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The diagram illustrates a chemical reaction involving several compounds. The initial compound 19 undergoes a reaction with LiAlH₄ to produce compounds 41, 42, and 43. The reactions are shown as follows:

- 19 $\xrightarrow{LiAlH₄}$ 41, 42, 43

Compounds 41, 42, and 43 have the following substituents:

- 41: $R = Br$
- 42: $R = TBDPS$
- 43: $R = MOM$

The table below lists the solvent and the diastereomeric ratio (dr) for compounds 44 and 45:

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>dr (44:45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>Et₂O</td>
<td>98: 2</td>
</tr>
<tr>
<td>TBDPS</td>
<td>THF</td>
<td>5: 95</td>
</tr>
<tr>
<td>MOM</td>
<td>THF</td>
<td>70: 30</td>
</tr>
</tbody>
</table>
Prediction of the diasterofacial selectivity in nucleophilic additions to aldehydes and ketones having a chiral centre in the β-position:

Chelation (Retz) or Acyclic Control (Evans)

- Good diasteroselectivities are only observed for substrates possessing electronegative substituents at the β-position.
A Particular case: Reduction of β-hydroxy ketones by boranes

\[ \text{Et}_2\text{BOMe}, \text{NaBH}_4 \rightarrow \]

\[ \text{R}^1\text{OH} \text{CO} \text{R}^2 \rightarrow \text{OH} \text{Et} \text{B} \text{Et} \rightarrow \text{R}^1\text{O} \text{CO} \text{R}^2 \]

\[ \text{Me}_4\text{NBH(OAc)}_3 \rightarrow \]

\[ \text{MeOH} \text{COEt} \rightarrow \text{MeOH} \text{COEt} \rightarrow \text{MeOH} \text{COEt} \]

\[ \text{Et}_2\text{BOMe}, \text{NaBH}_4 \rightarrow \text{OH} \text{OH} \text{R}^1 \text{R}^2 \]

\[ 1,3\text{-syn} \]

\[ \text{Favored} \]

\[ \text{AcO} \text{B} \text{H} \rightarrow \text{AcO} \text{B} \text{Ac} \rightarrow \text{AcO} \text{B} \text{Ac} \]

\[ \text{Favored} \]

\[ \text{1,3-diaxial delivery} \]

\[ \text{1,3-anti} \]

\[ \text{dr} = 98:2 \]

\[ \text{Me} \text{OH} \text{CO} \text{Et} \rightarrow \text{Me} \text{OH} \text{CO} \text{Et} \rightarrow \text{Me} \text{OH} \text{CO} \text{Et} \]

\[ \text{dr} = 95:5 \]
Regioselective aldol reaction:
Regioselective aldol reaction:

- Increasing selectivity:

Use of only one carbonyl compound with α-protons

\[
\text{H}_{\text{acetoxy}} + \text{Ph}_{\text{carboxyl}} \rightarrow \text{Ph}_{\text{acetoxy}} + \text{Ph}_{\text{carboxyl}}
\]

Activation of the desired C-H

\[
\text{O} \quad \text{O} \quad \text{O} \quad \text{O}
\text{R} \quad \text{R} \quad \text{R} \quad \text{R}
\]

pKₐ
9  11  13  19-20  24-25

Formation of the enolate by oxidative insertion

\[
\text{Br}_{\text{acetoxy}} \quad \text{Zn} \rightarrow \left[ \text{BrZn}_{\text{acetoxy}} \right] \left[ \text{OZnBr} \right]
\]
Formation of the enolate by controlled deprotonation

OM
Me

OM
Me

Kinetic product

Two protons
less steric protection

One proton
sterically protected

thermodinamic product
A very strong and not nucleophilic base is necessary LDA, LiHMDS, tBuOK...

**Kinetic control**
- Very sterically demanding base
- Very low temperature
- Slow addition of the carbonyl compound to the base
- Aprotic solvent

Example: LDA, -78 °C, THF

**Thermodinamic control**
- Relatively small base
- Higher temperatures
- Time for the equilibration is necessary
- Prootic or dipolar solvent

Example: tBuOK, tBuOH, 50 °C

![Chemical structures and reactions](image-url)
**E/Z Enolate geometry in substituted non-cyclic substrates**

\[
\begin{align*}
\text{O} & \quad \text{R} \quad \text{LDA} \quad \text{OLi} \\
\text{R} & \quad \text{OLi} \\
\text{OR} & \quad \text{OLi}
\end{align*}
\]

- **Favored for \( R^1 = \text{OR} \)**

1. \( R^1 \text{OC}(\text{THF, No)}\)
2. \( R^1 \text{OC}(\text{THF, No)} \rightarrow \text{LDA} \rightarrow \text{OLi} \)
3. \( R^1 \text{OC}(\text{THF, No)} \rightarrow \text{LDA} \rightarrow \text{OLi} \)

\( 6 \) (trans) \( 91:9 \) with HMPA, 16.84

\( 7 \) (cis)

**Additional Examples**

- **Ph\text{OC} \quad \text{Cy}_{2}\text{BCl, Et}_{3}\text{N} \quad \text{PhOCy}_{2} \quad 99\% \ E**
- **Et\text{OC} \quad \text{Bu}_{2}\text{BCl, DIPEA} \quad \text{EtOBu}_{2} \quad 98\% \ Z**

*LDA → E enolate*
*LDA+HMPA → Z enolate*

**Bulky Lewis acid+not bulky base → E**
*Not bulky Lewis acid+bulky base → Z*
The Zimmerman Model

\[ R\text{-}\text{ac} Me \rightarrow MX \rightarrow R\text{-}\text{ac} Me + R\text{-}\text{ac} Me \]

**Z-enolate** **E-enolate**

**E-enolates give anti products**

Favored

Disfavored

**Unfavorable steric interaction**

**Anti product**

**Z-enolates give anti products**

Favored

Disfavored

**Unfavorable steric interaction**

**Syn product**

**Enantiomer**
Reaction of the non chiral enolate with chiral ketones or aldehydes

\[
\begin{align*}
\text{E enolate} & \quad \text{highly Felkin diastereoselection} \\
\text{Z enolate} & \quad \text{Moderate anti-Felkin diastereoselection}
\end{align*}
\]
Reaction of the chiral enolate with non chiral ketones or aldehydes

Z-enolates
Reaction of the chiral enolate with non chiral ketones or aldehydes

E-enolates

Felkin

Anti-Felkin

E-enolate

R-CHO

Felkin product
disfavored

Anti Felkin product
favored

1,2-anti

1,3-anti
Evans Aldol Chemistry

\[ \text{Me} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{Bn} \quad \xrightarrow{n-\text{Bu}_2\text{BOTf} \quad \text{H-Pr}_2\text{NEt}} \quad \text{Me} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{Bn} \quad \xrightarrow{\text{PhCHO}} \quad \text{Me} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{Bn} \quad \xrightarrow{\text{easy to remove}} \quad \text{Ph} \quad \text{OH} \quad \text{O} \quad \text{Me} \quad \text{Bn} \]

Very selective Z enolate

Felkin product
**Chiral auxiliary** - allows enantioselective synthesis via diastereoselective reaction
- Add chiral unit to substrate to control stereoselective reaction
- Can act as a built-in resolving agent (if reaction not diastereoselective)
- **Problems** - need point of attachment
  - adds additional steps
  - cleavage conditions must not damage product!
Chiral auxiliaries are optically active compounds that introduce chirality in otherwise racemic compounds.

The temporary stereocenter then forces the asymmetric formation of a second stereocenter using steric hindrance or directing groups to determine chirality.

After the creation of the second stereocenter the original auxiliary can be removed in a third step and recycled.

E. J. Corey

Evans

Enders (SAMP)
Chiral auxiliary and addition to the carbonyl group

- We have seen many examples of substrate control in nucleophilic addition to the carbonyl group (Felkin-Ahn & chelation control)
- If molecule does not contain a stereogenic centre then we can use a chiral auxiliary
- The chiral auxiliary can be removed at a later stage

- Opposite diastereoisomer can be obtained from reduction of the ketone
- Note: there is lower diastereoselectivity in the second addition as the nucleophile, ‘H’ is smaller
Chiral auxiliary in synthesis

- The chiral auxiliary, 8-phenylmenthol, has been utilised to form the pheromone, frontalin
- Aggregation pheromone of the *Southern Pine Beetle* - the most destructive beetle to pine forests in southeastern United States
Chirale Auxillare
8-Phenylmenthol

- 8-Phenylmenthol
  - Phenylring schirmt eine Seite ab
  - Doppelbindung muss mit Lewissäure (AlCl₃) aktiviert werden
  - Von Corey et al entwickelt
Chirale Auxillare
8-Phenylmenthol

- Beispiele
Problem: Propose a synthesis of the compound in the box using the given reagents.
Scheme 3.24
Scheme 11.11

1) LDA
2) MeI
3) O₃
73% → TBDPSO

>98% ee

73

H₂, Ra-Ni
73%
overall
93% ee
Evans Aldol Chemistry

\[
\text{MeCO\(\stackrel{\text{O}}{\text{N}}\)NMe} \quad \xrightarrow{n\text{-Bu}_2\text{BOTf} \atop \text{i-Pr}_2\text{NEt}} \quad \text{MeCO\(\text{NMe}^+\)O} \quad \xrightarrow{\text{PhCHO}} \quad \text{MeCO\(\text{NMe}^+\)O} \quad \xrightarrow{\text{MeCHO}} \quad \text{MeCO\(\text{NMe}^+\)O}
\]

Very selective Z enolate

easy to remove
Stereoselective synthesis: chiral reagents

Chiral reagents

- **Chiral reagent** - stereochemistry initially resides on the reagent
- **Advantages** - No coupling / cleavage steps required
  - Often override substrate control
  - Can be far milder than chiral auxiliaries
- **Disadvantages** - Need a stoichiometric quantity (not atom economic)
  - Frequently expensive
  - Problematic work-ups
Binol derivative of LiAlH₄

- Reducing reagent based on BINOL and lithium aluminium hydride
- Selectivity is thought to arise from a 6-membered transition state (surprise!!)
- Largest substituent (RL) adopts the pseudo-equatorial position and the small substituent (RS) is axial to minimise 1,3-diaxial interactions
The Aldol Reaction

- Previously we saw the use of a chiral auxiliary to control the stereochemistry.
- Now an example where the reagent is used to control the stereochemistry.

\[
\text{ketone} + \text{ketone} \xrightarrow{(-)-\text{DIP-Cl, } \text{Et}_3\text{N}} \text{product}
\]

\(-\)-DIP-Cl = \(-\)-\text{IpcCl} = \(-\)-B-chlorodiisopinocampheylborane derived from pine.

- Proposed transition state:
  - reduce diaxial interaction between R and methyl group.
  - adopts pseudo-equatorial position to reduce 1,3-diaxial ring strain.
  - proceeds via the boron enolate (cf chiral auxiliary).
  - again boron acid aids organ.
  - oxidative O-B cleavage.

\[
\text{work-up } \xrightarrow{\text{H}_2\text{O}_2} \text{product}
\]
Brown Allylation and Crotylation

- hydroboration (2nd year)
  - boron adds to least substituted end and least hindered face

- (-)-lpc-OMe
  - can readily form E-crotyl reagent as well

- allyl nucleophile

- Z-crotyl nucleophile

- (+)-lpc-allyl

- Note how pinene frequently used for chiral reagents
- Reason is it is a reasonably cheap, naturally occurring source of chirality
- Available in both enantiomers (but one twice the price)
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Proceeds via a chair-like 6-membered transition state
I recommend that you practice drawing those chairs
The crotyl variant behaves in the same manner except two stereocentres are fixed
**Asymmetric Deprotonation**

**Epoxides**

- Prochiral epoxides can be transformed into *enantiomerically* enriched allylic epoxides

\[
\text{Base} \quad \xrightarrow{\text{Conditions}} \quad \text{Yield (e.e.)}
\]

- THF, reflux: 65 % (31 %)
- THF, 0 °C: 77 % (92 %)

**Proposed mechanism**

(R)-disfavoured

(S)-favoured

- bulk of epoxide "below" paper along with pyrrolidine
- bulk of epoxide, "above" paper

*confusing: but remember base in same position in both pictures but epoxide changed, base perpendicular to page*
Asymmetric Horner-Wadsworth-Emmons Reaction

- Many other possible chiral reagents
- An interesting example is an asymmetric reaction that forms an \( sp^2 \) centre!
- Asymmetric as desymmetrises a prochiral substrate

\[
\begin{align*}
\text{Ketone} & \quad + \quad \text{Prochiral Substrate} \\
\text{1. BuLi} & \quad 2. \text{AcOH} & \quad \rightarrow \\
\end{align*}
\]

What have we learnt?
- Asymmetric reagents can be used to instal chirality to a molecule
- It is possible to use a reagent to control the selectivity of carbonyl reduction
- Chiral boron reagents are readily formed and are excellent for addition reactions to carbonyls
- Chiral lithium amides are good bases for desymmetrisation or resolution reactions
- An asymmetric Wittig reaction can be readily achieved even though it forms an \( sp^2 \) centre
• **Chiral catalysis** - ideally a reagent that accelerates a reaction (without being destroyed) in a chiral environment thus permitting one chiral molecule to generate millions of new chiral molecules...
Enzymes
Typical Chiral Ligands for Asymmetric Catalysis

(R,R)-DIOP  
Kagan

(R,R)-DIPAMP  
Knowles

(S,S)-CHIRAPHOS  
Bosnich

(R,R)-BDPP  
Bosnich

(R,R)-NORPHOS  
Brunner

CAMPHOS  
Pfaltz

BPPFA  
Kumada

DUPHOS  
Burk

BPPM  
Achiwa

(R)-BINAP  
Noyori

(R)-BIPHEMP (R = Ph)  
Schmid

(R)-BICHEP (R = C₈H₁₅)  
Miyashita

JOSIPHOS  
Togni
Catalytic enantioselective reduction

- An efficient catalyst for the reduction of ketones is **Corey-Bakshi-Shibata catalyst** (CBS)
- This catalyst brings a ketone and borane together in a chiral environment
- The reagent is prepared from a **proline** derivative
- The reaction utilises ~10% heterocycle and a stoichiometric amount of borane and works most effectively if there is a big difference between each of the substituents on the ketone
- The mechanism is quite elegant...

```
[Chemical structures and reactions]
```
Mechanism of CBS reduction

- Interaction of amine & borane activates borane
- It positions the borane
- It increases the Lewis acidity of the endo boron

Catalyst turnover

Coordination of aldehyde activates aldehyde and places it close to the borane

Chair-like transition state; largest substituent is pseudo-equatorial
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R</th>
<th>ee [%]</th>
<th>Solvent, T [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>H</td>
<td>94</td>
<td>THF, 23</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>H</td>
<td>94</td>
<td>PhCH₃, 25</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>H</td>
<td>97</td>
<td>THF, 23</td>
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<tr>
<td></td>
<td></td>
<td>Me</td>
<td>75</td>
<td>PhCH₃, 23</td>
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<tr>
<td>4</td>
<td></td>
<td>H</td>
<td>97</td>
<td>THF, 23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>97</td>
<td>THF, 23</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Me</td>
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<tr>
<td>6</td>
<td></td>
<td>H</td>
<td>87</td>
<td>THF, 0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>H</td>
<td>96</td>
<td>THF, 23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>92</td>
<td>PhCH₃, 27</td>
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<tr>
<td>8</td>
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<td>Me</td>
<td>86</td>
<td>THF, 0</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>H</td>
<td>94</td>
<td>THF, 25–30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>93</td>
<td>THF, 0–5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Config. (ee [%])</th>
<th>T [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>96.5</td>
<td>2</td>
</tr>
<tr>
<td>S</td>
<td>95.3</td>
<td>32</td>
</tr>
<tr>
<td>R</td>
<td>97.3</td>
<td>-10</td>
</tr>
<tr>
<td>R</td>
<td>86[a]</td>
<td>-15</td>
</tr>
<tr>
<td>R</td>
<td>84</td>
<td>-10</td>
</tr>
<tr>
<td>R</td>
<td>91</td>
<td>23</td>
</tr>
<tr>
<td>R</td>
<td>97.6</td>
<td>23</td>
</tr>
<tr>
<td>R</td>
<td>94[n = 2]</td>
<td>0[b]</td>
</tr>
<tr>
<td>R</td>
<td>96.7[n = 3]</td>
<td>0[b]</td>
</tr>
</tbody>
</table>

[a] 0.25 equiv of B-Me-4. [b] The reaction time was 25 min.
Asymmetric transfer hydrogenation (Noyori)
Asymmetric transfer hydrogenation (Noyori)

![Chemical structures and reactions](image-url)
Frustrated Lewis Pairs

Classical Lewis Pairs

Frustration

„Frustrated Complex“

Dative adduct
Evans Bisoxazolidines

- C₂-symmetric
- Chelating substrate is necessary

\[
\begin{align*}
\text{5a} & \quad \overset{C_6H_6, -78 \degree C}{\underset{10 \text{ mol} \% \text{ 1}}{\longrightarrow}} \quad \text{(S)-7} \\
\text{5b} & \quad \overset{\text{10 mol} \% \text{ catalyst}}{\underset{\text{catalyst}}{\longrightarrow}} \quad \text{12b}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Time (h)b (temp, °C)</th>
<th>Endo/Exo%</th>
<th>Endo ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="SbF%E2%82%86">Cu(phen)</a>₂</td>
<td>20 (−15)</td>
<td>85:15</td>
<td>99</td>
</tr>
<tr>
<td><a href="OTf">Cu(phen)</a>₂</td>
<td>30 (−15)</td>
<td>96:4</td>
<td>97</td>
</tr>
<tr>
<td><a href="SbF%E2%82%86">Zn(phen)</a>₂</td>
<td>8 (25)</td>
<td>86:14</td>
<td>−64</td>
</tr>
<tr>
<td>[Fe(phen)]I₂I₂</td>
<td>40 (−15)</td>
<td>76:24</td>
<td>−32</td>
</tr>
<tr>
<td>[Mg(phen)⁺]I₂I₂</td>
<td>15 (0)</td>
<td>80:20</td>
<td>0</td>
</tr>
</tbody>
</table>

*J. Am. Chem. Soc. 1999, 121, 7559–7573*