Stereoselective Organic Synthesis

Prabhat Arya

Professor and Leader, Chemical Biology Program
Dean, Academic Affairs, Institute of Life Sciences
(An Associate Institute of University of Hyderabad Supported by Dr. Reddy’s)
University of Hyderabad Campus
Gachibowli, Hyderabad 500046, India

Adjunct Professor, Biochemistry, McGill University
Member, Ottawa Institute of Systems Biology

tel: (+91) (40) 6657 1500
e mail: prabhata@ilsresearch.org
website: http://www.ilsresearch.org
Stereoselective Nucleophilic Addition to Carbonyl Group and Enantioselective Oxidation
Outline

• Nucleophilic addition to carbonyl group
• Cram, Felkin-Anh, chelation and dipolar models
• 1,2 Asymmetric induction in carbonyl addition
• 1,3 Asymmetric induction in carbonyl addition
• Enantioselective carbonyl reduction (Masamune, Corey)
• Diastereoselective oxidation
• Enantioselective oxidation (Sharpless and Jacobsen)
• Enantioselective synthesis examples
Examples of Stereoselective Nucleophilic Addition to Carbonyl Group

1,2 Asymmetric Induction
Cram’s Rule

1,2 Asymmetric Induction

Increase in stereoselectivity
large difference between S and M

Decrease in stereoselectivity
increasing the size of R

- no chelating groups in the substrate other than the carbonyl group
- no polar group is attached to the chiral centre

Cram’s Rule: J Am Chem Soc 5828 (1952)
The Cyclic Model for 1,2 Asymmetric Induction

1,2 Asymmetric Induction

Use models here

J Am Chem Soc, 2748 (1959)
The Dipolar Model (Cornforth’s Model)

1,2 Asymmetric Induction

\[
\text{S} \quad \text{L} \quad \text{Nu} \quad \text{M} \\
\text{Cl} \quad \text{R} \\
\text{Me} \quad \text{H} \\
\text{Cl} \quad \text{Ph} \\
\text{Cl} \quad \text{Ph}
\]

\[
\text{M-Nu} \rightarrow \\
\text{S} \quad \text{L} \quad \text{Nu} \quad \text{OH} \\
\text{Cl} \quad \text{R} \\
\text{Me} \quad \text{H} \\
\text{Cl} \quad \text{Ph} \\
\text{Cl} \quad \text{Ph}
\]

Use models here

J Chem Soc, 112 (1959)
1,2 Asymmetric Induction

Cram Model

Felkin-Anh Model

Use models here
1,2 Asymmetric Induction
1,2 Asymmetric Induction

Use models here

1,2 Asymmetric Induction

Felkin Anh Products

MeLi or MeMgBr  dr: 2:1
MeTi(OiPr)_3  dr: 88:12

Taken from Book: Classics in Stereoselective Synthesis, Chapter 2
1,2 Asymmetric Induction

Felkin Anh Like

Use models here

dr: >100:1

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
1,2 Asymmetric Induction

Take from Book: *Classics in Stereoselective Synthesis*, Chapter 2
1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents
Use models here

\[ \text{E-crotyl} \]

\[ \text{Z-crotyl} \]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5
1,2 Asymmetric Induction: Diastereoselective Allylation with Chiral Boron Reagents
Enantioselective Organoborane Approach to Carbon-Carbon Bond Formation

Stereoelectronic Effect

Use models here

Use models here

Matched case (with RR tartrate), dr (A+B) = 91 : 9

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5
Use models here

$\text{from SS tartrate}$

mismatched case (with SS tartrate), $\text{dr (A+B)} = 2 : 98$

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5
Favored Transition State

Disfavored Transition State
Derived from (+) pinene

Use models here

matched case (+) pinene reagent
dr (A+B) = 98 : 2

mismatched case (-) pinene reagent
dr (A+B) = 5 : 95

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5
Derived from (+) pinene

Use models here

matched case (+) pinene reagent
\[ \text{dr (A+B)} = 92 : 8 \]

mismatched case (-) pinene reagent
\[ \text{dr (A+B)} = 5 : 95 \]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 5
**Favored Transition State**

**Disfavored Transition State**

*Si phase attack*

*Re phase attack*
**Favored Transition State**

- Si phase attack

**Disfavored Transition State**

- Re phase attack

Felkin

- favored

anti Felkin

Use models here
Disfavored Transition State

Si phase attack

Re phase attack

Favored Transition State

Felkin

anti Felkin

Use models here

Favored

anti Felkin

favored

A

B
1,3 Asymmetric Induction: Stereogenic Centre \( \beta \) to the Carbonyl Group
Use models here

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
Use models here

\[ \text{Felkin control} \]

\[ \text{chelation control} \]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
Regents-based Alteration in 1,3 Asymmetric Induction

Use models here

[Chemical reaction diagram]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
Regents-based Alteration in 1,3 Asymmetric Induction

External hydride delivery

Internal hydride delivery

Use models here

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 2
Enantioselective Reducing Agents
Catalytic Chiral Reducing Agent

Use models here

S-Proline

0.1 eq A/BH₃, THF

A and BH₃ are not reducing agents
The Proposed Catalytic Cycle

Use models here

An Enantioselective Synthesis α Amino Acids

Enantioselective Oxidation
Simple Oxidizing Agents

DMSO-DCC Oxidation

DMSO-Oxalyl Chloride Oxidation (Swern)
Oxidation of C=C Bond

\[ \text{R} = \text{H} + \text{MnO}_4 \rightarrow \text{R} - \text{H} + \text{MnO}_4^- + \text{H}_2\text{O} \rightarrow \text{R} - \text{H} + \text{MnO}_2 \]

\[ \text{R} = \text{H} + \text{OsO}_4 \rightarrow \text{R} - \text{H} + \text{OsO}_4^- + \text{H}_2\text{O} \rightarrow \text{R} - \text{H} + \text{R}_3\text{N} + \text{OsO}_4 \]
Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Murray Approach

\[
\text{OTBS}\quad \text{TBSO}\quad \text{OTBS} \quad \text{DMDO} \quad 100\% \quad \text{OTBS}\quad \text{TBSO}\quad \text{OTBS} \\
\text{dr: } >99:1
\]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Still Approach

\[
\text{mCPBA} \quad \text{NaHCO}_3 \quad 74\% \\
\text{NaOH then} \quad \text{H}_2\text{O}_2 \quad 94\%
\]

\[dr = 20:1:1\]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Directing Groups

\[ \text{OH} \quad \xrightarrow{\text{mCPBA or t-BuOOH, VO (ac ac)_2}} \quad \text{OH} \quad + \quad \text{OH} \]

with t-BuOOH, VO (ac ac)_2  \quad dr = 98:2

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Directing Groups

\[ \text{NHAc} \quad \text{mCPBA} \quad 91\% \quad \text{NHAc} \quad \text{O} \quad + \quad \text{NHAc} \quad \text{O} \quad dr = 99:1 \]

\[ \text{NHAc} \quad \text{mCPBA} \quad 85\% \quad \text{NHAc} \quad \text{O} \quad \text{HO} \quad \text{OH} \quad \text{HO} \quad \text{OH} \]
Directing Groups

\[
\text{Me} \quad \text{nBu} \quad \text{tBuOOH} \quad \text{VO (acac)}_2 \quad \text{A}_{1,2}^- \text{ strain minimized} \quad \text{dr} = 98:2
\]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Directing Groups

\[
\text{Me} \quad \text{OH} \quad \xrightarrow{\text{mCPBA}} \quad [\text{Me} \quad \text{H} \quad \text{H} \quad \text{Me}] \quad \xrightarrow{\text{dr} = 95:5} \quad \text{Me} \quad \text{OH}
\]

\text{A}_{1,3}^- \text{ strain minimized}

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Application to Lasacolid Synthesis

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Enantioselective Sharpless Epoxidation

Use models here

L-tartrate attack from the bottom face
D-tartrate attack from the top face
2-5 mol% Ti(OR)$_4$
2-6 mol% $RR$-Tartrate
$t$-BuOOH, mol sieve, $-20^\circ$C
The Proposed Mechanism

Use models here

Approach from behind
Application to Venustatriol Synthesis

\[ \text{D-(-) DET, Sharpless Conditions} \rightarrow \text{> 90\% ee} \]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Jacobson Epoxidation
The image depicts a chemical reaction involving the reaction of phenylalkene with manganese(III) peroxomalonate (NaOCl) catalyzed by a chiral manganese(III) complex. The reaction shows an 84% yield and 92% ee. The chemical structures and reaction conditions are illustrated with the catalyst and products. The reaction is taken from the book "Classics in Stereoselective Synthesis," Chapter 9.
Enantioselective Synthesis of BRL 55834

\[
\begin{align*}
&\text{C}_2\text{F}_5\text{N} & \text{Me} & \text{Me} \\
&\text{C}_2\text{F}_5\text{O} & \text{Me} & \text{Me} & \text{C}_2\text{F}_5 \\
\end{align*}
\]

\[
\begin{align*}
&\text{K}_2\text{O} & \text{Bu} \\
&\text{C}_2\text{F}_5\text{N} & \text{Me} & \text{Me} & \text{C}_2\text{F}_5 \\
\end{align*}
\]

\[
\begin{align*}
&\text{tBu} & \text{O} & \text{Me} & \text{Me} & \text{tBu} \\
&\text{tBu} & \text{Cl} & \text{tBu} & \text{tBu} & \text{tBu} \\
\end{align*}
\]

\[
\begin{align*}
&\text{N} & \text{N} & \text{Mn} \\
&\text{tBu} & \text{C}_2\text{F}_5 & \text{Me} & \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
&\text{NaOCl} \\
&\text{4 mol\%} \\
&\text{75\%} \\
&\text{94\% ee} \\
\end{align*}
\]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9
Enantioselective Synthesis of Indinavir

\[
\text{N} \quad \text{N} \quad \text{Mn} \quad \text{tBu} \quad \text{tBu} \quad \text{tBu} \quad \text{Cl}
\]

NaOCl

3 mol% 71%

84-86% ee

\[
\text{N} \quad \text{N} \quad \text{Me}
\]

\[
\text{N} \quad \text{N} \quad \text{CONHtBu}
\]

\[
\text{Ph} \quad \text{O} \quad \text{OH}
\]

\[
\text{Py} \quad \text{CONHtBu} \quad \text{OH} \quad \text{Ph} \quad \text{N} \quad \text{H}
\]

Taken from Book: *Classics in Stereoselective Synthesis*, Chapter 9