



syn-Selective boron mediated aldol condensations for the asymmetric synthesis of β -hydroxy- α -amino acids

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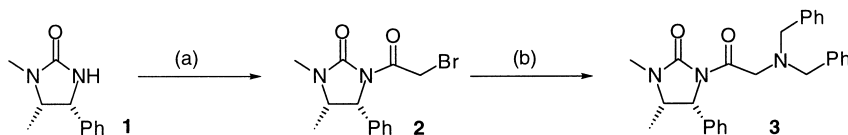
Abstract

Imidazolidinone-bound glycine enolate derivatives have been shown to undergo aldol condensation with aromatic and aliphatic aldehydes in good yields and with excellent stereocontrol (62–84%, 93–95% d.e.). Removal of the pendant imidazolidinone auxiliary and hydrogenolysis affords the β -hydroxy- α -amino acid derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: aldol; β -hydroxy- α -amino acids; glycine enolates; boron; imidazolidinone; asymmetric synthesis.

α -Amino- β -hydroxyacid derivatives have been shown to act effectively in enzymatic inhibition¹ and are important precursors to many β -lactam antibiotics.² Reports in the literature for the formation of these compounds have focused primarily on racemic syntheses,³ with only a few reports addressing the enantioselective preparation of the *anti*- and *syn*-aldol diastereomers.⁴ Herein we wish to report boron-mediated aldol condensations of a dibenzylated glycine enolate derivative for the enantioselective preparation of *syn* β -hydroxy- α -amino acids.⁵

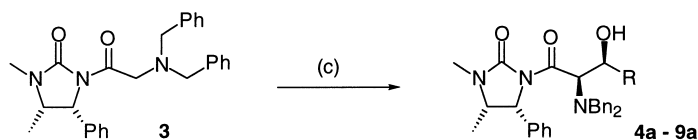
The protected glycine template (**1**) was prepared from the commercially available imidazolidinone (**1**) via acylation to the α -bromo-amide (**2**), followed by nucleophilic displacement with dibenzylamine (Scheme 1).



Scheme 1. Reagents and conditions: (a) BrCOCH_2Br , 2,6-lutidine, -30°C , CH_2Cl_2 , 99%; (b) $(\text{PhCH}_2)_2\text{NH}$, THF, 74%

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The 9-BBN vinyloxyborane of (**3**) reacts in a highly diastereoselective fashion with aromatic and aliphatic aldehydes to produce the *syn*-aldol derivatives (**4a–9a**) (Scheme 2). Selected results obtained for the aldol condensation with the chiral glycine derivative (**3**) and a range of aldehydes is provided in Table 1.



Scheme 2. Reagents and conditions: (c) 9-BBNOTf, Et₃N, CH₂Cl₂, 0°C, 1 h, then RCHO, 2 h, pH7 (phosphate buffer), MeOH, H₂O₂ (aq), 0°C, 1h.

Table 1
Aldol products derived from (**3**)

Aldehyde	Product	Yield (%)	2'R3'S:2'S3'R:Others a : b : c	Diastereomeric Excess (%)
Benzaldehyde	4a	84	1 : 0: 0	>95
4-Methoxybenzaldehyde	5a, b	66	32: 1: 0	94
4-Fluorobenzaldehyde	6a	62	1: 0: 0	>95
4-Nitrobenzaldehyde	7a	72	1: 0: 0	>95
Butyraldehyde	8a	69	1: 0: 0	>95
2-Furaldehyde	9a, b	65	94:6: 0	88

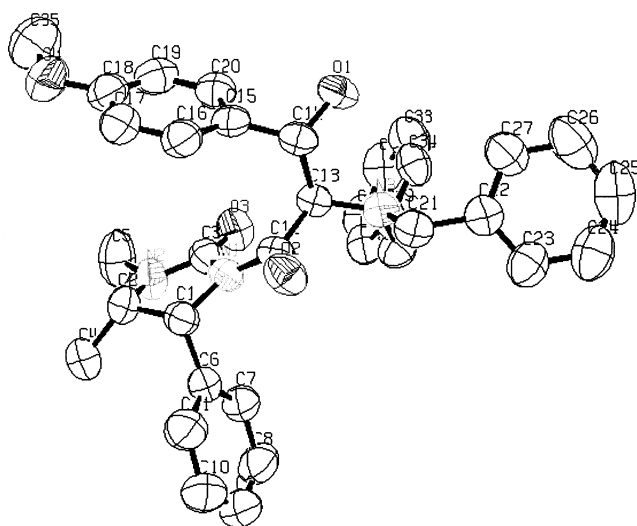


Figure 1. Molecular structure of **5a**, 2'(R), 3'(S)

Absolute stereochemical assignments are made on the analogous ^1H NMR chemical shifts and coupling constants⁶ of H2' and H3' to the 4''-methoxy derivatives (**5a**) and (**5b**) both having been confirmed by X-ray crystal data (Figs. 1 and 2).

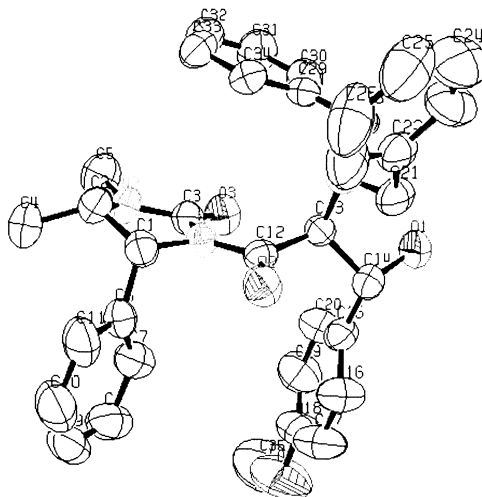


Figure 2. Molecular structure of **5b**, 2'(*S*), 3'(*R*)

Assuming (*Z*)-boron enolate generation under the reaction conditions, the stereoselectivity observed for the 9-BBN enolates can be explained by invoking a chair-like transition state. The chiral auxiliary adopts a conformation in which the dipole-dipole repulsion between the two oxygen atoms of the enolate is minimized, thus hindering approach of the aldehyde from the α -face (Fig. 3).⁷

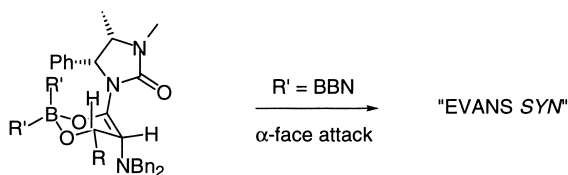
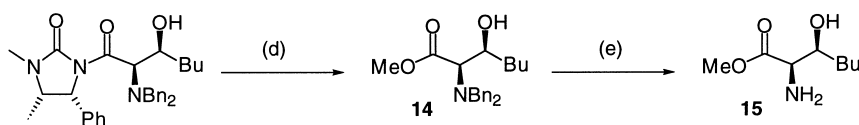


Figure 3.

Removal of the imidazolidinone auxiliary,⁸ exemplified in the formation of (**14**), followed by hydrogenation using Pearlmanns catalyst⁹ afforded the corresponding β -hydroxy- α -amino acid derivative (**15**) in high yield, with no observed epimerization (Scheme 3).¹⁰



Scheme 3. Reagents and conditions: (d) NaOMe, MeOH, 77%; (e) Pd(OH)₂/C, H₂, MeOH, 96%

In conclusion, the imidazolidinone derivative (**3**) offers a new and practical chiral glycine enolate equivalent. The simplicity of the experimental procedures, the excellent levels of optical purity obtained and the uniformity of the chemical yields make this an attractive procedure for the preparation of β -hydroxy- α -amino acid derivatives.

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