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Sugar-Assisted Kinetic Resolution of Amino Acids and Amplification of Enantiomeric Excess of Organic Molecules

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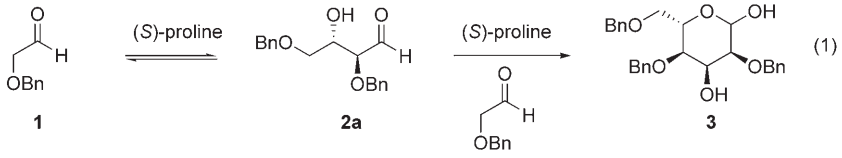
Abstract: The origins of biological homochirality have intrigued researchers since Pasteur's discovery of the optical activity of biomolecules. Herein, we propose and demonstrate a novel alternative for the evolution of homochirality that is not based on autocatalysis and forges a direct relationship between the chirality of sugars and amino acids. This process provides a mechanism in which a racemic mixture of an amino acid can catalyze the formation of an optically active organic molecule in the presence of a sugar product of low enantiomeric excess.

Keywords: amino acids · asymmetric amplification · homochirality · kinetic resolution · sugars

Introduction

The origins of biological homochirality have intrigued researchers since Pasteur's discovery of the optical activity of biomolecules.[1] In 1953, Frank proposed that evolution of high asymmetry from a small imbalance of enantiomers could be achieved by a combination of autocatalytic and inhibition processes.[2] This was first experimentally accomplished by Soai and co-workers.[3] Their original zinc addition experiment has been widely used to explain the origins of homochirality.

The circular polarization in star formation regions may have led to the initial asymmetry of organic molecules such as sugars and amino acids.[4] In fact, extraterrestrial amino acids have been found on the Murchison meteorite with enantiomeric excesses (*ee*s) of up to 9%.[5] The finding has led to speculation on the origins of homochirality by a process mediated by amino acids.[6–8] Furthermore, extraterrestrial sugars are also present on the Murchison meteorite.[9] In our earlier studies on the amino acid catalyzed formation of carbohydrates such as **2a** and **3**,[10] we found a remarkably high asymmetric amplification in the formation of the hexose product **3** (Reaction (1)).[11] In addition, a positive nonlinear effect that is dependent on the reaction conditions has been observed in the amino acid catalyzed α-aminoxylation of propionaldehyde.[7]



Hence, amino acids may have been the seed for the evolution of homochirality of carbohydrates. However, Frank's scheme is not applicable to Reaction (1) since the catalyst is not catalyzing its own formation. In fact, the amino acid is catalyzing the asymmetric formation of a sugar in a fashion similar to the way in which enzymes have asymmetrically assembled carbohydrates for millions of years.[12–13] Thus, there is a need to find an alternative mechanism for the origins of homochirality that is not based on autocatalysis. Bearing this in mind, and given the intense interest in the origins of homochirality, we became interested in finding a reaction model that could provide new insights on the origin of asymmetric amplification in amino acid catalyzed reactions. Here, we propose and demonstrate a novel alternative for the evolution of homochirality that forges a direct relation-

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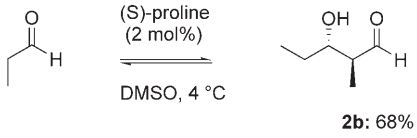
ship between the chirality of sugars and amino acids. This process provides a mechanism by which a racemic mixture of an amino acid can catalyze the formation of an organic molecule with an enantiomeric excess.

Results and Discussion

We first investigated the (*S*)-proline-catalyzed asymmetric formation of aldose precursor **2b** (Reaction (2)).[13d]



(2)

2b: 68% yield, 4:1 d.r., 98% *ee*

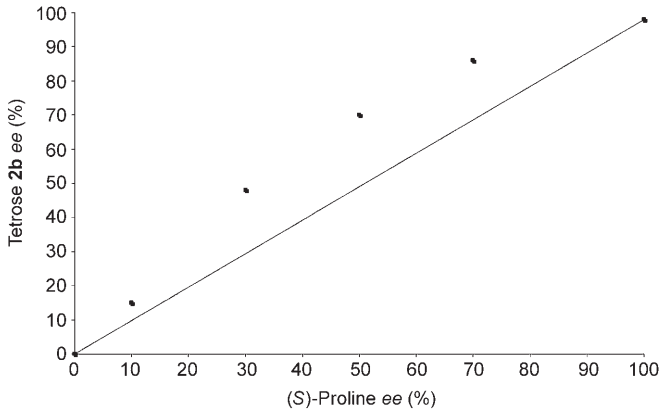
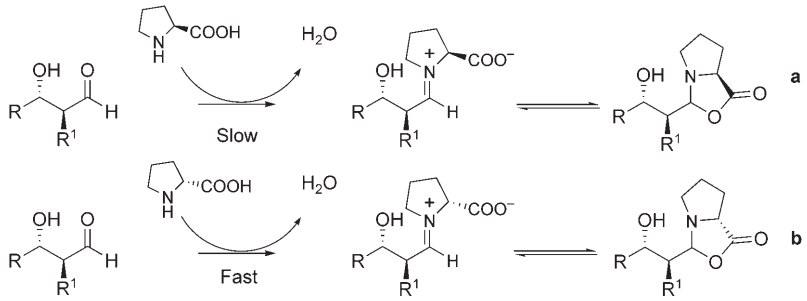


Figure 1. Relation between the enantiomeric excess of (*S*)-proline and that of the newly formed tetrose **2b** (■) in the catalytic asymmetric dimerization of propionaldehyde.

In initial experiments, we performed the amino acid catalyzed asymmetric synthesis of **2b** using different levels of enantioenriched (*S*)-proline as the catalyst (Figure 1). Notably, we found a significant asymmetric amplification of the enantiomeric excess in the amino acid catalyzed asymmetric formation of β-hydroxyaldehyde **2b**, even though, a single proline molecule takes part in the formation of aldose precursors **2** according to the proposed mechanisms and transition states of previously reported proline-catalyzed enantioselective aldol reactions.[10,11,13,14]

The results indicated to us that the asymmetric amplification in the amino acid catalyzed reactions was plausibly caused by chiral product **2b**. We therefore decided to test an alternative and novel explanation for the origins of homochirality that is consistent with transition state theory. The model is based on the intrinsic ability of chiral organic molecules such as sugars and β-hydroxyaldehydes **2**,[15] which are formed by amino acid catalysis, to react at different rates with the (*S*)- or (*R*)-amino acid and consequently "auto" kinetically resolve the catalyst without forming a new catalyst species (Scheme 1).



Scheme 1. Different reaction rates of (*S*)- and (*R*)-proline with sugars **2**.

This sugar-assisted kinetic resolution leads to asymmetric amplification of the chiral organic product in the next catalytic cycle because the free amino acid has a higher optical activity (Figure 2).

The product-assisted auto-kinetic resolution scheme is also applicable to sequential ($P_{n+1}=S_{n+1}$) and two parallel amino acid catalyzed reactions where the amino acid de-

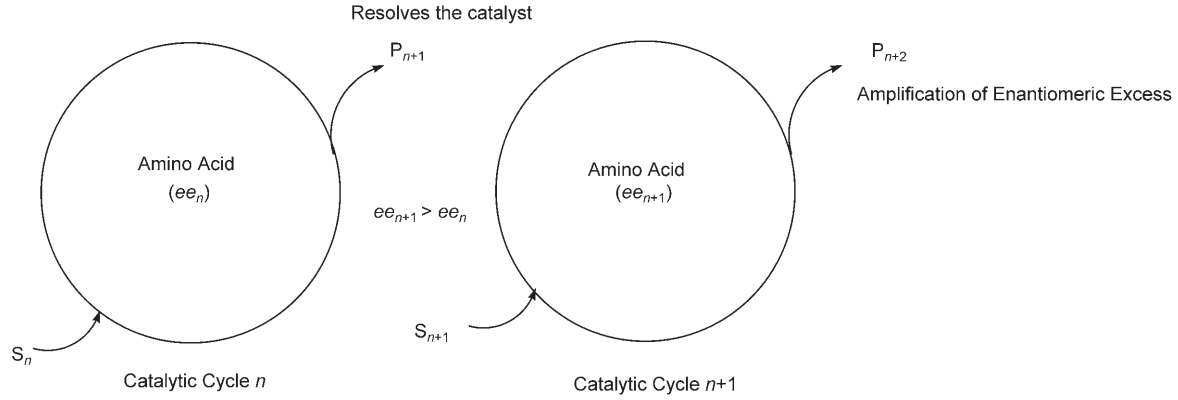
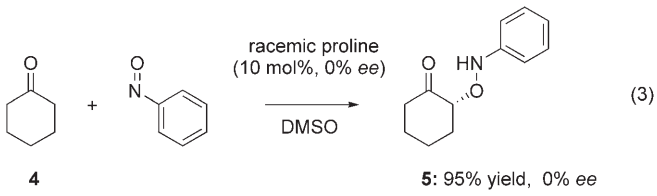


Figure 2. Proposed model for the catalytic asymmetric amplification.

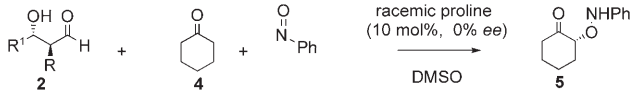
rived products P_{n+1} or P_{n+2} synergistically contributes to the asymmetric amplification of one of the products. The theory can be tested with a racemic amino acid as the catalyst. In this case, the presence of a chiral sugar P_1 with enantiomeric excess should be able to kinetically resolve the amino acid catalyst, which subsequently catalyzes the formation of optically active product P_2. This plausible scenario would suggest that a chiral sugar could have set the seed for the evolution of homochirality of sugars and amino acids. To further test our theory of a sugar-assisted kinetic resolution of an amino acid catalyst, we chose the racemic proline-catalyzed α-aminoxylation of cyclohexanone **4** that furnishes the corresponding racemic α-aminoxylated ketone **5** as the model reaction (Reaction (3)).[16]

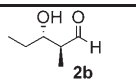
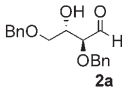
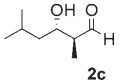
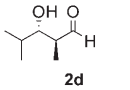
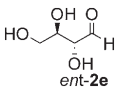
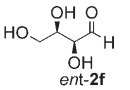
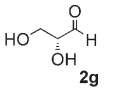


(3)

This proline-catalyzed reaction exhibits no asymmetric amplification and only one proline molecule takes part in the transition state.[16d,e] In an initial experiment, we added aldose precursor **2b** with 98% *ee* (1 mmol), which had been obtained by (*S*)-proline catalysis (Reaction (2)),[13d] to a mixture of racemic proline (10 mol%) in DMSO (1 mL) (Table 1, entry 1). After the mixture had been stirred for 1 h, the reaction mixture became homogeneous and cyclohexanone **4** (1 mmol) was added. Next, nitrosobenzene (0.5 mmol) in DMSO (1 mL) was slowly added by syringe pump to the reaction mixture. The reaction was quenched by directly purifying the reaction mixture by silica-gel column chromatography. Remarkably, product **5** was isolated in 57% yield with 27% *ee* (Table 1, entry 1). Thus, a product-assisted kinetic resolution of the amino acid catalyst by the aldehyde **2b** had occurred. The added aldose precursor **2b** was recovered with 97% *ee* as determined by chiral-phase GC analyses. Notably, increasing the pre-mixing time of **2b** with racemic proline to 4 h increased the *ee* of **5** to 66% *ee* (Table 1, entry 2). In addition, no product **5** was furnished without a catalytic amount of racemic proline. The addition of different aldose precursors **2a–d**, which had been furnished by (*S*)-proline catalysis, to the racemic proline-catalyzed model reaction (vide infra) furnished the optically active ketone product **5** in all cases (Table 1). Of the investigated aldose precursors, **2b** and **2d** reacted fastest with (*R*)-proline and created the highest concentration of free (*S*)-proline, which led to the highest asymmetric induction of ketone **5**. We also performed the premixing of the simplest sugars glyceraldehyde and tetroses **2** with proline under prebiotic conditions, which was followed by removal of the water and α-aminoxylation of **4**. In all cases, a sugar-assisted kinetic resolution of the amino acid catalyst had occurred, and optically active ketone **5** was furnished. To further establish that the sugars **2** were responsible for the in situ kinetic resolution and not just any chiral additive,[17] we investigated the racemic proline-catalyzed α-aminoxylation reaction in the presence of several natural chiral molecules (Table 2).

Table 1. Product-assisted in situ kinetic resolution of racemic proline.



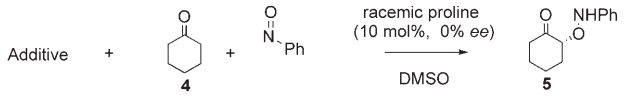
Entry	Sugar	d.r.[a]	*ee* [%][b]	Product	Yield [%][c]	*ee* [%][d]
1	 **2b**	4:1	98	**5**	57	27
2	**2b**	4:1	98	**5**	51[e]	66[e]
3	 **2a**	4:1	99	**5**	26	5
4	 **2c**	4:1	>99	**5**	48	10
5	 **2d**	>19:1	>99	**5**	55	27
6	 *ent*-**2e**	>19:1	>99	**5**	45[f]	−5
7	 *ent*-**2f**	>19:1	>99	**5**	24[f]	−2
8	 **2g**		>98	**5**	47	7

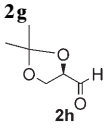
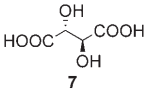
[a] The diastereomeric ratio (d.r.) (*anti*:*syn*) determined by NMR analyses. [b] The *ee* determined by chiral-phase GC analyses. [c] Yield of pure product isolated. [d] The *ee* determined by chiral-phase HPLC analyses. [e] The mixture was premixed for 4 h. [f] The mixture was premixed in water for 15 min.

We found that the enzyme-like kinetic resolution of the amino acid exclusively occurred in the presence of natural C-3 and C-4 sugars or aldose precursor **2**, which can be formed by proline catalysis. None, of the other chiral natural products **7–10** were able to resolve the amino acid catalyst. Hence, a free aldehyde moiety is essential for the kinetic resolution of the amino acid. Moreover, the C-6 sugar glucose **8**, which is preferentially in its pyranose form, was unable to kinetically resolve the amino acid catalyst. This is in accordance with the fact that the tetroses **2f** and **2g** have a faster equilibrium between the furananose form and the open form, which have a free reactive aldehyde moiety, than the pyranose ring of glucose **8**. Next, we performed the experiment with different levels of enantiomeric purity of tetrose **2b** (Table 3).

Notably, even though **2b** with low optical activity was added, the racemic proline catalyzed the formation of optically active ketone **5**. Thus, the optical purity of the tetrose **2** does not have to be high to create an imbalance between

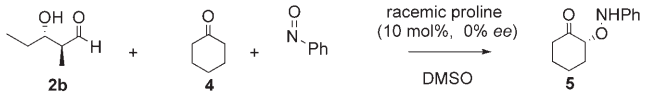
Table 2. Influence of chiral aldose precursors, sugars, amino acids, α-hydroxy acids and nucleotides on the racemic proline catalyzed reaction.



Entry	Additive	d.r.[a]	*ee* [%][b]	Product	Yield [%][c]	*ee* [%][d]
1	**2b**	4:1	98	**5**	51[e]	66
2	*ent*-**2e**	>19:1	>99	**5**	45[f]	−5
3	*ent*-**2f**	>19:1	>99	**5**	24[f]	−2
4	**2g**		>98	**5**	47	7
5	 **2h**		>98	**5**	6	17
6	 **7**		>99	**5**	64	0
7	D-glucose **8**		>99	**5**	47[f]	<1
8	D-glucose **8**		>99	**5**	49[g]	<1
9	(*S*)-alanine **9**		>99	**5**	59	0
10	D-2-deoxy-thymidine **10**		>99	**5**	64	0

[a] The d.r. (*anti*:*syn*) determined by NMR analyses. [b] The *ee* determined by chiral-phase GC analyses. [c] Yield of pure product isolated. [d] The *ee* determined by chiral-phase HPLC analyses. [e] The mixture was premixed for 4 h. [f] The mixture was premixed in water for 15 min. [g] The mixture was premixed in water for 48 h at 120 °C.

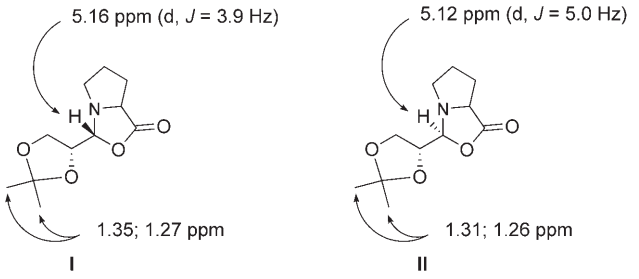
Table 3. Influence of the *ee* of **2b** in the product-assisted in situ kinetic resolution of racemic proline.



Entry	Sugar	d.r.[a]	*ee* [%][b]	Product	Yield [%][c]	*ee* [%][d]
1	**2b**	4:1	98	**5**	57	27
2	**2b**	4:1	86	**5**	55	24
3	**2b**	4:1	70	**5**	41	20
4	**2b**	3:1	48	**5**	67	10
5	**2b**	3:1	15	**5**	72	3.5

[a] The d.r. (*anti*:*syn*) determined by NMR analyses. [b] The *ee* determined by chiral-phase GC analyses. [c] Yield of pure product isolated. [d] The *ee* determined by chiral-phase HPLC analyses.

the two enantiomers of the amino acid. In fact, this small imbalance of enantiomeric excess of the amino acid catalyst is enough to give rise to asymmetric amplification (Figure 1). The kinetic resolution of the amino acids is plausible due to a combination of inhibition and reaction between sugars **2** and the proline catalyst.[18] For example, stirring racemic proline in the presence of glyceraldehyde **2h** or tetrose **2e** for 1 h followed by the α-aminoxylation reaction (vide infra) did not give ketone **5**. ^{1}H NMR analysis of the reaction between glyceraldehyde **2h** and (*S*)-proline in [D_6]DMSO showed that complete conversion to the corresponding oxazolidinone **I** had occurred within this time. The clear shift of the oxazolidinone C-2 ring-proton at $\delta =$ 5.16 ppm (d, $J = 3.9$ Hz) and the higher field shift of the methyl groups of the acetonide at $\delta = 1.35$ and 1,27 ppm, respectively, established the formation of **I**. Notably, performing the same experiment with (*R*)-proline furnished the corresponding diasteromeric oxazolidinone **II** with a clear shift of the C-2 ring-proton at $\delta = 5.12$ ppm (d, $J = 5.0$ Hz) and the higher field shift of the methyl groups of the acetonide at $\delta = 1.31$ and 1.26 ppm, respectively.



We next mixed racemic proline together with aldehyde **2g** and found that the ratio between oxazolidinones **I** and **II** was 1:1.5 (Figure 3). Thus, (*R*)-proline forms the oxazolidinone at a faster rate than (*S*)-proline.

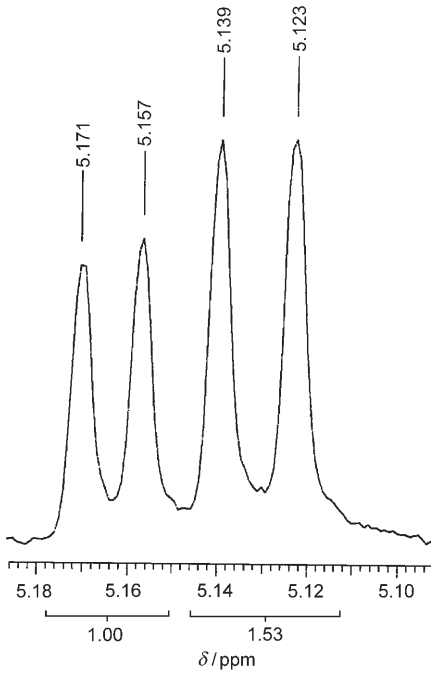


Figure 3. The ^{1}H NMR spectra of the C-2 protons of the oxazolidinones **I** and **II**, respectively, formed by mixing racemic proline with glyceraldehydes **2h** in [D_6]DMSO. The ratio between **I** and **II** is 1:1.5.

Moreover, kinetic experiments revealed that the (*S*)-proline-catalyzed α-aminoxylation reaction in the presence of the (*S*)-proline-derived tetrose **2b** was faster than the corresponding (*R*)-proline-catalyzed reaction (Figure 4). Consequently, optically active ketone (2*R*)-**6** is formed in the racemic proline-catalyzed reaction in Tables 1–3.

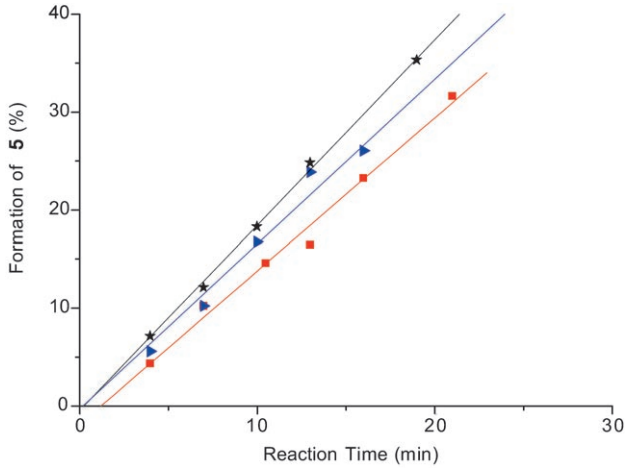


Figure 4. Relationship between the time and the asymmetric formation of **6** for the (*S*)-proline-catalyzed reaction (*, black), (*S*)-proline-catalyzed reaction in the presence of tetrose **2b** (▲, blue) and (*R*)-proline-catalyzed reaction in the presence of tetrose **2b** (■, red).

Conclusion

In summary, we have shown that sugar product **2**-assisted kinetic resolution as well as inhibition of an amino acid catalyst is the origin of the significant amplification of enantiomeric excess in the amino acid catalyzed formation of carbohydrates. The reaction scheme is complementary to the model of autocatalysis and provides a mechanism in which an optically inactive amino acid can mediate the formation of organic molecules with enantiomeric excesses in the presence of a sugar product with low enantiomeric excess. Thus, we have found that the optical enrichment of products derived by amino acid catalysis may be influenced by the action of simple sugars and amino acids. The symbiotic behavior of these additives, in combination with the likely presence of each in the prebiotic milieu, suggests that their cooperative action could have contributed to the early achievement of highly enantioenriched products under prebiotic conditions and may be an explanation for the origin of homochirality where the initial asymmetry may have been set by an amino acid or sugar.

Experimental Section

General: Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), Merck 60 F254 silica gel plates were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (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 by using Merck 60 silica gel (particle size 0.040–0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400 instrument. 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 ($\delta = 0$ ppm) for ^{1}H NMR spectra, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. GC was carried out using a Varian 3800 GC instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda =$ 589 nm, 1 dm cell). Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

(*S*)-Proline-catalyzed asymmetric synthesis of (2*S*, 3*S*)-3-hydroxy-2-methylpentanal (2b): Propionaldehyde (1 mL, 13.7 mmol) was added to a vial containing (*S*)-proline (30 mg, 0.26 mmol) and DMSO (2 mL). The reaction was left to stir at 4 °C for 16 h. The reaction mixture was readily purified by silica-gel chromatography (pentane/EtOAc 3:1) to furnish pure **2b** in 68 % yield with 98 % *ee*. Analytical data of this compound are identical in every aspect to previously reported values.[13d] The *ee* was determined by GC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol according to the method of Yamamoto et al.[19] GC: $T_{det} = 275$ °C, flow = 1.8 mL min^{-1}, $t_i = 100$ °C, hold 35 min, $t_f = 200$ °C rate = 80 °C min^{-1}, hold 10 min, major isomer: $t_r = 35.514$ min, minor isomer $t_r = 35.778$ min. The cross-aldol adducts **2c** and **2d** were synthesized according to MacMillan's[13d] and our[10] procedures by utilizing (*S*)-proline (10 mol %) as the catalyst.

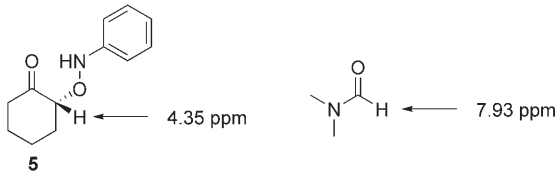
Typical experimental procedure for the proline-catalyzed asymmetric synthesis of (2*S*, 3*S*)-3-hydroxy-2-methylpentanal (2b): Propionaldehyde (1 mL, 13.7 mmol) was added to a vial containing proline (30 mg, 0.26 mmol, the *ee* of the proline was varied according to Figure 1) and DMSO (2 mL). The reaction was left to stir at 4 °C for 16 h. The reaction mixture was readily purified by silica-gel chromatography (pentane/EtOAc 3:1) to furnish pure **2b**. The *ee* was determined as described above.

Typical experimental procedure for the racemic proline-catalyzed synthesis of 5 in the presence of aldose precursors 2: A solution of aldose precursors **2** (1 mmol, with an *ee* according to Tables 1 and 2) or glyceraldehyde **2g** (0.75 mmol) and racemic (*R*),(*S*)-proline (6 mg, 10 mol %) in DMSO (1 mL) was left to stir for 1–2 h. Next, cyclohexanone **4** (1 mmol) was added to the homogeneous reaction mixture followed by slow addition with a syringe pump over 1 h of a solution of nitrosobenzene (54 mg, 0.5 mmol) in DMSO (1 mL). Next the reaction mixture was let to stir for an additional 0.5 h (3 h when tetrose **2a** was used). The reaction was quenched by putting the reaction mixture directly on a silica-gel column (pentane/EtOAc 10:1), which furnished the pure **5** and **2** after chromatography. Analytical data of **5** are identical to previously reported values.[16a,d] The *ee* was determined by chiral-phase HPLC analysis (Diacel Chiralpak AD, *n*-Hex/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): minor isomer: $t_r = 27.208$ min, major isomer: $t_r = 31.791$ min.

Typical experimental procedure for the racemic proline-catalyzed synthesis of 5 in the presence of sugars 2 or glucose: A solution of erythrose, threose **2** (0.25 mmol, with an *ee* according to Table 1 and Table 2), or glucose (2 mmol) and racemic (*R*),(*S*)-proline (6 mg, 10 mol %) in H_2O (1 mL) was left to stir for 15 min. The water was removed under reduced pressure and DMSO was added (1 mL). Next, cyclohexanone **4** (1 mmol) was added to the homogeneous reaction mixture followed by slow addition with syringe pump over 1 h of a solution of nitrosobenzene (54 mg, 0.5 mmol) in DMSO (1 mL). The reaction mixture was then left to stir for an additional 0.5 h (3 h when tetrose **2a** was used). The reaction was quenched by putting the reaction mixture directly on a silica-gel column (pentane/EtOAc 10:1), which furnished pure **5** and **2** after chromatography. Analytical data of **5** are identical to previously reported values.[16a,d] The *ee* was determined by chiral-phase HPLC analysis (Diacel Chiralpak AD, n-Hex/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): minor isomer: $t_r = 27.208$ min, major isomer: $t_r = 31.791$ min.

Typical experimental procedure for the racemic proline-catalyzed synthesis of 5 in the presence of a chiral derivative: A solution of chiral natural product (1 mmol, with an *ee* according to Table 2) and racemic (*R*),(*S*)-proline (6 mg, 10 mol %) in DMSO (1 mL) was left to stir for 1–2 h. Next, cyclohexanone **4** (1 mmol) was added to the homogeneous reaction mixture followed by slow addition with syringe pump over 1 h of a solu-

tion of nitrosobenzene (54 mg, 0.5 mmol) in DMSO (1 mL). The reaction mixture was then left to stir for an additional 0.5 h (3 h when tetrose **2a** was used). The reaction was quenched by putting the reaction mixture directly on a silica-gel column (pentane/EtOAc 10:1), which furnished pure **5** and **2** after chromatography. Analytical data of **5** are identical to previously reported values.[4] The *ee* was determined by chiral-phase HPLC analysis (Diacel Chiralpak AD, n-Hex/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): minor isomer: $t_r = 27.208$ min, major isomer: $t_r = 31.791$ min.



5

Typical experimental procedure for the kinetic study of the (*S*)-proline-catalyzed formation of ketone 5 (Figure 4, *, black): A solution of nitrosobenzene (54 mg, 0.5 mmol) in DMSO (1 mL) was slowly added with syringe pump to a homogeneous mixture containing (*S*)-proline (6 mg, 10 mol %), cyclohexanone (1 mmol), and DMF (0.155 mmol, 12 µl, internal standard) in DMSO (1 mL). Aliquots (25 µL) were taken out from the homogeneous reaction mixture and diluted with $CDCl_3$ and the progress of the reaction was monitored by ^{1}H NMR analyses. The ratio of the area of the quintet at $\delta = 4.35$ ppm corresponding to the C*H*ONHAr proton of **5** and the area of the broad singlet at $\delta = 7.93$ ppm corresponding to a formamide proton of DMF ($A_5/A_{\text{internal standard}}$) was directly correlated to the known calibration curve and gave the product formation as a function of time.

Typical experimental procedure for the kinetic study of the (*S*)-proline- and (*R*)-proline-catalyzed formation of ketone 5 in the presence of tetrose 2b (Figure 4, ▲, blue and ■, red, respectively): A solution of tetrose **2b** (1 mmol, 98 % *ee*) and (*S*)- or (*R*)-proline (6 mg, 10 mol %) in DMSO (1 mL) was left to stir for 1 h. The reaction mixture became homogeneous after it had been stirred for 2 min. Next, cyclohexanone **5** (1 mmol) and DMF (0.155 mmol, 12 µL, internal standard) was added, followed by slow addition with a syringe pump over 1 h of a solution of nitrosobenzene (54 mg, 0.5 mmol) in DMSO (1 mL). Aliquots (25 µL) were taken out from the homogeneous reaction mixture and diluted with $CDCl_3$, and the progress of the reaction was monitored by ^{1}H NMR analyses. The ratio of the area of the quintet at $\delta = 4.35$ ppm corresponding to the C*H*ONHAr proton of **5** and the area of the broad singlet at $\delta = 7.93$ ppm corresponding to formamide proton of DMF ($A_5/A_{\text{internal standard}}$) was directly correlated to the known calibration curve and gave the product formation as a function of time.

Typical experimental procedure for the NMR experiments between glyceraldehyde 2g and proline: A solution of glyceraldehyde **2h** (0.347 mmol, >98 % *ee*) and (*S*)- or (*R*)-proline (0.087 mmol) in DMSO (1 mL) was left to stir for 1 h in [D$_6$]DMSO (1 mL). Next, ^{1}H NMR analysis was performed, which showed that all (*S*)- or (*R*)-proline had reacted with aldehyde **2g** and formed the corresponding oxazolidinones **I** or **II**, respectively.

Typical experimental procedure for the NMR experiments between glyceraldehydes 2g and racemic proline: A solution of glyceraldehyde **2h** (0.043 mmol, >98 % *ee*) and (*S*),(*R*)-proline (0.087 mmol) in DMSO (1 mL) was left to stir for 15 min in [D$_6$]DMSO (1 mL). Next, ^{1}H NMR analysis was performed, which showed that the ratio between the corresponding oxazolidinones **I** and **II** was 1.53.

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