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

Rajeswari Thayumanavan, Fujie Tanaka,* and Carlos F. Barbas III*

Departments of Chemistry and Molecular Biology and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

ftanaka@scripps.edu; carlos@scripps.edu

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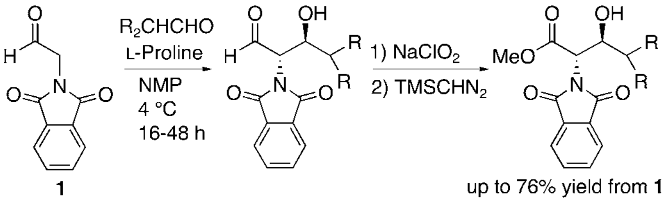
ABSTRACT



up to 76% yield from **1**
anti:syn = up to >100:1
up to >99.5% ee

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 (aminoacetaldehyde) derivative have been performed under organocatalysis using L-proline or (*S*)-5-pyrrolidine-2-yl-1*H*-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 diastereo- 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

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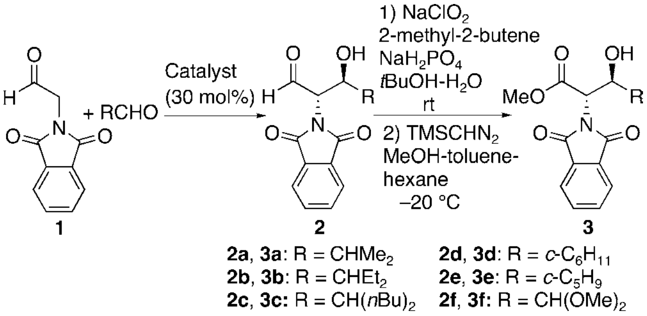
reactions of these aldehyde donors provide β-hydroxy-α-amino aldehydes that can be easily transformed into β-hydroxy-α-amino acids.

Although glycinate Schiff bases have been used as donors in asymmetric aldol reactions for the synthesis of β-hydroxy-α-amino acid ester derivatives,$^{3c-e,h}$ 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,$^{8a-d}$ Mannich,^{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).

Scheme 1. Direct Asymmetric Aldol Reactions of **1** to Afford β-Hydroxy-α-amino Aldehydes **2** and the Conversion of **2** to β-Hydroxy-α-amino Acid Esters **3**



First, we examined the aldol reaction of **1** with isobutyraldehyde under various conditions (Table 1). A mixture of aldehyde **1** (2 mmol), isobutyraldehyde (5 equiv with respect to **1**), and L-proline (30 mol % with respect to **1**) in DMSO (4 mL) was stirred at room temperature (rt) for 16 h (entry 1). The desired aldol product **2a** was obtained in 62% yield with high diastereoselectivity (dr = 10:1) and enantioselectivity (95% ee); side products were the dehydration product of **2a** and the self-aldol product of aldehyde **1**. We previously demonstrated that α,α-disubstituted aldehydes were less reactive than α-monosubstituted aldehydes as donors in the L-proline-catalyzed aldol reactions.^{8b} In the reaction of **1** and isobutyraldehyde, only **1** acted as the donor. No formation of self-aldol product of isobutyraldehyde and of α,α-dimethyl-β-hydroxy-γ-amino aldehyde was observed. The reactions in DMF and in *N*-methylpyrrolidone (NMP) also gave good results in terms of yield, dr, and ee (entries 2 and 3). The same reaction in NMP afforded a higher yield (86%) of **2a** than the reaction in DMSO primarily as a consequence of suppression of side products formation. Although a longer reaction time was required, the reaction performed in NMP at 4 °C provided excellent diasteroselectivity (dr = >100:1) and enantioselectivity (>99.5% ee) (entry 4). When higher concentrations were used, a shorter reaction time afforded the same yield with excellent diastero- and enantioselectivities (entries 5 and 6). Aldehyde **2a** could be used without purification in additional transformations. Oxidation of the crude aldol product **2a** with NaClO$_2$ and then esterification afforded **3a** (Scheme 1) in good yield with high diastereo- and enantioselectivities (73% from **1**, dr > 100:1, >99.5% ee) (entry 7). The reaction in the presence of (*S*)-5-pyrrolidine-2-yl-1*H*-tetrazole^{6b,c,i,j} (**4**) also afforded **2a** in excellent yield with excellent diastereo- and enantioselectivities (entry 8), whereas reaction with another aldol catalyst, (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/(*S*)-(+)-camphorsulfonic acid,^{8b,e} gave **2a** in low yield when the same reaction time was used, albeit with >99% ee for *anti*-**2a**.

Slow addition of the donor aldehyde was not required to obtain **2a** in good yield when 5−10 equiv of the acceptor aldehyde with respect to the donor aldehyde **1** was used in the reaction with L-proline or **4**; the formation of the self-aldol product of aldehyde **1** was minimized. This result stands in contrast to the aldol reactions of α-oxyaldehydes: aldol

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Table 1. Direct Asymmetric Aldol Reactions of Glycine Aldehyde Derivative **1** and Isobutyraldehyde in Various Conditions to Afford **2a** and Its Conversion to **3a**

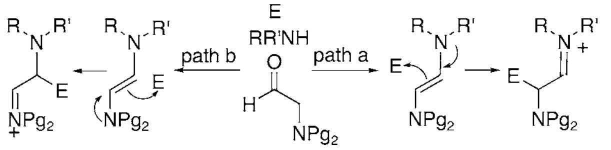
entry	catalyst	solvent	concn[a]	temp	time	yield (%)[b]	dr (anti:syn)[c]	ee (%)[d]
1	L-proline	DMSO	0.5 M	rt	16 h	62 (**2a**)	10:1 (**2a**)	95 (**2a**)
2	L-proline	DMF	0.5 M	rt	48 h	75 (**2a**)	5:1 (**2a**)	88 (**2a**)
3	L-proline	NMP	0.5 M	rt	3 days	86 (**2a**)	>10:1 (**2a**)	94 (**2a**)
4	L-proline	NMP	0.5 M	4 °C	6 days	93 (**2a**)	>100:1 (**2a**)	>99 (**2a**)
5	L-proline	NMP	1.0 M	4 °C	3 days	91 (**2a**)	>100:1 (**2a**)	>99 (**2a**)
6	L-proline	NMP	2.0 M	4 °C	36 h	87 (**2a**)	>100:1 (**2a**)	>99.5 (**2a**)
7	L-proline	NMP	2.0 M	4 °C	36 h	73 (**3a**)	>100:1 (**3a**)	>99.5 (**3a**)
8	**4**[e]	NMP	2.0 M	rt	16 h	76 (**3a**)	>100:1 (**3a**)	99.5 (**3a**)

[a] Concentration of aldehyde **1** in the reaction mixture. [b] Yield of **2a** or of **3a** (from **1**) as indicated in parentheses. See Scheme 1. [c] Diastereomeric ratio of **2a** without purification or of purified **3a**. The dr was determined by ^{1}H NMR. Anti isomer = (2*S**,3*S**)-isomer. [d] Enantiometic excess of (2*S*,3*S*)-**2a** or of (2*S*,3*S*)-**3a**. The ee of (2*S*,3*S*)-**2a** was determined by chiral-phase HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine. The ee of (2*S*,3*S*)-**3a** was determined by chiral-phase HPLC analysis. [e] Catalyst **4** = (*S*)-5-pyrrolidine-2-yl-1*H*-tetrazole.

reactions 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 α-oxyaldehyde.[6a]

The use of phthalimidoacetaldehyde (**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[11] followed by ozonolysis provides a crystalline product that is stable for at least several months at room temperature. *tert*-Butyloxycarbonyl (Boc) and benzoyl-protected glycine aldehyde derivatives were less optimal as donors in this reaction as compared to phthalimidoacetaldehyde (**1**).

Scheme 2. Possible Pathways of an Enamine Intermediate in the Reaction with α-Amino Aldehydes



To determine the relative stereochemistry and absolute configuration, aldol product **2a** was transformed into 3-hydroxyleucine (**5**) via oxidation of the aldehyde with $NaClO_2$ and deprotection of the phthalimide with hydrazine. Aldol **2a** obtained from the L-proline-catalyzed reaction afforded (2*S*,3*S*)-**5**,[2c−e,12] as determined by ^{1}H NMR spectra and by optical rotation, and the data were identical with the literature values. The stereochemical course of the aldol reaction to afford (2*S*,3*S*)-**2a** is in accordance with the transition states suggested for other L-proline-catalyzed aldol reactions.[8e,13]

Procedures 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 (2*S*,3*S*)-**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).[14] The reaction with di-*n*-butylacetaldehyde, 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 aldehydes 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

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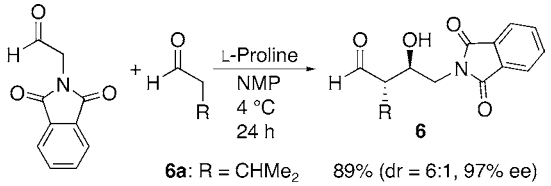
(14) Diastereomeric ratio of the aldol products decreased by epimerization at C2 when they were stored or when they were purified by silica gel column chromatography. See refs 9b,c. Column chromatography did not completely separate the anti and syn isomers of **3**.

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**[d]

		2		**3**			
entry	R	product	dr (anti:syn)[b]	product	yield (%)[c]	dr (anti:syn)[d]	ee (%)[e]
1	$CHEt_2$	**2b**	>10:1	**3b**	75	>10:1	94
2[f]	$CH(n\text{Bu})_2$	**2c**	10:1	**3c**	68	7:1	93
3	$c\text{-}C_6H_{11}$	**2d**	15:1	**3d**	73	5:1	98
4	$c\text{-}C_5H_9$	**2e**	14:1	**3e**	62	16:1	98[g]
5[h]	$CH(OMe)_2$	**2f**	5:1	**3f**	69	1:1	86 (syn, 68)

[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 ^{1}H 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 ^{1}H NMR analysis.[14] [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.

Scheme 3. Direct Asymmetric Aldol Reactions to Afford β-Hydroxy-γ-amino Aldehydes



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6a: R = $CHMe_2$ 89% (dr = 6:1, 97% ee)
6b: R = nBu 92% (dr = 6:1, 95% ee)

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[3c,h] and chiral zirconium catalysts[3g] provided excellent results for providing β-hydroxy-α-amino acid derivatives when α-monosubstituted aldehyde acceptors and arylaldehyde 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.[9b,11f] While we have focused our efforts here on the preparation of β-hydroxy-α-amino acids, we envision that this new class of aldol reactions will provide expedient entry to amino- and aza-sugar syntheses using a two-step protocol involving another organocatalytic addition or a Mukaiyama aldol addition step. Given our development of naked aldehyde chemistry in Michael and Mannich reaction manifolds as well,[5d,8a−d,9,10] the application of amino aldehydes through organocatalysis has tremendous synthetic promise. These studies will be reported in due course.

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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.

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