DOI: 10.1002/adsc.200505323

Amino Acid-Catalyzed Asymmetric Carbohydrate Formation: Organocatalytic One-Step *De Novo* Synthesis of Keto and Amino Sugars

Ismail Ibrahem, Weibiao Zou, Yongmei Xu, Armando Córdova*

Department of Organic Chemistry, The Arrhenius Laboratory, Stockholm University, 106 91 Stockholm, Sweden
Fax: (+46)-8-154-908, e-mail: acordova@organ.su.se, acordova1a@netscape.net

Received: August 17, 2005; Accepted: October 20, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A direct *de novo* synthesis of ketoses and amino sugars by amino acid-catalyzed asymmetric aldol, Mannich and Michael reactions with dihydroxyacetone phosphate mimics as donors is presented. Proline, proline derivatives and thiazolidine-4-carboxylic acids catalyzed the asymmetric assembly of keto sugars and amino sugars in high yield with up to >99% ee. The organocatalytic C_3+C_n methodology presented herein is a direct entry to the *de novo* synthesis of orthogonally protected C_4, C_5, and C_6 ketoses, carbohydrate derivatives, amino and aza sugars and the total synthesis of polyoxamic acids. The addition of water significantly accelerated and improved the enantioselectivity of the proline-mediated biomimetic asymmetric C–C bond-forming reactions.

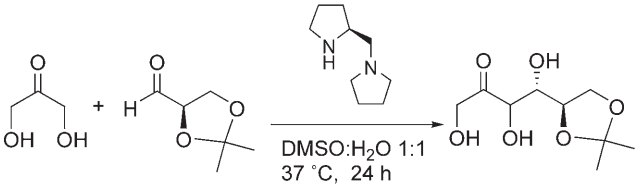
Keywords: amino acids; asymmetric catalysis; carbohydrate synthesis; dihydroxyacetone; ketoses; proline derivatives

Introduction

Carbohydrates are involved in life-essential metabolic processes, signal transduction and the immune response.[1] They are also the building blocks of several fundamental oligo- and polysaccharides. The amino acid-mediated asymmetric neogenesis of sugars is an ancient process,[2] which enzymes have catalyzed for billions of years.[3] The biosynthesis of sugars is accomplished *via* enzyme-catalyzed pathways from simple achiral precursors with absolute stereocontrol.[1a] For example, one of the key transformations in the gluconeogenesis is the aldolase enzyme-catalyzed aldol reaction between dihydroxyacetone phosphate (DHAP) and glyceraldehydes 3-phosphate that furnish fructose 1,6-diphosphate.[1a,3a,b]

The rapidly growing development of glycobiology and carbohydrate-based pharmaceuticals sets demands for the increased development of reaction design and methodological advancement for the selective construction of natural and unnatural carbohydrates.[4] In this context, the *de novo* synthesis of carbohydrates is of immense importance.[5,6] However, most conventional monosaccharide syntheses start from the chiral pool and involve multiple steps and they require protective group strategies and subsequent reduction-oxidation steps.[7] The reduction of protective group strategies can be accomplished by the utilization of aldolase enzymes as catalyst for the highly selective *de novo* synthesis of carbohydrates.[3,8]

Organocatalysis has experienced a renaissance in asymmetric catalysis and recently amino acid catalysis was added to the repertoire of carbohydrate synthesis.[9–11] For example, amino acids have been used as catalysts for the *de novo* synthesis of C_6 aldoses with excellent enantioselectivity.[12] In this context and inspired by the high selectivity of the DHAP-dependent aldolase enzymes, we recently reported an organocatalytic one-step *de novo* synthesis of C_6 ketoses [Eq. (1)].[11f]

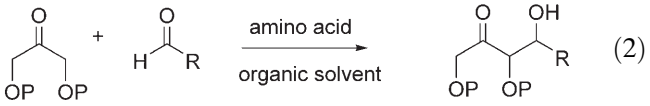


(1)

However, the chiral amine-catalyzed reaction between 1,3-dihydroxyacetone and other acceptor aldehydes than protected (*R*)-glyceraldehyde gave the desired

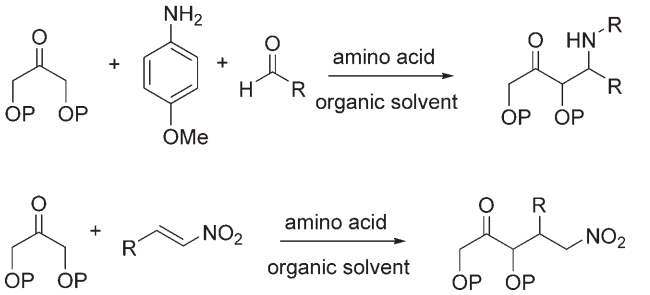
products with low enantiomeric excesses. Moreover, only trace amounts of products were observed in organocatalytic Mannich reactions with dihydroxyacetone as the donor.

Protected dihydroxyacetone derivatives have been employed as synthetic equivalents of 1,3-dihydroxyacetone for the synthesis of carbohydrate derivatives and polyhydroxylated compounds.[5] In addition, protected 1,3-dihydroxyacetone derivatives have the advantages of circumventing dimerization unlike 1,3-dihydroxyacetone, and are soluble in organic solvents. Thus, our focus turned towards employing protected dihydroxyacetone derivatives as DHAP mimics in direct organocatalytic aldol reactions [Eq. (2)].



(2)

Furthermore, amino acid-mediated enantioselective reactions have the advantage as compared to aldolase enzyme-catalyzed reactions of not being limited to aldehydes as electrophiles. Thus, the use of DHAP mimics could plausibly be extended to organocatalytic asymmetric Mannich and Michael reactions [Eq (3)].[13,14]



(3)

We most recently reported a highly enantioselective one-step *de novo* synthesis of carbohydrates using dimethyl-1,3-dioxan-5-one (**1**) as a DHAP mimetic in proline-catalyzed aldol and Mannich reactions.[15]

In this paper, we present (i) the development of the direct organocatalytic asymmetric aldol reactions between protected dihydroxyacetone **1** and different acceptor aldehydes and its application in a one-step *de novo* synthesis of C_4, C_5 and C_6 ketoses; (ii) the organocatalytic three-component asymmetric Mannich reaction with **1** as the donor and its application in a *de novo* synthesis of orthogonally protected amino sugars; (iii) the expeditious formal total synthesis of polyoxamic acids; (iv) the proline-catalyzed asymmetric Michael reaction with DHAP mimetic **1** as the donor and its application to the synthesis of aza-sugars; and (v) the kinetics and mechanisms of the water-accelerated amino acid-catalyzed C–C bond-forming reactions.

Results and Discussion

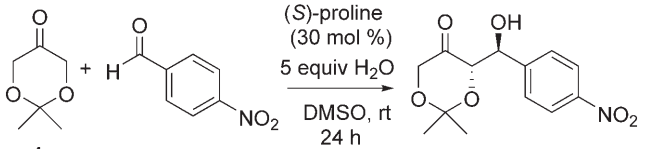
Aldol Reactions

To begin with, we investigated the direct (*S*)-proline-catalyzed asymmetric aldol reaction between dimethyl-1,3-dioxan-5-one (**1**) and *p*-nitrobenzaldehyde in DMSO [Eq. (4)]. The reaction was slow and the desired aldol product **2a** was isolated in 58% yield with 12:1 dr and 73% ee after 7 days reaction time [Eq. (9)]. Water is known to have a beneficial effect in proline-catalyzed aldol reactions.[16] Hence, we performed the above reaction in wet DMSO. Thus, vigorously stirring ketone **1** (1.5 mmol), *p*-nitrobenzaldehyde (0.5 mmol) and water (2.5 mmol, 45 μL) in the presence of a catalytic amount of (*S*)-proline (0.15 mmol) for 24 h furnished the desired aldol product **2a** in 72% yield with 18:1 dr (*anti*:*syn*) and 93% ee [Eq. (5)].

1 **2a**

58% yield, 12:1 dr, 73% ee

(4)



1 **2a**

72% yield, 18:1 dr, 93% ee

(5)

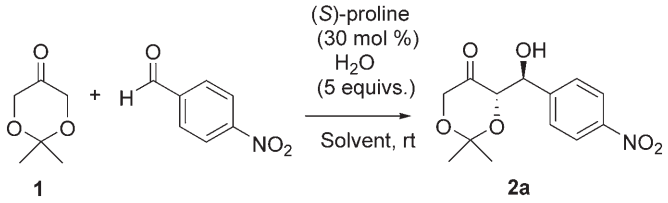
The preliminary aldol experiments with ketone **1** demonstrated the importance of water to accomplish high stereoselectivity and enantioselectivity in the amino acid-catalyzed asymmetric aldol reactions.

Solvent Screen

We next performed a solvent screen for the proline-catalyzed aldol reaction between **1** and *p*-nitrobenzaldehyde (Table 1).

The reaction worked in several of the solvents tested. However, the reactions in NMP (*N*-methylmorphilidinone) and dioxane only furnished trace amounts of **2a**. The fasted reaction rates were obtained in DMSO and the highest enantioselectivity in DMF. Importantly, water (1–10 equivalents) accelerated and increased the enantioselectivity of the proline-catalyzed asymmetric

Table 1. Solvent screen for the biomimetic aldol reaction.



1 2a

Entry	Solvent	Time [h]	Yield [%][a]	dr[b]	ee [%][c]
1	DMSO	24	72	18:1	93
2	DMSO	168	58[d]	12:1[d]	73[d]
3	DMF	240	90	1:1	99
4	NMP	216	trace	n.d.	n.d.
5	Acetonitile	216	85	2:1	98
6	$CHCl_3$	216	84	1:1	94
7	Dioxane	216	trace	n.d.	n.d.

[a] Isolated yield of the pure products after silica gel chromatography.
[b] dr = *anti*/*syn* ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis.
[d] Reaction performed without 5 equivs. of water.
n.d. = not determined.

C–C bond-forming reactions with DHAP mimetics. For example, the aldol reactions without addition of water were sluggish and progressed at a significantly lower rate as compared to the reaction with 5 equivalents of water (Figure 1). Furthermore, the enantiomeric excess of the desired aldol products from proline-catalyzed reactions between **1** and aromatic acceptor aldehydes were increased by 20%.

The beneficial effect of a small amount of water can be explained by a faster hydrolysis of intermediates of the catalytic cycle,[16] which increases turnover and suppresses catalyst inhibition.

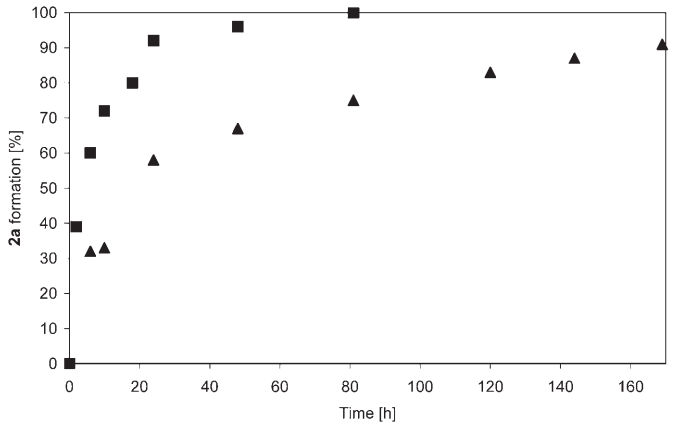
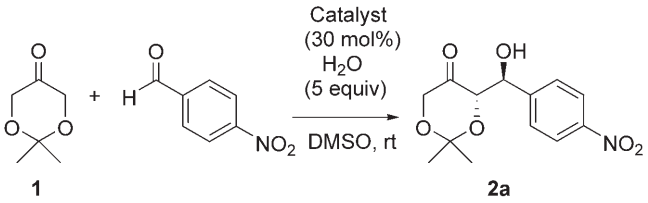


Figure 1. Product **2a** formation as a function of time for the proline-catalyzed enantioselective aldol reaction between ketone **1** and *p*-nitrobenzaldehyde with no water added (▲) and 5 equivalents of water present (■).

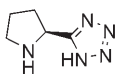
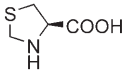
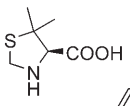
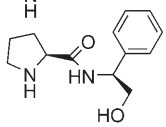
Catalyst

We next screened a series of cyclic five-membered amino acid derivatives and proline-derived dipeptides for their ability to mediate the direct organocatalytic one-step *de novo* synthesis of carbohydrate derivatives (Table 2).

Table 2. Catalyst screen for the biomimetic aldol reaction.



1 2a

Entry	Catalyst	Time [h]	Yield [%][a]	dr[b]	ee [%][c]
1	(*S*)-proline	24	72	18:1	93
2	(*S*)-proline	456	70[d]	2:1[d]	83[d]
3	(*S*)-pro-(*S*)-pro	240	45	2:1	<5
4	(*S*)-pro-(*S*)-pro	456	88[e]	2:1[e]	60[e]
5	(*S*)-pro-(*S*)-ala	120	traces	n.d.	n.d.
6	(*S*)-hydroxyproline	24	48	4:1	>99
7		96	50	5:1	>99
8		189	33	4:1	>99
9		189	32	4:1	>99
10		576	32	1:1	28

[a] Isolated yield of the pure products after silica gel chromatography.
[b] dr = *anti*/*syn* ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis.
[d] 10 mol% proline was used.
[e] Reaction performed in DMF without 5 equivs. of water.
n.d. = not determined.

We found that several of the cyclic amino acids catalyzed the reaction with excellent enantioselectivity.[17] For example, hydroxyproline was able to catalyze the formation of **2a** in 45% yield with 4:1 dr and >99% ee after 24 h. In addition, proline-derived dipeptides were able to catalyze the formation of **2a**. However, the reaction conditions are very important to achieve a high asymmetric induction. For example, (*S*)-pro-(*S*)-pro mediated the formation of **2a** in 88% yield with 2:1 dr and 60% ee when the reaction was performed in DMF and no water was added. Proline was the most efficient organocatalyst tested in Table 2. In addition, lowering the catalyst amount to 10% significantly increased the reaction time as well as decreased the ee of **2a** from 93 to 83%.

Substrate Scope

Based on the solvent and catalyst screen, we chose to perform the organocatalytic asymmetric aldol reactions between DHAP mimetic **1** and different acceptor aldehydes with proline as the catalyst and in wet DMSO (Table 3).

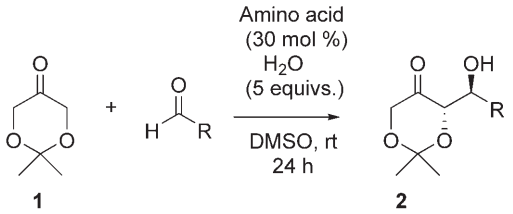
The reactions proceeded smoothly and aldol products **2a**–**2i** were isolated in high yield and up to >19:1 dr and 93–=98% ee. In particular, the reactions with aliphatic acceptor aldehydes were highly diastereoselective and enantioselective. For example, protected ribulose **2c** was synthesized in 85% yield with >19:1 dr and = 98% ee (entry 4). Furthermore, the (*S*)-proline-catalyzed diastereoselective aldol reaction between **1** and protected (*R*)-glyceraldehyde furnished the corresponding D-tagatose in 74% yield with >19:1 dr and = 98% ee (entry 5). In addition, (*R*)-proline catalysis furnished D-psicose in 68% yield with >19:1 dr and = 98% ee (entry 6). Hence, amino acid catalysis provides a new entry for a one-step synthesis of C_3+C_n sugars with excellent stereoselectivity. The unique feature of these results is that a single reaction sequence can convert a protected dihydroxyacetone into a carbohydrate in one step with enzyme-like stereoselectivity when an amino acid is employed as the catalyst. In the cases of aromatic acceptor aldehydes, the reactions proceeded with moderate diastereoselectivity and excellent enantioselectivity. For example, aldol product **2f** was isolated in 77% yield with 2:1 dr and 96% ee (Entry 7). Moreover, the (*S*)-proline-catalyzed self-aldol reaction of ketone **1** furnished the protected dendroketose in 61% yield and 95% ee. The reactions were operationally simple and can be performed on a gram-scale.

Determination of the Absolute Stereochemistry

The absolute and relative configurations of the known ketoses **2d** and **2e** confirmed that (*S*)-proline and other cyclic 5-membered amino acid derivatives catalyzed the asymmetric assembly of protected D-tagatose **2d** and (*R*)-proline mediated the formation of D-piscose **2e**, respectively.[5] Thus, the stereoselectivity of (*S*)-proline and (*R*)-proline are complimentary to tagatose aldolase and fuculose aldolase, respectively.[3b] Moreover, the acetonide protective groups were readily removed by standard acidic conditions to give the corresponding natural D-ketoses (Scheme 1).

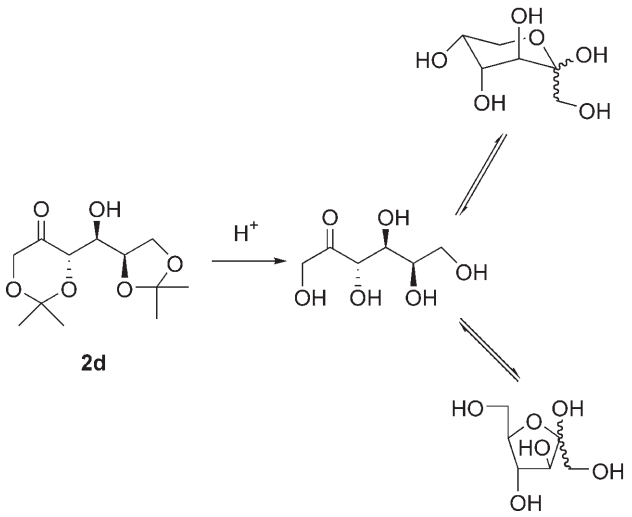
Furthermore, the optical rotation and spectral data of the *anti*-aldol product **2e** demonstrated that the absolute and relative stereochemistry of the aldol products derived by (*S*)-proline and its derivatives catalysis is in accordance with previous reported (*S*)-proline-catalyzed reactions.[5]

Table 3. Direct proline-catalyzed de novo synthesis of ketoses and polyhydroxylated compounds **2**.



Entry	Amino Acid	R	Prod.	Yield [%][a]	dr[b]	ee [%][c]
1	(*S*)-proline	4-NO_2-C_6H_4	**2a**	72	18:1	93
2	(*S*)-proline	4-NO_2-C_6H_4	**2a**	58[d]	12:1[d]	73[d]
3	(*S*)-proline	C_6H_5	**2b**	80	1:1	97
4	(*S*)-proline	$BnOCH_2$	**2c**	85	>19:1	98
5	(*S*)-proline		**2d**	74	>19:1	>98[e]
6	(*R*)-proline		**2e**	68	>19:1	>98[e]
7	(*S*)-proline	4-CN-C_6H_4	**2f**	77	2:1	96
8	(*S*)-proline	4-Cl-C_6H_4	**2g**	77	2:1	95
9	(*S*)-proline	4-Br-C_6H_4	**2h**	75	2:1	94
10	(*S*)-proline	*i*-Pr	**2i**	90	>19:1	99

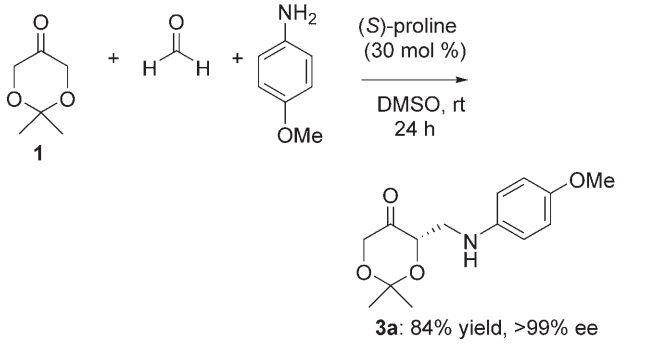
[a] Isolated yield of the pure products after silica gel chromatography.
[b] dr = *anti*/*syn* ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis. Bn = benzyl.
[d] No water was added.
[e] Based on the ee value of the starting protected (*R*)-glyceraldehyde and chiral shift reagents.



Scheme 1. Deprotection of D-tagatose.

Asymmetric Mannich Reactions

Amino and aza sugars are of immense importance as enzyme inhibitors and aminoglycosidase mimics.[18] They are usually prepared in multi-step synthetic sequences. Retro-synthetic analysis suggested that amino acid-catalyzed asymmetric three-component Mannich reactions with DHAP mimetic **1** would be a potential one-step entry to orthogonally protected amino sugars [Eq. (3)]. In an initial experiment, ketone **1** (1.5 mmol), formaldehyde (1 mmol, 36% aqueous solution) and *p*-anisidine (1.1 mmol) were vigorously stirred in the presence of a catalytic amount of (*S*)-proline (0.15 mmol) [Eq. (6)]. After 24 h the desired protected amino sugar **3a** was isolated in 84% yield and >99% ee.[15a]

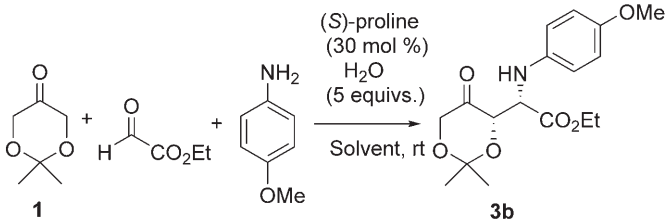


(6)

Solvent Screen

We next investigated the one-pot direct proline-catalyzed three-component Mannich reaction between **1**, *p*-anisidine and α-ethyl glyoxylate in different solvents (Table 4).

Table 4. Solvent screen for the biomimetic Mannich reaction.



Entry	Solvent	Time [h]	Yield [%][a]	dr[b]	ee [%][c]
1	DMSO	24	77	16:1	>99
2	DMF	24	28	19:1	96
3	NMP	24	35	19:1	82
4	TFE	24	60	>19:1	88
5	$CHCl_3$	24	22	19:1	8

[a] Isolated yield of the pure products after silica gel chromatography.
[b] Dr = *anti*/*syn* ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis.
n.d. = not determined.

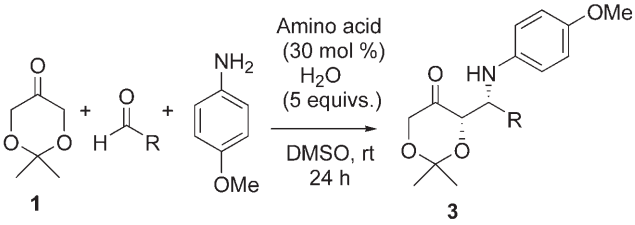
We found that proline was able to catalyze the formation of **3b** in all solvents tested. The order of reactivity of the solvents was in the following order: DMSO, TFE, NMP and DMF. The highest enantioselectiviy was obtained in DMSO and DMF. The proline-catalyzed Mannich reaction in chloroform furnished nearly racemic amino acid derivative **3b**.

Substrate Scope and Formal Total Synthesis

Encouraged by this result we decided to investigate the proline-catalyzed three-component Mannich reactions between donor **1**, *p*-anisidine and different acceptor aldehydes in wet DMSO (Table 5).

The proline-catalyzed asymmetric Mannich reactions proceeded with excellent chemoselectivity and the corresponding products **3a**–**3 g** were isolated in good yield and in several cases with >92% ee. The addition of water (5 equivalents) was of significant importance. For example, the (*S*)-proline-catalyzed Mannich reaction between **1**, *p*-anisidine and α-benzyloxyacetaldehyde without addition of water furnished trace amounts of the corresponding *p*-methoxyphenyl (PMP) protected amino sugar **3c** (Entry 3). In contrast, addition of 5 equivalents of water to the reaction mixture significantly accelerated the reaction and protected 4-amino-4-deoxy-*threo*-pentulose **3c** was isolated in 70% yield in a 6:1 dr (*syn*:*anti*) and 98% ee (Entry 4). Moreover, the (*R*)-

Table 5. Direct proline-catalyzed three-component asymmetric Mannich reactions with DHAP mimetic **1**.

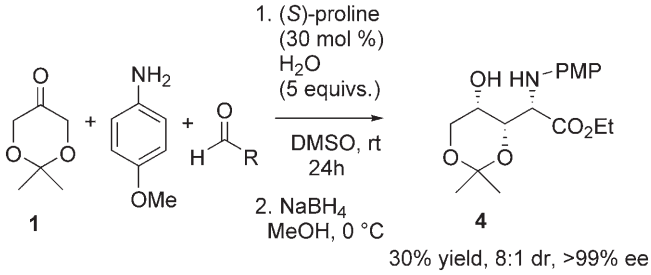


Entry	Amino Acid	R	Prod.	Yield [%][a]	dr[b]	ee [%][c]
1	(*S*)-proline	H	**3a**	84		>99
2	(*S*)-proline	CO_2Et	**3b**	77	16:1	>99
3	(*S*)-proline	$BnOCH_2$	**3c**	traces[d]	n.d.[d]	n.d.[d]
4	(*S*)-proline	$BnOCH_2$	**3c**	70	6:1	98
5	(*S*)-proline		**3d**	40	3:1	98[e]
6	(*R*)-proline		**3e**	55	>19:1	98[e]
7	(*S*)-proline	Ph	**3f**	80	3:1	76
8	(*S*)-proline	*i*-Pr	**3g**	60	4:1	48

[a] Isolated yield of the pure products after silica gel chromatography.
[b] dr = *syn*/*anti* ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis.
[d] Not determined.
[e] Based on the ee value of the starting protected (*R*)-glyceraldehyde.
Bn = benzyl.

proline-catalyzed three-component Mannich reaction between DHAP mimetic **1**, *p*-anisidine and *R*-isopropylideneglyceraldehyde proceeded with high chemo- and diastereoselectivity and furnished the corresponding protected D-4-amino-4-deoxysorbose **3e** in 55% yield with >19:1 dr and = 98% ee. In this case, (*R*)-proline was more efficient than (*S*)-proline. However, the proline-catalyzed Mannich reactions with benzaldehyde and *i*-butyraldehyde furnished the corresponding product **3f** and **3 g** with 75% ee and 48% ee, respectively. Thus, only moderate ees were obtained in these cases. The proline-catalyzed one-pot three-component Mannich reactions between α-glyoxylate, ketone **1**, and *p*-anisidine furnished the desired amino acid derivative **3b** in 77% yield with 16:1 dr and >99% ee (Entry 2). The reaction is readily scaled up and the amino acid-catalyzed asymmetric assembly of **3b** was performed on a gram scale.

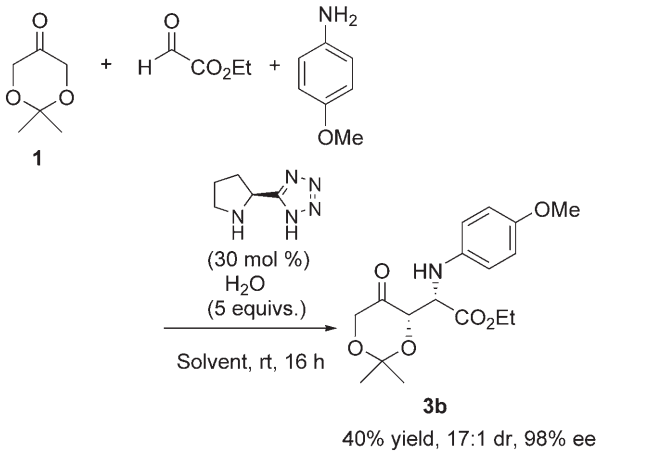
Polyxamic acids are naturally occurring and parts of polyoxindes.[19] Previous total syntheses of polyoxamic



Scheme 2. The highly chemo- and enantioselective one-step synthesis of protected polyoxamic acid **4**.

acids involve around six to eight steps.[20] However, *retro*-synthetic analysis suggests that amino acid-catalyzed asymmetric Mannich reactions between **1** and α-ethyl glyoxylate would be a novel short entry for the synthesis of polyoxamic acids. Thus, *in situ* chemoselective reduction of the keto functionality of the amino acid derivative **3b** derived by (*S*)-proline catalysis furnished the desired polyoxamic acid **4** in 30% yield as a predominant diastereomer and >99% ee (Scheme 2). Our reaction constitutes a novel one-step total synthesis of orthogonally protected polyoxamic acids such as **4**. Importantly, either enantiomer of the polyoxamic acid **4** can be formed by simply utilizing (*S*)- or (*R*)-proline as the catalyst.

The direct catalytic three-component asymmetric Mannich reaction was also catalyzed by praline-tetrazole with excellent chemo- and enantioselectivity [Eq. (7)].[21]



(7)

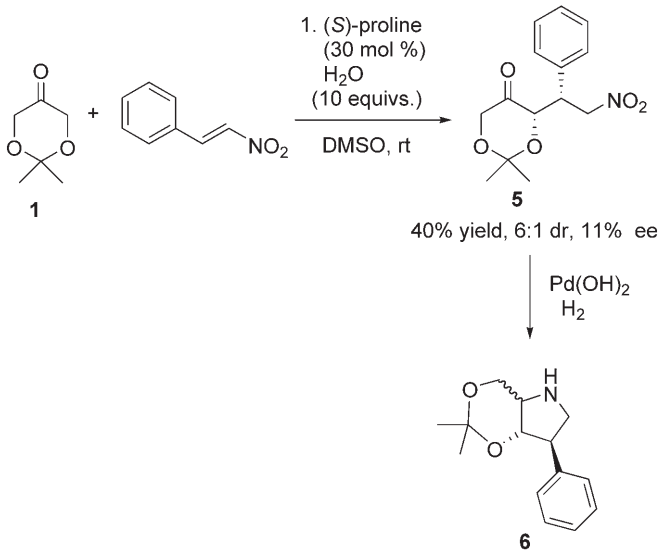
Determination of the Absolute Stereochemistry

The relative stereochemistries of the Mannich products **3** were assigned by NMR analysis and the absolute configuration based on correlation to the established previous (*S*)-proline-catalyzed Mannich reactions.[13] For example, (S)-proline asymmetrically assembled the corre-

sponding the L-amino sugar **3a** as determined by synthesis.[13g] The relative configuration of the products was *syn* and (*S*)-proline mediated the asymmetric assembly of (*S*)-amino acid derivative **3b**.

Michael Reactions

We next turned our attention towards a plausible synthesis of polyhydroxylated pyrrolidines, which are used as enzyme inhibitors, *via* amino acid-catalyzed Michael reactions between DHA mimetic **1** and nitrostyrenes [Eq. (3)]. In an initial experiment, ketone **1** (1.5 mmol), H_2O (5 mmol) and phenylnitrostyrene (0.5 mmol) in DMSO (2.0 mL) were reacted in the presence of a catalytic amount of (*S*)-proline. After 8 days of vigorous stirring the desired Michael product **5** was isolated in 40% yield with 6:1 dr and 11% ee [Eq. (8)].[22]



(8)

The Michael adduct was readily transformed to the corresponding pyrrolidine **6** by hydrogenation. Thus, the amino acid-catalyzed Michael reactions with **1** as the donor constitutes a novel entry to important hydroxy-substituted pyrrolidines or aza sugars.

Mechanism

The mechanism of the proline-catalyzed aldol reactions with DHAP mimetic **1** is depicted in Scheme 3a. The donor **1** reacts with proline, resulting in iminium formation. The iminium intermediate can either form an enamine or an oxazolidinone intermediate.[23] The oxazolidinone formation leads to catalyst inhibition and consequently decrease of the turnover. Next, the acceptor aldehyde reacts with the chiral enamine and C–C bond formation occurs resulting in an iminium intermediate, which also potentially undergoes oxazolinone formation. Hydrolysis of the product iminium intermediate by water gives the enantiomerically enriched aldol product and the catalytic cycle can be repeated.

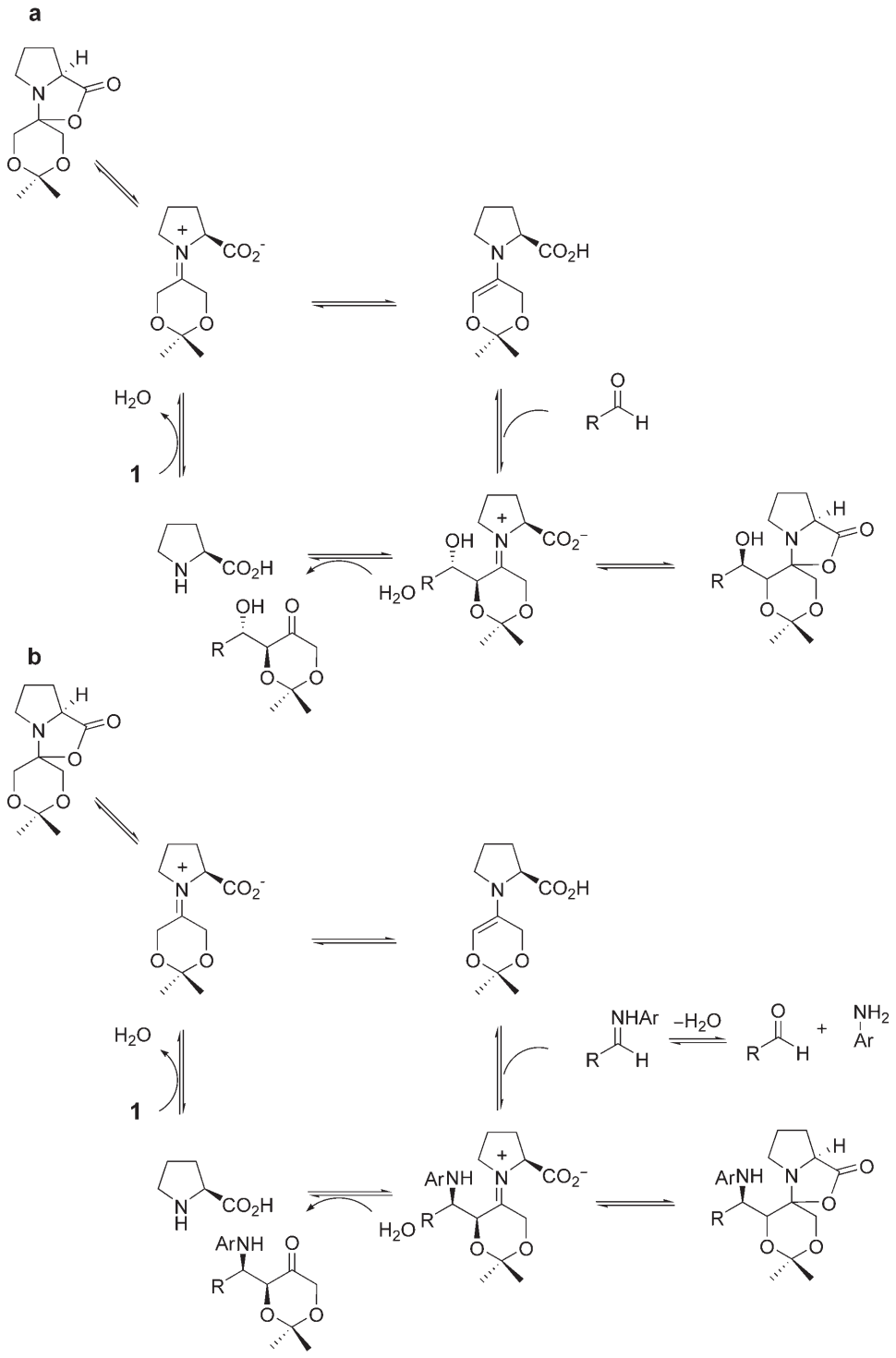
The same reaction mechanism is true for the proline-catalyzed direct asymmetric Mannich reactions (Scheme 3b). However, in this case, the chiral enamine intermediate reacts with the *in situ* generated imine to give an enantiomerically enriched Mannich product (after hydrolysis).

The stereochemistry of the (*S*)-proline-catalyzed aldol reactions with **1** was explained in terms of a *Re*-facial attack on the aldehyde by the *Si*-face of the enamine (Figure 2, **I**). The stereochemistry of the (*S*)-proline-catalyzed Mannich reactions with **1** was explained in terms of an *Si*-facial attack on the imine with a *trans*-configuration by the *Si*-face of the enamine (Figure 2, **II**). The six-membered transition states **I** and **II** are stabilized by hydrogen bonding between the oxygen atom of the aldehyde and the nitrogen atom of the imine and the carboxylic group of proline, respectively. The switch of facial selectivity between the aldehyde and imine is explained by the fact that a *Re*-facial attack on the imine would lead to steric repulsion with the pyrrolidine moiety of the enamine. Hence, proline affords β-hydroxy ketones **2** with *anti*-configuration and β-amino ketones **3** with a *syn*-stereochemistry.[13b,q,24]

The small excess of water will potentially facilitate proton-transfer in the transition state, which both lowers the LUMO of the incoming electrophile as well as directs the enantioselectivity of the newly formed stereocenters. Thus, the higher Brønsted acidity of the amino acid when water is added to the polar aprotic organic solvent plausibly accounts for the observed higher stereoselectivity of the water accelerated carbohydrate synthesis and Mannich reactions. Moreover, a small amount of water stabilizes the carbanion that is formed in the transition states **I** and **II**.

Conclusion

In summary, we disclose the *de novo* synthesis of ketoses by amino acid-catalyzed C–C bond-forming reactions with dihydroxyacetone mimetic **1** as the donor. The cyclic five-membered amino acids catalyzed the asymmetric assembly of keto sugars and amino sugars with enzyme-like selectivity to yield the desired carbohydrates in high yield with up to >99% ee. The organocatalytic C_3+C_n methodology presented herein is a direct entry to a one-step *de novo* synthesis of orthogonally protected C_4, C_5 and C_6 ketoses. In comparison to aldolase enzymes, organocatalysis has a broader scope with respect to the electrophile. Thus, orthogonally protected amino sugars and nitro sugars are synthesized by proline-medi-



Scheme 3. a) The reaction mechanism of the proline-catalyzed direct asymmetric aldol reactions with **1** as the donor. **b**) The reaction mechanism of the proline-catalyzed direct asymmetric Mannich reactions with **1** as the donor.

ated asymmetric Mannich and Michael reactions. A novel one-step formal total synthesis of polyoxamic acids was also accomplished. We found that an important water effect existed in the proline-catalyzed biomimetic aldol, Mannich and Michael reactions. The addition of water (1–10 equivs.) significantly accelerates and improves the enantioselectivity of the proline-mediated asymmetric reactions with protected dihydroxyacetones as donors, which is due to suppression of catalyst inhibition during the catalytic cycle and more efficient

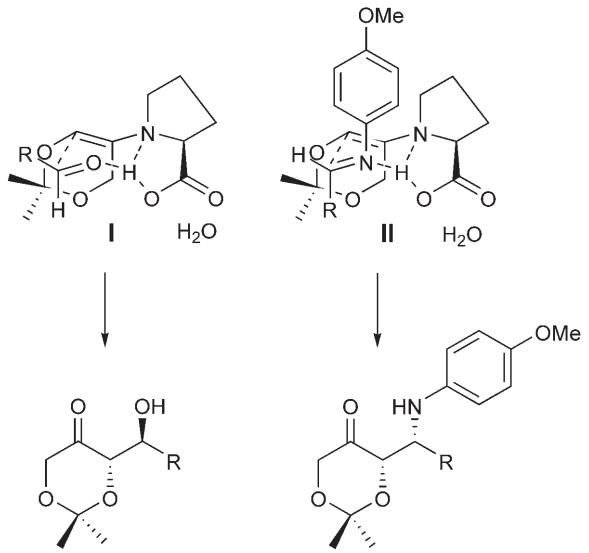


Figure 2. Proposed transition states **I** and **II** for the proline-catalyzed asymmetric aldol and Mannich reactions, respectively.

stabilization of the carbanion in the transition state, respectively. In addition, the high stereoselectivity of the amino acid-catalyzed carbohydrate synthesis makes it an attractive alternative to biocatalytic carbohydrate synthesis. The reaction constitutes an environmentally benign route for the expeditious synthesis of valuable carbohydrates.

Experimental Section

General Methods

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2.H_2O$ (10 g), concentrated H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concentrated H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H NMR and ^{13}C NMR spectra were recorded on Varian AS 400 and 300. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. GC was carried out using a Varian 3800 GC Instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (δ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical Experimental Procedure for the Proline-Catalyzed Asymmetric Biomimetic Aldol Reactions with 1 as the Donor

The aldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. Next, the ketone **1** (1.5 mmol) and water (2.5 mmol, 45 μL) were added to the flask and the mixture was vigorously stirred for 24 h at room temperature. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous-phase was back-extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated. The pure protected sugars **2** were obtained by silica gel column chromatography (toluene: EtOAc mixtures).

Typical Experimental Procedure for the Proline-Catalyzed Asymmetric Biomimetic Three-Component Mannich Reactions with 1 as the Donor

The aldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %), *p*-anisidine (0.55 mmol) and 2 mL DMSO. Next, the ketone **1** (1.5 mmol) and water (2.5 mmol, 45 μL) were added to the flask and the mixture was vigorously stirred for 24 h at room temperature. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous-phase was back-extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated. The pure protected amino sugars **3** were obtained by silica gel column chromatography (toluene:EtOAc mixtures). In the case of Mannich product 3a, neutral aluminum oxide was used for the column chromatography.

One-Pot Three-Component Asymmetric Synthesis of Protected Polyoxamic Acid 4

The α-ethyl glyoxylate (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %), *p*-anisidine (0.55 mmol) and 2 mL DMSO and the reaction mixture was stirred for 20 minutes. Next, the ketone **1** (1.5 mmol) and water (2.5 mmol, 45 μL) were added to the flask and the mixture was vigorously stirred for 24 h at room temperature. The reaction temperature was decreased to 0 °C and the mixture diluted with MeOH (2.0 mL). Next, $NaBH_4$ was slowly added to the reaction mixture which was stirred at 0 °C. After 15 minutes the reaction mixture was slowly added to a mixture of EtOAc (15.0 mL) and 2 N HCl (2.0 mL), the whole was cooled to 0 °C, and stirred for 20 minutes. Then the reaction mixture was dried with $MgSO_4$ and filtered. The organic phase was concentrated and purified by silica gel column chromatography (toluene:EtOAc, 1:1) to give polyoxamic acid **4** as a clear oil; yield: 52 mg (30%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 3.74 (s, 3H), 3.79 (m, 1H), 3.86 (dd, *J* = 12.1, 2.1 Hz, 1H), 4.01 (d, *J* = 1.8 Hz, 1H), 4.07 (m, 1H), 4.12–4.24 (m, 2H), 4.33 (m, 1H), 6.78 (s,

4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 18.9, 29.4, 55.8, 61.7, 62.6, 65.5, 65.9, 66.6, 99.6, 114.9, 118.4, 139.9, 154.7, 171.2; $[\alpha]_D^{26}$: −16.4 (*c* = 1.0, $CHCl_3$); MALDI-TOF MS: *m/z* = 362.1582; calcd. for $C_{17}H_{25}O_6N$ ($M + Na^+$): 362.1580.

Proline-Catalyzed Asymmetric Biomimetic Michael Reactions with 1 as the Donor and Asymmetric Synthesis of Aza Sugar 6

To a suspension of L-proline (30 mol %) in DMSO (1 mL) and H_2O (10 equivs.) was added the dioxanone (0.75 mmol) and nitroolefin (0.25 mmol). The resulting mixture was allowed to stir until TLC indicated complete conversion. The reaction was quenched with brine and extracted with ethyl acetate (3 × 10 mL), the combined organic phase was dried over anhydride Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel column chromatography (pentane:EtOAc,15:1 → 4:1) to give the Michael product **5**; yield: 28 mg (40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.21 (m, 5H, Ar), 4.92 (dd, 1H, *J* = 12.8, 9.2 Hz), 4.67 (dd, 1H, *J* = 12.8, 6.8 Hz), 4.58 (dd, 1H, *J* = 3.6, 1.2 Hz), 4.12 (ddd, 1H, *J* = 9.2. 6.8, 4.0 Hz), 3.90–3.86 (m, 2H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 206.72, 134.82, 129.39, 128.49, 128.07, 101.13, 76.34, 74.54, 66.99, 43.22, 24.01, 23.22; HPLC (Daicel Chiralpak AS, *iso*-hexanes/*i*-PrOH = 90:10, flow rate 0.5 mL/min, λ = 230 nm): major isomer: t_R = 17.71 min; minor isomer: t_R = 21.69 min; $[\alpha]_D^{25}$: −33.4 (*c* 1.0, $CHCl_3$).

A mixture of nitroketone **5** (28 mg, 0.1 mmol) and 20% $Pd(OH)_2$on carbon (4 mg) in 5 mL of methanol was hydrogenated at 90 psi for 2 days. The solution was filtered through celite and concentrated to give aza sugar **6** as a liquid; yield: 20 mg (86%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41–7.18 (m, 5H, Ar), 4.29 (dd, 1H, *J* = 5.1, 2.1 Hz), 4.21–4.10 (m, 2H), 3.86 (dd, 1H, *J* = 9.3, 8.4 Hz), 3.31–3.23 (m, 1H), 2.91 (1H, *J* = 9.9 Hz), 2.83–2.75 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.44 MHz): δ = 141.69, 128.66, 127.47, 126.82, 98.06, 75.36, 64.37, 63.24, 59.05, 48.56, 28.66, 19.73.

Typical Experimental Procedure for the Catalyst Screen

The *p*-nitrobenzaldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. Next, the ketone **1** (1 mmol) and water (2.5 mmol, 45 μL) were added to the flask and the reaction mixture was vigorously stirred for the time shown in Table 3 at room temperature. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous phase was back-extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated. The pure protected aldol product 2a was obtained by silica gel column chromatography (toluene:EtOAc, 7:1).

Experimental Procedure for the Measurements of the Formation of 2a as a Function of Time

Several reactions were started in parallel and run for different reaction times, which are shown in Figure 1 (■). The *p*-nitrobenzaldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. Next, the ketone **1** (1 mmol) and water (2.5 mmol, 45 μL) were added to the flask and the reaction mixture was vigorously stirred at room temperature. After one of the times shown in Figure 1 (■) an aliquot of the reaction mixture (10 μL) was dissolved in $CDCl_3$ and the conversion of *p*-nitrobenzaldehyde and formation of **2a** were determined by NMR analysis.

A series of parallel reactions were also started in parallel and run for different reaction times, which are shown in Figure 1 (▲). The *p*-nitrobenzaldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. Next, the ketone **1** (1 mmol) was added to the flask and the reaction mixture was vigorously stirred at room temperature. After one of the times shown in Figure 1 (▲) an aliquot of the reaction mixture (10 μL) was dissolved in $CDCl_3$ and the conversion of *p*-nitrobenzaldehyde and formation of **2a** were determined by NMR analysis.

Acknowledgements

Support by Prof. J.-E. Bäckvall and Stockholm University is gratefully acknowledged. We thank the Swedish National Research Council, Lars Hierta Foundation, Carl-Trygger Foundation and Wenner-Gren Foundation for financial support.

References and Notes

[1] a) J. M. Berg, J. L. Tymoczko, L. Stryer, *Biochemistry*, W. H. Freeman & Co., New York, **2002**; b) B. Ernst, G. W. Hart, P. Sinay (Eds), *Carbohydrates in Chemistry and Biology*, Wiley-VCH, New York, **2000**.

[2] a) S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151; b) A. Córdova, I. Ibrahem, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772; c) A. Córdova, M. Engqvist, I. Ibrahem, J. Casas, H. Sundén, *Chem. Commun*. **2005**, 2047; c) J. Kofoed, M. Machuqueiro, J. -L. Reymond, T. Darbre, *Chem. Commun.* **2004**, *26*, 1540.

[3] a) W.-D. Fessner, in: *Stereoselective Biocatalysis*, (Ed.: R. N. Patel), Marcel Dekker, New York, **2000**, p. 239; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352; c) A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C.-H. Wong, I. A. Wilson, *Science* **2001**, *294*, 369.

[4] P. Wang, C. Bertozzi (Eds), *Glycochemistry: Principles, Synthesis and Applications*, Marcel Dekker, New York, **2001**.

[5] For synthesis of ketoses see: a) M. Majewski, P. Nowak, *J. Org. Chem*. **2000**, *65*, 5152; b) M. Majewski, P. Nowak, *Synlett* **1999**, 1447; c) D. Enders, S. J. Ince, *Synthesis* **2002**, 619; d) D. Enders, M. Voith, S. J. Ince, *Synthesis* **1996**, 1775; e) D. Enders, O. F. Prokopenko, G. Raabe, J. Runsink, *Synthesis* **1996**, 1095; for an excellent review for the use of protected dihydroxyacetones in synthesis, see: f) D. Enders, M. Voith, A. Lenzen, *Angew. Chem. Int. Ed*. **2005**, *44,* 1330 and references cited therein.

[6] For the synthesis of aldoses, see: a) K. C. Nicolaou, H. J. Mitchel, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576; b) D. A.

Evans, E. Hu, J. S. Tedrow, *Org. Lett.* **2001**, *3*, 3133; c) S. G. Davies, R. L. Nicholson, A. D. Smith, *Synlett* **2002**, 1637; d) S. J. Danishefsky, C. J. Maring, *J. Am. Chem. Soc.* **1985**, *107*, 7761; e) S. G. Davies, R. L. Nicholson, A. D. Smith, *Org. Biom. Chem*. **2004**, *2*, 3385; reviews of the catalytic asymmetric aldol reaction, see: f) D. A. Evans, J. V. Nelson, T. Taber, in: *Topics in Stereochemistry*, Vol. 13, Wiley, Chicester, **1982**, p. 1; g) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36; for examples of direct metal organic catalytic aldol reactions, see: h) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed.* **1997**, *36*, 1871; i) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Oshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466; j) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; k) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497; l) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392; for examples of the *de novo* synthesis of aldoses *via* Sharpless AD, see: m) S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless, W. J. Walker, *Science* **1983**, *220*, 249; n) M. M. Ahmed, B. P. Berry, T. J. Hunter, D. J. Tomcik, G. A. O'Doherty, *Org. Lett*. **2005**, 7, 745.

[7] S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, **1983**.

[8] a) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1994**, *116*, 8422; b) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 7585; c) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc*. **1995**, *117*, 2947; d) J. Liu, C.-H. Wong, *Angew. Chem. Int. Ed.* **2002**, *41*, 1404; e) M. G. Silvestri, G. Desantis, M. Mitchell, C- H. Wong, *Topics in Stereochemistry*, **2003**, *23*, 267; f) R. Schoevaart, F. Van Rantwijk, R. A. Sheldon, *J. Org. Chem.* **2000**, *65*, 6940; g) H. J. M. Gijsen, L. Qiao, W. Fitz, C.-H. Wong, *Chem. Rev.* **1996**, *96*, 443; k) W. D. Fessner, V. Helaine, *Current Opinion in Biotechnology* **2001**, *12*, 574.

[9] Reviews, see: a) P. I. Dalko, L. Moisan, *Angew Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; d) P. Merino, T. Tejero, *Angew. Chem. Int. Ed.* **2004**, *43*, 2995.

[10] For a summary of amino acid-catalyzed sugar synthesis, see: U. Kazmaier, *Angew. Chem. Int. Ed*. **2005**, *44*, 3509.

[11] For selected direct organocatalytic aldol reactions, see: a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615; b) U. Eder, R. Sauer, G. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496; c) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; d) W. Notz, B. List, *J. Am. Chem. Soc*. **2000**, *122*, 7386; e) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573; f) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, *67*, 3034; g) Z. Tang, F. Jiang, L. -T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Jiang, Y.-Z Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; h) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem*. **2002**, *67*, 301; i) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; j) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; k) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed.* **2004**, *43*, 2420; l) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; m) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591; n) A. Córdova, *Tetrahedron Lett*. **2004**, *45*, 3949. o) J. Casas, H. Sundén, A. Córdova, *Tetrahedron Lett*. **2004**, *45*, 6117; p) I. Ibrahem, A. Córdova, *Tetrahedron Lett*. **2005**, *46*, 2839; q) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2004**, *43*, 2152; r) S. Saito, M. Nakadai, H. Yamamoto, *Tetrahedron* **2002**, *58*, 8167; s) Z. Tang, F. Jiang, L. -T. Yu, X. Cui, L. -Z. Gong, A. -Q. Mi, Y. -Z. Jiang, Y. -D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262; t) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983; u) A. Hartikaa, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, *15*, 1831; v) A. Berkessel, B. Koch, J. Lex, *Adv. Synth. Catal.* **2004**, *346*, 1141; x) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem*. **2005**, *3*, 84; y) Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435; z) J. Koefed, J. Nielsen, J.-L. Reymond, *Biorg. Med. Chem. Lett*. **2003**, *13*, 2445.

[12] a) A. B. Northrup, D. W. C. MacMillan D. W. C. *Science* **2004**, *305*, 1752; b) J. Casas, M. Engqvist, I. Ibrahem, B. Kaynak, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 1343; c) E. Reyes, A. Córdova, *Tetrahedron Lett.* **2005**, In press.

[13] Amino acid-catalyzed asymmetric Mannich reactions, see: a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; b) B. List, P. Porjaliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827; c) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199; d) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842; e) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558; f) T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301; g) I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 6528; h) A. Córdova, S. -i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; i) A. Córdova, C. F. Barbas III, *Tetrahedron Lett*. **2002**, *43*, 7749; j) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987; k) A. Córdova, *Synlett* **2003**, 1651; l) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; m) N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507; n) A. Münch, B. Wendt, M. Christmann, *Synlett* **2004**, 2751; o) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 4476; p) I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839; q) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron* **2005**, in press; for a review see: r) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.

[14] For examples of amino acid and derivatives thereof-catalyzed asymmetric Michael reactions, see: a) S. Hannesian, V. Pham, *Org. Lett.* **2000**, *2*, 2975; b) B. List, P. Pojarliev, H. J. Martin, *Org. Lett*. **2001**, *3*, 2423; D. Enders, A. Seki, *Synlett* **2002**, 26; c) J. M. Betancort, C. F. Barbas III, *Org. Lett*. **2001**, *3*, 3737; d) J. M. Betancort, K. Sakthivel,

R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441; e) J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Synthesis* **2004**, 1509; f) A. Alexakis, O. Andrey, *Org. Lett*. **2002**, *4*, 3611; g) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559; g) M. T. Hechavarria Fonseca, B. List, *Angew. Chem. Int. Ed*. **2004**, *43*, 3958; h) W. Wang, J. Wang, H. Li, *Angew. Chem. Int. Ed*. **2004**, #43#*44*, 1369; i) N. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; j) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331; j) N. Halland, P. S. Aburel K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2003**, *42*, 661; k) N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2003**, *42*, 4955; l) N. Halland, P. S. Aburel K. A. Jørgensen, *Angew. Chem. Int. Ed*. **2004**, *43,* 1272; l) T. Ishii, S. Fujioku, Y. Sekiguchi, H. *Kotsuki, J. Am. Chem. Soc.* **2004**, *126*, 9558; m) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

[15] a) I. Ibrahem, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3363. This is also the first use of **1** in amino acid-mediated Mannich reactions. For the first report on the use of **1** in amino acid-mediated aldol reactions see: b) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210. Later on, independent reports appeared on aldol: c) J. T. Suri, D. B. Ramachary, C. F. Barbas III, *Org. Lett*. **2005**, *7*, 1383; and Mannich: d) B. Westermann, C. Neuhaus, *Angew. Chem. Int. Ed.* **2005**,44, 4077; e) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed*. **2005**, *44*, 4079.

[16] a) A. I. Nyberg, A. Usano, P. Pihko, *Synlett* **2004**, 1891; b) D. E. Ward. V. Jheengut, *Tetrahedron Lett*. **2004**, *45*, 8347.

[17] Simple primary amino acids, primary amino acid terminated peptides and their derivatives are also catalysts for the asymmetric aldol reaction with **1**, see: a) A. Córdova, W. Zou, I. Ibrahem, M. Engqvist, E. Reyes, W. W. Liao, *Chem. Commun*, **2005**, 3586; b) W. Zou, I. Ibrahem, P. Diedzic, H. Sundén, A. Córdova, *Chem. Commun*, **2005**, 4946.

[18] a) T. D. Heightman, A. T. Vasella, *Angew. Chem. Int. Ed.* **1999**, *38*, 750; b) G. C. Look, C. H. Fotsh, C.-H. Wong, *Acc. Chem. Res.* **1993**, *26*, 182; c) *Iminosugars as glycosidase inhibitors: Nojirimycin and beyond*, (Eds.: A. E. Stutz, A. E. Stu), Wiley-VCH, Weinheim, **1999**.

[19] K. Isono, K. Asahi, S. Suzuki, *J. Am. Chem. Soc.* **1969**, *91*, 7490.

[20] a) B. trost, A. Krueger, R. C. Bunt, J. Zombrano, *J. Am. Chem. Soc*. **1996**, *118*, 6520; b) A. Tarrade, D. Dauban, R. H. Dodd, *J. Org. Chem.* **2003**, *68*, 9521 and references cited therein.

[21] Primary amino acids, primary amino acid terminated peptides and their derivatives are also catalysts for the asymmetric Mannich reaction with **1** as the donor: I. Ibrahem, W. Zou, Y. Xu, A. Córdova, *Chem. Eur. J*, **2005**, *11*, 7024.

[22] Small peptides catalyze the Michael addition of **1** to nitrostyrenes: Y. Xu. W. Zou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, in press.

[23] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839.

[24] S. Bahmanyar, K. N. Houk, *Org. Lett.* **2003**, *5*, 1249 and references cited therein.

