Kinetic Resolutions

Material outline:
For the Scientist in you:
   Definitions
   Theoretical treatment

For the technician in you:
   Practical considerations
   Useful KR’s
   Oxidative KR of allylic alcohols
      An extreme example
   Acylation/deacylation
   Hydrogenation
      olefins
      ketones
      Dynamic kinetic resolution
   Epoxide ring opening
      A very extreme example
   Parallel kinetic resolution

General References:
Vedejs, ACIEE, 2005, 3974
Kagan, Topics in Stereochemistry, 1988, 18, 249
Some definitions and examples

**Resolution:** A process leading to the separation of enantiomers, or derivatives thereof.

Simplest examples: **Resolution by making diastereomeric derivatives**

\[
\text{CO}_2\text{H} + \text{CO}_2\text{H} \xrightarrow{(+)-Menthol} \text{enantiomers} \xrightarrow{\text{idemical mp, mobility on silica gel, bp, etc}} \text{diastereomers} \xrightarrow{\text{different mp, mobility on silica gel, bp, etc}}
\]

**Resolution via salt formation:**

Larrow, Jacobsen, OS, 1998, 75, 1
Kinetic Resolution: One enantiomer reacts faster than the other:

\[
\begin{align*}
\text{Fast} & : \quad k_{\text{fast}} \\
\text{Slow} & : \quad k_{\text{slow}}
\end{align*}
\]

- Racemic mixture:
  - Fast reacting enantiomer
  - Slow reacting enantiomer

\[
\Delta \Delta G^\ddagger_{(\text{slow} - \text{fast})} = \Delta G^\ddagger_{\text{(slow)}} - \Delta G^\ddagger_{\text{(fast)}}
\]

- Potential Energy Diagram:
  - (S) + (R)- SM
  - Minor product
  - Major product

K_{rel} = s = k_{\text{fast}}/k_{\text{slow}} = \exp(\Delta \Delta G^\ddagger/RT)
Relationships between $k_{rel}$, ee and conversion

\[ k_{rel} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \] (1)

**Important Points**

1. KR can give any arbitrarily high ee recovered sm with any $k_{rel} > 1$ if you sacrifice yield

2. KR can give high ee product only if very high $k_{rel}$ (needs to be more selective than ‘normal’ asymmetric reaction

*(Jacobsen, 2001)*
Some thoughts: if not the only, route to optically pure allylic alcohols. Another noteworthy aspect of this approach to chiral materials is that virtually any degree of enantiomeric purity can be obtained. For example, if the epoxidation of 2-methylhept-1-en-3-ol (entry 7) is carried to 60% conversion, the enantiomeric excess is calculated to be 99.9999999999%, and one can go much higher than this simply by proceeding to higher conversions. Such extreme en-

For the production of enantiomerically pure substances, kinetic resolution is generally regarded as a poor cousin to asymmetric synthesis. Kinetic resolution suffers from the disadvantage that at least half of the starting material is lost. However, we believe this work makes clear one striking advantage kinetic resolution holds over asymmetric synthesis. The enantiomeric excess realized in an asymmetric synthesis is simply a consequence of the energy difference ($\Delta \Delta G^*$) between two diastereomeric transition states; the only way to improve the % ee is to increase that energy difference. Kinetic resolution too depends on there being an energy difference between diastereomeric transition states, but the manner in which that energy difference is expressed is unique to kinetic resolutions. The energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This winnowing should continue until the last molecule of the more reactive enantiomer is swept away, and one is left with a substance possessed of absolute enantiometric purity.

-Shearless, JACS, 1981, 6237
Note that eq 1 may not always hold:

\[ k_{rel} = \frac{\ln((1-c)(1-ee))}{\ln((1-c)(1+ee))} \]  

(1)

It assumes rxn is first order in substrate, but consider simple enzyme kinetics:

\[
\begin{align*}
\text{Sub} + \text{Cat} & \xrightleftharpoons[k_1]{k_1} \text{Sub-Cat} \\
\text{Rate}_{(R-sub)} & = \frac{k_{2(R)}[\text{Reagent}][\text{Cat}][\text{Sub}]}{K_M + [\text{Sub}]} \\
\text{K}_M & = (k_{-1} + k_2)/k_1 \sim \text{dissociation constant} \\
\text{Sub} & = \text{substrate}
\end{align*}
\]

For \([\text{sub}] >> K_m\), rxn is 0 order in \([\text{sub}]\); equation 1 does not hold

For \([\text{sub}] << K_m\), rxn is 1st order, equation 1 needs modification:

\[
\text{Relative rate} = E = \frac{k_{\text{cat}(R)}K_{M(S)}}{k_{\text{cat}(S)}K_{M(R)}} = \frac{\ln((1-c)(1-ee))}{\ln((1-c)(1+ee))} 
\]

(2)

Eq. 2 is eq 1 normalized to binding affinity

Many (most?) KR’s would likely show enzyme kinetics if anyone looked. Therefore they may start out zero order, then change. Also, one enantiomer could be 1st order, while the other is 0th order!

Hallmark of trouble is if \(k_{rel}\) (as calculated by eq 1) changes as a function of conversion

The real question is: what yield of what ee?
Drawbacks to KR’s
Max 50% yield
Poor ‘atom economy’
Viewed by some as inelegant

KR’s may be useful if the following are true:
1. Very high ee needed
2. Racemate cheap; optically active hard to make
3. Resolving agent cheap
4. Products easily separable
5. Catalyst cheap and works well
Ready; Catalysis  Kinetic Resolution

with D-(-)-DET

with L-(+)-DET

General trend: asymmetric catalytic reaction disclosed; soon after KR disclosed

Sharpless, JACS, 1981, 6237
improved (addn MS3A): JOC, 1986, 1922
relative rates: JACS, 1988, 2978

Epoxidation is *enantiomer-selective and diastereoselective*
Ready; Catalysis

Kinetic Resolution

-one of many interconverting ground-state structures

![Reaction Mechanism Diagram](image)

rate = \frac{k[Ti(tartrate)(OR)_{2}][TBHP][substrate]}{[ligand~alcohol]^{2}}

-ground state and TS dimer
-inhibited by water (that's why MS3A)
-need to lose 2 ROH ligands, coordinate [O] and substrate
Examples: isolated products shown
(for a large list, see Adv. Syn Cat, 2001, 5, supporting info)
Ready; Catalysis

**Kinetic Resolution**

2° KR

(![](image))

\[ (+)-DIPT, \text{Ti(OiPr)}_4, \text{TBHP} \]

\[ k_{rel}^*: \]

\[ \begin{array}{c}
0.36 \\
\text{slow}
\end{array} \]

\[ \begin{array}{c}
0.62 \\
\text{fast}
\end{array} \]

\[ \begin{array}{c}
100 \\
\text{fast}
\end{array} \]

\[ \begin{array}{c}
2.04 \\
\text{slow}
\end{array} \]

\[ k_{rel}^*: \]

\[ \begin{array}{c}
\text{fast} \\
\sim 102
\end{array} \]

\[ \begin{array}{c}
\text{~102} \\
\text{~0.98 slow}
\end{array} \]

\[ \begin{array}{c}
\text{~0.98}
\end{array} \]

\[ \text{ee} = \%1 - \% \text{ent-1} \]

\[ \text{de} = \%(1 + \text{ent-1}) - \%(\text{epi-1} + \text{ent-epi-1}) \]

predict ee and de will increase with conversion because of a **secondary kinetic resolution**

<table>
<thead>
<tr>
<th>conversion</th>
<th>yield 1 (%)</th>
<th>ee 1 (%)</th>
<th>predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>48</td>
<td>99.4</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>93 (max)</td>
<td>99.96</td>
<td></td>
</tr>
<tr>
<td>99.9</td>
<td>91</td>
<td>99.664</td>
<td></td>
</tr>
<tr>
<td>99.999</td>
<td>85</td>
<td>99.99999</td>
<td></td>
</tr>
</tbody>
</table>

* krel calc using Schreiber, JACS, 1987, 1525
Experimental validation

\[
\begin{align*}
\text{OH} & \quad \text{ (+)-DIPT, Ti(OiPr)_4, TBHP} \\
\text{cis} & \quad \text{-25 °C} \\
\text{OH} \\
\hline \\
\text{time} & \quad \text{ee} & \quad \text{de} \\
3 \text{ h} & \quad 84 & \quad 92 \\
24 \text{ h} & \quad 93 & \quad 99.7 \\
140 \text{ h} & \quad >97 & \quad >99.7 \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OH} \\
\text{cis} & \quad \text{ (+)-DIPT, Ti(OiPr)_4, TBHP} \\
\text{BnO} & \quad \text{-25 °C} \\
\text{BnO} & \quad \text{cis} \\
\hline \\
\text{time} & \quad \text{ee} & \quad \text{de} \\
1 \text{ h} & \quad 93 & \quad >97 \\
3 \text{ h} & \quad 95 & \quad >97 \\
44 \text{ h} & \quad >97 & \quad >97 \\
\end{align*}
\]
Next-generation epoxidation??

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{OiPr} & \quad \text{OiPr} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

potential advantages:
- aqueous conditions
- substrate classes inaccessible with Sharpless:

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{R} & \quad \text{R} \\
\text{R'} & \quad \text{R'} \\
\end{align*}
\]

demonstrated with \( R = H \)
KR with \( R \) not \( H \)??

obvious disadvantage:
hard to beat tartrate

Yamamoto, ACIEE, 2005, 4389
Enzymatic acylation/deacylation of amines and alcohols
review: Chem Rev. 1992, 1071

\[ \text{R} \text{CHO} + \text{NH}_3 + \text{HCN} \rightarrow \text{R} \text{CN} \rightarrow \text{R} \text{CH}_2 \text{CO}_2\text{H} \]

- Porcine kidney acylase (R = straight chain)
- Acylase from mold Aspergillus oryzae (R = branched)

AA's produced by Degusa on commercial scale
**Enzymatic acylation/deacylation of amines and alcohols**

Review: Chem Rev. 1992, 1071

- Enzymes can be used to put Ac on or take Ac off. Isopropenyl acetate or vinyl acetate common acylating agents.

- Enzyme 'kits' are available for screening purposes from SigmaAldrich and Biocatalysts.

- Rxns can be performed in water or organic solvents (hexane common); need exclude water from esterification reactions.

General rule: an enzyme will work for almost any substrate!!:

Some examples from ester hydrolysis (for details, see tables 8 - 12 in review):
Some products from acylation:
Note cleavage of ester or acylation of alcohol gives enantiomeric product

\[
\text{EtO}_2\text{C} - \text{Ph} \quad \text{OAc} \\
48\% y, 98\% \text{ ee} \\
\text{ent alcohol: } 49\% y, >98\% \text{ ee}
\]

\[
\text{CH}_3 \\
\text{OAc} \quad \text{OAc} \\
36\%, >98\% \text{ ee} \\
\text{ent alcohol 32\%, 98\% ee}
\]

extension to desymmetrization (often with 2° KR)

\[
\text{OAc} \\
\text{OBn} \quad \text{OBn} \quad \text{OAc} \\
70\%, >95\% \text{ ee}
\]

\[
\text{OH} \\
98\% \text{ ee}
\]

46\% y, >95\% ee
ent alcohol, 43\% y, >95\% ee

43\% y, 92\% ee
35\% y, 99.4\% ee
Ready; Catalysis

Kinetic Resolution

chemical methods for KR of alcohols

Advantage: clever design
Idea extended to other asymmetric reactions
One of most selective small molecule cat’s
Disadvantages: $3000/mmol
Fighting lipases and Noyori hydrogenation

Fu, Accts, 2000, 412;
Accts, 2004, 542

'planar chiral' version of DMAP

\[
\begin{array}{c}
\text{NMe}_2 \\
\text{Fe} \\
\text{Ph}_5 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Unreacted alcohol, major enantiomer</th>
<th>( s )</th>
<th>% ee (% conversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Me</td>
<td>43</td>
<td>99 (55)</td>
</tr>
<tr>
<td>2</td>
<td>R = Et</td>
<td>59</td>
<td>99 (64)</td>
</tr>
<tr>
<td>3</td>
<td>R = t-Pr</td>
<td>87</td>
<td>97 (52)</td>
</tr>
<tr>
<td>4</td>
<td>R = t-Bu</td>
<td>95</td>
<td>96 (51)</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>32</td>
<td>98 (56)</td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>71</td>
<td>99 (53)</td>
</tr>
<tr>
<td>7</td>
<td>OH</td>
<td>65</td>
<td>95 (52)</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>&gt;200</td>
<td>99 (51)</td>
</tr>
</tbody>
</table>
Kinetic resolution via asymmetric hydrogenation (much more on asymmetric hydrogenation to come)

Recovered allylic alcohols:

only useful when complementary to Sharpless
Pretty tough to separate products

Noyori, JOC, 1988, 708
1st (best?) example of dynamic kinetic resolution: racemization faster than reaction

\[ \text{Products:} \]

- \( \text{OH} \)
- \( \text{NHAc} \)
- d.r. 99:1, 98% ee

- \( \text{OH} \)
- \( \text{NHAc} \)
- d.r. 99:1, 94% ee

- \( \text{OH} \)
- \( \text{NHAc} \)
- d.r. 94:6, 98% ee

- \( \text{OH} \)
- \( \text{NHAc} \)
- d.r. 1:99, 93% ee

Noyori, JACS, 1989, 9134; 1993, 144; 1995, 2931
Jacobsen Hydrolytic kinetic resolution: background

proposed TS for asymmetric epoxidation

Lewis-acid catalyzed epoxide opening?

Asymmetric ring-opening of meso epoxides

(salen)CrCl

(t-Bu)CrCl

TMSN₃

R₁

R₂

R₃

R₄

ee(%) 97 93 82 85 92

Jacobsen, Accts, 2000, 421
catalyst activation:

\[
\begin{array}{c}
\text{(salen)Co(II)} \\
\text{Aldrich: $93/5g}$
\end{array}
\]

\[\text{Co} \quad \xrightarrow{1/4O_2/\text{AcOH}} \quad \xleftarrow{-1/2 \text{H}_2\text{O}} \quad \text{OAc} \quad \text{Co} \]

\[\text{(salen)Co(III)OAc}\]

hydrolytic kinetic resolution

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{H}_2\text{O} \quad \xrightarrow{(R,R)-(\text{salen})\text{Co(OAc)} \ (0.5 - 2 \text{ mol\%})} \quad \xleftarrow{\text{R}} \quad \text{O} \quad \text{R} \\
\text{R} & \quad \text{OH} \\
& \quad \text{OH}
\end{array}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Unreacted epox (0.55 equiv H\textsubscript{2}O)</th>
<th>Product diol (0.45 equiv H\textsubscript{2}O)</th>
<th>(k_{rel})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yield ee</td>
<td>yield ee</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{3}</td>
<td>46 &gt;99</td>
<td>45 99</td>
<td>500</td>
</tr>
<tr>
<td>CH\textsubscript{2}Ph</td>
<td>46 &gt;99</td>
<td>40 95</td>
<td>96</td>
</tr>
<tr>
<td>t-Bu</td>
<td>41 &gt;99</td>
<td>40 95</td>
<td>79</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl</td>
<td>43 &gt;99</td>
<td>40 95</td>
<td>190</td>
</tr>
<tr>
<td>CH\textsubscript{2}OTBS</td>
<td>47 &gt;99</td>
<td>42 98</td>
<td>250</td>
</tr>
<tr>
<td>CO\textsubscript{2}Me</td>
<td>43 &gt;99</td>
<td>37 97</td>
<td>130</td>
</tr>
<tr>
<td>Ph</td>
<td>44 &gt;99</td>
<td>42 98</td>
<td>130</td>
</tr>
<tr>
<td>C≡CTBS</td>
<td>41 &gt;99</td>
<td>41 99</td>
<td>420</td>
</tr>
</tbody>
</table>

Procedure: JACS, 2002, 1307
Mechanism and improved procedure (CoOTs): JACS, 2004, 1360
Terminal epoxides undergo simple KR with Phenols; epibromohydrin is a special case:

\[
\text{PhOH} + \text{O}_2\text{CCH}_2\text{Br} \rightarrow \text{PhOCH}_2\text{CH}_2\text{Br} \quad (1 \text{ equiv}) \quad (1.05 \text{ equiv})
\]

\[
\begin{align*}
\text{PhOH} & \rightarrow \text{PhOCH}_2\text{CH}_2\text{Br} \quad \text{major} \\
\rightarrow & \text{PhOCH}_2\text{OCH}_2\text{Br} \quad \text{minor}
\end{align*}
\]

\[
\text{PhOCH}_2\text{CH}_2\text{Br} + \text{PhOCH}_2\text{OCH}_2\text{Br} \rightarrow \text{PhOCH}_2\text{OCH}_2\text{Ph}
\]

\[
\text{JACS, 1999, 6086}
\]
Parallel kinetic resolution: Theory

called 'parallel' because SM -> P1 is an (S)-selective KR, SM --> P2 is an (R)-selective KR

Parallel kinetic resolution: example

Often make great exam questions; rarely make useful synthetic methods

Hoveyda, Tet, 1995, 4383

\[
\begin{align*}
\text{Et} & \\
& \text{H} \\
& \text{OH}
\end{align*}
\]

48% y 98% ee

\[
\begin{align*}
\text{n-C}_6\text{H}_{13} & \\
& \text{EtMgBr} \\
& \text{cat}
\end{align*}
\]

\[
\begin{align*}
\text{fast} & \\
\text{slow}
\end{align*}
\]

\[
\begin{align*}
\text{n-C}_6\text{H}_{13} & \\
& \text{OH}
\end{align*}
\]

48% y 98% ee