Chapter 14. Principles of Catalysis

14. 1. General Principles

14.1.1. Definition of a Catalyst

14.1.2. Energetics of Catalysis

14.1.3. Reaction Coordinate Diagrams of Catalytic Reactions

14.1.4. Origins of Transition State Stabilization

14.1.5. Terminology of Catalysis

14.1.6. Kinetics of Catalytic Reactions and Resting States

14.1.7. Homogeneous vs. Heterogeneous Catalysis

14. 2. Fundamentals of Asymmetric Catalysis

14.2.1. Importance of Asymmetric Catalysis

14.2.2. Classes of Asymmetric Transformations

14.2.3. Nomenclature
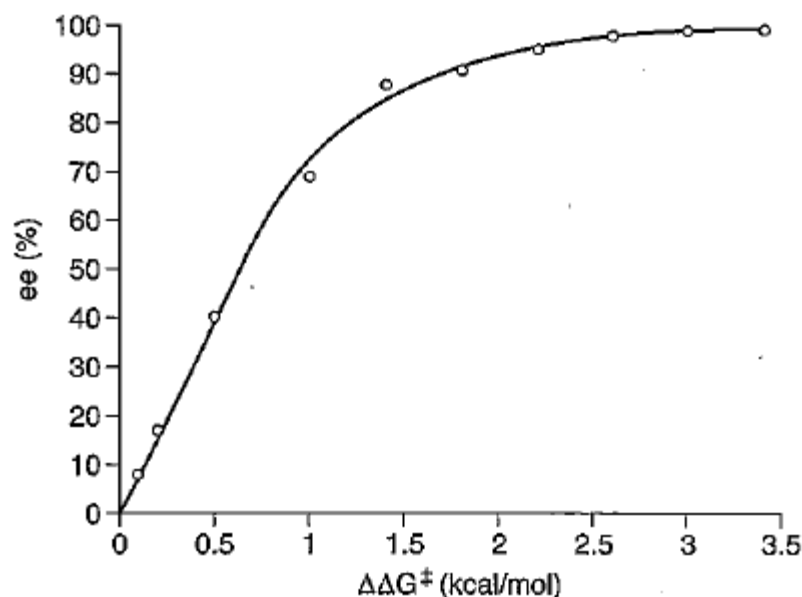
14.2.4. Energetics of Stereoselectivity

14.2.5. Transmission of Asymmetry

14.2.6. Alternative Asymmetric Processes:
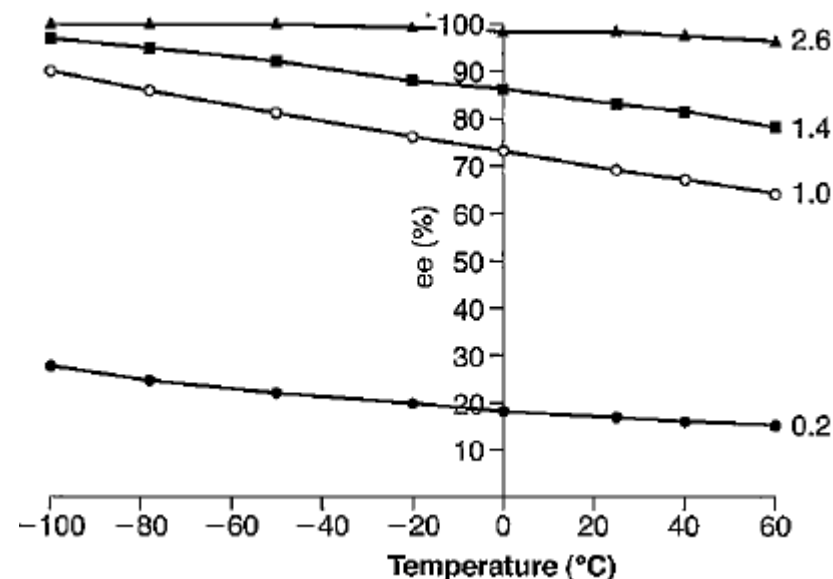 **Kinetic Resolution and Desymmetrizations**

14.2.4. Energetics of Stereoselectivity

$$\text{Enantomeric ratio} = \frac{[\text{Major enantiomer}]}{[\text{Minor enantiomer}]} = e^{-(\Delta\Delta G^{\ddagger}/RT)} \qquad (14.11)$$

- $\Delta\Delta G^{\ddagger} = 1.38$ kcal/mol => 10:1 ratio of product (at rt.)
- $\Delta\Delta G^{\ddagger} = 2$ kcal/mol => 90%ee

Figure 14.9.
Enantioselectivity as a function of the energy differences between the diastereomeric transition states ($\Delta\Delta G^{\ddagger}$) at 25 °C.

Figure 14.10.
Enantioselectivity as a function of temperature with $\Delta\Delta G^{\ddagger}$ values of 0.2, 1.0, 1.4, and 2.6 kcal/mol.

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14.2.4.1.1 Reaction with a Single Enantioselectivity-Determining Step

- simplest case:
  >direct reaction of catalyst. and prochiral substrate.
  >without coordination of subst. to cat. before enantioselectivity-determining step
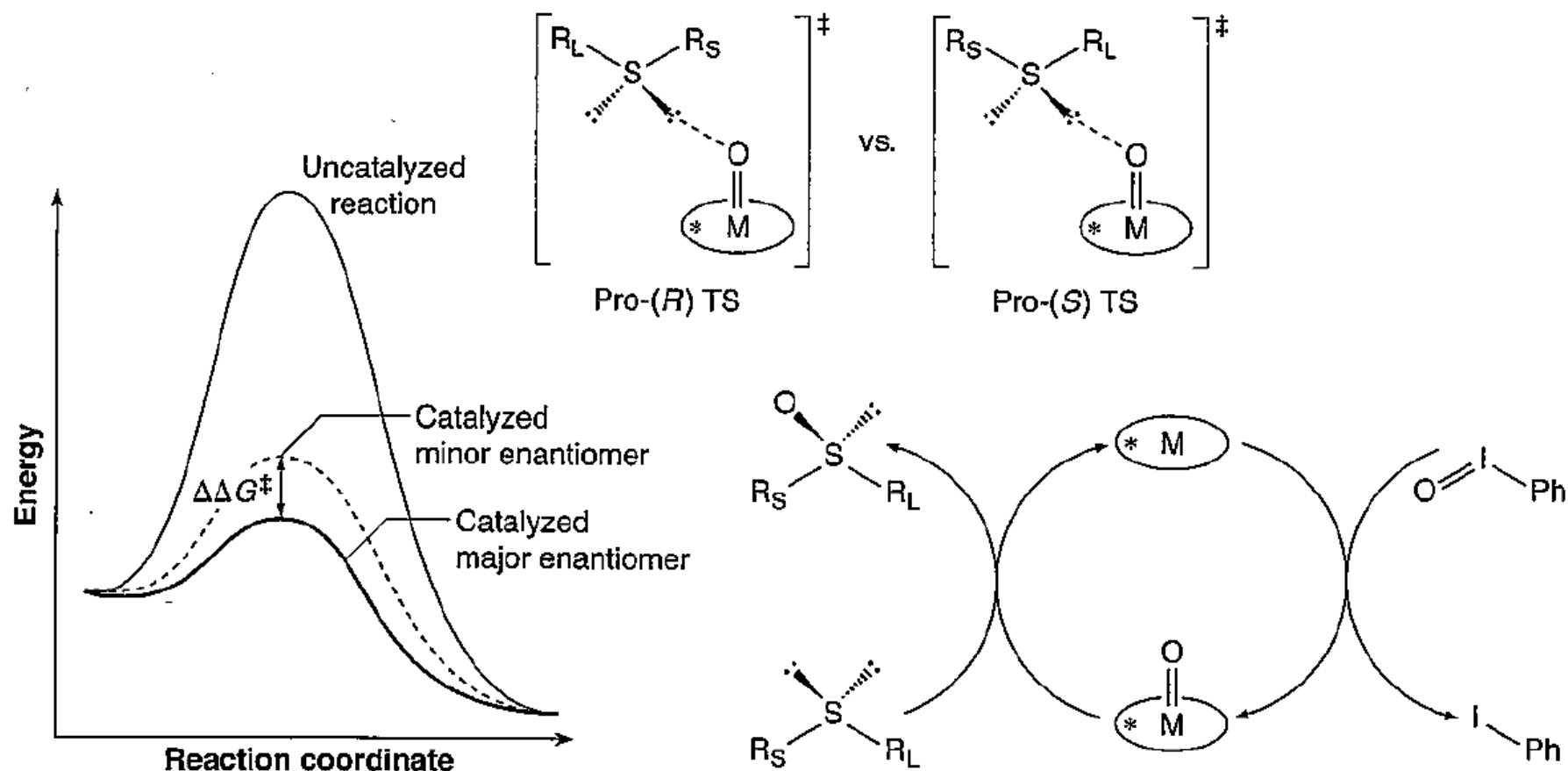- atom and group-transfer reactions (epoxidation, aziridination etc.)

Figure 14.11. Reaction coordinate of the oxidation step in the asymmetric sulfoxidation reaction.

- Prochiral substrates bind to catalyst in a separate step from enantioselectivity-determining step (**EDS**)
- **1)** interconversion of **I** and **I'** is slow relative to conversion to the product (Scheme 14.12.A)
  EDS = binding to the prochiral olefin faces to the metal
- **2)** interconversion of **I** and **I'** is significantly fast: (Scheme 14.12.B)
  EDS = reaction to form the product (**Curtin-Hammett conditions**)
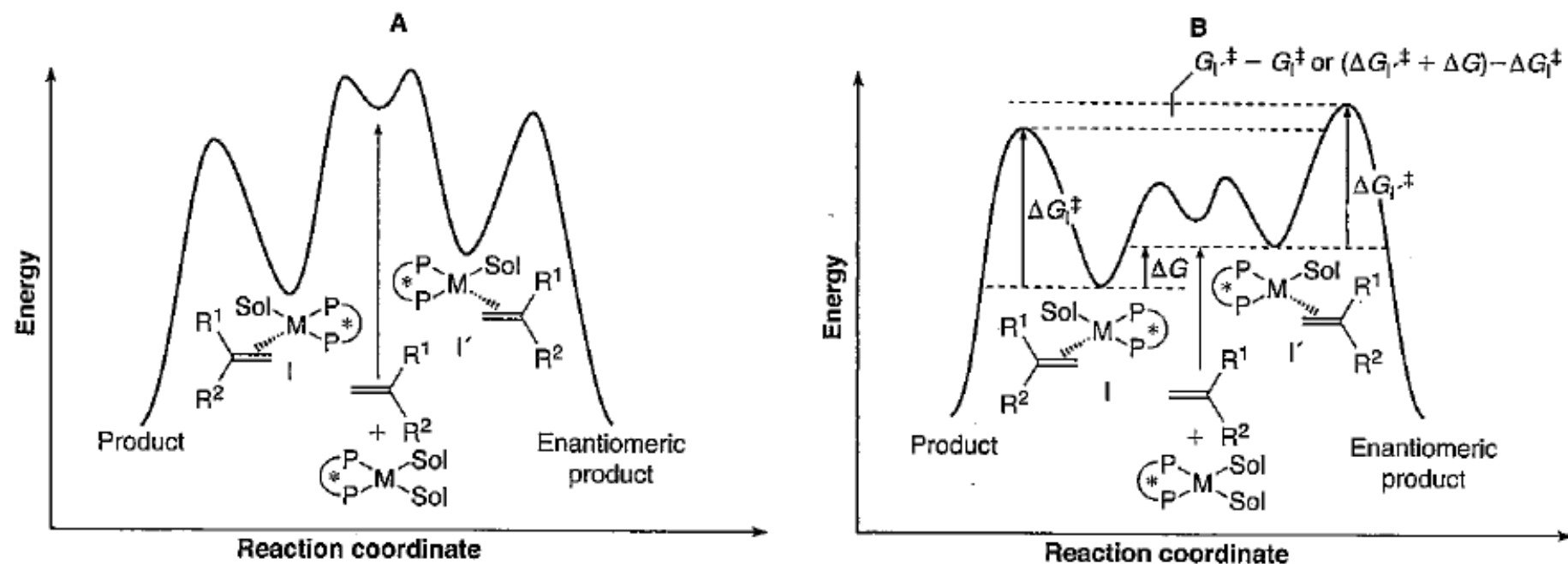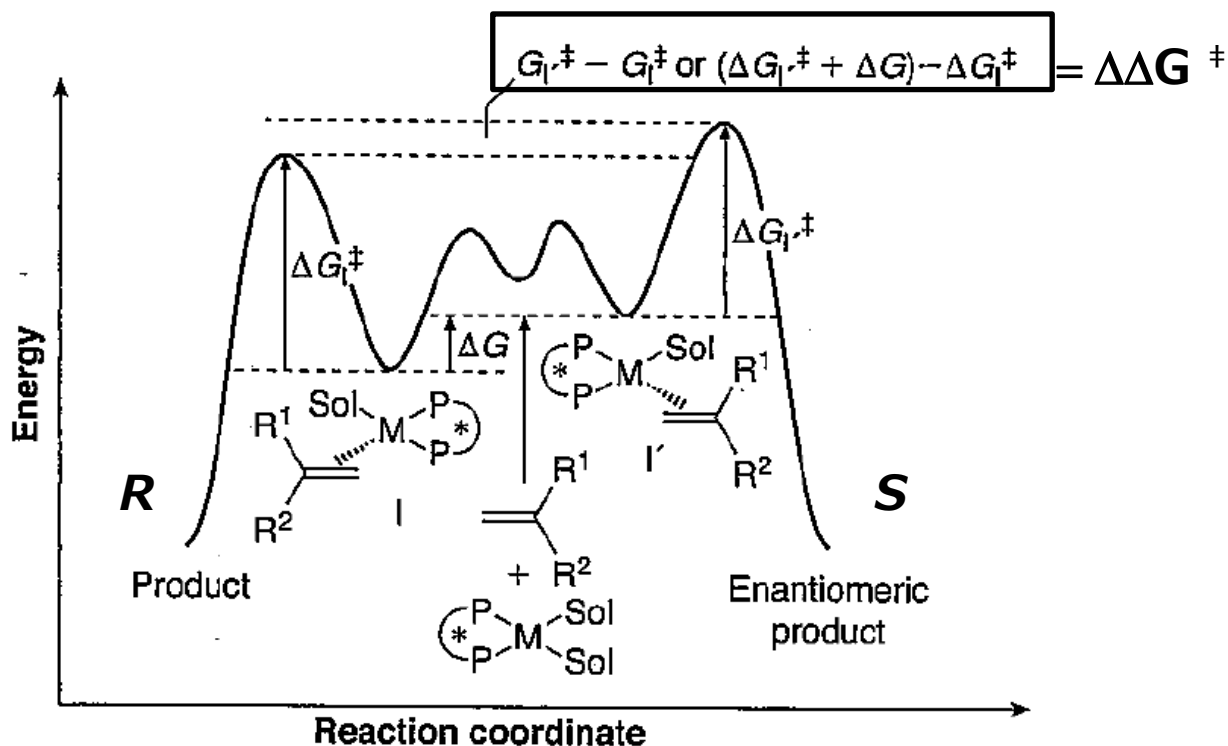

Figure 14.12.
Reaction coordinate diagrams illustrating reactions of diastereomeric olefin complexes. In scenario A, olefin binding is enantio-determining. In B, the diastereomeric olefin complexes are in rapid equilibrium and enantio-determination is the conversion of the olefin adducts to products. B is an example of Curtin–Hammett conditions.

# 14.2.4.1.1 The Curtin-Hammett Principle

- when competing reaction pathways <u>begin from rapidly interconverting isomers</u>,
  $\Rightarrow$ product ration is determined by the relative heights of the highest
  barriers leading to the two different products $(\Delta\Delta G^{\ddagger} = G_I^{\ddagger} - G_{I'}^{\ddagger})$

- $\dfrac{[R]}{[S]} = K_{eq}\left(\dfrac{k_i}{k_{i'}}\right) = \exp\left(-\dfrac{\Delta\Delta G^{\ddagger}}{RT}\right)$ $K_{eq} = \dfrac{[I]}{[I']}$ (14.13)

$$\boxed{G_{I'}^{\ddagger} - G_I^{\ddagger} \text{ or } (\Delta G_{I'}^{\ddagger} + \Delta G) - \Delta G_I^{\ddagger}} = \Delta\Delta G^{\ddagger}$$


enantioselectivity is controlled by the relative energy of the two diastereomeric
TSs (rather than the stabilities of the two diastereomeric intermediates)   6

$$(diphosphine)Rh^+(S)_2 \text{ catalyst}$$

Diphosphine = (S,S)-Chiraphos
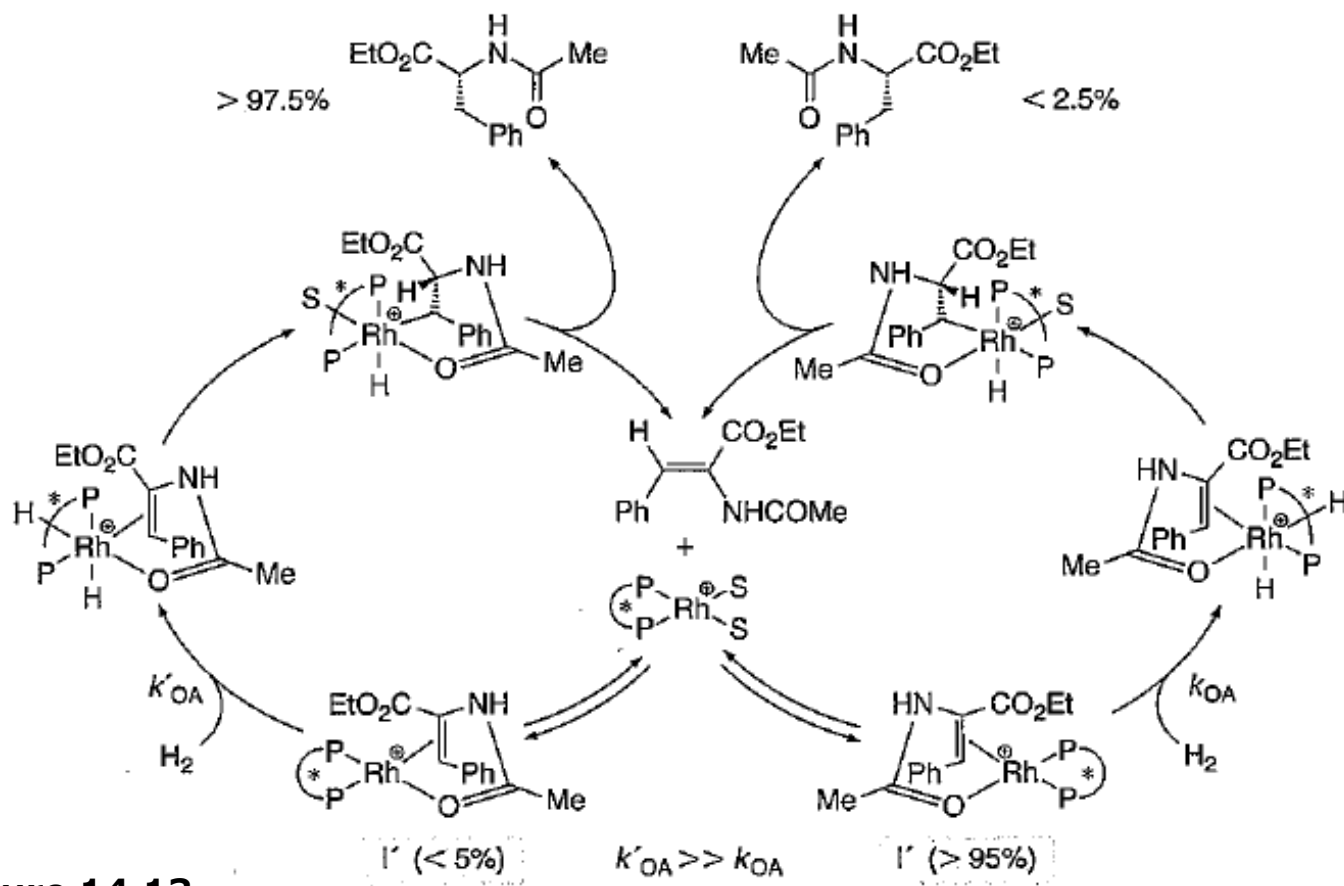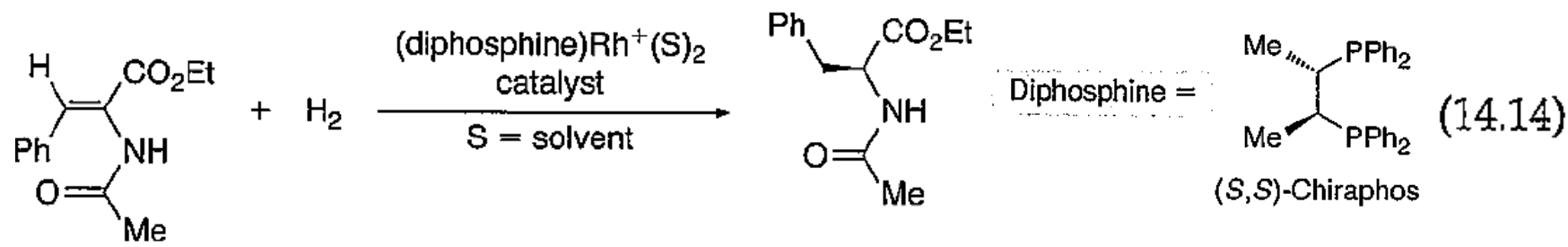
$$(14.14)$$

Figure 14.13.
Mechanism of the asymmetric hydrogenation, illustrating a reaction meeting the Curtin-Hammett conditions

Reaction (14.14)

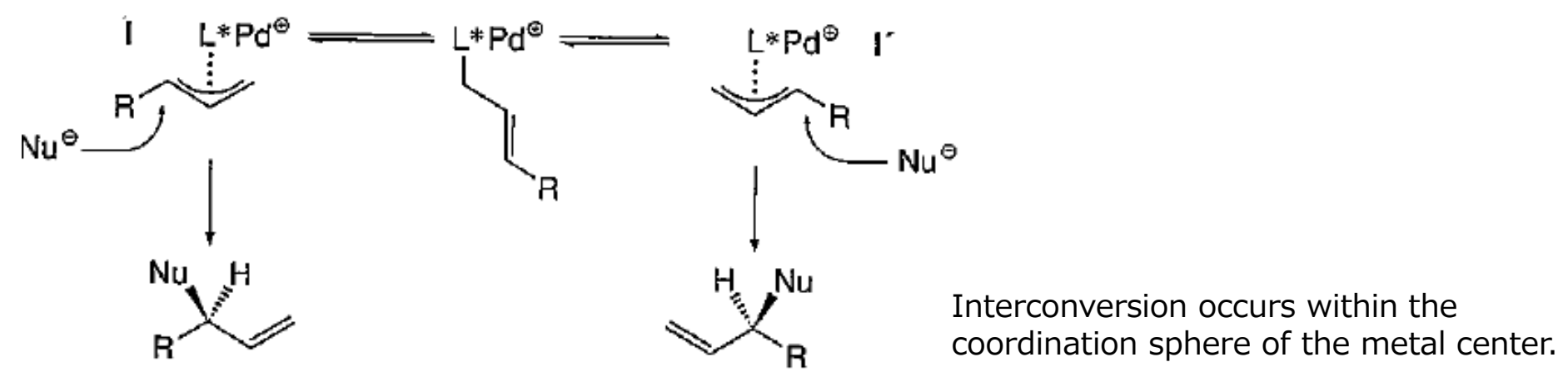$$\Delta G = \Delta G^{\ddagger}(I) - [\Delta G^{\ddagger}(I)' + \Delta G^{0}]$$
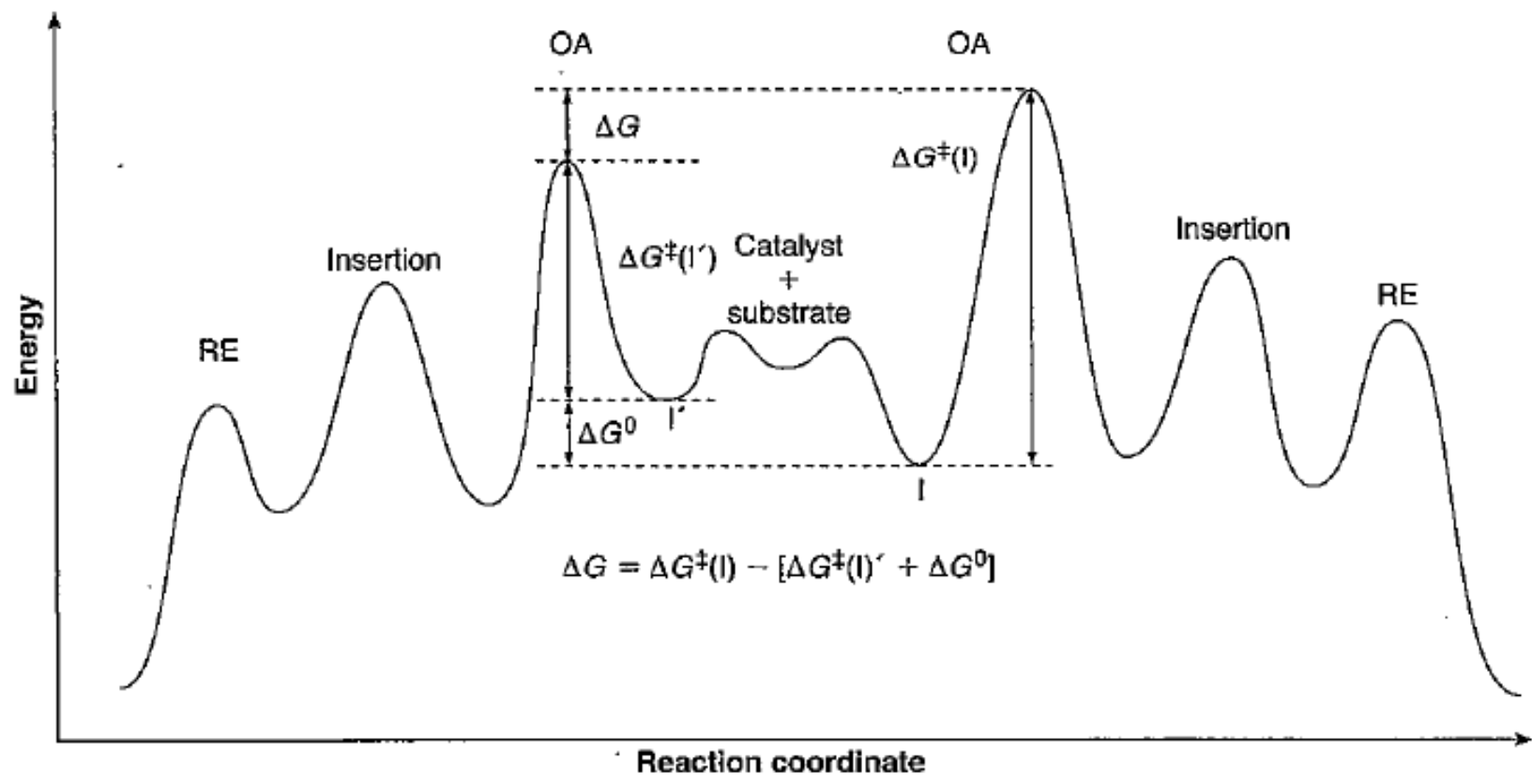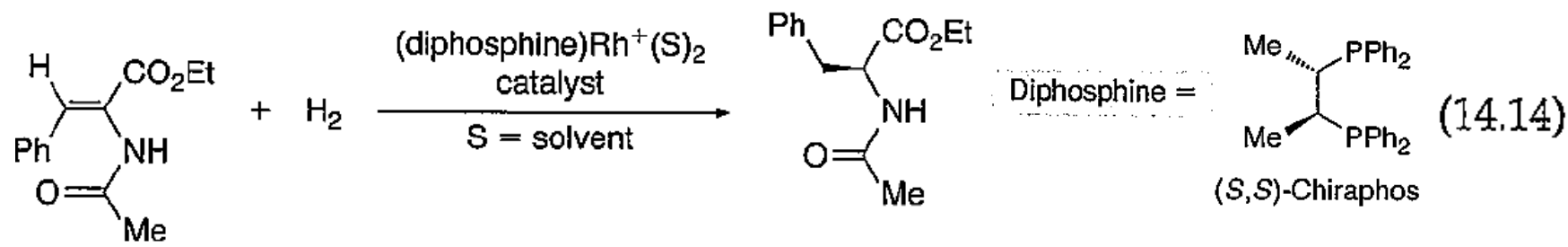
Figure 14.14.
Energy diagram for the asymmetric hydrogenation reaction under Curtin–Hammett conditions. The enantioselectivity-determining step is the oxidative addition (OA) of hydrogen.

Interconversion occurs within the coordination sphere of the metal center.

Figure 14.15.
Interconversion of the diastereomeric π-allyls **I** and **I'** occurs via an η^1-allyl. The enantioselectivity-determining step depends on the relative rates of $\pi-\sigma-\pi$ isomerization and nucleophilic attack.

- dilute conditions will help to achieve Curtin-Hammett conditions (unimolecular v.s. bimolecular)

- Halide ions catalyze the isomerization
- reversed enantioselectivity in the presence/absence of additives

(14.15)

9

1% Pd$_2$dba$_3$.CHCl$_3$ **5**

3% **6**

2

1a-e (X—⬡—OH)
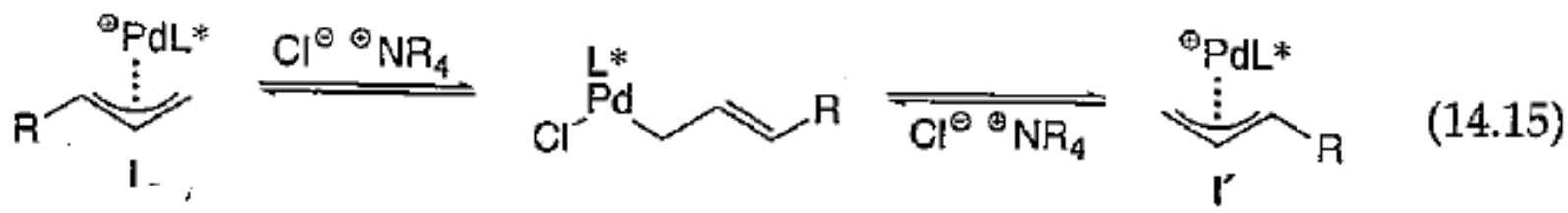
3a-e, **4a-e (S)**, **4a-e (R)** (2)
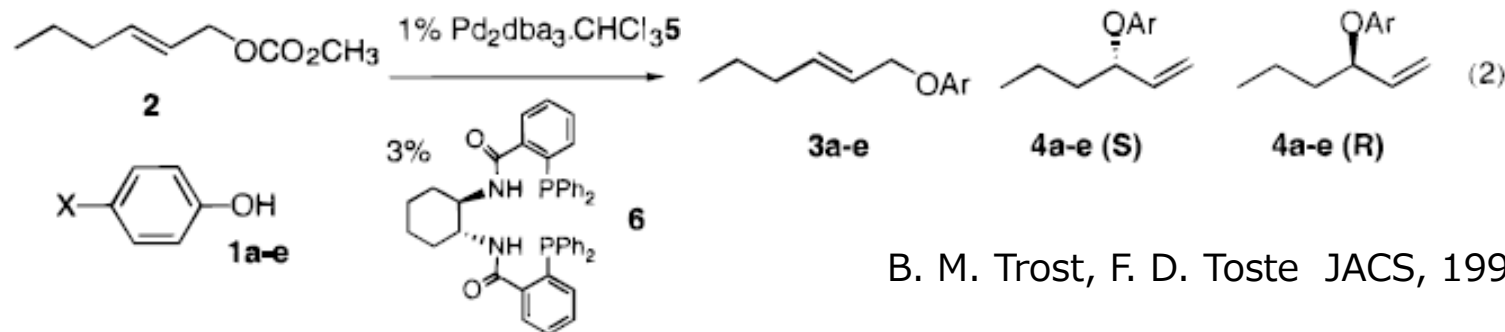
B. M. Trost, F. D. Toste JACS, 1999, 121, 4545

Table 4. Effect of Halide Ion on Enantioselectivity in the Reaction with Chiral Substrate **8** (Eq 4)

entry	solvent (concn ((M))	additive	4a:3a	% ee (R)
1	CH$_2$Cl$_2$ (0.5)		67:33	36
2	CH$_2$Cl$_2$ (0.5)	3% TBAT	71:29	50
3	CH$_2$Cl$_2$ (0.5)	3% Bu$_4$N$^+$ Cl$^-$	73:27	57
4	CH$_2$Cl$_2$ (0.5)	30% Bu$_4$N$^+$ Cl$^-$	80:20	65
5	CH$_3$CN (0.5)		80:20	53
6	CH$_3$CN (0.5)	3% Bu$_4$N$^+$ Cl$^-$	78:22	57
7	CH$_2$Cl$_2$ (0.1)	30% Me$_4$N$^+$ Cl$^-$	86:14	69
8	CH$_2$Cl$_2$ (0.1)	30% Et$_4$N$^+$ Cl$^-$	84:16	76
9	CH$_2$Cl$_2$ (0.1)	30% Bu$_4$N$^+$ Cl$^-$	84:16	83
10	CH$_2$Cl$_2$ (0.1)	15% Bu$_4$N$^+$ Cl$^-$	84:16	74
11	CH$_2$Cl$_2$ (0.1)	30% Hex$_4$N$^+$ Cl$^-$	84:16	86
12	CH$_2$Cl$_2$ (0.1)	30% Bu$_4$N$^+$ ClO$_4^-$	71:29	59
13	CH$_2$Cl$_2$ (0.1)	30% Bu$_4$N$^+$ Br$^-$	88:12	77
14	CH$_2$Cl$_2$ (0.1)	30% Bu$_4$N$^+$ I$^-$	84:16	75
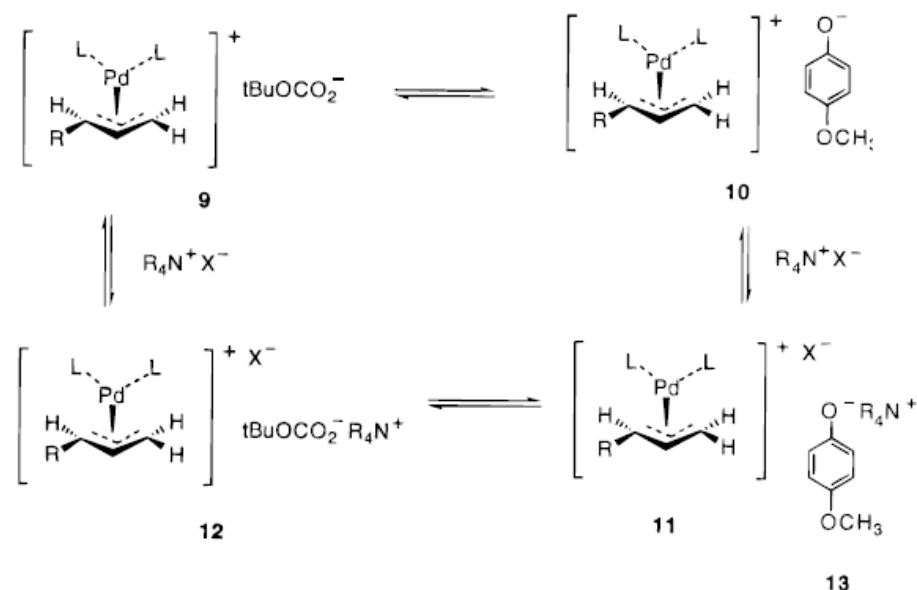
- Halide anion + diluted condition => Curtin-Hammett conditions
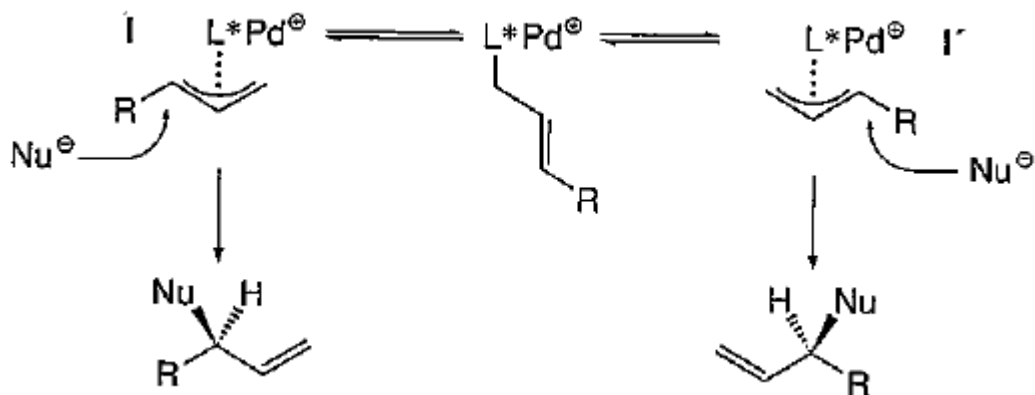- Ammonium cation lowers phenol nucleophilicity?

14.2.5.1 Effect of C$_2$ Symmetry

- it was often observed that C$_2$-symmetric catalyst were most effective
- Kagan: smaller number of metal-substrate adducts and TSs available
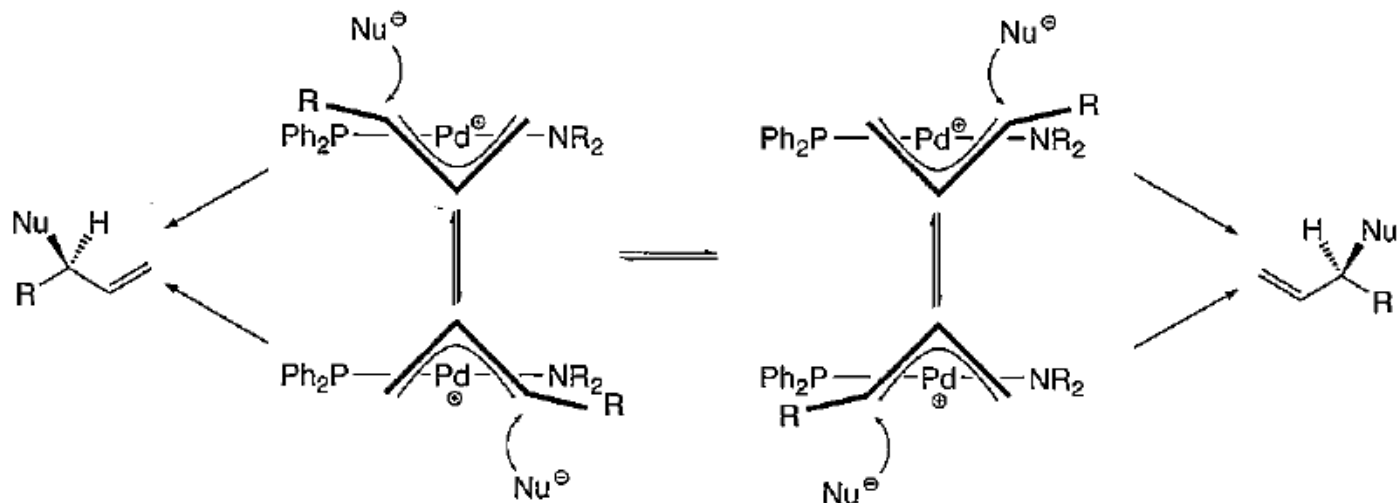
Figure 14.16.
The four diastereomeric π-allyl complexes containing an unsymmetical P–N ligand. These four diastereomeric complexes can be compared to the two diastereomeric π-allyl complexes containing a C$_2$-symmetric ligand (Figure 14.15).

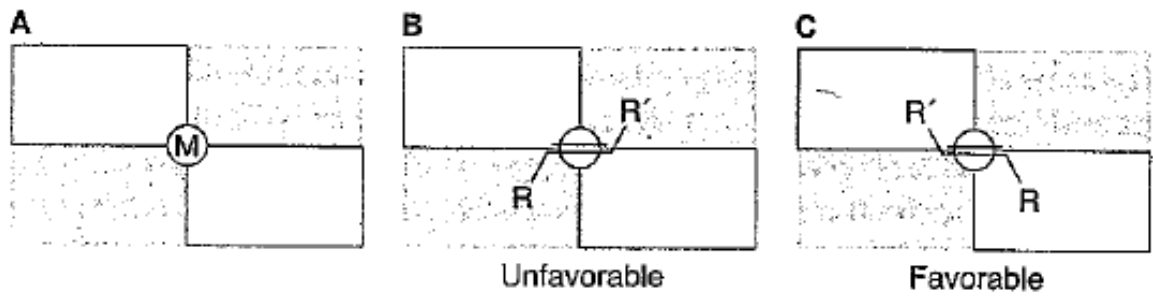**Figure 14.15.**
Interconversion of the diastereomeric π-allyls **I** and **I'** occurs via an η^1-allyl. The enantioselectivity-determining step depends on the relative rates of π–σ–π isomerization and nucleophilic attack.

14.2.5.2 Quadrant Diagrams

- generic model for steric biasing of chiral metal-ligand adducts
- shaded: hindered
- white: less hindered

Figure 14.17.
A. Quadrant diagrams for a C_2-symmetric catalyst. B. Unfavorable binding and C. favorable binding of an olefin in diastereomeric olefin complexes.

- stereogenic centers close to the metal: e.g.. Pybox (Fig. 14.18.A)
                    more distant from metal: e.g. Chiraphos (Fig. 14.18.B)
- chiraphos) Me: pseudo-equatorial
        two phenyls: pseudo-axial (edge) + pseudo-equatorial (face)

A (R, R)-PyBox   B (S, S)-Chiraphos   C Front view   D Rear view
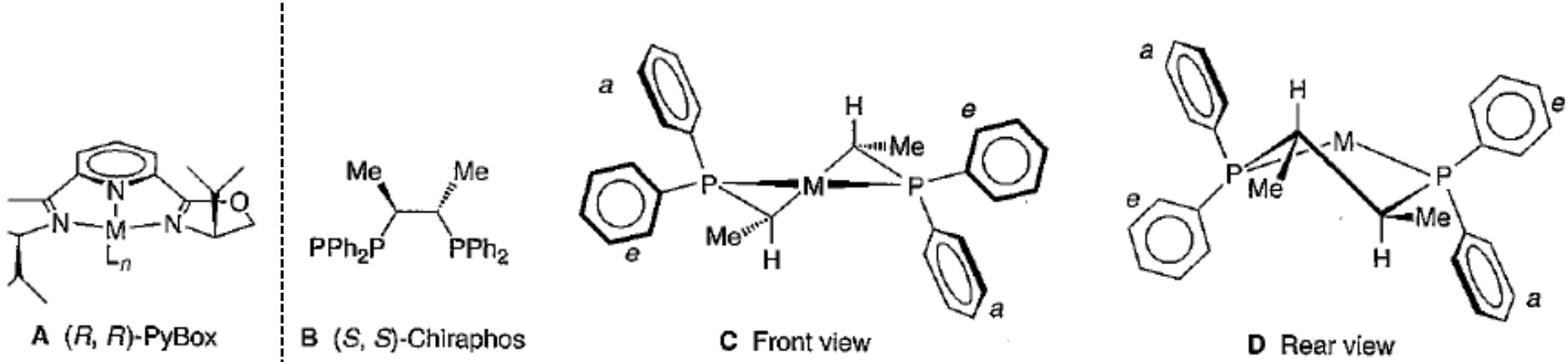
Figure 14.18.
PyBox and Chiraphos, illustrating the positioning of key substituents contributing to the chiral environment of the catalyst bearing these ligands.

14.2.6 Alternative Asymmetric Processes: Kinetic Resolutions and Desymmetrizations

14.2.6.1. Kinetic Resolutions

14.2.6.2. Dynamic Kinetic Resolution
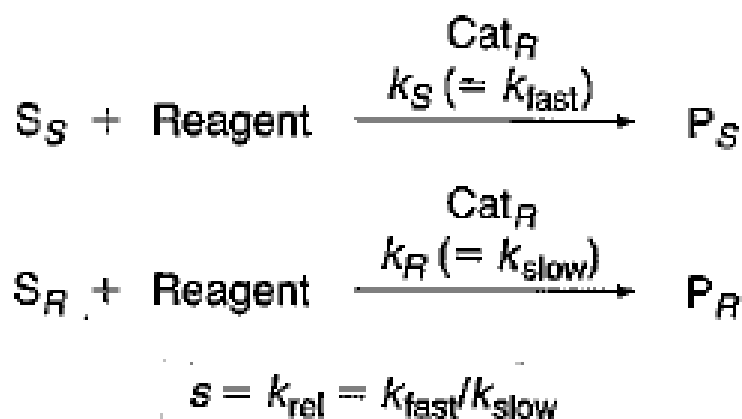
14.2.6.3. Dynamic Kinetic Asymmetric Transformations

14.2.6.4. Asymmetric Desymmetrizations

Kinetic Resolution (KR)

- reactions that occur at different rates with two enantiomers of a chiral substrate
- do not usually generate additional stereochemistry
- distinguish one enantiomer from another by creating new functionality
- maximum yield: 50%
- best option when racemate is inexpensive,
  no practical enantioselective route is available

$$S_S + Reagent \xrightarrow[\quad k_S (= k_{fast}) \quad]{Cat_R} P_S$$

$$S_R + Reagent \xrightarrow[\quad k_R (= k_{slow}) \quad]{Cat_R} P_R$$

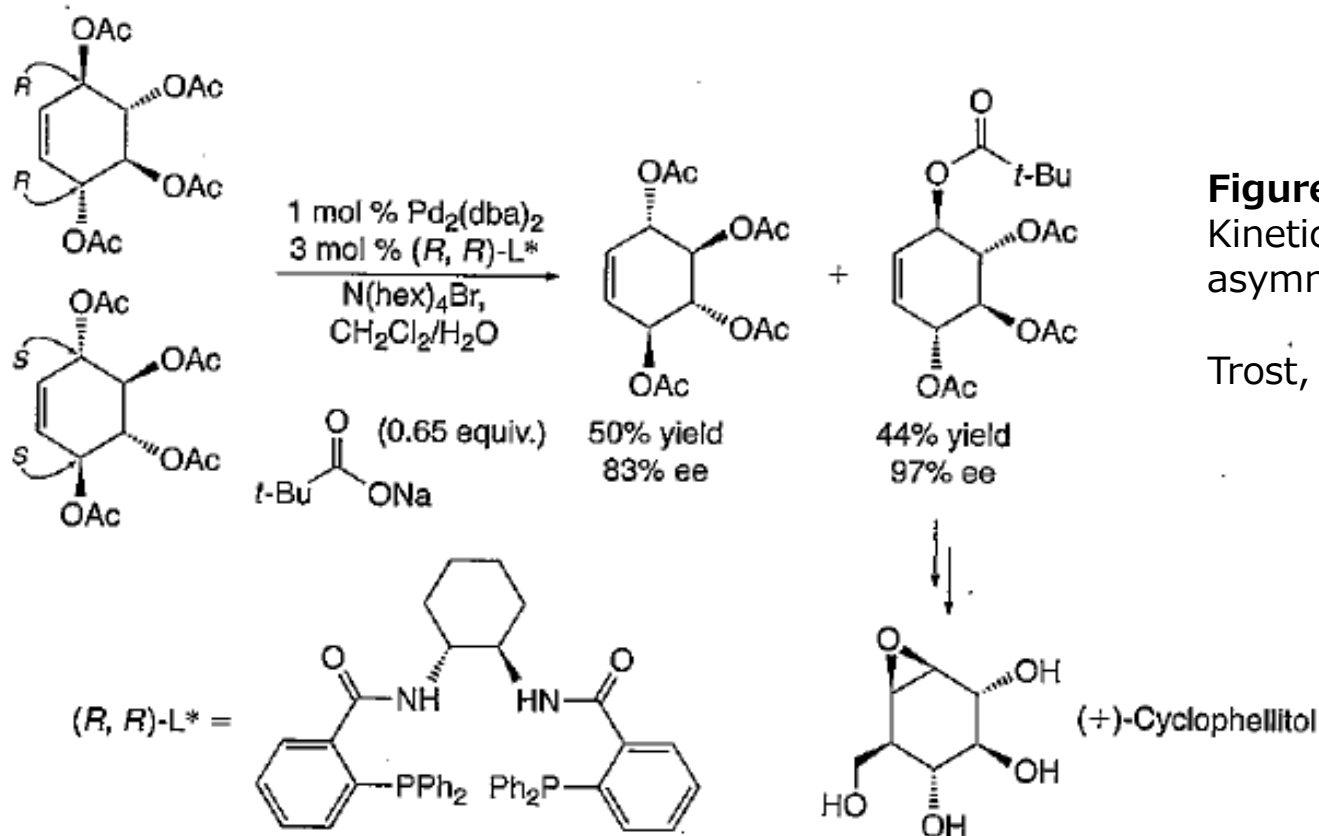$$s = k_{rel} = k_{fast}/k_{slow}$$

Figure 14.23.
Kinetic resolution involving the reaction of a racemic substrate, achiral reagent, and a resolved catalyst. The relative rate of reaction of the enantiomers determines the efficiency of the KR.
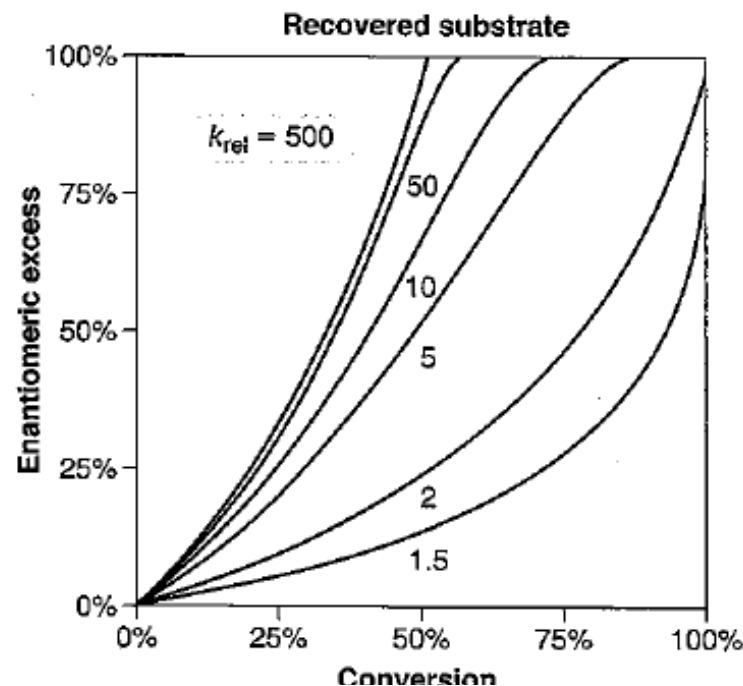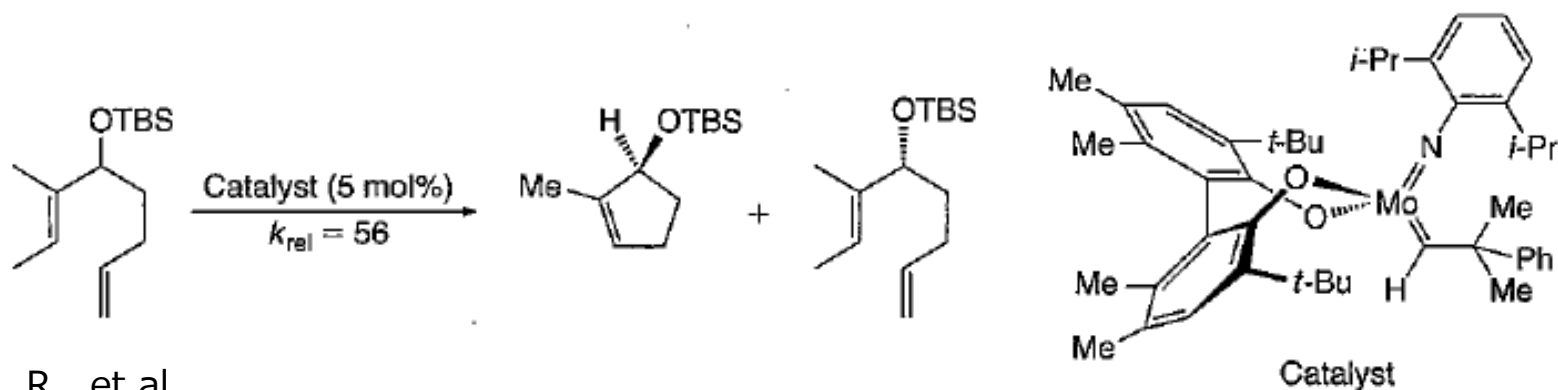
Figure 14.24.
Graph representing the ee (%) as a function of conversion (%) for different k_{rel} values.

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14.2.6.1.3. Examples of Kinetic Resolutions

Figure. 14.26.
Kinetic resolution in the asymmetric allylic substitution

Trost, B. M. et al. TL 1999, 40, 219

1 mol % Pd₂(dba)₂
3 mol % (R, R)-L*

N(hex)₄Br,
CH₂Cl₂/H₂O

(0.65 equiv.)
t-Bu   ONa

50% yield
83% ee

44% yield
97% ee

(R, R)-L* =

(+)-Cyclophellitol

Schrock, R. R.. et al.
JACS 1999 121 8251

Catalyst (5 mol%)
k_{rel} = 56

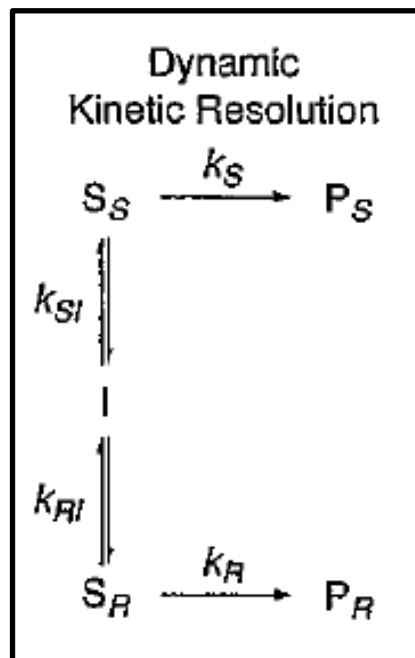**Figure 14.28.** Kinetic resolution in the asymmetric ring-closing metathesis.

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Dynamic Kinetic Resolution (DKR)
• KR in a fashion that allows the conversion of both enantiomers of the reactant into a single enantiomer of the product
• KR with a rapid racemization of the chiral substrate thorough an achiral intermediate (=**I**) or transition state
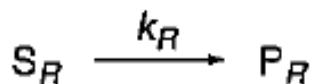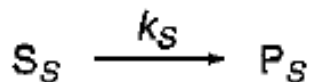
•In a typical DKR: $k_{rac} \geq k_{fast}$
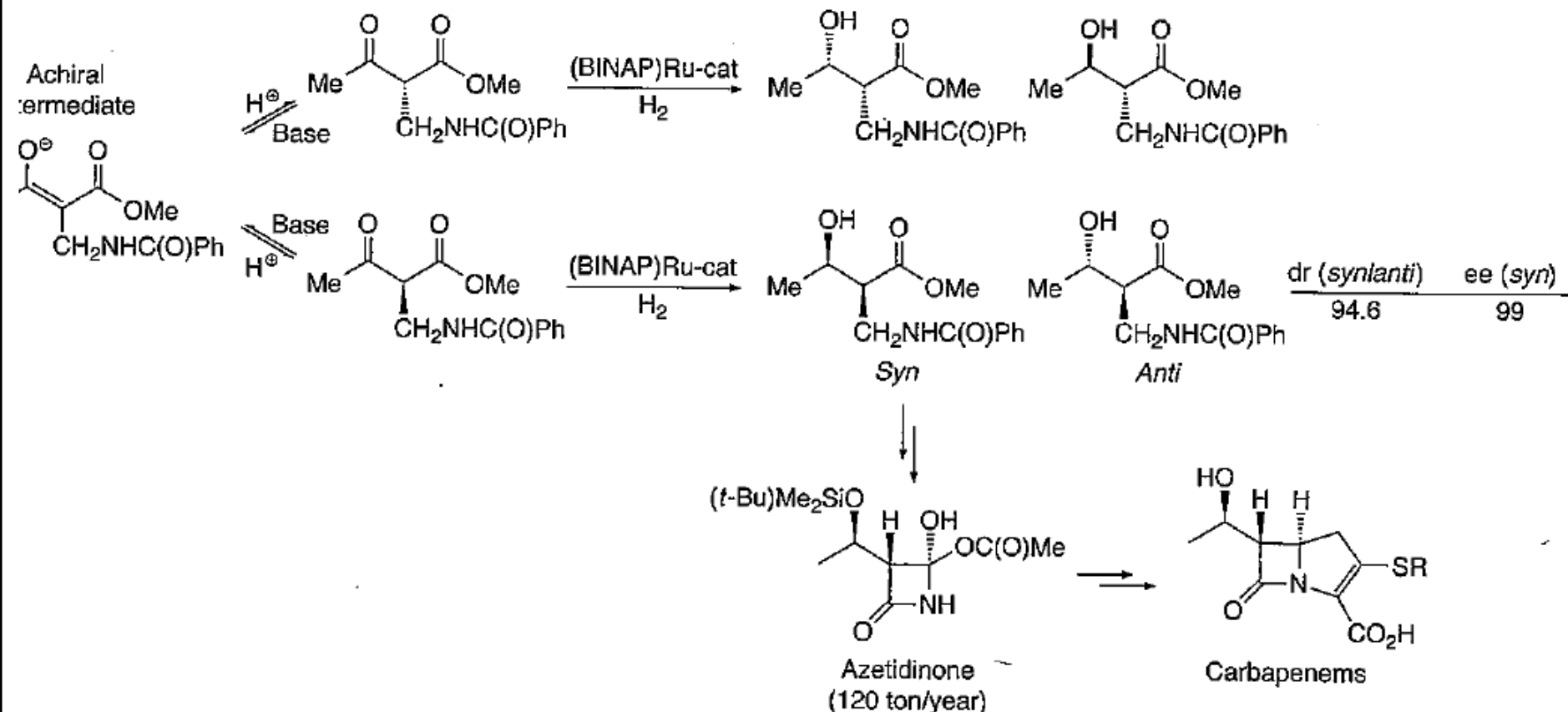
• if substrate fully equbriuming and $k_{fast}/k_{slow} \sim 20 \Rightarrow ee \sim 90\%$

Figure 14.29.
Comparison of a classical kinetic resolution with a dynamic kinetic resolution. In the dynamic kinetic resolution, I is an achiral intermediate or transition state.
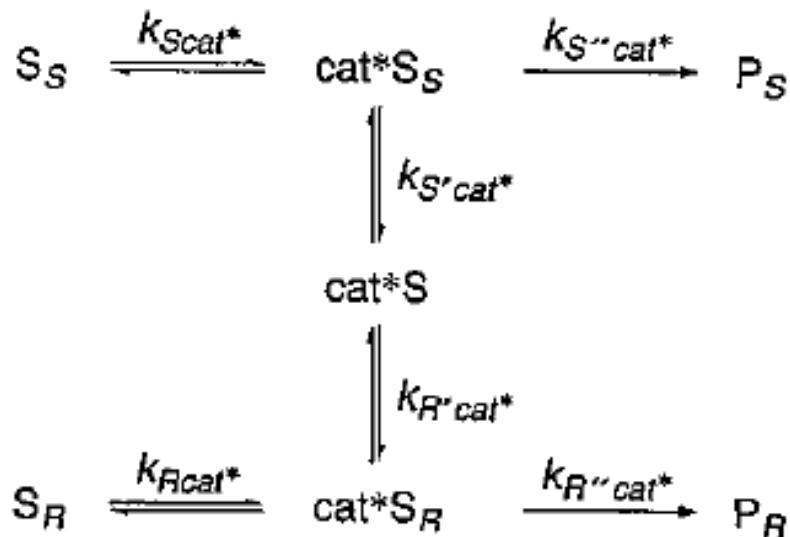
Figure 14.30.
DKR in the asymmetric reduction of α-substituted β-keto esters, illustrating the substrate racemization and the four possible diastereomeric products.

Noyori, R. et al. BCSJ 1995, 68, 36

14.2.6.3. Dynamic Kinetic Asymmetric Transformations (DyKAT)

• Mechanism of stereochemical interconversions distinguishes DKR and DyKAT
• **DKR**: catalyst that promotes racemization is achiral
  unrelated to resolution step
• **DyKAT**: interconversion of subst. stereochemistry occurs on asymmetric cat.
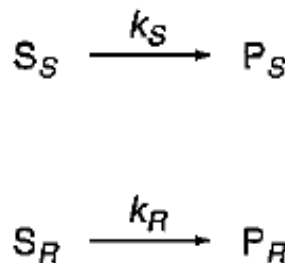 (epimerization)

DyKAT

Figure 14.31.
DyKAT reaction pathways involving epimerization. The (R)- and (S)-substrates and products are S_R, S_S, P_R, and P_S. The chiral catalyst is cat*.

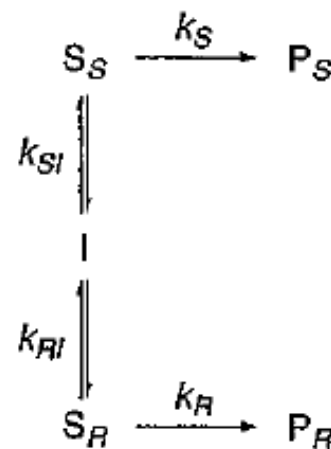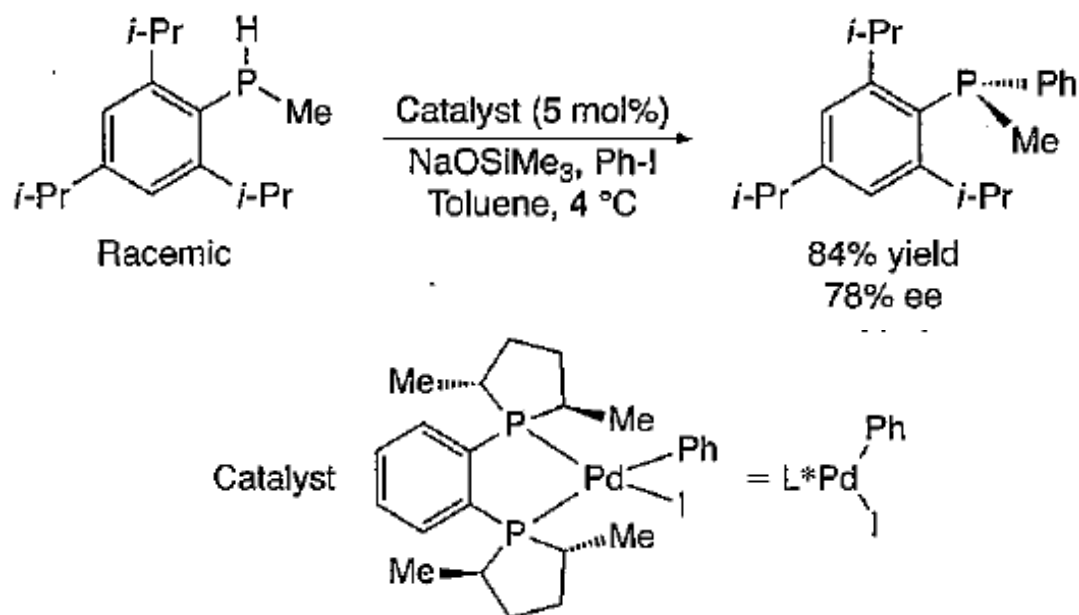**KR** — Classical Kinetic Resolution

**DKR** — Dynamic Kinetic Resolution

Figure 14.29.
Comparison of a classical kinetic resolution with a dynamic kinetic resolution. In the dynamic kinetic resolution, I is an achiral intermediate or transition state.

14.2.6.3. Examples of DyKAT

Catalyst (5 mol%)
NaOSiMe$_3$, Ph-I
Toluene, 4 °C

Racemic

84% yield
78% ee

Catalyst = L*Pd

D. S. Glueck et al. JACS 2002 124 13556

Figure 14.32.
DyKAT of racemic phosphine to generate a tertiary *P*-chirogenic phosphine.

L* = (*R, R*)-Me-DUPHOS

Base   Base

Inversion at P

Reductive elimination
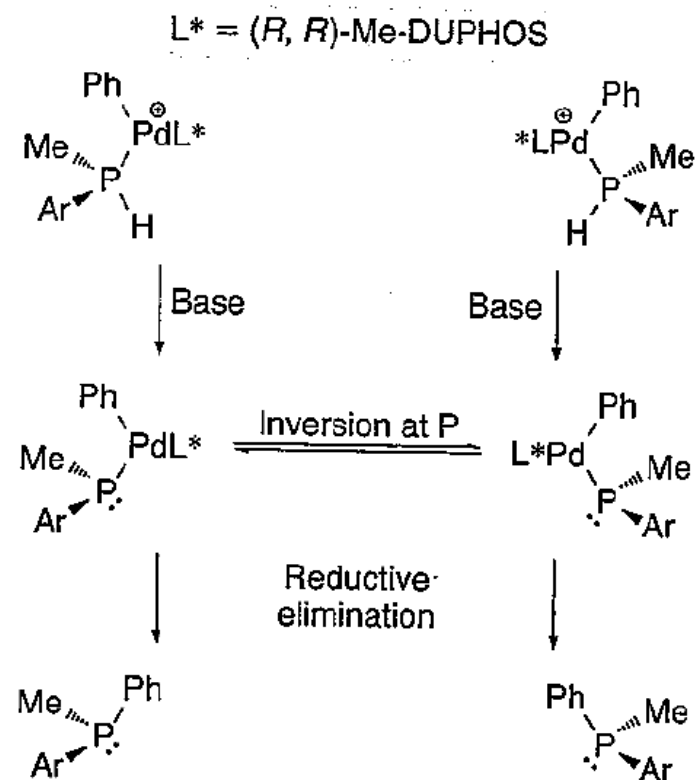
Figure 14.33.
Proposed mechanism of the DyKAT, where inversion of phosphorus is faster than reductive elimination.

14.2.6.4. Desymmetrization Reactions

• differential reactivity of enantiotopic FGs of subst. with chiral reagent or cat.
• catalyst differentiates between enantiotopic groups within single substrate
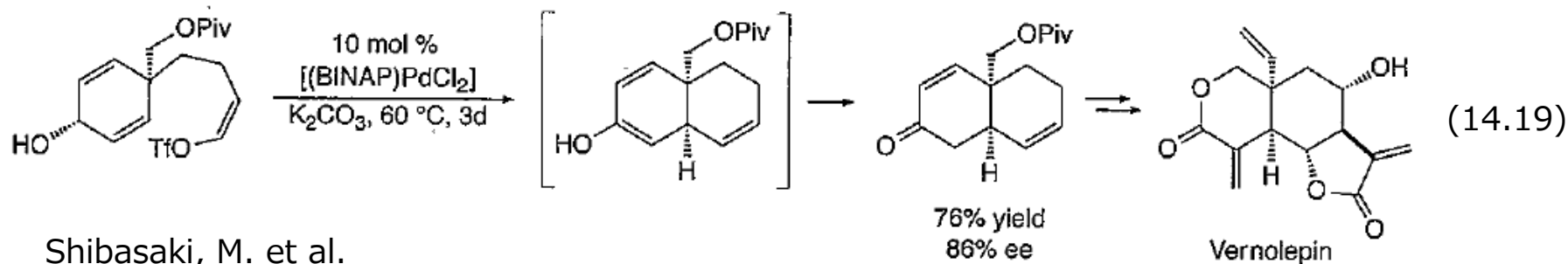 (cf. **KR**: differentiate between enantiomers of a racemic substrate)
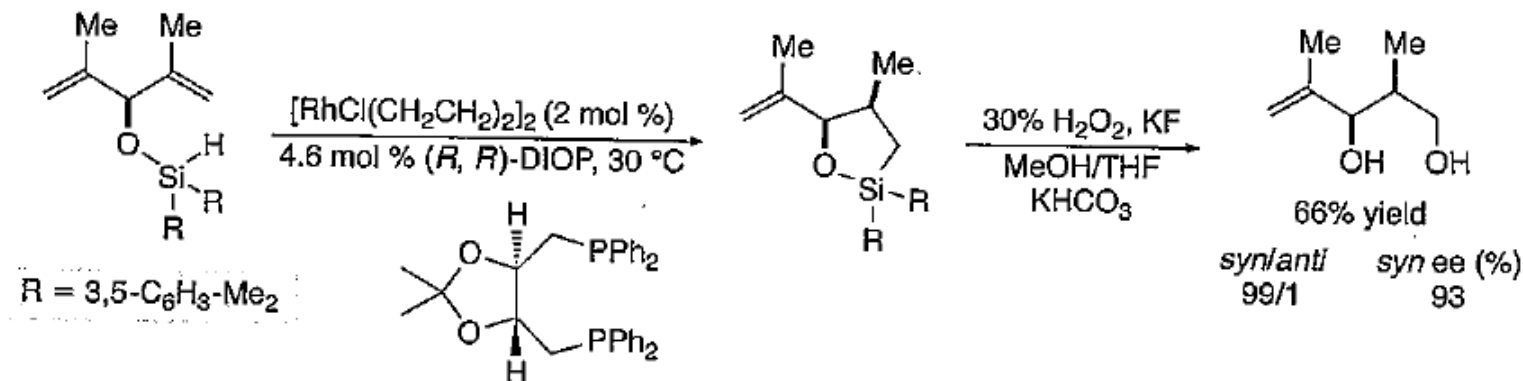
Figure. 14.34.
Desymmetrization of dienes by catalytic asymmetric hydrosilylation.
Oxidation of the product provides a valuable 1,3-diol

Ito, Y. et al.
TL 1990, 31, 7333

(14.19)

Shibasaki, M. et al.
TL 1993, 34, 4219