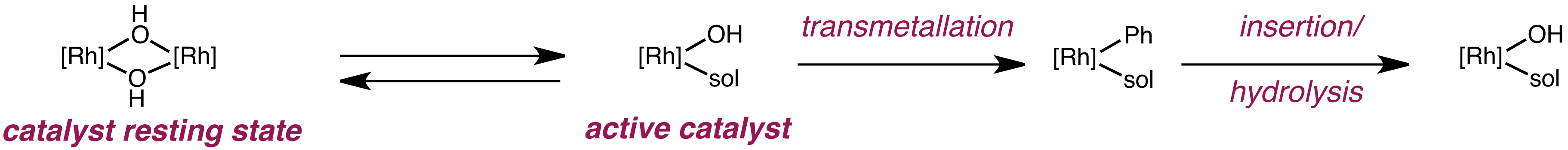
$PhB(OH)_2$

$B(OH)_3$

Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, T. *Chem. Asian J.* **2006**, *1*, 707.

Rhodium-Catalyzed 1,4-Additions

- Comparison of reaction kinetics: diene vs. phosphine ligand



catalyst resting state

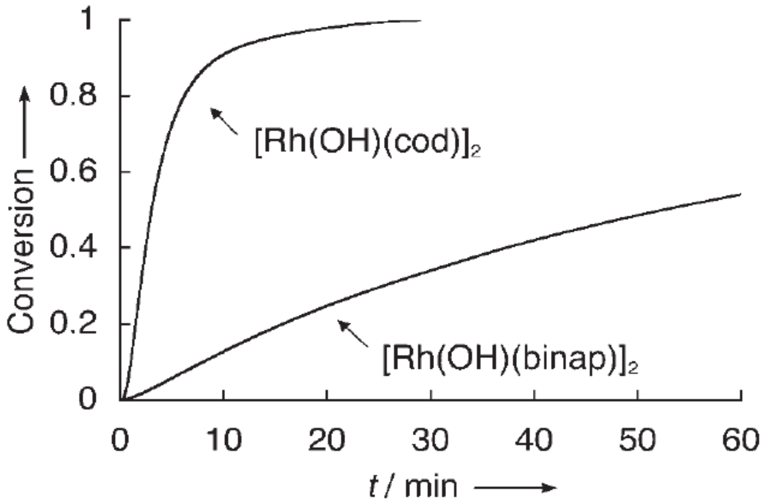
active catalyst

transmetallation

insertion/

hydrolysis

$[Rh(OH)(cod)]_2$	$K_{dimer} = 3.8 \times 10^2\ M^{-1}$	$K_1 = 6.7\ M^{-1}s^{-1}$	$K_2 = 16\ M^{-1}s^{-1}$
$[Rh(OH)(binap)]_2$	$K_{dimer} = 8 \times 10^2\ M^{-1}$	$K_1 = 0.5\ M^{-1}s^{-1}$	



$[Rh(OH)(cod)]_2$

equilibrium content of active catalyst is higher

transmetallation occurs faster

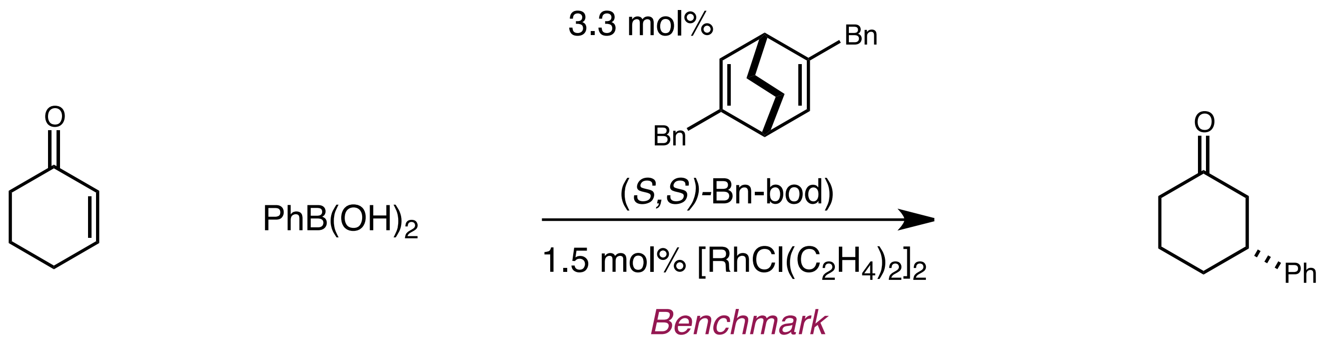
$[Rh(OH)(cod)]_2$ is 20 times more reactive

Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

Kina, A.; Yasuhara, Y.; Nishimura, T.; Iwamura, H.; Hayashi, T. *Chem. Asian J.* **2006**, *1*, 707.

Rhodium-Catalyzed 1,4-Additions: Catalyst Loading

- Catalyst loading can be decreased significantly



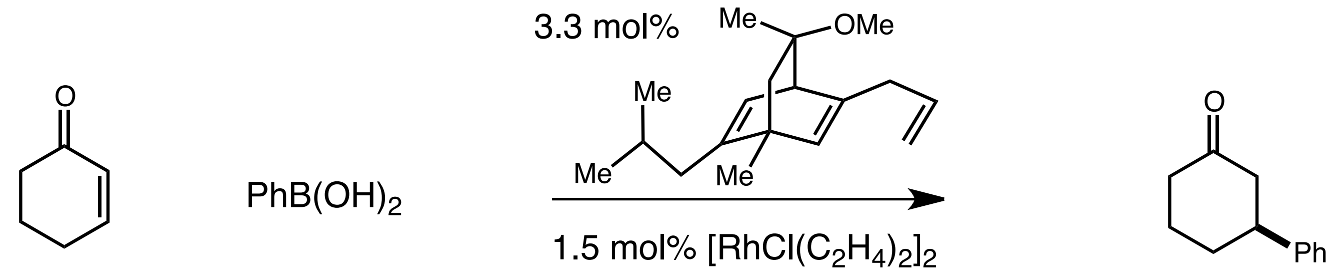
PhB(OH)$_2$	catalyst (mol% Rh)	yield (%)	ee (%)
PhB(OH)$_2$	1.0	quant	96
PhB(OH)$_2$	0.1	quant	96
PhB(OH)$_2$	0.05	79	96
PhB(OH)$_2$	0.01	0	--
(PhBO)$_3$	0.01	quant	96
(PhBO)$_3$	0.005	71	96

impurity in boronic acid deactivates catalyst

Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341.

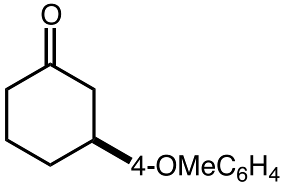
Rhodium-Catalyzed 1,4-Additions

- Carreira independently reports Rh-catalyzed 1,4 addition with C_1-symmetric ligand

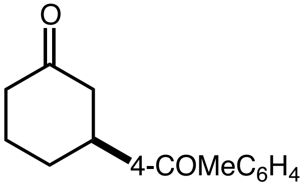


1.5 mol% $[RhCl(C_2H_4)_2]_2$
KOH, dioxanes/H_2O, 25 °C

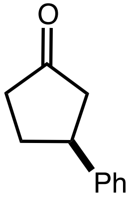
87% Y, 95% ee



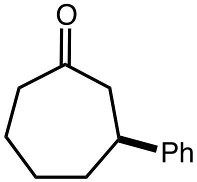
85% Y, 96% ee



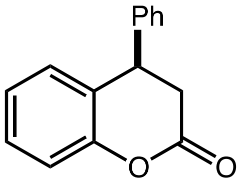
96% Y, 97% ee



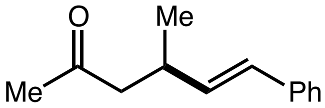
91% Y, 94% ee



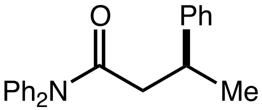
81% Y, 95% ee



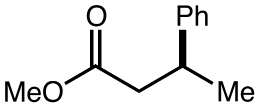
43% Y, 98% ee



68% Y, 89% ee



98% Y, 93% ee

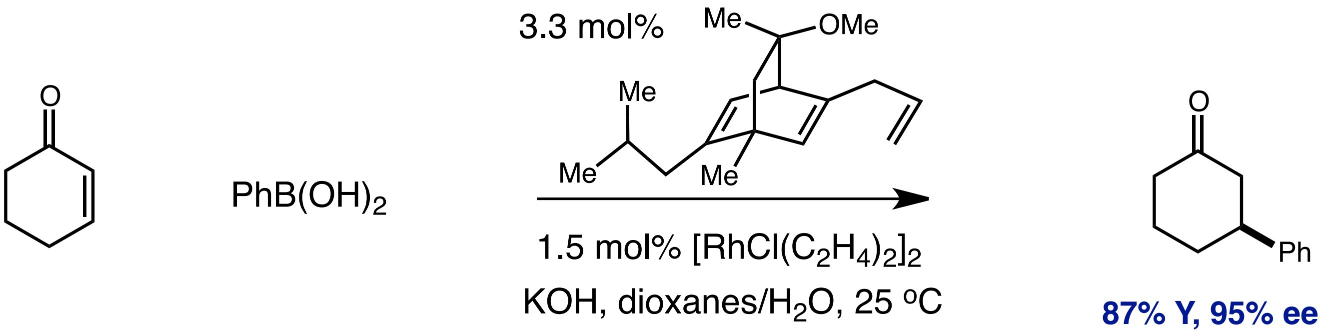


93% Y, 88% ee

Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. *Org. Lett.* **2004**, *6*, 3873.

Rhodium-Catalyzed 1,4-Additions

- Carreira independently reports Rh-catalyzed 1,4 addition with C_1-symmetric ligand

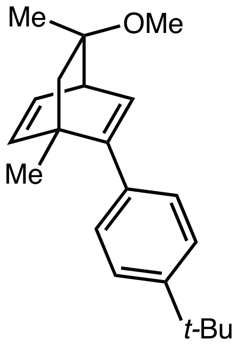


1.5 mol% $[RhCl(C_2H_4)_2]_2$

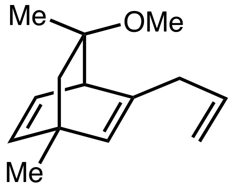
KOH, dioxanes/H_2O, 25 °C

87% Y, 95% ee

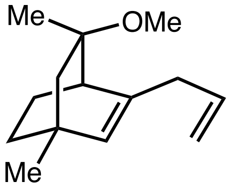
- Ligand modification gives insight in catalyst binding



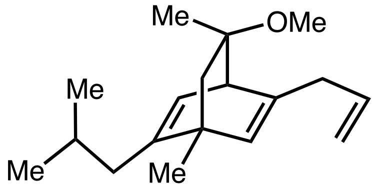
52% Y, 71% ee



93% Y, 58% ee



< 10% conversion



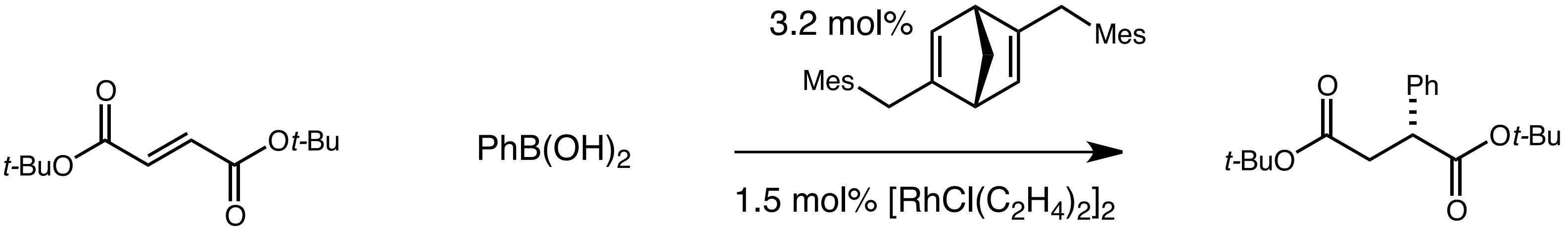
87% Y, 95% ee

Rigid diene structure required for activity

Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. *Org. Lett.* **2004**, *6*, 3873.

Rhodium-Catalyzed 1,4-Additions: Ligand Development

- Fumaric compounds are amenable to transformation

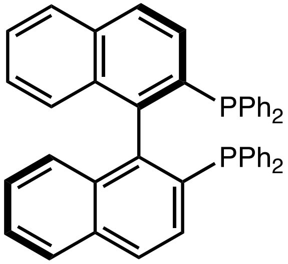


3.2 mol%

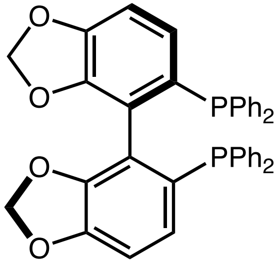
1.5 mol% $[RhCl(C_2H_4)_2]_2$
KOH, dioxanes/H_2O, 50 °C

90% Y, 90% ee

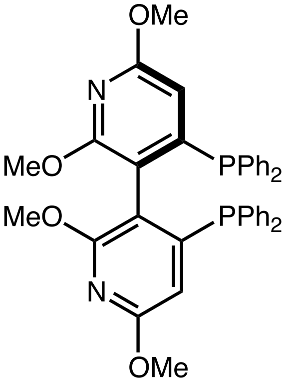
- Diene ligands are more selective than traditional ligands



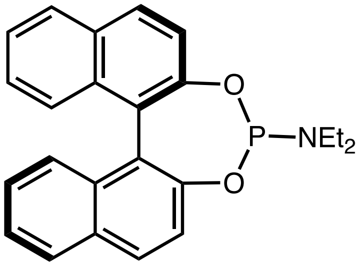
(*R*)-binap
96% Y, 21% ee



(*R*)-segphos
99% Y, 3% ee



(*S*)-P-phos
94% Y, 13% ee

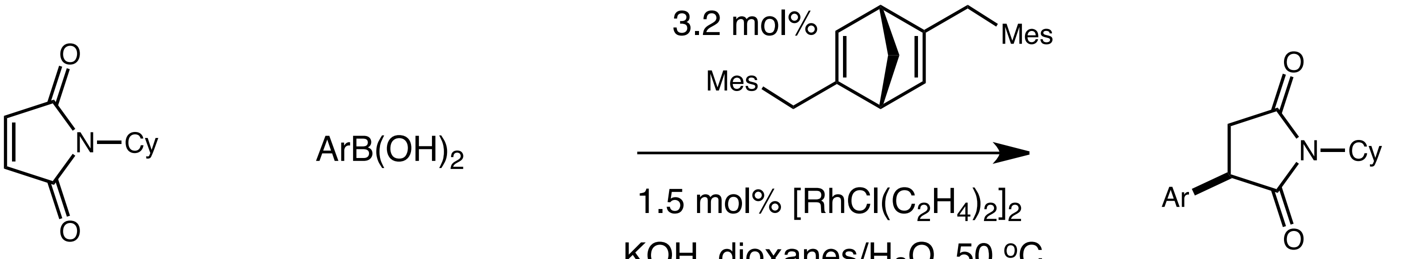


(*S*)-phosphoramidite
50% Y, 32% ee

Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425.

Rhodium-Catalyzed 1,4-Additions: Expansion of Scope

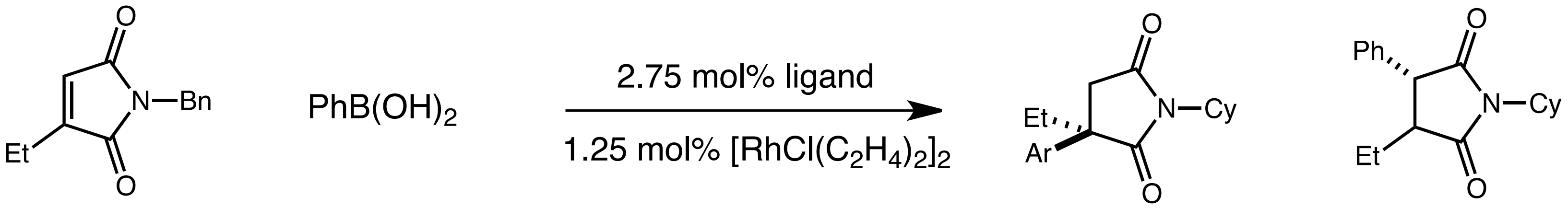
- Malemide compounds are amenable to transformation



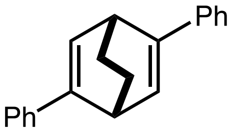
1.5 mol% $[RhCl(C_2H_4)_2]_2$
KOH, dioxanes/H_2O, 50 ^oC

77-95% Y, 82-92% ee

- Diene ligands and phosphine ligand display orthogonal reactivity



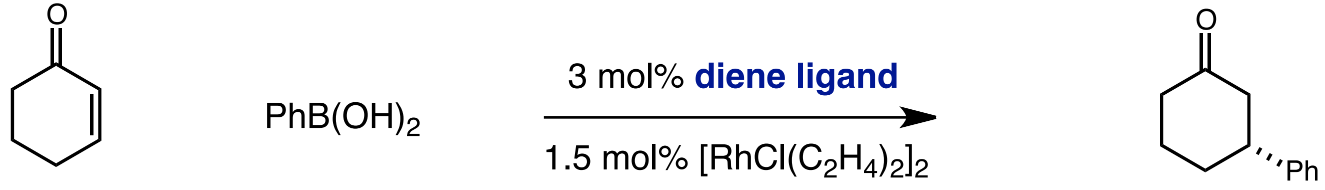
2.75 mol% ligand
1.25 mol% $[RhCl(C_2H_4)_2]_2$

(*R*)-Binap	**85%**	**15%**
	**10%**	**84%**

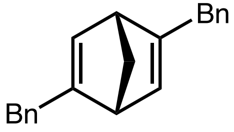
Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425.
Shintani, R.; Duan, W.-L.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628.

Rhodium-Catalyzed 1,4-Additions: Ligand Development

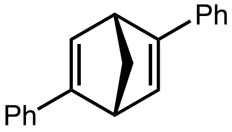
- Benchmark reaction: Phenyl boronic acid 1,4-addition to cyclohexenone



- Hayashi's C_2-symmetric ligands

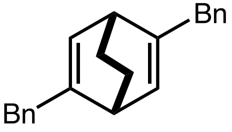


90% Y, 95% ee



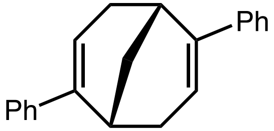
89% Y, 97% ee

not stable to air/light

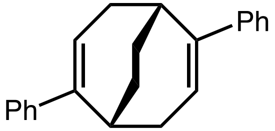


97% Y, 95% ee

stable



93% Y, 83% ee



98% Y, 90% ee

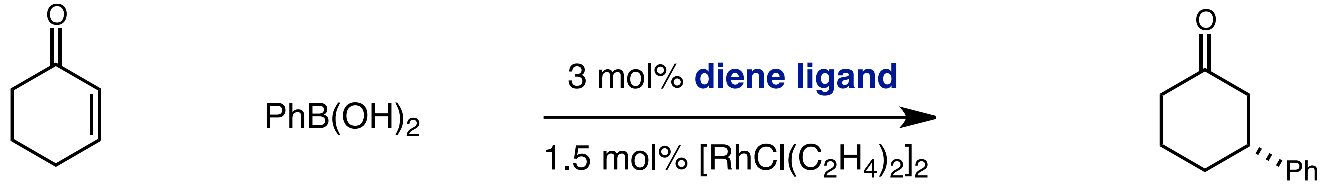
Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673.

Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503.

Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.

Rhodium-Catalyzed 1,4-Additions: Ligand Development

- Benchmark reaction: Phenyl boronic acid 1,4-addition to cyclohexenone

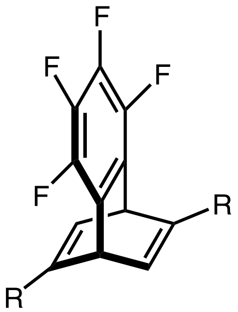

$PhB(OH)_2$

3 mol% **diene ligand**

1.5 mol% $[RhCl(C_2H_4)_2]_2$

98% Y, 99% ee

- Hayashi's state of the art ligand

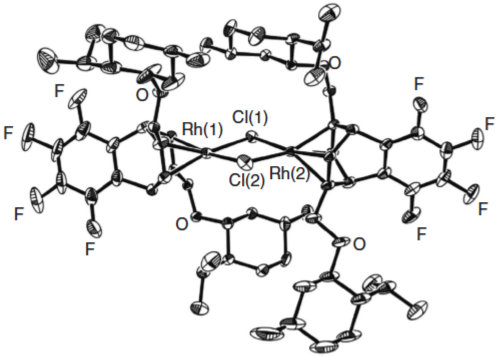


R = (–)-menthol

Ligand can be synthesized in 3 steps

High reactivity

High selectivity

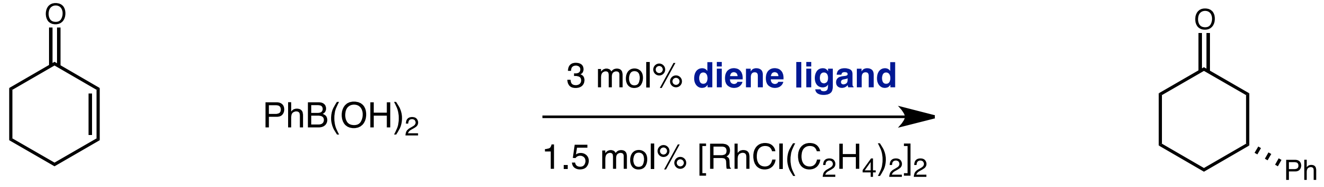


pre-catalyst

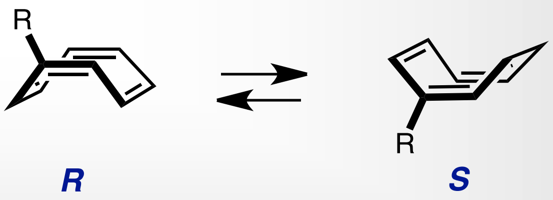
Nishimura, T.; Nagaosa, M.; Hayashi, T. *Chem. Lett*. **2008**, *37*, 860.

Rhodium-Catalyzed 1,4-Additions: Ligand Development

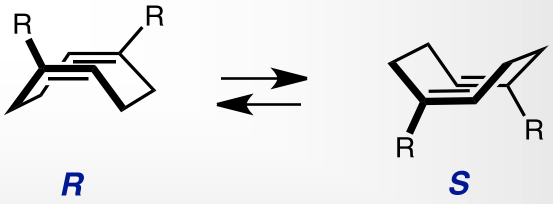
- Benchmark reaction: Phenyl boronic acid 1,4-addition to cyclohexenone



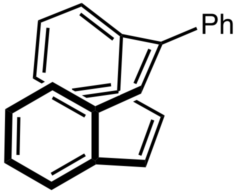
- Prochiral ligands



cyclooctatetraene

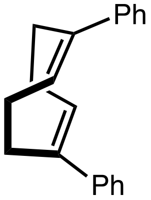


cyclooctadiaene



92% Y, 62% ee

Grützmacher



ligand dissociates and racemizes

90% Y, 43% ee

Using PhZnCl (fast) **89% Y, 81% ee**

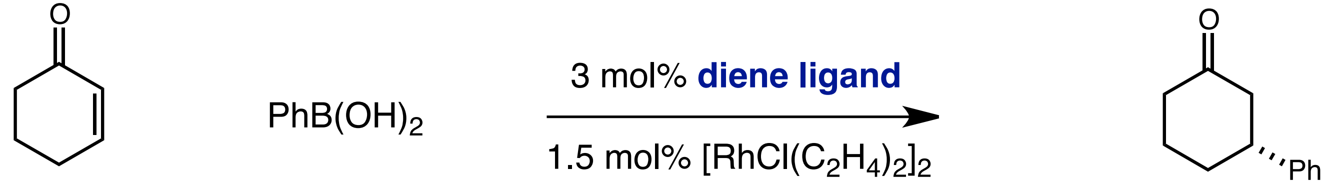
Hayashi

Kina, A.; Ueyama, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 5889.

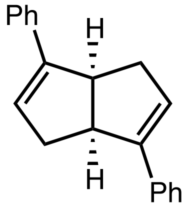
Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997.

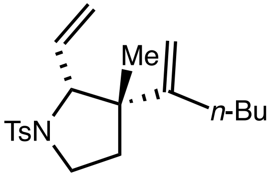
Rhodium-Catalyzed 1,4-Additions: Ligand Development

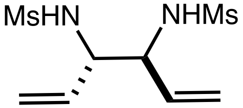
- Benchmark reaction: Phenyl boronic acid 1,4-addition to cyclohexenone



- Other ligands under development







95% Y, 88% ee

Laschat

96% Y, 91% ee

Xu and Lin

89% Y, 91% ee

Yu

96% Y, 95% ee

Du

Easy to synthesize

Norbornadiene mimics

Obtained from Rh allylic C-H activation/conjugated diene addn

Binding occurs through olefin

Complex has fast coordination/dissociation

Li, Q.; Dong, Z.; Yu, Z.-X.; *Org. Lett.* **2011**, *13*, 1122.

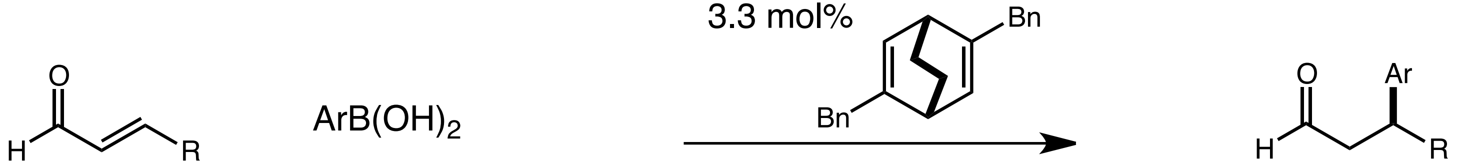
Wang, Y.; Hu, X.; Du, H. *Org. Lett.* **2010**, *12*, 5482.

Feng, C.-G.; Wang, Z.-Q.; Tian, P.; Xu, M.-H.; Lin, G.-Q. *Chem. Asian J.* **2008**, *3*, 1511.

Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331.

Rhodium-Catalyzed 1,4-Additions: Expansion of Scope

- 1,4-Addition into aldehydes

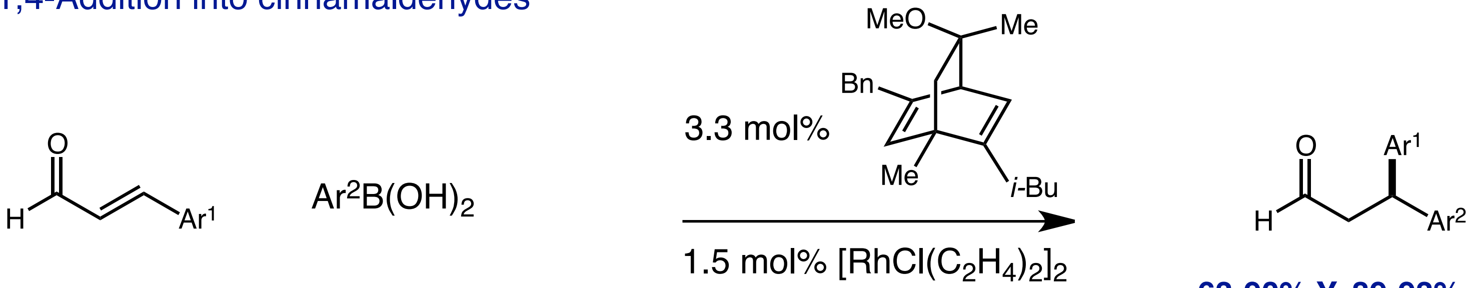


83-95% Y, 88-97% ee

R = alkyl, aryl

Ar = e⁻ rich, neutral, e⁻ poor

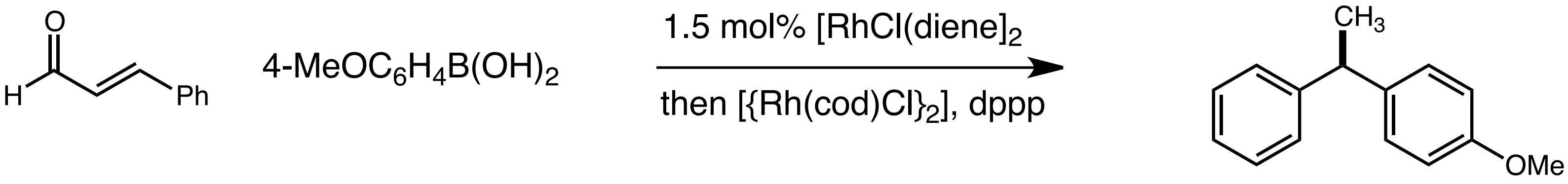
- 1,4-Addition into cinnamaldehydes



63-90% Y, 89-93% ee

$Ar^{1,2}$ = e⁻ rich, neutral, e⁻ poor

- 1,1-Diarylethanes via one-pot addition/decarbonylation



71% Y, 93% ee

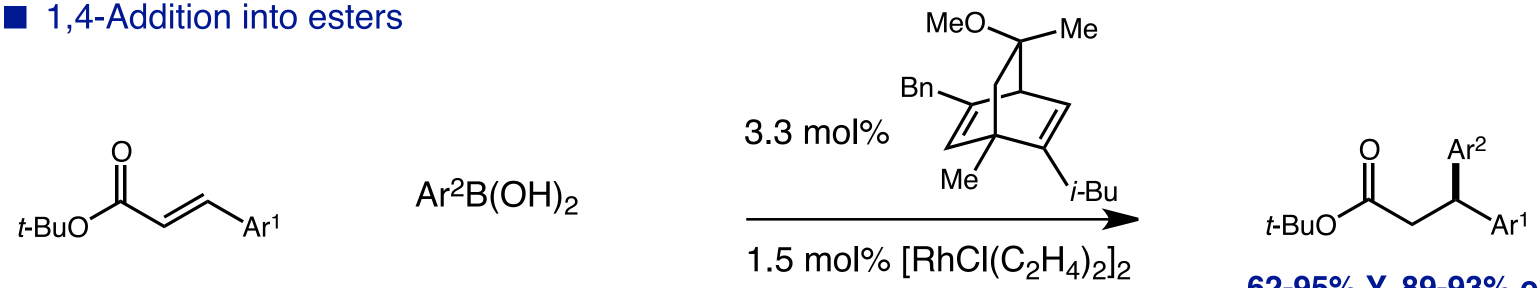
Hayashi, T.; Tokunaga, N.; Okamoto, K.; Shintani, R. *Chem. Lett.* **2005**, *34*, 1480.

Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.

Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 9331.

Rhodium-Catalyzed 1,4-Additions: Expansion of Scope

- 1,4-Addition into esters

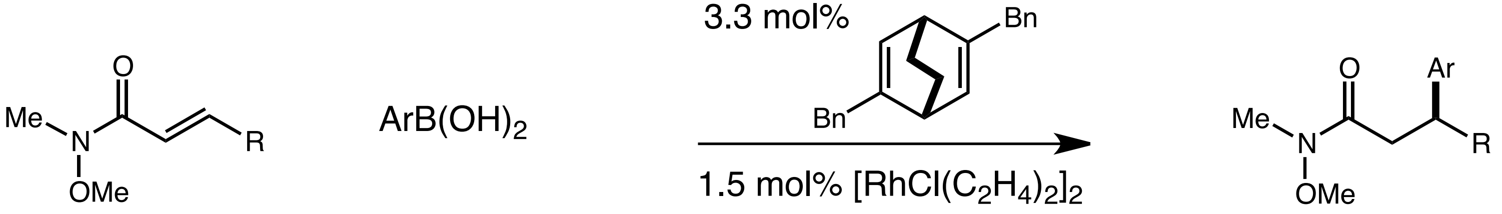


62-95% Y, 89-93% ee

$Ar^{1,2}$ = e⁻ rich, neutral, e⁻ poor

Ar^1 includes heteroaromatics

- 1,4-Addition into Weinreb amides

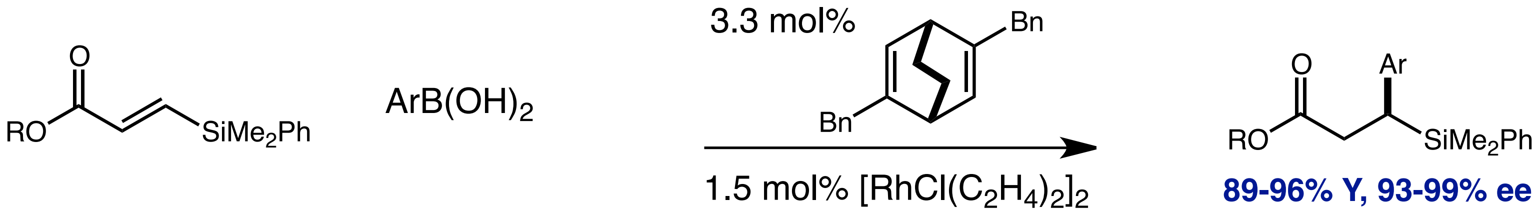


83-92% Y, 80-92% ee

R = alkyl, aryl

Ar = e⁻ rich, neutral

- 1,4-Addition into β-silyl carbonyls



89-96% Y, 93-99% ee

R = alkyl, aryl

Ar = e⁻ rich, neutral, e⁻ poor

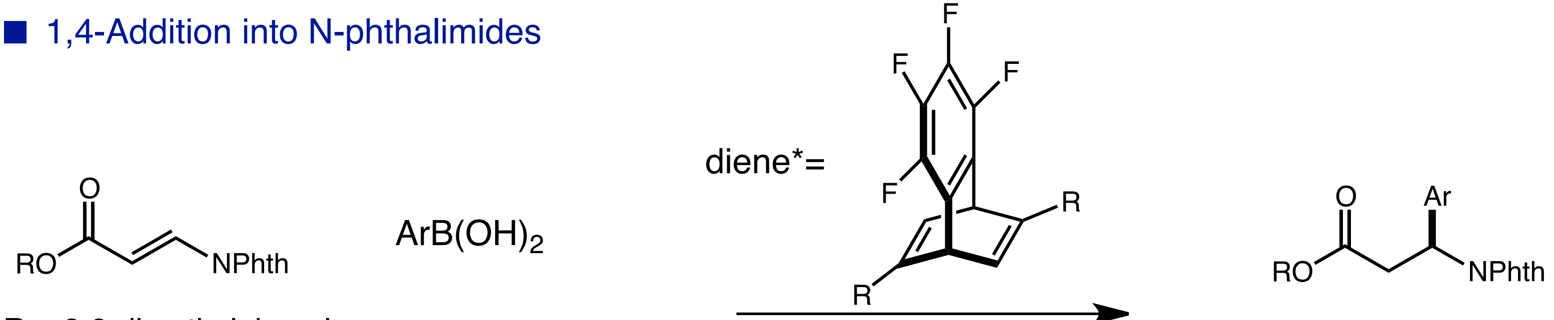
Shintani, R.; Kimura, T.; Hayashi, T. *Chem. Comm.* **2005**, 3213.

Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, 7, *3821.*

Shintani, R.; Okamoto, K. Hayashi, T. *Org. Lett.* **2005**, *7*, 4757.

Rhodium-Catalyzed 1,4-Additions: Expansion of Scope

- 1,4-Addition into N-phthalimides



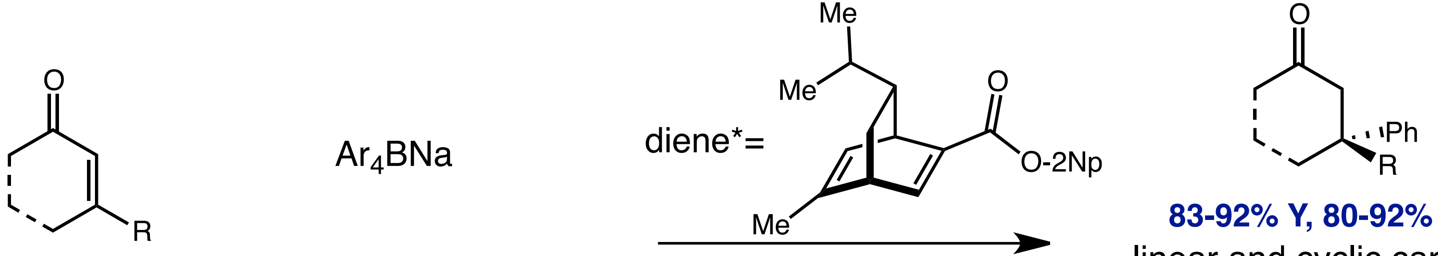
R = 2,6-dimethylphenyl

1.5 mol% $[RhCl(diene^*)_2]_2$

81-99% Y, 93-99% ee

Ar = e⁻ rich, neutral, e⁻ poor, vinyl

- 1,4-Addition to form quaternary centers



2.5 mol% $[RhCl(diene^*)_2]_2$

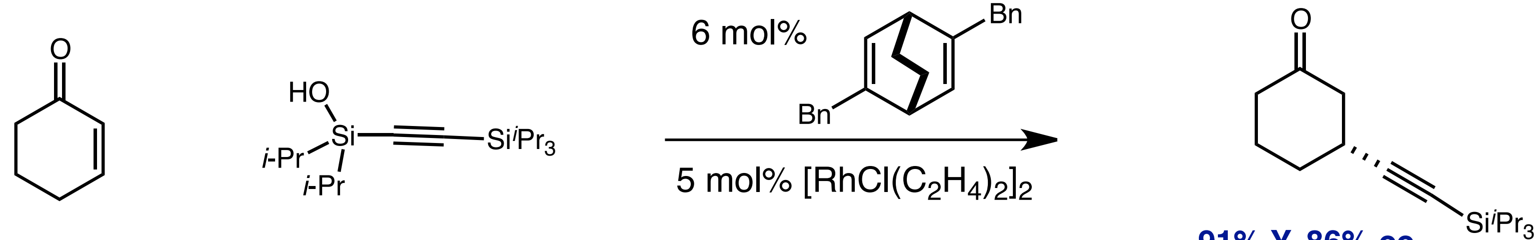
83-92% Y, 80-92% ee

linear and cyclic carbonyls

R = Me, Et, CO_2Me

Ar = e⁻ rich, neutral

- 1,4-Alkynylation of cyclic enones



5 mol% $[RhCl(C_2H_4)_2]_2$

91% Y, 86% ee

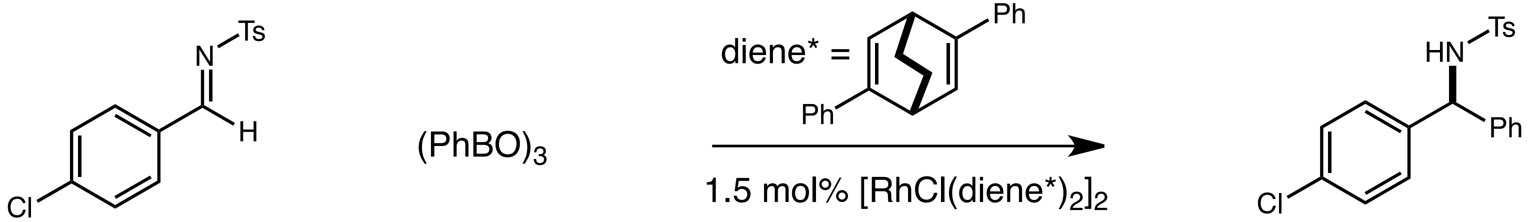
Nishimura, T.; Tokuji, S.; Sawano, T.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3222.

Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588.

Nishimura, T.; Wang, J. Nagaosa, M.; Okamoto, K.; Shintani, R.; Kwong, F.-Y.; Yu, W.-Y. Chan, A. S. C.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 464.

Rhodium-Catalyzed 1,2-Additions

- Seminal publication: Hayashi, 2004

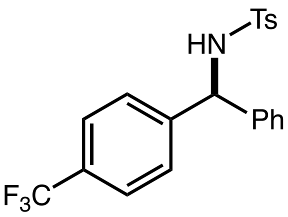


challenging with phosphine ligands

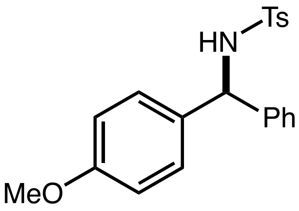
benchmark reaction

96% Y, 98% ee

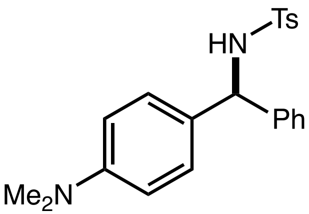
- Scope



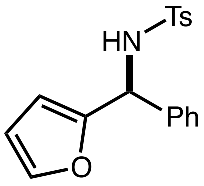
97% Y, 95% ee



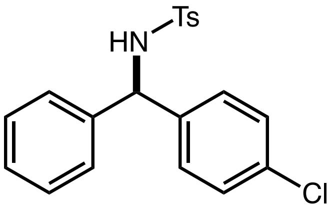
96% Y, 99% ee



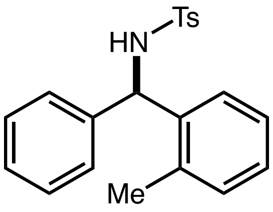
94% Y, 98% ee



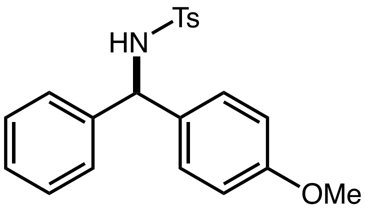
99% Y, 99% ee



99% Y, 99% ee



96% Y, 99% ee

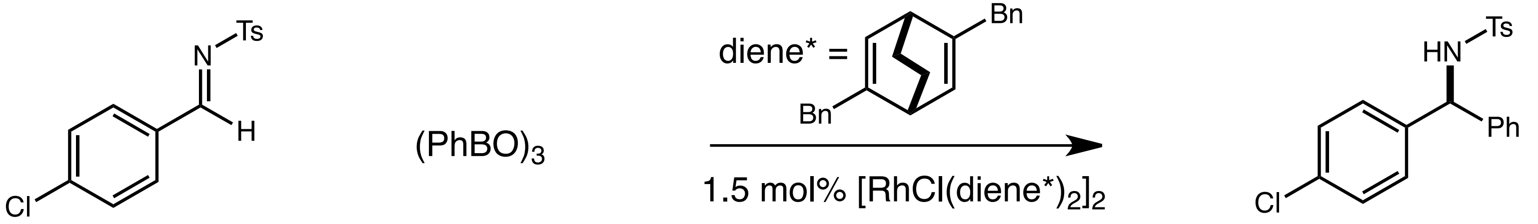


97% Y, 96% ee

Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.

Rhodium-Catalyzed 1,2-Additions

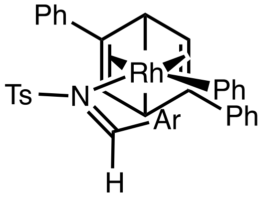
- Seminal publication: Hayashi, 2004



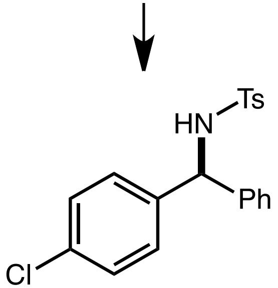
challenging with phosphine ligands
benchmark reaction

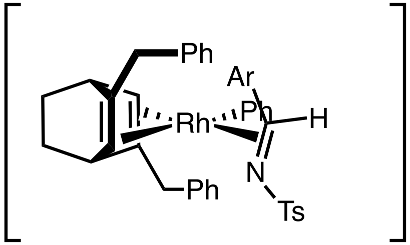
96% Y, 98% ee

- Stereochemical model

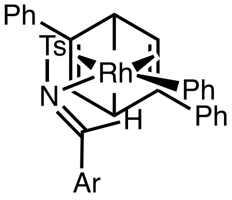


favored

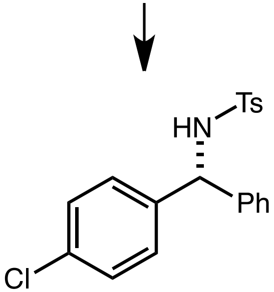




High enantioselectivity
results from Ts and Ar in
unsubstituted quadrants



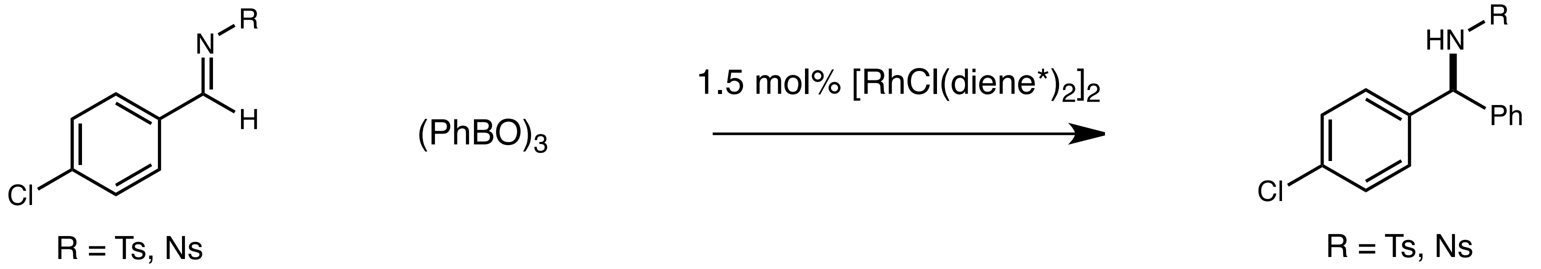
disfavored



Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.

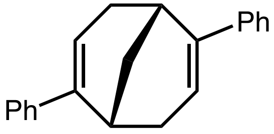
Rhodium-Catalyzed 1,2-Additions

- Benchmark reaction: 1,2 Ts- and Ns-imine addition

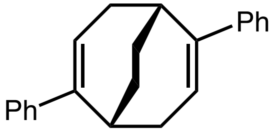


- Ligand development and survey

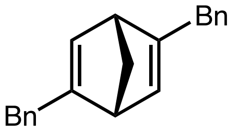
Ts



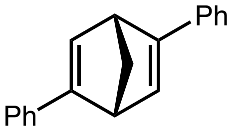
95% Y, 99% ee



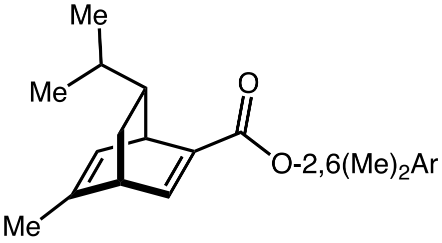
88% Y, 94% ee



98% Y, 92% ee

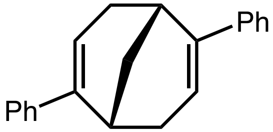


96% Y, 99% ee

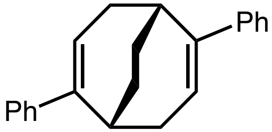


98% Y, 98% ee

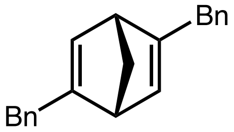
Ns



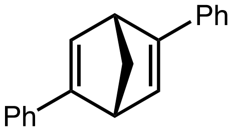
96% Y, 98% ee



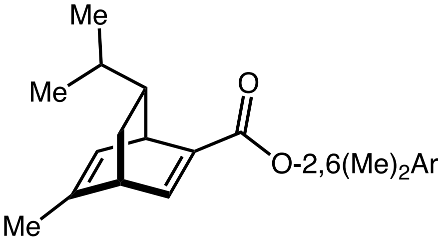
99% Y, 90% ee



88% Y, 81% ee



92% Y, 99% ee



96% Y, 99% ee

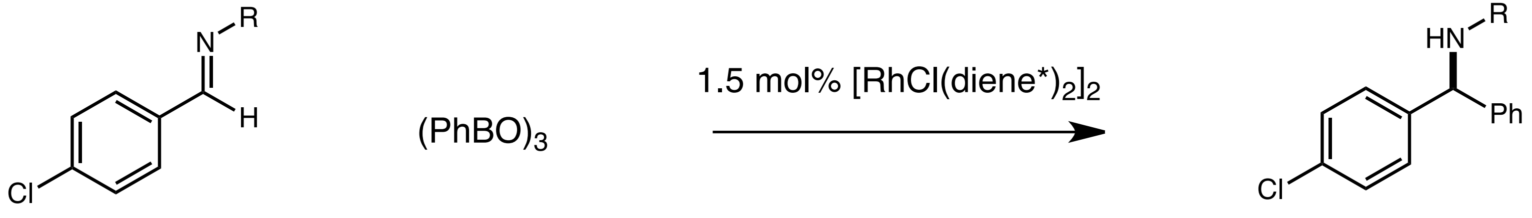
Otomaru, Y.; Hayashi, T.; Rawal, V. H. *Chem. Comm.* **2009**, *4815.*

Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.

Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673.

Rhodium-Catalyzed 1,2-Additions

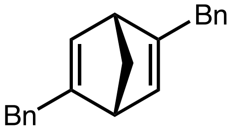
- Benchmark reaction: 1,2 Ts- and Ns-imine addition



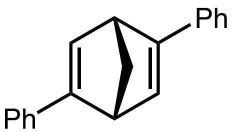
R = Ts, Ns

R = Ts, Ns

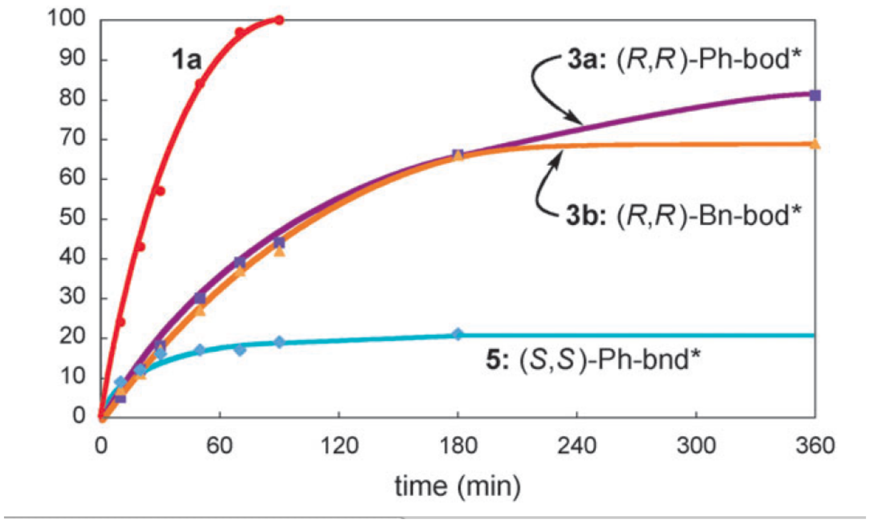
- Ligand effects on rate: electron deficient ligand (1a) accelerates transmetallation

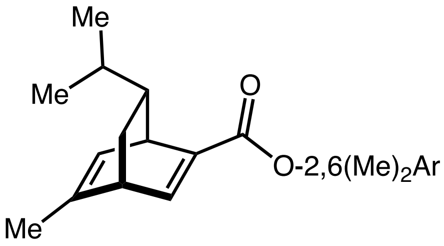


3b: 98% Y, 92% ee

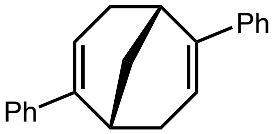


3a: 96% Y, 99% ee





1a: 98% Y, 98% ee



5: 95% Y, 99% ee

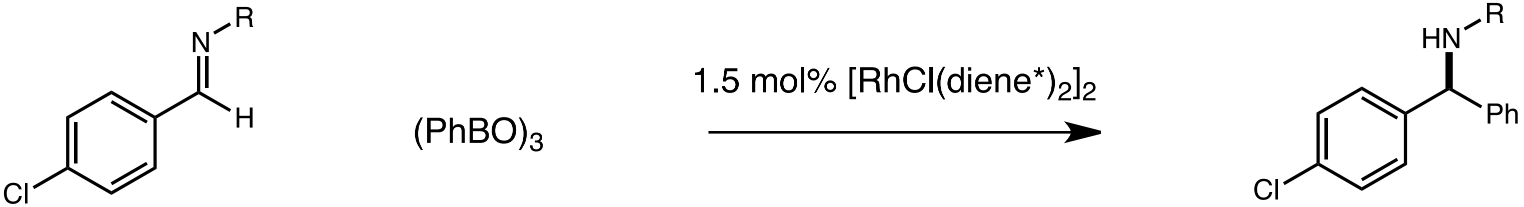
Otomaru, Y.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, *4815.*

Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307.

Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673.

Rhodium-Catalyzed 1,2-Additions

- Benchmark reaction: 1,2 Ts- and Ns-imine addition

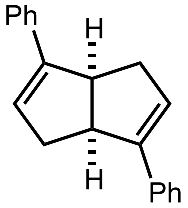


R = Ts, Ns

R = Ts, Ns

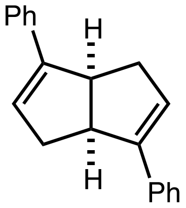
- Ligand development and survey

Ts



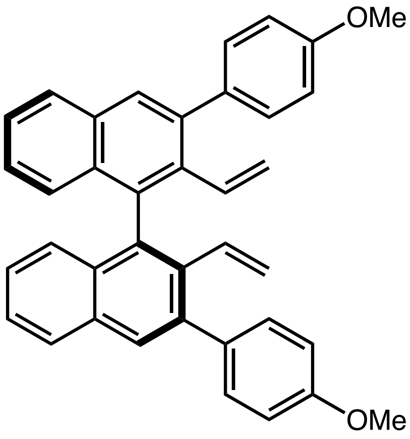
81% Y, 99% ee

Ns

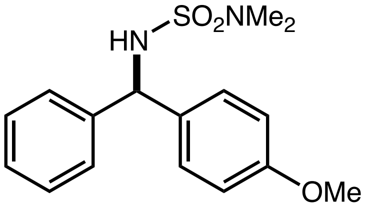


94% Y, 99% ee

Lin



Du



82% Y, 84% ee

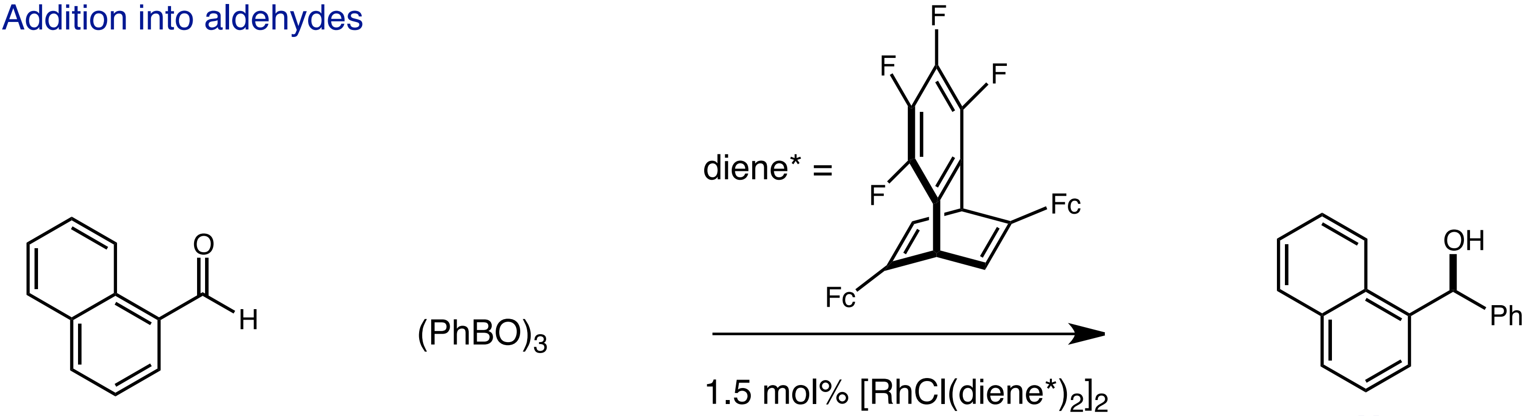
Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602.

Wang, L.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Synthesis* **2010**, 3263.

Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336.

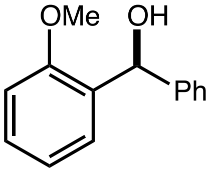
Rhodium-Catalyzed 1,2-Additions

- 1,2-Addition into aldehydes

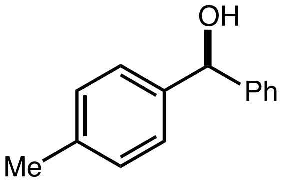


95% Y, 86% ee

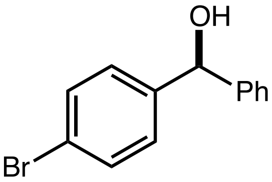
- Reaction scope



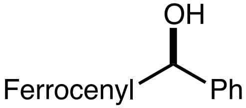
99% Y, 85% ee



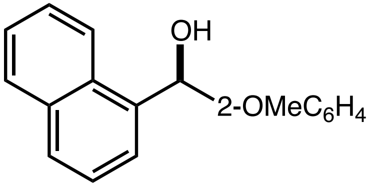
99% Y, 78% ee



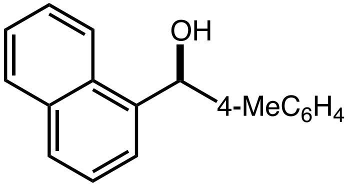
85% Y, 78% ee



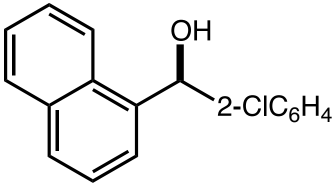
94% Y, 85% ee



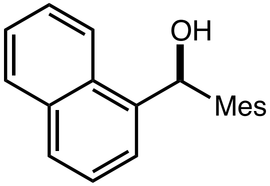
97% Y, 85% ee



90% Y, 85% ee



91% Y, 86% ee

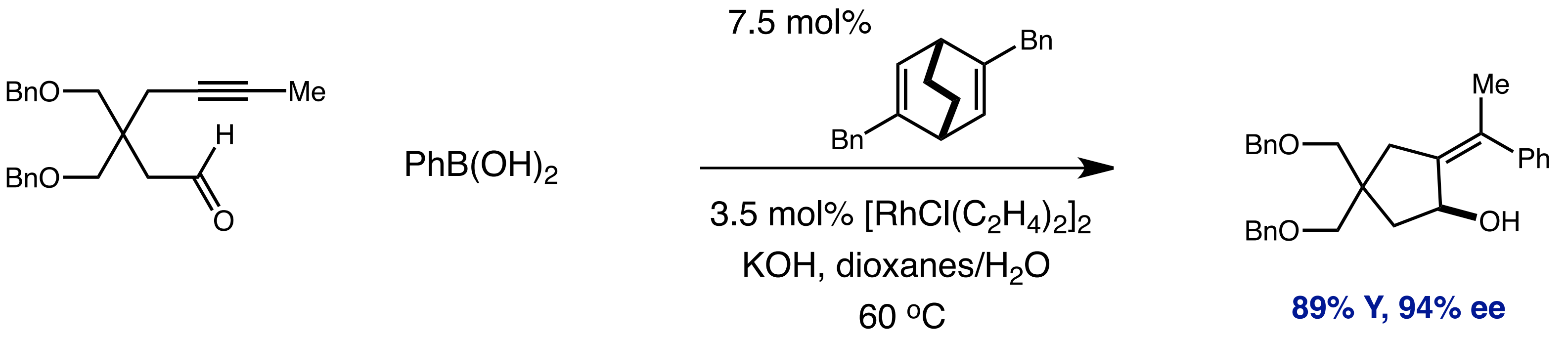


87% Y, 94% ee

Nishimura, T.; Kumamoto, H.; Nagaosa, M.; Hayashi, T. *Chem. Commun.* **2009**, *5713.*

Carborhodation with Chiral Diene Ligands

Rhodium-catalyzed addition/cyclization



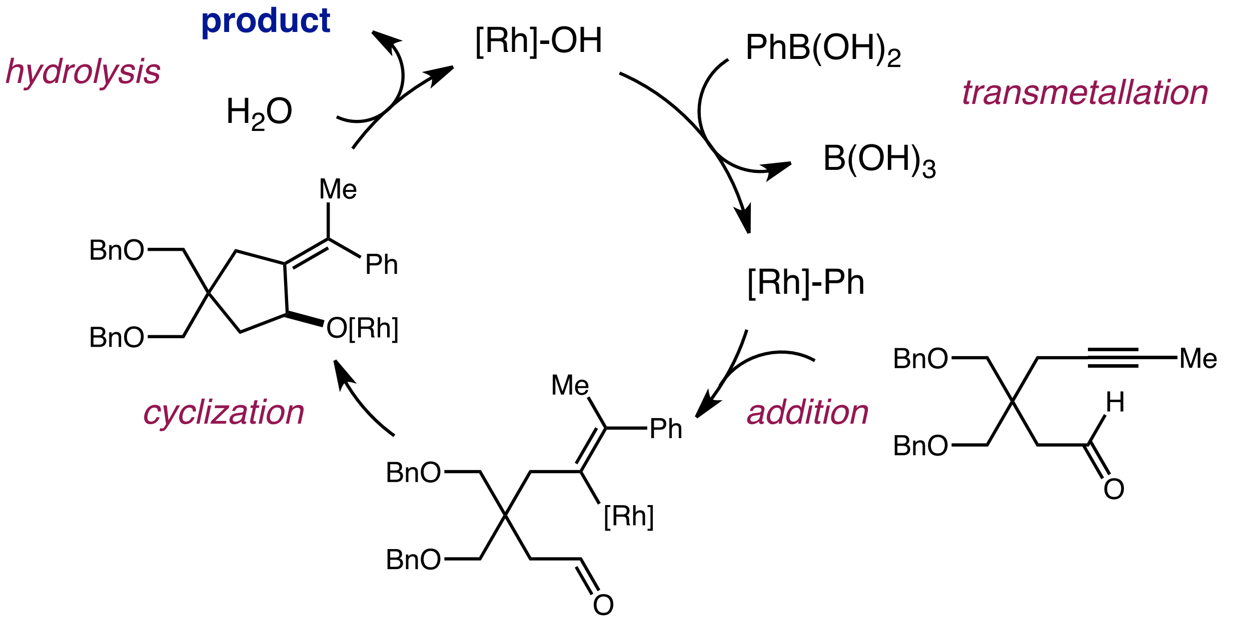
$PhB(OH)_2$

7.5 mol%

3.5 mol% $[RhCl(C_2H_4)_2]_2$
KOH, dioxanes/H_2O
60 °C

89% Y, 94% ee

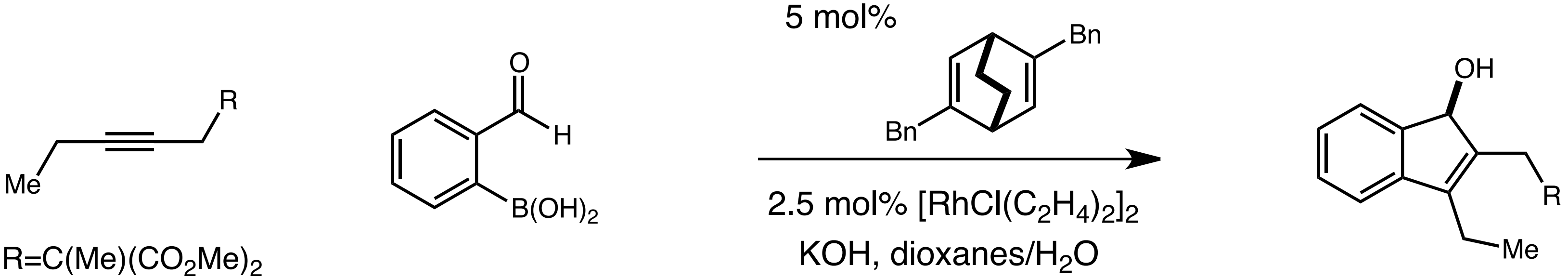
Catalytic cycle



Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54.

Carborhodation with Chiral Diene Ligands

- Rhodium-catalyzed addition/cyclization into alkynes



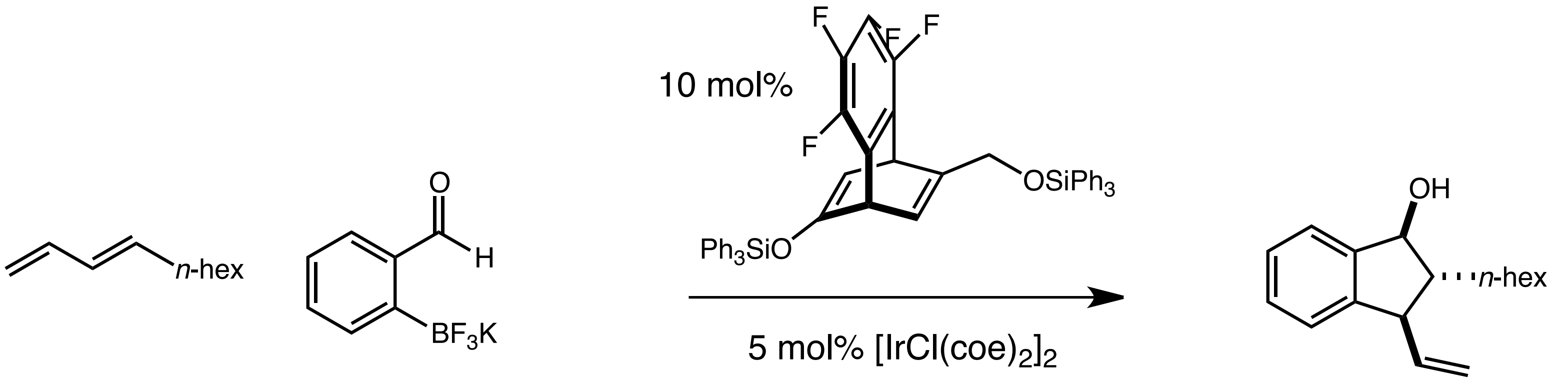
$R{=}C(Me)(CO_2Me)_2$

5 mol%

2.5 mol% $[RhCl(C_2H_4)_2]_2$
KOH, dioxanes/H_2O
35 °C

97% Y, 81% ee

- Rhodium-catalyzed addition/cyclization into alkenes



10 mol%

5 mol% $[IrCl(coe)_2]_2$
Et_3N, PhMe/H_2O, 60 °C

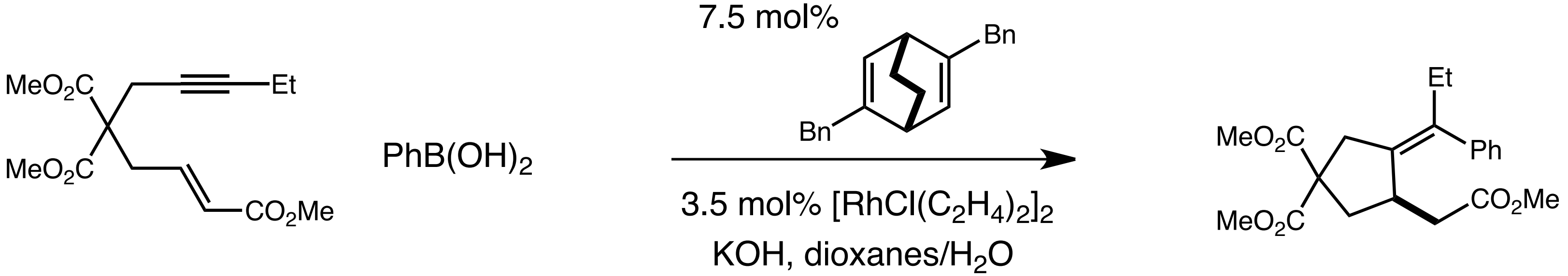
83% Y, 93% ee

Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1416.

Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *17*, 1778.

Carborhodation with Chiral Diene Ligands

- Rhodium-catalyzed addition/cyclization

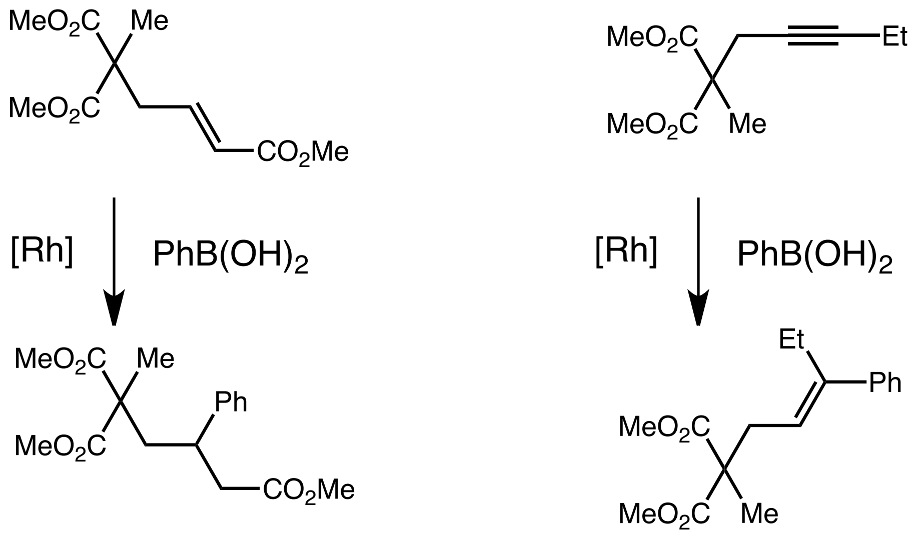


7.5 mol%

3.5 mol% [RhCl(C_2H_4)$_2$]$_2$
KOH, dioxanes/H_2O
60 °C

93% Y, 99% ee

- Rh/diene catalysts favor alkyne arylation over 1,4-addition

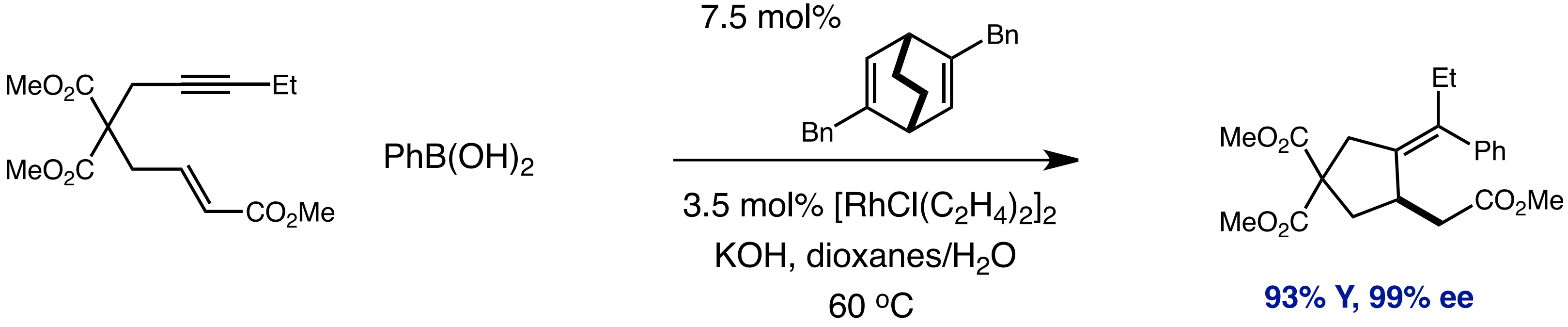


Binap	**76%**	**< 3%** (rec SM)
cod	**81%**	**80%**

Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3909.

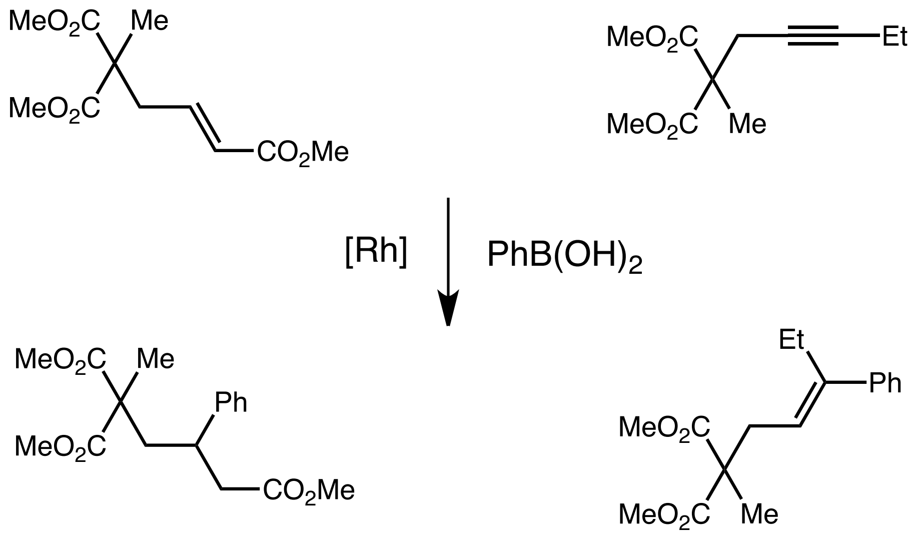
Carborhodation with Chiral Diene Ligands

- Rhodium-catalyzed addition/cyclization



93% Y, 99% ee

- Rh/diene catalysts favor alkyne arylation over 1,4-addition

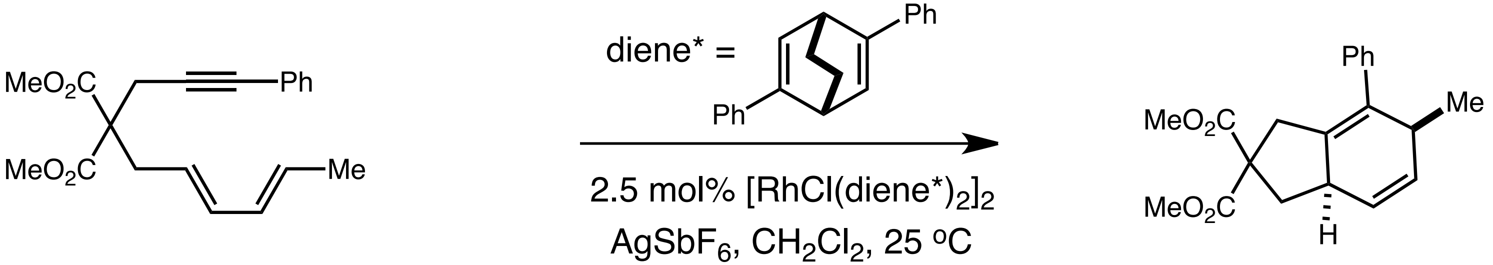


cod **7%** **76%**

Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3909.

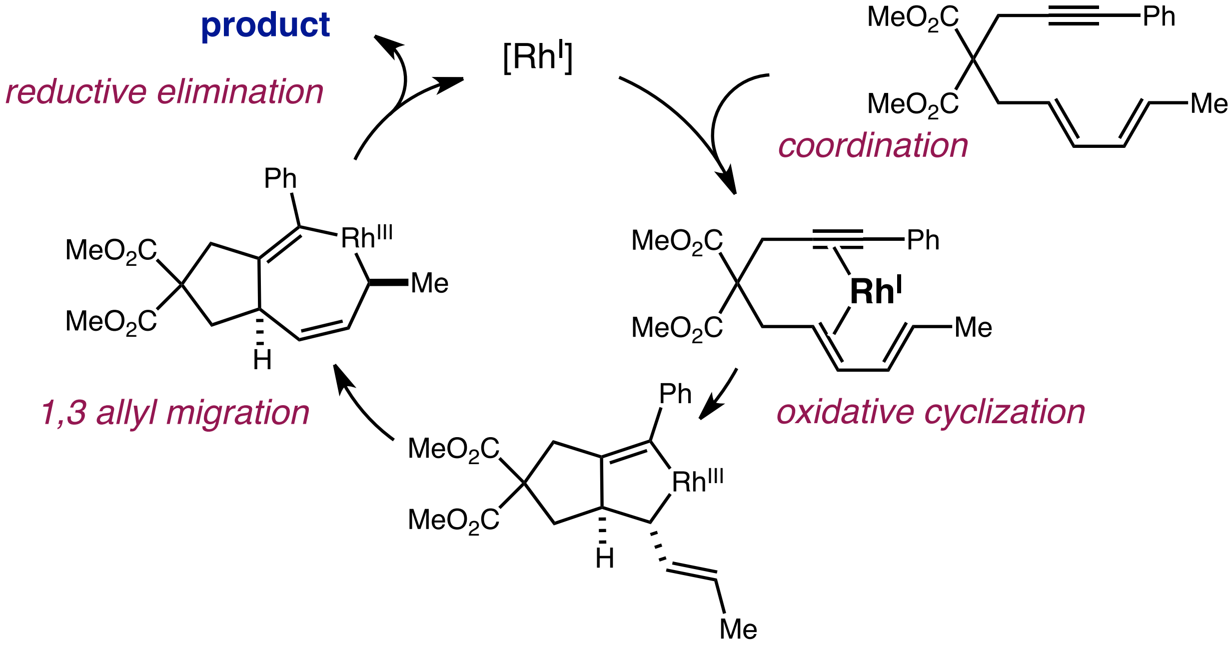
Carborhodation with Chiral Diene Ligands

- Rhodium-catalyzed [4+2]



87% Y, 94% ee

- Catalytic cycle



product

reductive elimination

[Rh^I]

coordination

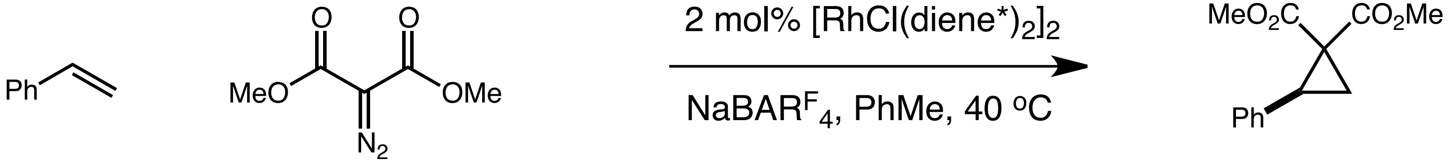
oxidative cyclization

1,3 allyl migration

Shintani, R.; Sannohe, Y.; Tsuji, T; Hayashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 7277.

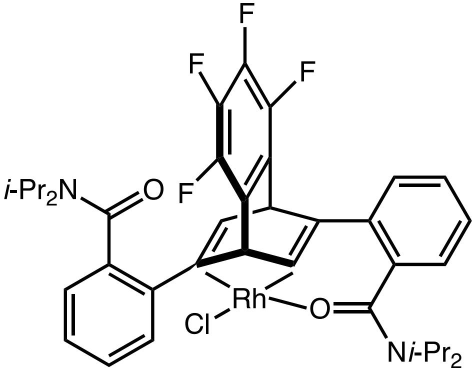
Carborhodation with Chiral Diene Ligands

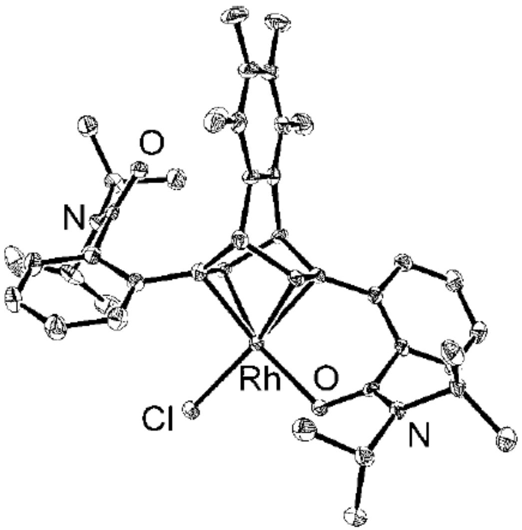
- Rhodium-catalyzed cyclopropanation



86% Y, 89% ee

- Rh/diene catalyst

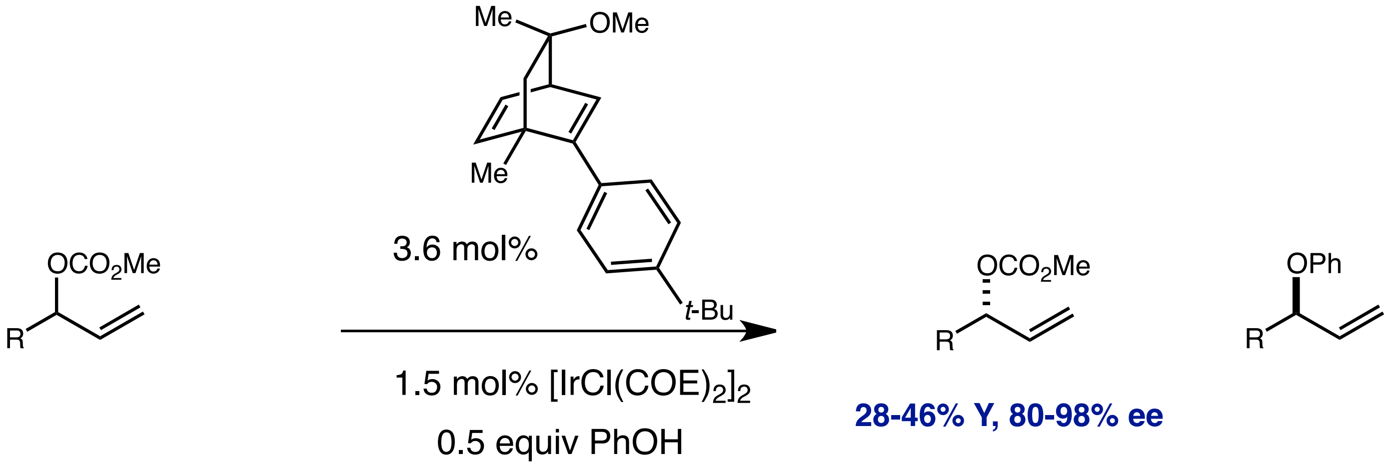




Nishimura, T.; Maeda, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7324.

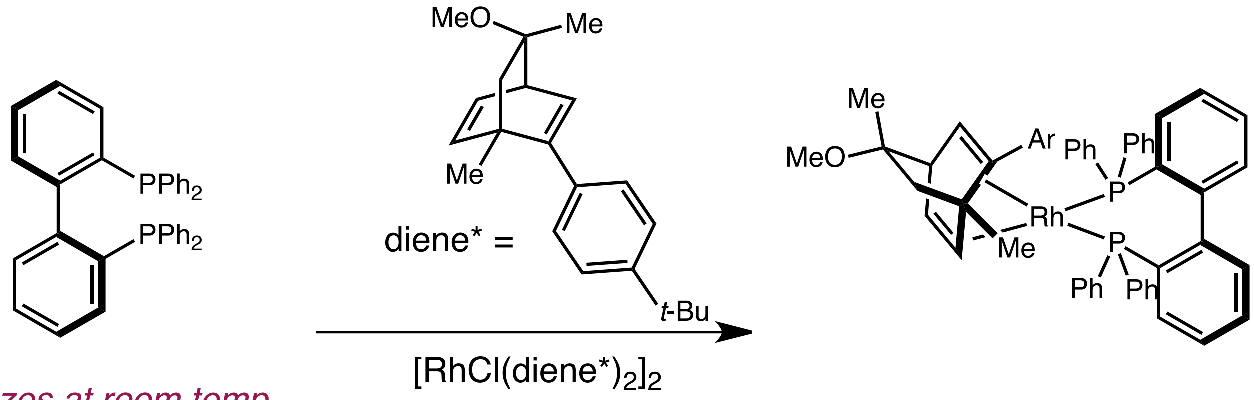
Chiral Dienes in Resolutions

- Carreira's seminal publication: kinetic resolution of allyl carbonates

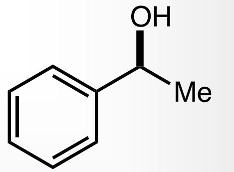


28-46% Y, 80-98% ee

- Resolution of BIPHEP



racemizes at room temp



57% Y, 12% ee

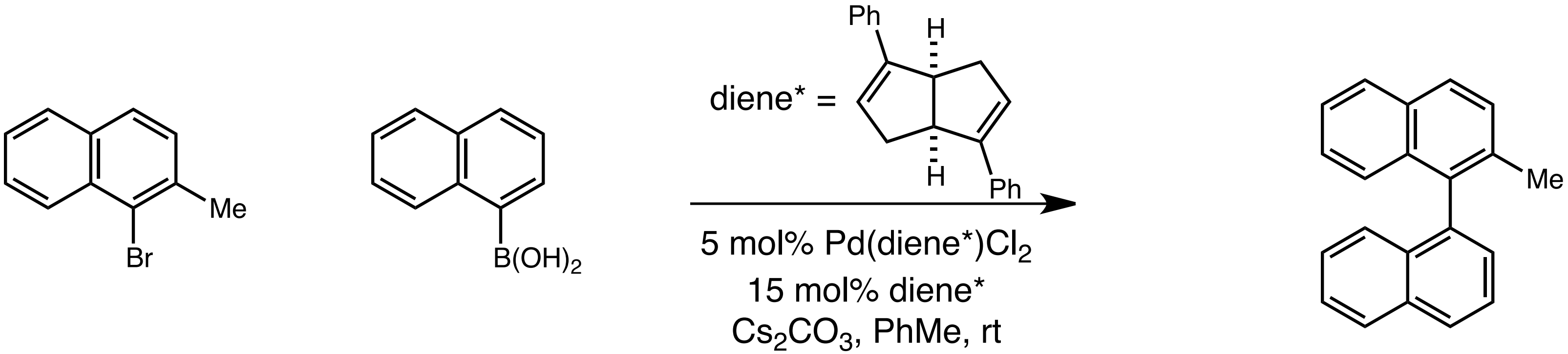
hydroboration of styrene

Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

Faller, J. W.; Wilt, J. C. *J. Organomet. Chem.* **2006**, *691*, 2207.

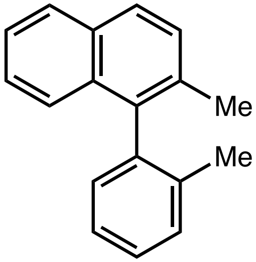
Chiral Dienes in Suzuki–Miyaura Coupling

- First enantioselective reaction employing Pd-diene catalyst

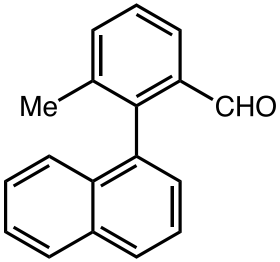


78% Y, 90% ee

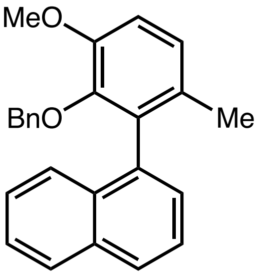
- Scope



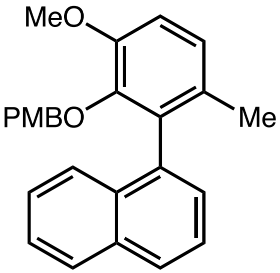
90% Y, 84% ee



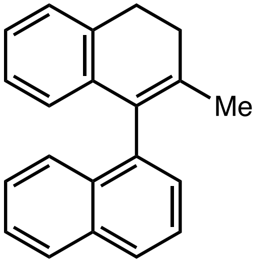
90% Y, 73% ee



93% Y, 65% ee



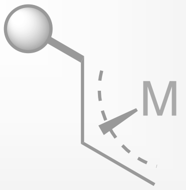
83% Y, 65% ee



72% Y, 48% ee

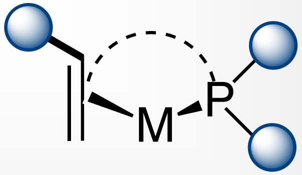
Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5546.

Classes of Chiral Olefins

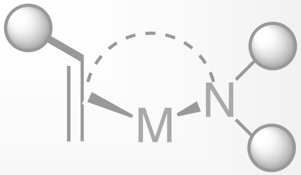


π-allyl

diene



phosphane-olefin

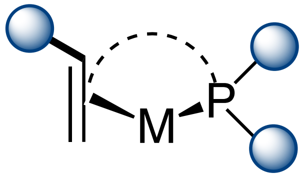


amine-olefin

Chiral Phosphane-Olefin Ligands

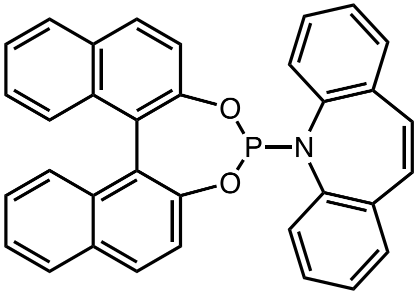
- Hybrid ligands combine advantages of phosphanes and olefins

good chiral environment
about metal

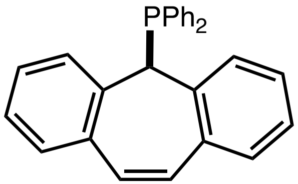


strong coordination ability

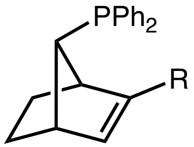
- Classes of chiral phosphane-olefin ligands



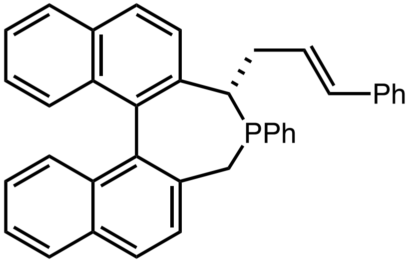
Carreira



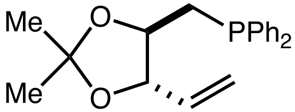
Grützmacher



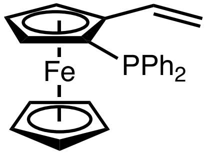
Hayashi



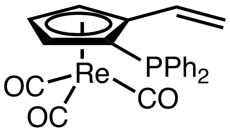
Widhalm



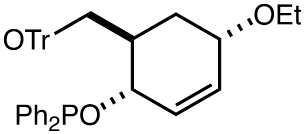
Du



Stepnicka



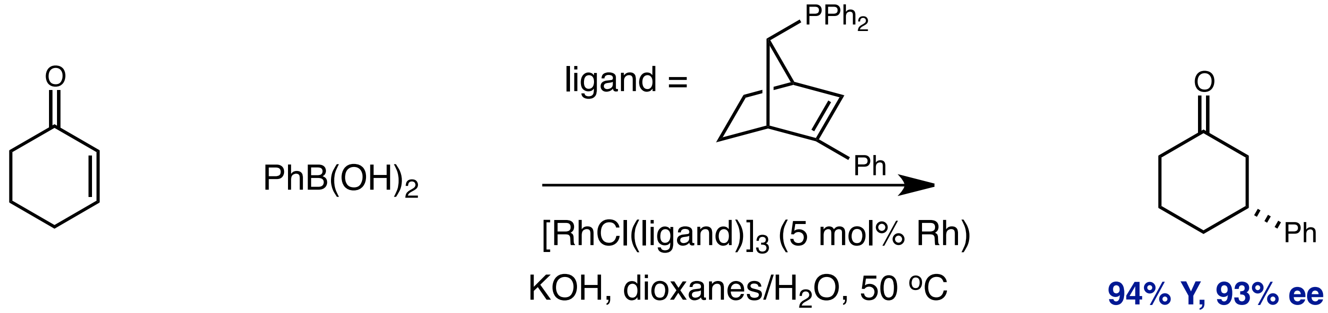
Bolm



Boysen

Chiral Phosphane-Olefin Ligands

- Phosphane-olefin ligands also participate in 1,4-additions



$PhB(OH)_2$

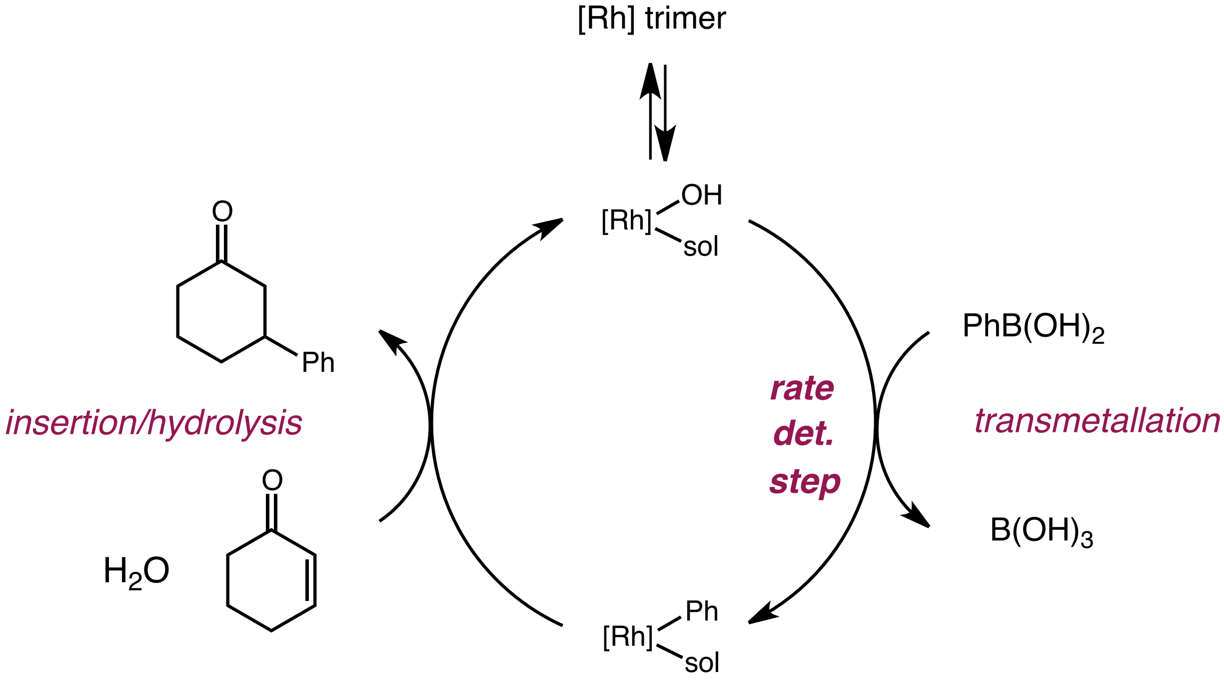
ligand =

$[RhCl(ligand)]_3$ (5 mol% Rh)

KOH, dioxanes/H_2O, 50 ^oC

94% Y, 93% ee

- Reactivity is similar to diene ligand



[Rh] trimer

[Rh]–OH / sol

$PhB(OH)_2$

transmetallation

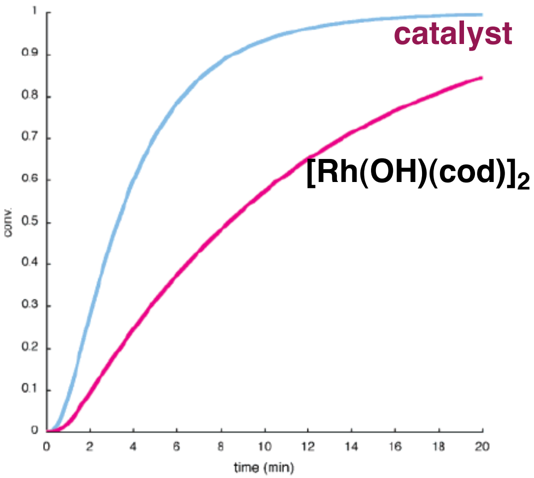
$B(OH)_3$

rate det. step

[Rh]–Ph / sol

H_2O

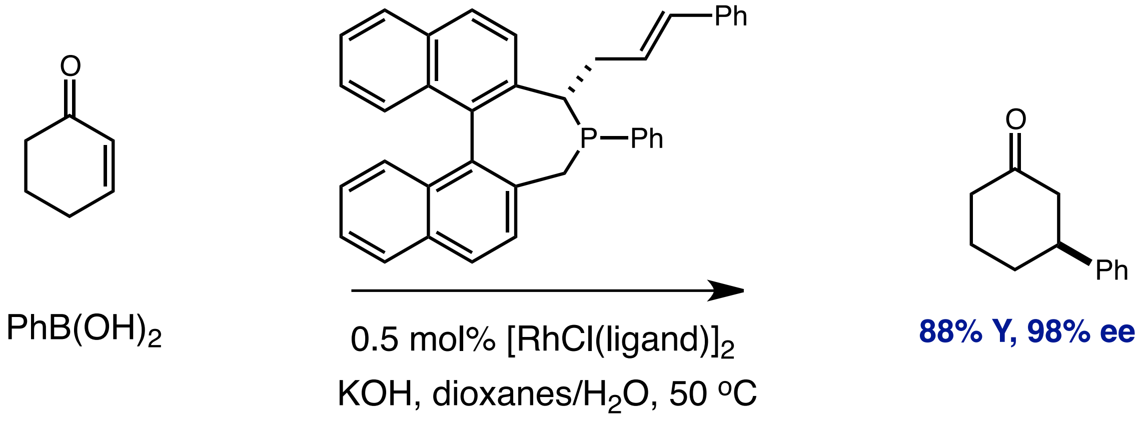
insertion/hydrolysis



Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130.

Chiral Phosphane-Olefin Ligands

- Wilhalm's ligand improves reactivity/selectivity

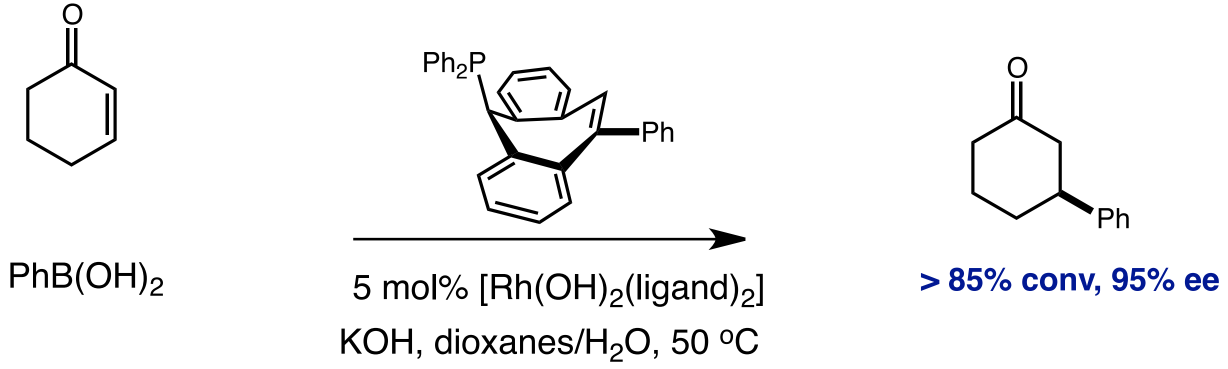


$PhB(OH)_2$

0.5 mol% $[RhCl(ligand)]_2$
KOH, dioxanes/H_2O, 50 °C

88% Y, 98% ee

- Tropp ligands are versatile



$PhB(OH)_2$

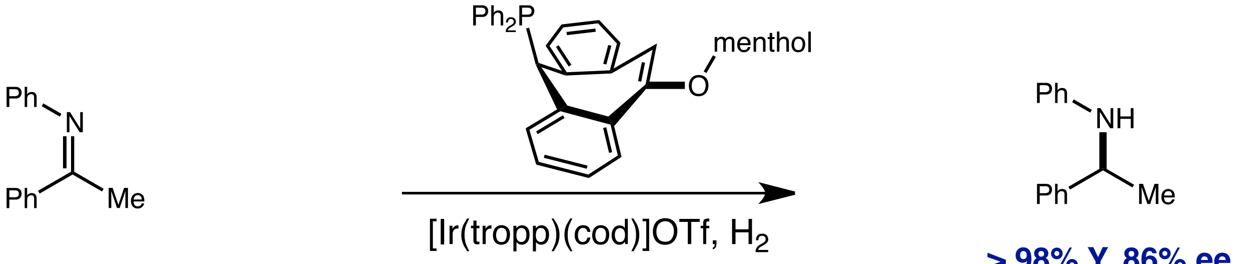
5 mol% $[Rh(OH)_2(ligand)_2]$
KOH, dioxanes/H_2O, 50 °C

> 85% conv, 95% ee

Kasak, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, 17*, 3084.*
Piras, E.; Lang, F.; Ruegger, H.; Stein, D.; Worle, M.; Grutzmacher, H. *Chem. Eur. J.* **2006**, *12*, 5849.

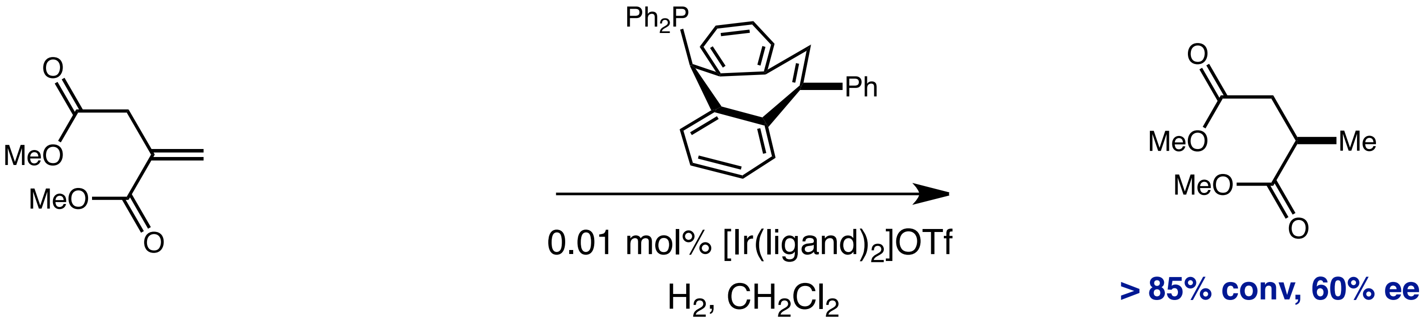
Chiral Phosphane-Olefin Ligands

- Hemilability of tropp ligand facilitates hydrogenation



> 98% Y, 86% ee

- Olefin hydrogenation



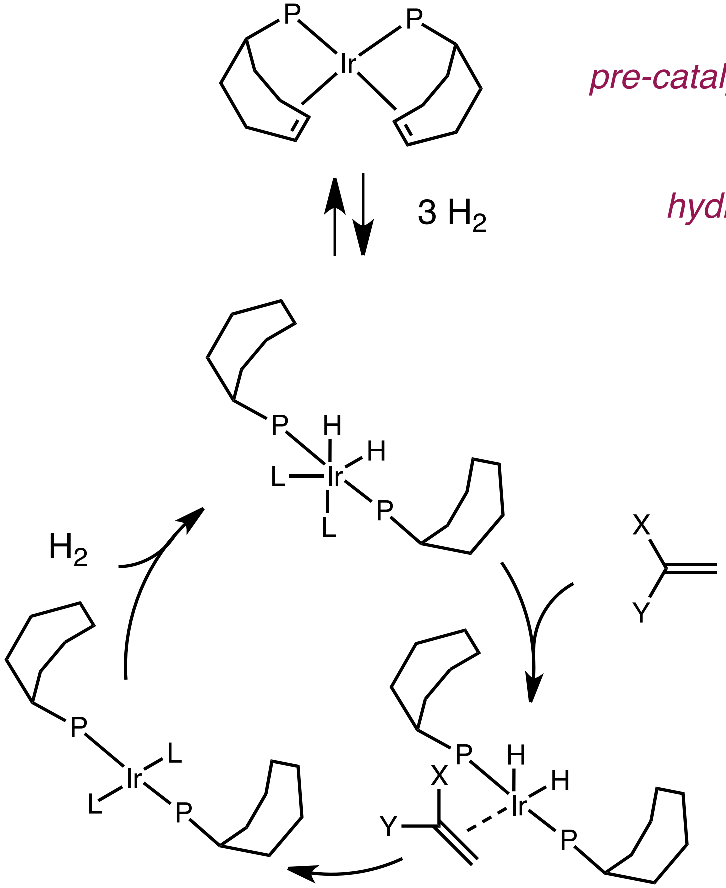
> 85% conv, 60% ee

Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Bohler, C.; Ruegger, H.; Schonberg, H.; Grutzmacher, H. *Chem. Eur. J.* **2004**, *10*, 4198.

Piras, E.; Lang, F.; Ruegger, H.; Stein, D.; Worle, M.; Grutzmacher, H. *Chem. Eur. J.* **2006**, *12*, 5849.

Chiral Phosphane-Olefin Ligands

- Hemilability of tropp ligand facilitates hydrogenation



pre-catalyst is bound to P and olefin

hydrogenation is reversible

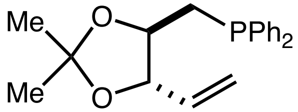
tropp ligand is hydrogenated
in active catalyst

Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Bohler, C.; Ruegger, H.; Schonberg, H.; Grutzmacher, H. *Chem. Eur. J.* **2004**, *10*, 4198.

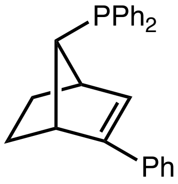
Piras, E.; Lang, F.; Ruegger, H.; Stein, D.; Worle, M.; Grutzmacher, H. *Chem. Eur. J.* **2006**, *12*, 5849.

Chiral Phosphane-Olefin Ligands

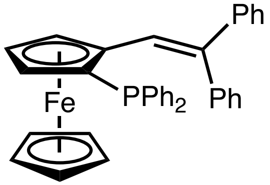
- Pd-allyl chemistry is now also possible



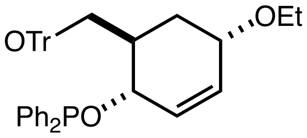
98% Y, 95% ee



87% Y, 96% ee



100% Y, 43% ee



90% Y, 61% ee

Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054.

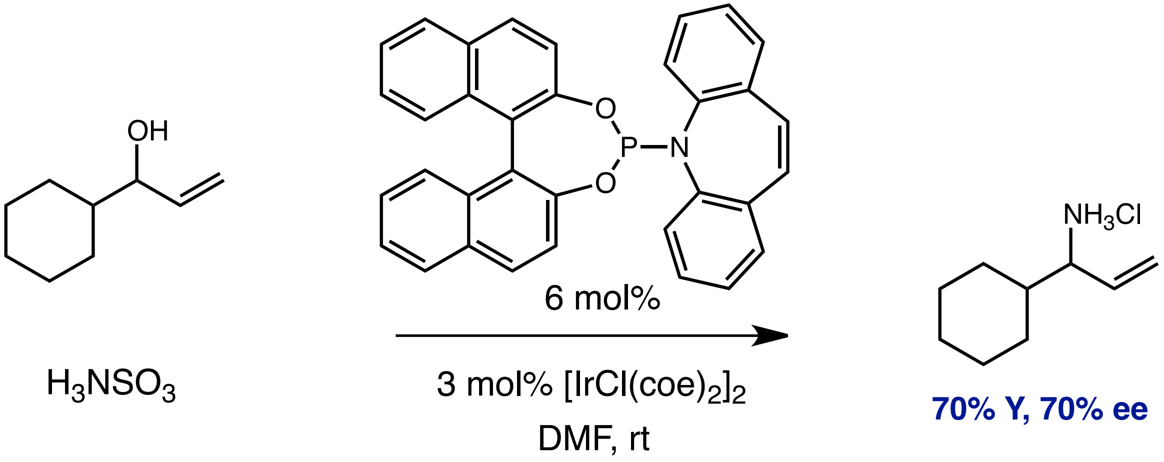
Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212.

Kasak, P.; Arion, W. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084.

Shintani, R.; Duan, W.-L.; Okamoto, K.; Hayashi, T. *Tetrahderon: Asymmetry* **2005**, *16*, 3400.

Chiral Phosphane-Olefin Ligands

- Carreira demonstrates allylic amination with Ir/P-olefin system



H_3NSO_3

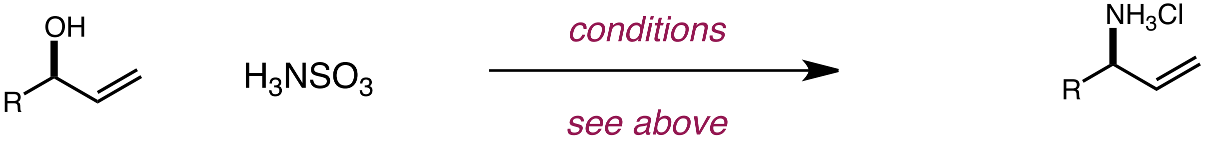
6 mol%

3 mol% $[IrCl(coe)_2]_2$

DMF, rt

70% Y, 70% ee

- Stereoretentive allylic amination



H_3NSO_3

conditions

see above

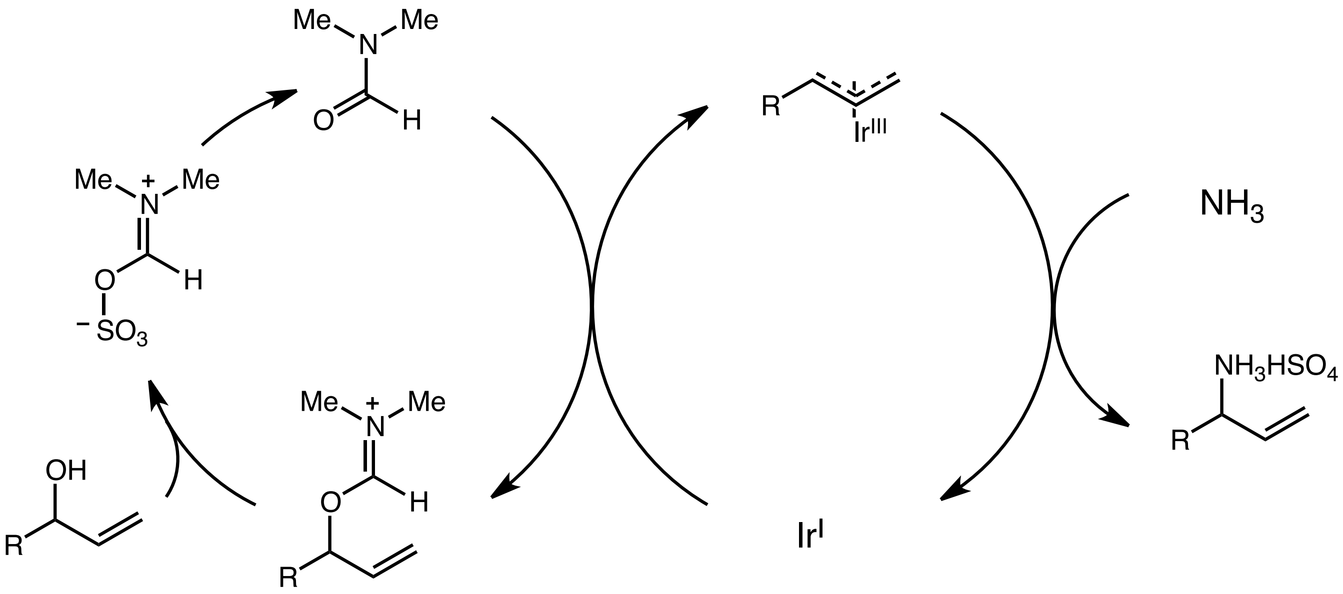
46-70% Y, 74-98% enantio-retention

Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917.

Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139.

Chiral Phosphane-Olefin Ligands

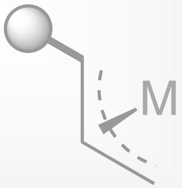
- Carreira demonstrates allylic amination with Ir/P-olefin system



Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917.

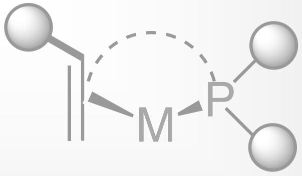
Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139.

Classes of Chiral Olefins

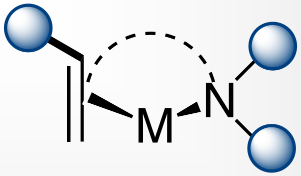


π-allyl

diene



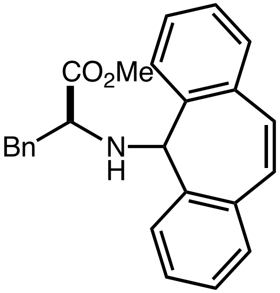
phosphane-olefin

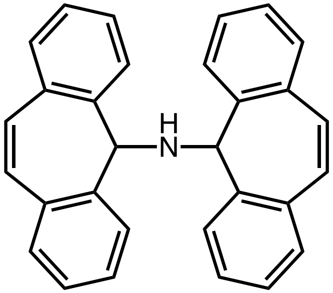


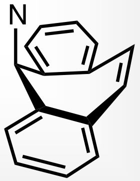
amine-olefin

Chiral Amine-Olefin Ligands

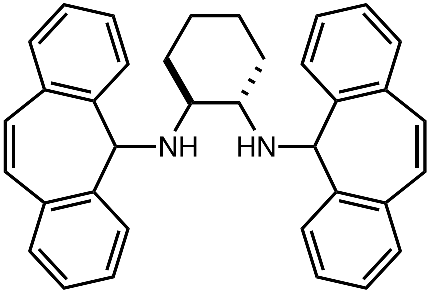
- Ligand lability is a challenge
- Unlike phosphane ligands, less prone to oxidation
- Based on phosphanyl-dibenzo-cycloheptene (tropp) framework

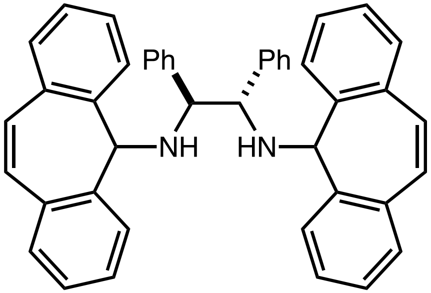






tropp





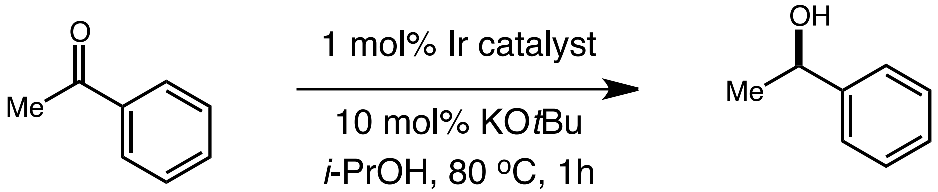
Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207.

Vogt, M.; de Bruin, B.; Berke, H.; Trincado, M.; Grützmacher, H. *Chem. Sci*. **2011**, *2*, 723.

Grützmacher, H.; Büttner, T.; Maire, P.; Ramseier, M.; Scheschkewitz, D.; Zweifel, T. DE 102004027771, **2006**; EP 05011539.3

Chiral Amine-Olefin Ligands

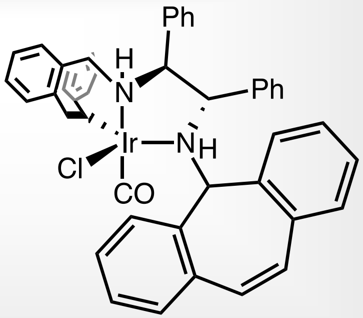
- Single example of asymmetric catalysis - Transfer hydrogenation



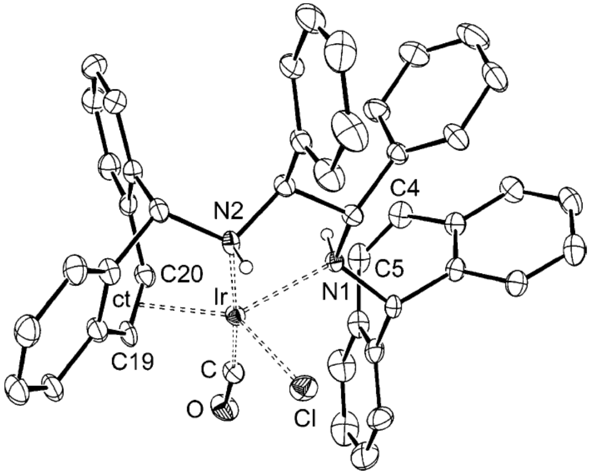
1 mol% Ir catalyst

10 mol% KO*t*Bu
i-PrOH, 80 ºC, 1h

>98% conv, 82% ee



(S,S)-[IrCl(CO)(trop$_2$dpen)]



Ir is bound to both N1 and N2 and C=C$_{tropp}$

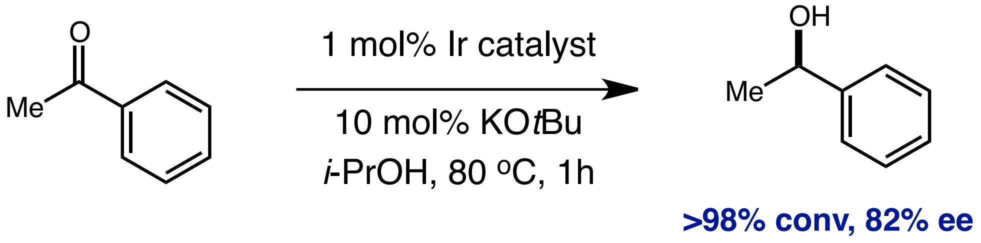
Ir–C=C$_{tropp}$ =1.968 Å

C=C$_{tropp}$ = 1.501 Å

Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207.

Chiral Amine-Olefin Ligands

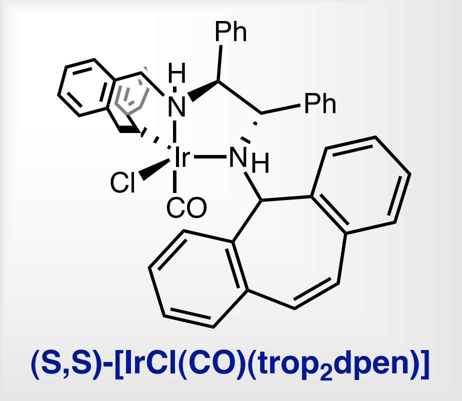
- Single example of asymmetric catalysis - Transfer hydrogenation



1 mol% Ir catalyst

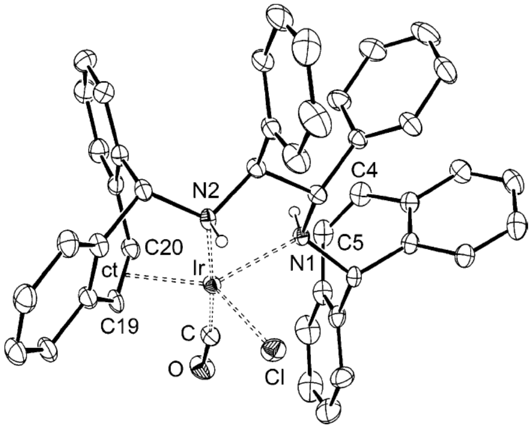
10 mol% KO*t*Bu
i-PrOH, 80 ºC, 1h

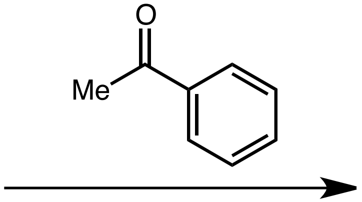
>98% conv, 82% ee



(S,S)-[IrCl(CO)(trop$_2$dpen)]

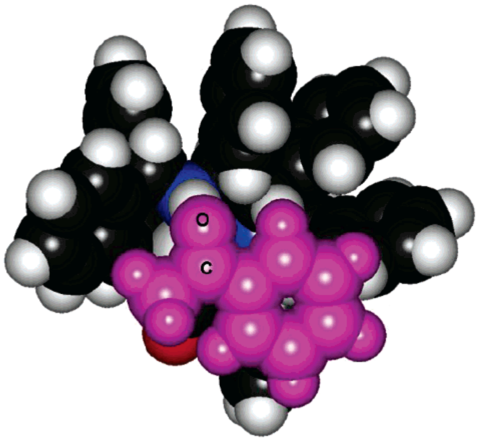
$$\mathrm{IrCl(CO)(trop_2dpen)} \xrightarrow{\mathrm{KO}t\mathrm{Bu}} \mathrm{Ir(CO)(trop_2dpen\text{-}H)} \xrightarrow{i\text{-}\mathrm{PrOH}} \mathrm{IrH(CO)(trop_2dpen)}$$





C=O H-bond to NH

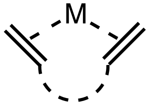
Ir-H is equatorial



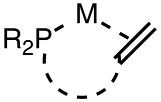
Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207.

Final Thoughts

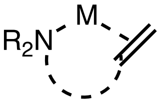
- Young and acelerating field
- Ligand classes:



diene

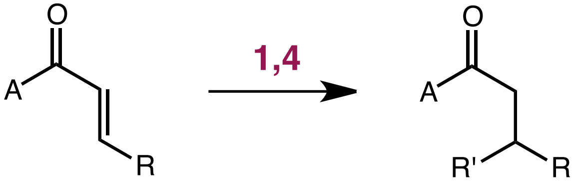


phosphane-olefin

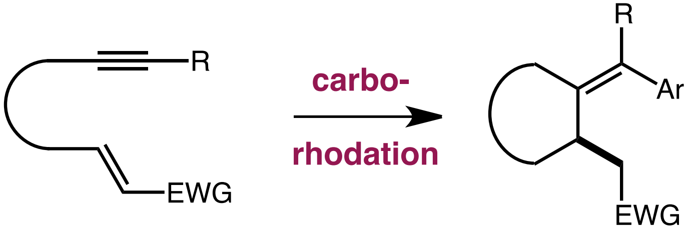


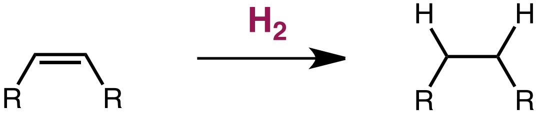
amine-olefin

- Late transition metals: Pd, Rh, Ir
- Reaction types:

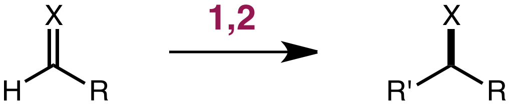


Cycloaddition





Chiral Resolution



- Advantages: novel/improved reactivity, low catalyst loading, mild conditions, chiral about metal
- Disadvantages: field is still at start of development, ligand synthesis challenging