Aldol reactions involving azetidin-2-one substrates have generally been concerned with the installation of the hydroxyethyl side chain of thienamycin and related penem and carbapenem antibiotics which are summarized by the representative example of condensation of the β-lactam enolate derived from 3 with acetaldehyde (Eq. 2). Chirality at the 4-position of azetidinone (4) determines the C-3 stereochemistry with 80-90% diastereoselectivity. However, little stereocontrol is observed for the introduction of the

\[ \text{N-OPMB} \xrightarrow{\text{LiHMDS, THF, -78 °C}} \text{N-OPMB} + \text{HO}_{\text{TBSO}} \xrightarrow{\text{then TBSO}} 97\% \text{(dr 1.2:1)} \]

(1)

Aldol reactions of unsubstituted β-lactams are rare. In conjunction with our program towards total syntheses of pyridinone natural products, we have studied the aldol reactions of unsubstituted azetidinone (1), a β-glycine enolate equivalent, as presented by the one-step preparation of complex β-lactams (2ab) (Eq. 1).
secondary hydroxy group in 4 (low anti:syn aldol ratios). Rare examples of related aldol reactions report varying degrees of enolate face selectivity and anti:syn diastereoselectivity. Furthermore, the lack of examples of aldol reactions employing unsubstituted β-lactams would suggest difficulties arising from enolate instability, and prompted us to investigate this potentially useful transformation.

Initially we uncovered problems with the appropriate choice for nitrogen protection as N-benzyl, N-(4-methoxy)benzyl, and N-silyl amides failed to provide consistently useful enolates. Inspired by reports of Miller and coworkers for the preparation and utility of N-alkoxy-β-lactams, we have found that the incorporation of the N-O bond in the hydroxamic acid derivative (1) has led to solutions of dependable enolates at –78 °C. Diastereoselection in the addition of azetidinone (1) to achiral aldehydes has been examined in Table 1. Complete deprotonation of 1 is effected by treatment with LiHMDS for 2 hours at –78 °C. Addition of the aldehyde leads to immediate formation of the aldol product in good to excellent yields and with high selectivity for the production of anti diastereomers. While the best stereocontrol was achieved with α-branched aliphatic aldehydes, benzylidene and unbranched aliphatic aldehydes provided anti products with good selectivity. Mechanistic considerations reveal that the planar lithium enolate of 1 may react with aldehydes through the closed chair-like transition state (5) which serves to activate the carbonyl yielding products with anti stereochemistry. The extent to which syn isomers are formed in certain cases was unanticipated. The minor products provide evidence for the competing anticlinal open transition state (6) where the aldehydic hydrogen is oriented over the β-lactam ring to minimize steric interactions in delivering syn stereochemistry. As substitution increases the steric bulk of R, transition state (6) is destabilized by nonbonded interactions with the enolate leading to reduced yields of syn isomers. We also note that the synclinal orientation of 7 rationalizes formation of the anti products. However, lithium cation coordination with formyl groups in 7 closely approximates the closed system relationships in 5.
Attempts to improve selectivity by the variation of reaction conditions have thus far proven unsuccessful. Enolization with NaHMDS led to reduced yields and slightly lower stereoselectivity. All attempts to utilize boron enolates resulted in no reaction. Likewise, transmetalation from the lithium enolates to magnesium, tin, or zinc, or the precomplexation of the aldehyde to a variety of Lewis acids resulted in either lower selectivity or recovered starting materials.

Table 1. Diastereoselection for Aldol Reaction of 1 with Achiral Aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Major Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>anti: syn&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td><img src="OPMB" alt="OH" /></td>
<td>93</td>
<td>4:1</td>
</tr>
<tr>
<td>2</td>
<td>O</td>
<td><img src="OPMB" alt="OH" /></td>
<td>93</td>
<td>5:1</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td><img src="OPMB" alt="OH" /></td>
<td>80</td>
<td>7:1</td>
</tr>
<tr>
<td>4</td>
<td>TBDPSO</td>
<td><img src="OPMB" alt="OH" /></td>
<td>87</td>
<td>8:1</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td><img src="OPMB" alt="OH" /></td>
<td>97</td>
<td>16:1</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td><img src="OPMB" alt="OH" /></td>
<td>79</td>
<td>19:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative stereochemistry was confirmed by analysis of vicinal ^1^H coupling constants: J<sub>H3-H5</sub> is greater for anti (6-9 Hz) than for syn products (1-4 Hz).

<sup>b</sup> Isolated yields after flash silica gel chromatography.

<sup>c</sup> Ratios were determined by integration of selected ^1^H NMR signals for crude product mixtures.
Prospects for stereocontrol from the aldehydic component were then examined with nonracemic $\alpha$-substituted aldehydes. Representative examples are shown in Table 2. Comparable anti:syn ratios were obtained with only slight preferences displayed between the two possible anti diastereomers. The products in Entries 1 and 2 were fully characterized following separation by silica gel chromatography. Confirmation of the stereochemistry of the newly formed hydroxyl stereocenter by modified Mosher analysis$^{10}$ supports preferred addition via the Felkin-Anh model. Entry 3 led to the isolation of two inseparable pairs of anti:syn diastereomers.

Table 2. Aldol Reactions of 1 with $\alpha$-Substituted Aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Major Product$^a$</th>
<th>Yield (%)$^b$</th>
<th>anti:syn$^c$</th>
<th>anti ratio$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBDPSO-CH$_3$H</td>
<td>TBDPSO-CH$_3$N$_2$-OPMB</td>
<td>80</td>
<td>&gt;19:1</td>
<td>1.4:1</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$H</td>
<td>CH$_3$N$_2$-OPMB</td>
<td>81</td>
<td>4:1</td>
<td>1.8:1</td>
</tr>
<tr>
<td>3</td>
<td>TBDPSO-CH$_3$H</td>
<td>TBDPSO-CH$_3$N$_2$-OPMB</td>
<td>81</td>
<td>11:1</td>
<td>1.1:1</td>
</tr>
</tbody>
</table>

$^a$ Absolute stereochemistry was confirmed by modified Mosher analysis of MTPA derivatives in Entries 1 and 2; Relative stereochemistry was confirmed by analysis of vicinal $^1$H coupling constants: $J_{HH}$ is greater for anti (6-9 Hz) than for syn products (1-4 Hz). $^b$ Isolated yields after silica gel chromatography. $^c$ Ratios were determined by integration of selected $^1$H NMR signals for crude product mixtures.

We have found this enolate methodology to be a valuable tool in our program leading to preparation of novel 5-substituted 4-hydroxy-2-pyridinones,$^{11}$ providing direct access to unique $\beta$-glycine derivatives. General transformations for C-terminal and N-terminal manipulations are illustrated below, and are compatible with demanding strategies for the synthesis of complex peptidomimetics.
In summary, azetidinone (I) is a source of reactive lithium enolate which provides for the convenient incorporation of the intact β-lactam ring system via aldol condensations with a wide variety of aldehydes and ketones. Subsequent transformations demonstrate that I may function as a valuable β-glycine enolate equivalent which allows for a rapid increase in molecular complexity.

**General procedure for the β-lactam aldol reactions:** To a –78 °C solution of β-lactam (I) (1.6 equiv.) in THF (0.1 M) was added LiHMDS (1.5 equiv. of a 0.88 M solution in THF) dropwise over 5 min. The resulting clear, pale yellow solution was stirred for 2 h at –78 °C, followed by addition of aldehyde (1.0 equiv.). After 15 min at –78 °C, the reaction was quenched by addition of saturated aqueous NH₄Cl, extracted with (C₂H₅)₂O, washed with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by silica gel flash chromatography.

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**REFERENCES AND NOTES**


5. Preparation of β-lactam (1) is as shown:

\[
\begin{align*}
\text{PMBO-NH}_2 & \xrightarrow{1) \text{3-chloropropionyl chloride, pyr, CH}_2\text{Cl}_2, 0 \degree\text{C, 95\%}} 1 \\
& \xrightarrow{2) \text{NaH, DMF, 0 \degree\text{C to 60 \degree\text{C, 53\%}}}} 1
\end{align*}
\]


9. Enolate formation was examined via deuterium incorporation following CH\textsubscript{3}OD quench at –78 \degree\text{C. Use of stoichiometric LiHMDS at –78 \degree\text{C for two hours led to 100\% deuterium incorporation. Other bases, including LDA, KHMDS, and NaHMDS were less effective. Lactam (1) is sparingly soluble in (C\textsubscript{2}H\textsubscript{5})\textsubscript{2}O at –78 \degree\text{C. Decomposition resulted when solutions of enolate were warmed from –78 \degree\text{C to –40 \degree\text{C. We tentatively suggest formation of dione (8) (1:1 mixture of isomers) via dimerization of the intermediate ketene as a principle pathway.}}

\[
\begin{align*}
1 & \xrightarrow{\text{LiHMDS, THF, –78 \degree\text{C to –40 \degree\text{C}}} 8
\end{align*}
\]

Similar ratios of anti:syn products were obtained following the addition of 12-crown-4 to solutions of lithium enolate. The latter observation offers support for the open transition state hypothesis.
