Week 14

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14.1 Kinetic Resolution and Related Asymmetric Processes

12/3: - Announcements.
    - Today: Last Tuesday's lecture.
        - Next time: Electron Transfer.
    - Exam 2 tomorrow.
        - Format like the practice exam.
        - Administered remotely.
        - Work alone, and closed note (honor code).
        - Available for 48 hours: Start of Wednesday til end of Thursday.
    - Do the teaching evaluations for both Alex and Masha!!
- Today: Kinetic selectivities.
- Consider a starting material (SM) that can evolve to a product A or B.

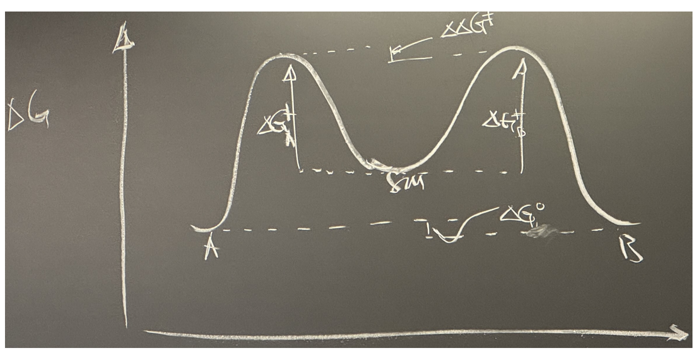


Figure 14.1: Thermodynamic vs. kinetic selectivity energy diagram.

- We can map this reaction onto a potential energy surface.
- If A and B are free to reversibly interconvert, then we can explain the product distribution in terms of the ΔG° between A and B.
    - In particular, $\Delta G = -RT\ln K_{\text{eq}}$ where $K_{\text{eq}} = [\text{A}]/[\text{B}]$.

- Today, we'll consider the case in which A and B do *not* reversibly interconvert.
  - In this case, what's important is the $\Delta\Delta G^\ddagger$ between the transition states.
  - Here, the selectivity is given as the ratio of the rate constants:

$$\text{selectivity} = \frac{[\text{A}]}{[\text{B}]} = \frac{k_\text{A}}{k_\text{B}} = \frac{\mathrm{e}^{-\Delta G^\ddagger_\text{A}/RT}}{\mathrm{e}^{-\Delta G^\ddagger_\text{B}/RT}} = \mathrm{e}^{-\Delta\Delta G^\ddagger/RT}$$

  - Note that $k_\text{A}/k_\text{B} = k_\text{rel}$. This quantity is important for determing dr's, er's, etc.

- A case in which kinetic selectivity is important: Catalytic kinetic resolution.

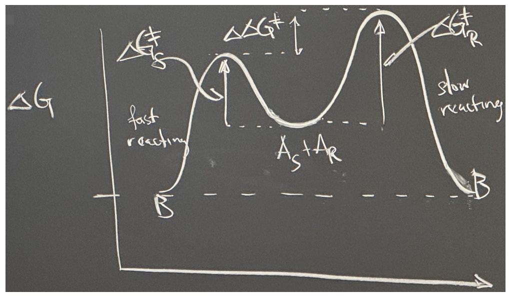


Figure 14.2: Catalytic kinetic resolution energy diagram.

- A is our starting material, a chiral racemic compound.
  - Thus, we can denote the starting materials as $\text{A}_\text{S} + \text{A}_\text{R}$.
  - As enantiomers, A_R and A_S have identical free energies.
- cat* is a **homochiral** catalyst.
- Then resolution to a product B can happen two different ways: Through a transition state that consumes the (S)-enantiomer, and through a transition state that consumes the (R)-enantiomer.
- When a homochiral catalyst acts on two enantiomers, it forms two different, diastereomeric adducts: $\text{A}_\text{S} \cdot \text{cat}^*$ and $\text{A}_\text{R} \cdot \text{cat}^*$.
  - Unlike enantiomers, diastereomers *are* different compounds that may have two different energies.
- What we've indicated in Figure 14.2 is that the (S)-enantiomer is converted faster than the (R)-enantiomer.
- Thus,

$$k_\text{rel} = \frac{k_\text{fast}}{k_\text{slow}} = \mathrm{e}^{-\Delta\Delta G^\ddagger/RT}$$

  - In the literature, k_rel is sometimes referred to as an **S-factor** (for "selectivity factor").
- Reference: Sheldon (2001).

- **Homochiral** (catalyst): A chiral catalyst of which we're using only a single enantiomer.

- There are many catalytic kinetic resolutions in the literature.
  - Radosevich developed one in grad school, when he was roughly our age!

- Example catalytic kinetic resolution.

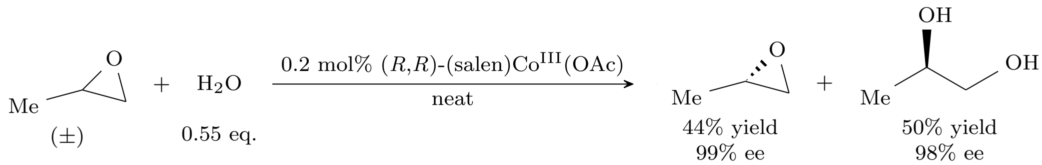


Figure 14.3: Hydrolytic kinetic resolution.

  - Take propylene oxide (racemic) and 0.55 eq. of water.
  - React them, neat, in the presence of a small amount of homochiral catalyst.
    - The structure of this complex is totally irrelevant to our aims, but we can look it up in the reference if we're curious.
    - This is our homochiral catalyst that will act on the two relatively inexpensive starting materials.
  - We run this reaction neat, and recover one enantiomer of our starting material in nearly quantitative yield with near perfect ee.
  - We also obtain a ring-opened *vic*-diol in nearly quantitative yield with near perfect ee.
  - $k_{\text{rel}} \approx 500$ here!
  - Reference: Tokunaga et al. (1997).
  - This is a **hydrolytic kinetic resolution**.
    - This is a very useful reaction for the resolution of terminal epoxides — and access to terminal 1,2-diols — because there exists no method to synthetically prefer a single enantiomer.
    - Propylene is so small that even the best chiral epoxidation catalysts aren't very selective here, so it's better to do a racemic epoxidation and then this.
  - Great atom economy.
- In a kinetic resolution like the above, the percent ee of both starting material and product is subject to change over time.
- To see this, let's build a theoretical model for a catalytic kinetic resolution.

$$\mathrm{A_S} + \mathrm{cat}^* \xrightarrow{k_{\text{fast}}} \mathrm{P} \qquad\qquad \mathrm{A_R} + \mathrm{cat}^* \xrightarrow{k_{\text{slow}}} \mathrm{P}$$

  - The net transformation involves the above two chemical reactions.
  - We can write differential rate laws for each enantiomer

$$\frac{\mathrm{d}[\mathrm{A_S}]}{\mathrm{d}t} = -k_{\text{fast}}[\mathrm{A_S}][\mathrm{cat}^*] \qquad\qquad \frac{\mathrm{d}[\mathrm{A_R}]}{\mathrm{d}t} = -k_{\text{slow}}[\mathrm{A_R}][\mathrm{cat}^*]$$

    - The consumption of the fast-reaction enantiomer will deplete [A].
  - Assuming [cat*] is approximately constant throughout the reaction, each of these differential rate laws can be independently integrated to

$$\ln\left(\frac{[\mathrm{A_S}]}{[\mathrm{A_S}]_0}\right) = -k_{\text{fast}}[\mathrm{cat}^*]t \qquad\qquad \ln\left(\frac{[\mathrm{A_R}]}{[\mathrm{A_R}]_0}\right) = -k_{\text{slow}}[\mathrm{cat}^*]t$$

  - Then, the key thing to note here is that for a racemic mixture, $[\mathrm{A_S}]_0 = [\mathrm{A_R}]_0$.
  - Thus, we can make this substitution and divide the above two integrated rate laws to get

$$k_{\text{rel}} = \frac{k_{\text{fast}}}{k_{\text{slow}}} = \frac{\ln([\mathrm{A_S}]/[\mathrm{A_S}]_0)}{\ln([\mathrm{A_R}]/[\mathrm{A_S}]_0)}$$

- This is a useful result, but we can make it even better. We'll start with a couple of definitions.
- **Conversion**: The ratio of how much of a reactant has reacted. *Denoted by* **c**. *Given by*

$$c := 1 - \frac{[A_S] + [A_R]}{[A_S]_0 + [A_R]_0} = 1 - \frac{[A_S] + [A_R]}{2[A_S]_0}$$

- **Enantiomeric excess**: A measurement of the degree to which a sample contains one enantiomer in greater amounts than the other. *Denoted by* **ee**. *Given by*

$$\text{ee} := \frac{[A_S] - [A_R]}{[A_S] + [A_R]}$$

- We can now do some algebra.
  - Indeed, it follows from the above definitions that

$$1 - \text{ee} = \frac{2[A_R]}{[A_S] + [A_R]} \qquad\qquad 1 + \text{ee} = \frac{2[A_S]}{[A_S] + [A_R]}$$

  - Then we can derive the following interesting relatinoships.

$$\frac{[A_R]}{[A_S]_0} = (1 - c)(1 - ee) \qquad\qquad \frac{[A_S]}{[A_S]_0} = (1 - c)(1 + ee)$$

  - We can now know the extent to which a reaction has evolved to consume one enantiomer or the other as a function of observables!
- Thus, we may define $\text{S} = k_{\text{rel}}$ as a function of conversion and ee.
  - For recovered starting material,

$$\text{S} = \frac{\ln[(1 - c)(1 - ee)]}{\ln[(1 - c)(1 + ee)]}$$

  - For the product,

$$\text{S} = \frac{\ln[(1 - c)(1 + ee)]}{\ln[(1 - c)(1 - ee)]}$$

- These relations allow us to relate conversion to ee for a catalyst of a given, set selectivity S. Specifically, we can parametrically plot ee as a function of conversion.
- Let's first do this for the percent ee in the recovered starting material.

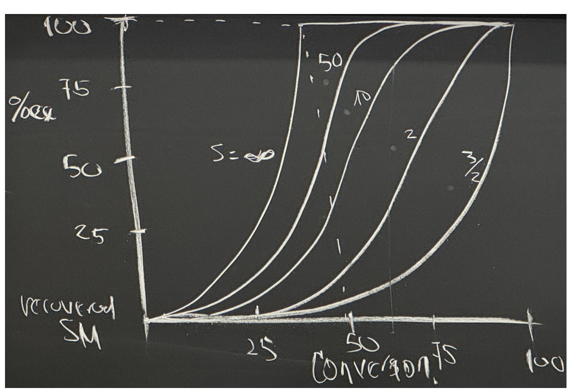


Figure 14.4: Starting material ee vs. conversion in a catalytic kinetic resolution.

- Consider first what happens in the limit that our selectivity factor is very large, i.e., that $\Delta\Delta G^\ddagger =$ large.
- If $S = \infty$, then 50% conversion will get us all we need.
  - This is because at this point, the enantiomer we don't want to recover will have been fully consumed.
- As the S-factor drops, we need higher conversions to get better ee's in the recovered starting material.
- What's cool about this is we can still get high ee's with bad catalysts... at the expense of conversion.
  - Essentially, with bad catalysts, we'll recover *less* enantiopure starting material (because some of it will have been consumed at higher conversions), but we *can* still recover essentially enantiopure starting material.

- For the product.

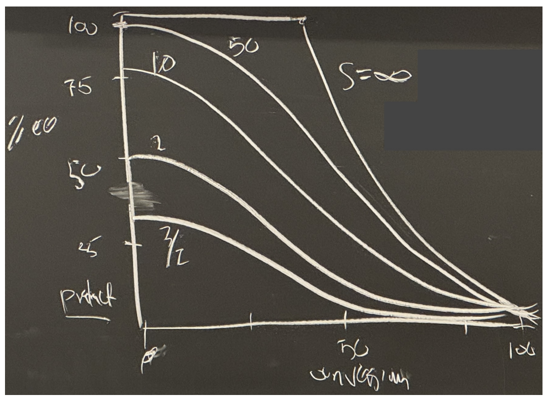
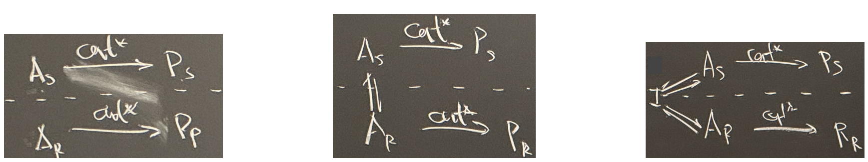


Figure 14.5: Product ee vs. conversion in a catalytic kinetic resolution.

- If $S = \infty$, the product will be enantiopure up until we begin converting some of the other enantiomer.
- If $S = 50$, we start at near-optimal purity, and then our bias will erode.
- What this implies is that for the purpose of kinetic resolution of the product, we need very good catalysts.
- That's what's remarkable about the Jacobsen catalyst: It's extremely selective for both the starting material *and* product.

- Let's now enter into some more complex kinetic regimes.



(a) Typical setup. (b) Direct interconversion. (c) Achiral intermediate.

Figure 14.6: Dynamic kinetic resolution models.

- As we've depicted it in Figure 14.2, our starting materials are equal in energy and not interconverting.
  - We can conceptualize this scenario as having a mirror plane between our starting materials and products that we *never* cross (Figure 14.6a).
- But what about when the starting materials do interconvert?
  - There are two ways in which this can happen: We can cross the mirror plane directly (Figure 14.6b), or through an achiral intermediate (Figure 14.6c).
- The 50% mass balance limit that is otherwise imposed is now lifted!
- Now our catalyst can sample both enantiomers via the epimerization.
- A_S interconverts with A_R, subject to a kinetically selective catalyst.

- Enantiomers under fast equilibrium are still under kinetic control, but with 100% theoretical yield.

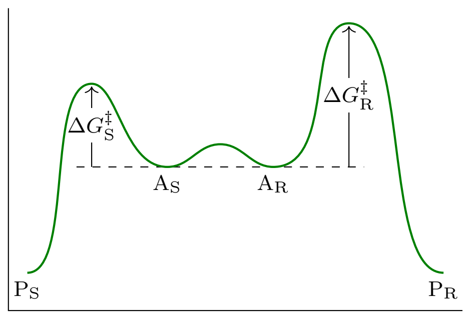


Figure 14.7: Dynamic kinetic resolution energy diagram.

- This is known as a **dynamic kinetic resolution**.

- Example dynamic kinetic resolution: Interconversion of chiral β-ketoesters prior to asymmetric hydrogenation.

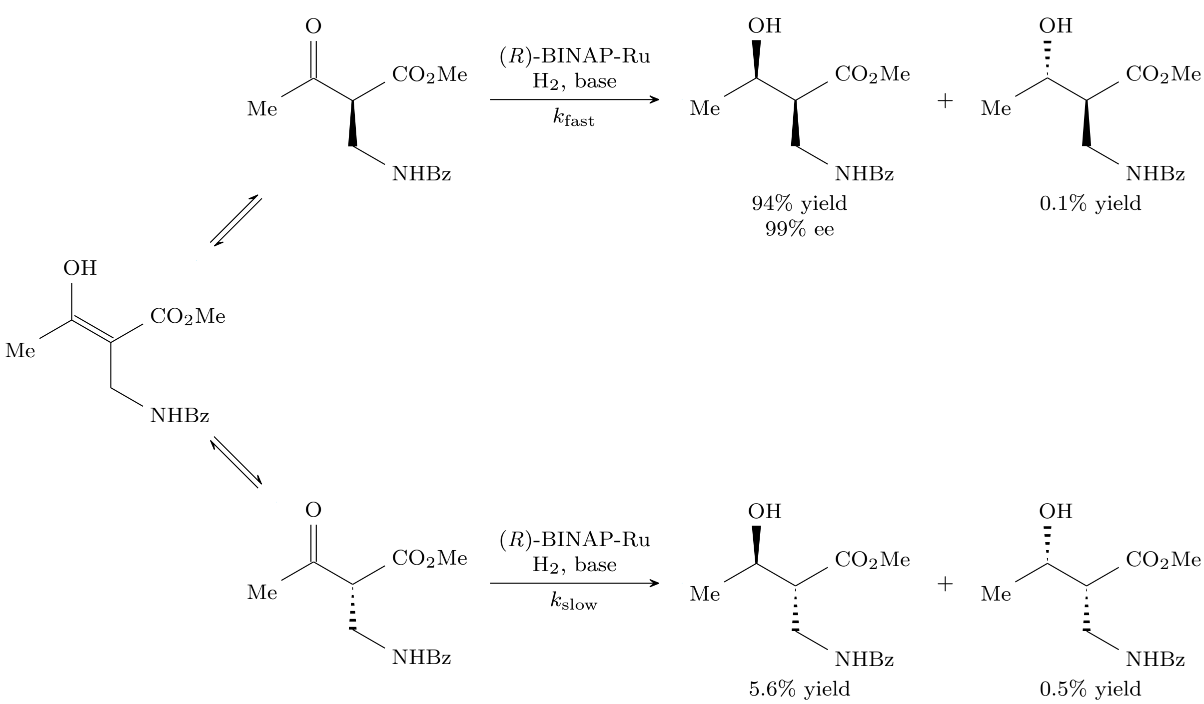


Figure 14.8: Noyori asymmetric hydrogenation.

- Consider a racemic sample of α-alkylated β-ketoester.
- Subject it to hydrogenation under **Noyori conditions**.
  - Both enantiomeric starting materials may become a *syn* or *anti* diastereomers.
  - Thus, in principle, you'd get a mess.
- Our mess is slightly alleviated by the fact that $k_{\text{fast}}/k_{\text{slow}} = 15$ for the ruthenium-BINAP catalyst.
  - This is about 2 kcal/mol of difference.
  - However, per Figure 14.5, this S-factor is not great.
- Our saving grace is the dynamic nature of this reaction.
  - When we actually run the experiment, we get fast enolization and interconversion through an achiral intermediate because of the base[1] in solution and the acidic α-proton.
  - Indeed, if the rate of enolization/racemation is denoted by k_{rac}, we have $k_{\text{rac}}/k_{\text{fast}} \approx 100$!
- Thus, we get 94% yield of one stereoisomer in 99% ee.
- Reference: Noyori et al. (1995).
  - See Table 3, Figure 19, and the associated discussions.
  - The whole paper is a good review of this chemistry, though.

- **Noyori asymmetric hydrogenation**: The asymmetric hydrogenation of a ketone using a homochiral ruthenium-BINAP catalyst, hydrogen gas, and a base.
- A related kinetic selectivity: Curtin-Hammett kinetics.

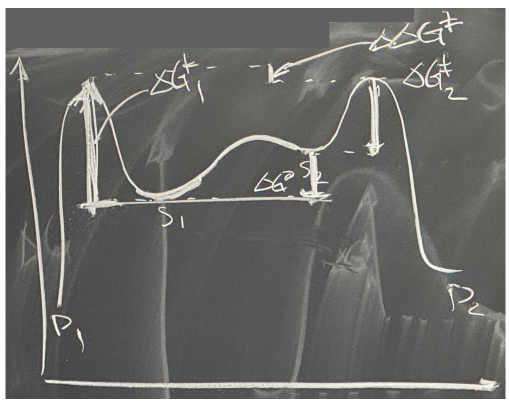


Figure 14.9: Curtin-Hammett selectivity derivation.

- Instead of (R)- and (S)-enantiomers, which rigorously have the same energy, we can consider other interconverting species with different energies.
- We can quantitate — with rate laws — the formation of the products.

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}t} = k_1[\mathrm{S}_1] \qquad\qquad \frac{\mathrm{d}[\mathrm{P}_2]}{\mathrm{d}t} = k_2[\mathrm{S}_2]$$

- Then taking a ratio gives

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \frac{k_1[\mathrm{S}_1]}{k_2[\mathrm{S}_2]}$$

- Note that

$$\frac{[\mathrm{S}_1]}{[\mathrm{S}_2]} = K_{\text{eq}}$$

so

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \frac{k_1}{k_2}K_{\text{eq}}$$

[1] It appears from the paper that there may not be a base; this may just be keto-enol tautomerization.

- Thus, with Arrhenius,

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \frac{\mathrm{e}^{-\Delta G_2^\ddagger/RT}}{\mathrm{e}^{-\Delta G_1^\ddagger/RT}}\mathrm{e}^{-\Delta G^\circ/RT} = \mathrm{e}^{(\Delta G_1^\ddagger - \Delta G_2^\ddagger - \Delta G^\circ)/RT}$$

- And then referencing Figure 14.9, we can see pictorially that

$$\Delta G_1^\ddagger - \Delta G_2^\ddagger - \Delta G^\circ = \Delta\Delta G^\ddagger$$

- Thus,

$$\frac{\mathrm{d}[\mathrm{P}_1]}{\mathrm{d}[\mathrm{P}_2]} = \mathrm{e}^{\Delta\Delta G^\ddagger/RT}$$

  if we have a fast equilibrium $\mathrm{S}_1 \rightleftharpoons \mathrm{S}_2$ (10 times faster than P_1 or P_2 formation).
- Essentially, if we have this fast starting equilibrium, then the product ratio is under kinetic control.

- Now suppose we drop S_2 down in free energy and leave the rest of the diagram unperturbed.
  - This change in one variable is compensated for by a change in the other variable, and we remain under kinetic control.
- Alex briefly discusses kinetic quench.
- Curtin-Hammett example 1 (Figure 6.4a).
  - P_1 is kinetically favored.
  - $[\mathrm{S}_1] > [\mathrm{S}_2]$.
  - Here, the $\mathrm{S}_1/\mathrm{S}_2$ ratio is irrelevant to product formation. This is "invisible" C/H kinetics. Mathematically,

$$\frac{[\mathrm{S}_1]}{[\mathrm{S}_2]} \neq \frac{[\mathrm{P}_1]}{[\mathrm{P}_2]}$$

- Curtin-Hammett example 2 (Figure 6.4b).
  - P_1 is kinetically favored.
  - $[\mathrm{S}_1] < [\mathrm{S}_2]$.
  - This is "classic" C/H kinetics.
  - Great example of this in Landis and Halpern (1987).
  - This scenario is actually pretty common.
- Curtin-Hammett example 3 (Figure 6.4c).
  - Here, $\Delta G_1^\ddagger = \Delta G_2^\ddagger$.
  - This scenario is pretty uncommon, but it is possible.
  - In this case, the equilibrium ratio *does* reflect the product ratio.
- Takeaway: It is far more likely that your equilibrium ratio of intermediates has no bearing on your ratio of products.