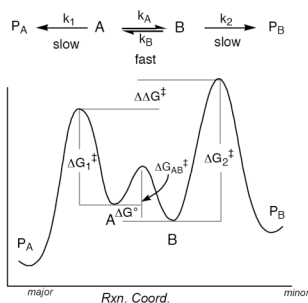
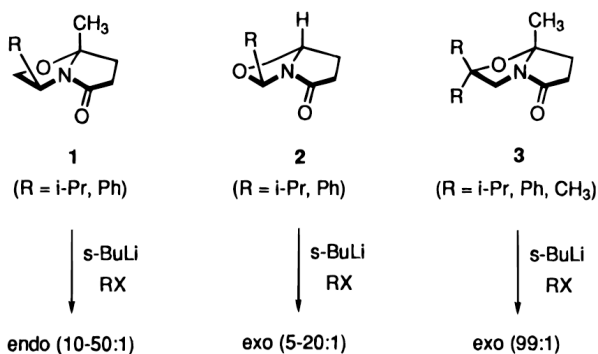


## I. Basic Principles

### IB. Kinetics & Thermodynamics of Organic Reactions

Boger Notes: p. 17 - 22 (Chapter II)

Problem of the Day:



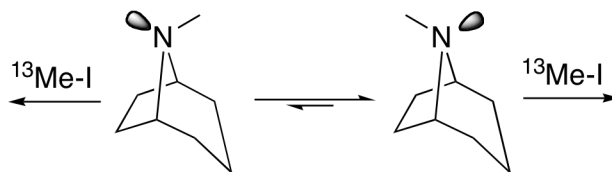
### Curtin-Hammett Principle

If the rates of reaction are much slower than the rate of interconversion, the Curtin-Hammett principle states that the product distribution is controlled by the difference in standard Gibbs energies of the respective transition states.

More specifically:

- If both conformers react at the same rate, the product distribution will be the same as the ratio of conformers at the equilibrium state.
- If the major conformer **B** is the faster reacting conformer, the product **P<sub>B</sub>** will form predominantly, and the ratio will not reflect the equilibrium distribution.
- If the minor conformer **A** is the faster reacting conformer, the product ratio will depend on all three variables  $k_1$ ,  $k_2$ , and  $K_{eq}$ , and the observed product distribution will not reflect the equilibrium distribution.
- Accordingly, the product formed can potentially derive from a conformer that you cannot even observe in the equilibrium distribution of the precursor(s).

### Conformational Control of Reactivity

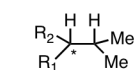


What factors determine the product distribution?

### Basic Principles of Asymmetric Transformations

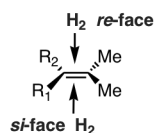
Federsel, H.-J. "Asymmetry on large scale: The roadmap to stereoselective processes." *Nature Rev. Drug Discovery* **2005**, 4, 685-697.

a (\*Sterogenic center)



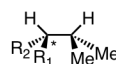
For example, *rac*-2,3-dimethylpentane is generated as incoming reactant does not show facial discrimination

Racemic process  
Hydrogen attacks with equal propensity from both sides of the substrate



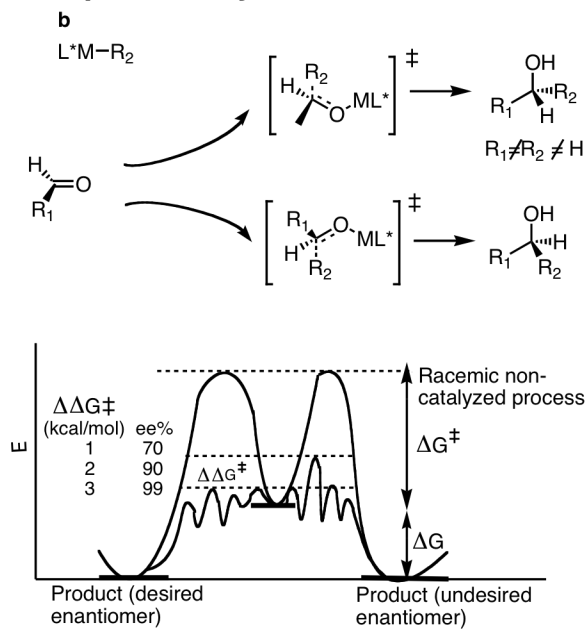
Prochiral olefin  $R_1 \neq R_2$   
For example,  $R_1 = \text{Et}$ ;  $R_2 = \text{Me}$

Asymmetric process;  
Hydrogen attack occurs preferentially from one face of the planar C-C double bond



For example, (3*S*)-2,3-dimethylpentane resulting from top or re-face approach of reactant

### Basic Principles of Asymmetric Transformations



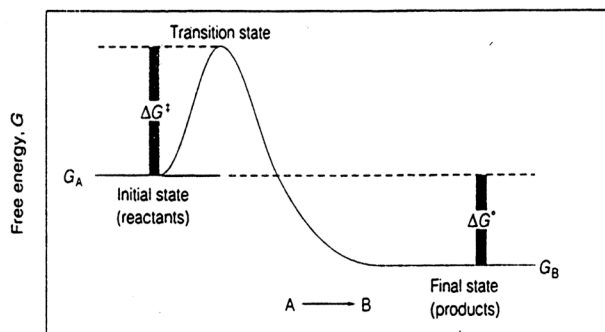
## Catalysis

- Catalysts increase reaction rate without themselves being changed
- Can accelerate a reaction in both directions
- Do not affect the state of equilibrium of reaction
  - simply allow equilibrium to be reached faster



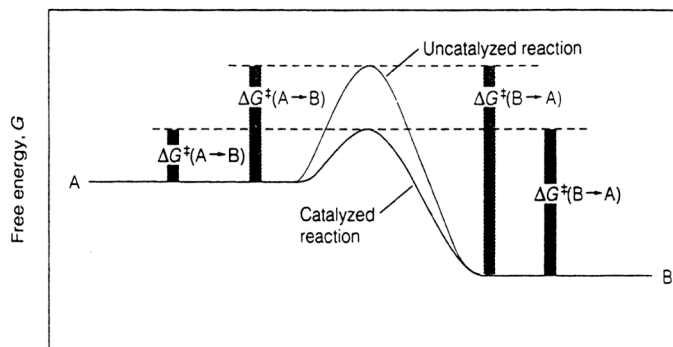
## Activation energy

- Molecules must be activated before they can undergo a reaction
  - Reactants must absorb enough energy from surroundings to destabilize chemical bonds (energy of activation)
- Transition state
  - Intermediate stage in reaction where the reactant molecule is strained or distorted but the reaction has not yet occurred



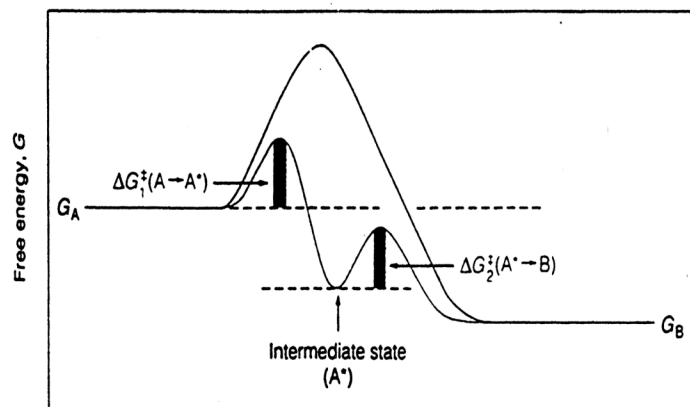
## Activation energy

- A catalyst lowers the energy of activation by:
  - Forcing molecules into conformations that favor the reaction
    - I.e. the catalyst may re-orientate molecules
- Change in free energy is identical to uncatalyzed reaction: **the catalyst does not change the thermodynamic equilibrium!**



## Activation energy

- Sometimes catalysts cause one large energy barrier to be replaced by two smaller ones
- Reaction passes through intermediate stage



## Energy and Time

How do you correlate rate constants to activation barriers?

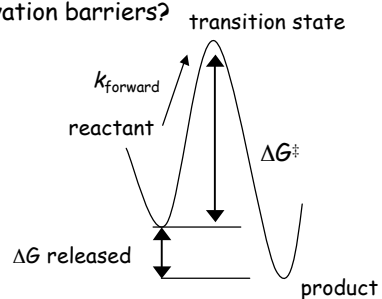
Arrhenius Equation

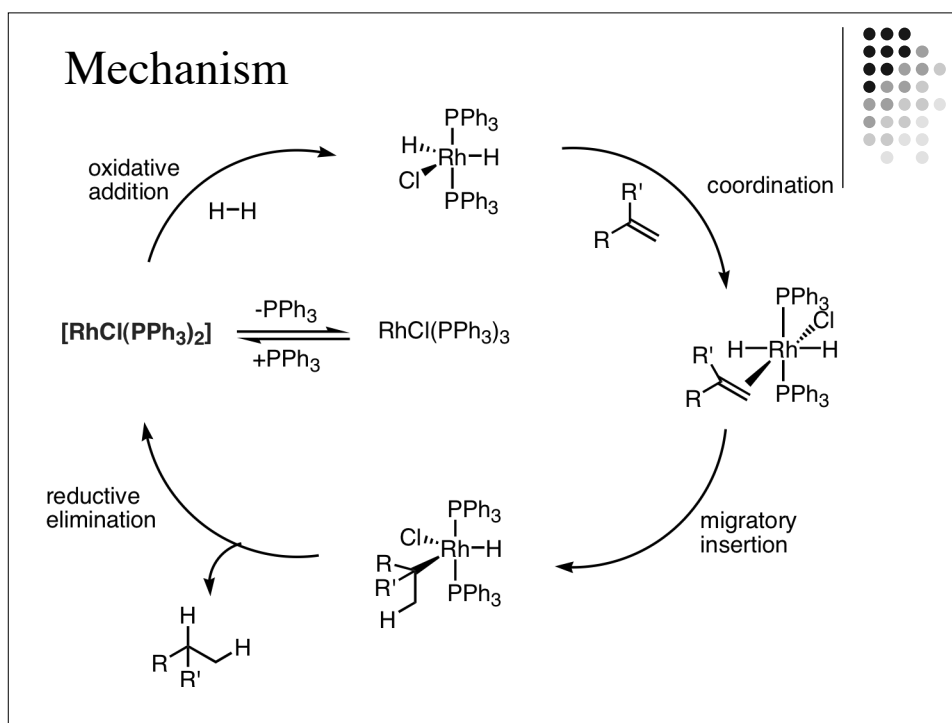
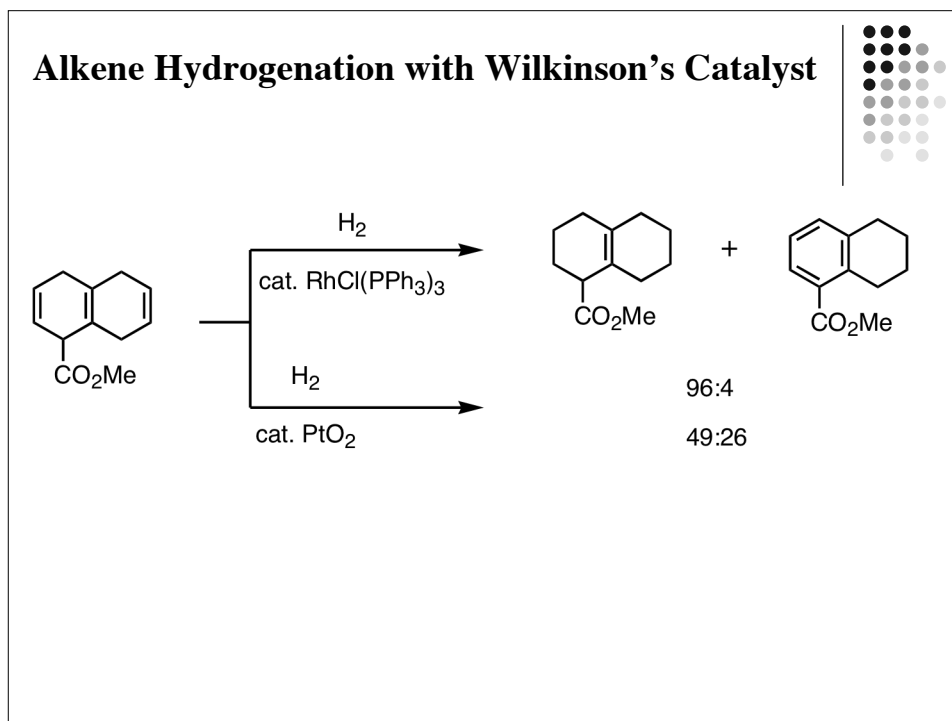
$$k \text{ (rate constant)} = A e^{(-E/RT)}$$

where  $A$  = "frequency factor", and  $e^{(-E/RT)}$  = activation energy

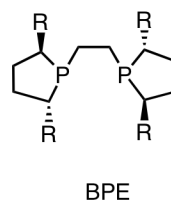
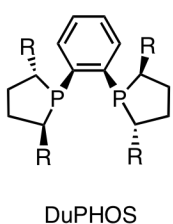
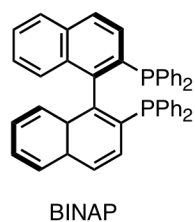
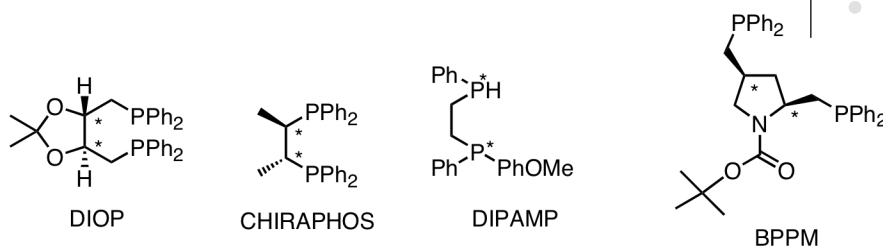
Eyring Absolute Rate Theory

$$k \text{ (rate constant)} = [k_b T/h] e^{(-\Delta G^\ddagger/RT)} = [k_b T/h] e^{(\Delta S^\ddagger/RT)} e^{(-\Delta H^\ddagger/RT)}$$

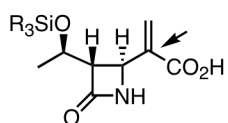
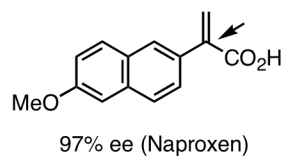
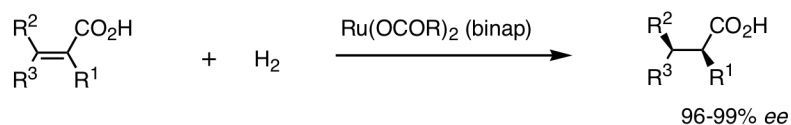




## Enantiomerically Enriched Phosphines

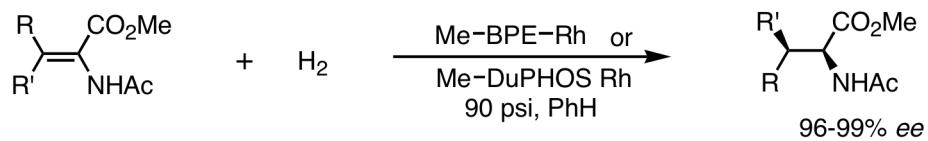


## Asymmetric Hydrogenation



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	ee
Me	Me	H	91
H		Me	87
H	Me	Ph	85
Ph	H	H	92
H	HOCH <sub>2</sub>	Me	93
H	CH <sub>3</sub>	COOCH <sub>2</sub> CMe	95

## Asymmetric Hydrogenation



## Monsanto L-DOPA Process



# Mechanism: Halpern, J. *Science* **1982**, *217*, 401-407.

Li, M.; Tang, D.; Luo, X.; Shen, W., "Mechanism of asymmetric hydrogenation of enamides with [Rh(bisp\*)]<sup>+</sup> catalyst: Model DFT study." *Int. J. Quant. Chem.* **2005**, *102*, 53-63.

