Advanced Organic Chemistry

روشهای سنتز مواد آلی

Dr Morteza Mehrdad
University of Guilan, Department of Chemistry,
Rasht, Iran
m-mehrdad@guilan.ac.ir
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Introduction

The reactions described in this chapter include some of the most useful methods for carbon-carbon bond formation:

- the aldol reaction,
- the Robinson annulation,
- the Claisen condensation and other carbon acylation methods,
- and the Wittig reaction and other olefination methods.
Pathway D: If the enolate has an $\alpha$-substituent that is a leaving group, cyclization can occur.
A second important reaction type considered in this chapter is **conjugate addition**, which involves addition of nucleophiles to electrophilic double or triple bonds.

The retrosynthetic dissection is at a bond that is to a carbonyl and to an anionstabilizing group.
2.1. Aldol Addition and Condensation Reactions:

2.1.1. The General Mechanism

- Are occurring in:
  - hydroxylic solvents
  - and under thermodynamic control.
    - are useful for:
      - the preparation of aldehyde dimers (aldols)
      - and certain, $\alpha,\beta$-unsaturated aldehydes and ketones.

For example, The mixed condensation of aromatic aldehydes with aliphatic aldehydes and ketones is often done under these conditions. The conjugation in the $\beta$-aryl enones provides a driving force for the elimination step.
2.1.2. Control of Regio- and Stereoselectivity of Aldol Reactions of Aldehydes and Ketones:

The term *directed aldol addition* is applied to reactions that are designed to achieve specific regio and stereochemical outcomes. Control of product structure requires that one reactant act exclusively as the *nucleophile* and the other exclusively as the *electrophile*.

The enolate that is to serve as the nucleophile is generated stoichiometrically, usually with *lithium* as the counterion in an aprotic solvent at low temperature.

Reaction conditions that involve other enolate derivatives as nucleophiles have been developed, including *boron enolates* and enolates with *titanium, tin, or zirconium* as the metal.
2.1.2.1. Aldol Reactions of Lithium Enolates

In the structures that follow, the reacting aldehyde is shown with R rather than H in the equatorial-like position, which avoids a 1,3-diaxial interaction with the enolate C(1) substituent. A consequence of this mechanism is that the reaction is stereospecific with respect to the E- or Z-configuration of the enolate. The E-enolate gives the anti aldol product, whereas the Z-enolate gives the syn-aldol.
The ratio of the location of the deuterium corresponds closely to the ratio of the stereoisomeric enolates for several aldehydes.
When it reacts with benzaldehyde only the syn aldol is formed. The product stereochemistry is correctly predicted if the TS has a conformation with the phenyl substituent in an equatorial position.
A similar preference for formation of the **syn aldol** is found for other Z-enolates derived from ketones in which **one of the carbonyl substituents is bulky**. Ketone enolates with less bulky substituents show a decreasing stereoselectivity in the order $t$-butyl $>$ $i$-propyl $>$ ethyl.

This trend parallels a decreasing preference for stereoselective formation of the Z-enolate.
The enolates derived from *cyclic ketones* are necessarily **E-isomers**. The enolate of cyclohexanone reacts with benzaldehyde to give both possible stereoisomeric products.

The stereoselectivity is about 5:1 in favor of the **anti isomer** under optimum conditions.
kinetic **stereoselection** in aldol additions of *lithium enolates*:

(1) The chair TS model provides a basis for analyzing the stereoselectivity observed in aldol reactions of ketone enolates having one bulky substituent. The preference is

\[
\begin{align*}
Z\text{-enolate} & \rightarrow \text{syn aldol}; \\
E\text{-enolate} & \rightarrow \text{anti aldol}.
\end{align*}
\]

(2) When the enolate has no **bulky** substituent, stereoselectivity is low.

(3) **Z-Enolates** are more **stereoselective** than **E-enolates**.

Ketones with one **tertiary alkyl** substituent give mainly the **Z-enolate**, less highly substituted ketones usually give mixtures of **E-** and **Z-enolates**.
When the enolate has no bulky substituent, stereoselectivity is low. 

Z-Enolates are more stereoselective than E-enolates.
E:Z ratio for 3-pentanone and 2-methyl-3-pentanone can be increased by use of a 1:1 lithium tetramethylpiperidide(LiTMP)-LiBr mixture for kinetic enolization.

<table>
<thead>
<tr>
<th></th>
<th>LDA</th>
<th>LiTMP</th>
<th>LiTMP + LiBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CH$_2$CCH$_2$CH$_3$</td>
<td>3.3:1</td>
<td>5:1</td>
<td>50:1</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CHCCH$_2$CH$_3$</td>
<td>1.7:1</td>
<td>2:1</td>
<td>21:1</td>
</tr>
<tr>
<td>(CH$_3$)$_3$CCCH$_2$CH$_3$</td>
<td>1: &gt;50</td>
<td>1: &gt;20</td>
<td>1: &gt;20</td>
</tr>
</tbody>
</table>

3-pentanone
2-methyl-3-pentanone
2,2-dimethyl-3-pentanone
When aldol addition is carried out under **thermodynamic conditions**, the product **stereoselectivity** is usually not as high as under **kinetic conditions**.

For example, with the product from the reaction of the enolate of **2,2-dimethyl-3-pentanone** and **benzaldehyde**. The greater stability of the anti isomer is attributed to the **pseudoequatorial position of the methyl group** in the chairlike product chelate. With larger substituent groups, the thermodynamic preference for the **anti isomer** is still greater.
For synthetic efficiency, it is useful to add MgBr₂, which accelerates the equilibration.
**Scheme 2.1. Examples of Directed Aldol Reactions**

**A. Lithium enolates**

1. 
   - **Path A**
   - Less-substituted ketone enolate

2. 
   - More highly substituted reactants

3. 
   - K control

4. 
   - 20
2.1.2.2. Aldol Reactions of Boron Enolates.

The O–B bond distances are shorter than for lithium enolates, and this leads to a more compact structure for the TS and magnifies the steric interactions that control stereoselectivity.
Boron enolates can be prepared by reaction of the ketone with a dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine. Use of boron triflates and a bulky amine favors the **Z-enolate**. The resulting aldol products are predominantly the **syn stereoisomers**.

The **E-boron** enolates of some ketones can be preferentially obtained by using dialkylboronon chlorides.
With the triflate reagents, the boron is **anti** to the enolizable group. With the bulkier dicyclohexylboron chloride, the boron favors a conformation **cis** to the enolizable group.

Z-Boron enolates can also be obtained from silyl enol ethers by reaction with the bromoborane derived from 9-BBN (9-bora bicyclo[3.3.1]nonane). This method is necessary for ketones such as 2,2-dimethyl-3-pentanone, which give E-boron enolates by other methods. **The Z-stereoisomer is formed from either the Z- or E-silyl enol ether.**
The E-boron enolate from cyclohexanone shows a preference for the *anti aldol* product. The ratio depends on the boron alkyl groups and is modest (2:1) with di-nbutylboron but greater than 20:1 for cyclopentyl-n-hexylboron.
The general trend is that boron enolates parallel lithium enolates in their stereoselectivity but show enhanced stereoselectivity.
B. Boron enolates

5e
\[ \text{PhCH}_2\text{CH}_2\text{CCH}_3 \]

5

\[ \text{R}_2\text{BO}_3\text{SCF}_3 \]

1) PhCH=O

-78°C, 5 h

2,6-lutidine

-78°C, 3 h

2) H_2O_2, pH 7

88%

6f
\[ \text{C}_2\text{H}_5 \]

(C\text{H}_11)_2\text{BO}_3\text{SCF}_3

Et\text{N(i-Pr)}_2

70%

7g
\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CN(CH}_3)_2 \]

1) (C\text{H}_11)_2\text{BI, Et}_3\text{N}

-78°C

2) PhCH=O

>97:3 syn

93%

a boron enolate of an amide

Section 2.1.3
Titanium enolates can be prepared from lithium enolates by reaction with a trialkoxytitanium(IV) chloride, such as \textit{tris (isopropoxy) titanium chloride}. \textit{Titanium enolates are} usually prepared directly from ketones by reaction with TiCl$_4$ and a tertiary amine. Under these conditions, the \textbf{Z-enolate} is formed and the aldol adducts have \textit{syn stereochemistry}. The addition step proceeds through a cyclic TS assembled around titanium.
Mixed aldehyde-aldehyde additions have been carried out using \( \text{TiCl}_4 \) and TMEDA.

The reaction gives *syn* adducts, presumably through a cyclic TS. Treatment of the *syn* adducts with 1 mol % \( \text{Ti(O-i-Pr)}_4 \) leads to equilibration to the more stable *anti* isomer.
Ketone-aldehyde additions have been effected using TiCl₄ in toluene. These reactions exhibit the same stereoselectivity trends as other titanium-mediated additions. With **unsymmetrical ketones**, this procedure gives the product from the **more substituted enolate**.

![Diagram of a chemical reaction](image)

unsymmetrical ketones

more substituted enolate.
Titanium enolates can also be used under conditions in which the titanium exists as an “ate” species. Crossed aldehyde-aldehyde additions have been accomplished starting with trimethylsilyl enol ethers, which are converted to lithium enolates and then to “ate” species by addition of Ti(O-n-Bu)₄. These conditions show only modest stereoselectivity.
If the number of anionic ligands exceeds the oxidation state of the metal, the complex has a formal negative charge on the metal and is called an “ate” complex.

The reaction works best with ketones having EWG substituents such as alkynones and haloketones. The reaction is thought to proceed through a cyclic intermediate that is stable until hydrolysis. This cyclic intermediate may be necessary to drive the normally unfavorable equilibrium of the addition step.
Tin(II) enolates can be generated from ketones and Sn(II)(O$_3$SCF$_3$)$_2$ in the presence of tertiary amines. The subsequent aldol addition is **syn selective and independent of enolate configuration**. The **syn stereoselectivity** indicates that reaction occurs through an **open TS**.

This preference arises from avoidance of **gauche interaction** of the aldehyde group and the enolate -substituent.

**Even cyclohexanone gives the syn product.**
Tin(II) enolates prepared in this way also show good reactivity toward ketones as the electrophilic component.

**Uncatalyzed** addition of trialkylstannyl enolates to benzaldehyde shows *anti* stereoselectivity.
The tri-n-butylstannyl enol derivative of cyclohexanone gives mainly *anti* product.

Zirconium *tetra-t-butoxide* is a mildly basic reagent that has occasionally been used to effect aldol addition.
Zirconium enolates can also be prepared by reaction of lithium enolates with \( \text{Cp}_2\text{ZrCl}_2 \), and they act as nucleophiles in aldol addition reactions.
A comparison of the anti:syn diastereoselectivity of the lithium, dibutylboron, and Cp₂Zr enolates of 3-methyl-2-hexanone with benzaldehyde has been reported. The order of stereoselectivity is:

\[
\text{Bu}_2\text{B} > \text{Cp}_2\text{Zr} > \text{Li}
\]

These results suggest that the reactions of the zirconium enolates proceed through a cyclic TS.
C. Titanium, tin and zirconium enolates

\[
\begin{align*}
\text{8}^\text{h} & \quad \overset{1)}{\text{TiCl}_4, \text{Et}_3\text{N}} \quad (\text{CH}_3)_2\text{CHCCH}_2\text{CH}_3 \\
& \quad \overset{2)}{(\text{CH}_3)_2\text{CHCH}==\text{O}} \quad \overset{\text{94\%, 92:8 \text{syn:anti}}}{\text{94\%}} \text{, 92:8 \text{syn:anti}}
\end{align*}
\]

\[
\begin{align*}
\text{9}^\text{g} & \quad \text{CH}_3\text{CH}_2\text{CCH}_2\text{CH}_3 + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}==\text{O} \\
\overset{\text{Sn(OTf)}_2}{\text{N-ethyl-piperidine}} & \quad \overset{\text{78\degree C}}{\text{86\% > 91:9 \text{syn:anti}}}
\end{align*}
\]

\[
\begin{align*}
\text{10}^\text{i} & \quad \overset{\text{OZr(Cp)}_2\text{Cl}}{\text{CH}_3\text{CCH}_2\text{CH}_3} + \text{PhCH==O} \\
\rightarrow & \quad \overset{\text{56\% \text{91:9 ds}}}{\text{56\% \text{91:9 ds}}}
\end{align*}
\]

\text{diastereoselectivity}
2.1.3. **Aldol Addition Reactions of Enolates of Esters and Other Carbonyl Derivatives.**

The enolates of other carbonyl compounds can be used in mixed aldol reactions. The silyl ethers of ester enolates, which are called **silyl ketene acetals**, show reactivity that is analogous to silyl enol ethers and are covalent equivalents of ester enolates.

These observations are explained in terms of a chairlike TS for the LDA/THF conditions and a more open TS in the presence of an aprotic dipolar solvent.
Despite the ability to control ester enolate geometry, the aldol addition reactions of unhindered ester enolate are not very stereoselective.
This stereoselectivity can be improved by use of a very bulky group.
2,6-Dimethylphenyl esters give E-enolates and anti aldol adducts.
The lithium enolates of \( \alpha \)-alkoxy esters exhibit high stereo-selectivity, which is consistent with involvement of a chelated enolate. The chelated ester enolate is approached by the aldehyde in such a manner that the aldehyde \( R \) group avoids being between the \( \alpha \)-alkoxy and methyl groups in the ester enolate.
Various combinations of **borylating reagents** and amines have been used and the E:Z ratios are dependent on the reagents and conditions. In most cases esters give **Z-enolates**, which lead to **syn** adducts, but there are exceptions.

Use of branched-chain alcohols increases the amount of **anti enolate**, and with t-butyl esters the product ratio is higher than 97:3.
Branched-chain esters also give mainly \textit{anti} adducts when the enolates are formed using dicyclohexyliodoborane.

Phenyl and phenylthio esters have proven to be advantageous in TiCl$_4$-mediated additions, perhaps because they are slightly more acidic than the alkyl analogs. The reactions show \textit{syn} diastereoselectivity, indicating that Z-enolates are formed.
N-acyloxazolidinones, can be used in conjunction with Bu$_2$BO$_3$SCF$_3$, Sn(O$_3$SCF$_3$)$_2$, or TiCl$_4$ for generation of enolates.

The stereoselectivity of the reactions is consistent with formation of a Z-enolate and reaction through a cyclic TS.
2.1.4. THE MUKAIYAMA ALDOL REACTION

The **Mukaiyama aldol reaction** refers to Lewis acid–catalyzed aldol addition reactions of silyl enol ethers, silyl ketene acetals, and similar enolate equivalents.

Lewis acids cause reaction to occur by coordination at the carbonyl oxygen, activating the carbonyl group to nucleophilic attack.
Lewis acids such as TiCl₄ and SnCl₄ induce addition of both silyl enol ethers, silyl ketene acetals to aldehydes.

Stereoselectivity increases with the steric bulk of the silyl enol ether substituent R¹.

Steric factors determine the amount of syn versus anti addition (BF₃).
In general terms, there are at least three possible mechanisms for catalysis:

- One is through **Lewis acid activation** of the electrophilic carbonyl component, similar to that discussed for BF$_3$, TiCl$_4$, and SnCl$_4$.
- Another is by **exchange with the enolate equivalent** to generate a more nucleophilic species.
- A third is activation of a catalytic cycle that generates **trimethylosilyl cation** as the active catalysts.
Aldol additions of silyl enol ethers and silyl ketene acetals can be catalyzed by (Cp)_2Zr^{2+} species including [(Cp)_2ZrO-t-Bu]^+ and (Cp)_2Zr(O_3SCF_3)_2

The catalytic cycle involves transfer of the silyl group to the adduct
Trimethylsilyl triflate can be formed by intermolecular transfer of the silyl group. When this occurs, the trimethylsilyl triflate can initiate a catalytic cycle that does not directly involve the Lewis acid.
Hindered bis-phenoxyaluminum derivatives are powerful cocatalysts for reactions mediated by TMS triflate and are believed to act by promoting formation of trimethylsilyl cations by sequestering the triflate anion.
Silyl enol ethers react with formaldehyde and benzaldehyde in water-THF mixtures using lanthanide triflates such as $\text{Yb(O}_3\text{SCF}_3)_3$. The catalysis reflects the strong affinity of lanthanides for carbonyl oxygen, even in aqueous solution.

![Chemical reaction diagram]

91% yield, 73:27 syn:anti
Indium(III) chloride is a borderline catalysts by these criteria, but nevertheless is effective. The optimum solvent is 95:5 isopropanol-water. Under these conditions, the reaction is **syn** selective, suggesting a cyclic TS.
The Lewis acids promote ionization of the acetal to an oxonium ion that acts as the electrophile. The products are β-alkoxy ketones.

In some cases, the enolate can be formed directly in the presence of the acetal with the Lewis acid also activating the acetal.
Dibutylboron triflate promotes both enol borinate formation and addition.

Reactions with acetals can serve to introduce β-alkoxy groups into complex molecules, as in the following reaction.
For example, photolysis of benzaldehyde dimethylacetal and 1-trimethylsilyloxy cyclohexene in the presence of a typical photoelectron acceptor, triphenylpyrylium cation, gives an excellent yield of the addition product.
addition reactions with silyl enol ethers as the nucleophile and TiCl₄ as the Lewis acid

fully substituted silyl enol ether

larger C(2) substituent syn to the hydroxy group

silyl ketene thioacetal
B. Catalytic Mukaiyama Reactions

lanthanide catalyst that is active in aqueous solution as a Lewis acid

MABR = bis(4-bromo-2,6-di-tert butylphenoxy) methyl aluminum
C. Reactions with acetals

10. \[ PhCHCH(OCH_3)_2 + CH_2=CC(CH_3)_3 \xrightarrow{TiCl_4, -78^\circ C} PhCH(C(CH_3)_3) + CH_2=CC(CH_3)_3(\text{BF}_3-\text{catalyzed reaction}) = 24:1 \]

84% yield, 2.5:1 syn:anti stereoselectivity

11. [\text{OTMS}]

\[ \text{PhCHCH(OCH}_3)_2 + (\text{CH}_3)_2\text{C(OCH}_3)_2 \xrightarrow{5 \text{ mol} \%} \text{PhCH} + \text{C(CH}_3)_2 \]

87%

12. [\text{OTMS}]

\[ \text{CH}_3(\text{CH}_2)_3\text{CCH}_3 + CH_2=CC(CH_3)_3 \xrightarrow{5 \text{ mol} \% \text{ Bu}_2\text{Sn(O}_3\text{SCF}_3)_2} \text{CH}_3(\text{CH}_2)_3\text{CCH}_2\text{CC(CH}_3)_3 \]

100%

13. [\text{TMSO}] + [\text{furan}]

\[ \text{Ph}_3\text{C}^+\text{ClO}_4^- \xrightarrow{-78^\circ C} \text{Ph}_3\text{C}^+\text{ClO}_4^- \]

80%

14. [\text{furan}]

\[ \text{CH}_3\text{CO}_2\text{CH}_3 + \text{CH}_3\text{CO}_2\text{CH}_3 \xrightarrow{\text{TiCl}_4, -50^\circ C} \text{Z}:\text{E} \text{ isomers at the new enone double bond} \]

no stereochemical issues

two cyclic reactants, gave a 2:1 mixture of stereoisomers
2.1.5. Control of Facial Selectivity in Aldol and Mukaiyama Aldol Reactions:

In the discussion of the stereochemistry of aldol and Mukaiyama reactions, the most important factors in determining the syn or anti diastereoselectivity were identified as the nature of the TS (cyclic, open, or chelated) and the configuration (E or Z) of the enolate.
2.1.5.1. STEREOCHEMICAL CONTROL BY THE ALDEHYDE.
If either the aldehyde or enolate contains a stereocenter, four stereoisomers are possible.
There are four possible chairlike TSs, of which two lead to syn product from the Z-enolate and two to anti product from the E-enolate.

If the substituted aldehyde is racemic, the enantiomeric products will be formed, making a total of eight stereoisomers possible.
In the **Felkin model** for nucleophilic addition to carbonyl centers the **larger-substituent is aligned anti to the approaching enolate** and yields the 3,4-syn product. If reaction occurs by an alternative approach, the stereochemistry is reversed, and this is called an **anti-Felkin** approach.
Cram's Rule

How does this center control the direction of attack at the trigonal carbon?
Less steric effects

Major product

Minor product
The interpretation of Felkin and Anh

This is the important interaction that must be minimized. Thus, in this approach the carbonyl substituent plays the major role.
Obtuse attack trajectory minimizes unfavorable interactions between these orbitals.
The obtuse angle of attack supports the nonpassive role of the R-group in ketones. Not only will there be steric interactions between the S or M groups and the R-group, but also interactions with the incoming nucleophile due to the attack trajectory. In this model one would predict an increase of stereodifferentiation as the size of R increases. This has been found experimentally.

Preferred conformation. Less interaction between the small group and the R-group. Note that this model "feels" the influence of increasing size of R.

In this coformer, an increased interaction is seen between the medium group and R. Also, there is more interaction with the nucleophile.
Cases for Modification of the Models

Compare the "normal" situation with the influence of a sterically bulky Lewis acid

As the bulk of the Lewis acid increases

This gives the Cram product

This gives the "anti-Cram" product
Dipolar Model

often described as the Cornforth model

Preferred direction of attack.

favored conformer

Preferred direction of attack.

favored conformer
Chelation Control


Het = heteroatom
M = metal

Preferred direction of attack
The Evolution of Models for Carbonyl Addition
If the alkyl group is branched, it occupies the “large” position. Thus, the t-butyl group occupies the “large” position, not the phenyl.
The **Felkin** TS is **A**. TS B represents a **non-Felkin** conformer, but with the same facial approach as **A**. The preferred TS for the Z-enolate is believed to be structure **C**. with larger R groups favoring TS C because of an increased $R^2/R^L$ interaction.
Mukaiyama reactions of $\alpha$-methyl aldehydes proceed through an open TS and show a preference for the 3,4-syn stereoisomer, which is consistent with a Felkin TS.
The stereoselectivity of aldol addition is also affected by **chelation**. α and β-Alkoxy aldehydes can react through chelated structures with Li⁺ and other Lewis acids that can accommodate two donor groups.
Studies with **α-alkoxy** and **β-alkoxy aldehydes** with lithium enolates found only modest diastereoselectivity.
Several α-methyl-β-alkoxyaldehydes show a preference for 2,3-syn-3,4-anti products on reaction with Z-enolates.

Both α- and β-alkoxy aldehydes give chelation controlled products with SnCl₄ and TiCl₄, but not with BF₃. If there is an additional substituent on the aldehyde, the chelate establishes a facial preference for the approach of the nucleophile.
In each instance, the silyl enol ether approaches *anti* to the methyl substituent on the chelate. This results in a 3,4-*syn* relationship between the hydroxy and alkoxy groups for α-alkoxy aldehydes and a 3,5-*anti* relationship for β-alkoxy aldehydes with the main chain in the extended conformation.
A crystal structure is available for the SnCl₄ complex of 2-benzylxoxy-3-pentanone. The steric shielding by the methyl group with respect to the C=O is evident in this structure (Figure 2.1). NMR studies indicate that the reaction involves formation of trimethylsilyl chloride from the chelated intermediate. This step is followed by conversion to the more stable aldol chelate.
With $\alpha$-and $\beta$-benzyloxyaldehydes, the t-butylthio ketene acetals also gave chelation-controlled addition.
This reaction occurs through a TS in which the aldehyde is chelated, but the silyl thioketene acetal is not coordinated to the Ti (open TS).
The BF$_3$-catalyzed reactions occur through an open TS, whereas the TiCl$_4$ reactions are chelation controlled.
In the reaction of α-methylthiobutanal, where the methylthio group has the potential for chelation, BF₃ gave 100% of anti product, whereas TiCl₄ gave a 5:1 syn:anti ratio.

Chelation-controlled product is formed from reaction of α–benzyloxypropanal and the TBDMS silyl ketene acetal derived from ethyl acetate using 3% LiClO₄ as catalyst.
The reaction is believed to occur through a cationic complex, with the chloride ion associated with a second aluminum as \((\text{CH}_3)_2\text{AlCl}_2\). Interestingly, although TiCl\(_4\) induced chelation control with the benzyloxy group, it did not do so with the TBDMS group.
In the case of α-alkoxy aldehydes the preferred TS appears to be F and G for the E- and Z-enolates, respectively. The reactant conformation is believed to be determined by minimization of dipolar repulsion between the alk oxy substituent and the carbonyl group.
A BF$_3$-catalyzed reaction was found to be 3,5-anti selective for several β-substituted 5-phenylpentanals. This result can be rationalized by a TS that avoids an unfavorable alignment of the C=O and C–X dipoles.
The same stereoselectivity was observed with a more complex pair of reactants in which the β-substituent is a cyclic siloxy oxygen.

β-substituent is a cyclic siloxy oxygen
Thus we see that steric effects, chelation, and the polar effects of $\alpha -$ and $\beta$-substituents can influence the facial selectivity in aldol additions to aldehydes. These relationships provide a starting point for prediction and analysis of stereoselectivity based on structural effects in the reactant aldehyde. These general principles have been applied to the synthesis of a number of more complex molecules. Table 2.3 summarizes the relationships discussed in this section.

**Table 2.3. Summary of Stereoselectivity for Aldol Addition Reactions**

<table>
<thead>
<tr>
<th>Cyclic TS</th>
<th>Open TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-syn for $X^\alpha = \text{medium}$</td>
<td>3,4-syn for $X^\alpha = \text{medium}$</td>
</tr>
<tr>
<td>$E$-enolate 2,3-anti, 3,4-syn</td>
<td></td>
</tr>
<tr>
<td>$Z$-enolate 2,3-syn, 3,4-anti</td>
<td></td>
</tr>
</tbody>
</table>

$X^\alpha = \text{alkoxy}$

$E$-enolate 2,3-anti, 3,4-weak

$Z$-enolate 2,3-syn, 3,4-anti

$Y^\beta = \text{alkoxy}$ 3,5-anti