Aldol Reactions: E-Enolates and Anti-Selectivity

Matthew Grant Anderson
Utah State University

Follow this and additional works at: https://digitalcommons.usu.edu/gradreports

Part of the Organic Chemistry Commons

Recommended Citation
https://digitalcommons.usu.edu/gradreports/1312

This Report is brought to you for free and open access by the Graduate Studies at DigitalCommons@USU. It has been accepted for inclusion in All Graduate Plan B and other Reports by an authorized administrator of DigitalCommons@USU. For more information, please contact digitalcommons@usu.edu.
ALDOL REACTIONS:
E-ENOLATES AND ANTI-SELECTIVITY

Prepared By:

---------------------------
MATTHEW GRANT ANDERSON

A non-thesis paper submitted in partial fulfillment of the requirement for a Plan B Degree of Masters of Science in Organic Chemistry

UTAH STATE UNIVERSITY
Logan, Utah

2005
Contents

Page

CONTENTS...........................................................................................................i
LIST OF TABLES, FIGURES AND SCHEMES.................................................ii,iii
ABSTRACT...........................................................................................................iv

CHAPTER I.
ALDOL REACTIONS:E-ENOLATES AND ANTI SELECTIVITY.........1

CHAPTER II.
SECTION 1. MODELS OF E-ENOLATE FORMATION.........................12
SECTION 2. PATERSON ENOLATE PAPER .................................................15
SECTION 3. BROWN’S ENOLIZATION PAPER.................................18
SECTION 4. COLLUM’S ENOLIZATION PAPER..............................23

CHAPTER III. E-ENOLATES AND ANTI ALDOLS FROM
TOTAL SYNTHESIS......................................................................................29

REFERENCES.................................................................................................37
**List of tables, figures and schemes**

<table>
<thead>
<tr>
<th>Definition of stereocontrol. Figure 1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zimmerman Model. Figure 2a, 2b</td>
<td>3,4</td>
</tr>
<tr>
<td>Metal-oxygen bond lengths. Table 1</td>
<td>5</td>
</tr>
<tr>
<td>DuBois transition states. Figure 3</td>
<td>6</td>
</tr>
<tr>
<td>Evans auxiliary. Figure 4</td>
<td>8</td>
</tr>
<tr>
<td>Ghosh auxiliary. Figure 5</td>
<td>9</td>
</tr>
<tr>
<td>Corey Lewis Acid. Figure 6</td>
<td>10</td>
</tr>
<tr>
<td>Noyori Model. Figure 7</td>
<td>11</td>
</tr>
<tr>
<td>Ireland Model. Figure 8</td>
<td>12</td>
</tr>
<tr>
<td>Rotamers. Figure 9</td>
<td>14</td>
</tr>
<tr>
<td>Paterson enolate scheme. Figure 10</td>
<td>16</td>
</tr>
<tr>
<td>Trends in enolization. Table 2</td>
<td>17</td>
</tr>
<tr>
<td>Enolization of <em>iso</em>-propyl ethyl ketone. Table 3</td>
<td>19</td>
</tr>
<tr>
<td>Enolization of 3-pentanone. Table 4</td>
<td>20</td>
</tr>
<tr>
<td>Enolization of ethyl <em>tert</em>-butyl ketone. Table 5</td>
<td>21</td>
</tr>
<tr>
<td>Enolization of ethyl phenyl ketone. Table 6</td>
<td>22</td>
</tr>
<tr>
<td>Lithium Species. Figure 11</td>
<td>24</td>
</tr>
<tr>
<td>Selectivity of enolization. Figure 12</td>
<td>25</td>
</tr>
<tr>
<td>Effect of added LiCl. Figure 13</td>
<td>26</td>
</tr>
<tr>
<td>Effect of added LiBr. Figure 14</td>
<td>27</td>
</tr>
</tbody>
</table>
Trends in enolization. Table 7 ................................................................. 27
Retrosynthetic Analysis. Scheme 1 ............................................................ 30
Synthesis of Fragment 7. Scheme 2 ............................................................. 31
Synthesis of Fragment 8. Scheme 3 ............................................................ 32
Synthesis of fragment 9. Scheme 4 ............................................................ 32
Lithium Aldol Coupling Between Fragment 8 and 9. Scheme 5 .................... 34
Lithium Aldol Coupling Between Fragment 52 and 56. Scheme 6 ................. 35
Abstract

A common structural motif in complicated natural product molecules is an alkyl group at an alpha position to a carbonyl and an alcohol at the beta position anti to each other. This arrangement occurs in bioactive molecules that are important for medical research such as spongistatin A at the C15-C16 position and in (-)-baconipyrone C at C12-C13. Bioactive molecules such as these generally occur in such a low concentration in the organism in which they originate that deriving them from the natural source for research is not practical so efficient syntheses are sought. Reactions that produce 1,2 syn aldol products have been perfected under most circumstances, but methods to produce 1,2 anti aldol products without bulky alkyl groups on the enolizable compound still need to be perfected. In the case of 3-pentanone under conditions of E-enolization the yield is only approximately 70:30 E:Z. Anti aldol reactions generally result from E-enolates but in the case of the enolate of 3-pentanone without large alkyl groups to enforce a particular geometry in the pericyclic transition state between the enolate and carbonyl compound the yield of 70:30 E:Z goes down to 64:36 anti:syn. Quoting Erick M. Carrera¹ “additions that produce anti substituted aldol adducts remain elusive and intractable”. Since the best yields of E-enolates and anti aldol reactions rely on the short Lewis Acid-oxygen bond length to maximize steric interactions in the transition states perhaps different Lewis Acids can be developed that have shorter LA-oxygen bond lengths.
Chapter I

Aldol Reactions: E-Enolates and Anti Selectivity

An aldol addition is the nucleophilic attack on a carbonyl by an enolate to create a beta hydroxy carbonyl compound. If the reaction is followed by dehydration that results in the formation of a double bond the reaction is called an aldol condensation. The aldol reaction is arguably the most important reaction for lengthening a carbon chain that contains chiral centers. The enolates that participate in an aldol reaction can be formed under two types of conditions, either thermodynamic deprotonation or kinetic deprotonation. A thermodynamically formed enolate generally has the most substituted double bond or conjugated double bond and is more stable because of this substitution. The kinetically formed enolate is formed by having the most easily (accessible) removable proton abstracted and is generally less substituted. If the thermodynamic product is desired then a larger or more loosely held counterion such as sodium or potassium is used as this allows for proton exchange and the reaction is done in a protic solvent at warmer temperatures and the enolate is allowed to come to equilibrium with its most stable form. But since equilibrium conditions exist the enolates can rearrange or the ensuing aldol product can return to their starting materials. Generally the stereoselectivity of an aldol reaction using thermodynamically formed Z-enolate is higher than for the kinetically formed E-enolates. When the kinetically deprotonated enolate is desired a smaller more tightly bound counterion such as titanium, lithium or boron is used as this decreases the rate of proton exchange, and an aprotic solvent and cold temperatures (generally from -100°C to -35°C) are also used. Usually a sterically hindered strong
base is employed which cannot act as a nucleophile. It is possible to achieve a great deal of regioselectivity in deprotonation\textsuperscript{3}. In addition to thermodynamic and kinetically formed enolates based on kinetic acidity as well as degrees of substitution of the double bond there is another definition based on whether the alkyl group is on the same side of the double bond as the enolate oxygen or on the opposite side. If the alkyl group is on the same side of the double bond as the oxygen this is referred to as the \textit{Z} (\textit{zusammen} = together) configuration, this configuration is generally more stable. If the alkyl group is on the opposite side of the double bond from the oxygen this is referred to as the \textit{E} (\textit{entgenen} = opposite) configuration and is generally less stable. \textit{Z}-enolates predominantly give syn addition in aldol reactions whereas the \textit{E}-enolate predominantly gives the anti addition product. The anti and syn terms refer to the orientation of the \( \alpha \) and \( \beta \) substituents and are with respect to the lowest energy conformation of the molecule. However if a \( \sigma \) bond is rotated this \textit{syn anti} description is no longer clear.

If the stereochemical outcome of an aldol\textsuperscript{4} reaction is determined by either the enolate or carbonyl compound this is referred to as being substrate controlled. If the stereochemical outcome of a reaction is based on either a chiral base or a Lewis Acid this is referred to as being reagent controlled (figure 1). Using a chiral reagent can override inherent substrate control.

\textbf{Figure 1.} Substrate control if stereoinduction from \( R_1 \cdot R_2 \) or \( R_3 \). Auxiliary control if stereoinduction from \( R_1 = \text{a auxiliary} \). Reagent control if stereoinduction from \( ML_n \) or added Lewis Acid.
When an achiral enolate and an achiral carbonyl compound react they form up to two new chiral centers, one on the α carbon and one on the β carbon provided the enolate is substituted at its α position. This is referred to as simple diastereoselection. Since an achiral enolate is planar there is no facial preference for the achiral carbonyl compound provided there are no effects by the Lewis acids if they are employed. Using the Zimmerman Model the four stereoisomers can generally be predicted (figure 2a, 2b) by assuming a closed chair like transition state where the metal chelates to both oxygens.

**Figure 2a.** The Zimmerman Model for E-enolates.
Figure 2b. The Zimmerman Model for Z-enolates.

Diastereoselection is best when using smaller metal ions such as boron, titanium and lithium that form short metal-oxygen bonds as this gives a tighter transition state (table 1) and maximizes steric interactions. According to Heathcock\(^5\) boron is much less reactive than lithium, which leads to a later more product like transition state in which steric interactions are more important.
Table 1. Metal-oxygen and metal-ligand bond lengths.

<table>
<thead>
<tr>
<th>Metal</th>
<th>M-O Bond Length (Å)</th>
<th>L</th>
<th>M-L Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-O</td>
<td>1.36-1.47</td>
<td>Cr₃</td>
<td>1.51-1.58</td>
</tr>
<tr>
<td>Ti-O</td>
<td>1.62-1.73</td>
<td>Cl</td>
<td>2.18-2.21</td>
</tr>
<tr>
<td>Al-O</td>
<td>1.92</td>
<td>Cr₃</td>
<td>2.00-2.24</td>
</tr>
<tr>
<td>Li-O</td>
<td>1.92-2.00</td>
<td>O₂R₂</td>
<td>1.92-2.00</td>
</tr>
<tr>
<td>Zn-O</td>
<td>1.92-2.16</td>
<td>Cl</td>
<td>2.18-2.25</td>
</tr>
<tr>
<td>Mg-O</td>
<td>2.01-2.03</td>
<td>Br</td>
<td>2.43</td>
</tr>
<tr>
<td>Zr-O</td>
<td>2.16</td>
<td>C₅H₅</td>
<td>2.21</td>
</tr>
</tbody>
</table>

THF seems to be the optimum solvent for generating anti aldols but if very polar solvents like HMPA or DMPU are used this disrupts the pericyclic transition state and lowers anti selectivity. This model relies on the chelate being achiral. The stability of these transition states is mostly governed by the 1,3 diaxial interactions of the alkyl groups. In the case of the most favorable pathway for the reaction of the Z- enolate and an aldehyde the 1, 3 interactions are better if R₁ is axial and R₃ is equatorial **TS A** (figure 2b) rather than both groups being axial as in **TS C** or **D**. **TS A** becomes even more favorable as R₁ and R² become larger as this maximizes the 1,3 interactions, when R² is very large R² and R³ or R¹ and R² gauche interactions may override 1,3-diaxial interactions. For the most favorable reaction pathway for the E- enolate the same 1,3 interactions prevail **TS E and F** (figure 2a). As with the E- enolate the diastereoselectivity increases as R¹ and R² become more sterically demanding but selectivity can change as R² becomes very large. Since the E or Z enolate has no facial preference it can attack the achiral carbonyl from either the re or si face leading to equimolar quantities of each diastereomers. Therefore simple diastereo selection would not be practical for use on advanced intermediates. Since it would be very difficult to separate the diastereomers from simple diastereo selection
it may not be practical to use for making simple starting materials unless reagent control is employed such as a chiral Lewis Acid. Chiral Lewis Acids can have a facial preference for the pericyclic transition state.

A slightly more refined version of the Zimmerman model proposed by DuBois\(^6\) predicts (figure 3) a skewed conformation of the transition state. This explains the greater stereo selectivity of the Z-enolate over that of the E-enolate. This model explains why Z-enolates are more stereoselective even when \(R^1\) is not large.

**Figure 3. DuBois model transition states.**

Another transition state model is the Noyori Open Chain Model which assumes that the oxygens are not brought near each other in the transition state by chelation and are as far apart as possible. This model can be invoked when both the E and Z-enolate give syn addition. There are numerous other transition\(^7^{,8}\) state models that have been postulated but the above mentioned examples predict the stereochemical outcome in the vast majority of cases. In fact entire aldol review articles written by the foremost experts in the field invoke only the Zimmerman model.\(^9\)

A second type of stereoselection is diastereoface selection. If either the carbonyl compound or the enolate contain a chiral center near the site of reactivity it
can affect the facial selectivity of an achiral reacting partner. This chiral center is preserved during the reaction leading to a product that has up to three chiral centers.

A third type of stereoselection is double stereo differentiation. This occurs when both reacting partners have a chiral center leading to a product that has up to a total of four chiral centers, the two being preserved during the reaction as well as the two newly created centers. If the chiral centers complement each other in the transition state this leads to a greater amount of facial selectivity and is referred to as consonance or as both reacting partners being matched. If the two chiral centers work against each other in the transition state this is referred to as dissonance or as having the reacting partners being mismatched. An advantage of using either diastereoface selection or double stereo differentiation rather than chiral auxiliaries is that they rely on the inherent chirality of either the enolate or carbonyl compound to affect stereo induction, and do not have any groups that have to be installed in the case of auxiliaries.

To provide a greater amount of facial discrimination in aldol reactions either auxiliaries or chiral auxiliaries can be attached to the carbonyl compound before enolization and then removed after the reaction. Perhaps a better example of how chiral auxiliaries affect facial selectivity comes from the alkylation of an enolate rather than an aldol reaction. In the Evans total synthesis of cytovirin the (1S,2R)-norephedrin derived (figure 4) enolate 2 (referred to as Evans type Oxazolidinones) has the si face inaccessible because of the phenyl and methyl substituents on the norepedrin making only the re face accessible. If the absolute configuration of the methyl and phenyl groups were opposite this would then make only the si face
accessible. Generally Evans type chiral auxiliaries contain a dipole moment inducing atom such as the oxygen of a carbonyl as well as steric discriminating groups (in this case methyl and phenyl). The steric discriminating groups generally prevent the enolate from adopting an E configuration during deprotonation so there are only rare examples of E-enolate auxiliaries and in turn very few anti aldol additions using chiral Evans Oxazolidinones type auxiliaries.

But with different types of auxiliaries there have been exceptions. One such example comes from Ghosh and Onishi\(^\text{12}\) (figure 5).

**Figure 4.** A chiral auxiliary popularized by Evans.
In their paper they describe the synthesis of anti aldol ester molecule D starting with cis-1-arylsulfonamideo-2-indanol (molecule A) via Z-enolate C. For this particular reaction the trend shows an increase in anti selectivity with larger $R^1$ groups on the aldehyde.

If boron is used as a chelate when using chiral auxiliaries it can only chelate to two oxygens because it is only bidentate. First it chelates with the carbonyl on the
auxiliary and the enolate oxygen but upon entering into the pericyclic transition state of the Zimmerman Model it disassociates from the auxiliary carbonyl and forms an association with the incoming carbonyl oxygen. So with bidentate metals the chiral auxiliary is held free in either an axial or equatorial position. In the case of tridentate metals such as titanium they can chelate to both carbonyl of the auxiliary and the enolate oxygen holding them rigid, and upon entering into the pericyclic transition state it can chelate to the incoming carbonyl compound. A drawback of auxiliaries is that they must be installed and then removed adding extra steps.

In the case of simple diastereoselection previously given (figure 2a) the two most favorable pathways for the E-enolate lead to an equimolar amount of two diastereomers as there is no facial preference in the transition state for the achiral boron ligands. But if the boron has chiral ligands such as that used by Corey (figure 6) they will have a preferred orientation in the transition state and make TS A (figure 2a) preferred over TS B leading only to one diastereomer being produced.

**Figure 6.** A chiral Lewis Acid reagent used by Corey to make TS A pathway in figure 2a predominate.

In a Mukaiyama aldol reaction the enolate relies on a silane group as a counterion. It is probably best not to describe the silane group as counterion as it is stably covalently bonded to the oxygen forming a stable enol ether. Since these enol ethers are weak nucleophiles the carbonyl compound they are reacted with must be
activated with a strong Lewis Acid such as titanium chloride to make the reaction proceed. Also the reaction proceeds poorly at cold temperatures and both E and Z-enolates give syn aldols. The silane group cannot chelate as in the previous models so the Noyori Open Chain Model can be used to predict the stereochemistry outcome (figure 7).

**Figure 7.** Product as determined by the Noyori Open Chain Model.
Chapter II
Section 1

Models of E-Enolate Formation

Since E-enolates lead preferentially to syn addition in aldol reactions they will be discussed further. Also there are fewer examples of E-enolates in the literature since they are kinetically formed and less stable and harder to prepare than the thermodynamically formed Z-enolates counterparts. Unfortunately most examples of either type of enolate formation from text books and journals rely on large alkyl groups such as iso-propyl, tert-butyl, phenyl or benzyl groups to help control formation of the enolate and in turn the stereo chemistry of the aldol product. But there are generally not any of these large substituents present in the structure of large natural product molecules of interest to total synthesis chemists. Therefore these examples are not totally applicable to natural product synthesis. In theory, according to the Ireland\textsuperscript{14} Model (figure 8) it should be easy to prepare E-enolates by simply choosing a lithium amine base with large ligands thus causing repulsion of the largest $\alpha$ group on the enolizable compound.

\textbf{Figure 8.} Enolization as predicted by the Ireland model.

But this must not be the case as there are currently very few examples of this type of reagent based E-enolization given in the literature for the preparation of anti
aldols. The Ireland Model is an oversimplification since it involves a monomeric lithium species. In actuality they would exist as aggregates of oligomers. Experimentally generating lithium E-enolates with lithium amines have at best average to poor yields\(^5,\^{11,15}\) in the case of enolates with small alkyl substituents. In the case of diethyl ketone where there are no bulky alkyl groups to enforce the conformation favorable to E-enolization the yield is only 70:30 E:Z and since the lithium-oxygen bond is longer than that of the boron enolate the steric interactions are not maximized in the pericyclic transition state. So for diethyl ketone with 70:30 E:Z the yield of anti:syn aldol goes down to 64:36. Using lithium amine bases the yields go up to 95% for ester E-enolates the ester oxygen must contribute to stability. Lithium enolates are not the reagent of choice for generating E-enolates but they are very successful at generating Z-enolates and syn addition. It was shown by Collum \textit{et al} in 1991 that lithium E-enolates may isomerize into Z-enolates over time.\(^{17}\) Perhaps a more accurate model\(^{16}\) of enolization is provided by figure 9 conformation \textbf{A}.

With the methyl gauche\(^{18}\) to the carbonyl \textbf{A} is less stable by 800 cal mol\(^-1\) than conformation \textbf{B} having the methyl group nearly eclipsed to the carbonyl, disregarding solvent effects the entropy savings of going from the \textbf{B} to the \textbf{A} conformation for ethyl, \textit{n}-propyl, \textit{iso}-propyl and phenyl is -700, -600 and -300 cal mol\(^-1\) respectively. In conformation \textbf{A} the methyl group is driven away from the incoming base and is eclipsed over the oxygen during deprotonation which is more favorable than having it eclipse the R group leading preferentially to the Z-enolate. In addition to the conformation \textbf{B} (figure 9) as being more stable the corresponding E-enolates are also less stable. Using a bulky R group should increase the amount of Z-enolate formed.
The most success forming E-enolates has been achieved using dicyclohexylboryl chloride as the Lewis Acid and triethyl amine as the base at cold temperatures. But this method is not completely perfected yet as without a large $R^1$ group to force the Lewis Acid to be cis to the least substituted side of the carbonyl during deprotonation the yields are only as high\(^\text{17}\) as 12:79 Z:E in the case of diethyl ketone. The only way to improve on these low yields for enolates with non bulky substituents may be to develop Lewis Acids that will have shorter metal-oxygen bonds that will maximize the steric interactions of small alkyl groups such as methyl and ethyl in the transition states.

Several papers will now be reviewed in an attempt to explain the good results obtained with boron enolates and the problems associated with using lithium as a counterion.
Section 2

Ian Paterson and Jonathan M. Goodman’s journal article Enolisation of Ketones by Dialkylboron Chlorides and Triflates: a Model for the Effect of Reagent Leaving Group, Substrate Structure and Amine Base studied how the dihedral angle between the different leaving groups on the dialkyl boron and the carbonyl oxygen, as well as electronic effects, affect the regio and stereoselective enolization of ketones. When a dialkyl boron chloride with the sterically hindered alkyl groups cyclohexyl (cHex) or isopinocamphenyl (Ipc) form a Lewis acid complex (figure 10) with the carbonyl oxygen of a ketone, for example ethyl iso-propyl ketone, the chlorine leaving group will orient itself cis to the less substituted side of the carbonyl as the less substituted side is better able to stabilize the developing partial negative charge of the leaving group. The authors give charge stabilization rather then steric as the main reason for this orientation. Also the LG-B bond will eclipse the carbonyl double bond. The authors state this is because of the anomeric effect which is assumed to mean that this orients the oxygen lone pair orbital and the boron anti bonding orbital in a favorable alignment so transfer of electrons can occur. Indication of an anomeric effect comes from a shorter B-O bond than expected. The developing negative charge on the chlorine as it begins to depart will induce a partial negative charge on the α carbon adjacent to it, activating it towards deprotonation by either NEt₃ or tPr₂NEt. In addition to activation towards deprotonation by inducing a partial negative charge, the chlorine does not have a great enough steric bulk to impede the approach of the base structure 1 (figure 10). In this transition state the
ethyl group is forced by the boron to be anti to the carbonyl if drawn in a Newman Projection.

**Figure 10.**

For this example the E:Z = 3:97. Unfortunately without any bulky groups to force the boron complex to the least substituted side the greatest E-selectivity is 79:21 in the case of diethyl ketone. When bulky groups such as iso-propyl or tert-butyl groups are used they force the boron complex over the less substituted side giving high E-selectivity up to 97:3, see Table 2 for trends.

In the same system used above using triflate as the leaving group the sterics of the triflate force the boron complex to be cis to the less substituted side. The bulk of
the triflate impedes the approach of the amine base so deprotonation is directed trans to it (molecule 3).

Table 2. Trends in enolization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>L₂BCl</th>
<th>L₂BOTf</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me(CO)Et</td>
<td>-----</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>Et(CO)Et</td>
<td>21:79</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>iBu(CO)Et</td>
<td>12:88</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>iPr(CO)Et</td>
<td>3:97</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>tBu(CO)Et</td>
<td>3:97</td>
<td>25:75</td>
</tr>
</tbody>
</table>

Also with the triflate trans to the deprotonation site the alkyl group can be in its lower energy conformation and eclipse the carbonyl and upon deprotonation will yield the Z-isomer (molecule C). With both the triflate and the chlorine boron complex the dihedral angle between the B-LG and carbonyl double bond is said to play an important role. Having a greater dihedral angle in the case of the triflate leaving group gives it less of a preference for the least substituted side of the carbonyl based on charge stabilization. Please note that in figure 10 the triflate does indeed orient itself over the iso-propyl side regardless of sterics. In this paper for E-enolate formation the proton is always abstracted from the less substituted side. It will have to be investigated in further papers if deprotonation can be forced to occur on the more substituted side expanding the range of enolate building blocks. Another shortcoming of this paper is the yields for E-enolates are low unless the carbonyl is substituted with large alkyl groups such as tert-butyl or iso-propyl. This is not a flaw in the paper itself, but is an inherent flaw for E-enolizations. Unfortunately there probably would not be any bulky groups such as these in a large molecule of interest to natural product synthesis chemists unless they were installed as auxiliaries.
Section 3

Herbert C. Brown’s paper Enolboration. 4. An Examination of the Effect of the Leaving Group (X) on the Stereoselective Enolboration of Ketones with Various $R_2BX/Et_3N$. New reagent for the Selective Generation of either Z or E Enol Borinates from Representative Ketones, studies mainly the effect of a leaving group ability on the complexed dialkyl boron and its effect on either E or Z-enolization. It has previously been determined that $R_2BOTf$ reagents predominantly form Z-enolates while $R_2BOCl$ gives mainly E-enolates. It is postulated by the authors that leaving group ability may be the cause of this selectivity, triflate being a strong leaving group while chlorine is a relatively poor leaving group. The authors want to test this hypothesis by selecting leaving groups of intermediate ability such as mesylate and iodine, as well as varying other parameters such as the steric requirements of the alkyl groups on the boron and ketones with alkyl groups of varying steric requirements.

For the first set of data in table 3 and equation 3 boron complexes having as alkyl groups either 9-borabicyclo[3.3.1]nonane (9-BBN), and the more sterically demanding di-cyclohexyl substituents (cHex) with the 5 different leaving groups, and their effects on ethyl isopropyl enolization by triethylamine were studied. According to the authors in this case and all proceeding data sets regardless of whether triflate or chlorine was used the proton was abstracted from the least substituted side of the carbonyl. In this data set the highest E selectivity is 97:3 E:Z with the cyclohexyl as the alkyl groups and chlorine as the leaving group. The bulky alkyl groups on boron force the methyl group to be anti to oxygen upon deprotonation, but if this conformation was solely enforced by sterics then it would also be enforced with
triflate as the leaving group since it is bulkier than chlorine. So as the authors will prove the leaving group ability also plays a major role. The lowest E selectivity of 12:88 E:Z is obtained with the sterically smaller 9-BBN as the alkyl group and triflate as the leaving group.

\[ \text{R}_2\text{BX}, \text{Et}_3\text{N} \rightarrow \text{OBR}_2 \quad \text{and/or} \quad \text{OBR}_2 \quad \text{and/or} \quad \text{OBR}_2 + \text{Et}_3\text{N}^*\text{HX} \]

(eq 3)

<table>
<thead>
<tr>
<th>X</th>
<th>Z</th>
<th>E</th>
<th>Yield %</th>
<th>Z</th>
<th>E</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTf</td>
<td>88</td>
<td>12</td>
<td>96</td>
<td>25</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>OMs</td>
<td>82</td>
<td>18</td>
<td>94</td>
<td>23</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
<td>I</td>
<td>73</td>
<td>27</td>
<td>97</td>
<td>32</td>
<td>68</td>
<td>98</td>
</tr>
<tr>
<td>Br</td>
<td>57</td>
<td>43</td>
<td>96</td>
<td>11</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>Cl</td>
<td>46</td>
<td>54</td>
<td>95</td>
<td>&lt;3</td>
<td>&gt;97</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 3. Trends in enolization of iso-propyl ethyl ketone.

For the second set of data in table 4 (eq. 4) the enolization of diethyl ketone was studied; the only difference from the first set of data (eq 3) is that there is an ethyl group rather than an iso-propyl group on the ketone. But this affects selectivity greatly, under optimum conditions for E-enolate formation (chlorine as the leaving group and cyclohexane as the ligands). There is only a yield of 79:21 E:Z. In the previous data set the yield was 97:3 E:Z. This change in selectivity cannot be explained easily. According to figure 4 of chapter 2 the iso-propyl group should make TS A1 more favorable but instead it seems to improve the yield. And using this same model\textsuperscript{16} transition state B2 that leads to the formation of E-enolate should be
favored by the smaller R group ethyl, but instead it increases the yield of Z isomer. With 9-BBN as the alkyl groups the Z isomer is almost exclusively produced. The authors attribute this to the smaller size of the alkyl group being more important than the nature of the leaving group.

![Chemical structure](image)

Table 4. Trends in enolization of 3-pentanone.

<table>
<thead>
<tr>
<th>9-X-9-BBN</th>
<th>cHex₂BX</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Z</td>
</tr>
<tr>
<td>OTf</td>
<td>&gt;97</td>
</tr>
<tr>
<td>OMs</td>
<td>&gt;97</td>
</tr>
<tr>
<td>I</td>
<td>&gt;97</td>
</tr>
<tr>
<td>Br</td>
<td>&gt;97</td>
</tr>
<tr>
<td>Cl</td>
<td>&gt;97</td>
</tr>
</tbody>
</table>

The third set of data in table 5 was collected from the enolization of ethyl tert-buty1 ketone. Using triflate as the leaving group and cyclohexane as the ligands the yield is 97:3 E:Z which seems rather high, since according to the Paterson model given in section 2 of chapter II the triflate because of steric reasons will generally orient itself over the smaller group and direct deprotonation trans to it. Since there is no trans hydrogen for the base to abstract the overall yield of the reaction should not be so high at 85%, as the triflate is supposed to repel the base because of steric.

According to the authors the use of the large tert-buty1 group has been used to give the E-enolate exclusively. But this also contradicts the model of deprotonation given in figure 4 of chapter 2 where large R groups should favor the formation of Z-enolate.
Data in table 6 was collected for the enolization of propiophenone. Using 9-BBN as the alkyl groups and triflate as the leaving group the amount of Z isomer formed is surprisingly as high as 3:97 E:Z. Since the triflate is forced by the phenyl group to be cis to the ethyl side it would seem that it would not allow the ethyl group to adopt a Z conformation upon deprotonation. But perhaps because of the small size of the alkyl groups it allows for a very large dihedral angle between the LG-B and carbonyl double bond, and allows the ethyl to assume a Z orientation. Using 9-BBN as the alkyl groups and chlorine as the leaving group the yield of E isomer is rather high at 48:52 E:Z. Perhaps the small size of the 9-BBN group allows the boron to be trans to the phenyl side which would allow the methyl group to assume either a E or Z conformation upon deprotonation. Using cyclohexane as the ligands the yield goes up to 97% E isomer. Perhaps the lower yield with 9-BBN as the alkyl group could be attributed to the smaller size of this alkyl group which allows for a greater dihedral
angle which would allow the ethyl group to assume either a E or Z configuration upon deprotonation.

\[
\text{O} \quad \text{R}_2\text{BX, Et}_3\text{N} \quad \text{Ph} \quad \text{OBR}_2 \quad \text{and/or} \quad \text{OBR}_2 \quad \text{Ph} \quad + \quad \text{Et}_3\text{N}^*\text{HX}
\]

(eq 6)

Table 6. Trends in enolization of ethyl phenyl ketone.

<table>
<thead>
<tr>
<th>9-X-9-BBN</th>
<th>cHex_2BX</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Z E Yield%</td>
</tr>
<tr>
<td>OTf</td>
<td>&gt;97 &lt;3 97</td>
</tr>
<tr>
<td>OMs</td>
<td>&gt;97 &lt;3 96</td>
</tr>
<tr>
<td>I</td>
<td>&gt;97 &lt;3 98</td>
</tr>
<tr>
<td>Br</td>
<td>83 17 96</td>
</tr>
<tr>
<td>Cl</td>
<td>52 48 97</td>
</tr>
</tbody>
</table>

In all cases except for the enolization of ethyl *iso-*propyl ketone, *tert-*butyl ketone and propiophenone using the smaller 9-BBN gives a lower yield for E-enolates. Perhaps the *iso-*propyl, *tert-*butyl and phenyl groups are very effective at directing the boron complex to be trans to them. This study shows that the better leaving group does favor the formation of Z-enolates while the poorer leaving groups favor E-enolate formation. The smaller 9-BBN substituent on boron favors Z selectivity while the bulkier cyclohexane groups favor E selectivity.

Perhaps it is the size of the leaving group rather than leaving group ability that contributes to E selectivity? Perhaps using alkyl groups on the boron larger that cyclohexane could improve E selectivity further?
Section 4

David Collum and associates' article\textsuperscript{17} \textit{Effects of Lithium Salts on the Stereochemistry of Ketone Enolization by Lithium 2,2,6,6-Tetramethylpiperadine (LiTMP). A Convenient Method for Highly $E$-Selective Enolate Formation}, studies the $E/Z$ composition as a function of time and also the effect of various amounts of added lithium bromide or lithium chloride on the ratio of $E/Z$ enolate formed. In 1984 Corey and Gross\textsuperscript{24} found that for the enolization of 3-pentanone with the sterically hindered base LOBA (1,1,3,3-tetramethylbutyl-\textit{tert}-butylamide) $E/Z$ is 70:30. However, if the enolate is trapped as it is formed, the percent composition is increased to 98:2 $E/Z$. Taking these results into account Collum \textit{et al} postulated that trapping the enolate as a silane breaks up the lithium enolate and lithium enolate-LiTMP aggregates into smaller dimers and monomers\textsuperscript{25} (figure 11) that can participate more effectively in an Ireland Model type deprotonation.
Figure 11. X=cyclohexanolate, Br or Cl. Reaction composition of the enolate of cyclohexanone determined in a proceeding Collum\textsuperscript{25} paper.

And the trapping may also prevent E to Z isomerization if it is occurring. But it is not the addition of silane that facilitates this higher yield but rather the lithium chloride it generates.

First of all the authors study the E/Z composition as a function of the total percent conversion (figure 12). At the onset of the reaction E/Z equals 30:1 but this ratio goes steadily down over the course of the reaction. Nearing 100% conversion the ratio is approximately E/Z equals 9:1. The authors postulate that this decline is mostly caused by a change in mechanism brought about by the formation of lithium species aggregates over time rather than isomerization. In the initial stages of the
reaction the kinetic pathway via the Ireland Model is favored but as more enolate forms they begin to form aggregates that disfavor this kinetic pathway.

**Figure 12.** Selectivity of 3-pentanone enolization at -78°C in THF.

Since lithium halides increase the amount of E-enolate formation data was collected from the enolization of 3-pentanone with LiTMP in the presence of either lithium chloride or lithium bromide. The second set of data was collected (figure 13)
by varying the amount of lithium chloride from 0.0 equivalents to 2.0 equivalents. The optimum amount of E-enolate is formed using 0.35 equivalents of salt. For the addition of lithium bromide the optimum amount of salt is approximately 1.1 equivalents (figure 14).
Figure 14. Selectivity of 3-pentanone enolization in the presence of LiBr at -78°C in THF.

For the variation of parameters of ketone, base, TMS and amount of lithium bromide added optimum conditions were found (equation 7 and table 7).

Table 7. E/Z enolization selectivity for selected lithium dialkyl amides in THF at -78°C.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>R₁,R₂</th>
<th>LDA</th>
<th>LOBA/TMSCI</th>
<th>LiTMP</th>
<th>LiTMP-LiBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Et, Me</td>
<td>3.3:1</td>
<td>50:1</td>
<td>5:1</td>
<td>50:1</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr, Me</td>
<td>1.7:1</td>
<td>2:1</td>
<td>1&gt;20</td>
<td>21:1</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu, Me</td>
<td>1:50</td>
<td>1:50</td>
<td>1&gt;20</td>
<td>1&gt;20</td>
</tr>
<tr>
<td>12</td>
<td>Me, Ph</td>
<td>13:1</td>
<td>12:1</td>
<td></td>
<td>32:1</td>
</tr>
</tbody>
</table>
The authors did not postulate on the exact mechanism or change in mechanism brought about by the addition of a salt, but simply say that it effects the lithium enolate aggregates in such a way as to favor the kinetic pathway and that the addition probably results in the formation of LiTMP-LiX that can participate in an Ireland Model transition state more easily.
Discodermolide is one of the most effective tubulin polymerizing agents known. But it only occurs at a concentration of 0.002% weight in sponges so extracting it from sponges for cancer research is not practical. In addition the sponge is rare and occurs at such a great ocean depth that it must be harvested with an unmanned submersible. So an effective synthetic route was sought. This synthesis by Paterson and associates has an overall yield of 10.3%. Their paper\textsuperscript{26} \textit{A Practical Synthesis of (+) Discodermolide and Analogs: Fragment Unions by Complex Aldol reactions}, contains a total of five aldol reactions. In scheme 1 molecules 7, 8 and 9 have the C4-C5, C12-C13 and C19-C20 bonds constructed respectively using standard E-enolate and anti selective aldol methodology.
Scheme 1. Retrosynthetic analysis.

The major coupling that forms the C6-C7 bond between molecule 7 and 52 (scheme 6) is also formed in this manner. The major coupling at C16-C17 was made using lithium enolate methodology. The reaction starts with the synthesis of fragment 7, which has the 1,2 anti configuration on C5 and C6 installed using substrate (scheme 2) based anti selective aldol reaction via a E-enolate. Alpha chiral ketone (S)-10 is first complexed with cHex$_2$BCl at 0°C and then deprotonated with triethylamine to afford E-enolate 14 which was then cooled to -78°C. To this solution was then added acetaldehyde. The most favorable pathway for E-enolates was followed in the Zimmerman Model (re attack) to yield a 1,2 anti aldol. The aldol reaction was then
followed by in situ reduction giving a yield over two steps of 86% with a yield of the desired diastereomer of 97%.

**Scheme 2.** Synthesis of fragment 7.

For the construction of fragment 8 (scheme 3) the same reagents were used in the enolate/aldol step except the carbonyl compound is methacrolein rather than acetaldehyde, the same transition state is followed giving a yield of 95%, with greater than 97% yield of the desired diastereomer molecule 20.

Synthesis of fragment 9 (scheme 4) begins with the E-enolization of benzyl protected chiral ketone (S)-12 which is then coupled to chiral aldehyde 29 under the same standard E-enolate forming conditions. For these two steps the yield is 99% and a greater than 97% yield of the desired diastereomer.


The major coupling between molecules 8 and 9 (Scheme 5) begins with the enolization of molecule 8 using optimum lithium E-enolate forming methodology of LiTMP/LiBr reagents. The reaction was performed at -100°C to prevent the
epimerization of the $\alpha$ methyl group on the aldehyde 9. This could possibly be caused by the extreme reactivity of lithium. Perhaps the epimerization occurs in the pericyclic transition state. Also, at higher temperatures, the enolate experiences $\alpha$ elimination to yield the aromatic substituted enolate. This could also be caused by the reactivity of the lithium ion. The reaction proceeds via the most favorable pathway for E-enolates in the Zimmerman model. The transition state is also said to follow Felkin-Ahn selectivity which means that if molecule 9 the medium sized R group (in this case methyl) will be gauche to the carbonyl during the attack of the nucleophile which will be delivered over the least hindered hydrogen side of the Newman Projection. The enolization and aldol reaction have a yield of 81% with greater than 97% excess of the desired diastereomer.
Scheme 5. Lithium aldol coupling between fragment 8 and 9.

In order to get the desired stereochemistry at C7 on molecule 58 the enolate of ketone 7 would have to attack the carbonyl of molecule 52 from the si face. But using cHex$_2$BCl as a Lewis Acid the nucleophilic attack occurred over the least sterically crowded face of the molecule giving re addition with only 12:88 of the desired enantomer with an overall yield of 67%. It was thought that it was the size of the cyclohexyl ligands that made re attack favorable so boron with the larger isopinocampenyl (ipc) ligand was used and the amount of desired enantomer went up to 84:12 with an overall yield of 87%. Using these larger ligands overrides the inherent selectivity of the aldehyde.
Scheme 6. Lithium aldol coupling between fragment 56 and 52.

reaction conditions: $\text{L}_2\text{BCL}_2, \text{Et}_3\text{N}$
(1) $L = \text{cHex}$ or
(2) $L = (+)-\text{Ipc}$

Yield:
- 57:58 Yield 67%
- 88:15 Yield 67%
- 16:84 Yield 87%
References


