Stereoselective Synthesis

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Reference Texts:


“Stoichiometric Asymmetric Synthesis” by Mark Rizzacasa and Michael Perkins, Sheffield Academic Press 2000
10 Minute Problem

i. Indicate which of the following compounds are chiral and mark any stereocentres

ii. For the stereocentres bearing 4 different groups assign the configuration as $R$ or $S$

iii. Give the structures for the enolates A and B and explain the stereochemical outcomes of the following aldol reactions using transition state models
Not a stereocentre
\[
\text{BrMgTMP} \quad \text{MgBr} \\
\text{HMPA} \\
\text{Enolate A} \\
\text{95 % ds} \\
\text{Enolate B} \\
\text{>95 % ds}
\]
**Ethyl Ketone Aldol Reactions**

\[
\begin{align*}
&\text{LDA} & \text{Me}_3\text{SiO} & \rightarrow & \text{syn-anti} \\
&\text{TMEDA} & \text{Me}_3\text{SiO} & \rightarrow & \text{syn-syn}
\end{align*}
\]

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>% syn-anti</th>
<th>% syn-syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph, 'Bu, 'Pr</td>
<td>&gt;95</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>Ph CH₂</td>
<td>87</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Ph₂CH</td>
<td>&gt;90</td>
<td>&lt;10</td>
<td></td>
</tr>
</tbody>
</table>

**Mechanism:**

1. Lithium enolate of the ketone reacts with an aldehyde to form a six-membered transition state.
2. The stereochemistry of the product depends on the orientation of the substituents.
3. The transition state for syn-syn products is sterically hindered, leading to lower yield.

**Key Points:**
- The use of lithium diisopropylamide (LDA) and TMEDA as bases.
- The importance of steric hindrance in determining stereochemistry.
- The reaction is highly stereoselective with syn-anti ratios ranging from >95 to <5.

**Synthesis Examples:**
- **Ph, 'Bu, 'Pr:** High syn-anti ratio (>95:5).
- **Ph CH₂:** Moderate syn-anti ratio (87:13).
- **Ph₂CH:** High syn-anti ratio (>90:10).

**Notes:**
- The use of TMEDA is crucial for the reaction's selectivity.
- The reaction conditions are optimized for selectivity and yield.
$\text{BrMgTMP}$

Enolate A

Enolate B

$i$. $\text{BrMgTMP}$

$\text{ii. Ti(OiPr)}_3\text{Cl}$

$\text{HMPA}$

$\text{Me}_3\text{SiO}$

$\text{tBu}$

$\text{O}$

$\text{Ph}$

$95 \% \text{ ds}$

$>95 \% \text{ ds}$

$\text{syn-anti}$

$\text{syn-syn}$
Ethyl Ketone Aldol Reactions

\[ \text{Reaction 1: } \text{anti: syn} = 88:12 \]

\[ \text{Reaction 2: } \text{anti: syn} = 86:14 \]

\[ \text{Reaction 3: } \text{anti: syn} = >98:2 \]

\[ \text{Reaction 4: } \text{anti: syn} = >98:2 \]
Titanium (IV) Aldol Reactions

1. LDA
2. ClTi(OiPr)$_3$
3. EtCHO

R = Si(t-Bu)(CH$_3$)$_2$

99 : 1

syn-syn

syn-anti
Direct formation of Titanium (IV) enolates

\[
\text{BnOCH}_2\text{Cl} \quad 99 \% \text{ Yield, } >99 \% \text{ ds}
\]

i. TiCl\(_4\), –78 °C, 2 min
ii. \(\text{iPr}_2\text{NEt}\)
iii. BnOCH\(_2\)Cl
Aldol Reaction of Titanium (IV) enolates

1. $\text{TiCl}_4$, $-78 \degree \text{C}$, 2 min
2. $\text{iPr}_2\text{NEt}$
3. $\text{CH}_3\text{C}_2\text{CHCHO}$

$\text{MeCH}_2\text{CHMe}$

95% Yield, 92% ds

$\text{MeCH}_2\text{CHMe}$

95% Yield, 93% ds

$\text{syn-syn}$

$\text{syn-anti}$
Aldol Reaction of Titanium (IV) enolates

i. TiCl₄, –78 °C, 2 min
ii. iPr₂NEt
iii. CH₃₂CHCHO

96 % Yield, 96 % ds
82 % Yield, 95 % ds

syn-syn

syn-anti
Aldol Reaction of Titanium (IV) enolates

\[
\text{i. } \text{TiCl}_4, -78 \, ^\circ\text{C}, \text{2 min} \\
\text{ii. } \text{iPr}_2\text{NEt} \\
\text{iii. CH}_3\text{)(CHCHO} \\
\]

87 % Yield, 94 % ds
Generation of Boron enolates

- Boron enolates are now regarded as highly versatile and effective intermediates in stereoselective synthesis and are generally prepared from the carbonyl compound by treatment with a dialkylboron triflate and a tertiary amine (usually triethylamine or diisopropylethylamine) according to the Mukaiyama method usually leading to the formation of the $Z$-($O$) enolate.

- Formation of the $E$-($O$) enolate has been possible by modification of the Mukaiyama procedure. An early report is that of Masamune and Van Horn who found that either the $Z$-($O$) or $E$-($O$) enolate of cyclohexyl ethyl ketone could be formed by variation of the boron triflate used in the enolisation procedure.
Generation of Boron enolates

- This selectivity has been explained in terms of deprotonation of diastereomeric Lewis acid complexes where the Lewis acid is either *cis* or *trans* relative to the acidic α-hydrogens.

- This rationalises the observation that the larger the ligands on the boron the more *E-(O)* enolate is formed. It has also been found that use of the boron chloride reagents instead of the triflates favours the formation of *E-(O)* enolate and a general protocol for the formation of this enolate has been developed by Brown.
**Generation of Boron enolates**

- From a practical perspective the selective formation of the $Z$(O) enolate can be generally achieved by using the boron triflate with small ligands ($n$Bu or Et) and a sterically hindered base, whereas the $E$(O) enolate can be formed by reaction of the boron chloride with large ligands (cyclohexyl) and a small base ($\text{Et}_3\text{N}$ or $\text{Me}_2\text{NEt}$).
**Classic Boron Aldols**

![Chemical reaction diagram]

- Reaction with $n$-Bu$_2$BOTf and $i$-Pr$_2$NEt.
- Product distribution:
  - Ph: 40 : 1
  - Et: 50 : 1
  - $i$Pr: 100 : 1

- $R = \text{Si}(t\text{-Bu})(\text{CH}_3)_2$
- $R = t\text{BuMe}_2\text{Si}$

- Product formation with $H_2O_2$ and NaOH or Buffer.
- Conditions: THF or MeOH.

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**Formulas:**

- Initial substrate: $\text{RCOR} \rightarrow \text{Me}$
- Aldol condensation:
  - $\text{RCOR} \rightarrow \text{OR}$
- Diastereomeric mixture:
  - $\text{Me} \rightarrow \text{OR}$
  - $\text{H} \rightarrow \text{OR}$

---

**Equation:**

$R = \text{Si}(t\text{-Bu})(\text{CH}_3)_2$
**Classic Boron Aldols**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Oxazolidinone</th>
<th>Aldehyde</th>
<th>Aldol Product</th>
<th>Ratio syn isomers</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.30</td>
<td>i(^{\prime})PrCHO</td>
<td>4.32</td>
<td>497 : 1</td>
<td>78</td>
</tr>
<tr>
<td>4.31</td>
<td>i(^{\prime})PrCHO</td>
<td>4.33</td>
<td>&lt;1 : 500</td>
<td>91</td>
</tr>
<tr>
<td>4.30</td>
<td>PhCHO</td>
<td>4.32</td>
<td>141 : 1</td>
<td>75</td>
</tr>
<tr>
<td>4.31</td>
<td>PhCHO</td>
<td>4.33</td>
<td>&lt;1 : 500</td>
<td>95</td>
</tr>
<tr>
<td>4.30</td>
<td>(n)BuCHO</td>
<td>4.32</td>
<td>&gt;500 : 1</td>
<td>88</td>
</tr>
<tr>
<td>4.31</td>
<td>(n)BuCHO</td>
<td>4.33</td>
<td>&lt;1 : 500</td>
<td>89</td>
</tr>
</tbody>
</table>
Classical Boron Aldols
**Classic Boron Aldols**

![Chemical structures and reactions involving Boron aldol reactions.](image)

- Reaction of $\text{BnO-}C\equiv C$ with $\text{(C}_6\text{H}_{11})_2\text{BCl}$ and $\text{Et}_3\text{N}$ to form a major product with 93% yield and 97% ds.

- A $A^{1,3}$ strain is minimised for the major product formation.

- The reaction is disfavoured by lone-pair repulsion.
Classic Boron Aldols

\[
\begin{align*}
\text{(C}_6\text{H}_{11})_2\text{BCl} & \quad \text{Me}_2\text{NEt} \\
\text{Bn} & \quad \text{Me} \\
\end{align*}
\]

93 % Yield 84% ds

\[
\begin{align*}
\text{(C}_6\text{H}_{11})_2\text{BCl} & \quad \text{Me}_2\text{NEt} \\
\text{Bn} & \quad \text{Me} \\
\end{align*}
\]

89 % Yield 83% ds

\[
\begin{align*}
\text{BnO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

OP1 OP2

\[
\begin{align*}
\text{BnO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

OP1 OP2