Direct Organocatalytic Asymmetric Aldol Reactions of α-Amino Aldehydes: Expedient Syntheses of Highly Enantiomerically Enriched anti-β-Hydroxy-α-amino Acids

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ABSTRACT

A simple and efficient method for the synthesis of highly enantiomerically enriched β-hydroxy-α-amino acid derivatives has been developed. Direct asymmetric aldol reactions of a glycine aldehyde (aminocetaldehyde) derivative have been performed under organocatalysis using L-proline or (S)-5-pyrrolidine-2-yl-1H-tetrazole. The reactions afforded anti-β-hydroxy-α-amino aldehydes in good yield with high diastereoselectivity (dr up to >100:1) and high enantioselectivity (up to >99.5% ee), which were easily transformed into β-hydroxy-α-amino acid derivatives.

β-Hydroxy-α-amino acids are components of natural products with wide-ranging biological properties, including antibiotic, anticancer, and immunosuppressant activities.1–4 They are also precursors for pharmaceuticals and useful chiral building blocks in organic synthesis.2 Consequently, tremendous efforts have been directed toward the development of syntheses of optically pure β-hydroxy-α-amino acids and their derivatives.2–4 Nonetheless, demand still exists for highly efficient diastere- and enantioselective syntheses of β-hydroxy-α-amino acid derivatives. One successful method for the synthesis of optically pure β-hydroxy-α-amino acids involves the use of threonine aldolases and serine hydroxymethyl transferases.2b,4 These enzymes catalyze asymmetric aldol reactions between glycine donor and aldehyde acceptors, reactions that constitute one of the simplest strategies to access β-hydroxy-α-amino acids. On the basis of these enzyme-catalyzed aldol reactions, we examined reactions in which we used glycine aldehyde derivatives as donors. Aldol
reactions of these aldehyde donors provide β-hydroxy-α-amino aldehydes that can be easily transformed into β-
hydroxy-α-amino acids.

Although glycinate Schiff bases have been used as donors in asymmetric aldol reactions for the synthesis of β-hydroxy-
α-amino acid ester derivatives, glycine aldehyde derivatives have not been examined as donors in direct asymmetric
aldol reactions previously. Asymmetric organocatalysis with l-proline and other small molecules has received renewed
attention because of its broad applicability, simplicity, and efficiency.\(^5\)–\(^10\) Reactions involved in organocatalysis are also
environmentally benign. We previously reported the use of naked aldehyde donors in organocatalytic aldol\(^8\)–\(^4\) Man-
nich,\(^9\) and Michael\(^10\) reactions. Thus, the use of α-amino aldehydes in these reactions should provide the corresponding
reaction products. Here we report simple and efficient, direct asymmetric aldol reactions of the glycine aldehyde derivative
1 (Scheme 1).

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(7) (a) Slow addition of the donor aldehyde was not required to
Optimization of the crude aldol product 2a with NaClO₂ and then esterification afforded 3a (Scheme 1) in good yield with high diastereose- and enantioselectivities (73% from 1, dr > 100:1, > 99.5% ee) (entry 7). The reaction in the presence of (S)-5-pyrrolidinyl-2-yl-1H-tetrazole\(^8\)–\(^11\) (4) also afforded 2a in excellent yield with excellent diastereo- and enantio-selectivities (entry 8), whereas reaction with another aldol catalyst, (S)+(−)-1-(2-pyrrolidinylmethyl)pyridinium(S)+(−)-camphorsulfonic acid,\(^8\)–\(^11\) gave 2a in low yield when the same reaction time was used, albeit with > 99% ee for anti-2a. Slow addition of the donor aldohydric was not required to obtain 2a in good yield when 5–10 equiv of the acceptor
aldehyde with respect to the donor aldohydric 1 was used in the reaction with l-proline or 4; the formation of the self-
aldehyde product of aldohydric 1 was minimized. This result stands in contrast to the aldol reactions of α-oxoaldehydes:
Table 1. Direct Asymmetric Aldol Reactions of Glycine Aldehyde Derivative 1 and Isobutyraldehyde in Various Conditions to Afford 2a and Its Conversion to 3a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>conc</th>
<th>temp</th>
<th>time</th>
<th>yield (%)</th>
<th>dr (anti:syn)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-proline</td>
<td>DMSO</td>
<td>0.5 M</td>
<td>rt</td>
<td>16 h</td>
<td>62 (2a)</td>
<td>10:1 (2a)</td>
<td>95 (2a)</td>
</tr>
<tr>
<td>2</td>
<td>L-proline</td>
<td>DMSO</td>
<td>0.5 M</td>
<td>rt</td>
<td>48 h</td>
<td>75 (2a)</td>
<td>5:1 (2a)</td>
<td>88 (2a)</td>
</tr>
<tr>
<td>3</td>
<td>L-proline</td>
<td>NMP</td>
<td>0.5 M</td>
<td>rt</td>
<td>3 days</td>
<td>86 (2a)</td>
<td>&gt;10:1 (2a)</td>
<td>94 (2a)</td>
</tr>
<tr>
<td>4</td>
<td>L-proline</td>
<td>NMP</td>
<td>0.5 M</td>
<td>4 °C</td>
<td>6 days</td>
<td>93 (2a)</td>
<td>&gt;100:1 (2a)</td>
<td>&gt;99 (2a)</td>
</tr>
<tr>
<td>5</td>
<td>L-proline</td>
<td>NMP</td>
<td>1.0 M</td>
<td>4 °C</td>
<td>3 days</td>
<td>91 (2a)</td>
<td>&gt;100:1 (2a)</td>
<td>&gt;99 (2a)</td>
</tr>
<tr>
<td>6</td>
<td>L-proline</td>
<td>NMP</td>
<td>2.0 M</td>
<td>4 °C</td>
<td>36 h</td>
<td>87 (2a)</td>
<td>&gt;100:1 (2a)</td>
<td>&gt;99 (2a)</td>
</tr>
<tr>
<td>7</td>
<td>L-proline</td>
<td>NMP</td>
<td>2.0 M</td>
<td>4 °C</td>
<td>36 h</td>
<td>73 (2a)</td>
<td>&gt;100:1 (2a)</td>
<td>&gt;99 (2a)</td>
</tr>
<tr>
<td>8</td>
<td>4*</td>
<td>NMP</td>
<td>2.0 M</td>
<td>rt</td>
<td>16 h</td>
<td>76 (2a)</td>
<td>&gt;100:1 (3a)</td>
<td>99.5 (2a)</td>
</tr>
</tbody>
</table>

*Catalyst 4 = S-(5)-pyrrolidine-2-yl-1H-tetrazole.

procedure developed here were easily performed on a semipreparative scale. The aldol reaction to afford 2a was performed on a 10.5 mmol scale (2 g of aldehyde 1), and the resulting aldol products were further transformed to (25,3S)-5 (940 mg, 60% from 1).

To study the scope of the reaction, we used a series of acceptor aldehydes. Results of reactions with α,α-disubstituted aldehyde acceptors are shown in Table 2. Reactions with 2-ethylbutyraldehyde, cyclohexanecarboxaldehyde, and cyclopentanecarboxaldehyde provided aldol products at 4 °C and these product aldehydes were transformed to the corresponding methyl esters in good yields (62–75% from 1) with high enantioselectivities (94–98% ee) (entries 1, 3, and 4). The diastereoselectivities of the aldol reactions were also high (dr >10:1 to 15:1). The reaction with di-n-butylacetate aldehyde, an aldehyde bearing a bulky group, was slow at 4 °C and was performed at room temperature (entry 2). This case also provided the desired product with high enantioselectivity (93% ee). The reaction with α-dimethoxy acetaldehyde, available in aqueous solution, afforded the desired aldol product with low diastereoselectivity, but 86% ee in the presence of water (entry 5). Thus, the aldol reaction of 1 was efficient for the synthesis of a broad range of enantiomERICALLY enriched γ-branched-β-hydroxy-α-amino acid derivatives. In all reactions in Table 1, again only 1 acted as the donor.

Aldehyde reaction partner selection was key in order to assign donor and acceptor roles to aldehydes in the aldol reaction. Aldol reactions between 1 and α-nonbranched alddehydes such as isovaleraldehyde and hexanal afforded β-hydroxy-γ-amino aldehydes 6 under conditions identical to those used in Table 2 (Scheme 3). No formation of


(14) Diastereomeric ratio of the aldol products decreased by epimerization at C2 when they were stored or when they were purified by silica gel column chromatography. See refs 9b,c. Column chromatography did not completely separate the anti and syn isomers of 3.


Reaction of α-oxyaldehydes with isobutyraldehyde afforded the desired aldol products in moderate yields (along with a significant amount of the self-aldol product of α-oxyaldehyde), even after slow addition (over 36 h) of the donor. The use of phthalimidoacetalddehyde (1) was a key for this reaction. The enamine intermediates in the reactions of N-protected glycine aldehydes may react via one or both pathways shown in Scheme 2. Protection of the α-amino group of glycine aldehyde as a phthalimide allowed the selective reaction via path a. Aldehyde 1 can be synthesized in large scale in two steps; reaction of allylamine with phthalic anhydride followed by ozonolysis provides a crystalline product that is stable for at least several months at room temperature. tert-Butyloxyacrylonitrile (Boc) and benzyl-protected glycine aldehyde derivatives were less optimal as donors in this reaction as compared to phthalimidoacetaldehyde (1).

To determine the relative stereochemistry and absolute configuration, aldol product 2a was transformed into 3-hydroxylysine (5) via oxidation of the aldol with NaClO2 and deprotection of the phthalimide with hydrazine. Aldol 2a obtained from the L-proline-catalyzed reaction afforded (25,3S)-5,9,12 as determined by 1H NMR spectra and by optical rotation, and the data were identical with the literature values. The stereochemical course of the aldol reaction to afford (25,3S)-2a is in accordance with the transition states suggested for other L-proline-catalyzed aldol reactions.10,13
-hydroxy-R-amino aldehydes was detected. In these instances, aldehyde 1 acted as the acceptor. Slow addition of aldehyde 1 to isovaleraldehyde in the presence of the catalyst did not change the outcome of the reaction.

In conclusion, using easily accessible reagents and inexpensive chiral catalysts, we have developed a simple, scalable, and environmentally safe synthetic route to highly enantiomerically enriched anti-β-hydroxy-α-amino acid derivatives. While asymmetric aldol reactions of glycinate Schiff base and its silicon enolate using chiral quaternary ammonium salt catalysts and chiral zirconium catalysts provided excellent results for providing β-hydroxy-α-amino acid derivatives when α-monosubstituted aldehyde acceptors and arylandehyde acceptors were used, respectively, our aldol reaction of 1 was efficient to afford γ-branched β-hydroxy-α-amino acid derivatives using α,α-disubstituted aldehyde acceptors. Of note, the use of a glycyl aldehyde (aminoacetaldehyde) is versatile from a synthetic perspective because the aldehyde functionality resident in the products can be readily transformed through oxidation or reduction or can serve as an electrophilic handle for a wide variety of other transformations.

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Supporting Information Available: Detailed experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 2. Direct Asymmetric Aldol Reactions of Glycine Aldehyde Derivative 1 and Conversion of Aldol Products 2 to β-Hydroxy-α-amino Acid Esters 3

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>2 product</th>
<th>dr (anti:syn)</th>
<th>3 product</th>
<th>yield (%)</th>
<th>dr (anti:syn)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHEt₂</td>
<td>2b</td>
<td>&gt;10:1</td>
<td>3b</td>
<td>75</td>
<td>&gt;10:1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>CH(nBu)₂</td>
<td>2c</td>
<td>10:1</td>
<td>3c</td>
<td>68</td>
<td>7:1</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₄</td>
<td>2d</td>
<td>15:1</td>
<td>3d</td>
<td>73</td>
<td>5:1</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>C₅H₉</td>
<td>2e</td>
<td>14:1</td>
<td>3e</td>
<td>62</td>
<td>16:1</td>
<td>98²</td>
</tr>
<tr>
<td>5</td>
<td>CH(OEt)₂</td>
<td>2f</td>
<td>5:1</td>
<td>3f</td>
<td>69</td>
<td>1:1</td>
<td>86 (syn, 68)</td>
</tr>
</tbody>
</table>

a Unless otherwise noted, a mixture of 1 (2 mmol), acceptor aldehyde (10–20 mmol), and L-proline (0.6 mmol) in N-methylpyrrolidone (NMP) (1 mL) was stirred at 4 °C for 16–48 h for the aldol reaction. See Scheme 1. b Diastereomeric ratio of 2 determined by 1H NMR analysis of the reaction mixture without purification. c Isolated yields of 3 (from 1). d Diastereomeric ratio of 3 after purification using silica gel column chromatography, determined by 1H NMR analysis. e Enantiomeric excess of anti-3 determined by chiral-phase HPLC analysis, unless noted otherwise. f Reaction was performed at room temperature. g ee of anti-2e determined by HPLC analysis of the corresponding oxime prepared with O-benzylhydroxylamine. h Reaction mixture included water. See text.

β-hydroxy-α-amino aldehydes was detected. In these instances, aldehyde 1 acted as the acceptor. Slow addition of aldehyde 1 to isovaleraldehyde in the presence of the catalyst did not change the outcome of the reaction.

In conclusion, using easily accessible reagents and inexpensive chiral catalysts, we have developed a simple, scalable, and environmentally safe synthetic route to highly enantiomerically enriched anti-β-hydroxy-α-amino acid derivatives. While asymmetric aldol reactions of glycinate Schiff base and its silicon enolate using chiral quaternary ammonium salt catalysts and chiral zirconium catalysts provided excellent results for providing β-hydroxy-α-amino acid derivatives when α-monosubstituted aldehyde acceptors and arylandehyde acceptors were used, respectively, our aldol reaction of 1 was efficient to afford γ-branched β-hydroxy-α-amino acid derivatives using α,α-disubstituted aldehyde acceptors. Of note, the use of a glycyl aldehyde (aminoacetaldehyde) is versatile from a synthetic perspective because the aldehyde functionality resident in the products can be readily transformed through oxidation or reduction or can serve as an electrophilic handle for a wide variety of other transformations.

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