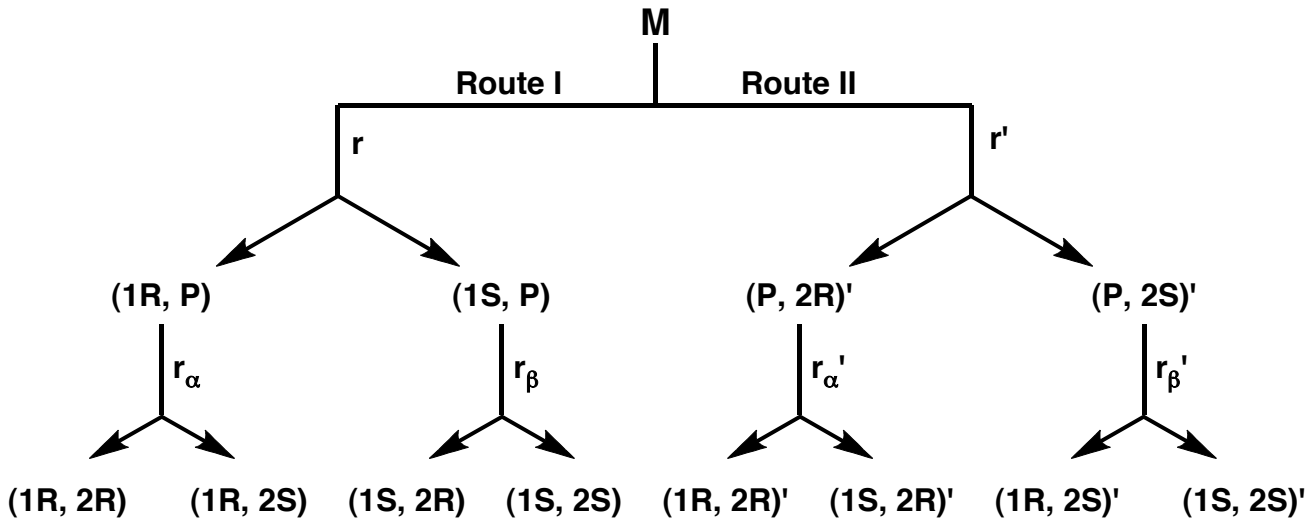
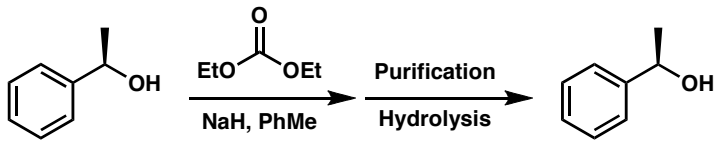
The Horeau Principle

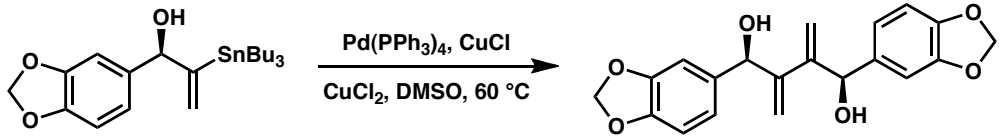
The Nature of Statistical Amplification in Enantioselective Synthesis



Stoltz Group Literature Meeting
John Enquist
Monday, December 18th, 2006
8:00 PM
147 Noyes



(60% *ee*) (86.5% *ee*)



88% *ee*

82% yield
8 : 1 dr
(99.2% *ee*)

The Horeau Principle: A Statistical Basis for Asymmetric Amplification

I.) Origins and explanation of the Horeau Principle.

- A.) Wolfgang Langenback's observations.
- B.) Horeau's original experiments and conclusions.
- C.) Critical assumptions, costs, and guiding concepts of Horeau's work.

II.) The Horeau Principle via chemical duplication.

- A.) Duplication as a method of chiral resolution or enantioenrichment.
- B.) Applications of duplication to the elucidation of substrate *ee*.
- C.) Duplications and their application to synthesis.

III.) Extensions of the Horeau Principle beyond duplication.

- A.) The Horeau Principle via multiple enantioselective catalysis.
- B.) Adding complexity to the Horeau Principle.

IV.) Conclusions.

Reviews:

Duplication and purification - Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*, **1981**, p. 430-434.
The Horeau Principle explained - Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.
Double Asymmetric synthesis - Baba, S. E.; Sartor, K.; Poulin, J.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 131, 525-533.
In the context of non-linear effects - Girard, C.; Kagan, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959.
The historical perspective - Heller, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 495-499.
Mathematical treatment and assumptions - Chandrasekhar, S. **2005**, *31*, 779-783.

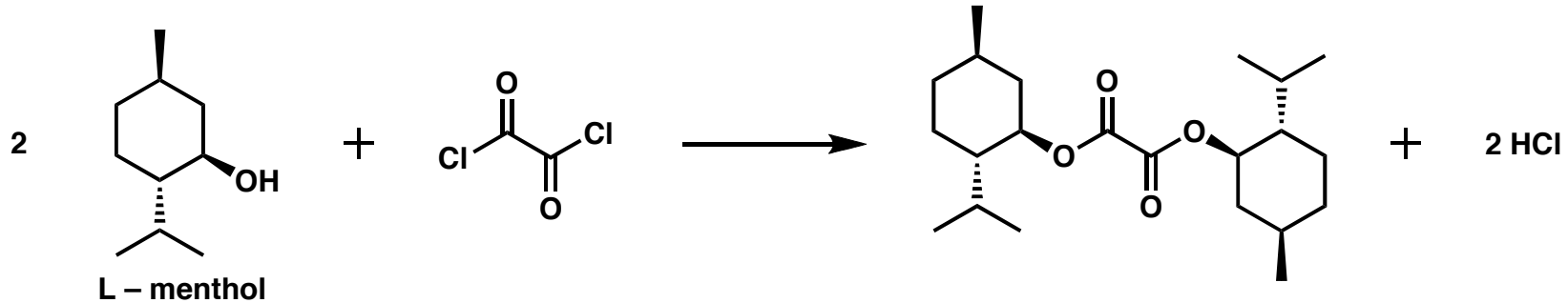
Langenback's Observations: The Origin of the Horeau Principle

An Idea Before its Time

- Langenback's original publication in 1936 postulated:

"*With every synthesis of an optically active compound from inactive starting materials, a degredation in optical purity takes place... The infinite repetition of these processes over a geological time period would have led to a complete loss of optical activity... if the degredation were not compensated for by an increase in optical purity in a different process.*"

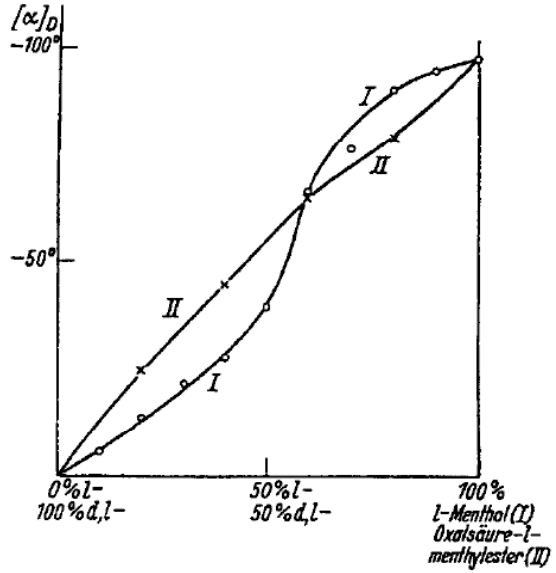
- To understand and indentify this phenomenon, Langenback investigated a simple dimerization process:



L – menthol
(0 - 100% *ee*)

- Analysis of the optical rotation of the product bis-ester revealed unusal behavior. Product rotation varied as a function of the *ee* of L-menthol.

- No stereocenters were formed... What factors influence optical rotation here?

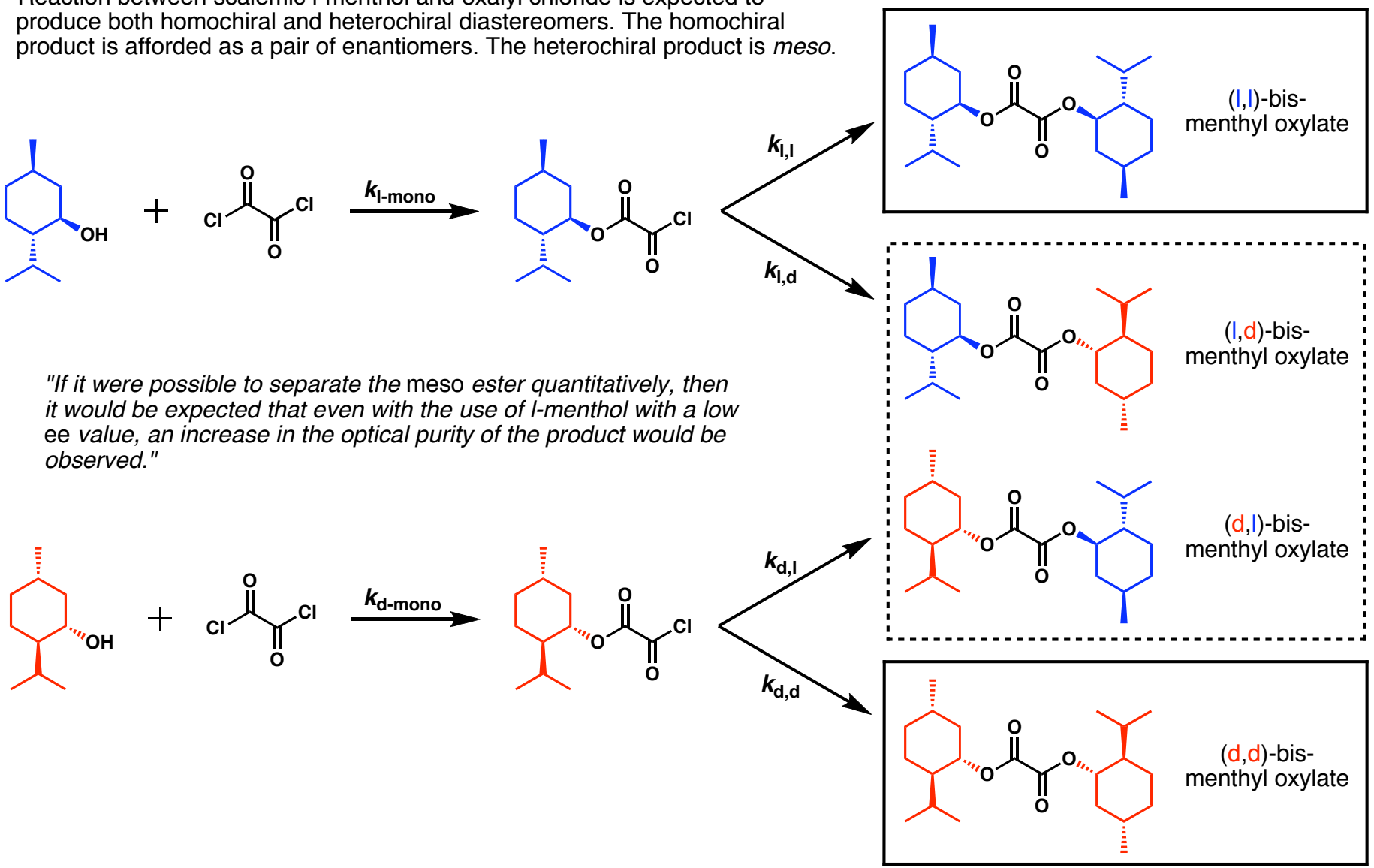


Heller, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 495-499.
Langenbeck, W. *Z. Phys. Chem. A* **1936**, *177*, 401-408.

Langenback's Observations: The Origin of the Horeau Principle

An Idea Before its Time

- Reaction between scalemic l-menthol and oxalyl chloride is expected to produce both homochiral and heterochiral diastereomers. The homochiral product is afforded as a pair of enantiomers. The heterochiral product is *meso*.



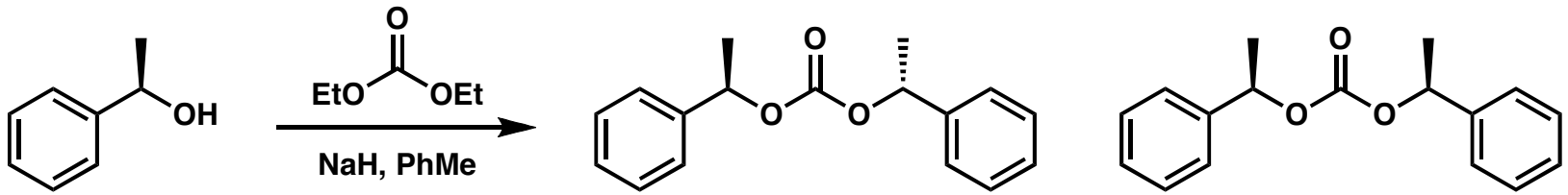
"If it were possible to separate the meso *ester quantitatively, then it would be expected that even with the use of l-menthol with a low* ee *value, an increase in the optical purity of the product would be observed."*

Heller, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 495-499.
Langenbeck, W. *Z. Phys. Chem. A* **1936**, *177*, 401-408.

Horeau's Experiments: Statistical Enantiomeric Enrichment

Dimerization as a Resolution Technique

• In 1973, Horeau performed experiments very similar to Langenbeck's duplications, but with the aid of separation techniques.



(60% *ee*)

Homochiral

2.10

:

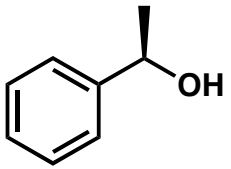
1

Heterochiral

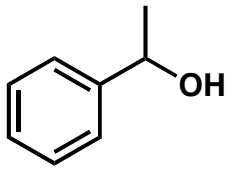
- Dimerization of a nonracemic molecule through an achiral linker provided a mixture of diastereomeric products.
- Separation of these diastereomers followed by liberation of the monomers yielded two different mixtures of the starting material.
- The *homochiral* diastereomer afforded enantioenriched monomer, whereas the *heterochiral* diastereomer afforded only racemic monomer.

Hydrolysis

Hydrolysis



67.7% yield
(86.5% *ee*)



32.2% yield
(0% *ee*)

Vigneron, J. P.; Dhaenes, M.; Horeau, A. *Tetrahedron*, **1973**, *29*, 1055-1059.
Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.

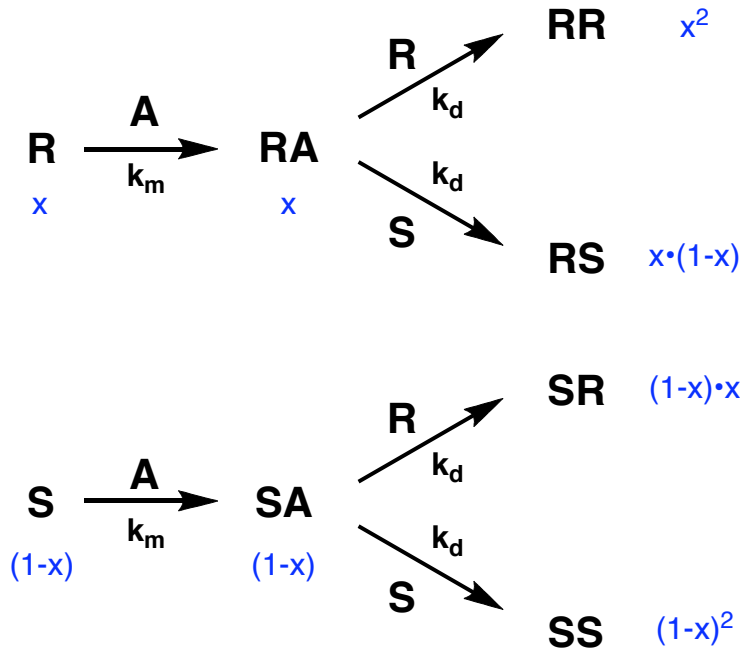
Horeau's Experiments: Statistical Enantiomeric Enrichment

Math and Theory

- For any scalemic mixture composed of molecules baring a single chiral center, the respective enantiomers are represented by the letters R and S. An achiral, bifunctional duplication reagent is represented by A.

- If the scalemic mixture is enriched with the R enantiomer, the total composition of R in the mixture can be represented as x, while the total composition of S is 1-x (where R+S=1).

- **Criticial Assumptions:**
  - The outcome of the first reaction must have *no* influence upon the second reaction. This means *no* chiral recognition between RA or SA and either incoming monomer.
  - There must be *no* difference in rate between enantiomers during the formation of RA or SA.
  - There must be *no* interference by side reactions.
  - Reactions must be irreversible.



- Following the above assumptions, we can conclude:

$$dr = \frac{\text{Homochiral Yield}}{\text{Heterochiral Yield}} = \frac{x^2 + (1-x)^2}{2 \cdot x \cdot (1-x)}$$

$$ee_p = \frac{RR - SS}{RR + SS} = \frac{x^2 - (1-x)^2}{x^2 + (1-x)^2}$$

$$er_p = \frac{RR}{SS} = \frac{x^2}{(1-x)^2} = \left(\frac{x}{(1-x)}\right)^2 = (er_i)^2$$

- If we take the value ee_i to be the initial enantiomeric excess of the starting material, we can find alternative expressions for ee_p and dr:

$$ee_p = \frac{2 \cdot ee_i}{1 + (ee_i)^2} \qquad dr = \frac{1 + (ee_i)^2}{1 - (ee_i)^2}$$

Vigneron, J. P.; Dhaenes, M.; Horeau, A. *Tetrahedron*, **1973**, *29*, 1055-1059.
Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.

Horeau's Experiments: Statistical Enantiomeric Enrichment

Costs and Benefits

- The *ee* of the dimer increases beyond that of the monomer quickly. This is an example of positive nonlinear behavior.

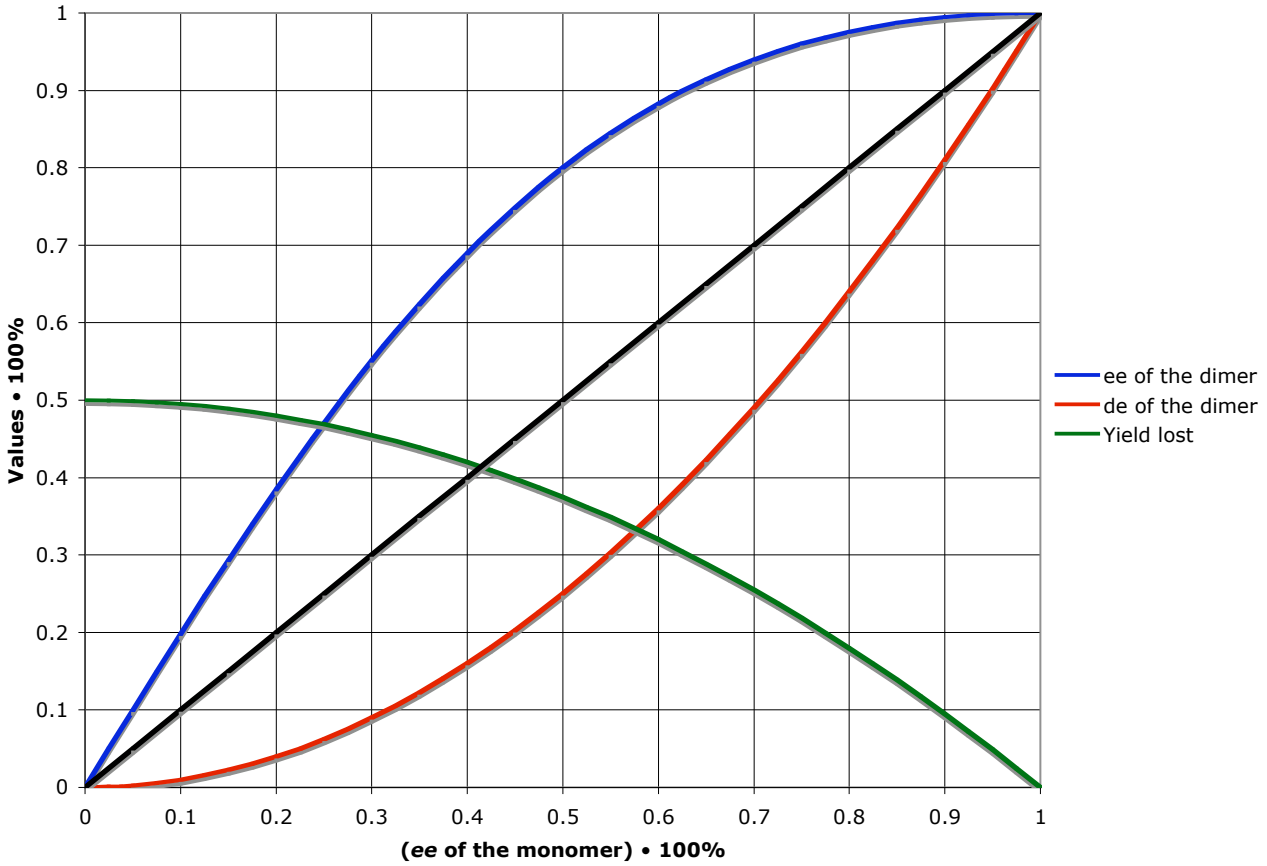
$$er_p = \frac{RR}{SS} = \left(\frac{R}{S}\right)^2 = (er_i)^2 \Longrightarrow er_p \geq er_i \quad \text{(for all R > S)} \qquad ee_p = \frac{2 \cdot ee_i}{1 + (ee_i)^2}$$

- The *de* (and hence dr) of the dimer increases more slowly, with high dr only achieved at large ee_i values.

$$dr = \frac{1 + (ee_i)^2}{1 - (ee_i)^2} \qquad de = (ee_i)^2 \leq ee_i \quad \text{for} \quad 0 \leq ee_i \leq 1$$

- The inherent cost of this duplication technique is a *loss in yield*. The removed *meso* diastereomer is half composed of the desired enantiomer!

$$\text{Yield loss} = \frac{1}{1 + dr}$$



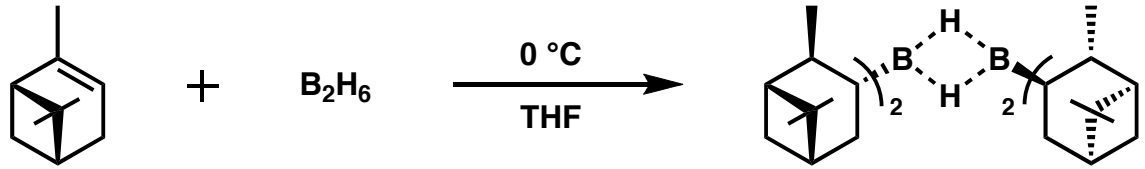
Vigneron, J. P.; Dhaenes, M.; Horeau, A. *Tetrahedron*, **1973**, *29*, 1055-1059.

Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.

Enantiomeric Enrichment via Duplication

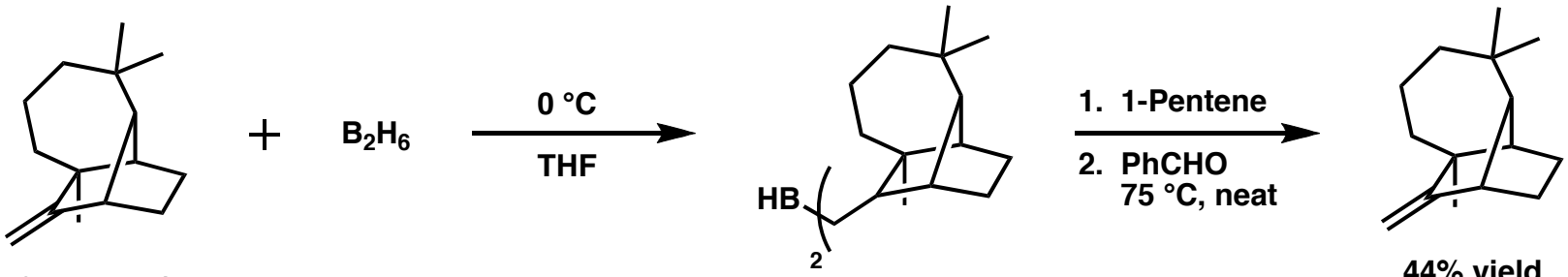
Applications and Synthesis

• Synthesis and enantioenrichment of diisopinocamphenylborane from scalemic (α)-pinene.



ee_i	ee_p	ee_{calc}
91.6	99.0	99.6
92.0	99.0	99.7
84.0	98.3	98.4

(Horeau Principle behavior observed despite newly forming chiral center)

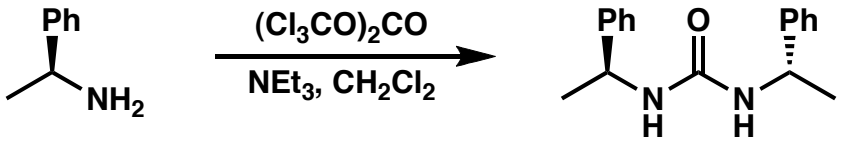


(86.3% ee_i)

44% yield
(98.5% ee_i)

Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945-947.
Prabhakar, K.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 3203-3206.

• Dimerization of (S)-methylbenzylamine was used in order to assay *ee* without need for a chiral auxiliary.



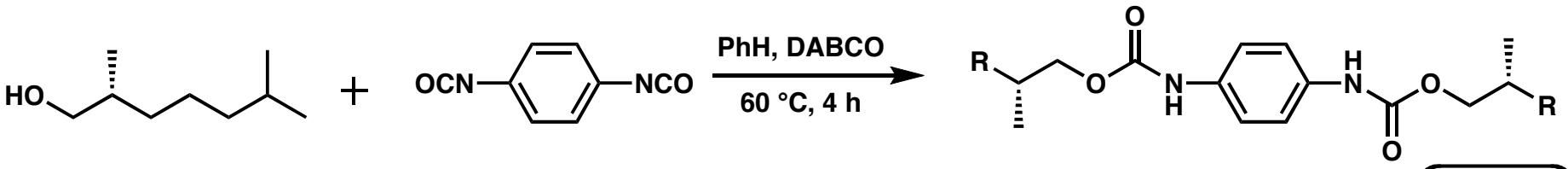
- ^{1}H NMR showed 99:1 dr in favor of the homochiral diastereomer for (+)-methylbenzylamine.
- (±)-methylbenzylamine gave a 1:1 dr.
- The amine ee_i was determined to be 99.1%

Grotjahn, D.; Joubran, C.; *Tetrahedron: Asymmetry* **1995**, *6*, 745-752.

Enantiomeric Enrichment via Duplication

Applications and Synthesis

• Low selectivity carboalumination produced substrates with modest *ee* values. Duplication made them synthetically useful.



(74% *ee*$_i$)

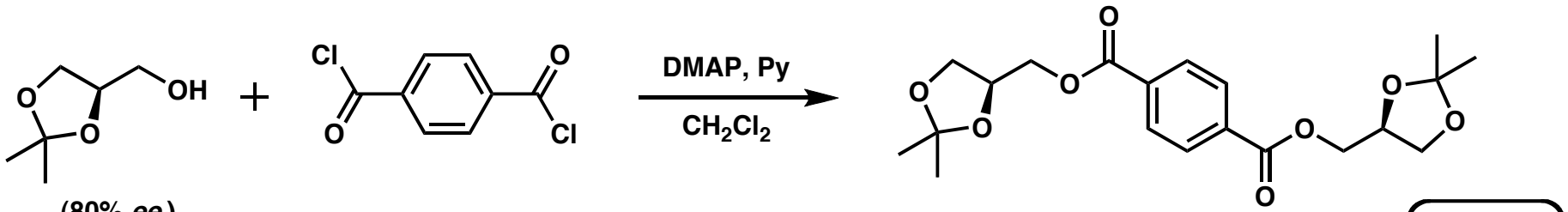
43% yield
(no reported dr)
(93.0% *ee*)

Calculated

3.4 : 1 dr
95.6% *ee*

Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253-3256.

• Horeau–type duplications are most effective when they are *transparent* to a synthetic route, or else can play a roll in the synthesis.

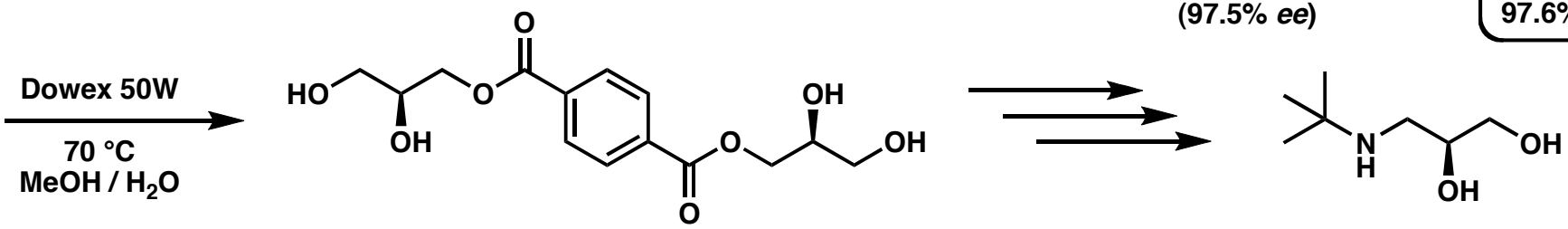


(80% *ee*$_i$)

87% yield
4.6 : 1 dr
(97.5% *ee*)

Calculated

4.5 : 1 dr
97.6% *ee*



82% yield

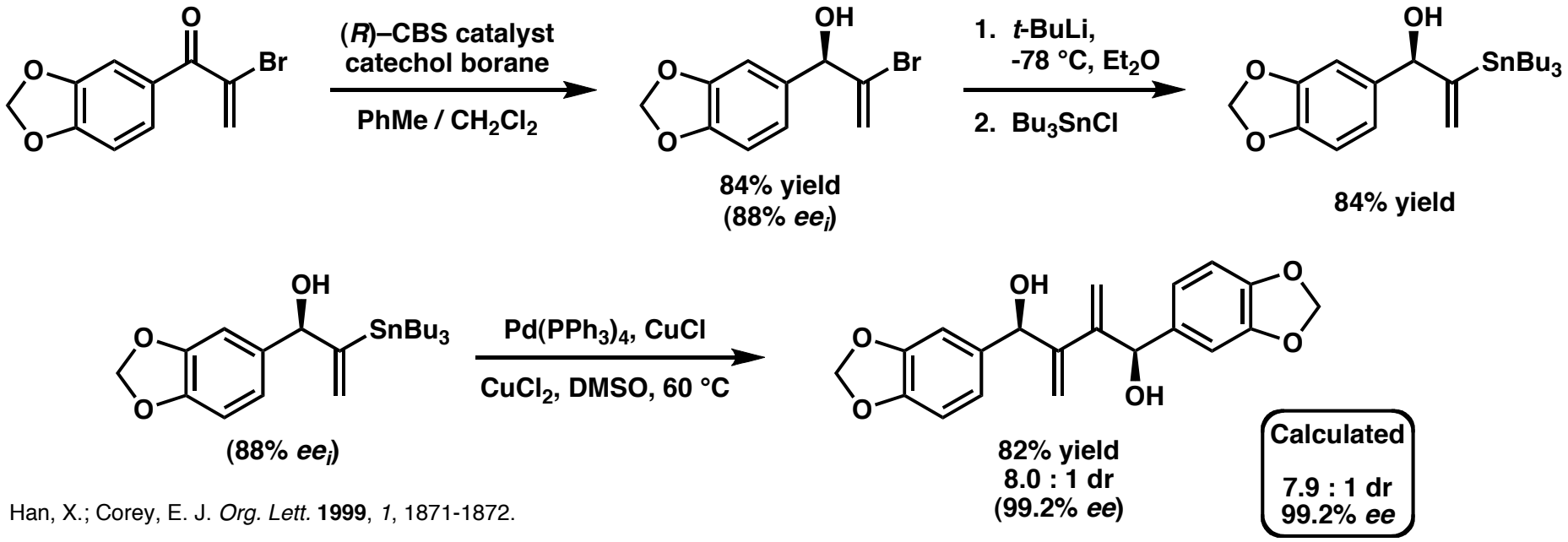
39.1% overall yield
97.5% *ee*

D'Arrigo, P.; Servi, S. *J. Org. Chem.* **1997**, *62*, 6394-6396.

Enantiomeric Enrichment via Duplication

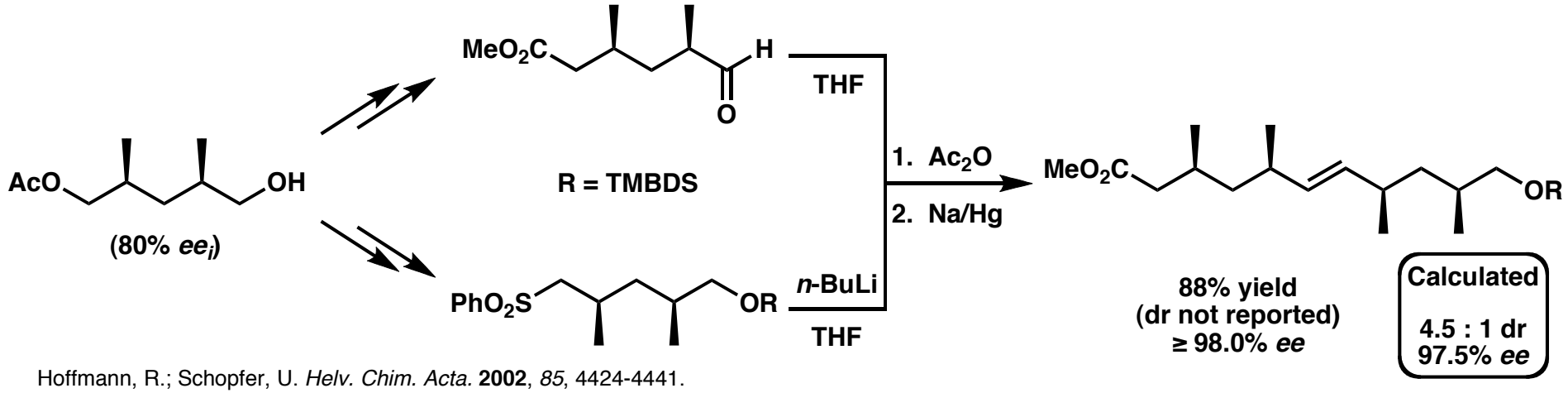
Duplication without Achiral Linkers

• The total synthesis of (–)-Wodeshiol by Corey benefits from Horeau-type *ee* amplification during the key dimerization:



Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871-1872.

• Derivitization and coupling of a common intermediate to boost modest *ee*:

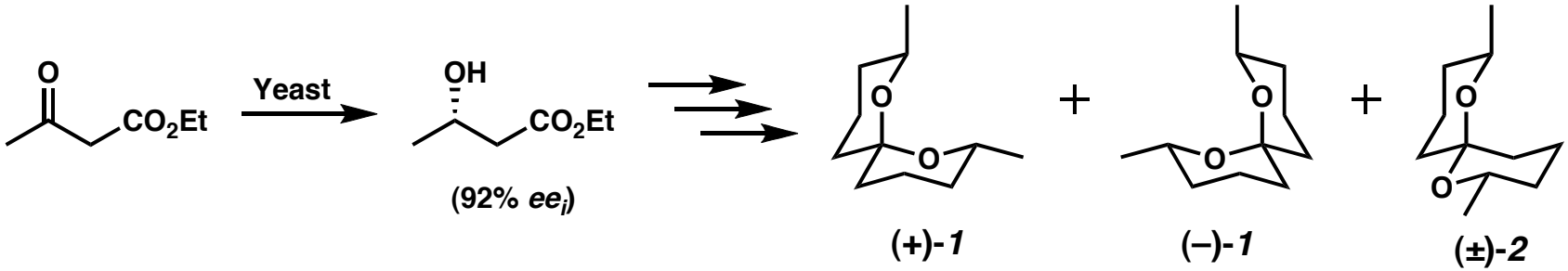


Hoffmann, R.; Schopfer, U. *Helv. Chim. Acta.* **2002**, *85*, 4424-4441.

Enantiomeric Enrichment via Duplication

Controversy over the Synthesis of Carpenter Bee Hormone

• **1981**: Mori and Tanida report the total synthesis of four stereoisomers of 2,8-Dimethyl-1,7-dioxaspiro[5,5]undecane.



• **1984**: Isaksson and coworkers separate the four naturally occuring stereoisomers via liquid chromatography. Their optical rotation values do not match those of Mori *et al.* exactly.

$[\alpha]^{24}$	**(+)-*1***	**(–)-*1***	**(+)-*2***	**(–)-*2***
Mori Values	+ 51.7°	- 51.6°	–	–
Isaksson Values	+ 44.6°	- 44.3°	+ 44.0°	- 44.6°

"We thus conclude that our isolated enantiomers are at least 98% optically pure. Mori and Tanida reported [larger] specific rotations... although their chiral starting material was of only 92% ee*... The reason for this is not clear to us."*

• **1986**: Mori and Tanida report multiple (re)syntheses of **(+)-*1*** and **(-)–*1*** in response to Isaksson's paper.

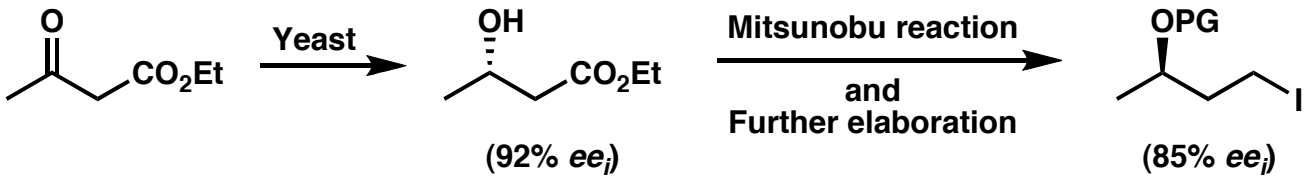
"[Isaksson] challenged our higher values, because we employed [starting material] of only 92% ee*... Apparently they thought that [this] should yield* ***(+)*****-1** *of 92%* ee*."*

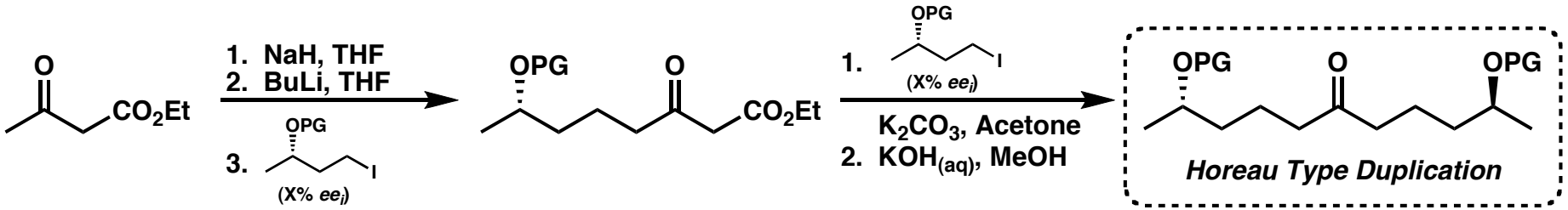
Mori, K.; Tanida. *Tetrahedron*, **1981**, *37*, 3221-3225.
Isaksson, R.; Liljefors, T. *J. Chem. Soc. Chem. Commun.* **1984**, 137-138.
Mori, K.; Watanabe, H. *Tetrahedron*, **1986**, *42*, 295-304.

Enantiomeric Enrichment via Duplication

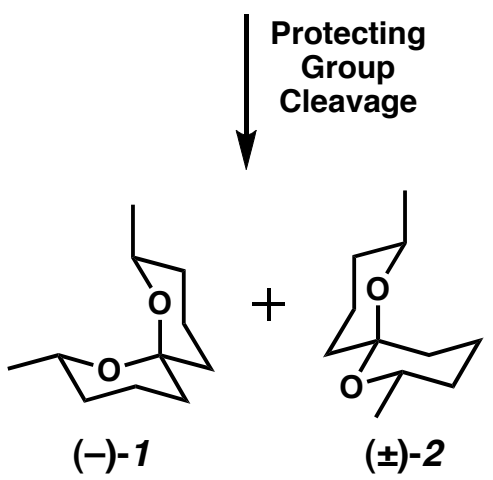
Controversy over the Synthesis of Carpenter Bee Hormone

• **1981, 1986**: Total synthesis and reexamination of 2,8-Dimethyl-1,7-dioxaspiro[5,5]undecane by Mori.





Alcohol Config.	X% ee_i	$[\alpha]^{24}$	Experiment % ee_p	Experiment dr	Calculated % ee_p	Calculated dr
S	92	- 51.6°	99.3	9 : 1	99.6	12 : 1
R	100	+ 59.2°	100	N/A	100	N/A
R	85	+ 58.7°	97.2	6.4 : 1	98.6	6.2 : 1



*"In conclusion... the specific rotations reported for **1** and **2** by Isaksson et al. must be in error. The reason for this is not clear to us."*

Mori, K.; Tanida. *Tetrahedron*, **1981**, *37*, 3221-3225.
Isaksson, R.; Liljefors, T. *J. Chem. Soc. Chem. Commun.* **1984**, 137-138.
Mori, K.; Watanabe, H. *Tetrahedron*, **1986**, *42*, 295-304.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

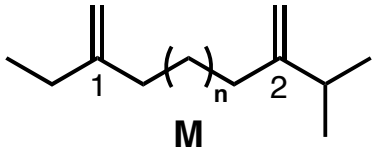
• Do Horeau-type distributions and effects play a role in the generation of two or more stereocenters from a *prochiral* molecule?

- For the case of a molecule **M** bearing two nonequivalent prochiral centers labeled 1 and 2, we assume total conversion of the *intermediates*:

$$\mathbf{r} = \frac{[1R, P] - [1S, P]}{[1R, P] + [1S, P]}$$

$$\mathbf{r_\alpha} = \frac{[1R, 2R] - [1R, 2S]}{[1R, 2R] + [1R, 2S]}$$

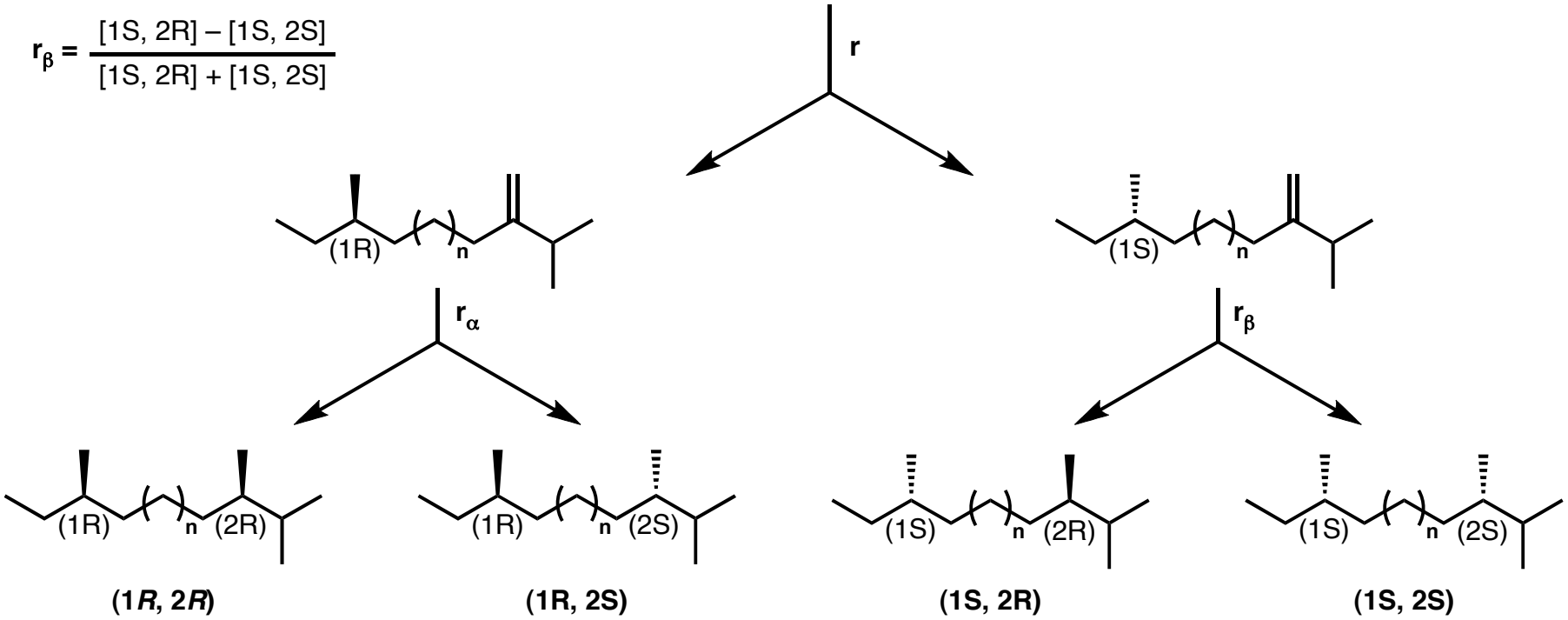
$$\mathbf{r_\beta} = \frac{[1S, 2R] - [1S, 2S]}{[1S, 2R] + [1S, 2S]}$$



M

Route I

Initial Attack at 1



(1*R*, 2*R*) **(1R, 2S)** **(1S, 2R)** **(1S, 2S)**

(1R, 2R) + (1S, 2S) – Diastereomer A

(1R, 2S) + (1S, 2R) – Diastereomer B

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

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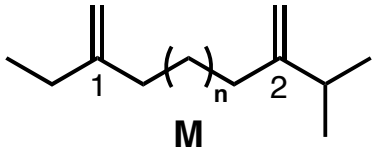


M

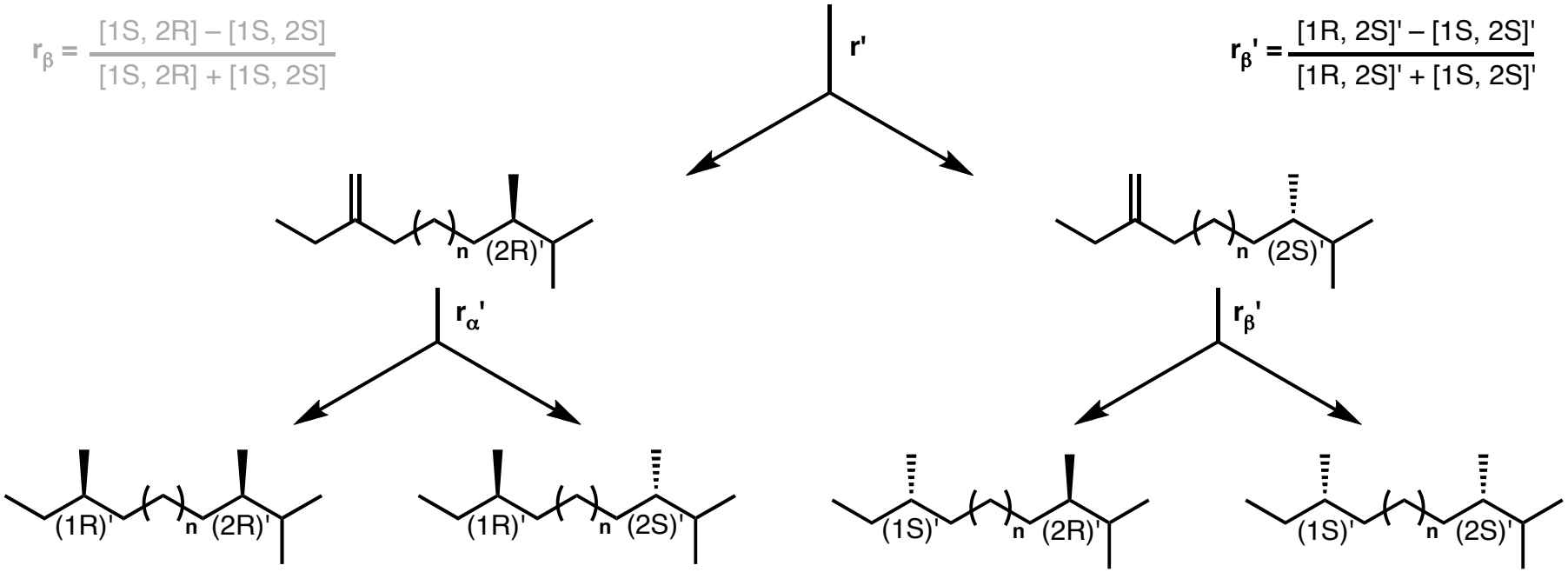
Route II

Initial Attack at 2

$$r' = \frac{[P, 2R]' - [P, 2S]'}{[P, 2R]' + [P, 2S]'}$$

$$r_\alpha' = \frac{[1R, 2R]' - [1S, 2R]'}{[1R, 2R]' + [1S, 2R]'}$$

$$r_\beta' = \frac{[1R, 2S]' - [1S, 2S]'}{[1R, 2S]' + [1S, 2S]'}$$



(1*R*, 2*R*)' **(1R, 2S)'** **(1S, 2R)'** **(1S, 2S)'**

(1R, 2R)' + (1S, 2S)' – Diastereomer A

(1R, 2S)' + (1S, 2R)' – Diastereomer B

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$$r = \frac{[1R, P] - [1S, P]}{[1R, P] + [1S, P]}$$

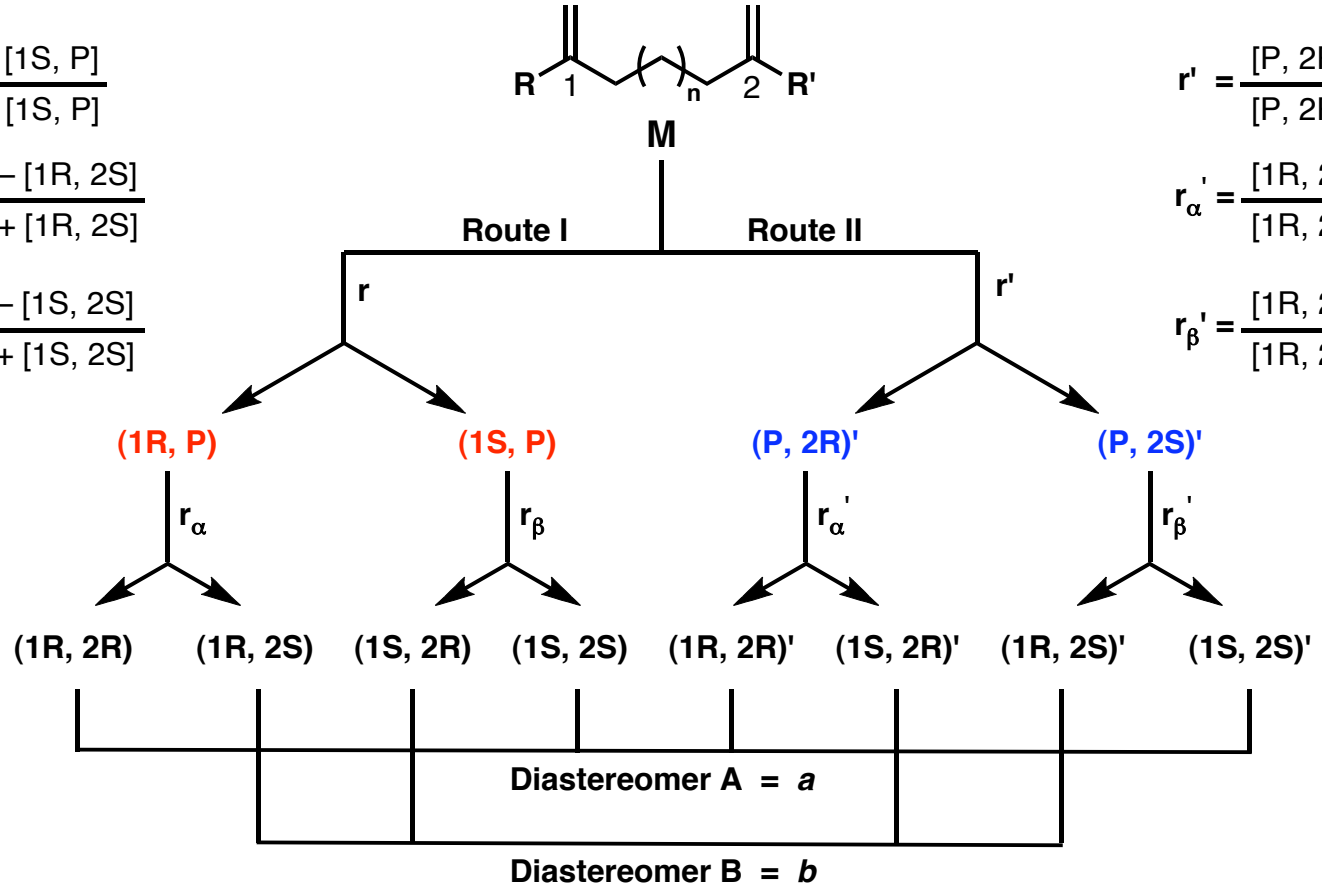
$$r_\alpha = \frac{[1R, 2R] - [1R, 2S]}{[1R, 2R] + [1R, 2S]}$$

$$r_\beta = \frac{[1S, 2R] - [1S, 2S]}{[1S, 2R] + [1S, 2S]}$$

$$r' = \frac{[P, 2R]' - [P, 2S]'}{[P, 2R]' + [P, 2S]'}$$

$$r_\alpha' = \frac{[1R, 2R]' - [1S, 2R]'}{[1R, 2R]' + [1S, 2R]'}$$

$$r_\beta' = \frac{[1R, 2S]' - [1S, 2S]'}{[1R, 2S]' + [1S, 2S]'}$$



• Additional definitions for the diastereomeric ratio, and a term (**i**) to weigh the relative contributions of Routes I and II:

$$\mathbf{dr} = \frac{a}{b} \quad \text{such that } a + b = 1$$

$$\mathbf{i} = \frac{[1R, P] + [1S, P]}{[1R, P] + [1S,P] + [P, 2R]' + [P, 2S]'}$$

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

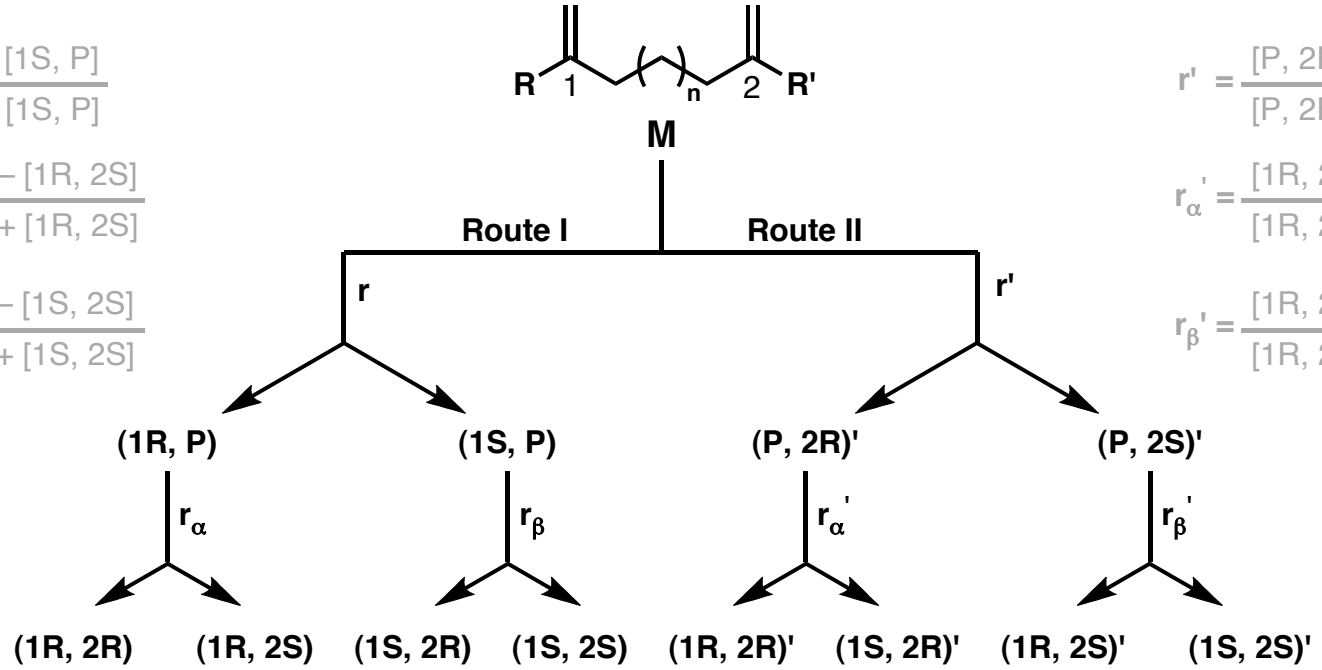
• Do Horeau-type distributions and effects play a role in the generation of two or more stereocenters from a *prochiral* molecule?

- For the case of a molecule **M** bearing two nonequivalent prochiral centers labeled 1 and 2, we assume total conversion of the *intermediates*:

$$r = \frac{[1R, P] - [1S, P]}{[1R, P] + [1S, P]} \qquad r' = \frac{[P, 2R]' - [P, 2S]'}{[P, 2R]' + [P, 2S]'}$$

$$r_\alpha = \frac{[1R, 2R] - [1R, 2S]}{[1R, 2R] + [1R, 2S]} \qquad r_\alpha' = \frac{[1R, 2R]' - [1S, 2R]'}{[1R, 2R]' + [1S, 2R]'}$$

$$r_\beta = \frac{[1S, 2R] - [1S, 2S]}{[1S, 2R] + [1S, 2S]} \qquad r_\beta' = \frac{[1R, 2S]' - [1S, 2S]'}{[1R, 2S]' + [1S, 2S]'}$$



• If the possibility for different stereoselectivities at *each* step is considered, the product *ee* and dr can be expressed as:

$$ee_A = \frac{([1R, 2R]+[1R, 2R]') - ([1S, 2S]+[1S, 2S]')}{([1R, 2R]+[1R, 2R]') + ([1S, 2S]+[1S, 2S]')} = \frac{i\,[(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') - (1-r_\beta')(1-r')]}{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') + (1-r_\beta')(1-r')]}$$

$$ee_B = \frac{([1R, 2S]+[1R, 2S]') - ([1S, 2R]+[1S, 2R]')}{([1R, 2S]+[1R, 2S]') + ([1S, 2R]+[1S, 2R]')} = \frac{i\,[(1-r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') - (1-r_\alpha')(1+r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]}$$

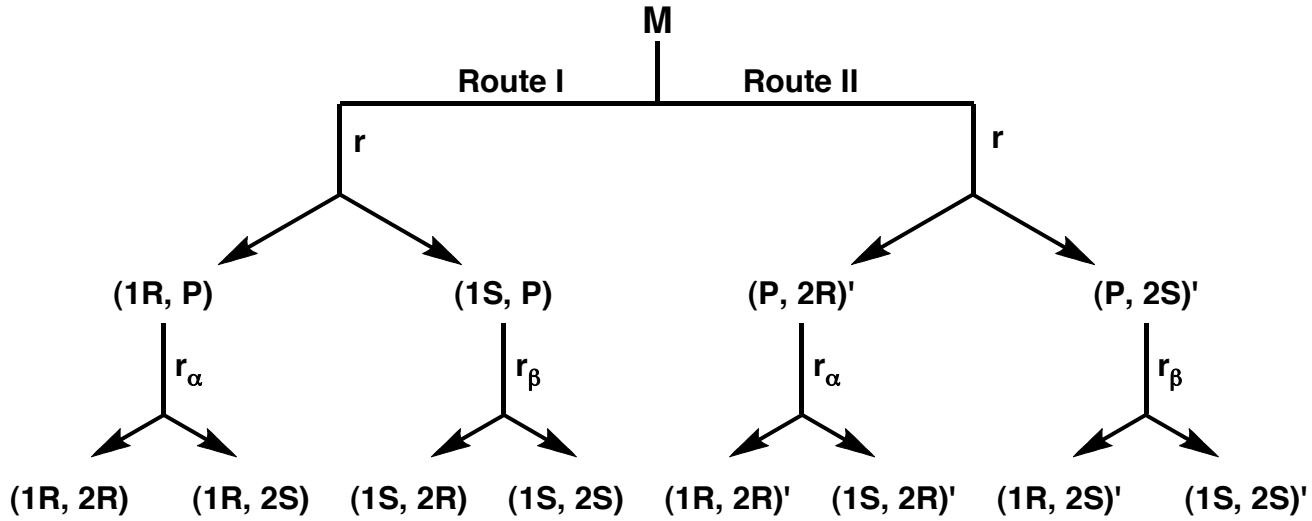
$$dr = \frac{([1R, 2R]+[1R, 2R]') + ([1S, 2S]+[1S, 2S]')}{([1R, 2S]+[1R, 2S]') + ([1S, 2R]+[1S, 2R]')} = \frac{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1+r') + (1-r_\alpha')(1-r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]}$$

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

• Limiting cases of Kagan's calculations for multiple chiral reactions.



• **Assumptions:**
Route I and Route II operate simultaneously and competitively, but have identical selectivities at corresponding steps.

$$\boxed{r = r' \qquad r_\alpha = r_\alpha' \qquad r_\beta = r_\beta'}$$

$$ee_A = \frac{i\,[(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') - (1-r_\beta')(1-r')]}{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') + (1-r_\beta')(1-r')]} \Rightarrow ee_A = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)}$$

$$ee_B = \frac{i\,[(1-r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') - (1-r_\alpha')(1+r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]} \Rightarrow ee_B = (2i-1)\frac{(1-r_\alpha)(1+r) - (1+r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)}$$

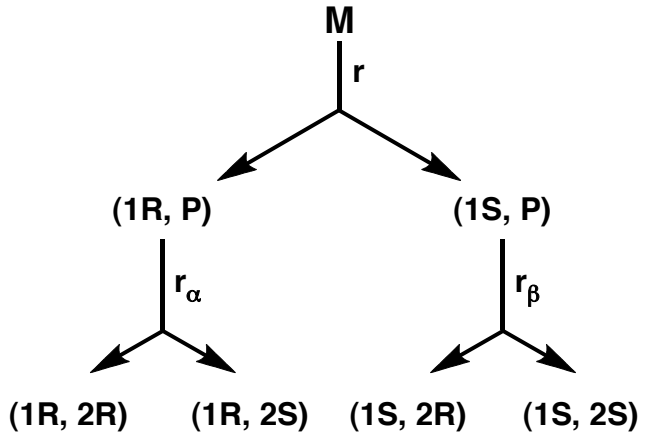
$$dr = \frac{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1+r') + (1-r_\alpha')(1-r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]} \Rightarrow dr = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)}$$

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

• Limiting cases of Kagan's calculations for multiple chiral reactions.



• **Assumptions:**
Route I and Route II are identical, or else one of the Routes dominates the reaction to the point of always occuring first:

$$\boxed{i = 1 \qquad r = r' \qquad r_\alpha = r_\alpha' \qquad r_\beta = r_\beta'}$$

$$ee_A = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)} \Rightarrow ee_A = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)}$$

$$ee_B = (2i-1)\frac{(1-r_\alpha)(1+r) - (1+r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)} \Rightarrow ee_B = \frac{(1-r_\alpha)(1+r) - (1+r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)}$$

$$dr = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)} \Rightarrow dr = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)}$$

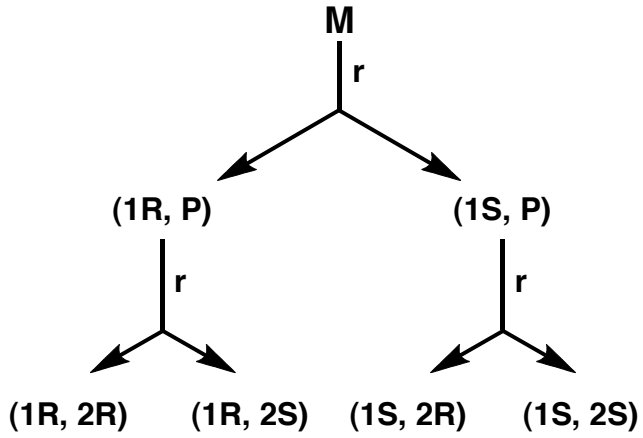
$$\Rightarrow \boxed{dr = \frac{ee_B - r}{r - ee_A}}$$

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

• Limiting cases of Kagan's calculations for multiple chiral reactions.



• **Assumptions:**
All stereoselectivities are identical, regardless of order of transformation or other existing stereocenters:

$$i = 1 \qquad r = r' = r_\alpha = r_\alpha' = r_\beta = r_\beta'$$

$$ee_A = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)} \Rightarrow ee_A = \frac{2r}{1 + r^2}$$

$$ee_B = \frac{(1-r_\alpha)(1+r) - (1+r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)} \Rightarrow ee_B = 0$$

$$dr = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)} \Rightarrow dr = \frac{1 + r^2}{1 - r^2}$$

$$\Rightarrow \quad ee_p = \frac{2 \cdot ee_i}{1 + (ee_i)^2} \qquad dr = \frac{1 + (ee_i)^2}{1 - (ee_i)^2}$$

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

- **Summary:**
  - In the case of a double enantioselective reaction, the *ee* of the major (**A**) and minor (**B**) diastereomers and the dr are:

$$ee_A = \frac{i\,[(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') - (1-r_\beta')(1-r')]}{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\alpha')(1+r') + (1-r_\beta')(1-r')]}$$

$$ee_B = \frac{i\,[(1-r_\alpha)(1+r) - (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') - (1-r_\alpha')(1+r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]}$$

$$dr = \frac{i\,[(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1+r') + (1-r_\alpha')(1-r')]}{i\,[(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)] + (1-i)\,[(1+r_\beta')(1-r') + (1-r_\alpha')(1+r')]}$$

Substrate Control

  - When the selectivities for the reactions are independent of the *initial* reaction site (Same selectivities along Route I and II):

$$ee_A = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1+r_\alpha)(1+r) + (1-r_\beta)(1-r)} \qquad ee_B = (2i-1)\frac{(1-r_\alpha)(1+r) - (1+r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)} \qquad dr = \frac{(1+r_\alpha)(1+r) - (1-r_\beta)(1-r)}{(1-r_\alpha)(1+r) + (1+r_\beta)(1-r)}$$

  - When the Routes and their selectivities are identical – OR – When one Route is highly favored ($\mathbf{r \neq r_\alpha \neq r_\beta}$):

$$\mathbf{dr = \frac{ee_B - r}{r - ee_A}}$$

  - When the selectivities are equal, and independent of all else ($\mathbf{r = r_\alpha = r_\beta}$):

$$\mathbf{ee_A = \frac{2r}{1 + r^2}} \qquad \mathbf{ee_B = 0} \qquad \mathbf{dr = \frac{1 + r^2}{1 - r^2}}$$

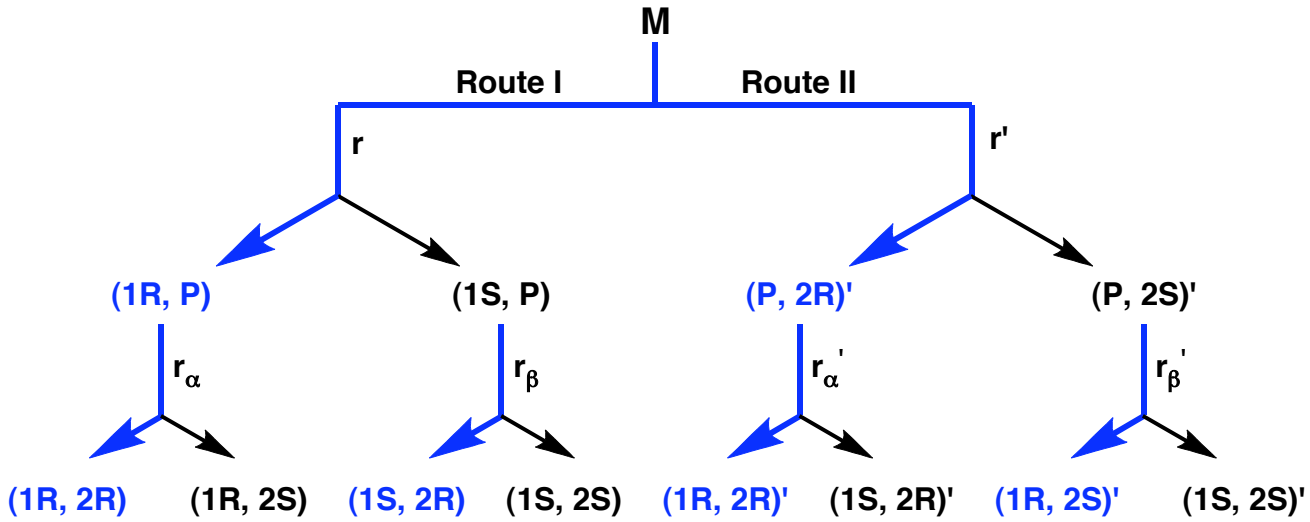
Catalyst Control

Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Remote Stereocenter Generation and Statistical Distributions

• Amplifications originating from double enantioselective reactions upon a bis-prochrial molecule:



• For a situation in which the chiral catalsyt or reagent employed favors the formation of the *R* stereocenter.

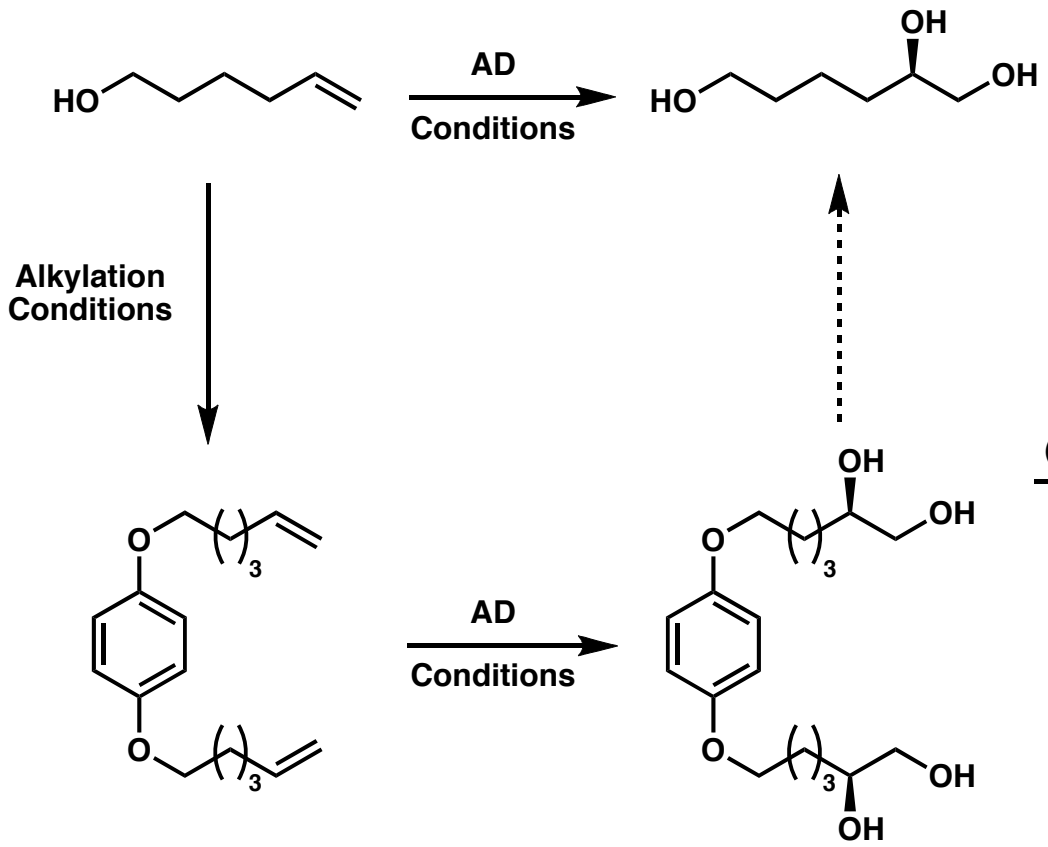
- Intial reaction creates an excess of **(1R, P)**, **(P, 2R)'** relative to **(1S, P)**, **(P, 2S)'**.
- Futher reaction of **(1R, P)** favors **(1R, 2R)**. Any **(1R, 2S)** produced has *no effect* on ee_A.
  (The same holds for the analogous path in Route II)
- Any reaction of **(1S, P)** generated in the first step favors **(1S, 2R)**, minimizing **(1S, 2S)**.
  (Again, also for Route II)

Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.
Baba, S.; Sartor, K.; Kagan, H. *Bull. Soc. Chim. Fr.* **1994**, 525-533.

Multiple Enantioselective Transformations

Synthesis and Multiple Prochiral Centers

• Obtaining enantioenriched 1,2-diols via asymmetric dihydroxylation of the corresponding terminal olefins afforded lower than anticipated *ee* values in some cases.



Ligand $(DHQD)_2$ –	Oxidant	% ee_p
-PHAL	$K_3Fe(CN)_6$	85.7
-PHAL	I_2	83.2
-PYR	$K_3Fe(CN)_6$	95.6
-PYR	I_2	89.0
-AQN	$K_3Fe(CN)_6$	84.0
-AQN	I_2	52.8

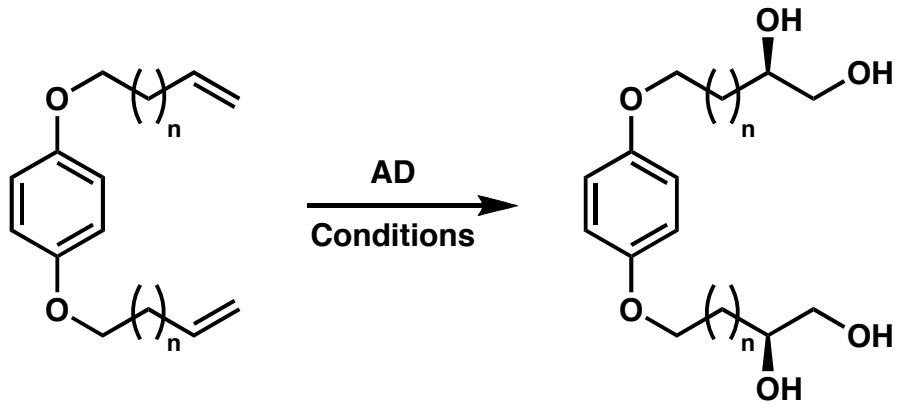
Ligand $(DHQD)_2$ –	Oxidant	% ee_p	dr
-PHAL	$K_3Fe(CN)_6$	98.9	6.7
-PHAL	I_2	97.0	4.1
-PYR	$K_3Fe(CN)_6$	99.4	9.5
-PYR	I_2	70.4	1.4
-AQN	$K_3Fe(CN)_6$	98.1	5.1
-AQN	I_2	97.6	4.6

Hoye, T.; Mayer, M. *J. Org. Chem.* **1998**, *63*, 8554-8557.

Multiple Enantioselective Transformations

Synthesis and Multiple Prochiral Centers

- Horeau-type amplification of 1,2-diols via double asymmetric dihydroxylation gave much better *ee* values for many conditions... But at a cost.



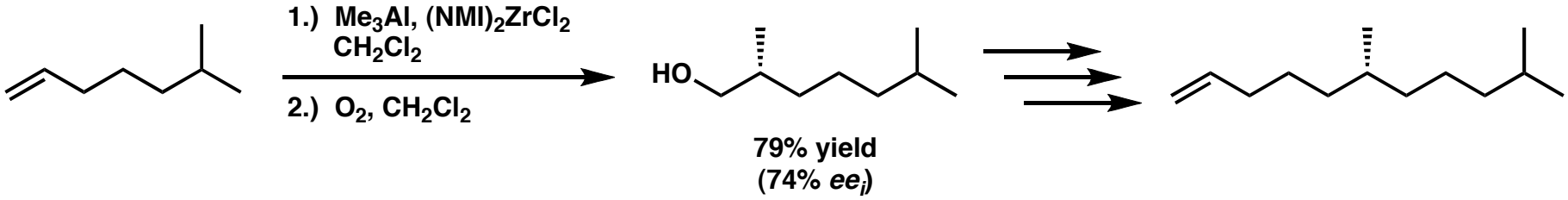
n	Ligand $(DHQD)_2$ –	Oxidant	% ee_p	dr	% ee_i (calculated)	% Yield lost to *meso*
0	-PHAL	$K_3Fe(CN)_6$	99.2	7.9	88.1	11.2
0	-PYR	$K_3Fe(CN)_6$	84.8	1.9	55.6	34.6
0	-AQN	$K_3Fe(CN)_6$	99.9	24.5	96.0	3.9
3	-PHAL	I_2	97.0	4.1	78.0	19.6
3	-PYR	$K_3Fe(CN)_6$	99.4	9.5	90.0	9.5
3	-PYR	I_2	70.4	1.4	41.2	41.2
5	-PHAL	$K_3Fe(CN)_6$	97.6	4.6	80.0	18.0
5	-PYR	I_2	89.7	2.3	62.3	30.6

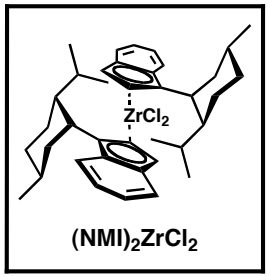
Hoye, T.; Mayer, M. *J. Org. Chem.* **1998**, *63*, 8554-8557.

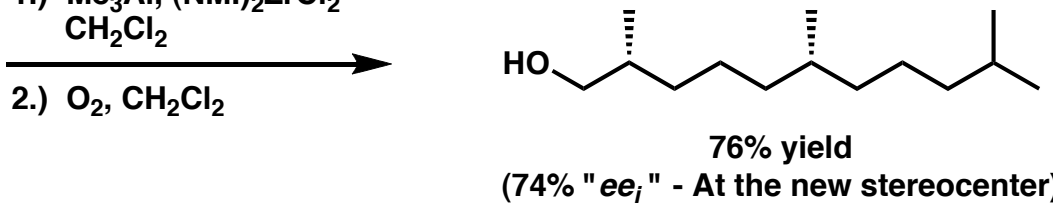
Multiple Enantioselective Transformations

Synthesis and Multiple Prochiral Centers

- Stepwise transformations show similar mathematical behavior in the absence of substrate control.







- Knowing the "local" *ee* values at each of the stereocenters individually allows for Horeau predictions, which can be checked against experimental findings:

Calculated Values

$$ee_p = \frac{2 \cdot ee_i}{1 + ee_i^2} = 95.6\% \qquad 96.7\% = ee_p$$

$$dr = \frac{1 + ee_i^2}{1 - ee_i^2} = 3.42 \qquad 3.32 = dr$$

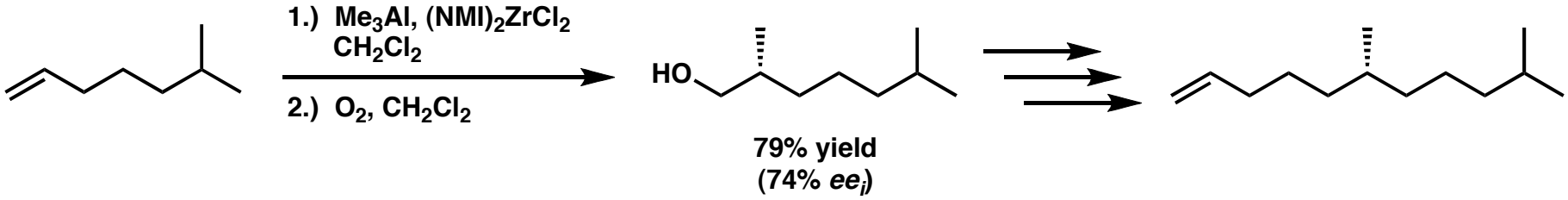
Experimentally Determined Values

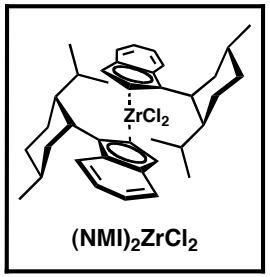
Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253-3256.

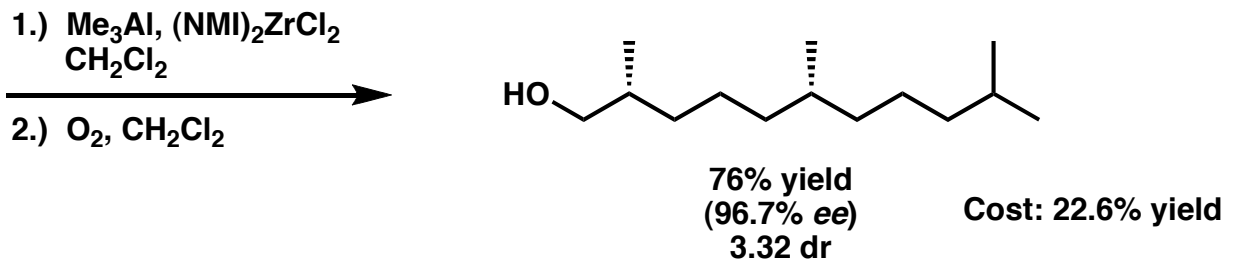
Multiple Enantioselective Transformations

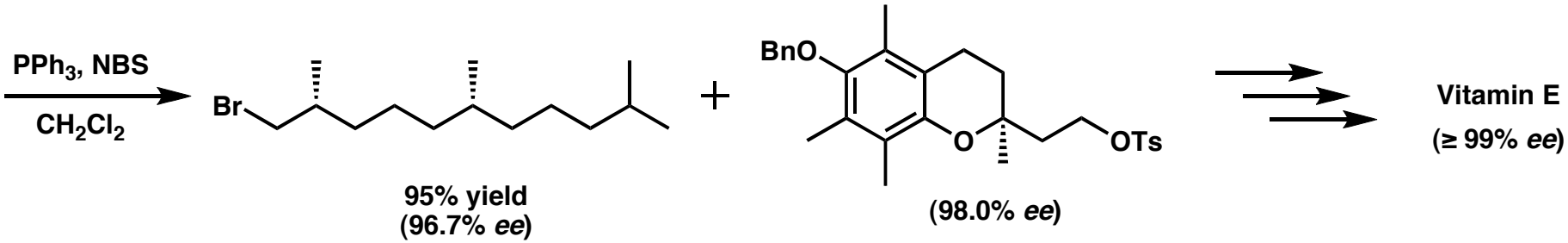
Synthesis and Multiple Prochiral Centers

• Stepwise transformations show similar mathematical behavior in the absence of substrate control.









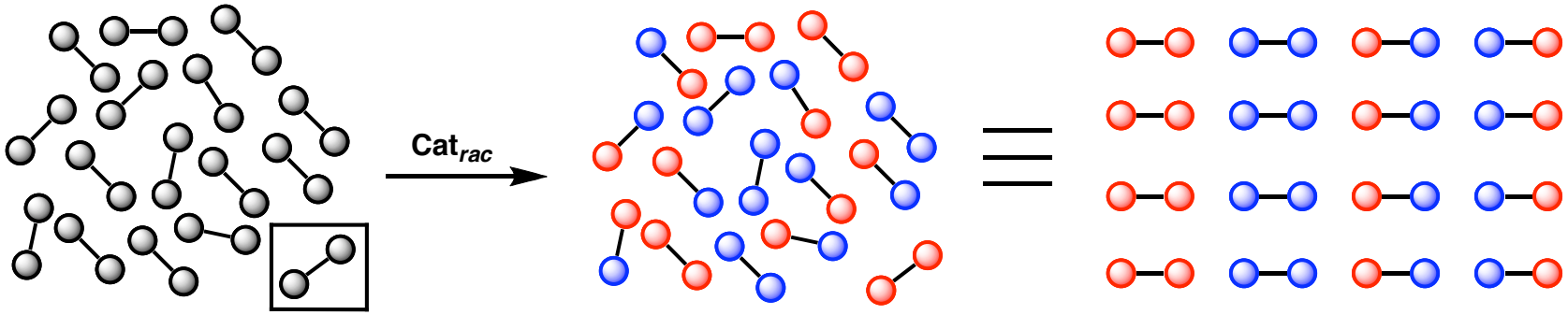
• Even in cases of sequential enantioselective reactions, amplification of product *ee* may result.

Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253-3256.

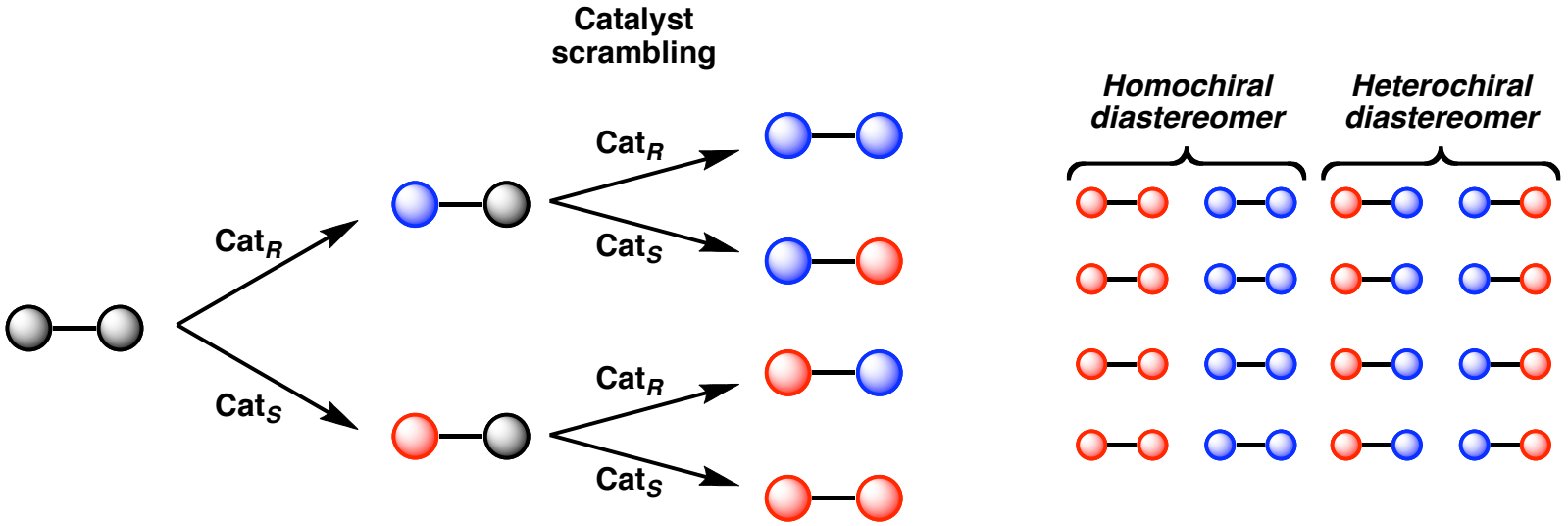
Multiple Enantioselective Transformations

Applications Beyond Amplification

- Is it possible to estimate the enantioselectivity of a chiral catalyst from its racemic mixture?



- Equal opportunity to interact with either sense of the catalyst at either step leads to a racemate. In the absence of substrate influence, equal quantities of the two diastereomers are expected. . .

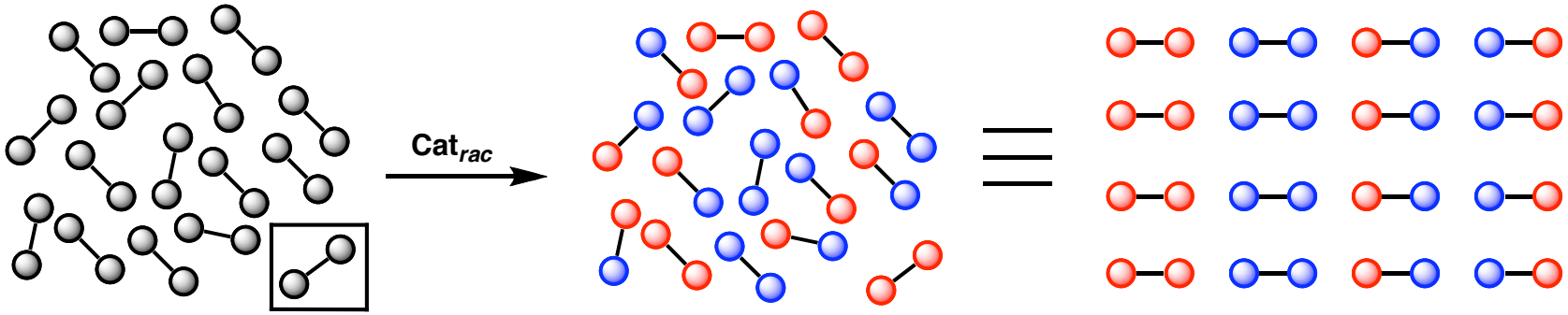


Lagasse, F.; Tsukamoto, M.; Kagan, H. *J. Am. Chem. Soc.* **2003**, *125*, 7490-7491.

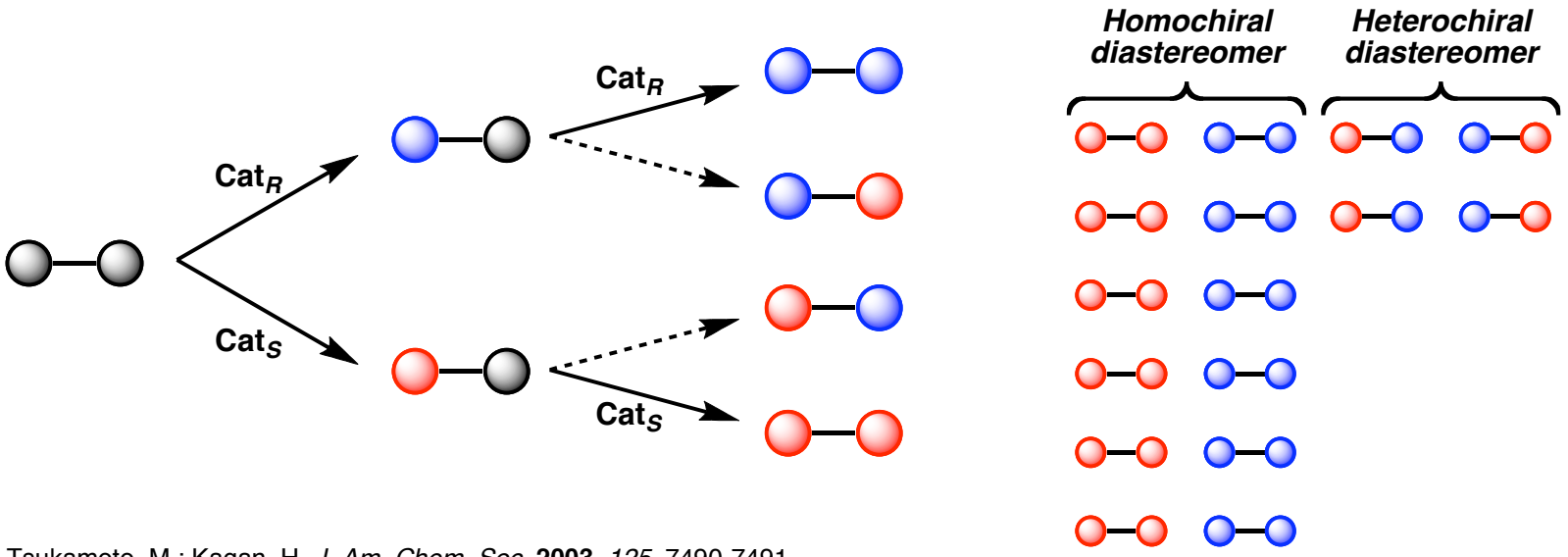
Multiple Enantioselective Transformations

Applications Beyond Amplification

- Is it possible to estimate the enantioselectivity of a chiral catalyst from its racemic mixture?



- What would occur if, after the initial reaction, the catalyst did *not* release the substrate? What if it could continue to act upon the remaining prochiral site?
- The heterochiral diastereomer would then be afforded *only* as a result of "catalyst errors", and **(dr ≠ 1)** would be expected.



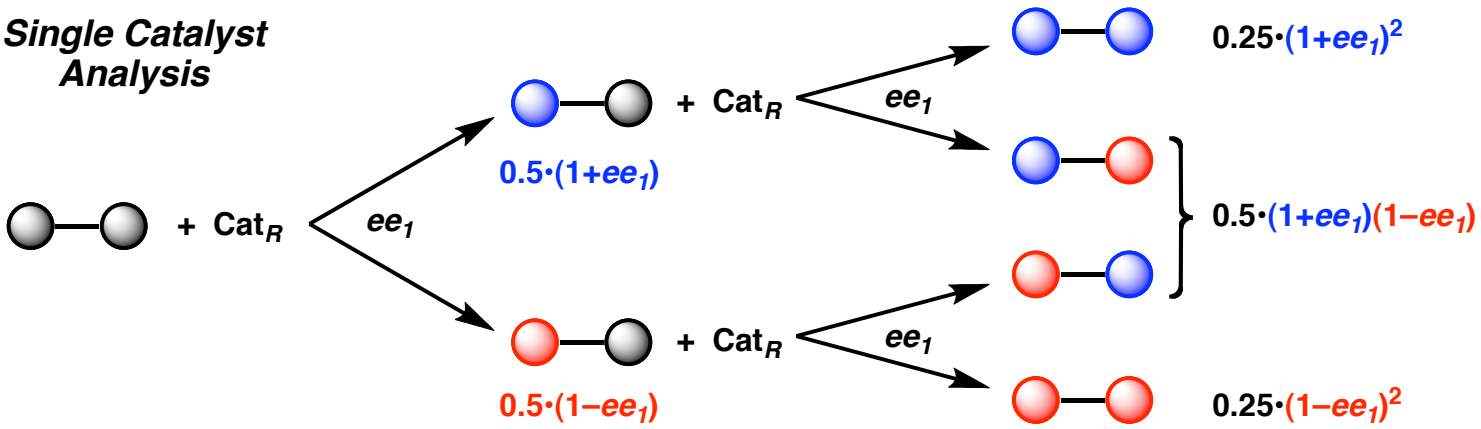
Lagasse, F.; Tsukamoto, M.; Kagan, H. *J. Am. Chem. Soc.* **2003**, *125*, 7490-7491.

Multiple Enantioselective Transformations

Applications Beyond Amplification

- Is it possible to estimate the enantioselectivity of a chiral catalyst from its racemic mixture?
- For a single catalyst of a racemic mixture interacting with both prochiral sites of a symmetric substrate:

Single Catalyst Analysis



Note: ee_2 in this case refers to the local selectivity at the second forming center.

- If the catalyst operates on both prochiral sites with equal selectivity, then $ee_1 = ee_2$ holds true.

$$ee_{homo} = \frac{2\cdot(ee_1)}{1 + (ee_1)^2} = 0$$

For every reaction of this molecule with **Cat$_R$** there occurs a corresponding reaction of another molecule with **Cat$_S$**.

$$dr = \frac{1 + (ee_1)^2}{1 - (ee_1)^2} \Rightarrow de_{homo} = (ee_1)^2$$

Both **Cat$_R$** and **Cat$_S$** will afford the same ratio of homorchiral to heterochiral products.

$$ee_1 \approx \sqrt{(de_{homo})}$$

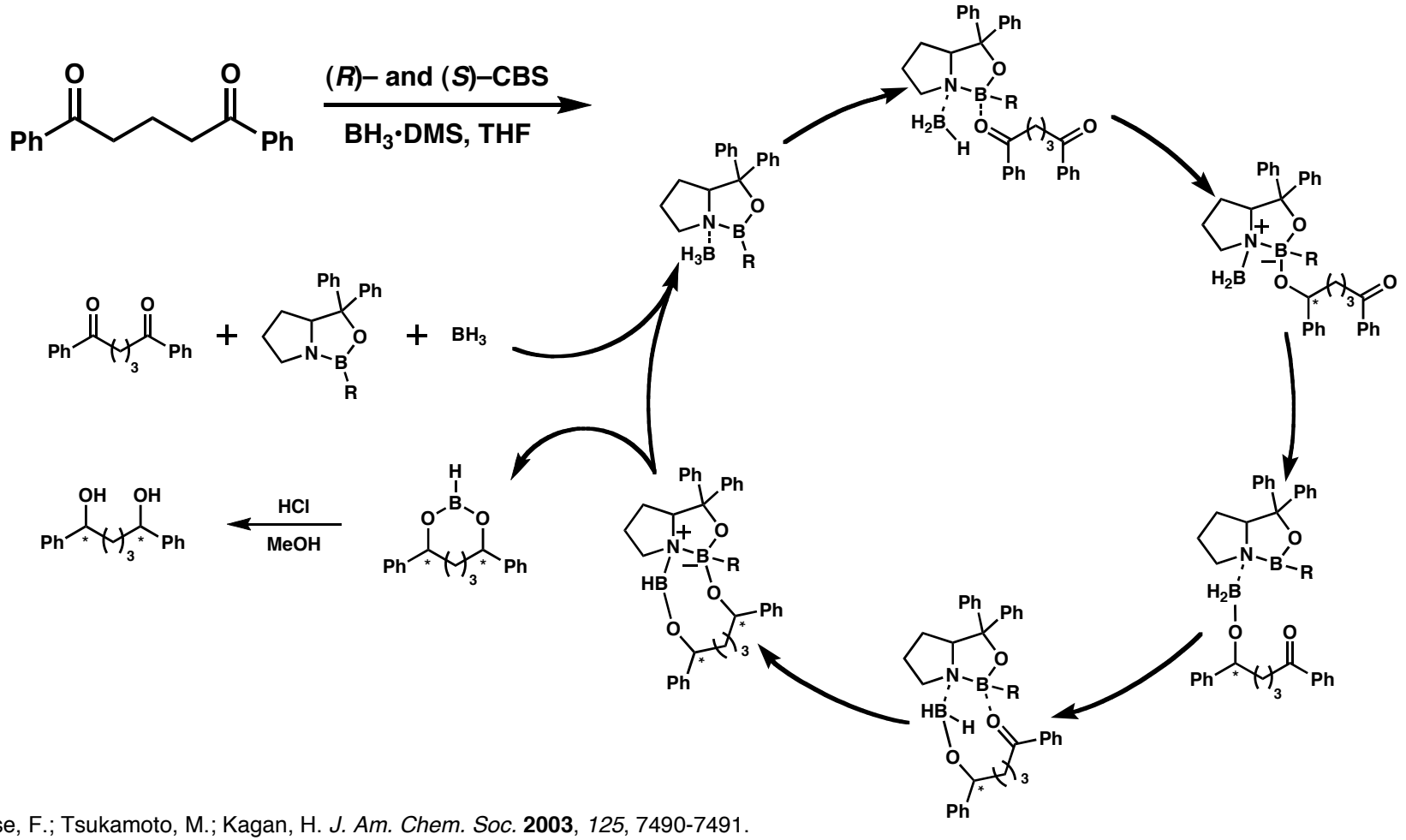
Lagasse, F.; Tsukamoto, M.; Kagan, H. *J. Am. Chem. Soc.* **2003**, *125*, 7490-7491.

Multiple Enantioselective Transformations

Applications Beyond Amplification

- Is it possible to estimate the enantioselectivity of a chiral catalyst from its racemic mixture?
- **Guiding conditions and critical assumptions:**

1.) For any given substrate with two prochiral sites, a single catalyst molecule must perform *both* reactions (No scrambling).
2.) After a single reaction, the newly formed stereocenter must have *no influence* on further selectivity (Zero substrate control).
3.) The catalyst selectivity must be *identical* at both prochiral sites, regardless of the order of reaction (***ee*$_1$ = *ee*$_2$**).



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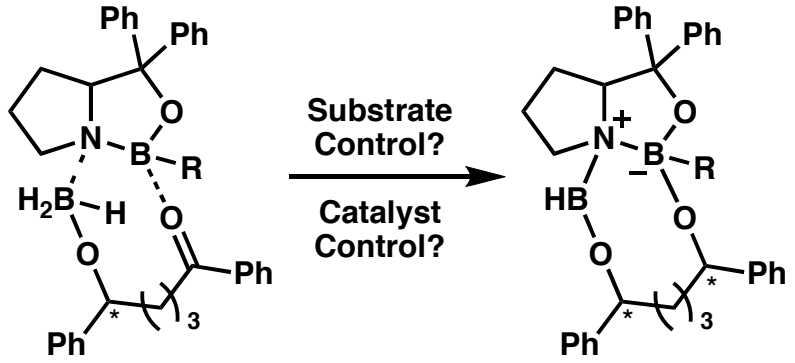
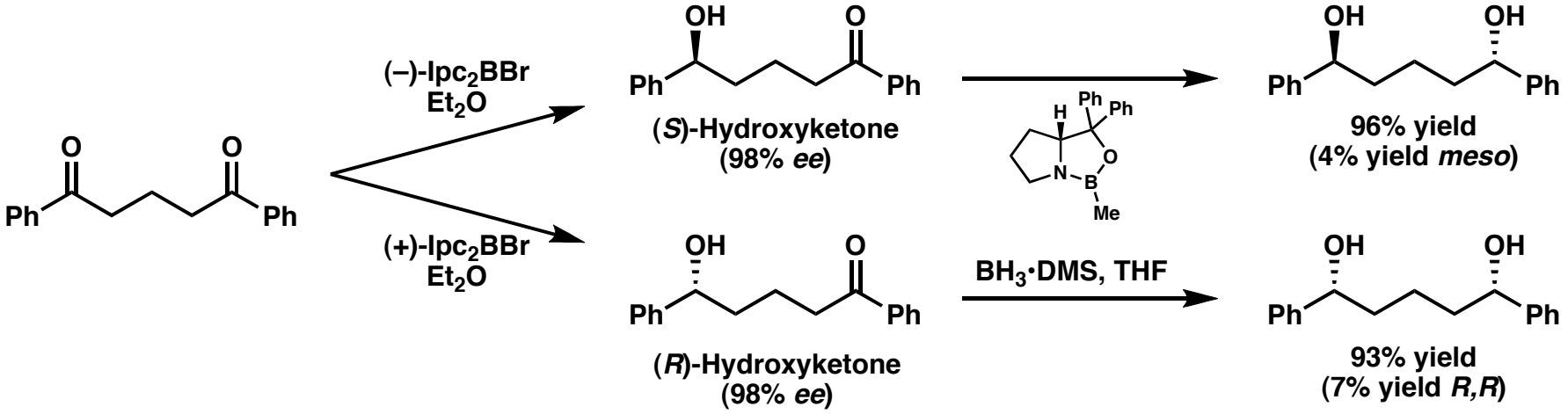


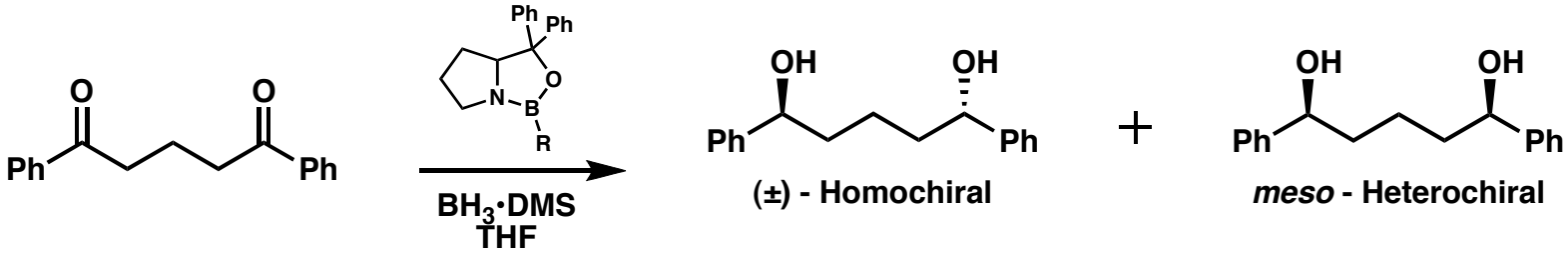


Lagasse, F.; Tsukamoto, M.; Kagan, H. *J. Am. Chem. Soc.* **2003**, *125*, 7490-7491.

Multiple Enantioselective Transformations

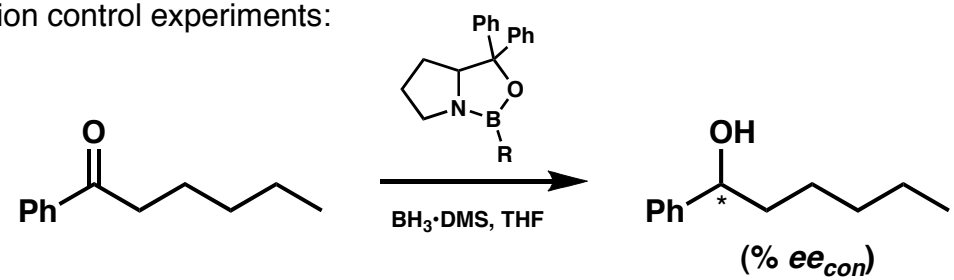
Applications Beyond Amplification

• Both racemic and enantioenriched catalysts were employed, and ***ee*$_1$** values were calculated from ***de*** data.



Catalyst R	Catalyst Config.	% de_{homo}	dr	% ee_1 (calculated)	% ee_{homo} (measured)	% ee_{homo} (calculated)
H	*R*	87.0	14.3	93.2	≥ 99.0	99.8
H	*rac*	86.0	13.3	92.7	—	—
Me	*S*	81.0	9.5	90.0	≥ 99.0	99.4
Me	*rac*	83.0	10.8	91.1	—	—
OMe	*R*	89.0	17.2	94.3	≥ 99.0	99.8
OMe	*rac*	82.0	10.1	90.6	—	—

• Single-reduction control experiments:



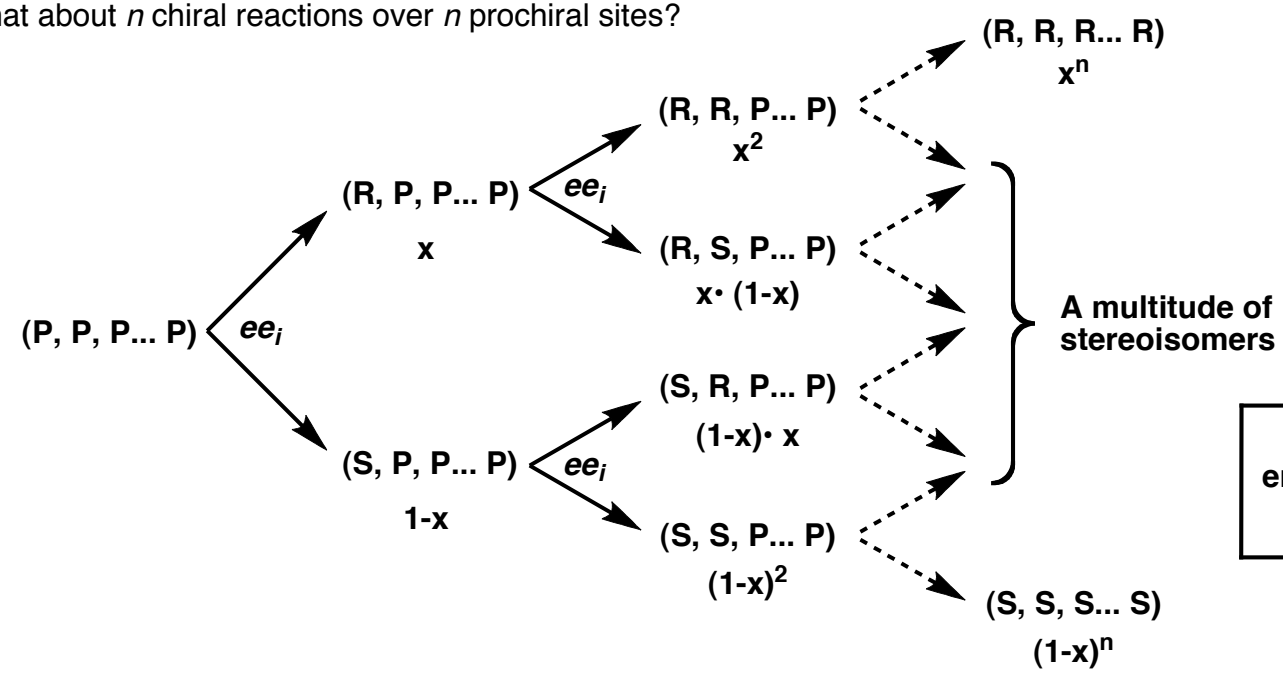
Catalyst R	Catalyst Config.	% ee_{con}	% ee_1 (calculated)
H	*R*	82.0	93.2
Me	*S*	87.0	90.0

Lagasse, F.; Tsukamoto, M.; Kagan, H. *J. Am. Chem. Soc.* **2003**, *125*, 7490-7491.

Multiple Enantioselective Transformations

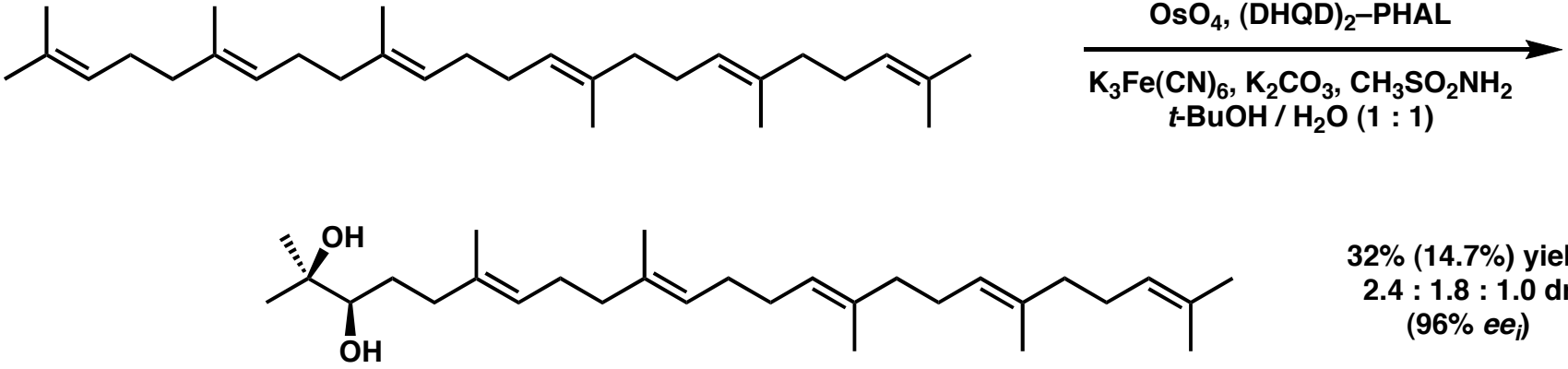
*n*th *Order Amplifications*

- What about *n* chiral reactions over *n* prochiral sites?



$$ee_p = \frac{x^n - (1-x)^n}{x^n + (1-x)^n}$$

$$er_p = \frac{x^n}{(1-x)^n} = \left(\frac{x}{(1-x)}\right)^n = (er_i)^n$$



32% (14.7%) yield
2.4 : 1.8 : 1.0 dr
(96% *ee*$_i$)

Crispino, G.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273-4273.
Crispino, G.; Ho, P. T.; Sharpless, K.B. *Science* **1993**, *259*, 64-66.
Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.

Multiple Enantioselective Transformations

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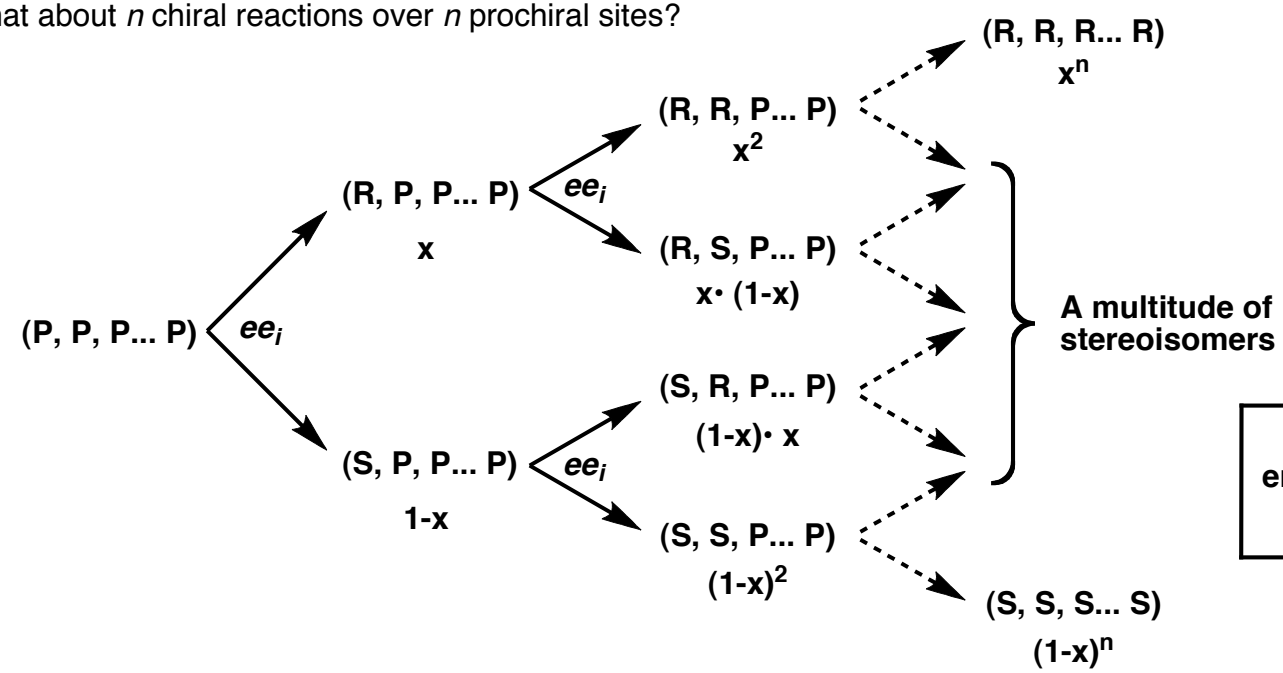
- What about *n* chiral reactions over *n* prochiral sites?



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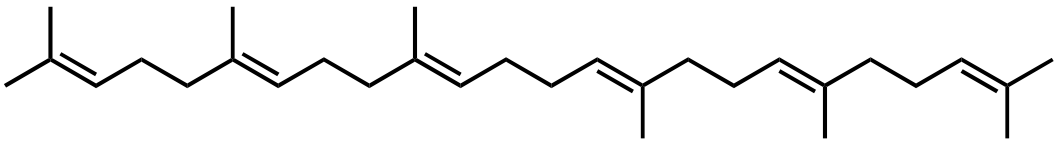
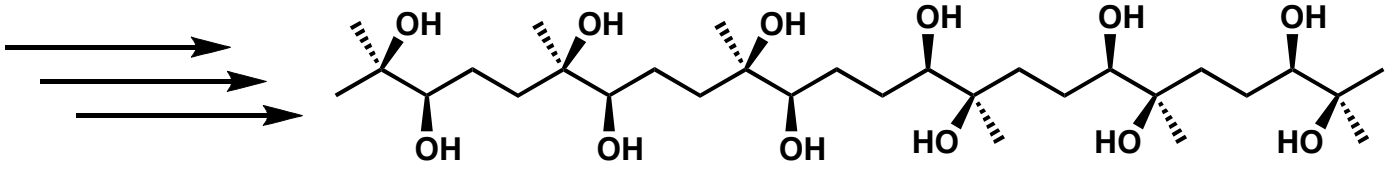


OsO_4, $(DHQD)_2$–PHAL

$K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$

t-BuOH / H_2O (1 : 1)



$er_p = 13{,}841{,}287{,}201 \approx 10^{10}$

$ee_p = 99.99999998\%$

78.9% yield

9.7% yield for *all others*

(34 products, 718 paths!)

Crispino, G.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273-4273.

Crispino, G.; Ho, P. T.; Sharpless, K.B. *Science* **1993**, *259*, 64-66.

Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515-524.

Summary and Conclusion

- Dimerization of a chrial compound, whether via an achiral linker or direct coupling, will result in a products boasting an *ee* value higher than the starting material employed. This occurs by virtue of the forming *meso* diastereomer, which allows for removal of racemic material.

- Multiple enantioselective transformations will result in an increase in product *ee* relative to the value expected for a single reaction. This occurs by virtue of the heterochiral diastereomer acting as a 'buffer' against formation of the undesired enantiomer.

- In both cases, the cost paid for an increase in *ee* is always material lost in the form of undesired diastereomers. The lower ee_i is, the higher this cost becomes.

- Horeau-type amplifications in *ee* are exponential in relation to the number of duplications or enantioselective transformations.

- *All* of the preceding cases assume *zero* substrate control! The equations discussed are *approximations* and may not be applicable to all cases. However, they serve as an excellent starting point for many systems, and have numerous extensions with interesting applications.

Dimerizations or Double Enantioselective Transformations with all $r = ee_i$

$$ee_p = \frac{2 \cdot ee_i}{1 + ee_i^2}$$

$$dr = \frac{1 + ee_i^2}{1 - ee_i^2}$$

Double Enantioselective Transformations with

$r \neq r_\alpha \neq r_\beta$

$$dr = \frac{ee_B - r}{r - ee_A}$$