

ALDOL REACTIONS OF UNSUBSTITUTED β -LACTAMS. STUDIES OF A β -GLYCINE ENOLATE EQUIVALENT[†]

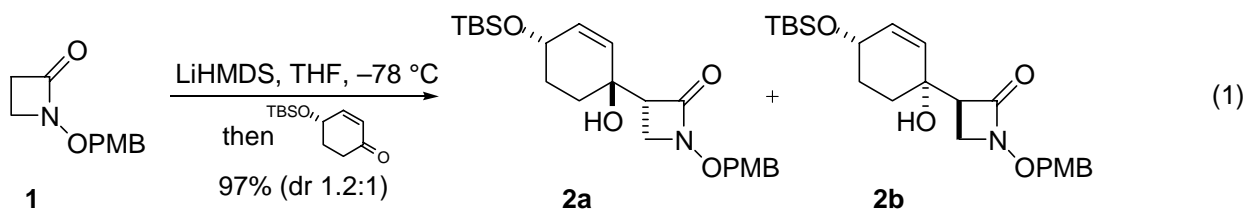
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Abstract – Aldol reactions of the lithium enolate of *N*-(4-methoxybenzyloxy)azetidin-2-one (**1**) were examined. High diastereoselectivity favoring the *anti* adduct was observed with achiral aldehydes. Modest α -stereocontrol with chiral aldehydes was realized. Application of this method for the efficient synthesis of novel β -amino esters is also described.

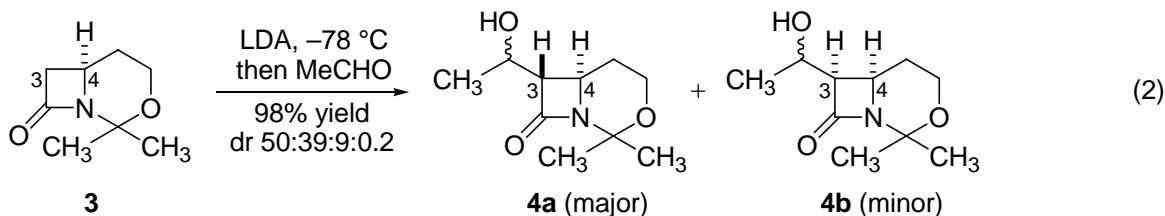
The β -lactam is an essential structural motif for a number of medicinally important natural and unnatural products.¹ Considerable effort has been focused on strategies for the *de novo* construction of the 4-membered system.^{1,2} The potential of this reactive ring as a synthetic intermediate has also been recognized, and methods for selective opening have been developed.³ However, general techniques for the incorporation of intact β -lactams are rare. In conjunction with our program towards total syntheses of pyridinone natural products,⁴ we have studied the aldol reactions of unsubstituted azetidinone (**1**),⁵ a β -glycine enolate equivalent, as presented by the one-step preparation of complex β -lactams (**2ab**) (Eq. 1).



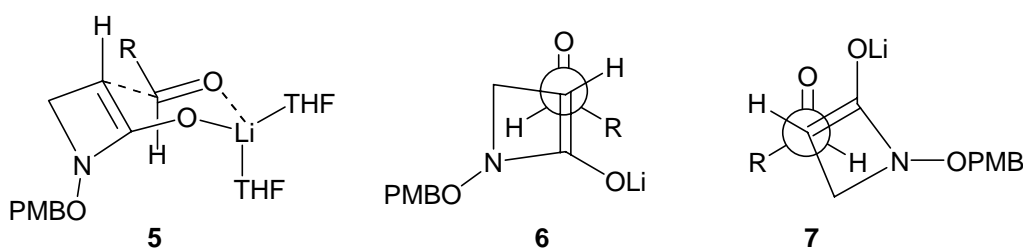
Aldol reactions involving azetidin-2-one substrates have generally been concerned with the installation of the hydroxyethyl side chain of thienamycin and related penem and carbapenem antibiotics which are summarized by the representative example of condensation of the β -lactam enolate derived from **3** with acetaldehyde (Eq. 2).⁶ 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

[†] Dedicated to Professor Leo A. Paquette in celebration of his 70th birthday.

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.⁷ 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,⁸ 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 $-78\text{ }^\circ\text{C}$. 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 $-78\text{ }^\circ\text{C}$. 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, benzylic 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.⁹

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

Entry	Aldehyde	Major Product ^a	Yield (%) ^b	<i>anti:syn</i> ^c
1			93	4:1
2			93	5:1
3			80	7:1
4			87	8:1
5			97	16:1
6			79	19:1

^a Relative stereochemistry was confirmed by analysis of vicinal ¹H coupling constants: J_{H3-H5} is greater for *anti* (6-9 Hz) than for *syn* products (1-4 Hz). ^b Isolated yields after flash silica gel chromatography. ^c Ratios were determined by integration of selected ¹H NMR signals for crude product mixtures.

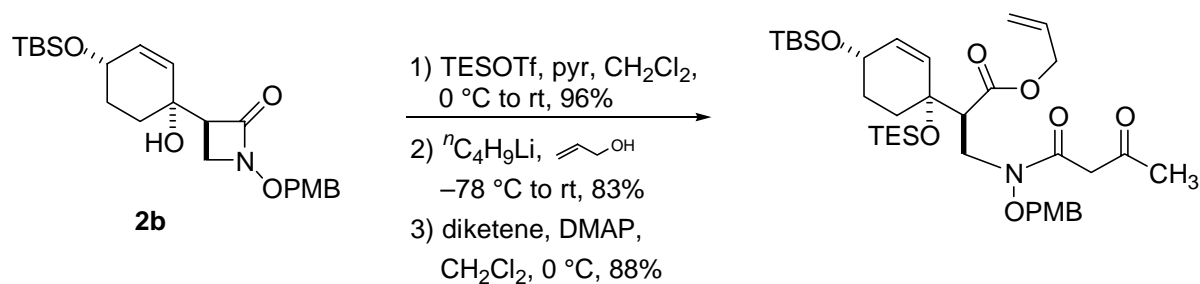
Prospects for stereocontrol from the aldehydic component were then examined with nonracemic α -substituted aldehydes. Representative examples are shown in Table 2. Comparable *anti:syn* ratios were obtained with only slight preferences displayed between the two possible *anti* diastereomers. The products 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 analysis¹⁰ supports preferred addition *via* the Felkin-Anh model. Entry 3 led to the isolation of two inseparable pairs of *anti:syn* diastereomers.

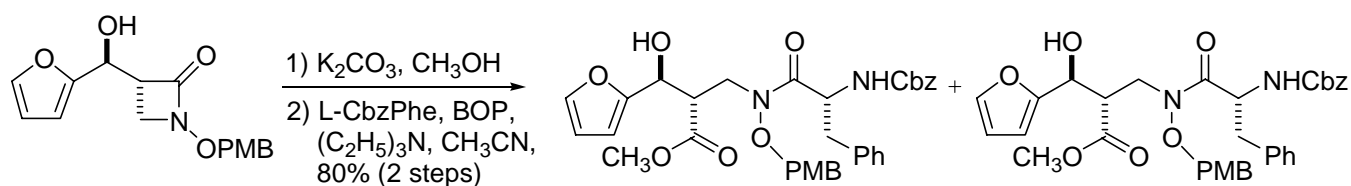
Table 2. Aldol Reactions of **1** with α -Substituted Aldehydes.

Entry	Aldehyde	Major Product ^a	Yield (%) ^b	<i>anti:syn</i> ^c	<i>anti</i> ratio ^c
1			80	>19:1	1.4:1
2			81	4:1	1.8:1
3			81	11:1	1.1:1

^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 ¹H coupling constants: J_{H3-H5} 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 ¹H 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 β -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 (**1**) 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 **1** 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 $-78\text{ }^\circ\text{C}$ solution of β -lactam (**1**) (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 $-78\text{ }^\circ\text{C}$, followed by addition of aldehyde (1.0 equiv.). After 15 min at $-78\text{ }^\circ\text{C}$, the reaction was quenched by addition of saturated aqueous NH_4Cl , extracted with $(C_2H_5)_2O$, washed with saturated aqueous $NaHCO_3$ and saturated aqueous $NaCl$, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by silica gel flash chromatography.

ACKNOWLEDGEMENTS

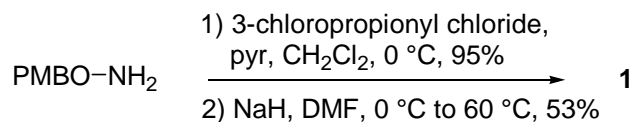
We gratefully acknowledge the National Institute of Health (GM-41560) for generous support of this work.

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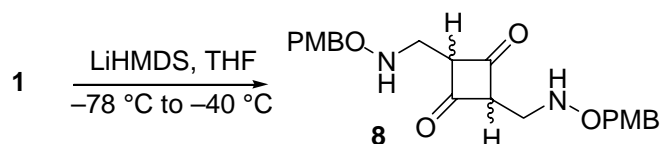
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Similar ratios of *anti:syn* products were obtained following the addition of 12-crown-4 to solutions of lithium enolate. The latter observation offers support for the open transition state hypothesis.

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