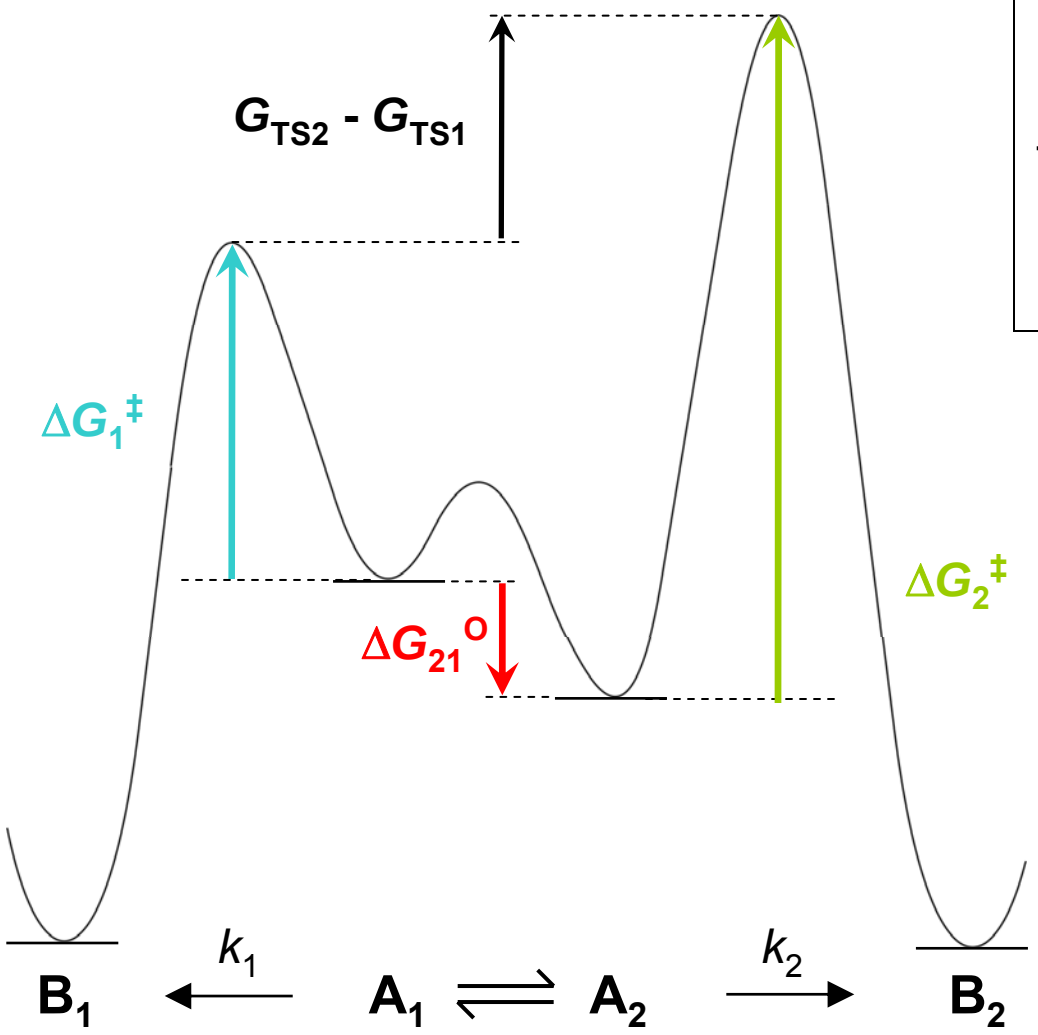
The Curtin-Hammett Principle

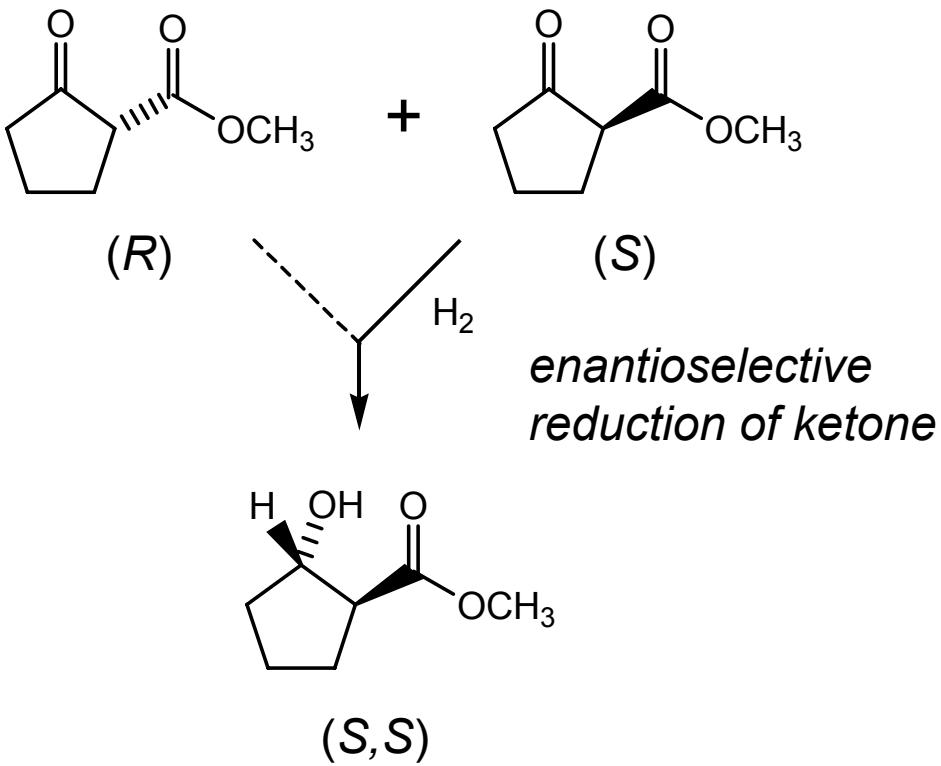


$$\frac{\frac{\partial[B_2]}{\partial t}}{\frac{\partial[B_1]}{\partial t}} = e^{\left(\frac{-(G_{TS2} - G_{TS1})}{RT}\right)}$$

So, relative reaction rates depend only on relative transition-state energies, and not on starting-material ground-state energies.

The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution

Question: How can enantioselective chemistry convert a racemic mixture into exclusively one diastereomer?

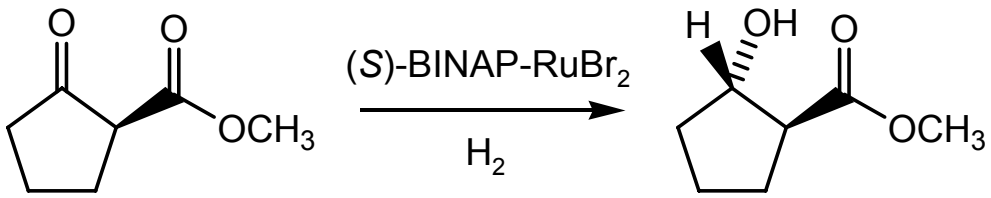


(*S*) to (*S*,*S*) makes sense—just incorporate new chiral center by enantioselective reduction.

But how to convert (*R*) to (*S*,*S*)?

Ryoji Noyori, Nagoya University
(Nobel Prize, 2001)

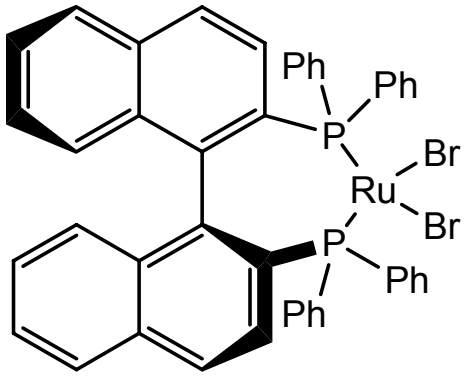
The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution



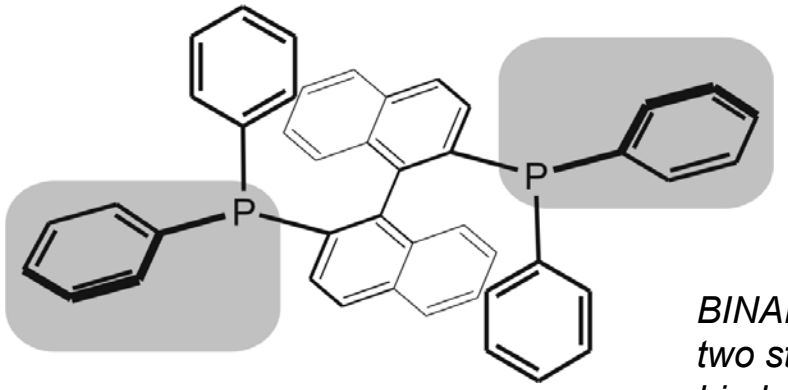
(*S*) (*S,S*)

(*R*) is converted to (*R*,*S*) much more slowly than (*S*) to (*S*,*S*) with this catalyst.

Diastereospecific yield of reaction on racemic mixture could not exceed 50%.



(*S*)-BINAP-$RuBr_2$



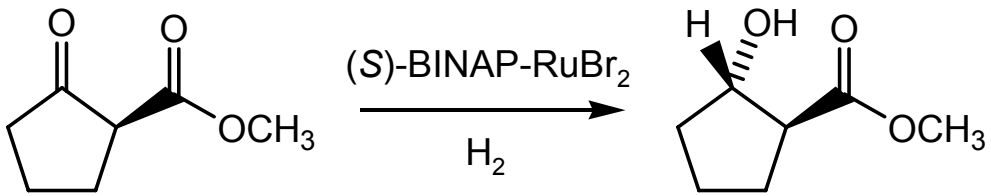
(*S*)-BINAP

BINAP ligand creates two sterically hindered quadrants.

Tokunaga, M.; Kitamura, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

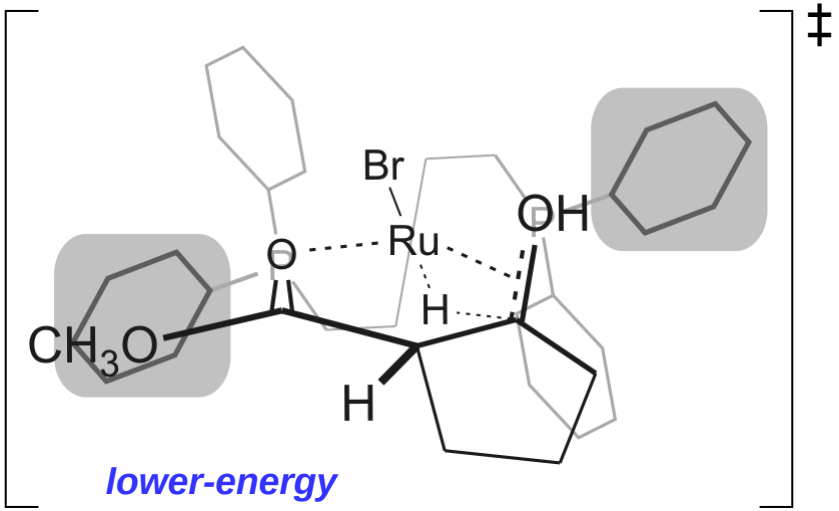
Noyori, R.; et al. *J. Am. Chem. Soc.* **1989**, *111*, 9134-9135.

The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution



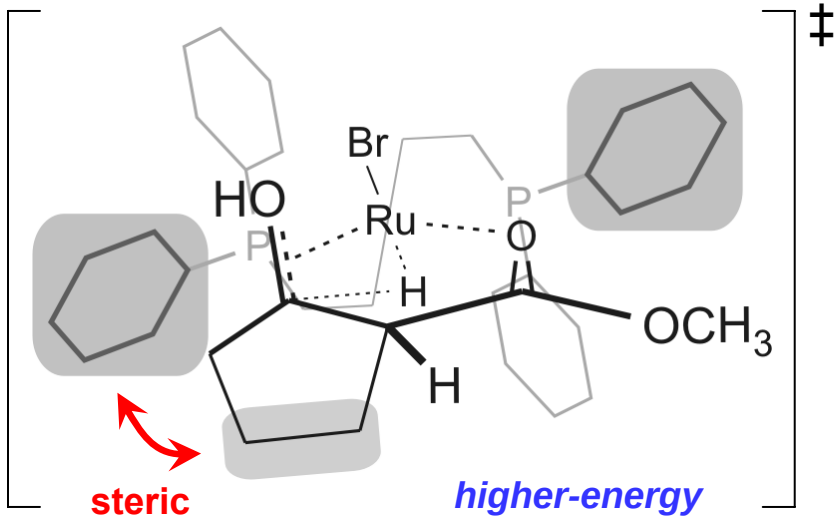
(*S*) (*S*,*S*)

(*R*) is converted to (*R*,*S*) much more slowly than (*S*) to (*S*,*S*) with this catalyst.



lower-energy (rate-determining) transition state

(***S***)-BINAP + (***S***)-ketoester

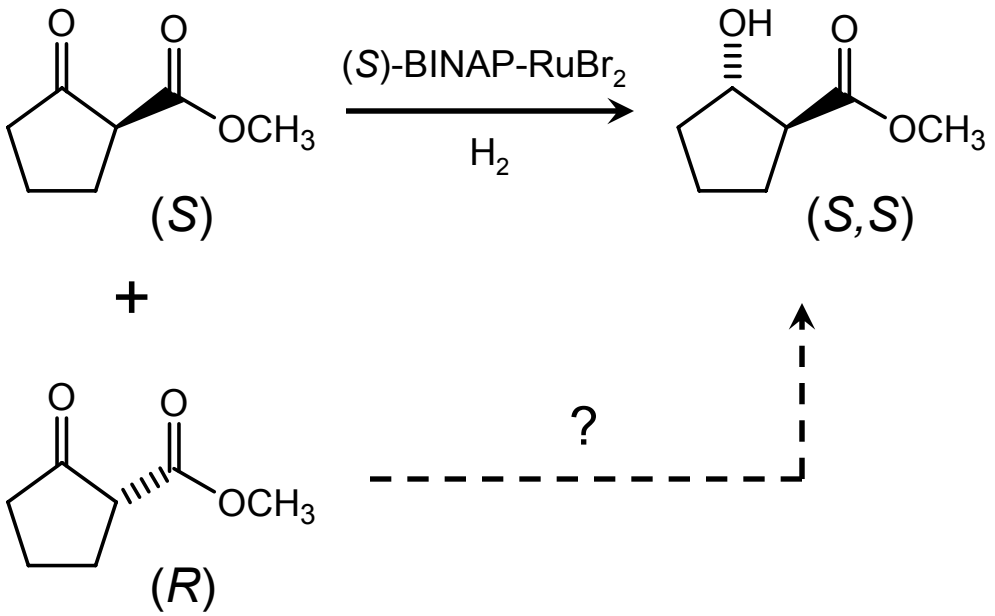


steric congestion

higher-energy (rate-determining) transition state

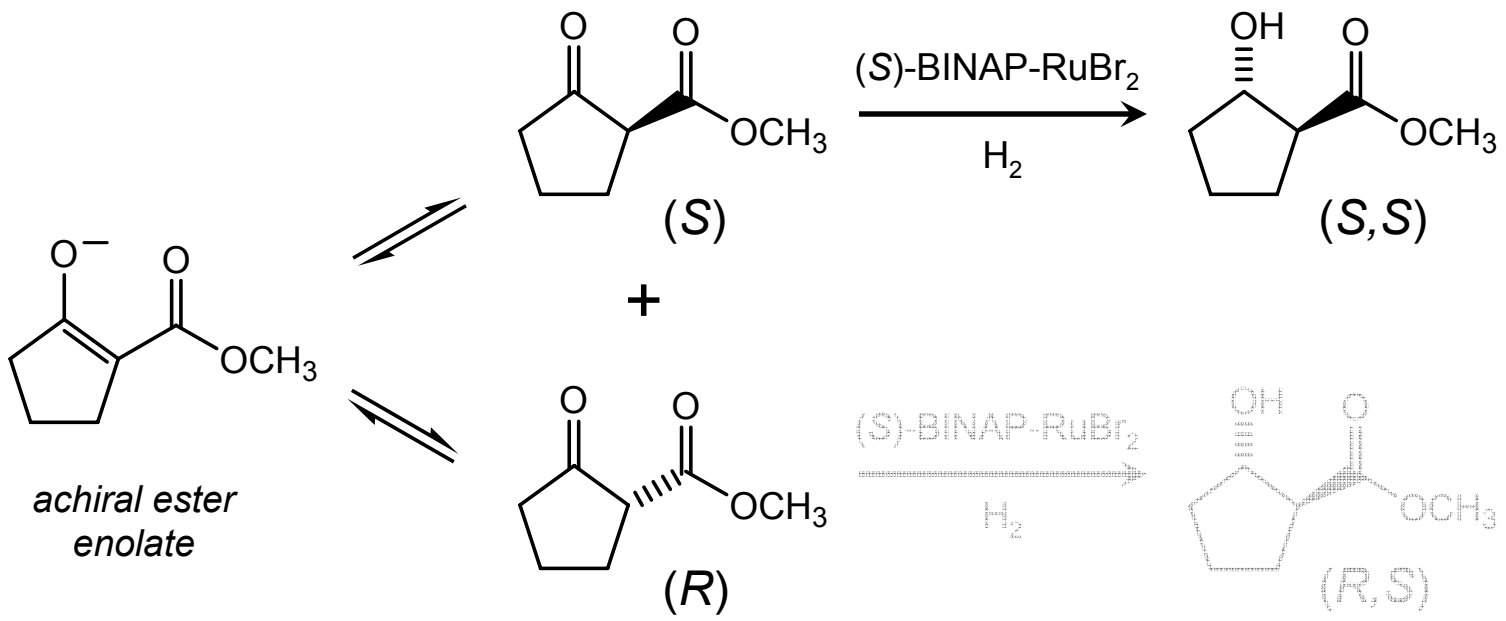
(***S***)-BINAP + (***R***)-ketoester

The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution



So, how to convert (*R*)-ketoester to (*S*,*S*)-β-hydroxyester?

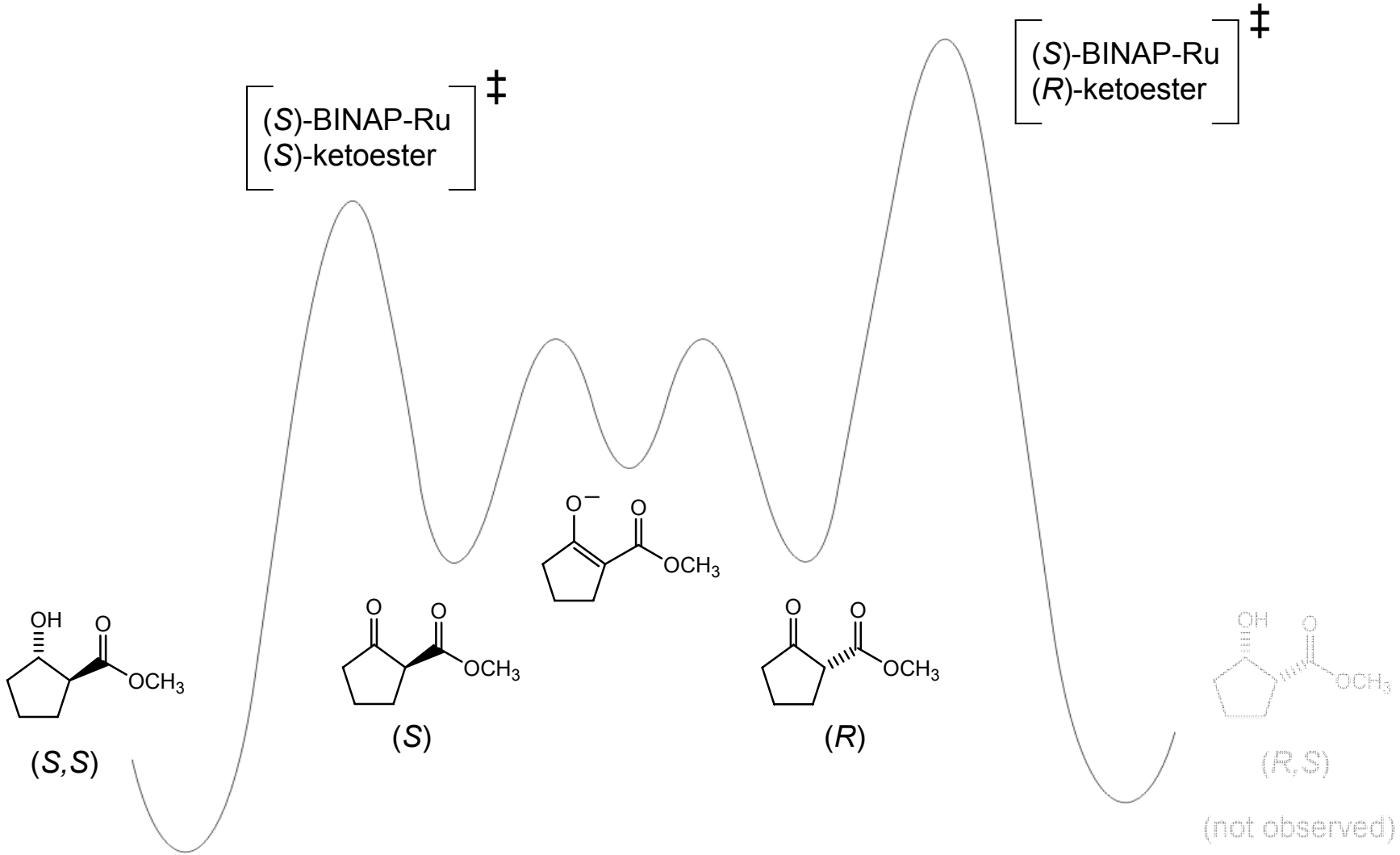
The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution



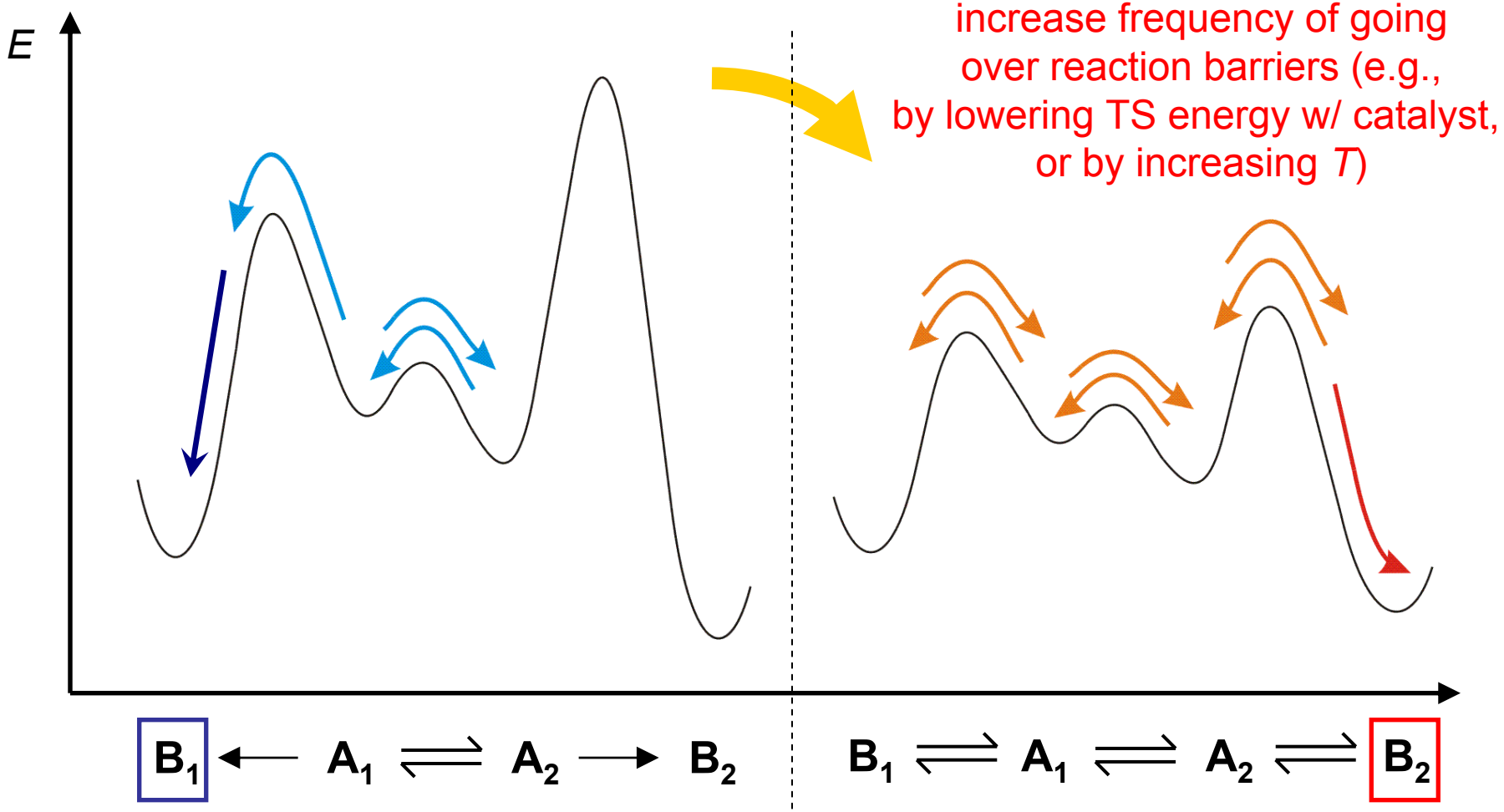
Equilibrate two enantiomeric starting materials through achiral enolate, by tuning Lewis acidity in solvent.

Curtin-Hammett ensures that all racemate goes to (*S*,*S*), as long as equilibration is faster than catalysis.

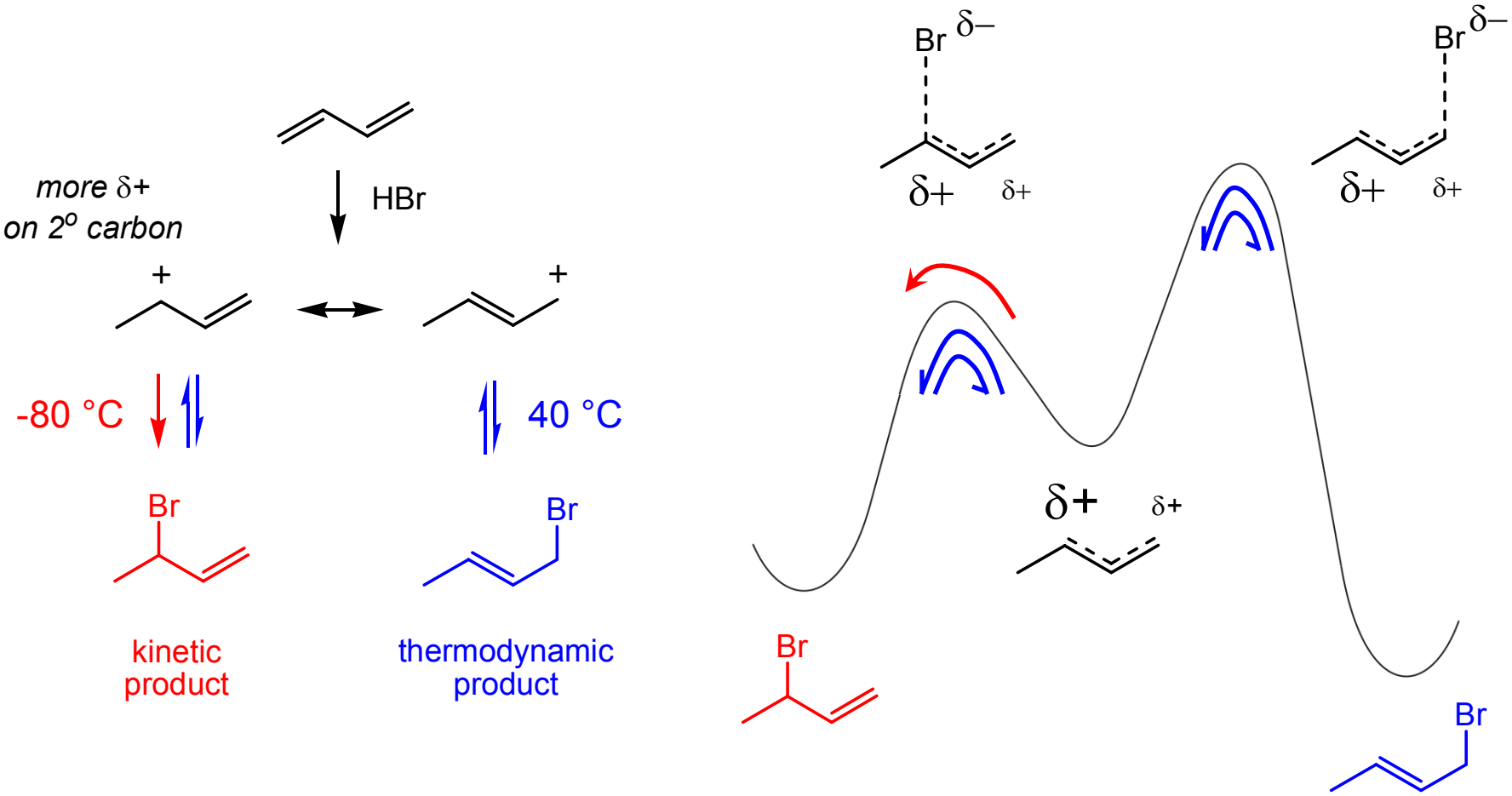
The Curtin-Hammett Principle
Example: Dynamic Kinetic Resolution



Kinetic vs. Thermodynamic Control

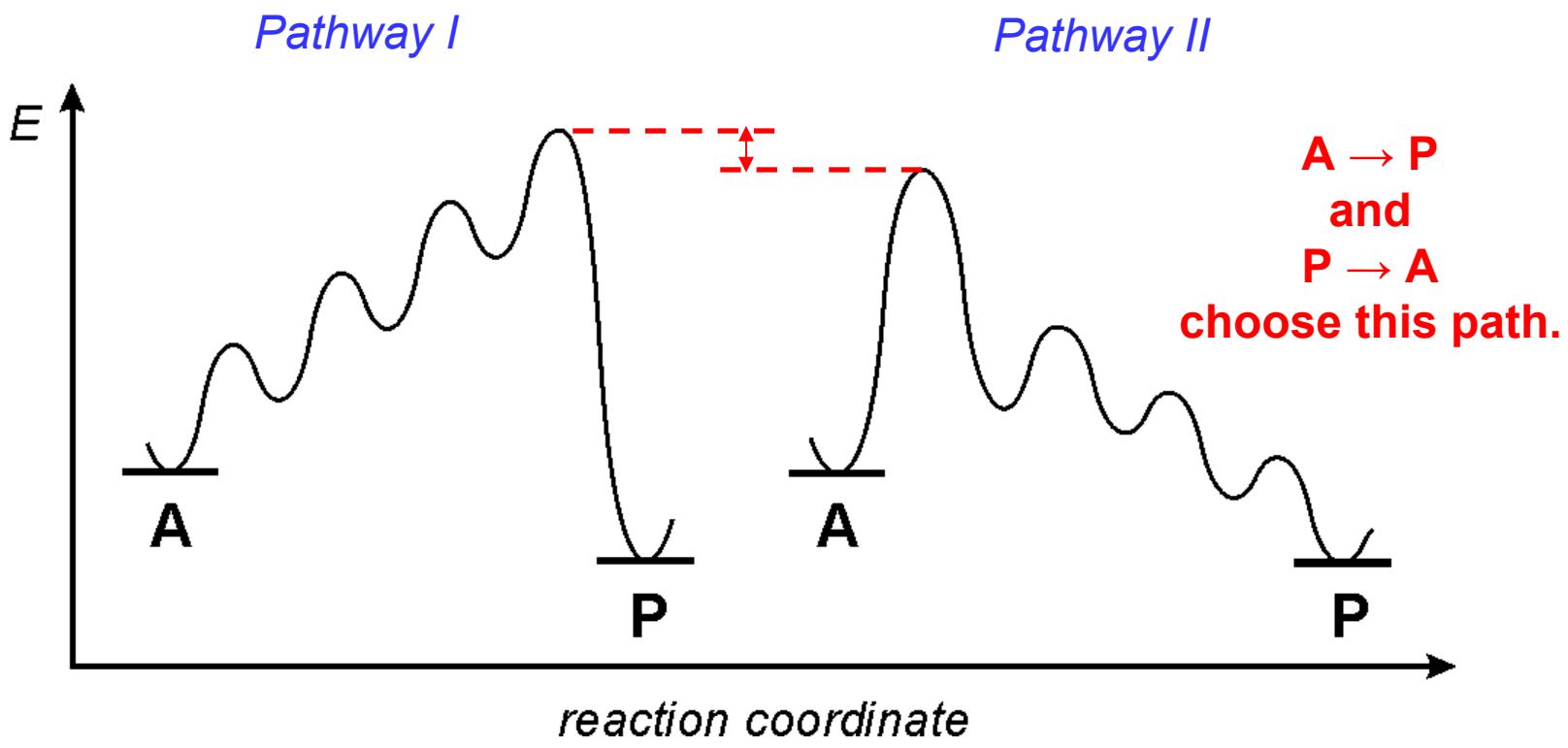


Kinetic vs. Thermodynamic Control



Principle of Microscopic Reversibility

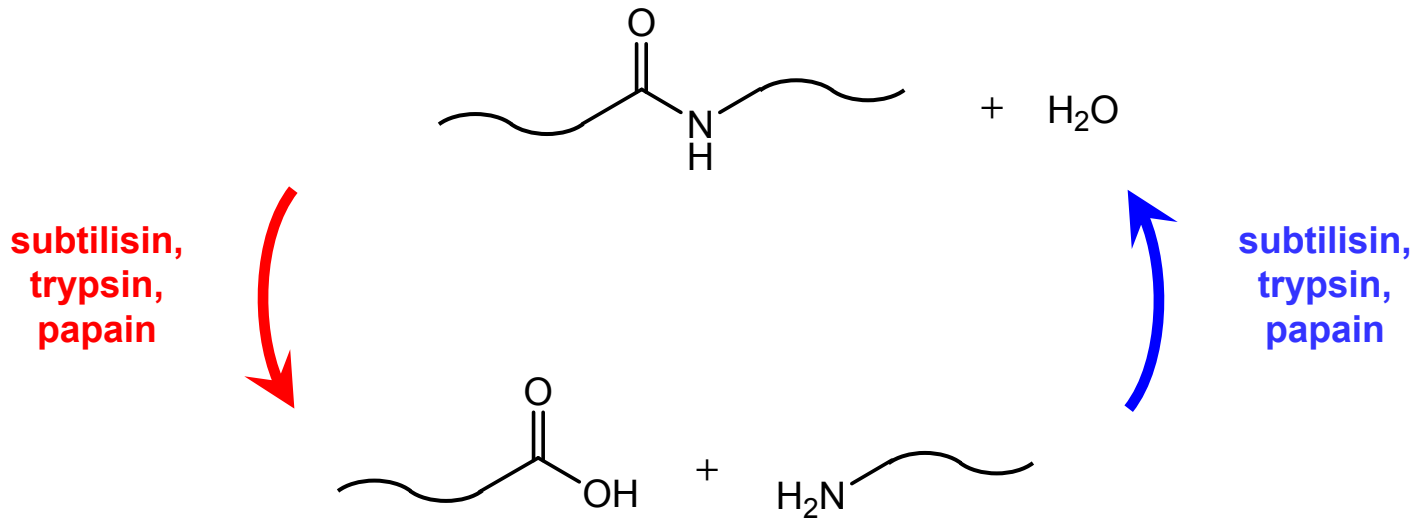
The lowest-energy pathway from reactant to product must also be the lowest-energy pathway from product to reactant.



If I were hiking, I'd take Pathway I from A → P, and Pathway II from P → A. But molecules aren't hikers. They'd always take Pathway II.

Principle of Microscopic Reversibility

An interesting corollary: Catalysts activate both forward and reverse reactions.



Enzymes that catalyze protein cleavage…

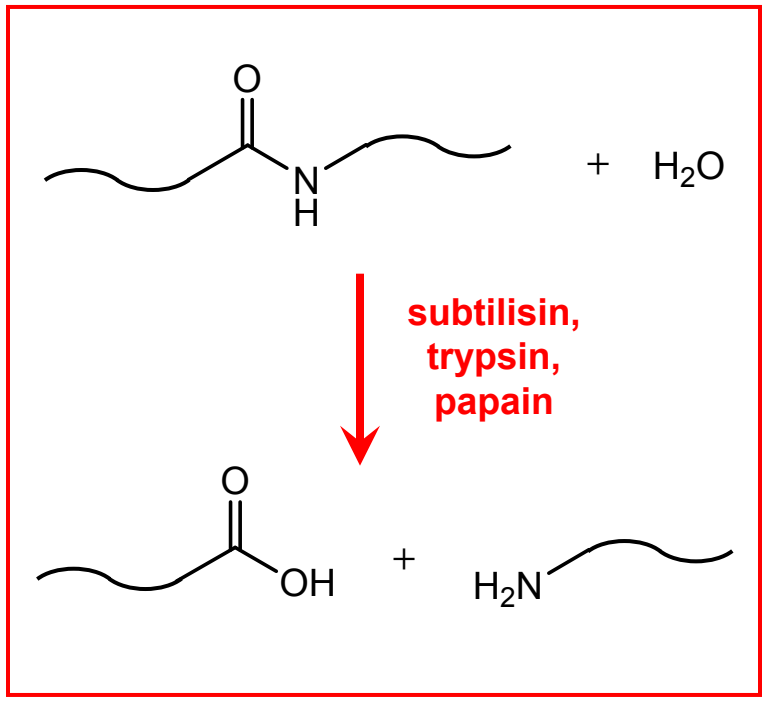
…also catalyze protein synthesis!

So, how does our body selectively degrade the proteins it wants to eat, and synthesize the proteins it wants to use?

Principle of Microscopic Reversibility

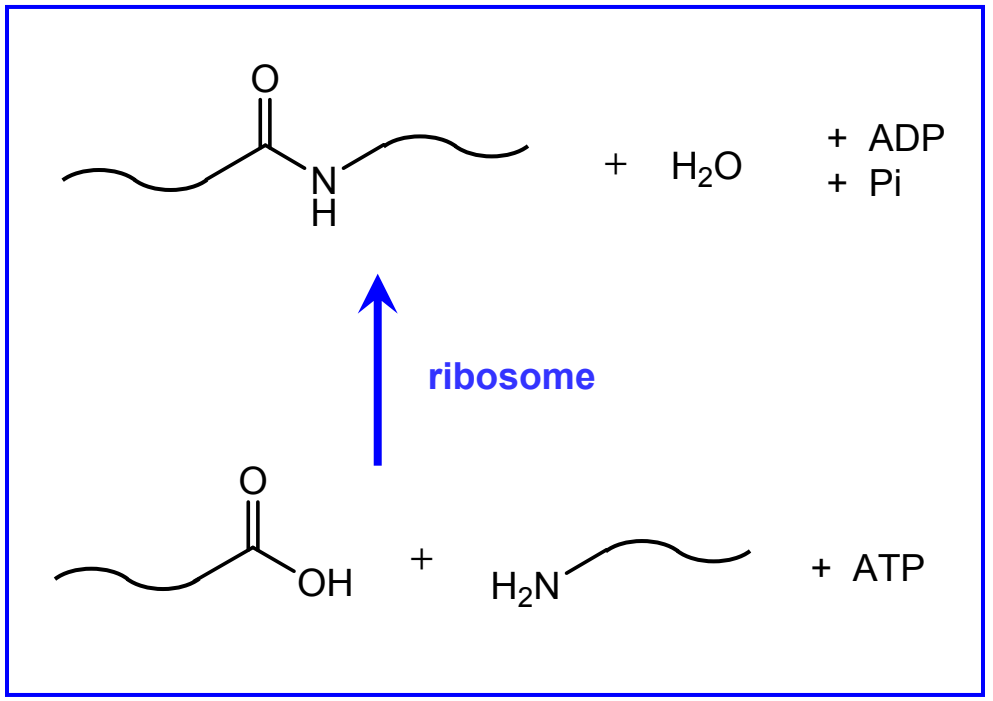
Answer: **Isolate different reactions in different places.**

In the gut…



…proteolysis is driven by water.

Inside cells…



…protein synthesis is driven by energy (ATP).

Enzymes work both ways, but thermodynamics drives reactions in desired directions.