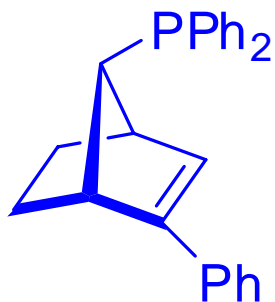


Development of Chiral Phosphine–Olefin Ligands and Their Use in Asymmetric Catalysis



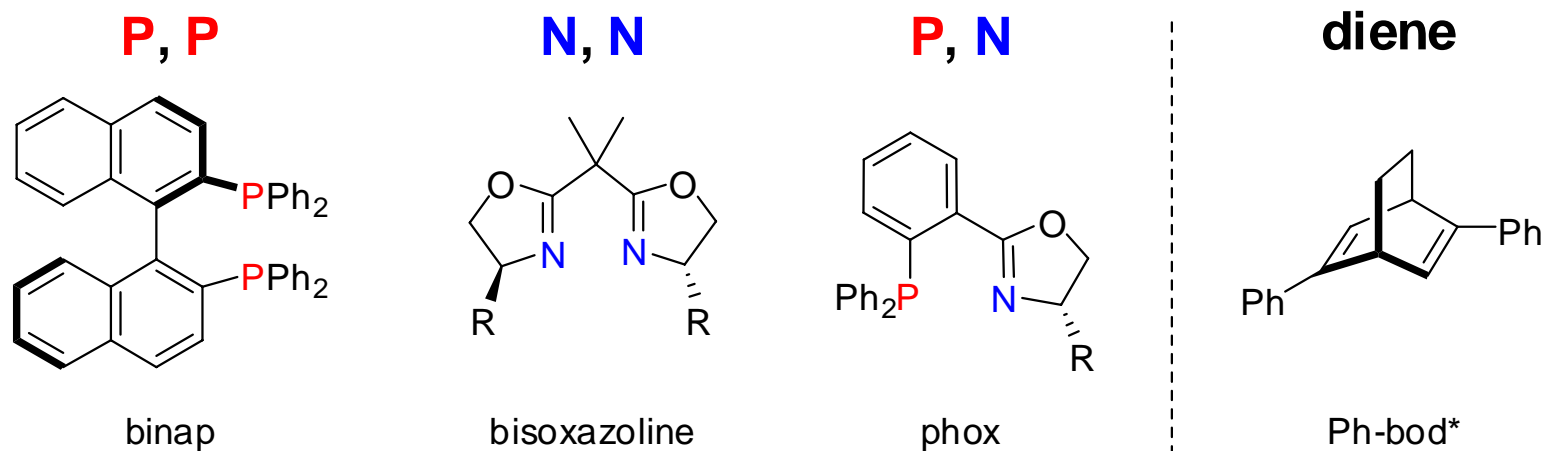
Wei-Liang Duan

July 31, 2007

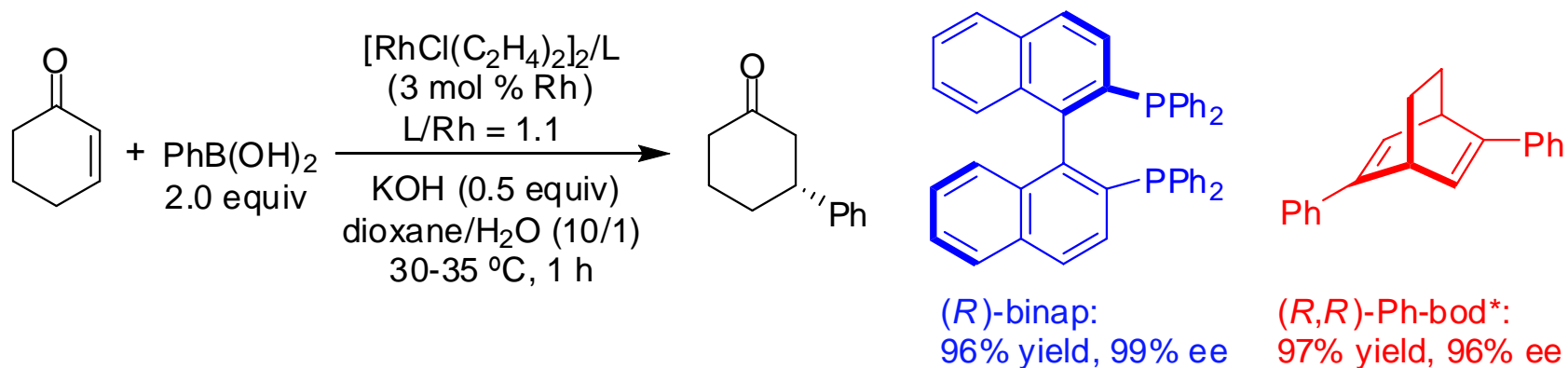
Research Works in Hayashi Group, Kyoto University
(Oct, 2003 – Mar, 2007)

Conventional Chiral Ligands in Asymmetric Catalysis

1



(*R*)-Binap and (*R,R*)-Ph-bod* in the Rhodium-Catalyzed 1,4-Addition of Phenylboronic to Cyclohexenone



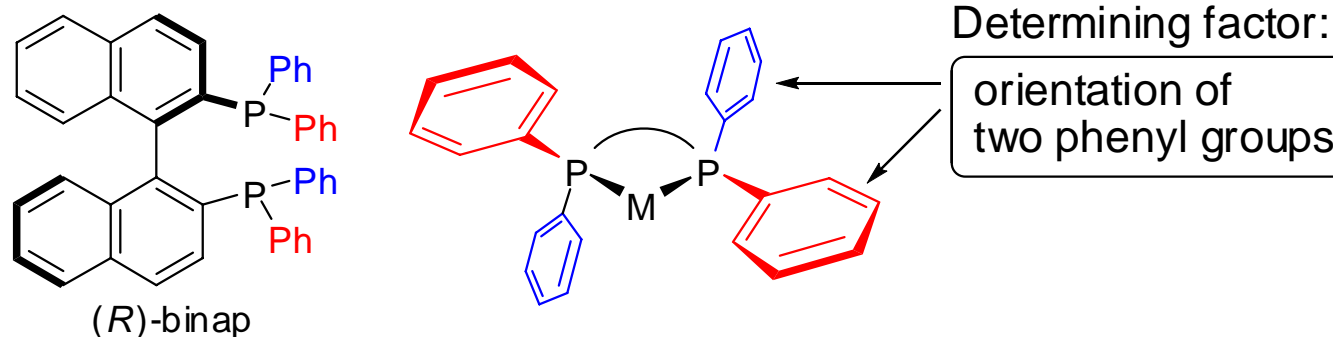
Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, 124, 5052.

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

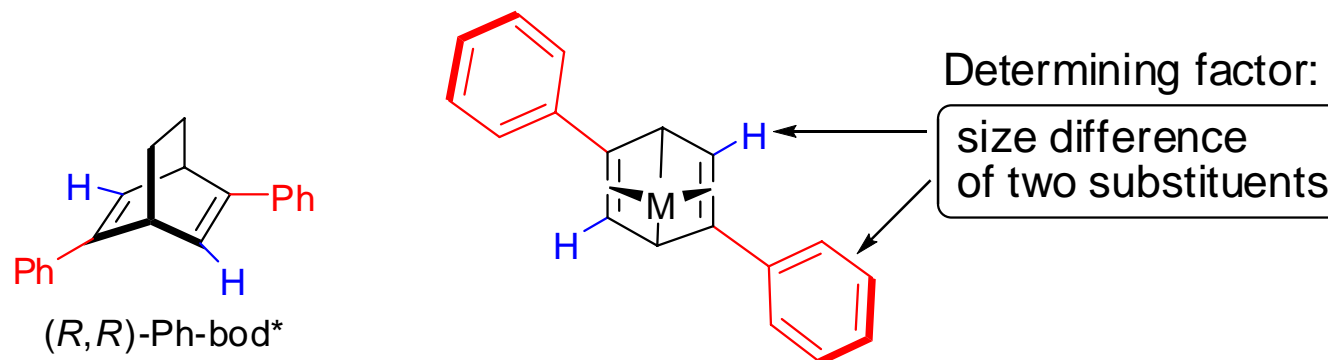
Chiral Environment of Metal–Ligand* Complexes

2

C_2 -Symmetric Bisphosphine Ligand

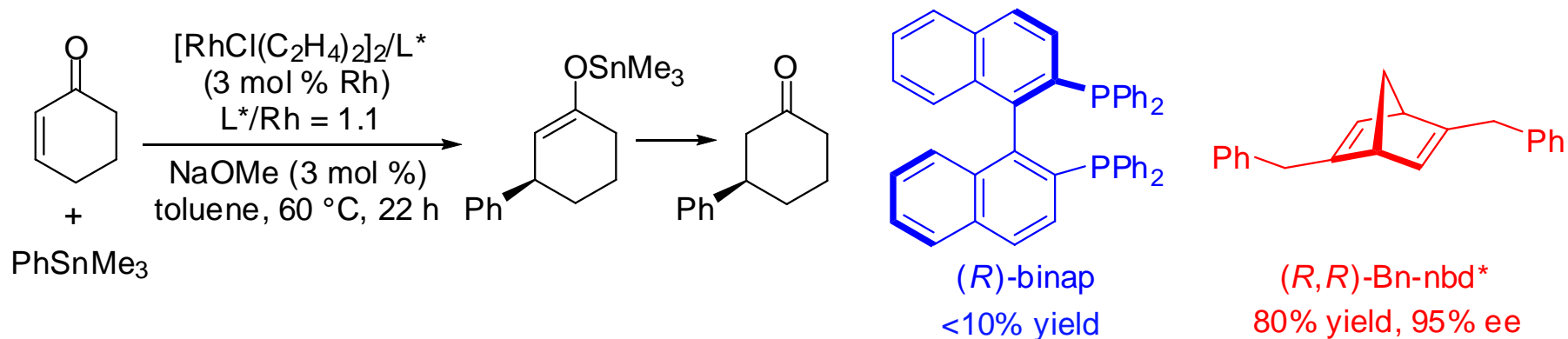


C_2 -Symmetric Diene Ligand

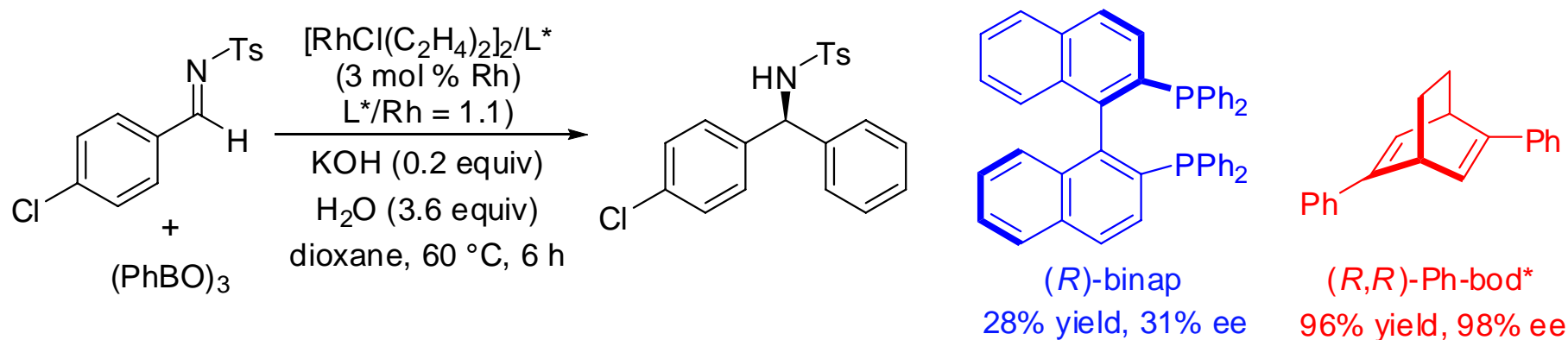


Chiral Diene Ligands vs Binap in Asymmetric Catalysis

3

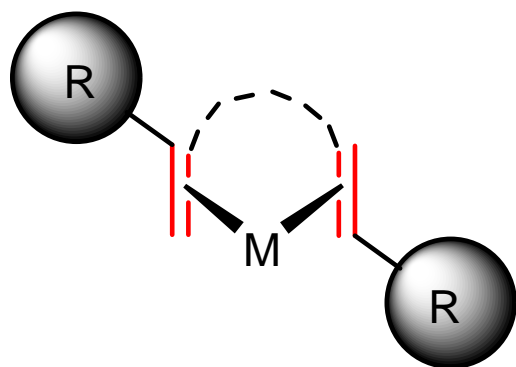


Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, 125, 11508.

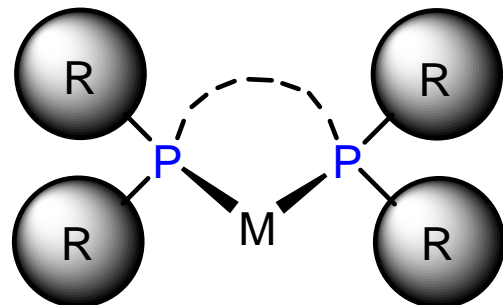


Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, 126, 13584.

Feature of Chiral Diene

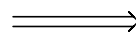


good chiral environment
low coordination ability



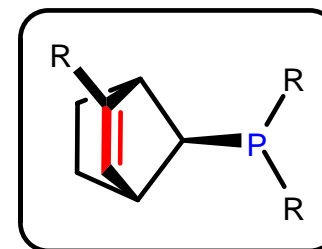
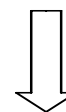
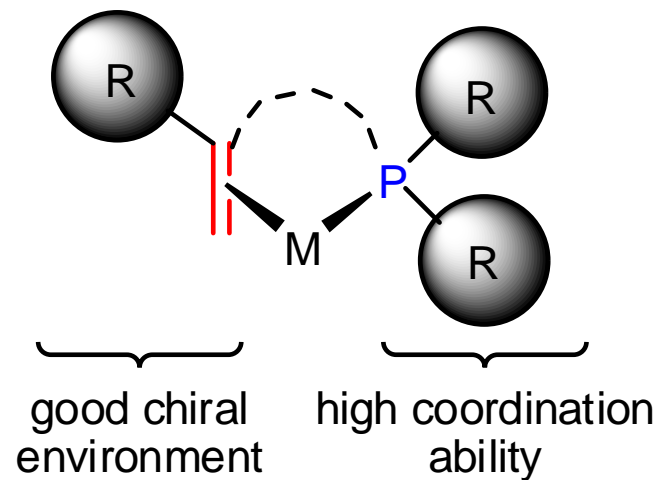
high coordination ability

combination



Design of Novel Chiral Phosphine–Olefin Ligands

4

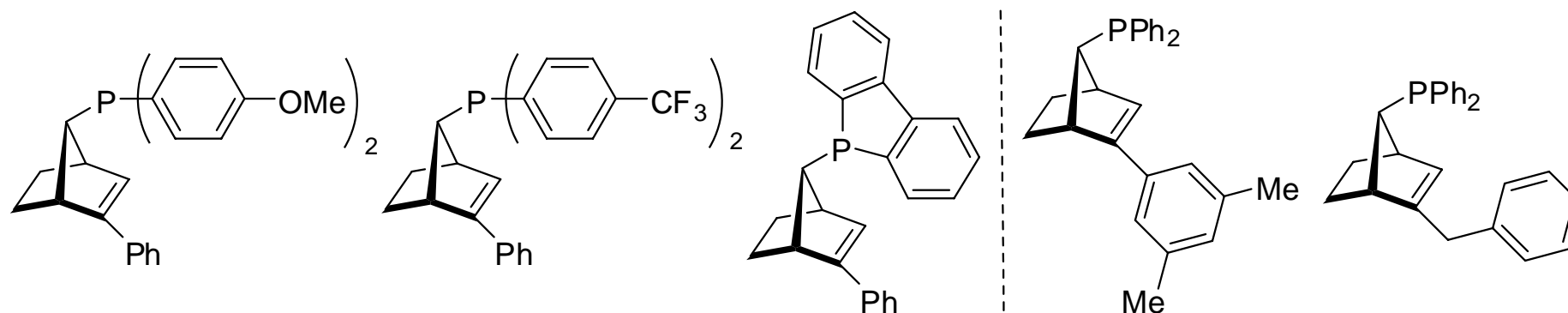
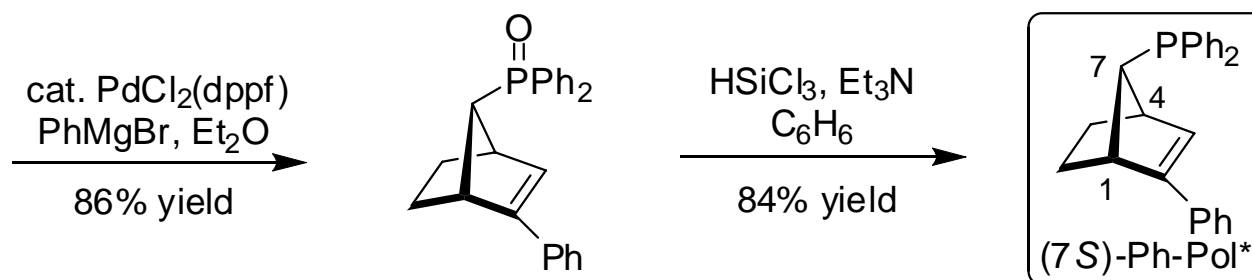
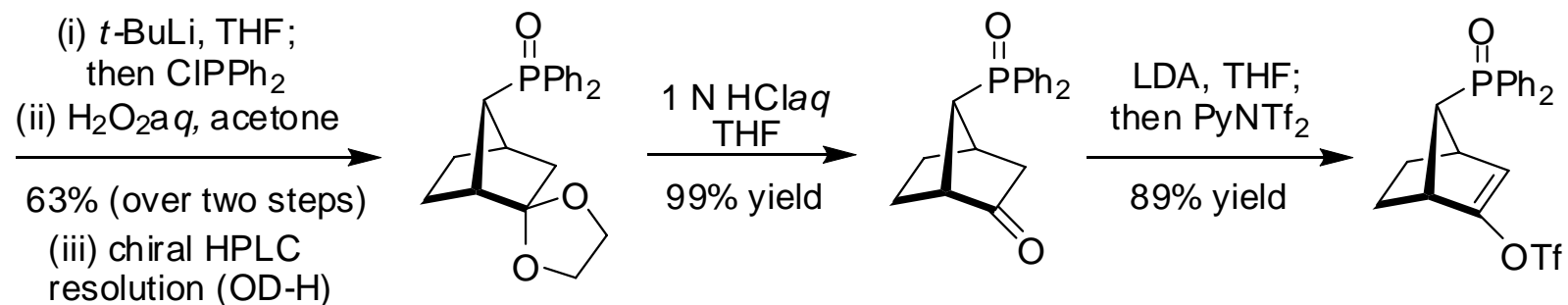
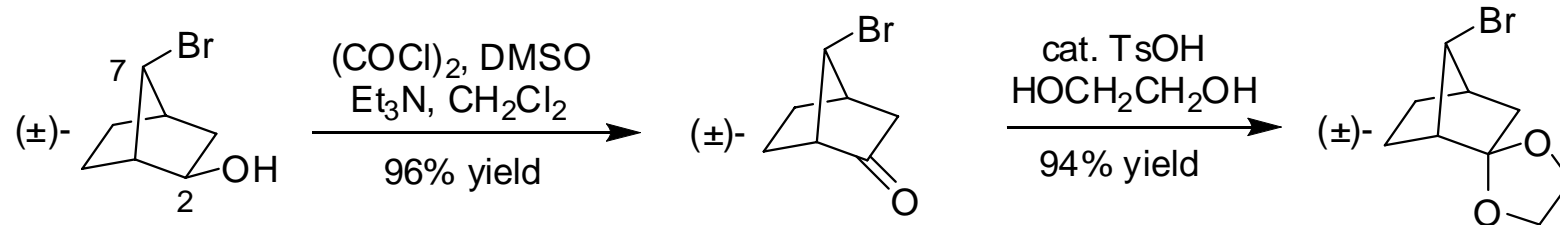


Our Target Structure

For the first example of chiral phosphine–olefin ligand:
Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhrer, C.; Rügger, H.;
Schönberg, H.; Grützmacher, H. *Chem. Eur. J.* **2004**, *10*, 4198.

Preparation of Phosphine–Olefin Ligands

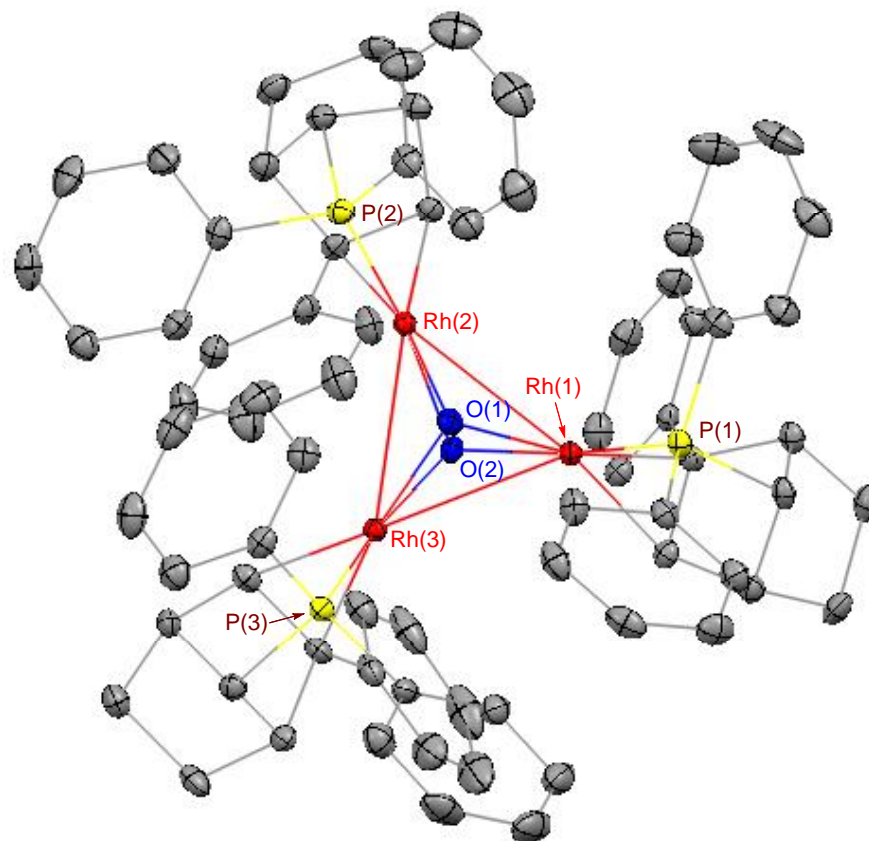
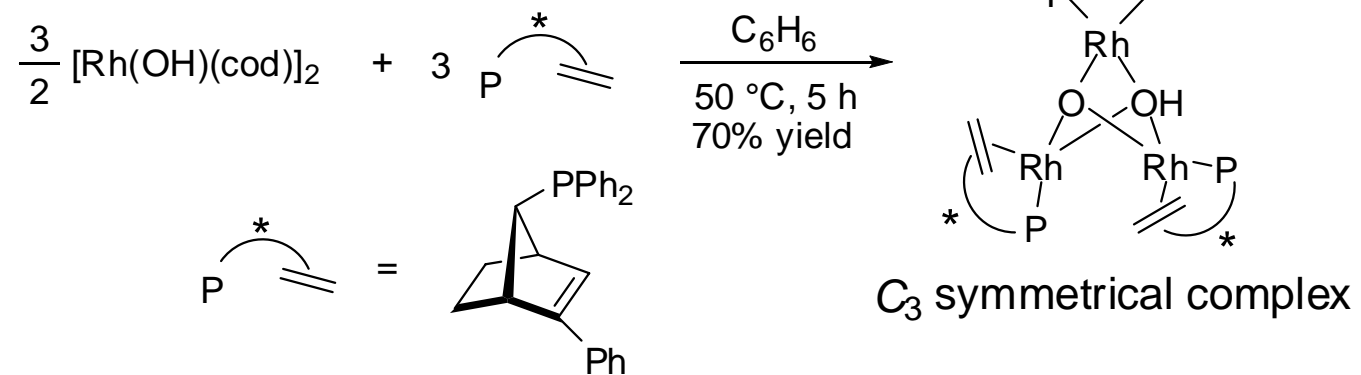
5



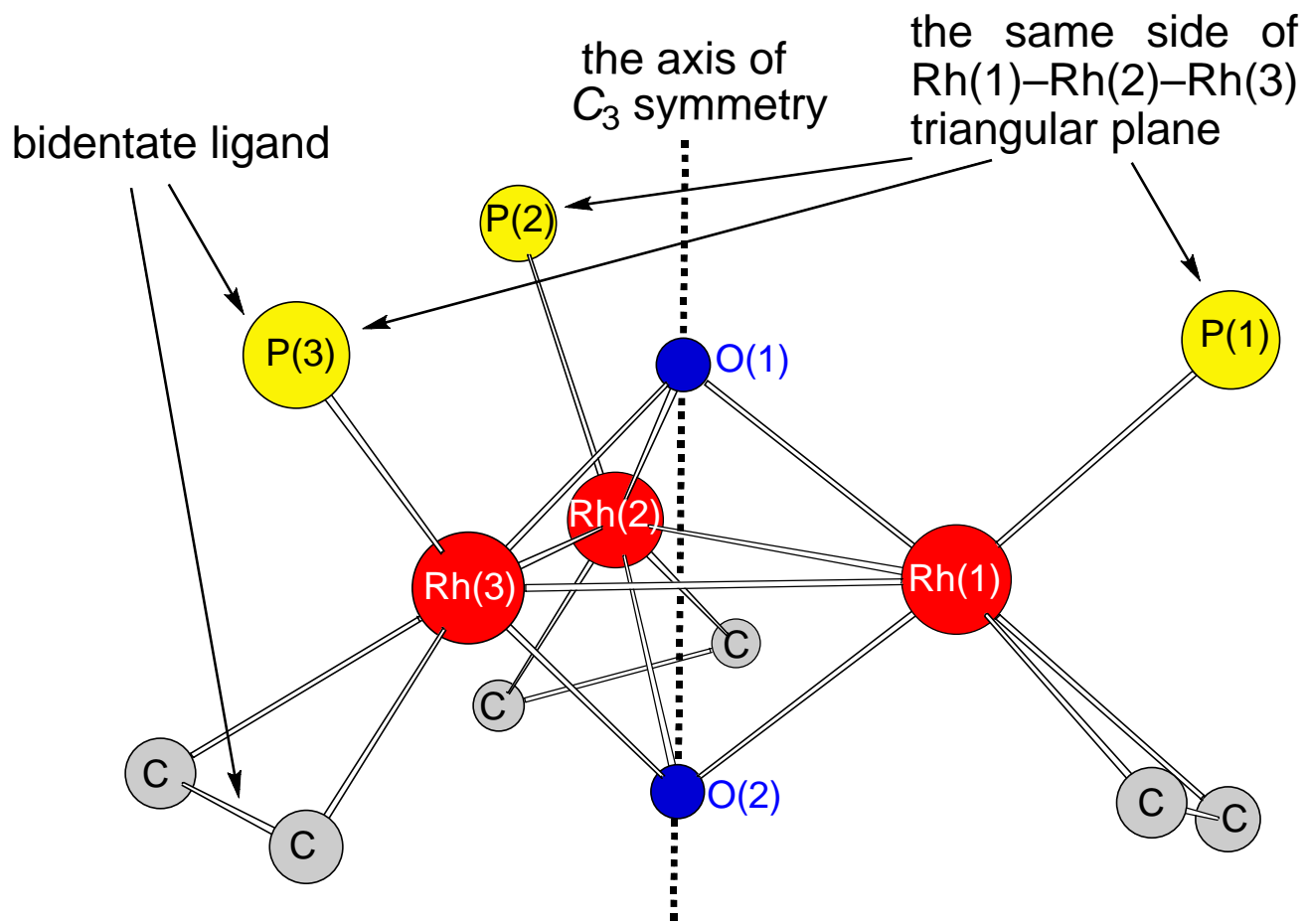
Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611.

Structure of a Rhodium/(7*S*)-Ph-Pol* Complex

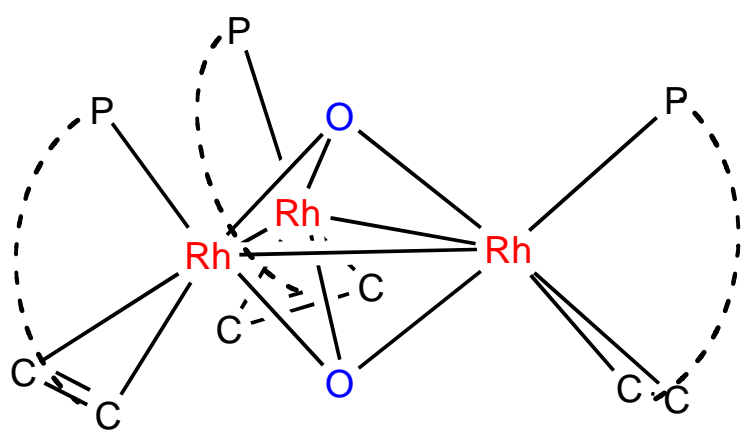
6



Structural Feature of Rh/Ph-Pol* Trimeric Complex

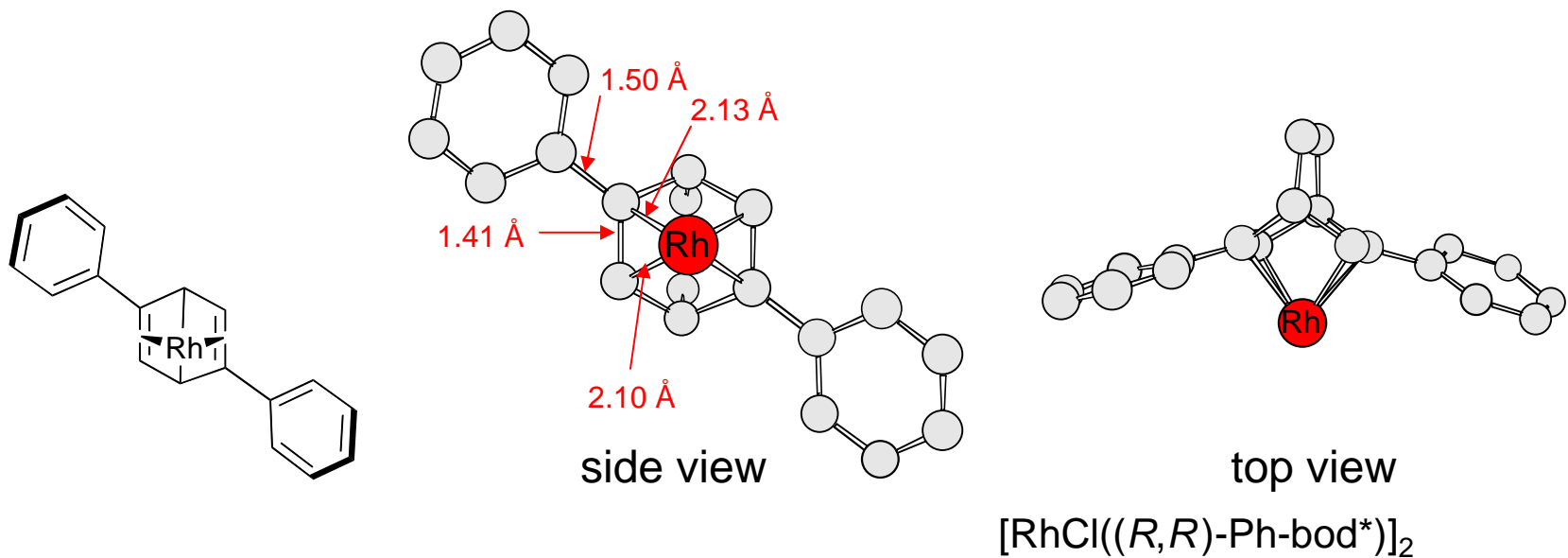
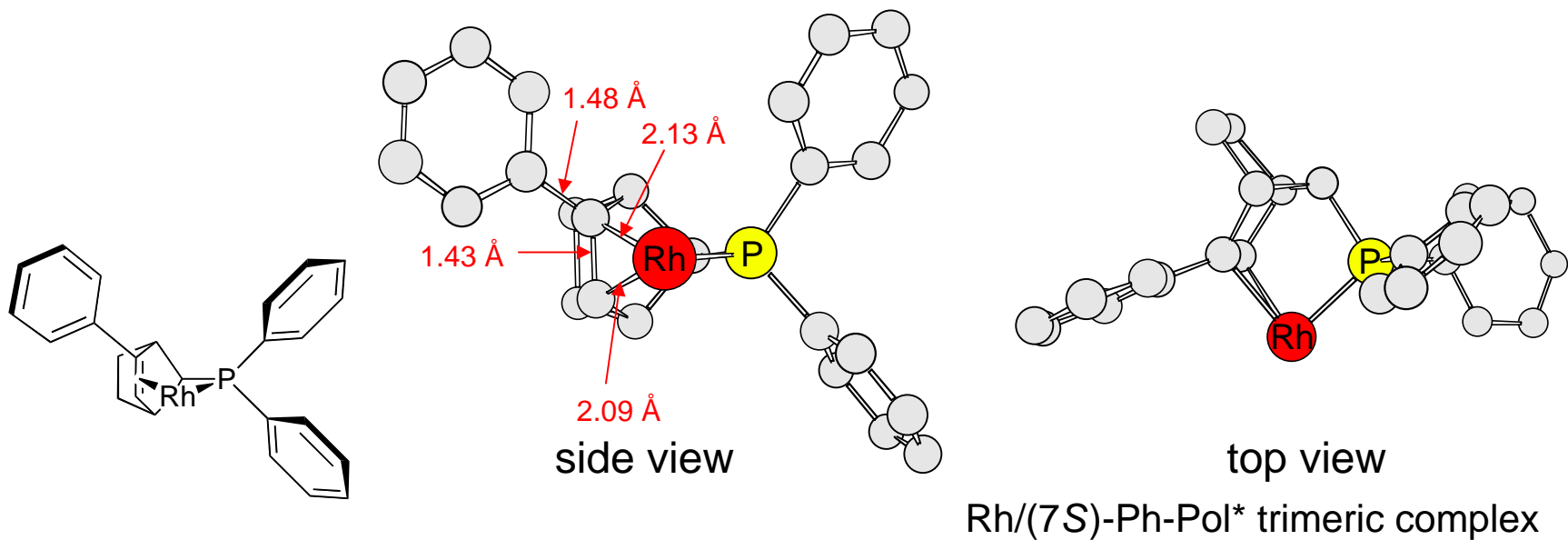


Rh/(7S)-Ph-Pol* trimeric complex



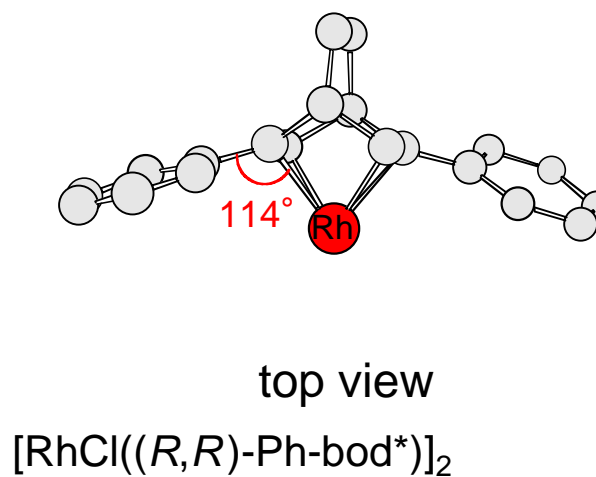
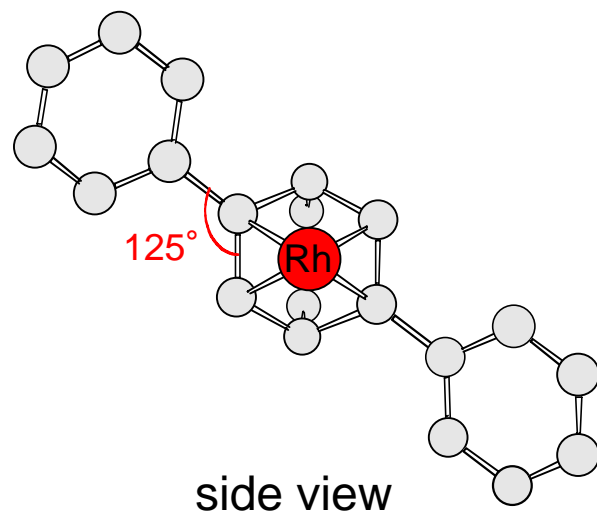
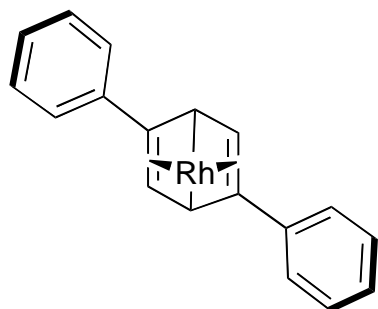
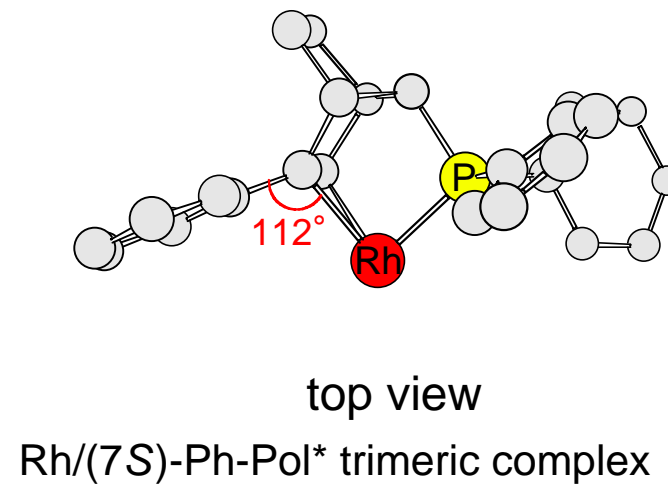
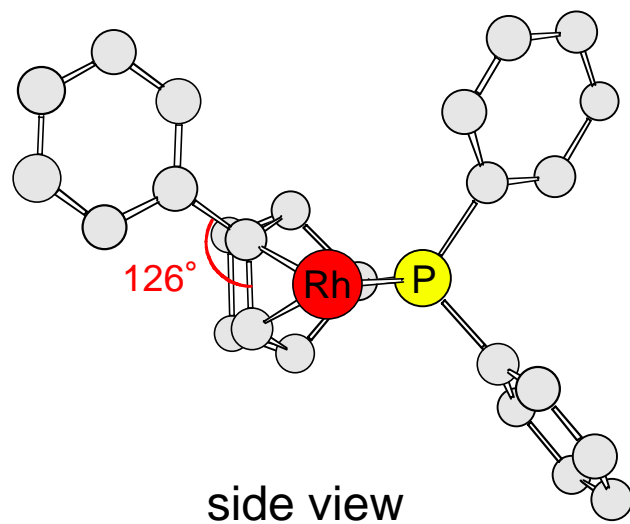
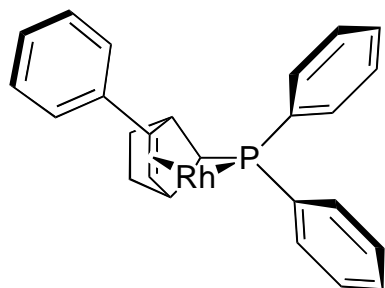
Comparison of Selected Bond Distances and Angles

8



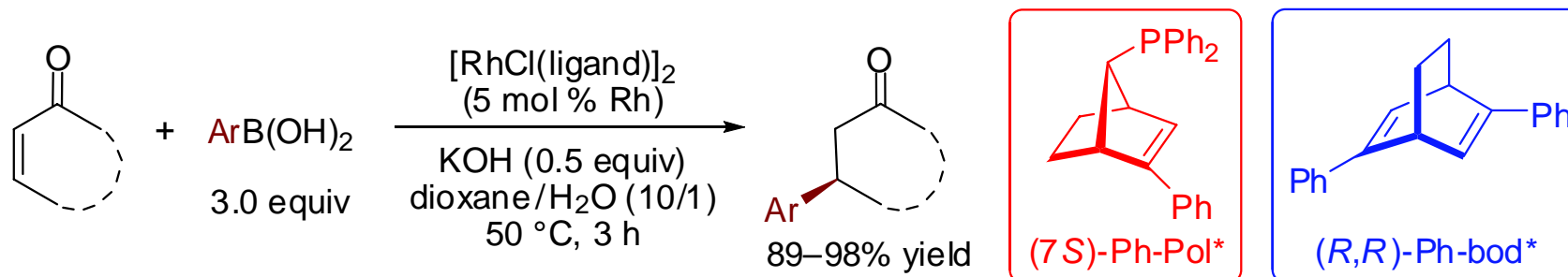
Comparison of Selected Bond Distances and Angles

8

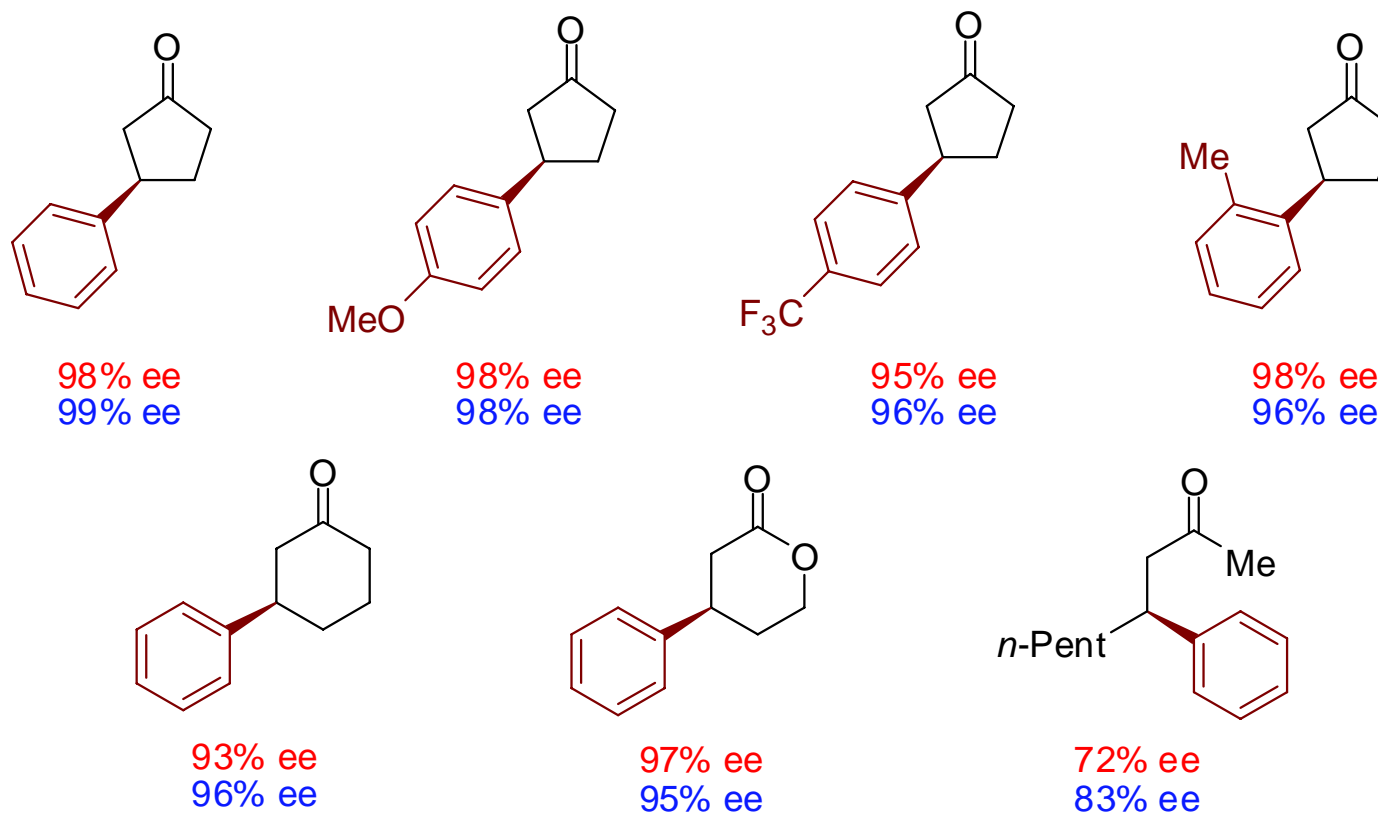


Phosphine–Olefin (*7S*)-Ph-Pol* vs (*R,R*)-Ph-bod* in the Rhodium-Catalyzed Asymmetric 1,4-Addition

9

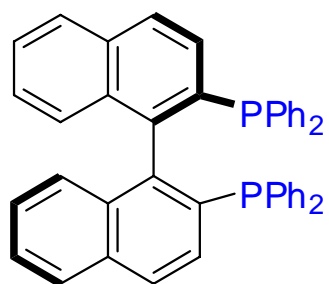
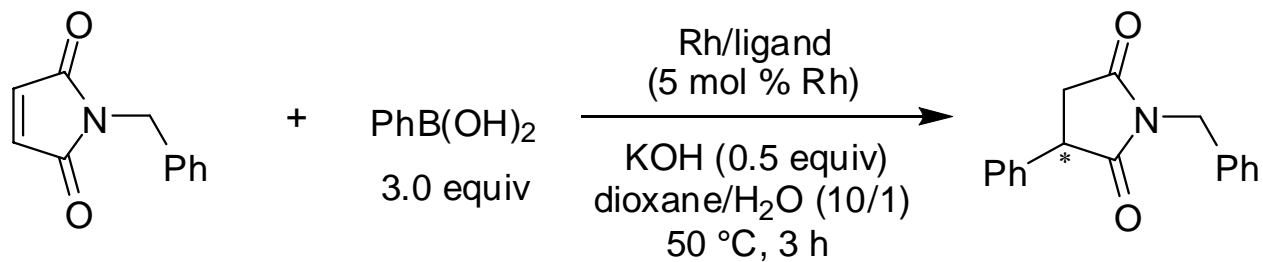


(7S)-Ph-Pol* vs *(R,R)*-Ph-bod*:
similar trend in chiral induction \longrightarrow stereocontrol by olefin chirality in *(7S)*-Ph-Pol*



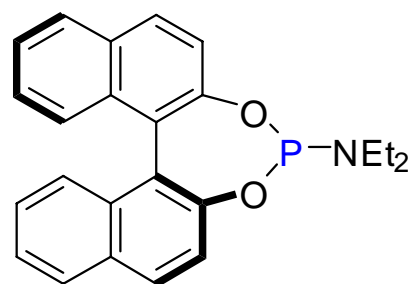
Ligand Effect in the Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid to 1-Benzylmaleimide

10



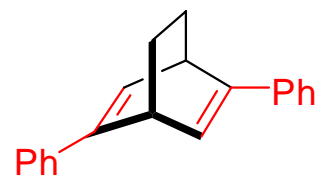
(*R*)-binap

70% yield, 58% ee



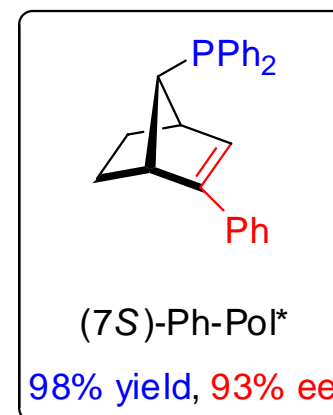
(*S*)-phosphoramidite-NEt₂

100% yield, 45% ee



(*R,R*)-Ph-bod*

18% yield, 91% ee

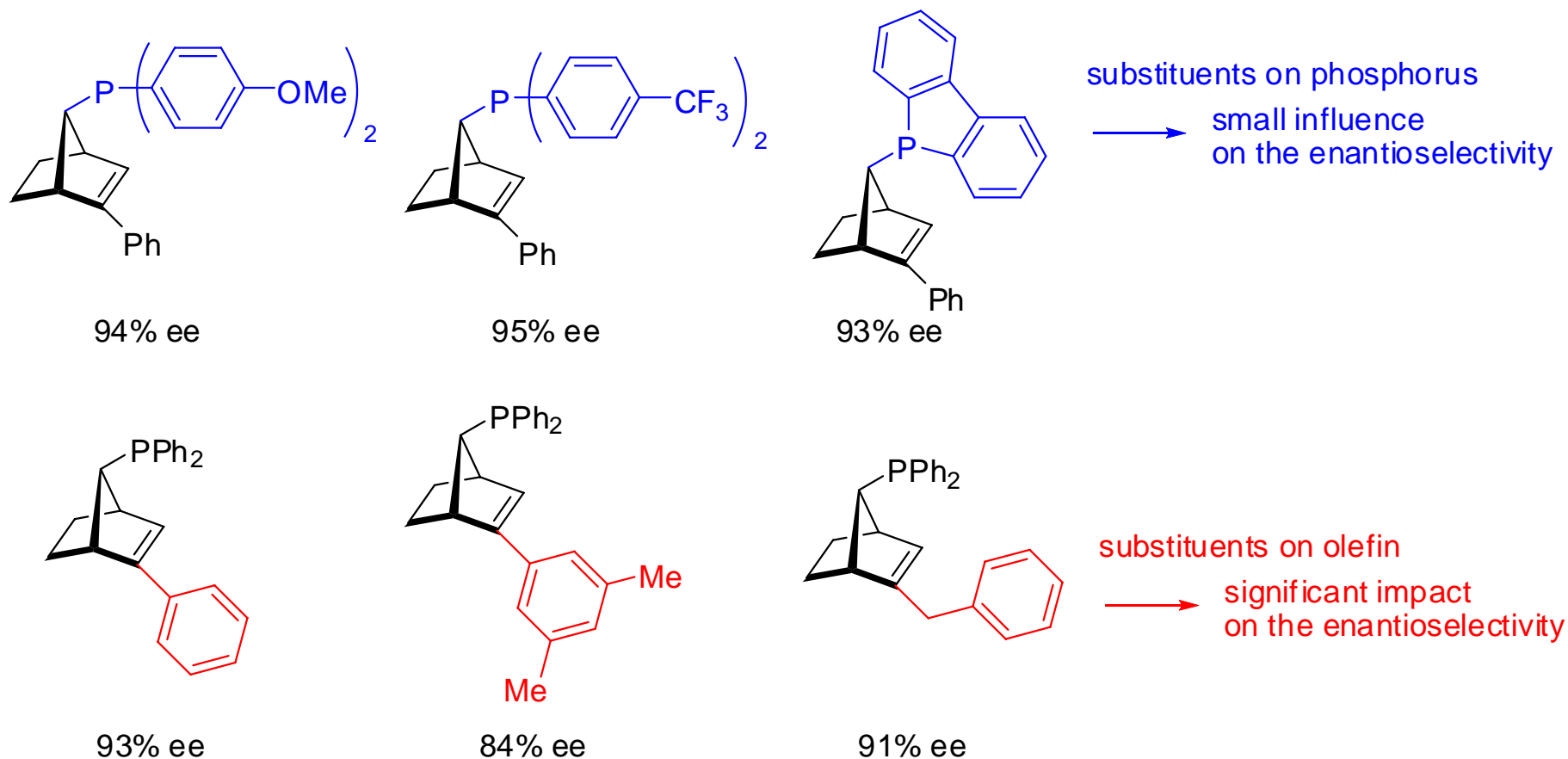
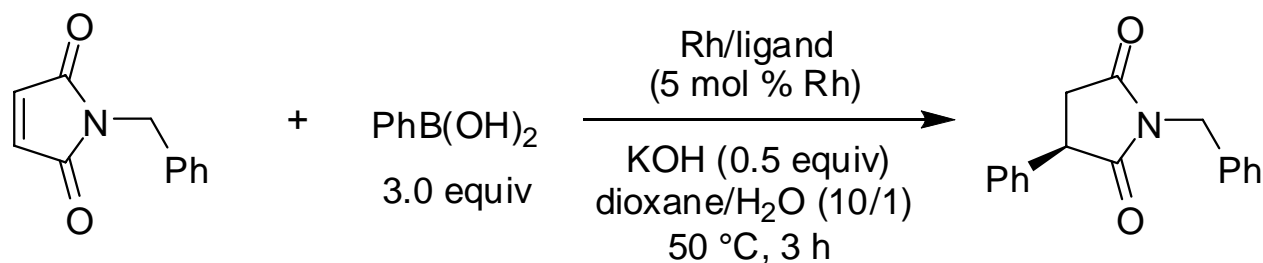


high yield

high ee

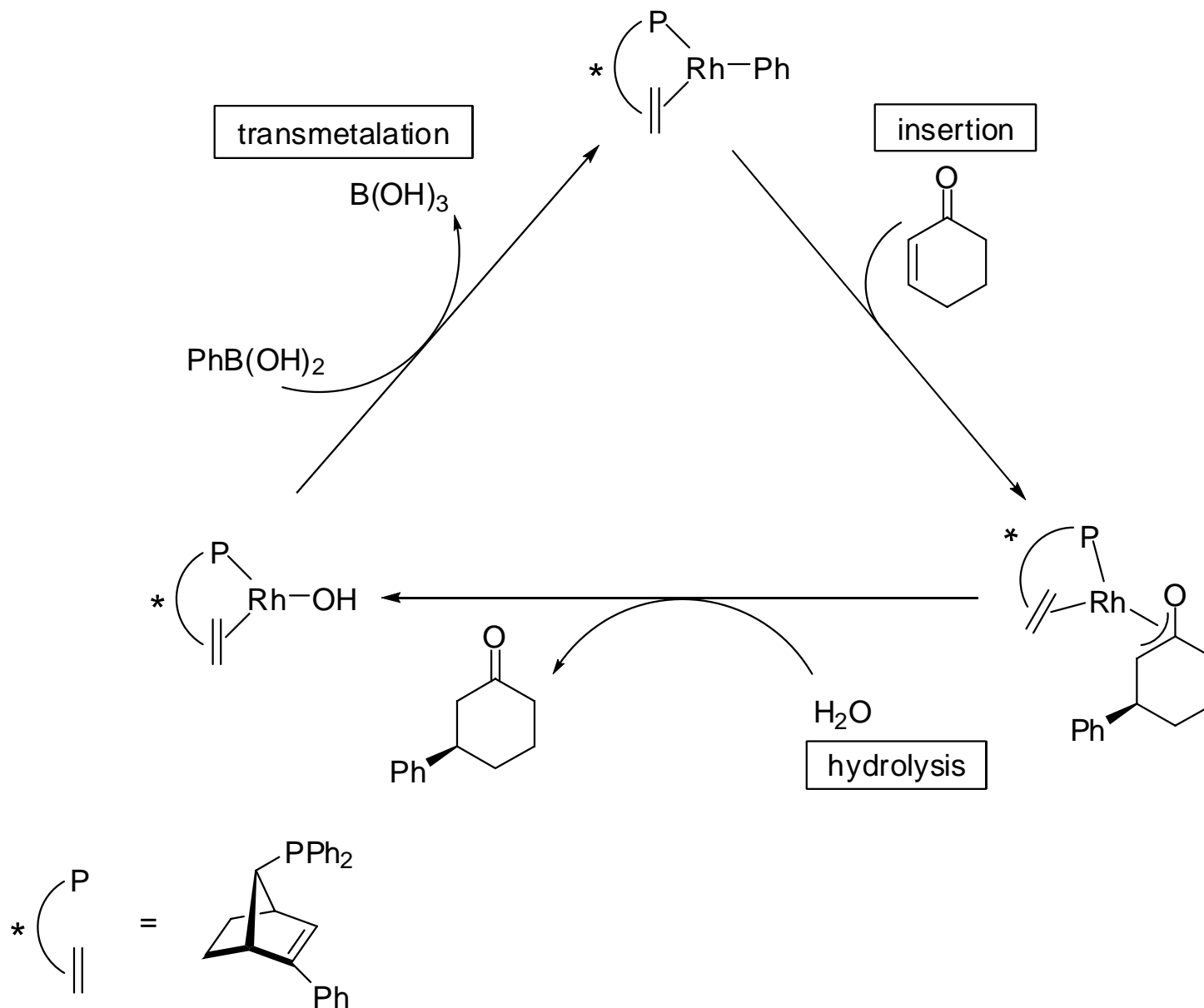
Phosphine vs Olefin: Ligand Substituent Effect in the Rhodium-Catalyzed Asymmetric 1,4-Addition

11

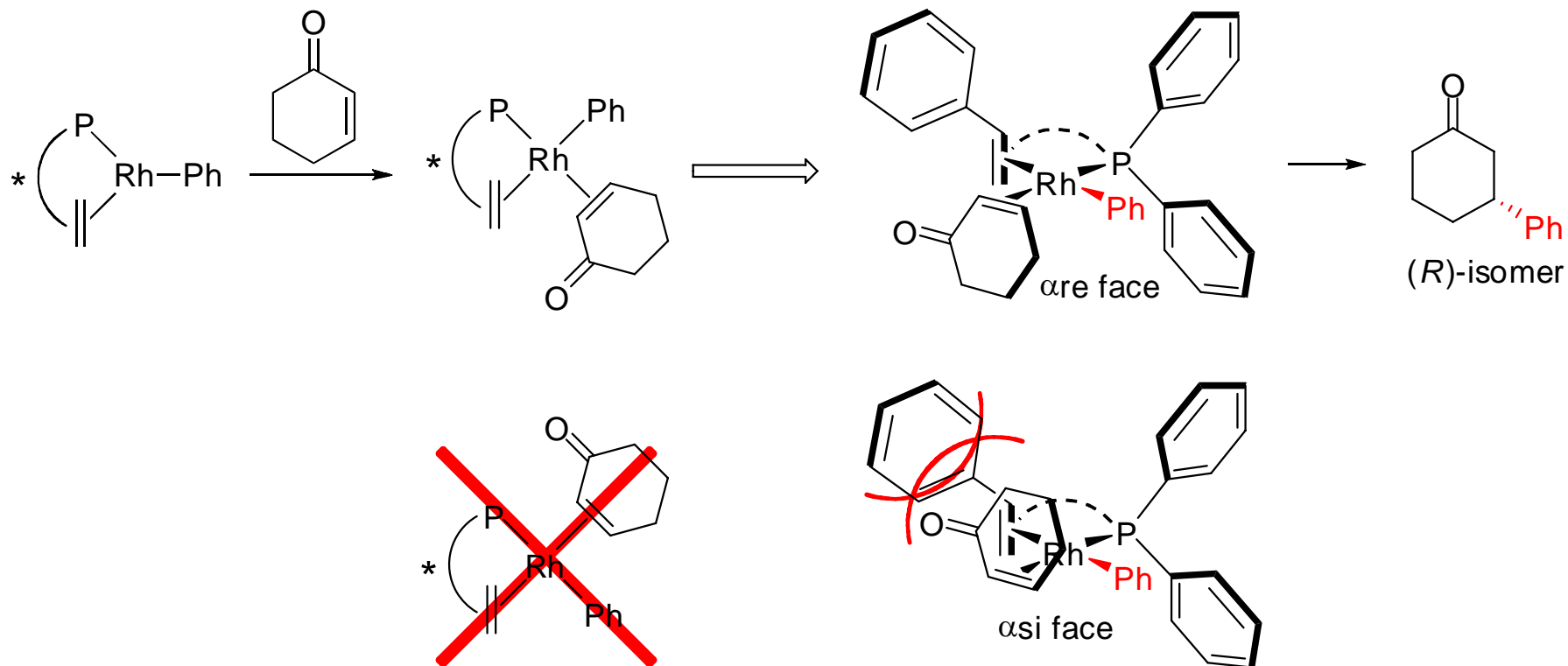


Proposed Catalytic Cycle

12

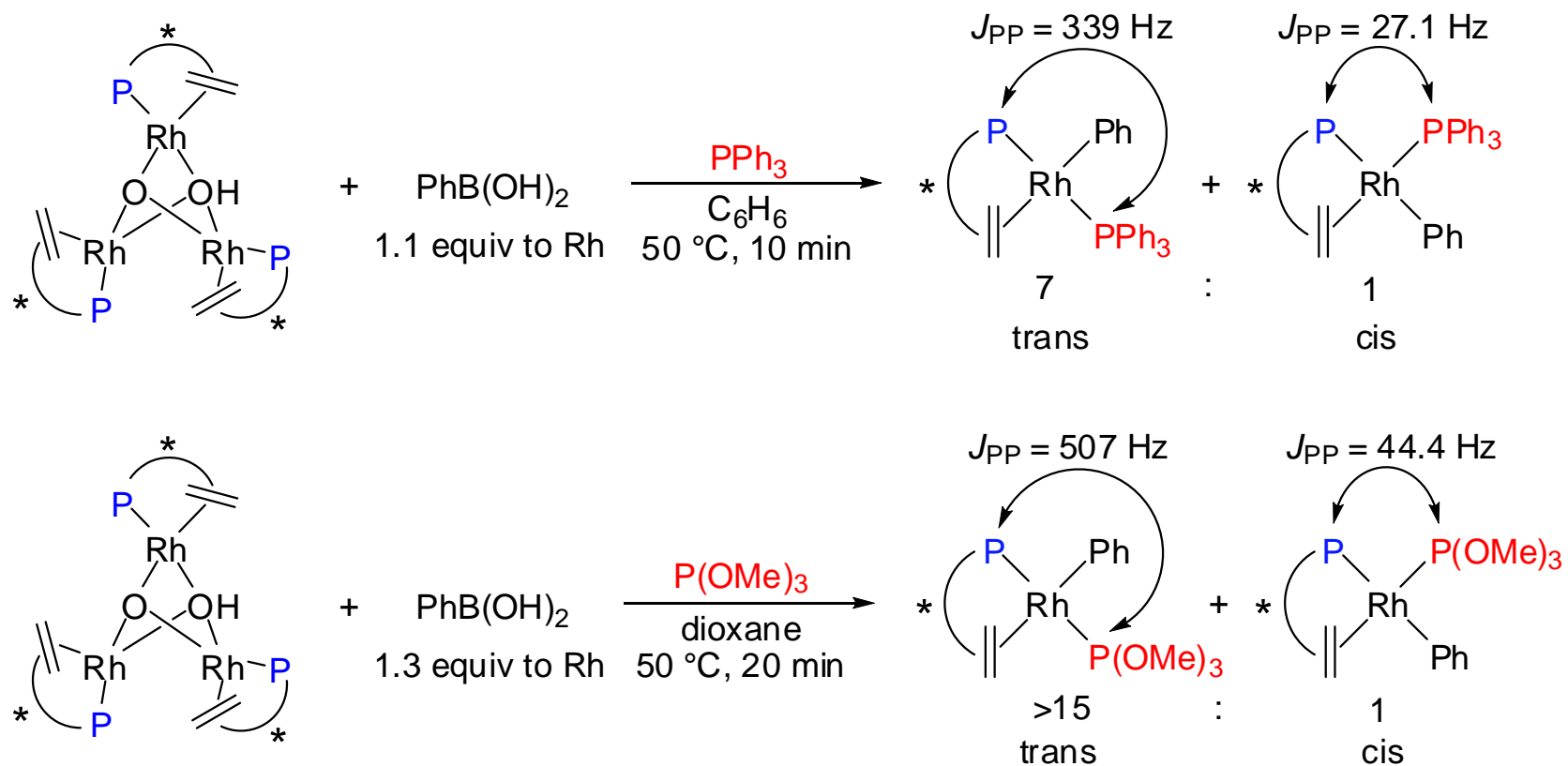
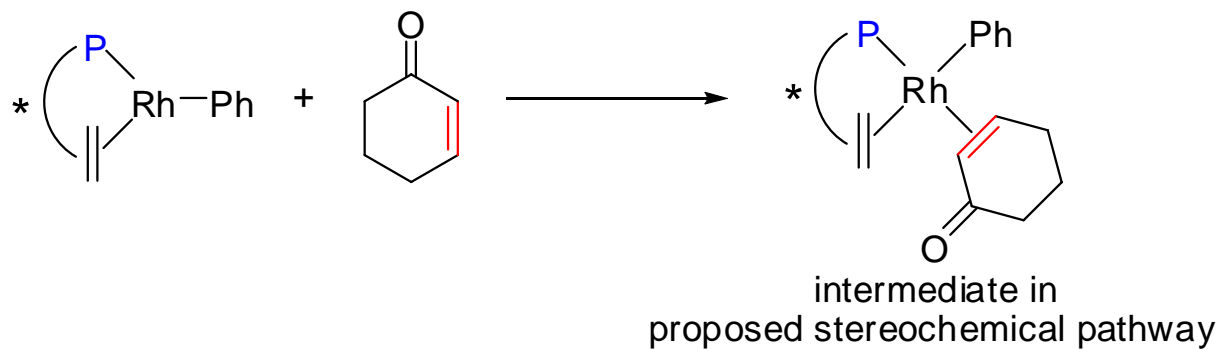


Proposed Stereochemical Pathway



Structural Insight of Phenyl–Rhodium Species

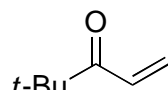
14



Observation of Reaction Intermediates in Catalytic Cycle by ^{31}P NMR

15

Rh-Ph
in dioxane at 50 °C



1 h

oxa- π -allylrhodium

H_2O

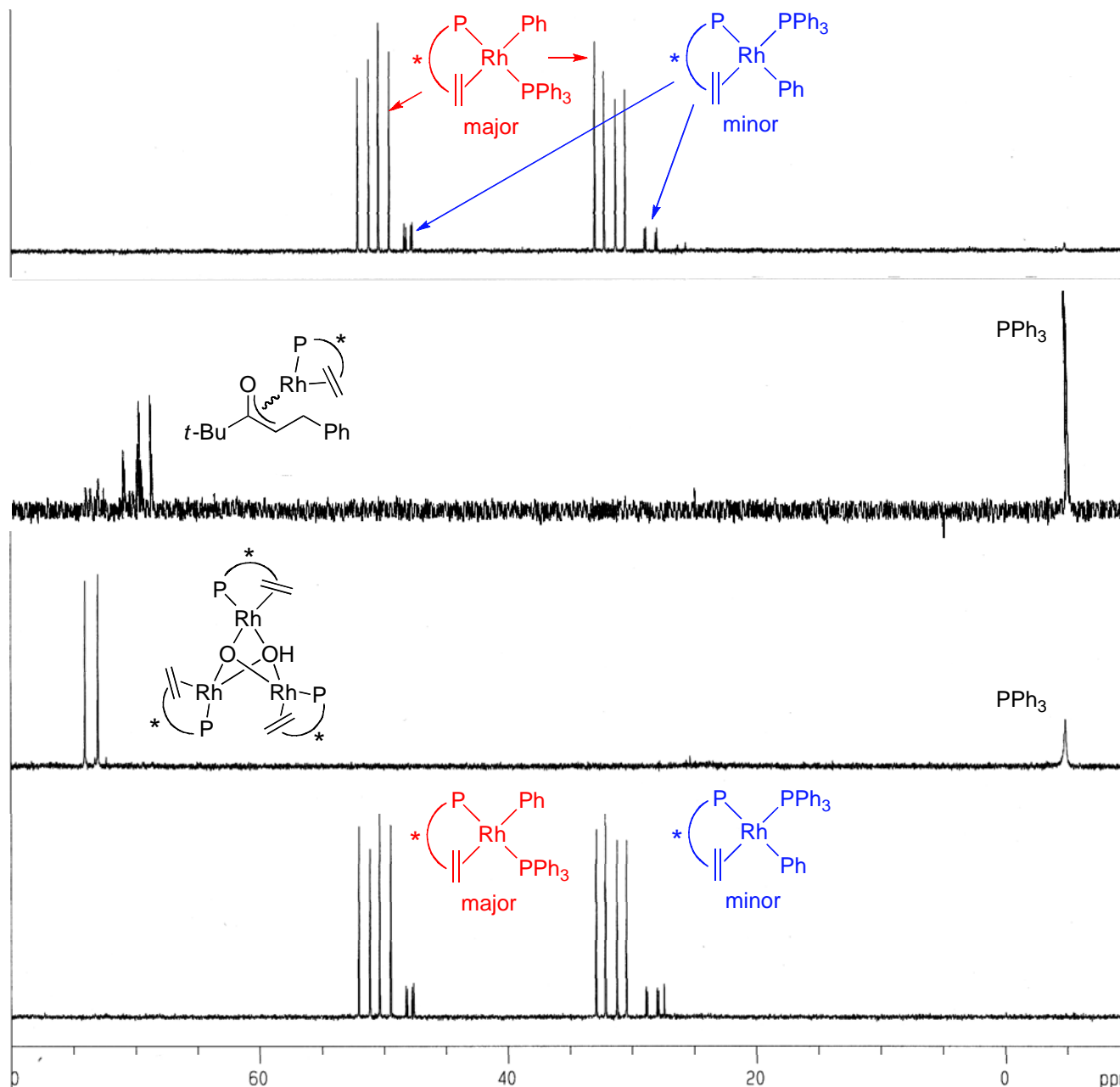
1 h

Rh trimer

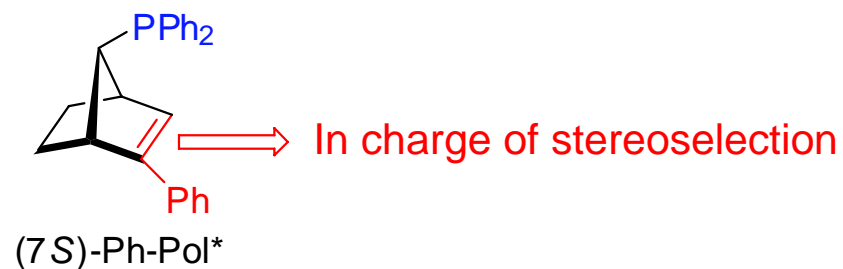
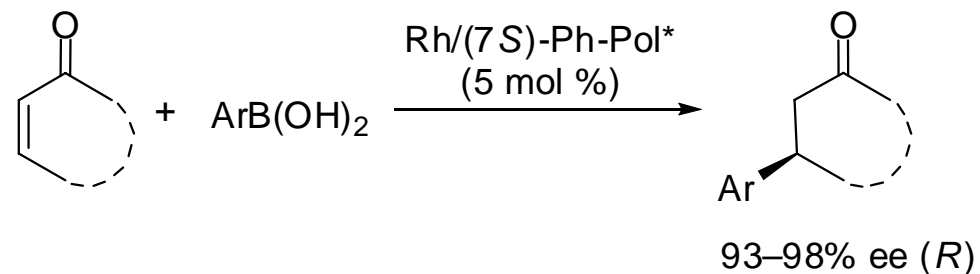
$\text{PhB}(\text{OH})_2$

10 min

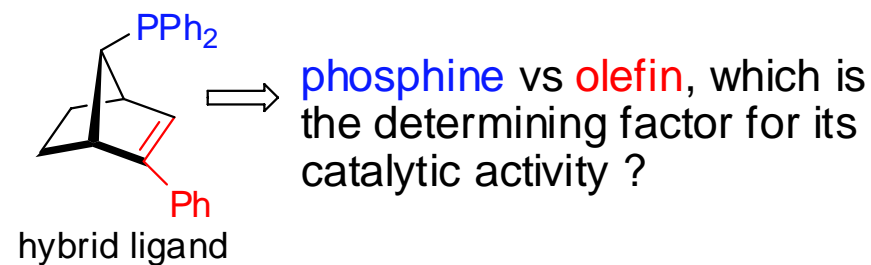
Rh-Ph



Summary for Experimental Results



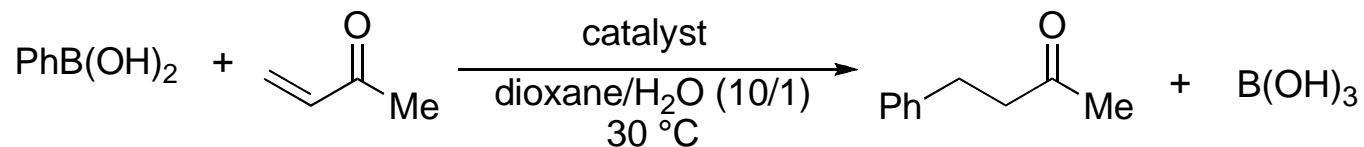
**How about
its catalytic activity ?**



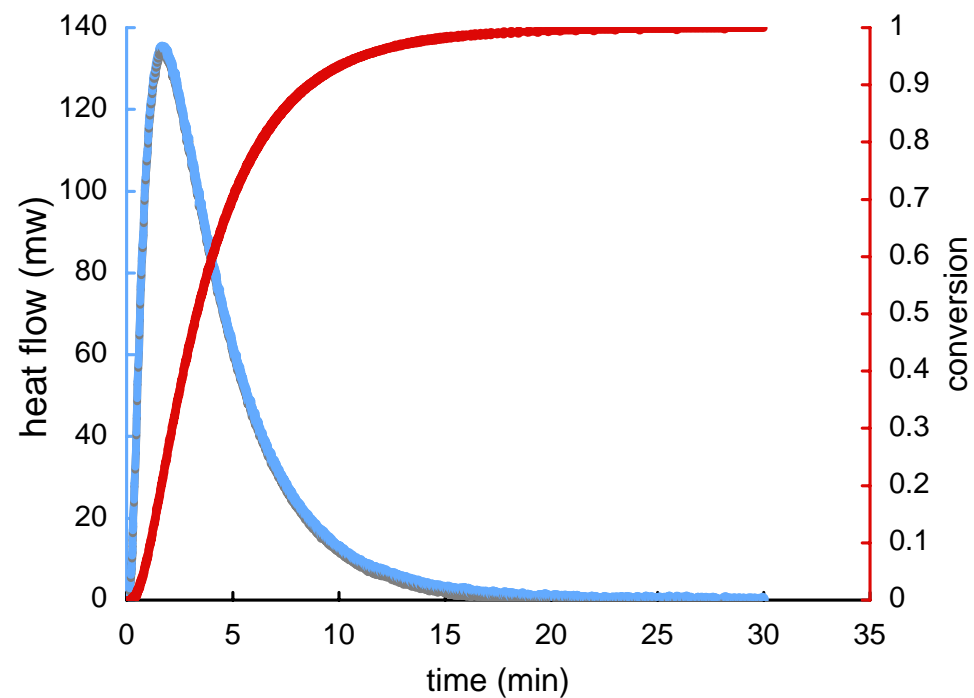
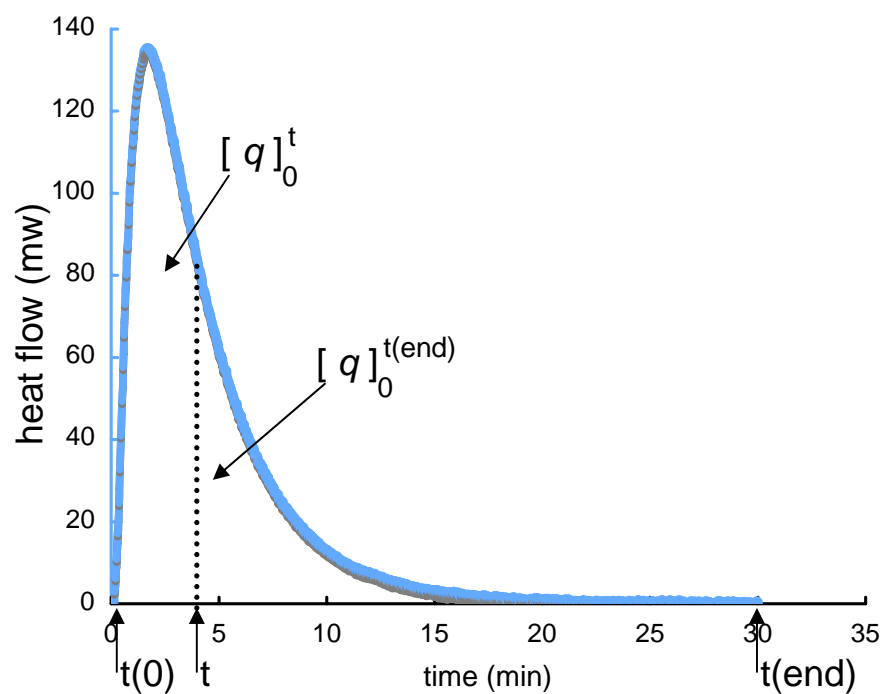
Kinetic Studies on the 1,4-Addition Reaction Catalyzed by Rh/(7S)-Ph-Pol* Using a Reaction Calorimeter

17

A pertinent review: Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.

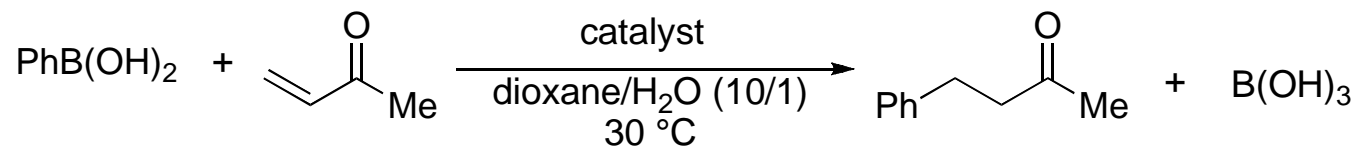


Heat \uparrow = Reaction rate \uparrow $\text{conv.} = \frac{[q]_0^t}{[q]_0^{t(\text{end})}}$

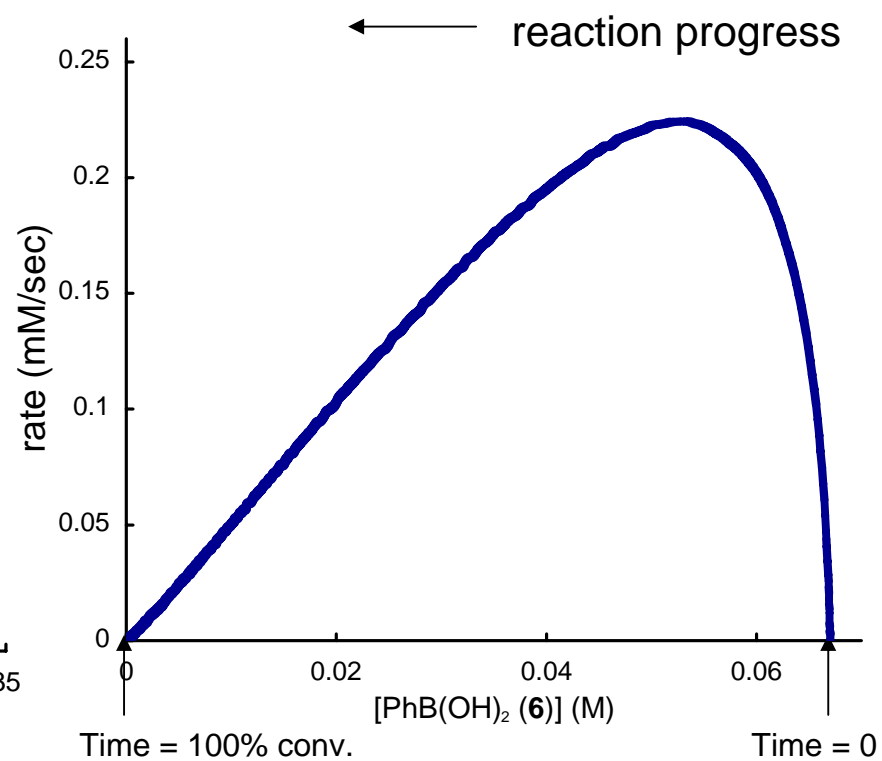
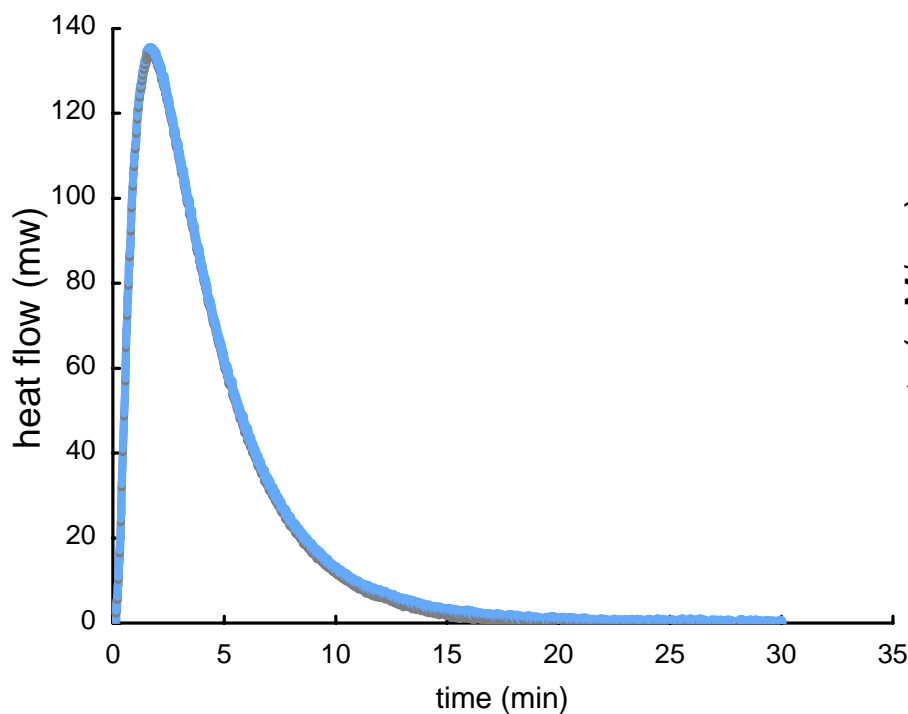


Quantitative Analysis Using the Graph of Rate vs [PhB(OH)₂]

18



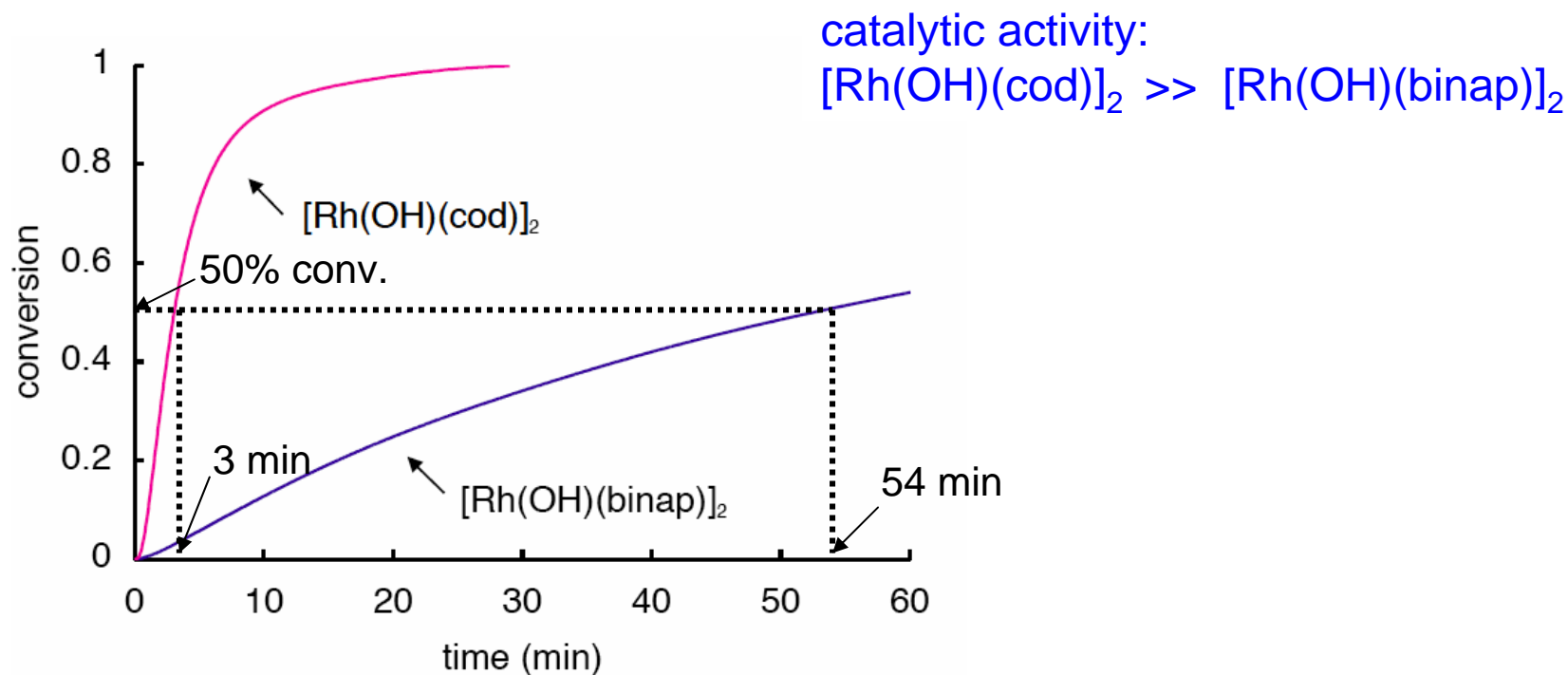
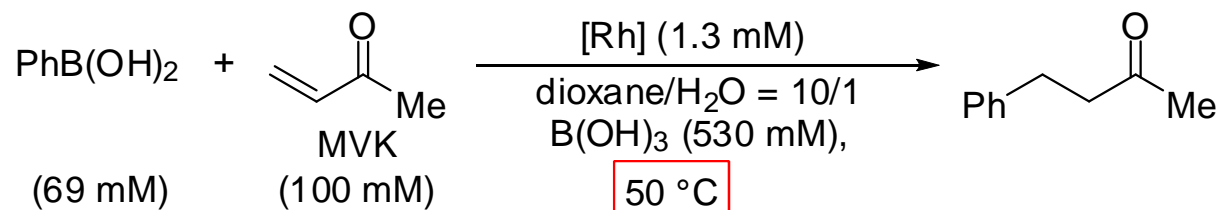
heat ↑ = reaction rate ↑



Previous Works:

19

Comparison of Catalytic Activity between Rh/cod and Rh/binap



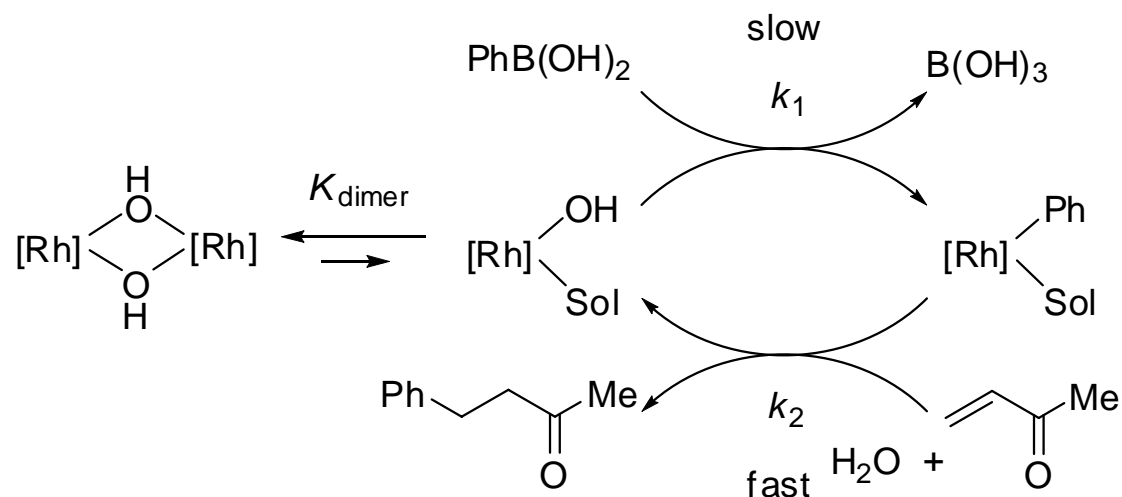
Kina, A.; Iwamura, H.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, 128, 3904.

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

Rate Equation in the Rh/binap and Rh/diene Systems



Catalytic Cycle for the Rh/binap or Rh/diene Systems



[Rh]: Rh/binap or Rh/cod

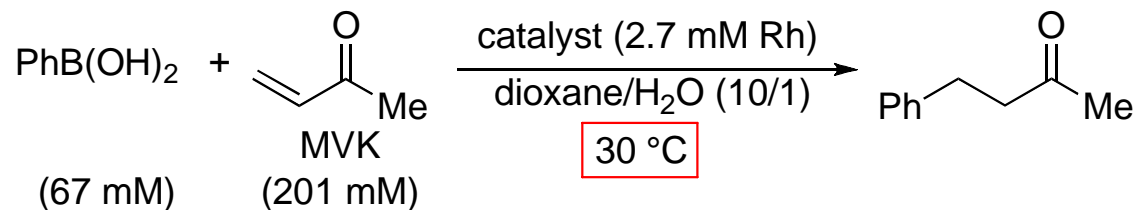
$$\text{binap: } K_{\text{dimer}} = 8 \times 10^2 \text{ M}^{-1}; k_1 = 0.5 \text{ M}^{-1}\text{s}^{-1}$$

$$\text{cod: } K_{\text{dimer}} = 3.8 \times 10^2 \text{ M}^{-1}; k_1 = 6.7 \text{ M}^{-1}\text{s}^{-1}$$

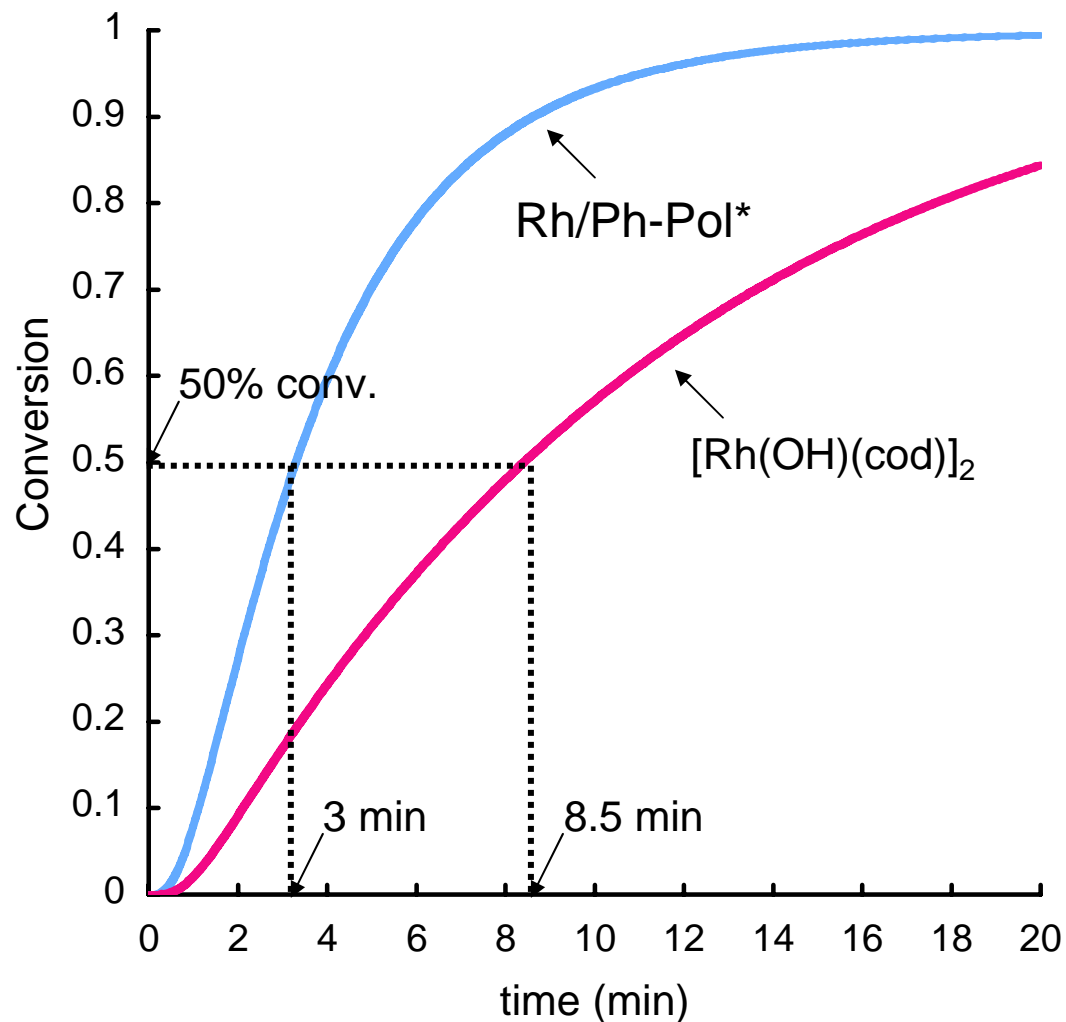
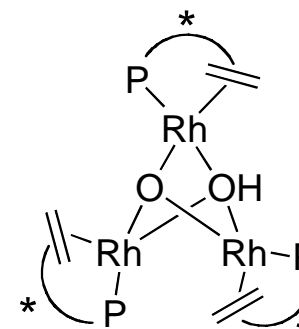
at 50 °C

Comparison of Catalytic Activity between Rh/Ph-Pol* and Rh/cod

21



Rh/Ph-Pol*:



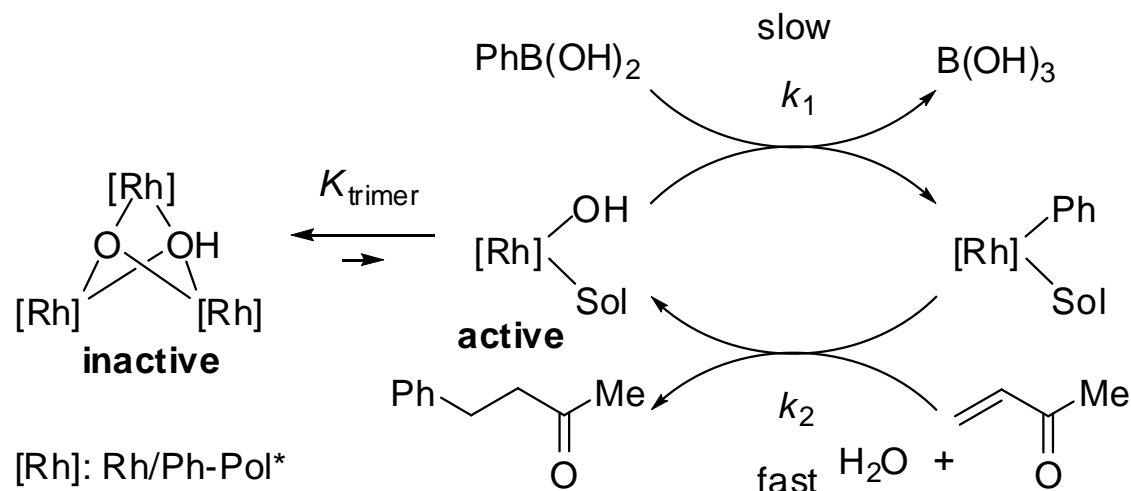
catalytic activity:
Rh/Ph-Pol* > [Rh(OH)(cod)]₂

Results of the Kinetic Experiments:

22

$$\text{rate} \propto [\text{PhB}(\text{OH})_2]^1 [\text{MVK}]^0 [\text{Rh}]^{0.4}$$

Proposed Catalytic Cycle for the Rh/Ph-Pol*-Catalyzed 1,4-Addition of Phenylboronic Acid to Methyl Vinyl Ketone (MVK)

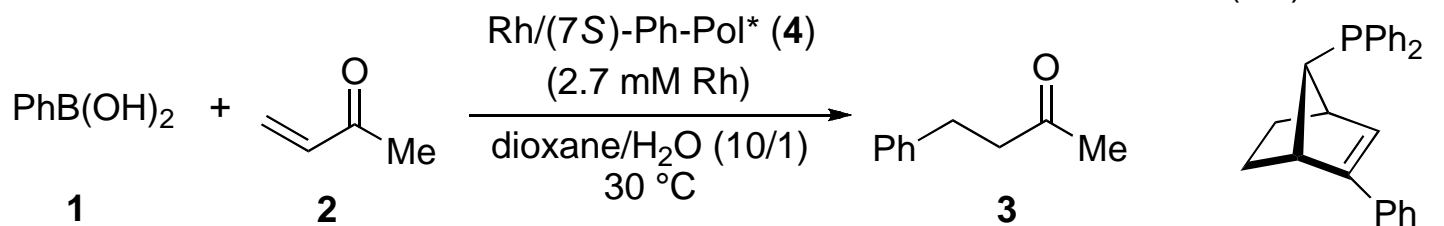


$$\text{rate} = \frac{k_1}{(3K_{\text{trimer}})^{1/3}} [\text{PhB}(\text{OH})_2] [\text{Rh}]_{\text{total}}^{1/3} \implies (7S)\text{-Ph-Pol}^*: \begin{array}{l} K_{\text{trimer}} = 9 \times 10^5 \text{ M}^{-2} \\ k_1 = 5 \text{ M}^{-1}\text{s}^{-1} \end{array} \quad (\text{at } 30 \text{ }^\circ\text{C})$$

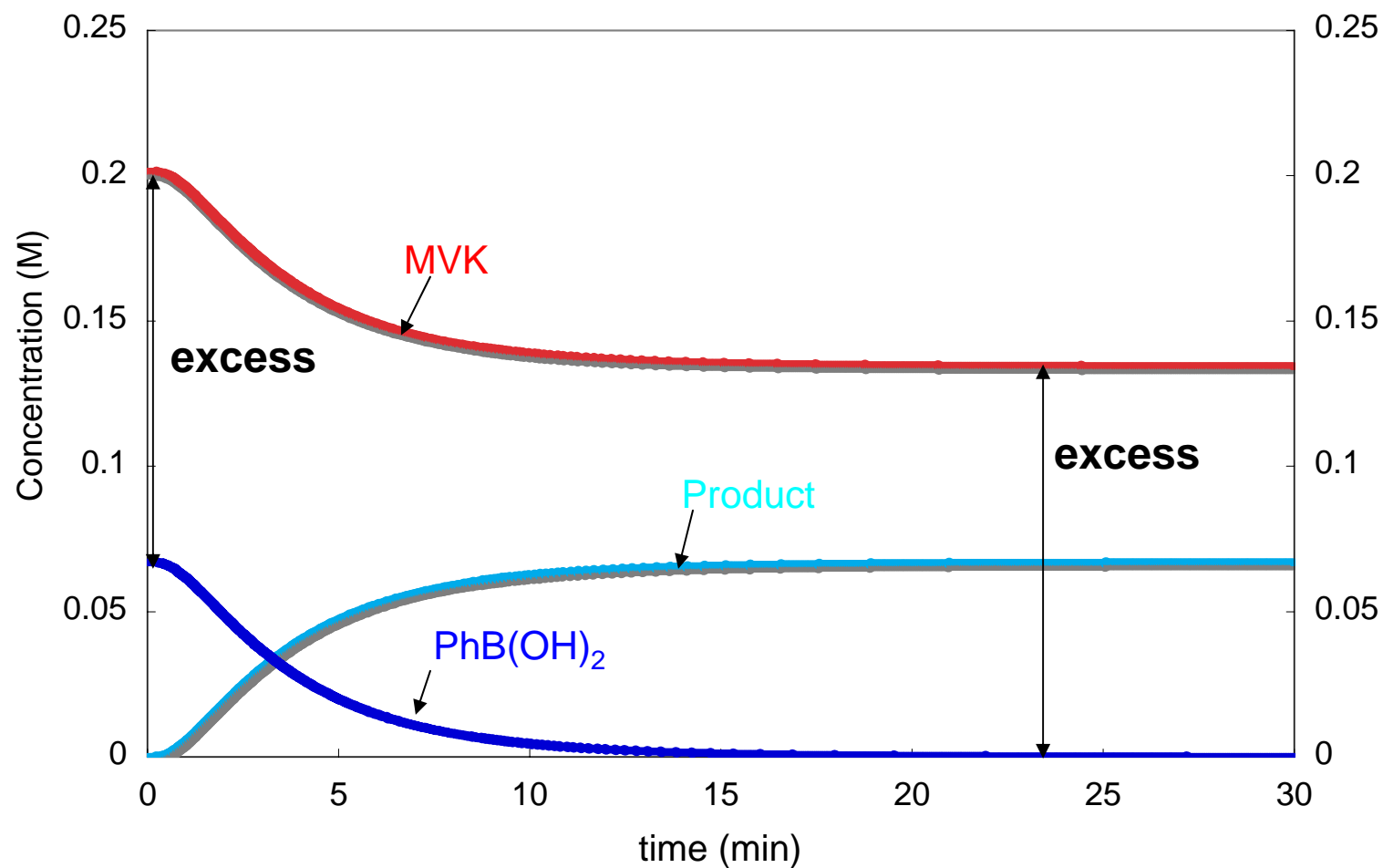
$$\text{cod:} \quad \begin{array}{l} K_{\text{dimer}} = 3.8 \times 10^2 \text{ M}^{-1} \\ k_1 = 1.3 \text{ M}^{-1}\text{s}^{-1} \end{array} \quad (\text{at } 30 \text{ }^\circ\text{C})$$

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

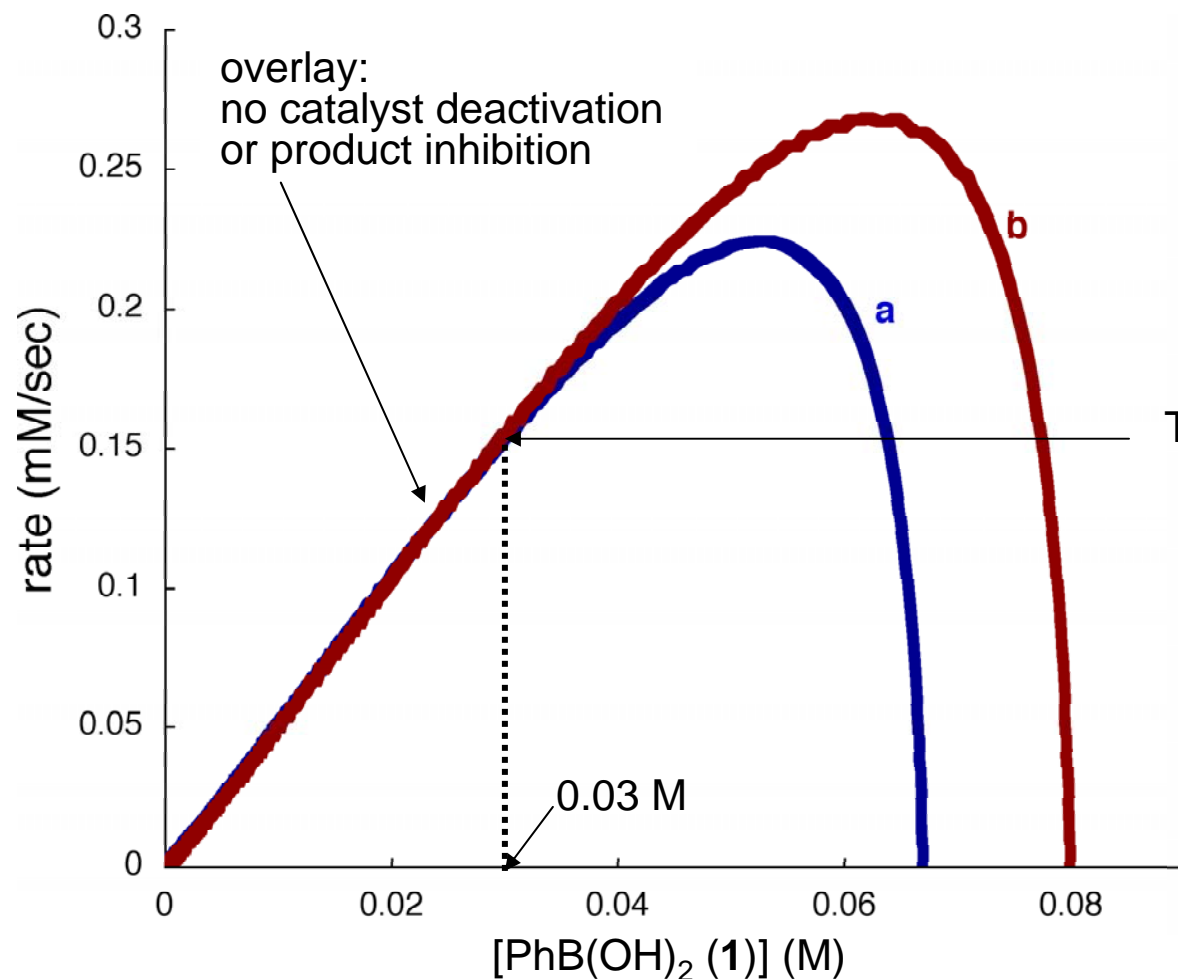
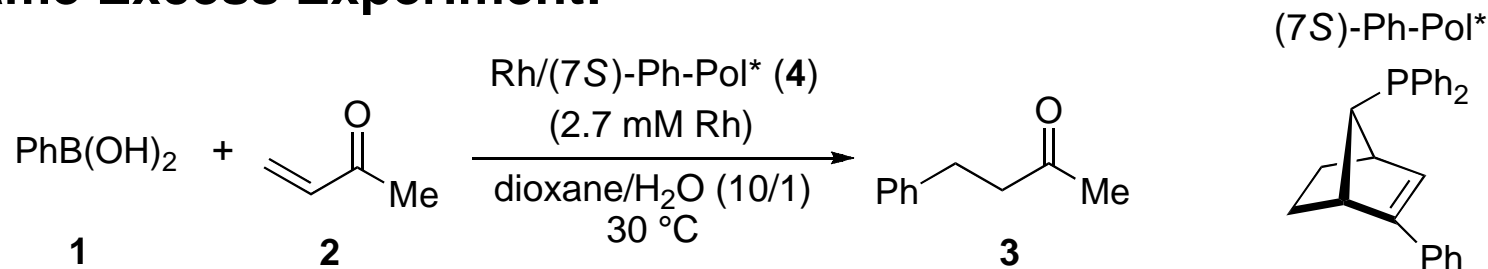
Defination of "Excess" in Kinetic Study



$$\text{["Excess"]} = [\text{MVK}]_0 - [\text{PhB(OH)}_2]_0 = [\text{MVK}]_t - [\text{PhB(OH)}_2]_t = \text{Constant}$$



The Same Excess Experiment:



a, --: [1]₀ = 67 mM, [2]₀ = 201 mM
 ([“excess”] = 134 mM).

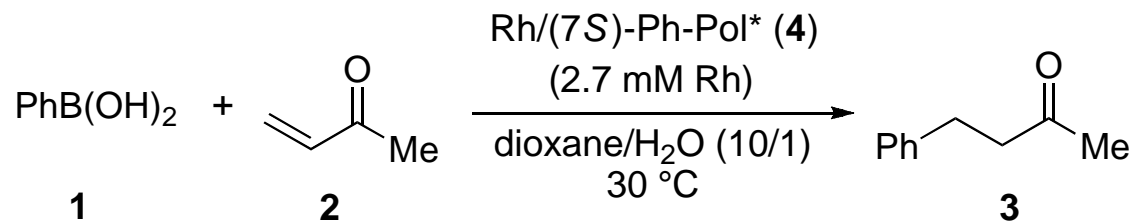
b, --: [1]₀ = 80 mM, [2]₀ = 214 mM
 ([“excess”] = 134 mM).

The same reaction rate (a and b)

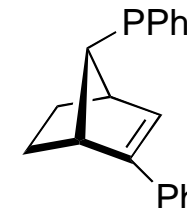
a: [1] = 30 mM, [2] = 164 mM
 [3] = 37 mM

b: [1] = 30 mM, [2] = 164 mM
 [3] = 50 mM
 cat 4: more turnovers

The Different Excess Experiment:

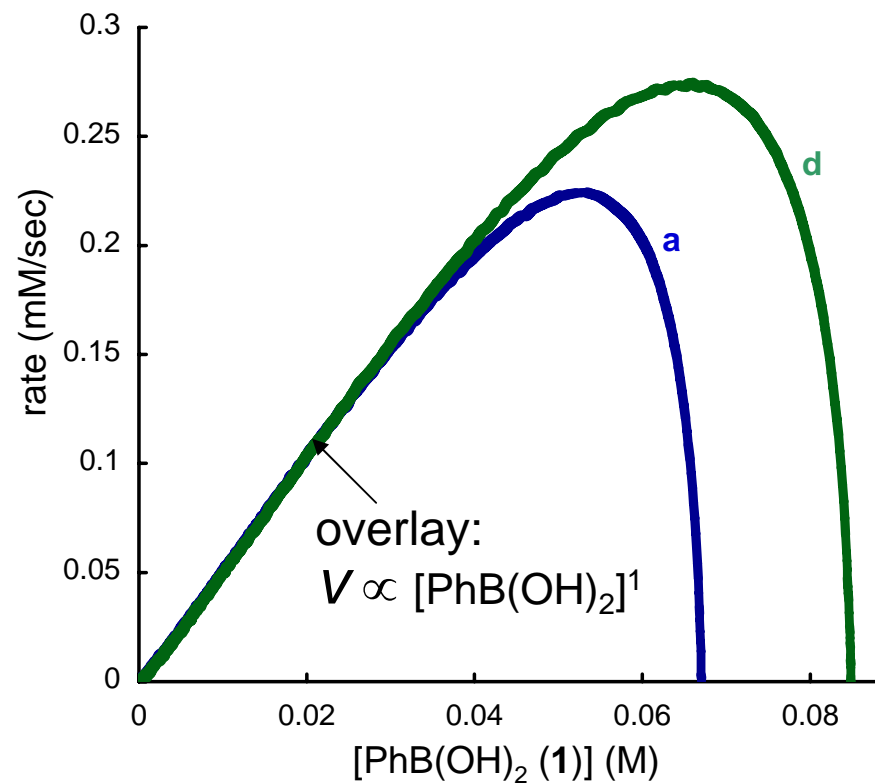
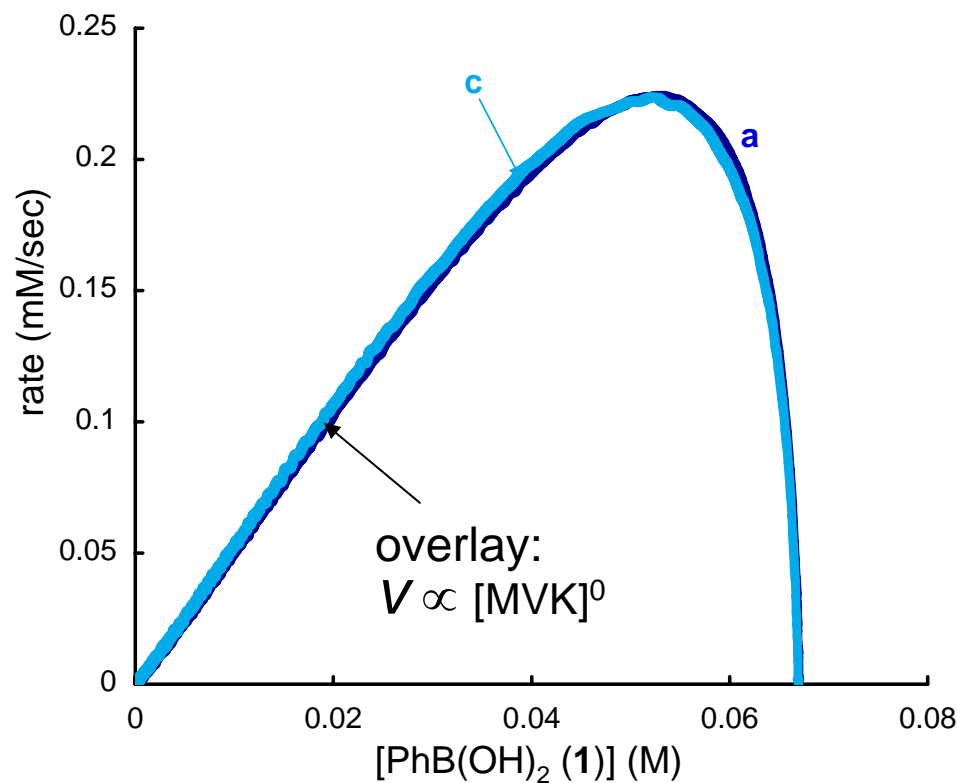


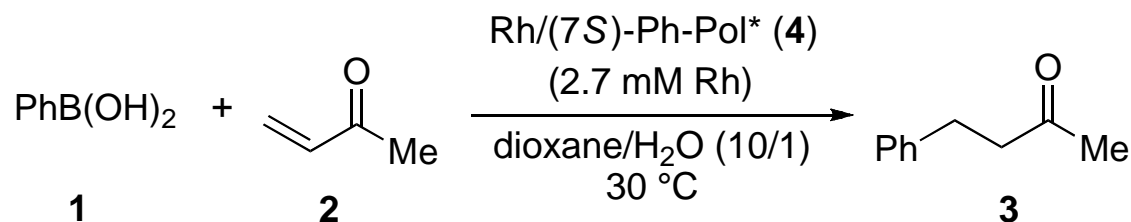
(7S)-Ph-Pol*



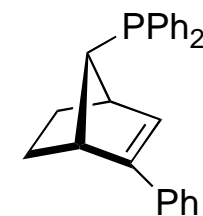
a, --: [1]₀ = 67 mM, [2]₀ = 201 mM, ([“excess”] = 134 mM).
 c, --: [1]₀ = 67 mM, [2]₀ = 101 mM, ([“excess”] = 34 mM).

a, --: [1]₀ = 67 mM, [2]₀ = 201 mM, ([“excess”] = 134 mM).
 d, --: [1]₀ = 85 mM, [2]₀ = 201 mM, ([“excess”] = 116 mM).



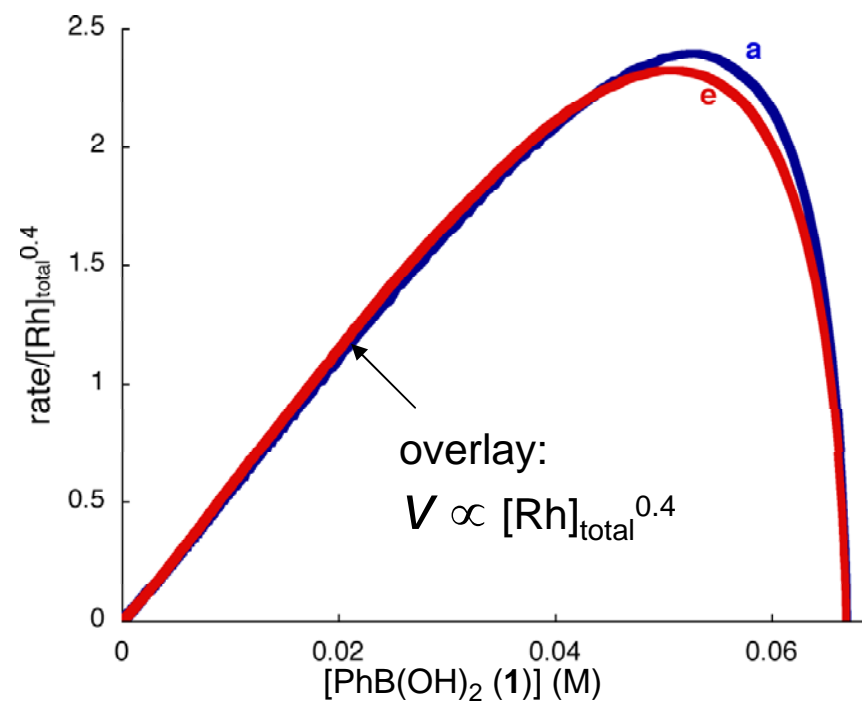
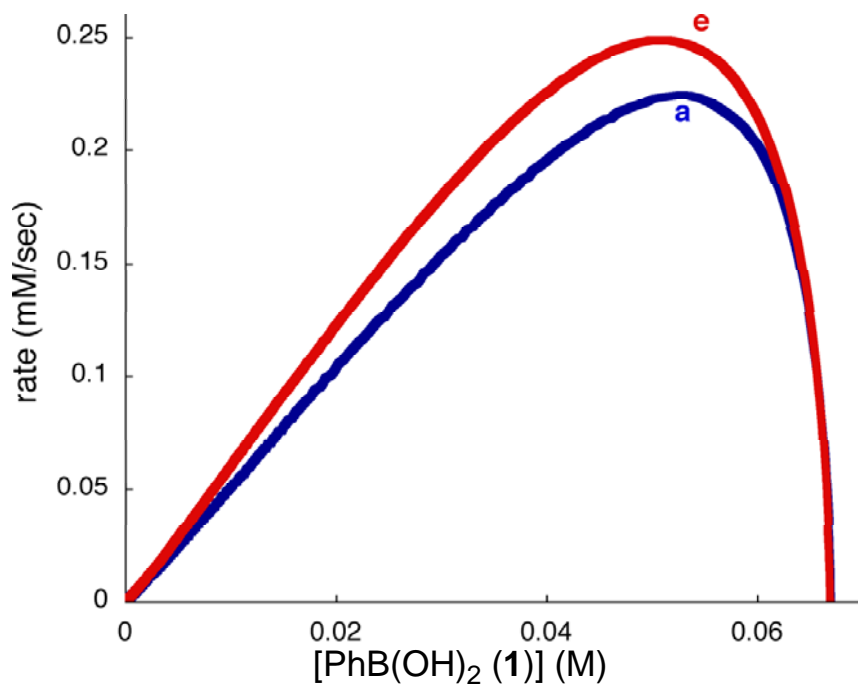
Order in $[\text{Rh}]_{\text{total}}$ 

(7S)-Ph-Pol*



a, --: $[\text{1}]_0 = 67\text{ mM}$, $[\text{2}]_0 = 201\text{ mM}$, $[\text{4}]_0 = 2.7\text{ mM Rh}$.

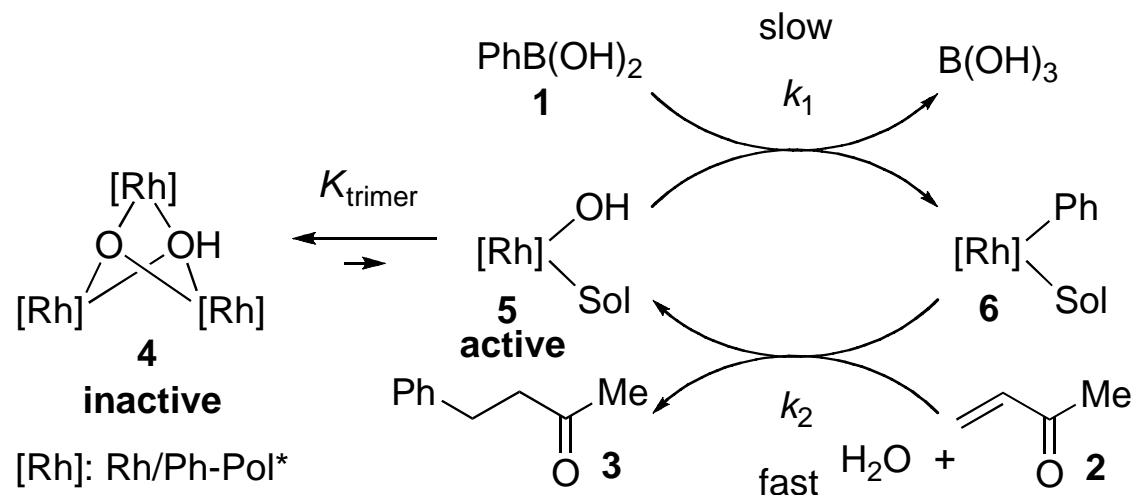
e, --: $[\text{1}]_0 = 67\text{ mM}$, $[\text{2}]_0 = 201\text{ mM}$, $[\text{4}]_0 = 3.8\text{ mM Rh}$.



$$V \propto [\text{PhB(OH)}_2]_1 [\text{Rh}]^{0.4}$$

Proposed Catalytic Cycle for the Rh/Ph-Pol*-Catalyzed 1,4-Addition of Phenylboronic Acid to Methyl Vinyl Ketone

27



$$\left. \begin{array}{l} \text{rate} = k_2[2][6] \\ [\text{Rh}]_{\text{total}} = 3[4] + [5] + [6] \end{array} \right\} \xrightarrow{k_2[2] \gg k_1[1]} \left. \begin{array}{l} \text{rate} = k_1[1][5] \\ [\text{Rh}]_{\text{total}} = 3[4] + [5] \end{array} \right.$$

$$\Downarrow K_{\text{trimer}} = \frac{[4]}{[5]^3}$$

$$\text{rate} = \frac{k_1}{(3K_{\text{trimer}})^{1/3}} [1][\text{Rh}]_{\text{total}}^{1/3} \xleftarrow{A=1} \text{rate} = \frac{k_1}{(6K_{\text{trimer}})^{1/3}} [1][\text{Rh}]_{\text{total}}^{1/3} \left\{ (1+A)^{1/3} + (1-A)^{1/3} \right\}$$

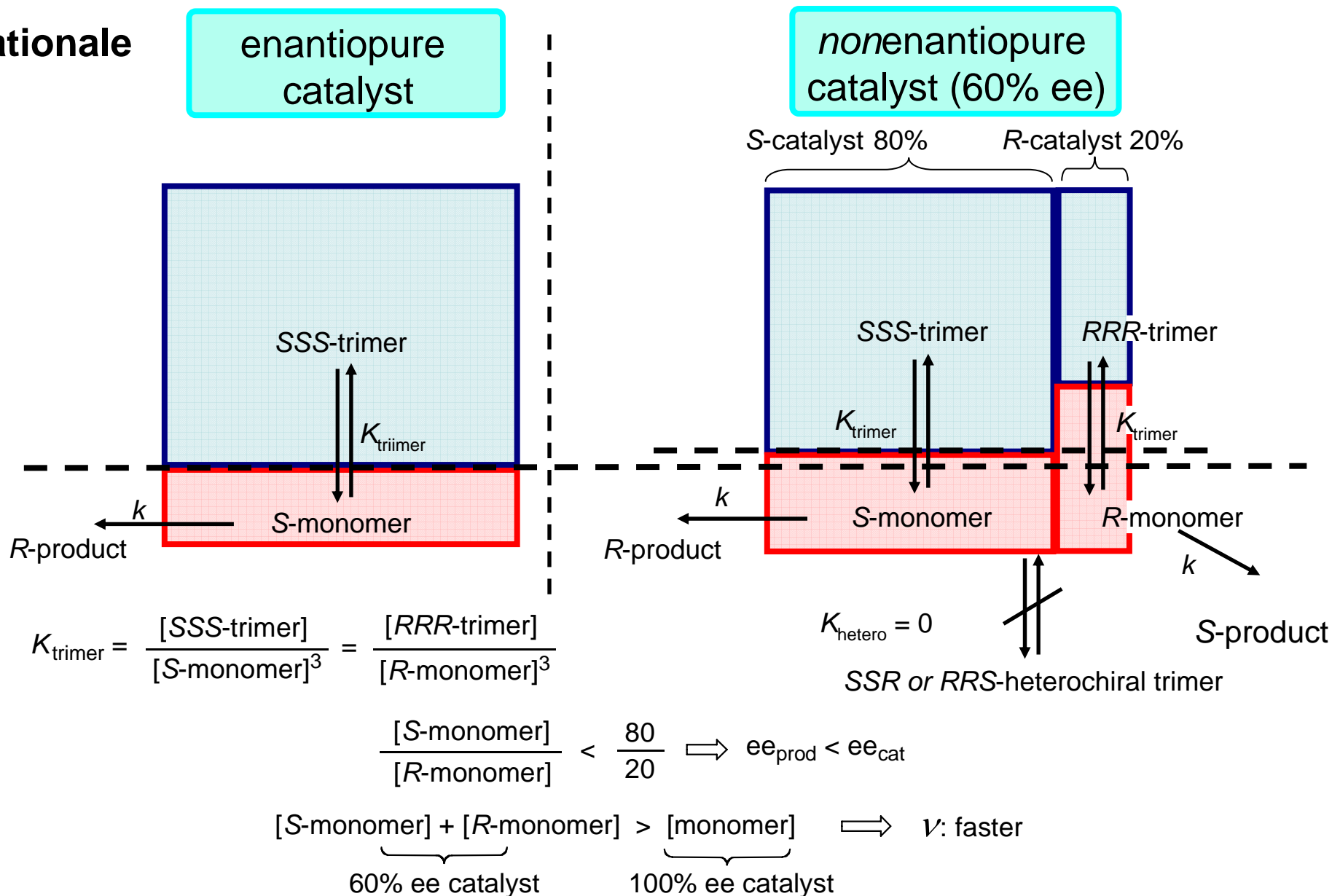
$$A = \left(1 + \frac{4}{81K_{\text{trimer}}[\text{Rh}]_{\text{total}}^2} \right)^{1/2}$$

Nonlinear Effect Studies on the Asymmetric 1,4-Addition Catalyzed by Rh/1a

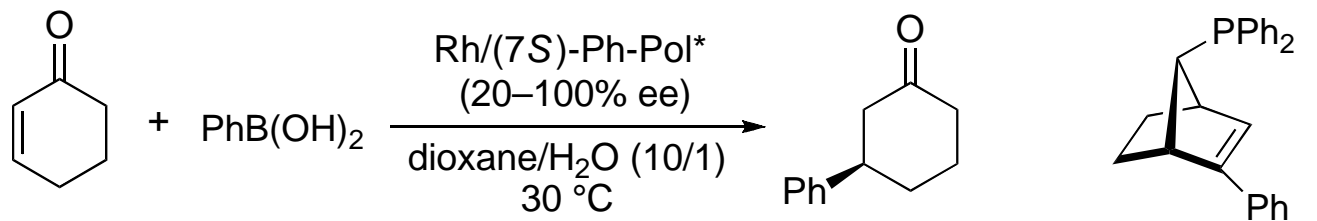
Rationale

enantiopure catalyst

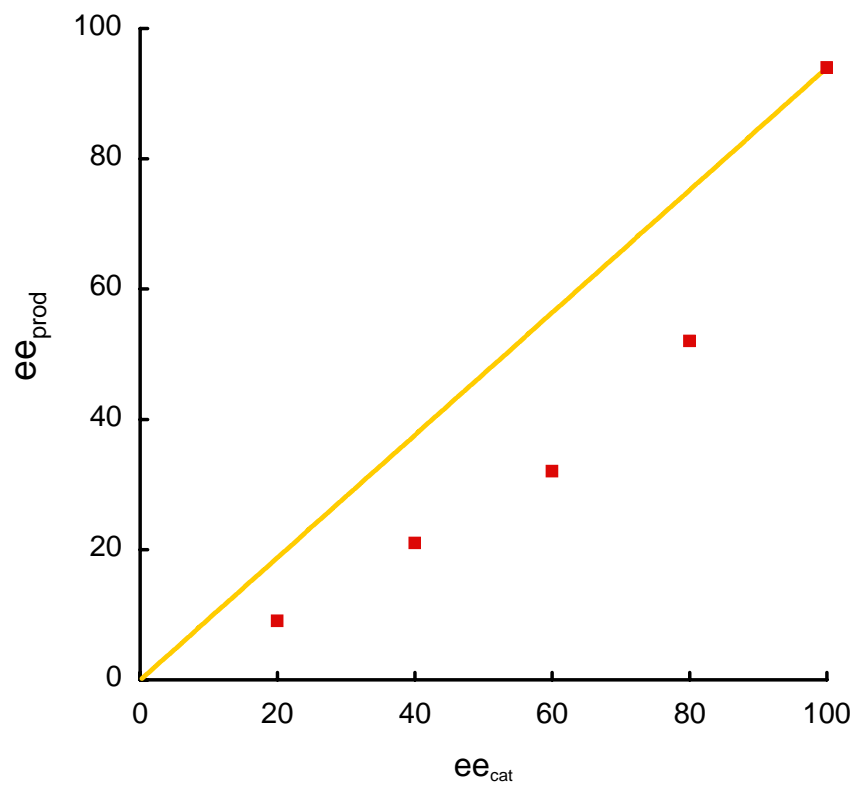
nonenantiopure catalyst (60% ee)



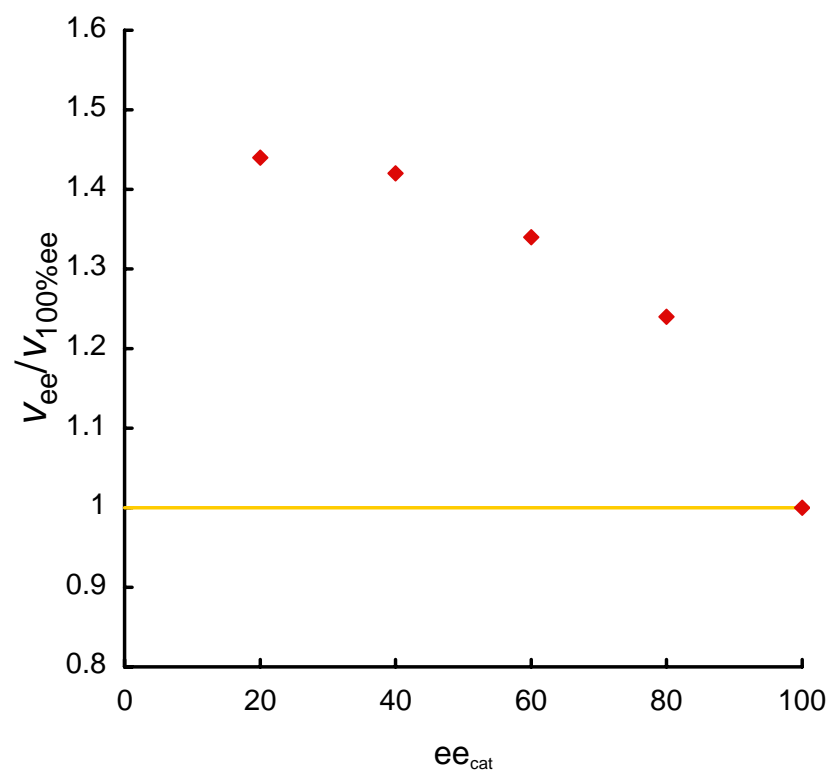
Experimental Results



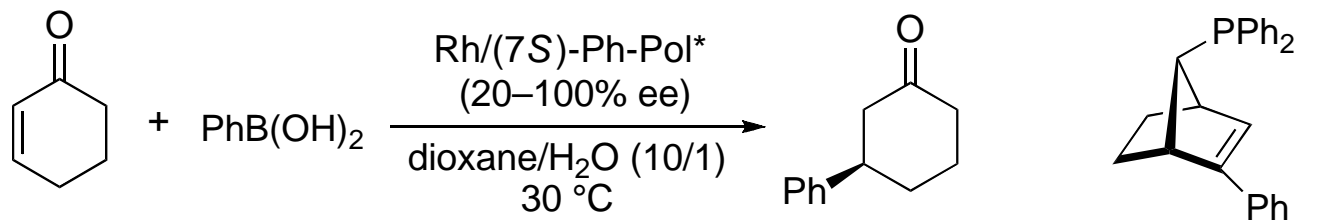
ee_{prod} vs ee_{cat}



v_{ee}/v_{100%ee} vs ee_{cat}

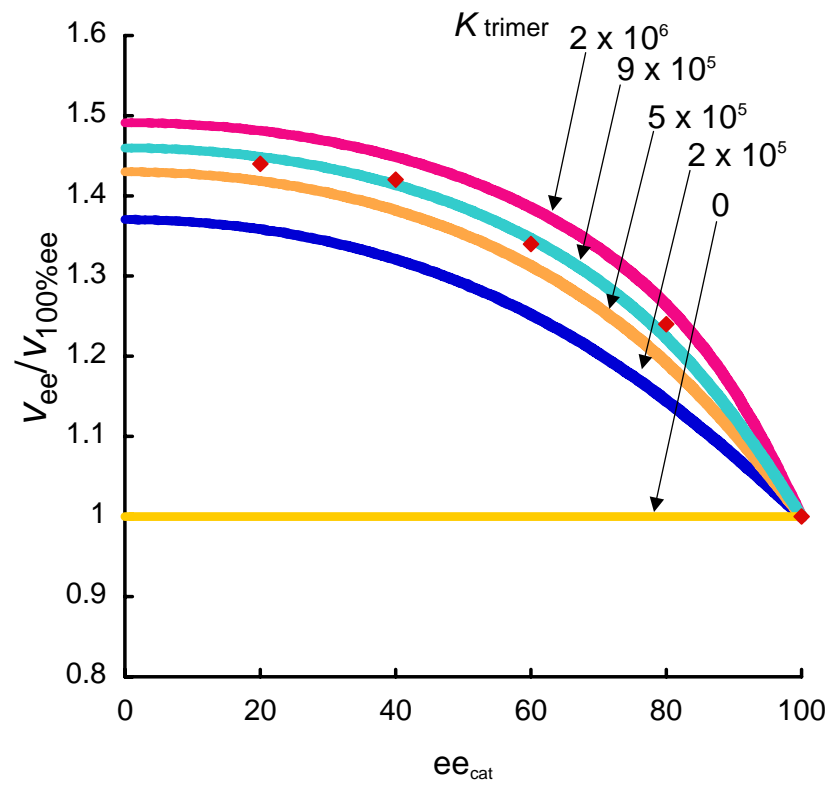
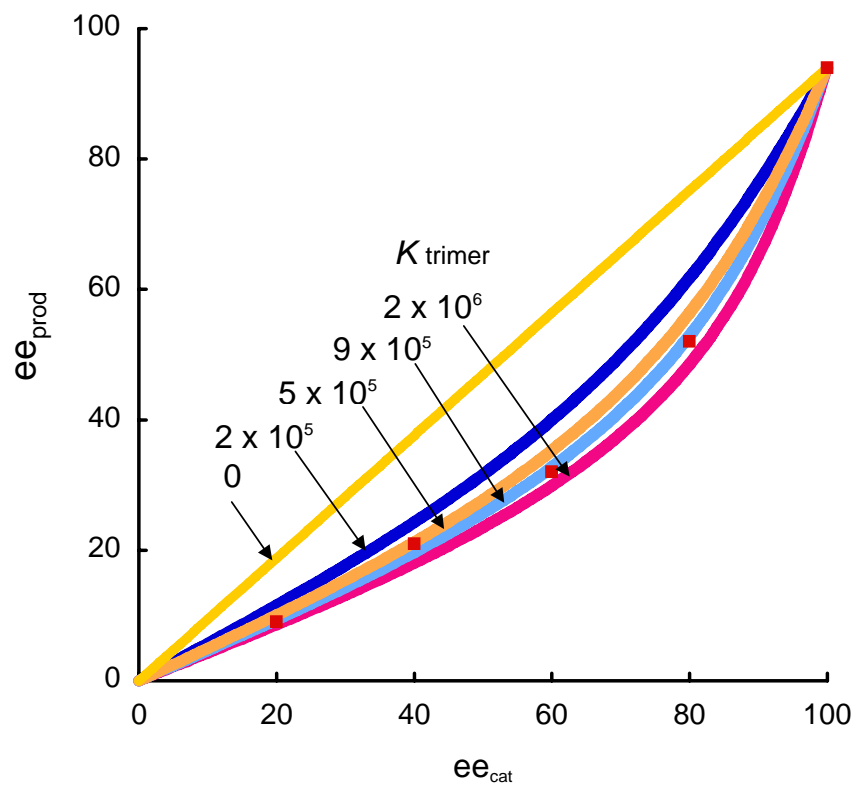


Simulation

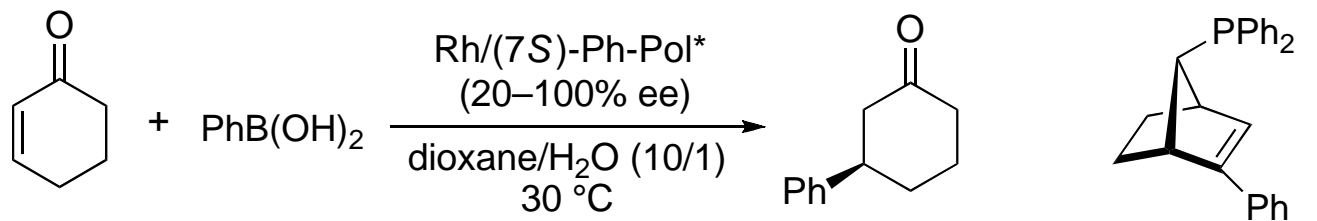


ee_{prod} vs ee_{cat}

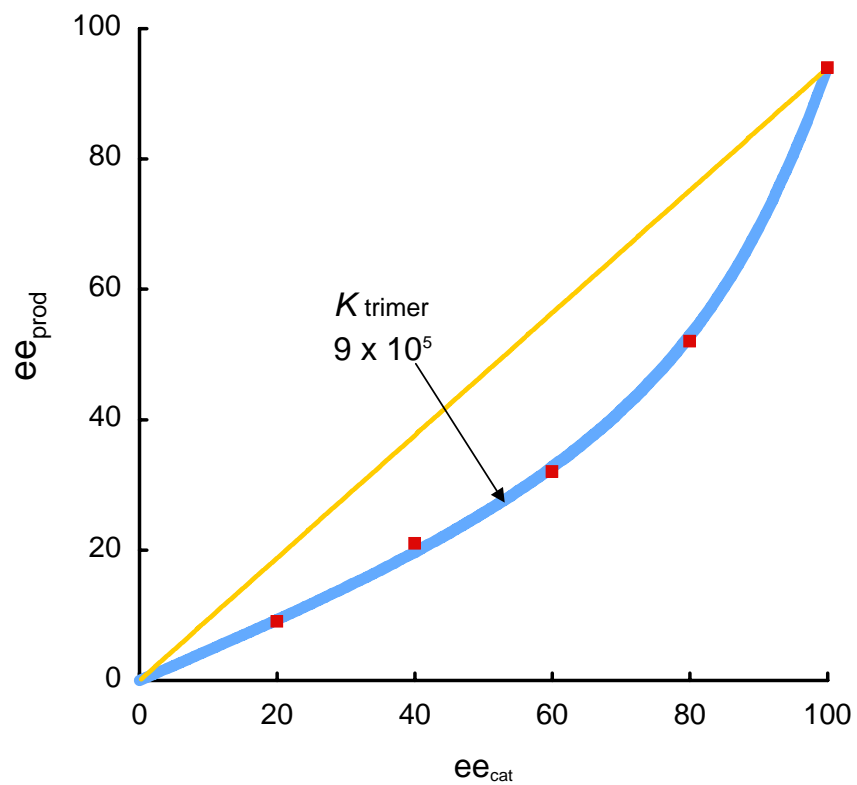
$v_{ee}/v_{100\%ee}$ vs ee_{cat}



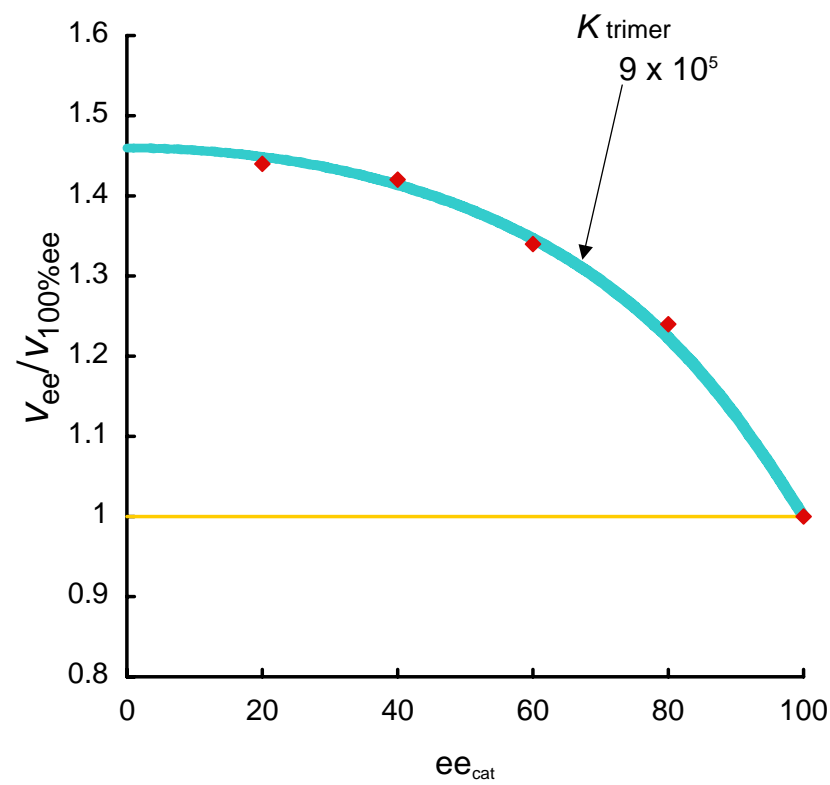
Simulation



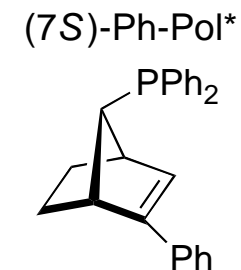
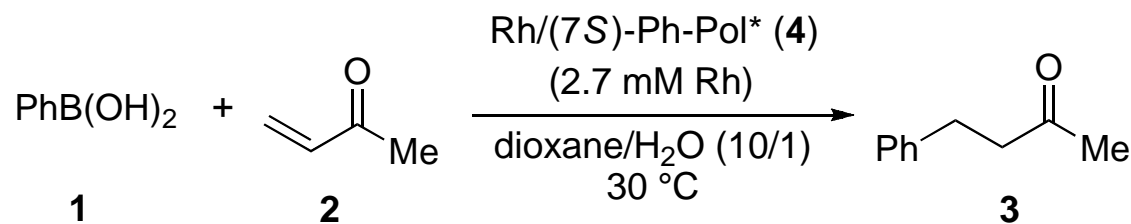
ee_{prod} vs ee_{cat}



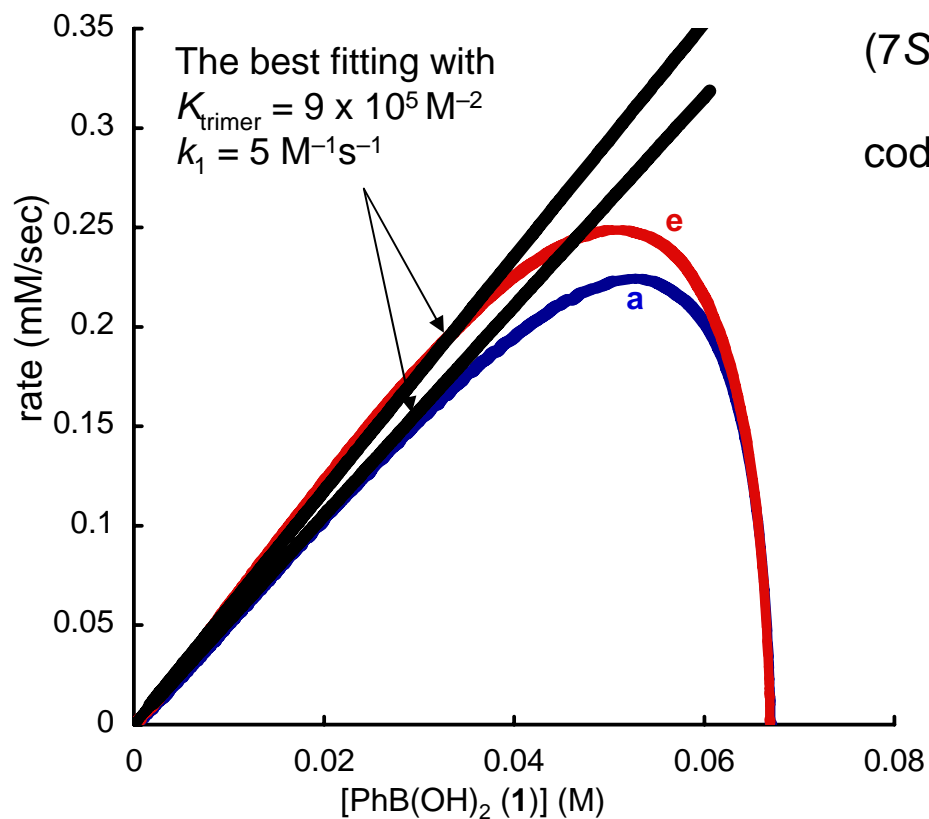
$v_{ee}/v_{100\%ee}$ vs ee_{cat}



Extracting the Value of k_1



$$\text{rate} = \frac{k_1}{(3K_{\text{trimer}})^{1/3}} [\text{1}][\text{Rh}]_{\text{total}}^{1/3} \xrightarrow{K_{\text{trimer}} = 9 \times 10^5 \text{ M}^{-2}} k_1 = 5 \text{ M}^{-1}\text{s}^{-1}$$

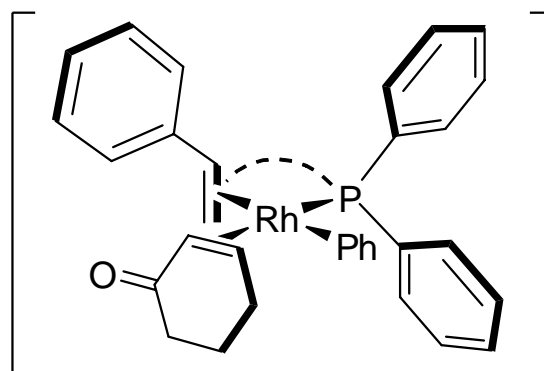
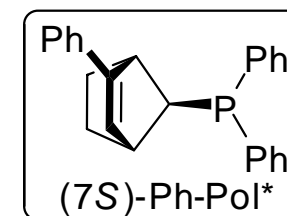
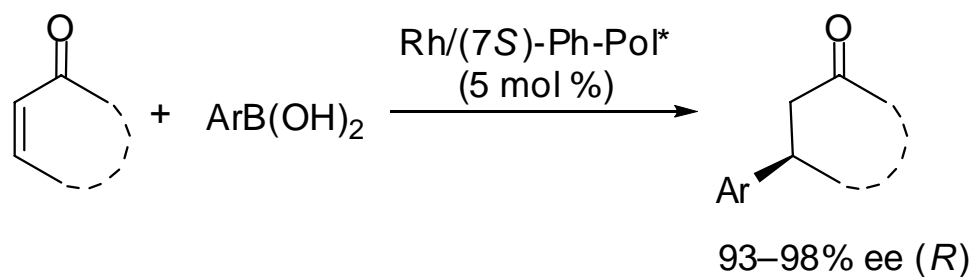


(7S)-Ph-Pol*: $k_1 = 5 \text{ M}^{-1}\text{s}^{-1}$; $K_{\text{trimer}} = 9 \times 10^5 \text{ M}^{-2}$

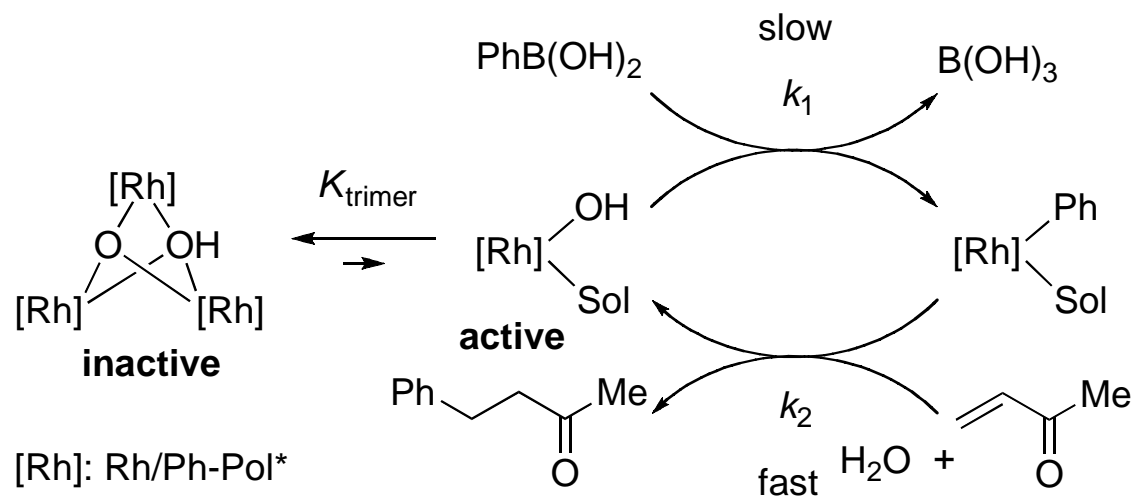
cod: $k_1 = 1.3 \text{ M}^{-1}\text{s}^{-1}$; $K_{\text{dimer}} = 3.8 \times 10^2 \text{ M}^{-1}$

Summary for Rhodium/Phosphine-Olefin Chemistry

Rhodium-Catalyzed 1,4-Addition



Kinetic Study



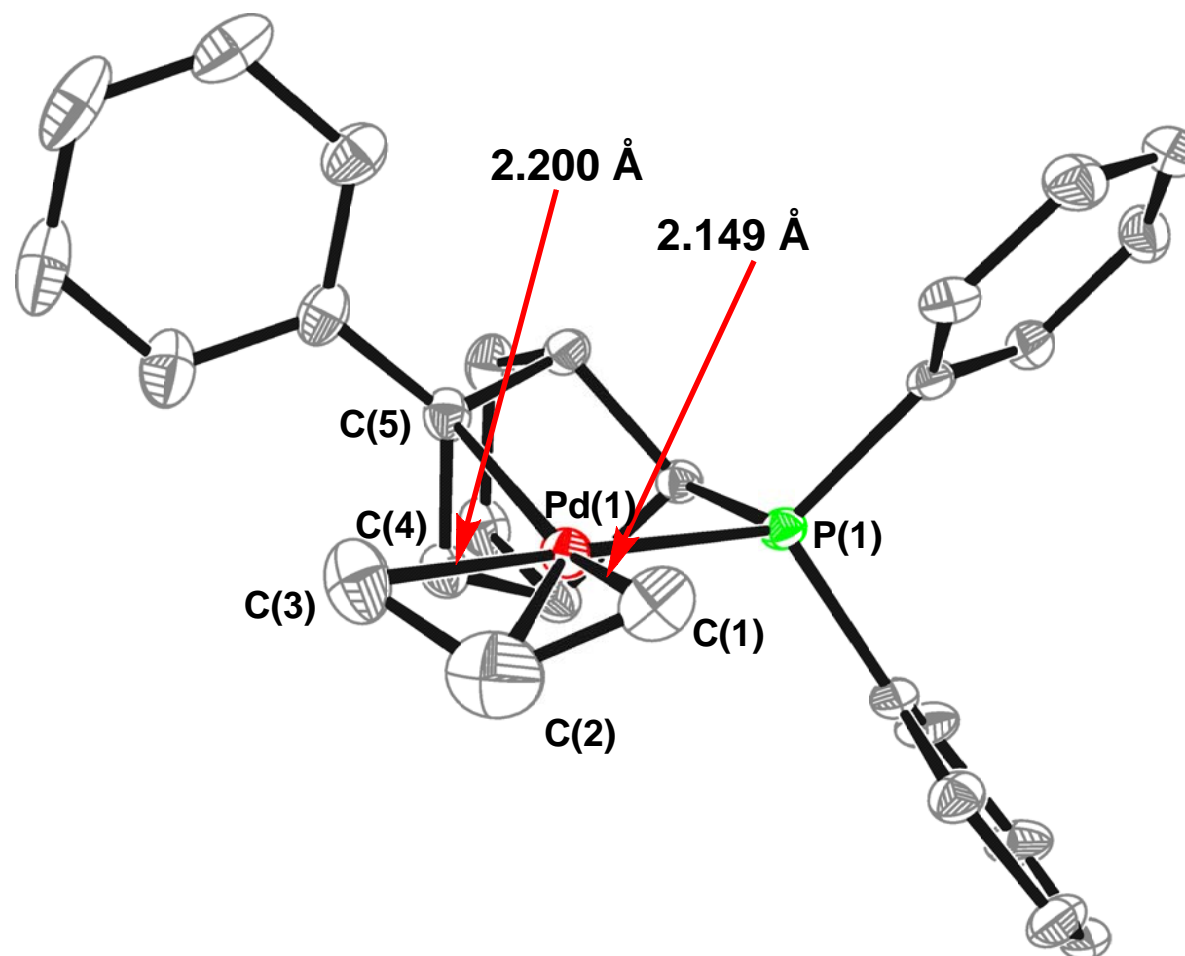
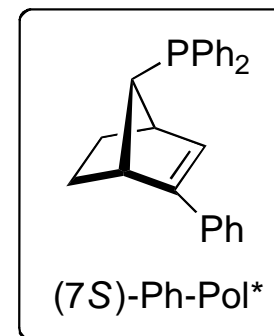
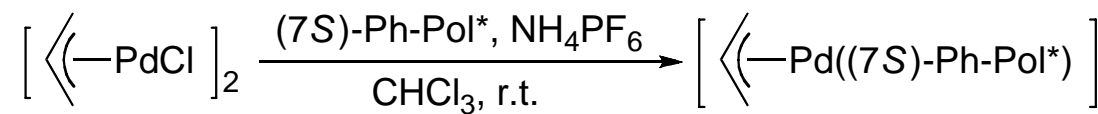
$$\text{reaction rate} \propto [\text{PhB(OH)}_2]^1 [\text{MVK}]^0 [\text{Rh}]^{0.4}$$

$$K_{\text{trimer}} = 9 \times 10^5 \text{ M}^{-2}$$

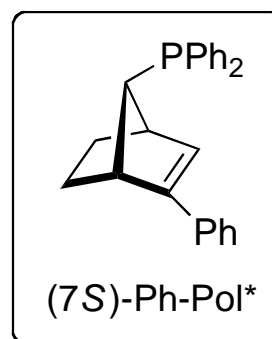
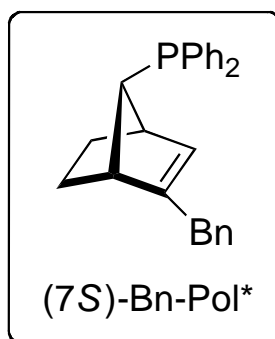
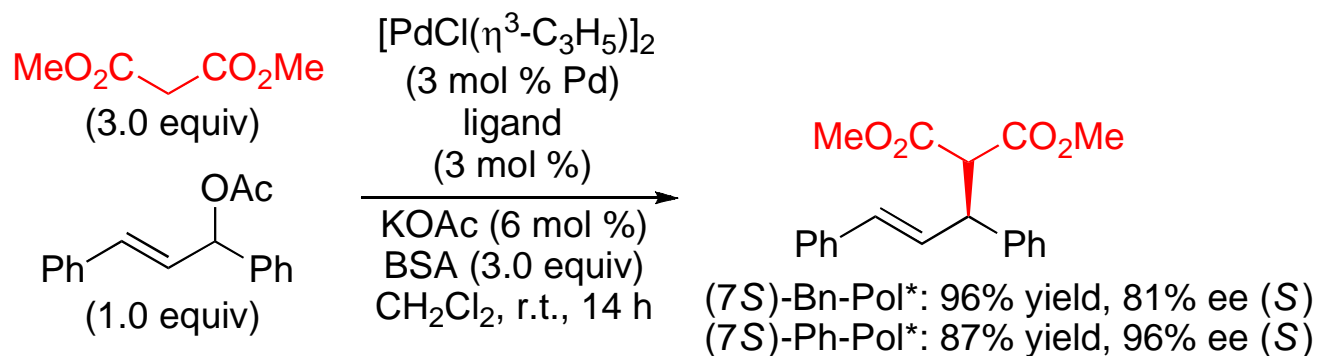
$$k_1 = 5 \text{ M}^{-1} \text{ s}^{-1}$$

π -Allyl-Pd/Chiral Phosphine–Olefin Complex

33

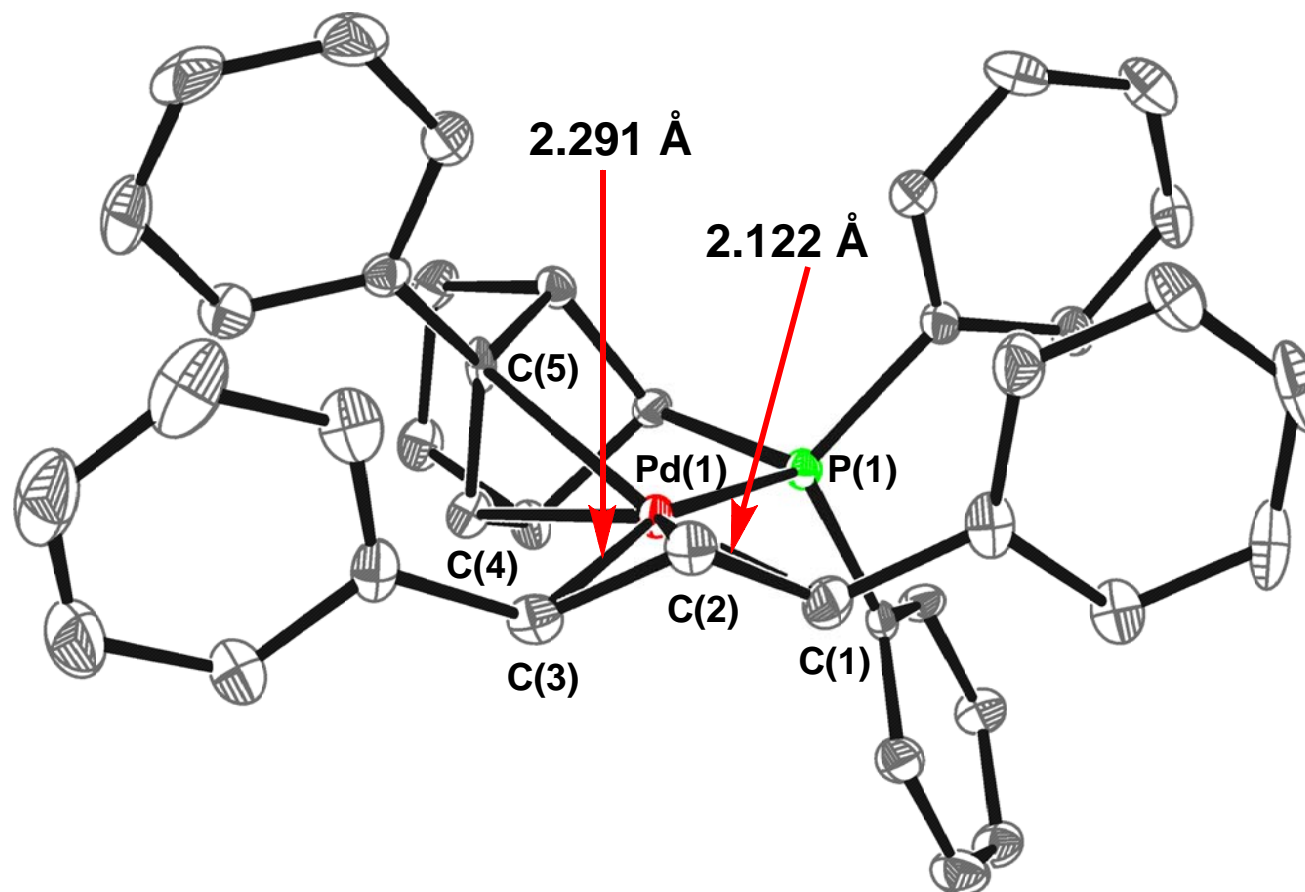
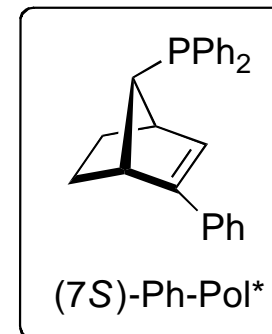
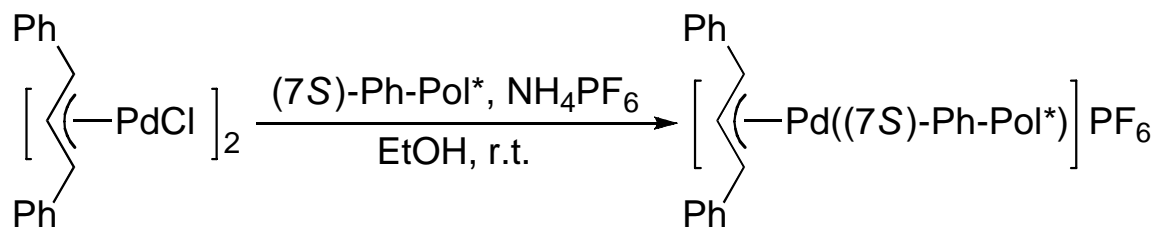


Palladium/Chiral Phosphine-Olefin Catalyzed Asymmetric Allylic Alkylation

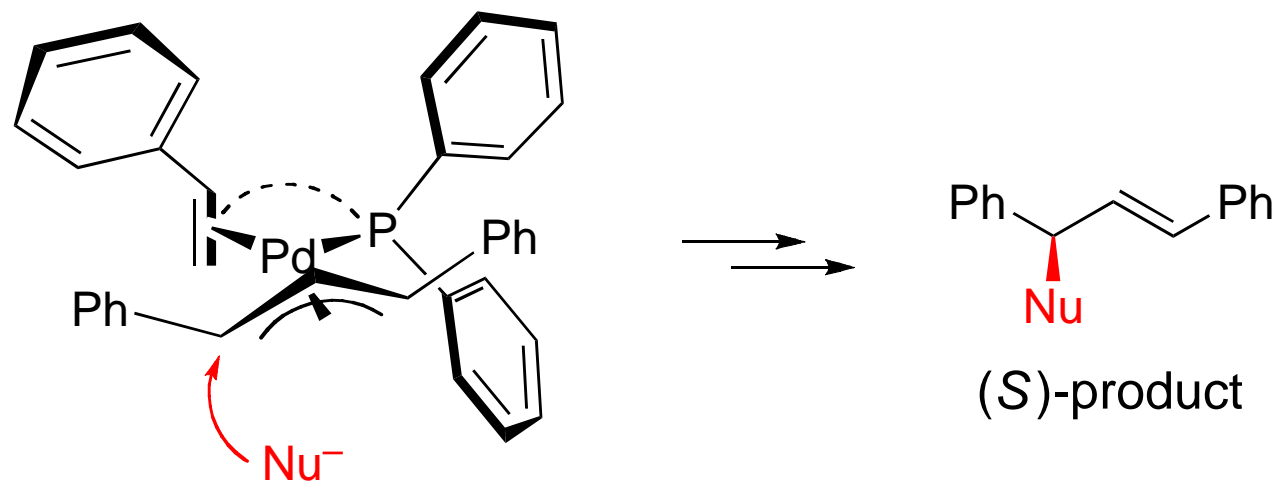


Shintani, R.; Duan, W.-L.; Okomoto, K.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, 16, 3400.

π -Allyl-Pd/Chiral Phosphine-Olefin Complex:



Proposed Stereochemical Pathway



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