A Brief Introduction to the Curtin-Hammett Principle

J. I. Seeman, *J. Chem,Ed.* **1986,** *63,* 42-48 *The Curtin-Hammett Principle and the Winstein-Holness Equation*

J. I. Seeman, *Chem. Rev.* **1983**, *83*, 84-134. *Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammet-Winstein-Holness Kinetics*
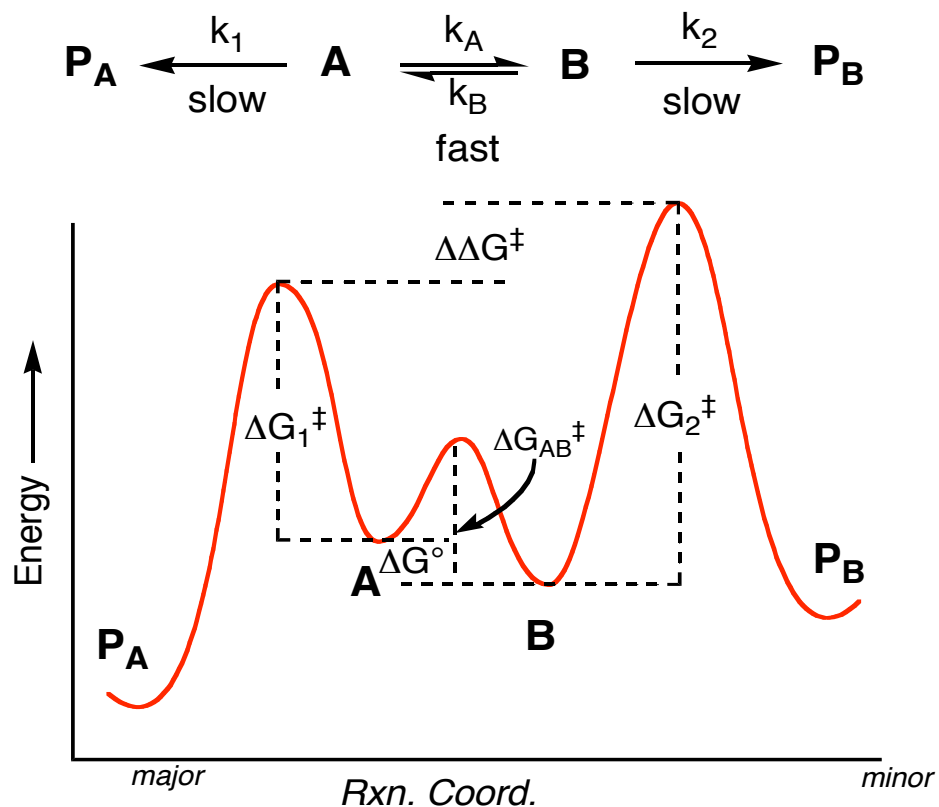
Curtin–Hammett Conditions

Curtin–Hammett Principle

"The product composition, P_A vs P_B is not solely dependent on relative proportions of the conformational isomers in the substrate;

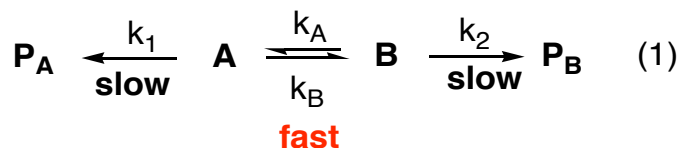*it is controlled by the difference in standard Gibbs energies ($\Delta\Delta G^*$) of the respective transition states."*

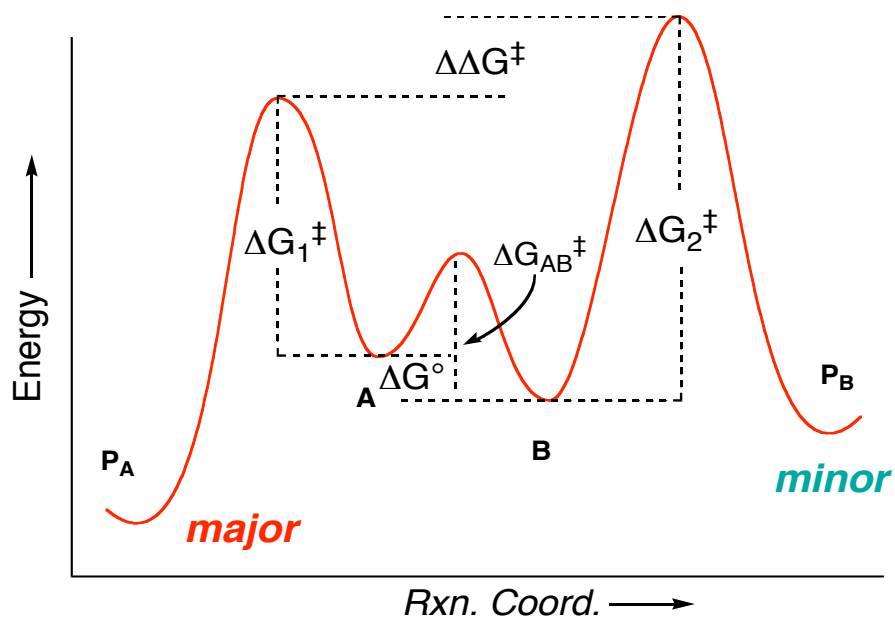The C-H principle may be extended to rapidly interconverting diastereomers, or constitutional isomers as well.

$$P_A \xleftarrow[\text{slow}]{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow[\text{slow}]{k_2} P_B$$

fast

Energy →

$\Delta\Delta G^\ddagger$

$\Delta G_1{}^\ddagger$ $\Delta G_{AB}{}^\ddagger$ $\Delta G_2{}^\ddagger$

$\Delta G°$

A   B

P_A P_B

major   Rxn. Coord.   *minor*

Chem 206, D. A. Evans

"Curtin–Hammett Conditions"

$$k_1, k_2 \ll k_A, k_B:$$

$$P_A \xleftarrow[\text{slow}]{k_1} \quad A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow[\text{slow}]{k_2} P_B \quad (1)$$
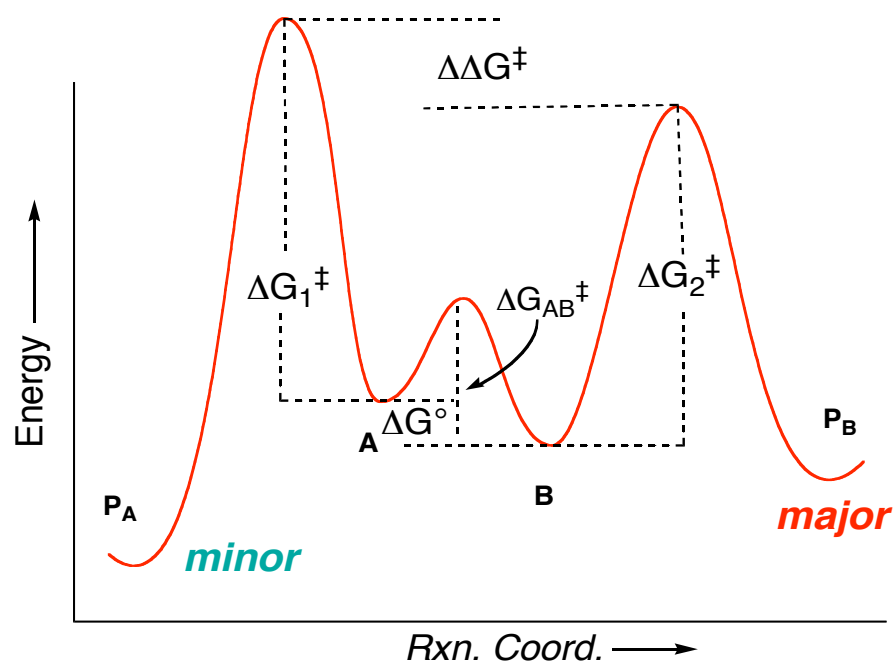
fast

Case 1: Less stable conformer leads to the **major** product.

If reaction rates are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the A/B ratio is constant throughout the course of the rxn.

Energy ⟶

$\Delta\Delta G^{\ddagger}$

$\Delta G_1^{\ddagger}$ $\Delta G_{AB}^{\ddagger}$ $\Delta G_2^{\ddagger}$

A ΔG°

B

P_A

P_B

major

minor

Rxn. Coord. ⟶

Case 2: Less stable conformer leads to the **minor** product.

If reaction rates are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the A/B ratio is constant throughout the course of the rxn.

$\Delta\Delta G^{\ddagger}$

$\Delta G_1^{\ddagger}$ $\Delta G_{AB}^{\ddagger}$ $\Delta G_2^{\ddagger}$

A ΔG°

B

P_A

P_B

minor

*major*

Energy ⟶

Rxn. Coord. ⟶

Curtin - Hammett Principle

The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies ($\Delta\Delta G^{\ddagger}$) of the respective transition states.

Case 2: Curtin-Hammett Conditons

k_1, k_2 << k_A, k_B: If the rates of reaction are much **slower** than the rate of interconversion, ($\Delta G_{AB}^{\ddagger}$ is small relative to $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$), then the ratio of A to B is constant throughout the course of the reaction.

$$P_A \xleftarrow[\text{slow}]{k_1} A \underset{k_B}{\overset{k_A}{\rightleftharpoons}} B \xrightarrow[\text{slow}]{k_2} P_B \qquad (1)$$

$$\text{fast}$$
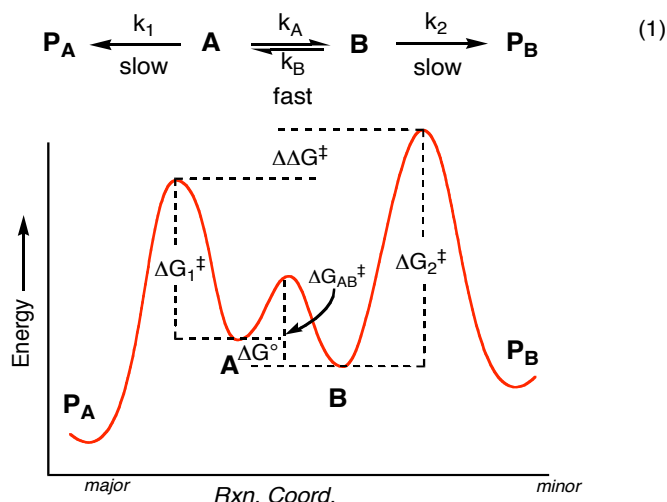
The Derivation:

Using the rate equations $\dfrac{d[P_A]}{dt} = k_1[A]$ and $\dfrac{d[P_B]}{dt} = k_2[B]$ we can write:

$$\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} \quad \text{or} \quad d[P_B] = \frac{k_2[B]}{k_1[A]} d[P_A] \qquad (2)$$

Since A and B are in equilibrium, we can substitute $K_{eq} = \dfrac{[B]}{[A]}$

$$\int d[P_B] = \frac{k_2}{k_1} K_{eq} \int d[P_A] \quad \text{Integrating, we get} \quad \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} \qquad (3)$$

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

To relate this quantity to ΔG values, recall that $\Delta G^{\circ} = -RT \ln K_{eq}$ or $K_{eq} = e^{-\Delta G^{\circ}/RT}$, $k_1 = e^{-\Delta G_1^{\ddagger}/RT}$, and $k_2 = e^{-\Delta G_2^{\ddagger}/RT}$. Substituting this into the above equation:

$$\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} = \frac{e^{-\Delta G_2^{\ddagger}/RT}}{e^{-\Delta G_1^{\ddagger}/RT}} (e^{-\Delta G^{\circ}/RT}) = e^{-\Delta G_2^{\ddagger}/RT} e^{-\Delta G^{\circ}/RT} e^{\Delta G_1^{\ddagger}/RT} \qquad (4)$$

Combining terms:

$$\frac{[P_B]}{[P_A]} = e^{-(\Delta G_2^{\ddagger} + \Delta G^{\circ} - \Delta G_1^{\ddagger})/RT} \quad \text{or} \quad \frac{[P_B]}{[P_A]} = e^{-\Delta\Delta G^{\ddagger}/RT}$$

Where $\Delta\Delta G^{\ddagger} = \Delta G_2^{\ddagger} + \Delta G^{\circ} - \Delta G_1^{\ddagger}$

Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

Within these limits, we can envision three scenarios:

• If both conformers react at the **same rate**, the product distribution will be the same as the ratio of conformers at equilibrium.

• If the **major conformer** is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.

• If the **minor conformer** is the faster reacting conformer, the product ratio will depend on all three variables in eq (2), and the observed product distribution will not reflect the equilibrium distribution.

This derivation implies that you could potentially isolate a product which is derived from a conformer that you can't even observe in the ground state!

"Non-Equilibrating Conformers"

k_1, k_2 >> k_A, k_B: If the rates of reaction are **faster** than the rate of interconversion, A and B cannot equilibrate during the course of the reaction, and the product distribution (P_B/P_A) will simply reflect the initial equilibrium composition.

$$\frac{[P_B]}{[P_A]} = \frac{[B]_o}{[A]_o}$$
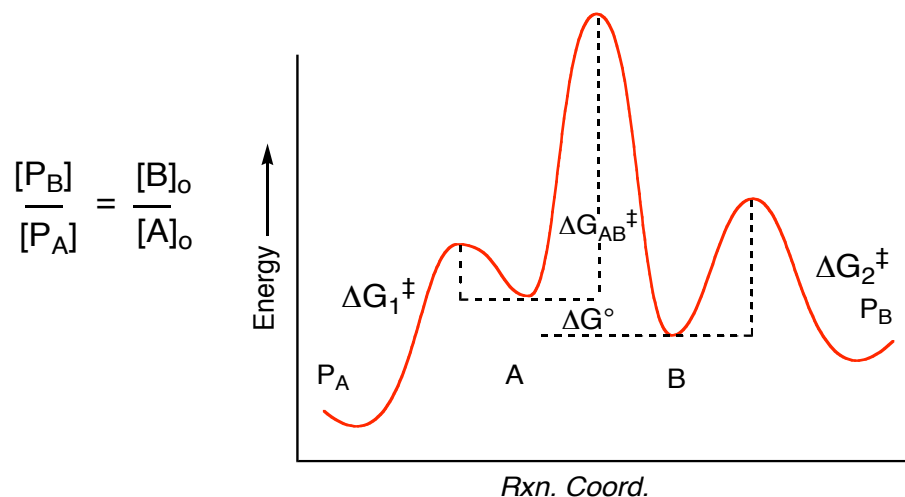
"Non-Equilibrating Conformers"
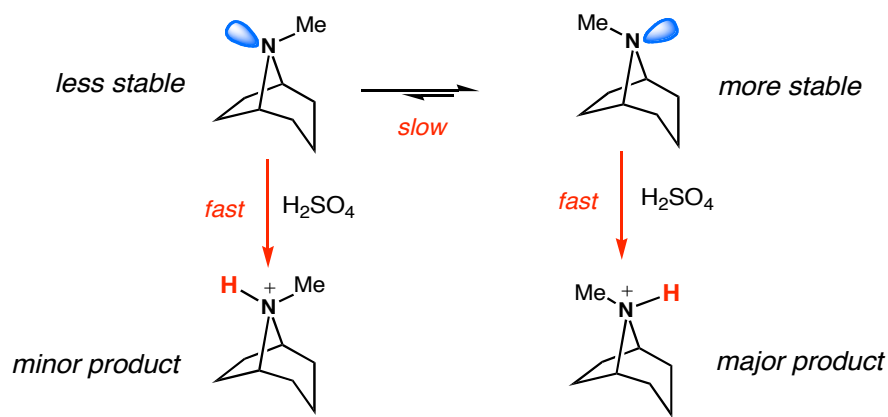
The rates of protonation are much faster than the rates of conformation interconversion

Introduction

Two new classes of potent nonnucleoside reverse transcriptase inhibitors were recently reported by the Merck Research Laboratories: the 3,4-dihydroquinazolin-2(1*H*)-ones[1] and the 1,4-dihydro-2*H*-3,1-benzoxazin-2-ones.[2] Efforts to enhance the clinical utility of these inhibitor classes by deriving compounds that express both high levels of antiviral activity and augmented pharmacokinetic profiles led to one promising compound from each class—L-738,372 and DMP-266. DMP-266 was ultimately
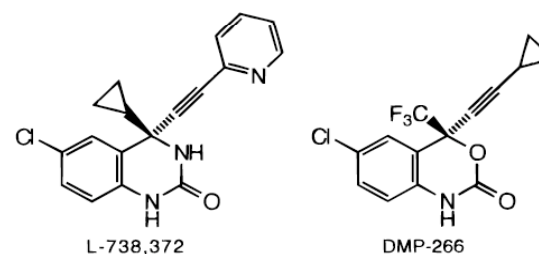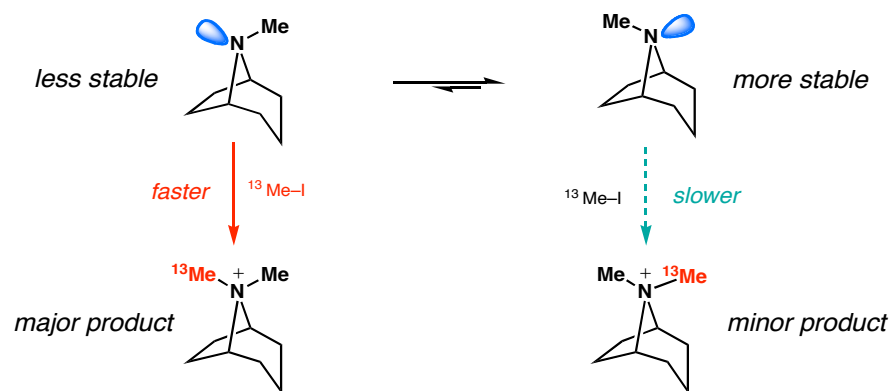

chosen for clinical evaluation[2] and has shown excellent preliminary results for the treatment of HIV when used in combination with indinavir.[3,4] The potential importance of
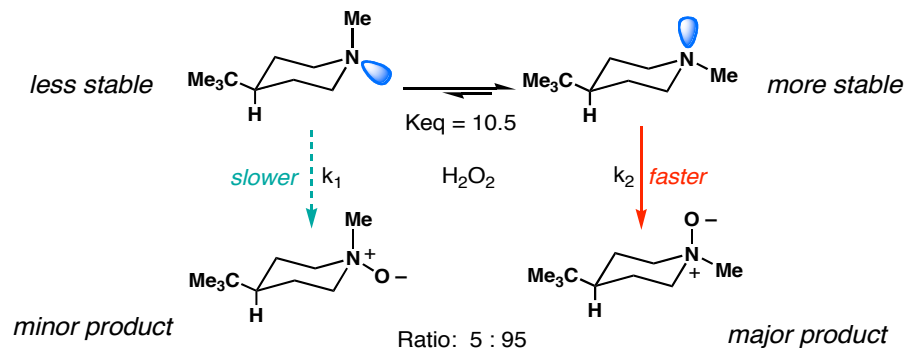
A Dramatic case from Merck

−78°C: low ee

−78°C ⟶ RT ⟶ −78°C: er = 50:1
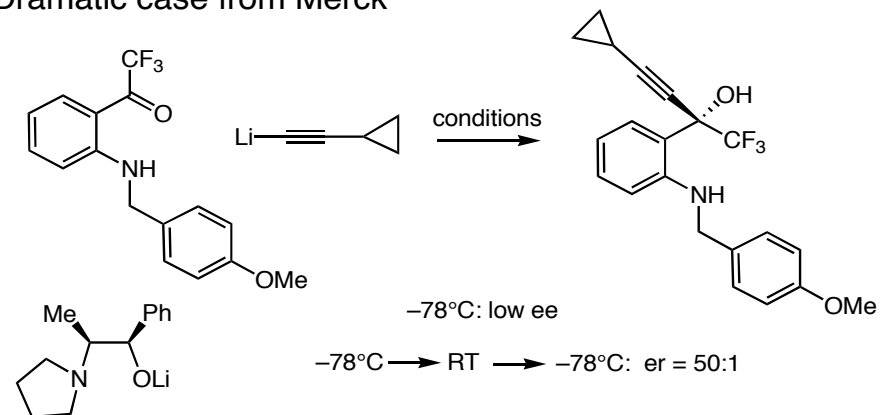
Tropane alkylation is a well-known example.

less stable   ⇌   *more stable*

faster ^{13}Me–I ^{13}Me–I   *slower*

major product   *minor product*

The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

JOC **1974** 319

Oxidation of piperidines:

less stable   ⇌   *more stable*

Keq = 10.5

slower k_1 H_2O_2 k_2 *faster*

*minor product*   Ratio: 5 : 95   *major product*

When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into $[P_B]/[P_A] = k_2K/k_1$, the ratio $k_2/k_1 \sim 2$.

Note that in this case, the more stable conformer is also the faster reacting conformer!

Tet. **1972** 573
Tet. **1977** 915

Enantioselective Lithiation:

i-Pr$_2$N   *s*-BuLi   *i*-Pr$_2$N
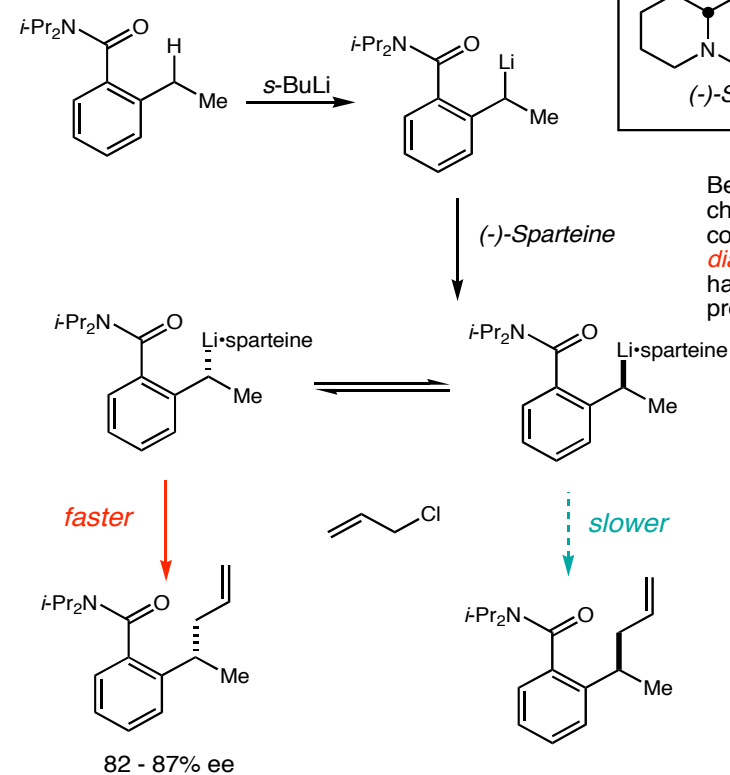
(-)-Sparteine

Because sparteine is chiral, these two complexes are *diasteromeric* and have different properties.

(-)-Sparteine

i-Pr$_2$N   Li•sparteine   ⇌   *i*-Pr$_2$N   Li•sparteine

faster   Cl   *slower*

*i*-Pr$_2$N   *i*-Pr$_2$N

82 - 87% ee

Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of (-)-sparteine results in racemic product.

Note that the two alkyllithium complexes MUST be in equilibrium, as the enantioselectivity is the same over the course of the reaction. If they were not equilibrating, the enantioselectivity should be higher at lower conversions.

This is a case of ***Dynamic Kinetic Resolution***: Two enantiomeric alkyl lithium complexes are equilibrating during the course of a reaction with an electrophile.

Beak, *Acc. Chem. Res*, **1996**, 552

The asymmetric hydrogenation of prochiral olefins catalyzed by Rhodium is an important catalytic process.

> 95% ee
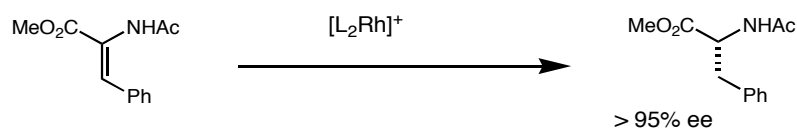
Enantioselectivities are generally very high when the ligand is a chelating diphosphine. (ee's are given for S,S-CHIRAPHOS)
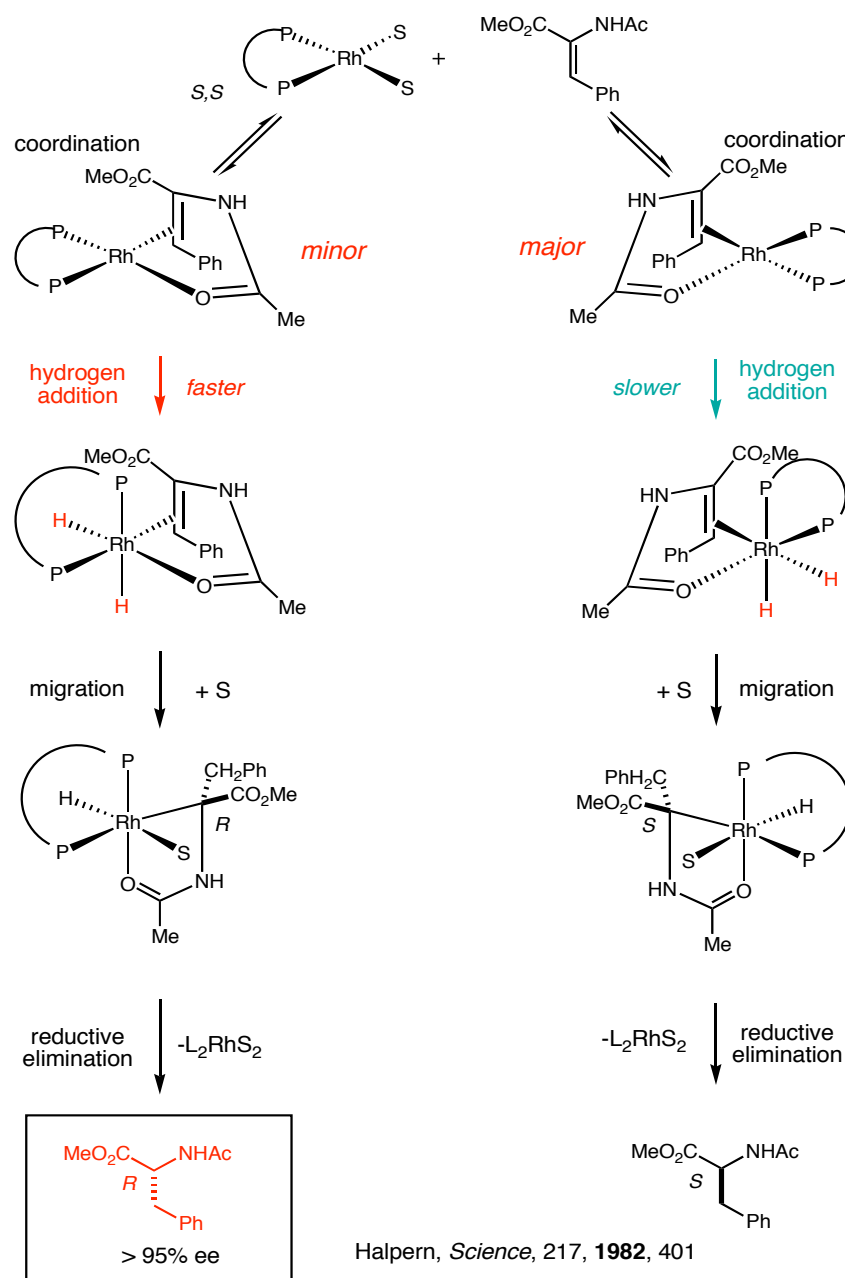
When a chiral ligand is used, there are two diastereomeric complexes which may be formed:

minor complex **1**

major complex **2**

(NMR, X-Ray)

H₂ fast

slow H₂

observed product
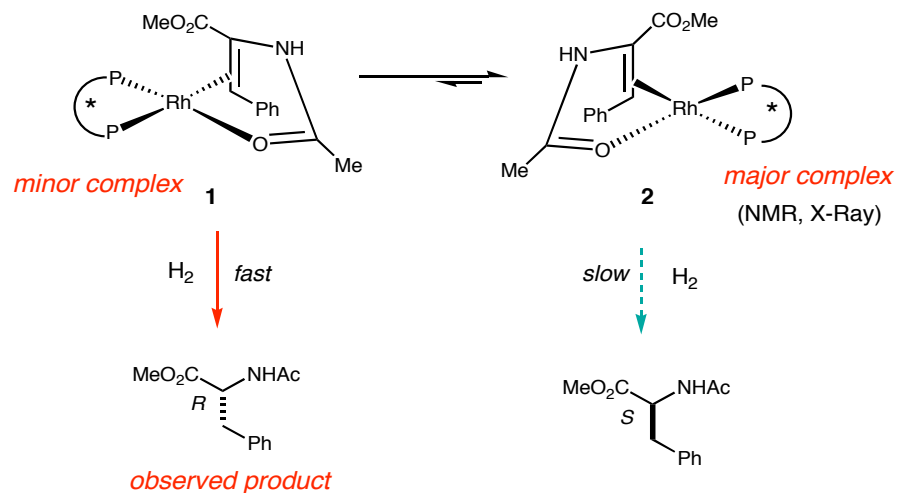
Observations:

• Complex 2 is the only diasteromer observed for the catalyst-substrate complex (1HNMR, X-Ray crystallography) in the absence of hydrogen

• The enantioselectivity is strongly dependant on the pressure of H₂, and degrades rapidly at higher hydrogen pressures

• The observed enantiomer is exclusively derived from the minor complex 2

*These observations may be explained using the **Curtin - Hammett Principle***

S,S

coordination

coordination

minor

major

hydrogen addition — *faster*

slower — hydrogen addition

migration + S

+ S migration

reductive elimination — -L₂RhS₂

-L₂RhS₂ — reductive elimination

> 95% ee

Halpern, *Science*, 217, **1982**, 401

The Curtin-Hammett treatment can be extended to ANY case where different products are formed from two rapidly intereconverting starting materials, whether they are conformers, tautomers or isomers.

$$P_A \xleftarrow{k_1} A \underset{k_B}{\overset{k_A}{\rightleftarrows}} B \xrightarrow{k_2} P_B$$

major   *minor*
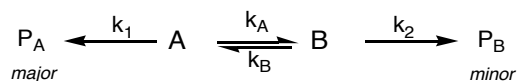
Stannylene ketals provide an efficient way to acylate the more hindered site of 1,2-diols.

Ratio 2:1

Ar= *p*-NO$_2$C$_6$H$_4$

TMS-Cl | faster   slower | TMS-Cl

Product Ratio 22:1
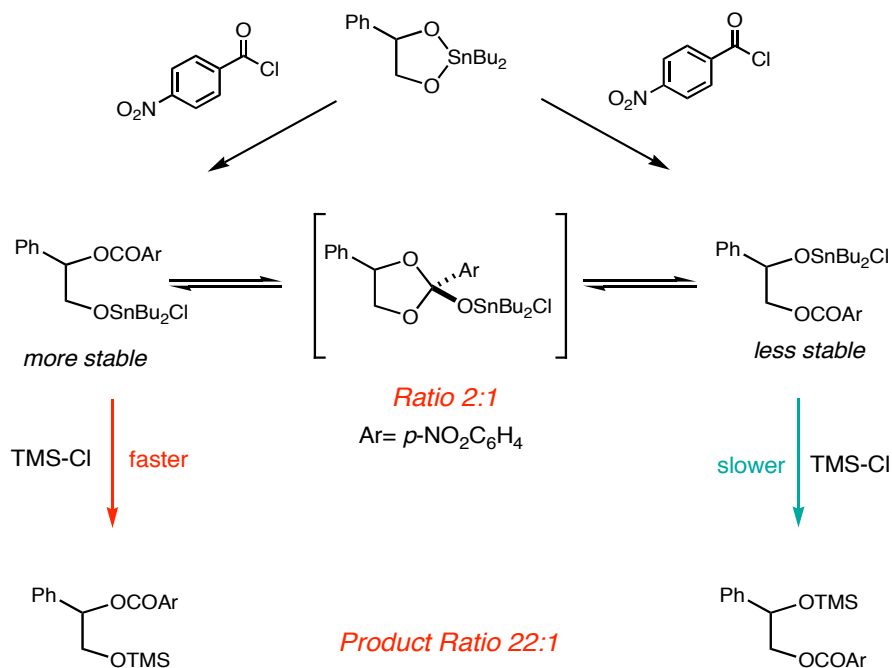
The two stannyl esters are in equilibrium at room temperature, and the more stable isomer is initially formed more slowly. The stannyl esters are allowed to equilibrate before quenching with TMS-Cl, which reacts more rapidly with the less hindered primary alkoxystannane.

JOC **1996**, 5257

"It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..."

David Y. Curtin, 1954

" Because Curtin is very generous in attributing credit, this is sometimes referrred to as the Curtin-Hammett principle rather than the Curtin principle."

Louis Plack Hammett, 1970

***Curtin - Hammett Principle:** The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.*

THE TAKE-HOME LESSON:

Never assume that the most stable conformation of a compound is the most reactive. It may be, but then again, it may not.