The Horeau Principle

*Fundamentals, Theory, & Selected Synthetic Applications*

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Group Meeting
6/18/21
Outline

1. Introduction
   a) Initial disclosure
   b) Basic theory of statistical duplication

2. Applications of Statistical Duplication in Synthesis

3. Past Statistical Duplication: Asymmetric Catalysis
   a) Advantages of setting multiple stereocenters
   b) A focus on the Horeau principle in catalyst control
   c) Why substrate control gets messy, fast

4. Synthetic Applications in Asymmetric Catalysis

5. Summary
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Horeau’s Initial Demonstration of Statistical Enantioenrichment

in 1973, Alain Horeau and co-workers reported the use of what would become known as the Horeau Principle as a technique to enrich the enantiomeric purity of a scalemic mixture

Horeau’s initial procedure consisted of 3 steps:

1. Coupling of scalemic starting material onto a bifunctional linker
2. Removal of the meso diastereomer
3. Hydrolysis of the chiral diastereomer

for an early, but less studied, report of this phenomenon, see: Langenbeck, W.; Triem, G. Z. Phys. Chem. A. 1936, 401-408.
by applying some straightforward algebra with a couple chemical assumptions, we can explain this phenomenon of “statistical duplication”

key assumptions:

1. formation of all diastereomers occurs with equal rates (no asymmetric induction)
2. the dimerization is clean and irreversible

the Horeau Principle provides a means to increase the e.e. of a scalemic starting material at the cost of yield (d.r.)
Theory Behind Horeau’s Initial Report

by applying some straightforward algebra with a couple chemical assumptions, we can explain this phenomenon of “statistical duplication”

\[
(S) \quad x \\
(R) \quad 1-x
\]

\[
(S) + (R) \rightarrow X \\
\text{loss of major enantiomer}
\]

<table>
<thead>
<tr>
<th>ee\text{,i}</th>
<th>ee\text{,p}</th>
<th>ee\text{,p}</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>30%</td>
<td>55%</td>
<td>23%</td>
</tr>
<tr>
<td>50%</td>
<td>80%</td>
<td>19%</td>
</tr>
<tr>
<td>75%</td>
<td>96%</td>
<td>11%</td>
</tr>
<tr>
<td>90%</td>
<td>99.4%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

\[
ee\text{,p} = \frac{2(\text{ee}\text{,i})}{1 + (\text{ee}\text{,i})^2}
\]

\[
dr = \frac{1 + (\text{ee}\text{,i})^2}{1 - (\text{ee}\text{,i})^2}
\]
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   a) Initial disclosure
   b) Fundamentals

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Han and Corey utilized this phenomenon in order to achieve a highly enantioselective synthesis of (-)-wodeshiol, hinging upon a key Pd-catalyzed homocoupling.

\[
eq p = \frac{2(ee)}{1 + (ee)^2} = \frac{2(0.88)}{1 + (0.88)^2} = 99.2\%
\]

84% yield

8:1 mixture

34% yield over 2 steps
Synthesis of Antibiotic FR-900848 via “The Horeau Gambit”

Falck and co-workers applied iterative Horeau duplications to afford a polycyclopropane antibiotic natural product in >99.9% e.e.

\[
\text{Bu}_3\text{Sn}-\text{OTBDPS} \xrightarrow{\text{asymmetric cyclopropanation}} \text{Bu}_3\text{Sn}-\text{OTBDPS} \quad 98\% \text{ yield}
\]

\[
\text{Bu}_3\text{Sn}-\text{OTBDPS} \quad 88-90\% \text{ e.e.}
\]

\[
\text{a}) \, ^{8}\text{BuLi}, -40 ^\circ \text{C} \quad \text{b}) \, [\text{CuPBU}_3]_4, \text{O}_2, -78 ^\circ \text{C}
\]

\[
\text{TBDPSO}^+ \quad 73\% \text{ yield}
\]

\[
\text{TBDPSO}^+ \text{OTBDPS} \quad 98\% \text{ e.e.}
\]

\[
\text{OTBDPS} \quad >99\% \text{ e.e.}
\]

\[
\text{OTBDPS} \quad (\text{theoretical: } 99.98\%)
\]

\[
\text{TBDPSO}^+ \text{Br} \quad 98\% \text{ e.e.}
\]

\[
\text{a}) \, ^{1}\text{BuLi}, -78 ^\circ \text{C} \quad \text{b}) \, [\text{CuPBU}_3]_4, \text{O}_2, -78 ^\circ \text{C}
\]

\[
\text{TBDPSO}^+ \text{Br} \quad 75\% \text{ yield}
\]

\[
\text{TBDPSO}^+ \text{OTBDPS} \quad >99\% \text{ e.e.}
\]

\[
\text{Me} \quad \text{OTBDPS} \quad >99\% \text{ e.e.}
\]

\[
\text{Me} \quad \text{OTBDPS} \quad \text{7 steps}
\]

\[
\text{Me} \quad \text{OTBDPS} \quad 65\% \text{ yield}
\]

\[
\text{FR-900848}
\]

Using Horeau’s Principle to Determine e.e.

by analyzing the diasteromeric composition of a Horeau-type dimerization reaction, the e.e. of the starting material can be easily calculated

\[
dr = \frac{1 + (ee)^2}{1 - (ee)^2}
\]

dr = \frac{1 + (ee)^2}{1 - (ee)^2}

phosphinic dichlorides form two heterochiral diastereomers, but react particularly cleanly

carbonates, oxalates, ureas, anhydrides, and silanes have been used as well

for more examples, see: Harned, A. M.; Tetrahedron 2018, 3797-3841.
Third-Order Statistical Amplification

perhaps unsurprisingly, formation of trimers instead of dimers leads to high degrees of enantiomeric enrichment

dimerization of the formylpinane would result in a theoretical e.e. of 94.0% - trimerization elevates the enantioenrichment to near-enantiopurity!

however, trimerization results in higher losses - an estimated 23% of the major enantiomer is lost
Fourth-Order Statistical Amplification

fourth-order Horeau amplification has been utilized to synthesize C₄-symmetric porphyrins with phenomenal levels of enantiopurity.

\[ \text{Horeau amplification predicts an e.r. of 1.57 billion: 1! (99.99999994\% e.e.)} \]
Fourth-Order Statistical Amplification

fourth-order Horeau amplification has been utilized to synthesize C₄-symmetric porphyrins with phenomenal levels of enantiopurity

![Chemical structure](image)

<table>
<thead>
<tr>
<th>eeᵢ</th>
<th>erₚ</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>74.8%</td>
<td>2340:1</td>
<td>58:42</td>
</tr>
<tr>
<td>83.4%</td>
<td>15040:1</td>
<td>70:30</td>
</tr>
<tr>
<td>91%</td>
<td>281000:1</td>
<td>84:16</td>
</tr>
<tr>
<td>99%</td>
<td>~10⁹:1</td>
<td>98:2</td>
</tr>
</tbody>
</table>

even samples of modest enantiopurity result in formation of nearly enantiopure porphyrins!

...but at a high cost
Aggarwal and co-workers demonstrated the Horeau principle at work to an extraordinary degree in an assembly-line synthetic protocol.

"On the basis of the Horeau principle, after nine homologations using the stannane (10^3 : 1 e.r.) on the boronic ester (∼10^2 : 1 e.r.) the enantiomeric ratio of the major diastereoisomer should be 10^{29} : 1, which is considerably greater than Avogadro’s number, and so the product is expected to be literally a single enantiomer."
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An Often More Applicable Scenario: Multiple Asymmetric Reactions

a perhaps more interesting side of the Horeau Principle is found when applied to sequentially setting two stereocenters on the same molecule, a situation very thoroughly described by Kagan and co-workers in 1994.
Multiple Asymmetric Reactions: Kagan’s Treatment

The Ideal Case: Total Catalyst Control

This scenario is fundamentally simplest under complete catalyst control (\(r = r_A = r_B = r' = r_A' = r_B\)).

\[
\text{ee}_A = \frac{2r}{1 + r^2} \quad \text{ee}_B = 0 \quad \text{dr} = \frac{1 + r^2}{1 - r^2}
\]

These are the same equations as from statistical duplication!
The Ideal Case: Total Catalyst Control

This scenario is fundamentally simplest under complete catalyst control \((r = r_A = r_B = r' = r_A' = r_B)\).

\[
\begin{align*}
\text{ee}_A &= \frac{2r}{1 + r^2} & \text{ee}_B &= 0 & dr &= \frac{1 + r^2}{1 - r^2}
\end{align*}
\]

These are the same equations as from statistical duplication!

The examples presented today will fall into this limiting case, generally characterized by the use of (pseudo)symmetric substrates.
Kagan’s Treatment of Substrate Control

**case 1:** both routes are identical, or one route does not occur

\[ ee_A = \frac{(1 + r_A)(1 + r) - (1 - r_B)(1 - r)}{(1 + r_A)(1 + r) + (1 - r_B)(1 - r)} \]

\[ ee_B = \frac{(1 - r_A)(1 + r) - (1 + r_B)(1 - r)}{(1 - r_A)(1 + r) + (1 + r_B)(1 - r)} \]

\[ dr = \frac{ee_B - r}{r - ee_S} \]
Kagan’s Treatment of Substrate Control

case 2: both routes are in competition, but have identical selectivities at corresponding steps

\[ i = \frac{1R + 1S}{1R + 1S + 2R + 2S} \]

\[ \text{ee}_A = \frac{(1 + r_A)(1 + r) - (1 - r_B)(1 - r)}{(1 + r_A)(1 + r) + (1 - r_B)(1 - r)} \]

\[ \text{ee}_B = (2i - 1) \frac{(1 - r_A)(1 + r) - (1 + r_B)(1 - r)}{(1 - r_A)(1 + r) + (1 + r_B)(1 - r)} \]

\[ \text{dr} = \frac{(1 + r_A)(1 + r) - (1 - r_B)(1 - r)}{(1 - r_A)(1 + r) + (1 + r_B)(1 - r)} \]
Noyori’s Demonstration of Asymmetric Hydrogenation

A few years before Kagan and co-workers published their statistical analysis of this principle, Noyori’s lab demonstrated its feasibility with Ru-catalyzed hydrogenation.

$$\text{RuCl}_2[(R)\text{-BINAP}] \, \text{MeMe} \, \text{O}\text{O} \rightarrow 72 \text{ atm H}_2, \text{rt}$$

99% “100% e.e.”

1% meso

98.5% e.e.

$$\text{RuCl}_2[(S)\text{-BINAP}] \, \text{MeMe} \, \text{OH} \, \text{O} \rightarrow \text{H}_2, \text{rt}$$

>99% e.e.

15% 85% >99% e.e.

Catalyst control >> substrate control

Noyori’s Demonstration of Asymmetric Hydrogenation

A few years before Kagan and co-workers published their statistical analysis of this principle, Noyori’s lab demonstrated its feasibility with Ru-catalyzed hydrogenation.

\[
\begin{align*}
\text{Me} & \text{Me} \quad \text{O} & \text{O} \\
\text{RuCl}_2[(R)\text{-BINAP}] & \quad \text{Me} & \text{Me} \\
\text{Me} & \text{Me} \quad \text{OH} & \text{OH} \\
72 \text{ atm } H_2, \text{ rt} & \quad 99\% \quad \text{“100\% e.e.”} \\
\text{Me} & \text{Me} \quad \text{OH} & \text{OH} \\
98.5\% \text{ e.e.} & \quad 1\% \quad \text{meso}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \text{Me} \quad \text{O} & \text{O} \\
\text{RuCl}_2[(S)\text{-BINAP}] & \quad \text{Me} & \text{Me} \\
\text{Me} & \text{Me} \quad \text{OH} & \text{OH} \\
\quad & \quad 26\% \quad \text{“100\% e.e.”} \\
\text{Me} & \text{Me} \quad \text{OH} & \text{OH} \\
74\% & \quad \text{meso}
\end{align*}
\]

\[
\begin{align*}
\text{ee} & = \frac{2(0.985)}{1 + (0.985)^2} = 99.99\% \text{ ee} \\
\text{dr} & = \frac{1 + (0.985)^2}{1 - (0.985)^2} = 66:1
\end{align*}
\]

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A Well-Characterized Example: Asymmetric Bis-Oxidation of 1,3-Dithianes

An early example from Aggarwal and co-workers provides a clean example of this principle at work.

\[
\text{ee} = \frac{2(0.30)}{1 + (0.30)^2} = 55\% \text{ ee}
\]

\[
\text{ee} = \frac{2(0.85)}{1 + (0.85)^2} = 98.7\% \text{ ee}
\]

**Synthesis of Chiral C$_2$-symmetric Ligands**

Horeau’s principle is often invoked for ligand synthesis, providing rapid access to C$_2$-symmetric ligand scaffolds with excellent enantiopurity.

1. **First Reaction Set**
   - a) (–)-IpcBH$_2$, -25 ºC
   - b) H$_2$O$_2$, NaOH
   - **yield:** 44% yield
   - **ee:** >96% e.e. (after recrystallization)

2. **Second Reaction Set**
   - a) (–)-IpcBH$_2$, -25 ºC
   - b) H$_2$O$_2$, NaOH
   - **yield:** 66% yield
   - **ee:** >99% e.e. (after recrystallization)

---

Same Idea, Different Form of Stereochemistry

multiple-olefinations are subject to the same stereochemical enrichment

NaH, -78 ºC

d.r. 60:1

not observed

\[
\text{dr} = \frac{1 + \text{(selectivity)}^2}{1 - \text{(selectivity)}^2} \quad \text{selectivity} = 99.2 : 0.8 (E:Z)
\]

\[
[E, E] : [Z, Z] = \frac{2(0.984)}{1 + (0.984)^2} = \sim 15000:1
\]
Horeau’s Principle in Asymmetric Catalysis: (-)-cyanthiwigin F

Enquist and Stoltz invoked Horeau’s Principle in asymmetric decarboxylative allylation as a key step in their highly enantioselective synthesis of (-)-cyanthiwigin F.

2 steps from diallyl succinate

78% yield
4.4:1 d.r.

99% e.e.


Sequential Asymmetric Reactions: Synthesis of Vitamin E

the same principle applies to performing two discrete asymmetric reactions, as evidenced in Huo and Negishi’s synthesis of Vitamin E

Sequential Asymmetric Reactions: Organocatalysis

the MacMillan group demonstrated a cascade approach to enal hydrofluorination using two distinct imidazolidinone organocatalysts

the high d.r. and e.e. observed with the enantiomeric enamine catalyst confirms:
1. the organocatalyst is exchanged prior to fluorination
2. the fluorination is predominantly catalyst-controlled

Sharpless’s asymmetric dihydroxylation of squalene demonstrates the multiplicative effect of the Horeau principle in asymmetric catalysis.

\[
\text{ee}_p = \frac{(1 + \text{ee}_R)^6 - (1 - \text{ee}_R)^6}{(1 + \text{ee}_R)^6 + (1 - \text{ee}_R)^6} = 99.999999986\% \text{ ee}
\]

(14 billion : 1 e.r.)
Summary

• The Horeau Principle provides a means to enrich a substrate’s enantiopurity, or improve the enantioselectivity of a reaction by coupling it to another

• The price for this amplification is diminished d.r., with material lost in the other diastereomer(s)
  • lower ee\textsubscript{i} values result in a higher cost

• Iterative amplification provides exponential purity/selectivity increases, but bears a greater d.r. cost

• In regimes of total catalyst control, this effect is easy to study and quantify,
  • This becomes significantly more challenging in the presence of substrate control, reversible reactions, or certain side processes