The Ivanov Reaction

\[
\text{Ph}-\text{CH}_2\text{OMgBr} \quad \text{PhCHO} \quad \text{Ph} \quad \text{CO}_2\text{H} \\
\text{syn} \quad 24\% \quad \text{anti} \quad 76\%
\]


To achieve high diastereo- and enantioselectivity, it is necessary to:

- control the enolization step
- use an auxiliary with a large diastereofacial bias
- control competing transition states, e.g.
  - half-chair vs. twist boat
  - closed vs. open
- use metal-derivatives that have clearly defined coordination geometries.
The stereochemical implications of the Zimmerman-Traxler transition state model for the aldol reaction can be summarized as follows:

Zimmerman-Traxler transition states represent the most frequently used models, but other possibilities have always to be considered as well:
Closed vs. Open Transition States

Enolization

(a) Lithium enolates

\[
\text{LDA, THF, } -78^\circ \text{C} \quad \xrightarrow{\text{(slight excess of base)}} \quad \text{OTBS, } + \text{OTBS}
\]

\[
\text{Z-silyl ketene acetal} \quad 6 : 94 \quad \text{vs.} \quad \text{E-silyl ketene acetal}
\]
Transition states for enolization:

![Diagram of transition states for enolization]

Kinetic ratios for LDA/THF enolization:

<table>
<thead>
<tr>
<th>R</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>95: 5</td>
</tr>
<tr>
<td>O-t-But</td>
<td>95: 5</td>
</tr>
<tr>
<td>Et</td>
<td>50: 50</td>
</tr>
<tr>
<td>t-Pr</td>
<td>40: 60</td>
</tr>
<tr>
<td>t-Bu</td>
<td>0: 100</td>
</tr>
<tr>
<td>Ph</td>
<td>0: 100</td>
</tr>
</tbody>
</table>
| NEt₂ | 0: 100 | *(cf. Dauben, JACS 1985, 107, 2264)*

b. Boron enolates

Selectivities:

The boron-halide coordinates to the carbonyl oxygen, thereby increasing the acidity of the $\alpha$-proton so that it can be removed by amine bases.

<table>
<thead>
<tr>
<th>$R$ = Et</th>
<th>$R$ = i-Pr</th>
<th>$R$ = t-Bu</th>
<th>$R$ = Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E : Z$</td>
<td>$E : Z$</td>
<td>$E : Z$</td>
<td>$E : Z$</td>
</tr>
</tbody>
</table>

with $\text{Chx}_2\text{B-Cl}$:

| $79 : 21^*$ | $97 : 3$   | $97 : 3$   | $97 : 3$ |

with $\text{Chx}_2\text{B-I}$:

44 : 56

68 : 32

3 : 97

3 : 97


* but:

w' $\text{Chx}_3\text{B(OTf)/NEt}_3$: $E : Z = 20 : 80$

with $\text{B-OTf-9-BBN}$:

3 : 97

12 : 88

90 : 10

3 : 97

with $\text{B-I-9-BBN}$:

3 : 97

27 : 73

3 : 97

3 : 97

at least a partial rationalization of these results is provided by the following transition state models:
Asymmetric Induction


Heathcock/Masamune auxiliaries:

Highly selective additions of these auxiliaries have been achieved via all four of the postulated pathways (JOC 1991, 56, 2499):
Evans’ Chiral Oxazolidinone Auxiliary

D. A. Evans, *JACS* 1981, 103, 2127


Experiments employing N-acyloxazolidinethione auxiliaries (sulfur has a higher affinity to titanium than oxygen), 2 equiv of TiCl$_4$ and 1 equiv of Hünig's base gave excellent selectivity for the “non-Evans” syn aldol product. Crimmins believes that the second equivalent of Lewis acid abstracts the chlorine ion and leads to a chelated transition state (in contrast to the acyclic transition state postulated by Heathcock). In addition, very high (>98:2) “Evans” syn aldol selectivities could be obtained by using 1 equiv of TiCl$_4$ in combination with sparteine (2.5 equiv). The role of sparteine is presently unknown.

An added advantage of oxazolidinethiones is that they are easily removed under mild conditions:

Two methods for the synthesis of 4-benzyloxazolidine-2-thione from 2-amino-3-phenyl-1-propanol (phenylalaninol) have been described. The appropriate amino alcohol is readily prepared from (R)-phenylalanine or (S)-phenylalanine by reduction with sodium borohydride and iodine in THF. Exposure of phenylalaninol to carbon disulfide and aqueous sodium carbonate for 15 min at 100 °C provided 4-benzyloxazolidine-2-thione in 63% yield. Alternatively, treatment of the amino alcohol with thiophosgene and triethylamine in dichloromethane for 30 min at 0 °C provided 95% of the oxazolidinethione. The former method often results in the oxazolidinethione contaminated with varying amounts of the corresponding thiazolidinethione.


Oxazolidinethiones can be N-acylated by a variety of standard methods including acylation of the lithium salt or sodium salt by treatment with an acyl chloride or mixed anhydride or by acylation with an acid chloride in the presence of triethylamine.

**Tin(II) Enolates of N-acyloxazolidinethiones.** Tin(II) enolates of oxazolidinethiones show moderate diastereoselectivity for the non-Evans aldol products presumably proceeding through a chelated transition state. The N-acetyl oxazolidinethiones are generally less selective than the corresponding thiazolidinethiones in diastereoselective acetate aldol reactions.


![Chemical structure](image1)

**Boron enolates of N-acyloxazolidinethiones.** Boron enolates of N-propionyloxazolidinethiones can be generated under standard enolization conditions with dibutyliaboron triflate and diisopropylethylamine. The boron enolates react with aldehydes to provide the Evans syn-aldol products with excellent diastereoselectivity. No oxidative workup was necessary in the examples reported.


![Chemical structure](image2)

The use of excess titanium (IV) chloride with N-glycolyloxazolidinethiones leads to the anti aldol adducts selectively. These aldol additions most likely proceed through an open transition state where the additional Lewis acid serves to activate the aldehyde for the aldol addition reaction.

\[
\begin{align*}
\text{TiCl}_4, & \quad 3 - 4 \text{ equiv.} \\
& \quad (\text{-})\text{-sparteine} \\
\text{CH}_2\text{Cl}_2, & \quad -78 \degree \text{C} \\
\text{CH} & \quad \text{CHO} \quad \text{or} \quad \text{CHO} \\
\text{60 - 75\%} \\
\rightarrow
\end{align*}
\]

indirect solution for anti-aldol (D. A. Evans, THL 1986, 27, 4957):

\[
\begin{align*}
\text{Bu}_2\text{BOTf, NEt}_3, & \quad 1. \text{LAH} \\
\text{OHC} & \quad \text{2. TsCl} \quad 3. \text{LAH} \\
\text{58\%}
\end{align*}
\]
For important modern concepts on **selective anti-aldol** processes, see work by


\[
\begin{align*}
\text{Ph} & \text{CHO} + \text{OTMS} \\
\text{Ph} & \text{OH} \quad \text{O} \quad \text{OPh} \\
\text{Ph} & \text{OH} \quad \text{O} \quad \text{OPh}
\end{align*}
\]

1. (c-C\textsubscript{3}H\textsubscript{7})\textsubscript{2}BOTf, NE\textsubscript{3}  
2. EtCHO  

\[
\text{Bn}^- \text{N} \quad \text{SO}_\text{Mes}
\]

90% yield  

\[dr = 96:4\]

and others:  
Double Diastereoselectivity

D. A. Evans, JACS 1985, 107, 4346.

Note: Reagent-based stereocontrol does not always superseed substrate control:

from: cytovaricin synthesis; Paterson, THL 1988, 29, 585.
Evans Bispropionate Synthon


\[ \text{Ph} \quad \text{Ph} \]
\[ \text{syn, syn} \quad \text{anti, syn} \quad \text{anti, anti} \]

\[ \text{OMe} \quad \text{OMe} \quad \text{OMe} \]
\[ \text{86\%} \quad \text{90\%} \]
Paterson's Ipc-Enolate (*TH 1990*, 46, 4663):

\[
\begin{array}{c}
\text{O} \quad \xrightarrow{(\text{lpc})_2\text{BOTf}} \quad \text{EtN} \\
\text{OBlpc}_2 \quad \xrightarrow{\text{MeCHO}} \quad \text{OH} \quad \text{O} \\
\end{array}
\]

\[\text{cf. Ch}_{2}\text{BOTf: } Z : E = 80 : 20\]

\[\text{syn : anti = 97 : 3}\]

\[82\% \text{ ee}\]

\[
\text{favored TS: (derived from (+)-pinene)}
\]

\[
\begin{array}{c}
\text{H} \\
\text{H} \\
\text{B} \\
\text{H} \\
\end{array}
\quad \equiv 
\]

\[
\begin{array}{c}
\text{S} \\
\text{M} \\
\text{L} \\
\text{S} \\
\end{array}
\]

→ This strategy is particularly useful for aldol reactions of large, chiral fragments in macrolide synthesis.

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Catalytic Asymmetric Aldol: **Eder-Sauer-Wiechert-Hajos** Process


