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Amine-Catalyzed Direct Aldol Reactions of Hydroxy- and Dihydroxyacetone: Biomimetic Synthesis of Carbohydrates

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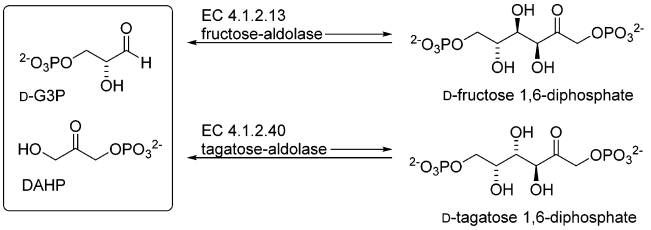
Supporting Information

ABSTRACT: This article presents comprehensive studies on the application of primary, secondary, and tertiary amines as efficient organocatalysts for the de novo synthesis of ketoses and deoxyketoses. Mimicking the actions of aldolase enzymes, the synthesis of selected carbohydrates was accomplished in aqueous media by using proline- and serine-based organocatalysts. The presented methodology also provides direct access to unnatural L-carbohydrates from the (*S*)-glyceraldehyde precursor. Determination of the absolute configuration of all obtained sugars was feasible using a methodology consisting of concerted ECD and VCD spectroscopy.

INTRODUCTION

Dihydroxyacetone (DHA) is one of the most employed donors in nature, playing a key role in many vital biotransformations. In particular, its phosphorylated form is an intermediate in glycolysis and gluconeogenesis. Dihydroxyacetone phosphate (DHAP) participates in an enzyme-catalyzed aldol reactions en route to carbohydrates.[1] For example, fructose 1,6-biphosphate aldolase (FruA) catalyzes in vivo the aldol addition of D-glyceraldehyde 3-phosphate (D-G3P) and dihydroxyacetone phosphate (DHAP) to give D-fructose 1,6-biphosphate (Scheme 1). This aldolase controls stereoselective construction

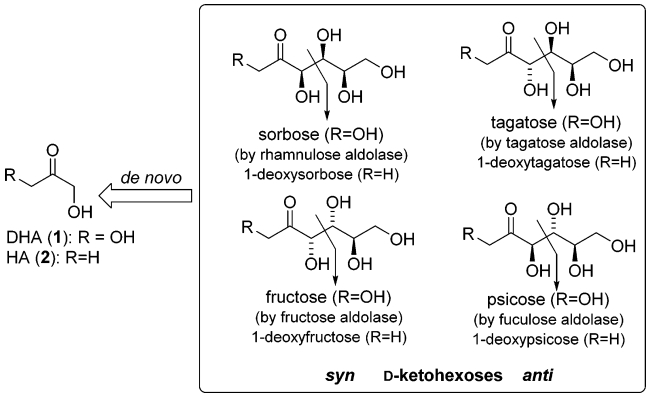
Scheme 1. Biosynthesis of Fructose and Tagatose by DHAP-Dependent Aldolases



of C−C bonds with two *syn*-configured hydroxy-substituted stereogenic centers. In contrast, construction of an *anti*-configured ketohexose (D-tagatose) is controlled in nature by tagatose aldolase (TagA; Scheme 1).

In general, aldolases can catalyze C−C bond formation between dihydroxyacetone phosphate and glyceraldehyde with simultaneous formation of two new stereocenters. As a consequence, four different ketohexose stereoisomers can be obtained in a short and efficient $C_3 + C_3$ strategy (Scheme 2).

Scheme 2. Stereochemical Complementarity of DHAP-Dependent Aldolases



Each aldol reaction generates a single product, whose stereochemistry at C-3 and C-4 is complementary to the others. In addition to one *R*-configured stereogenic center delivered from glyceraldehyde substrate, these reactions create two new stereogenic centers in the form of *syn*- (D-fructose and D-sorbose) or *anti*-ketohexoses (D-psicose and D-tagatose) (Scheme 2; R = OPO_3^{2-}).

Different aldolases catalyzing the formation of each of those stereoisomers are commercially available and may be adopted to the straightforward synthesis of natural carbohydrates and their derivatives.[2] In this manner, synthesis of the remaining diastereoisomeric sorbose and psicose molecules can be

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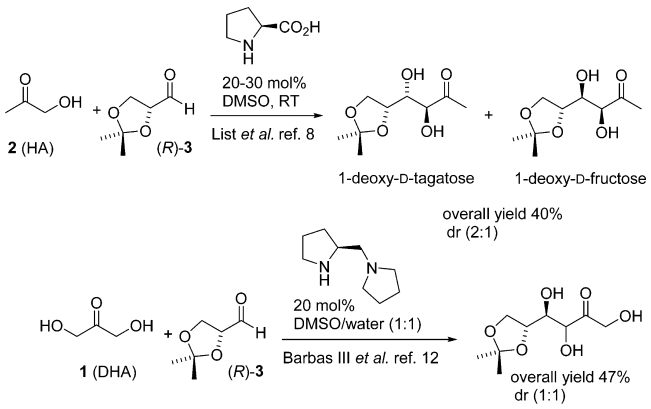
accomplished by using rhamnulose and fuculose aldolases, respectively (Scheme 2). All mentioned enzymes have a broad aldehyde specificity, while the need for the application of dihydroxyacetone phosphate constitutes an important limitation for their synthetic use. Only some aldolase antibodies are capable of using α-hydroxylated ketones such as hydroxyacetone as the donor.[3]

Although chemists developed DHAP-dependent aldolases into important tools for the asymmetric synthesis of carbohydrates, similar straightforward transformations promoted by small organic catalysts have remained elusive. In contrast to the simplicity of the presented attempts, existing methodologies for the synthesis of carbohydrates typically need several synthetic steps and tedious protecting group manipulation.[4] Interestingly, a versatile and simple $C_3 + C_3$ strategy utilizing a DHA donor, although most favored by nature, is still challenging for organic chemists. A promising strategy for the stereoselective application of hydroxy- and dihydroxyacetone is associated with the rapid development of organocatalytic methods.[5] In analogy to enzymes, organocatalysis allows for the direct catalytic aldol reaction of aldehydes and ketones without the use of preformed enolates.[6] This concept also allows the organocatalytic synthesis of some carbohydrates, but the state of the art in this area is not well recognized, especially for unprotected donors.[7]

In 2000 List and Notz described the first enamine-based enantioselective aldol addition of unprotected hydroxyacetone with several enolizable aliphatic aldehydes.[8] The authors demonstrated that protected (*R*)-glyceraldehyde reacted with unprotected hydroxyacetone by an (*S*)-proline-promoted direct aldol reaction. D-Tagatose and D-fructose derivatives were isolated with moderate diastereoselectivities of only 2:1 and poor overall yield (40%; Scheme 3). Although unselective, the synthesis of the *anti*- and *syn*-1-deoxyhexoses provided an indication of the utility of these types of asymmetric aldol reactions as applied to carbohydrate synthesis. According to the broadly accepted explanation, the *Si* face of the hydroxyacetone enamine attacks the *Re* face of the aldehyde to give the *anti* product (1-deoxytagatose). The enamine double bond is presumed to possess a *E* configuration, and the observed *anti* stereoselectivity is consistent with a chairlike transition state.[9] Further, enamine-based organocatalytic *anti*-[10] and *syn*-selective[11] direct aldol reactions of unprotected hydroxyacetone have been demonstrated for aromatic and nonchiral aliphatic aldehydes, whereas the diastereoselective reaction with optically pure glyceraldehyde has remained neglected.

Scheme 3. Amine-Catalyzed Aldol Reactions of Unprotected Hydroxy- and Dihydroxyacetone



In 2002, Barbas et al. reported for the first time an organocatalyzed cross-aldol reaction of unprotected DHA with acetonide of (*R*)-glyceraldehyde. The reaction was promoted by (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine in an aqueous phosphate buffer.[12] The authors observed unselective formation of all four possible stereoisomeric ketohexoses under physiological conditions by enamine catalysis. Further research also clearly demonstrated that unprotected DHA was not a useful substrate for the enamine-based aldol addition (Scheme 3).[13]

In contrast, application of protected DHA molecules has been far more promising in the field of carbohydrate synthesis. The best results in the direct synthesis of ketohexoses was described when (*S*)-proline was used as a catalyst for the reaction of protected DHA derivatives such as 2,2-dimethyl-1,3-dioxan-5-one.[14] Since (*S*)- and (*R*)-proline catalysts provide versatile access to *anti*-1,2-diols,[13−15] they mimic tagatose and fuculose aldolases. The reaction proceeds through an (*E*)-enamine leading to *anti*-configured aldols.

More recently, Luo et al. showed that *anti*-selective reaction of dioxanones with aromatic aldehydes can be promoted by chiral primary amines, thus confirming that the reaction stereoselectivity depends on *E*-configured enamines formed exclusively from cyclic ketones.[16] A parallel concept of application of primary amine based organocatalysts to *syn*-selective aldol reactions of unprotected dihydroxyacetone was presented by Barbas and co-workers.[17] These *syn*-selective reactions of DHA with aromatic aldehydes were carried out in the presence of tryptophan or threonine derivatives in combination with methyltetrazole.

Using the same principles, Barbas and co-workers reported that primary amino acid derivatives could catalyze the *syn*-aldol reaction of protected DHA with optically pure glyceraldehyde. *O*-*tert*-Butyl-D-threonine controlled the aldol reaction of *tert*-butyldimethylsilyl (TBS)-protected dihydroxyacetone with (*R*)-glyceraldehyde to form protected D-fructose with a high diastereoisomeric ratio (98:2).[18] Similarly, an *O*-*tert*-butyl-L-threonine-based amide can act as an efficient catalyst for the reaction of TBS-protected DHA with the acetonide of (*R*)-glyceraldehyde, providing the protected D-sorbose derivative in 86% yield and 3:1 *syn*:*anti* ratio.[19] Applying water-tolerant catalysts mimics L-rhamnulose and D-fructose aldolases, respectively.

Despite the fact that many authors have claimed to solve the problem of the biomimetic reaction of DHA, the presented catalysts were active and selective only for protected donors. Although the stereoselective synthesis of *syn*- and *anti*-aldols from DHA derivatives is well established, asymmetric reaction of unprotected donors needs further effort, especially for the synthesis of sugars. To address this problem and since divergent biomimetic access to all ketohexoses by using enamine organocatalysis and a C_3-dihydroxyacetone-based strategy from unprotected donors are still not possible, we present here our effort toward resolving this fundamental synthetic problem.

This article presents the first straightforward de novo synthesis of all 1-deoxyketohexoses of D and L series from hydroxyacetone and the currently elusive *syn*-selective formation of ketohexoses from unprotected dihydroxyacetone. In addition to their synthetic value, the presented organocatalysts truly mimic aldolase stereoselectivity and mode of action by

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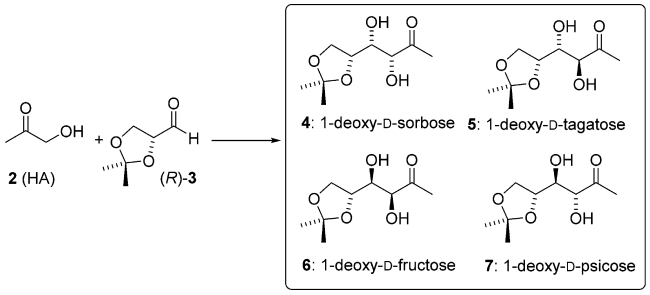
forming enamine intermediates in homogeneous aqueous solvents.

RESULTS AND DISCUSSION

Reaction of Hydroxyacetone (HA) Promoted by Primary and Secondary Amine Based Organocatalysts. The general lack in stereoselective synthesis of carbohydrates from unprotected donors inspired us to carry out comprehensive research in this field. We initially studied the reaction of hydroxyacetone (**2**) and (*R*)-glyceraldehyde acetonide (**3**) as a possible general method for the de novo synthesis of 1-deoxyketohexoses. Unselective asymmetric aldol reactions of these substrates may result in the formation of four differently configured 1-deoxyketohexoses (**4**−**7**; Scheme 4). For stereoselective control of the reaction, enamine should preferentially attack one of the aldehyde carbonyl group sites. Moreover, enamine formation and its reaction with aldehyde should be faster than the possible formation of the product under general base mechanism. To achieve high enantioselectivity of the aldol product, diastereoselective control of the C−C bond formation by chiral aldehyde should also be restrained.

Scheme 4. Four Possible Products of the Reaction of Hydroxyacetone and (*R*)-Glyceraldehyde



Following the results described by List,[8] and to investigate the application of both enantiomeric amino acids in various solvents, we started by re-examination of the (*S*)-proline-controlled aldol reaction. Preferential formation of (*E*)-enamine between hydroxyacetone and the proline molecule should result in selective formation of an *anti*-aldol. Indeed, we confirmed observed the reaction selectivity (Table 1, entry 1). Surprisingly, application of an enantiomeric *R*-configured catalyst resulted in a visible drop in reaction yield, thus confirming the additional influence of substrate stereochemistry and confirming the possible formation of matched/mismatched pairs (Table 1, entry 2).

Next, we turned our attention to the reaction in aqueous solvents, closely related to the biomimetic concept. In fact, synthetically useful direct aldol reactions in aqueous media are rare and are mostly limited to less demanding donors such as cyclohexanone and acetone.[20] In accord with our expectations, the direct aldol reaction of hydroxyacetone in wet DMF was less efficient and unselective in comparison to the reaction in dry solvents (Table 1, entry 5). Proline was an extremely poor catalyst of the reaction, providing unselective formation of the aldols as expected. The addition of water to the mixture completely suppressed stereoselective addition of enamine to aldehyde, probably because of competitive hydrogen bond formation between the carbonyl group of aldehyde and water instead of the catalyst. Interestingly, the reaction promoted by pyrrolidine catalyst resulted in a better yield (Table 1, entry 6).

Table 1. Direct Aldol Reaction of Hydroxyacetone 2 with (*R*)-Glyceraldehyde 3 Promoted by Secondary Amine-Based Catalysts

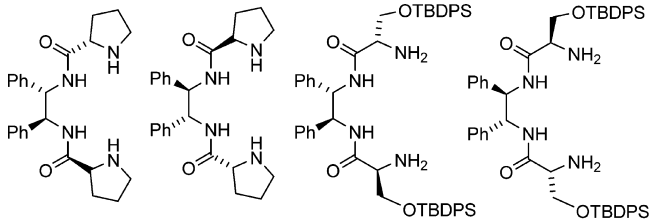
entry	catalyst[a]	solvent	yield (%)[b]	dr (**4**:**6**)[c]
1	(*S*)-proline	DMF	39	2.5:1
2	(*R*)-proline	DMF	trace	
3	(*S*)-proline	DMSO	30	2.5:1
4	(*S*)-proline	THF	45	2:1
5	(*S*)-proline	DMF/H_2O (9/1)	7	1:1
6	pyrrolidine	DMF/H_2O (9/1)	37	1:1
7	(*S*)-proline[d]		50	2:1
8	pyrrolidine[d]		60	1:7
9	(*S*)-serine	THF	8	2:1[e]
10	(*R*)-serine	THF	10	1:2[e]

[a]The reactions were performed with (*R*)-**3** (1 mmol), HA **2** (5 mmol), and catalyst (20 mol %) in the appropriate solvent (2 mL) at room temperature for 24 h. [b]Total yield of both *syn* stereoisomers. [c]Determined by ^{1}H NMR and chiral HPLC analysis. [d]The reactions were performed with neat (*R*)-**3** (4 mmol), HA **2** (2 mmol), and catalyst (20 mol %) at room temperature for 24 h. [e]dr refers to *syn* products (**4**:**6**).

Such better reactivity of pyrrolidine in comparison to that of proline was previously observed in aqueous solvents.[12] Most intriguing, however, was the reaction promoted by pyrrolidine without any solvent (Table 1, entry 8). The reaction afforded the *syn*-diol i.e. 1-deoxy-D-fructose (**6**) with a high level of stereoselectivity (*syn*:*anti* 7:1), clearly suggesting a different reaction mechanism. We assumed that the reaction selectivity resulted from formation of hydroxyacetone enol, which reacts with optically pure glyceraldehyde by the Felkin−Anh model. The proposed reaction mechanism will be presented and discussed below.

Learning from these studies, we attempted to synthesize carbohydrates. On the basis of our earlier success in the development of direct aldol reactions catalyzed by C_2-symmetrical bisamides in water,[21] we decided to apply this methodology to the elusive synthesis of ketohexoses. First, we decided to test previously developed organocatalytic mimics of the aldolases for *anti*- and *syn*-selective aldol reaction of hydroxyacetone with optically pure aldehyde. C_2-Symmetrical bis-prolinamides (**8**, **9**) and lipophilic bis-siloxyserinamides (**10**, **11**) readily available from (*S*,*S*)- and (*R*,*R*)-diphenylethylenediamine and amino acids have been used as enantioselective organocatalysts for the direct aldol reaction of unprotected hydroxyacetone with nonchiral aldehydes. Now, we screened all four catalysts in the aldol reaction of hydroxyacetone with glyceraldehyde acetonide (**3**) (Scheme 5).

Scheme 5. Organocatalysts Used in This Study for Biomimetic Direct Aldol Reaction of Hydroxy- (HA) and Dihydroxyacetone (DHA)



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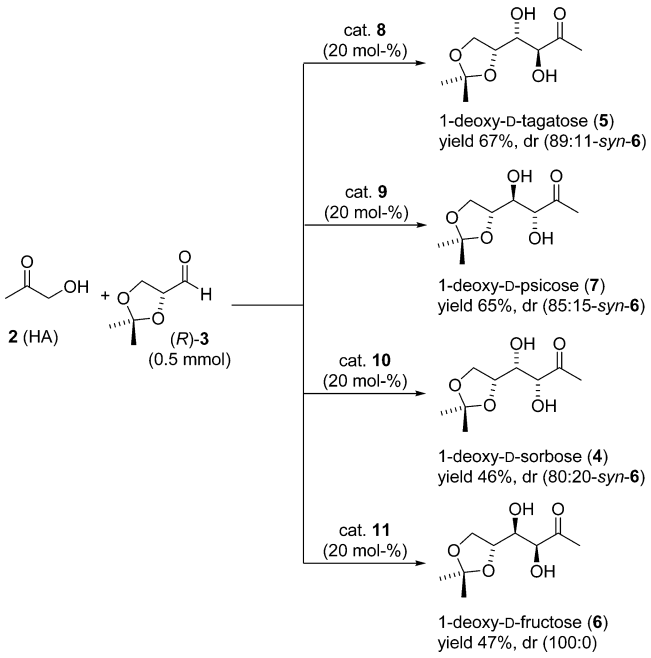
Our original design for organocatalysts involved both their application to the direct aldol reactions in water and the expected reaction selectivity.[22] Thus, we selected proline-based catalysts for the *anti*-aldol reaction on the basis of the presumption that (*E*)-enamine formation controlled by catalysts **8** and **9** will result in the formation of *anti*-aldols. In contrast, the design of organocatalysts **10** and **11** for the *syn*-aldols was based on the intermediacy of a (*Z*)-enamine in the transition state. According to this concept, we studied the direct aldol reaction of hydroxyacetone (**2**) with (*R*)-glyceraldehyde acetonide (**3**) catalyzed by enantiomeric amides containing secondary (**8**, **9**) and primary amine functions (**10**, **11**; Scheme 6).[21] Catalyst design and the unsuccessful application of simple

Scheme 6. Stereoselective Synthesis of 1-Deoxy-D-ketohexoses[a]



[a]Reactions were performed with (*R*)-**3** (0.5 mmol) and catalyst (20 mol %) in a THF/HA/water mixture (1/9/1, 2 mL) at room temperature for 24 h.

amides as well as other derivatives of amino acids have been tested and discussed in our previous works.[21−23] In this paper, we present only the successful application of the most reactive and stereoselective catalysts.

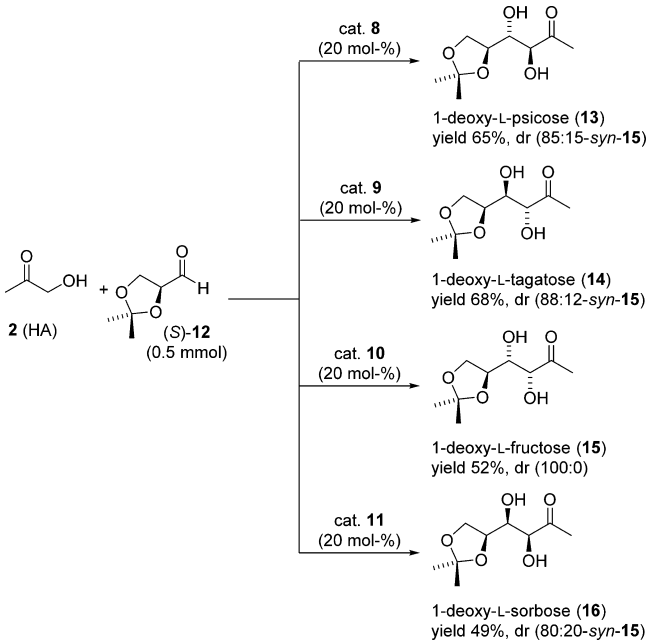
Using optimal conditions elaborated previously for the reaction of nonchiral aldehydes,[21] and performing the reaction at room temperature, we explored the scope of the reaction in the synthesis of deoxyketoses. To our delight, each of the four selected catalysts perfectly controlled the stereoselective formation of the expected sugar with a good yield. The first experiments showed that the reaction controlled by catalyst **8**, composed of (*S*,*S*)-diphenylethylenediamine and L-proline, resulted in a formation of protected 1-deoxy-D-tagtose (**5**) in good yield and 89:11 *anti*-favored dr when 20 mol % of organocatalyst was used (Scheme 6). Interestingly, the enantiomeric proline-based catalyst **9** delivered protected 1-deoxy-D-psicose (**7**) in good yield and high stereoselectivity (85:15; Scheme 6). Thus, according to our expectation (*S*)-proline controls the enantioselective formation of 4*S*-configured 3,4-*anti*-aldol while the enantiomeric (*R*)-proline-based catalyst **9** delivered a 4*R*-configured 3,4-*anti*-aldol. Application of the matched catalyst and aldehyde acceptor was essential for the formation of the expected sugars.

On the basis of the same principles, formation of the 4*S*-configured 3,4-*syn*-aldol was observed for the catalyst **10** composed of L-serine. Catalyst **10** provided 1-deoxy-D-sorbose (**4**) in good chemical yield, maintaining essentially the same diastereoselectivity (80:20) in comparison to proline-based catalysts. Finally, the reaction controlled by catalyst **11** resulted in exclusive formation of 1-deoxy-D-fructose (**6**).

It is important to mention that we have not observed any racemization of optically pure glyceraldehyde or hexoses during the reaction, and high enantiomeric excesses of all products have been confirmed by NMR experiments and chiral HPLC analysis. In fact, enantiomeric excesses of the resulting hexoses simply reflect the ee of the starting material. The presented experiments confirm that the elaborated methodology provides a practical and direct route to deoxyketohexoses by using organocatalysts mimicking all four DHAP-dependent aldolase enzymes (Scheme 2).

Encouraged by these results, we decided to investigate the possible synthesis of L-sugars by using the developed methodology. This would be a valuable achievement in light of the rare and tedious synthesis of this family of compounds.[24] To achieve this goal, the reactions of hydroxyacetone and (*S*)-glyceraldehyde precursor promoted by the same catalysts have been tested (Scheme 7).

Scheme 7. Stereoselective Synthesis of 1-Deoxy-L-ketohexoses[a]



[a]Reactions were performed with (*S*)-**12** (0.5 mmol) and catalyst (20 mol %) in a THF/HA/water mixture (1/9/1, 2 mL) at room temperature for 24 h.

To our delight, the reactions proceeded smoothly and aldol products **13**−**16** were isolated in good yields and high diastereoselectivities. The presented amino acid catalysis provides a new entry to a one-step de novo synthesis of 1-deoxy-L-psicose (65%), 1-deoxy-L-tagatose (68%), 1-deoxy-L-fructose (52%), and 1-deoxy-L-sorbose (49%). The application

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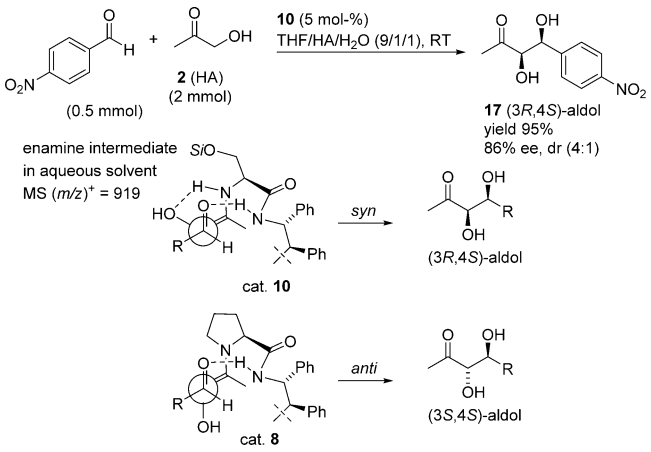
of *S*-configured aldehyde additionally confirmed that catalysts control enantioselective formation of the C-4 stereogenic center with additional control of *syn*- or *anti*-configured aldols (Scheme 7). This observation finally proved that the reaction proceeds via enamine formation which, in turn, may react preferentially with one site of the aldehyde molecule.

The stereochemistry of the presented organocatalytic carbohydrate synthesis is in accordance with previously reported principles for proline- and serine-based aldol reactions.[21] In the cross-aldol reaction, the *Si* face of the (*Z*)-enamine intermediate formed from catalyst **10** and HA approaches the *Re* face of the acceptor aldehyde, furnishing the desired (3*R*,4*S*)-*syn*-aldol adduct, as illustrated in Scheme 8.

Scheme 8. Possible Structures of Transition States Leading to *syn*- and *anti*-Aldols



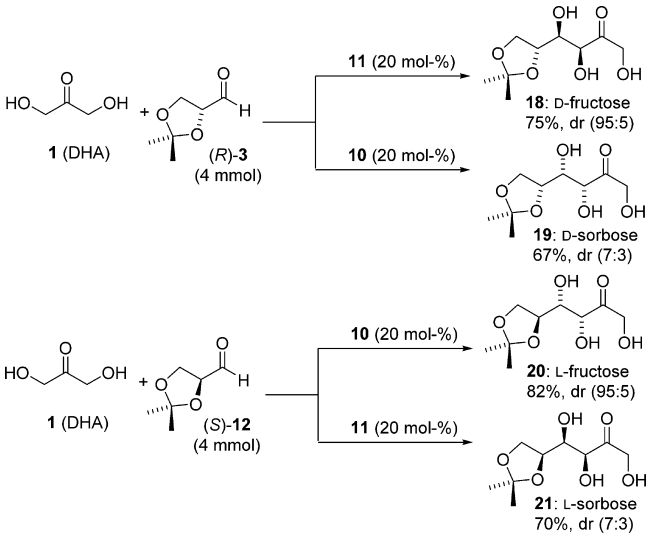
High reaction enantioselectivity observed for the reaction of 4-nitrobenzaldehyde (86% ee) confirmed that asymmetric induction is controlled by the enamine-based organocatalyst **10**.

Formation of an enamine in the reaction mixture was previously confirmed by high-resolution MS spectra: the signal at *m*/*z* 919 matches the expected molecular weight. The isotopic pattern of this signal corresponds with the calculated pattern of the expected enamine structure.[25] Organocatalyst **10** can form hydrogen-bond-stabilized (*Z*)-enamine. In contrast, preferential formation of (*E*)-enamine for the proline-based catalyst **8** resulted in preferential formation of *anti*-aldols (Scheme 8).

Reaction of Dihydroxyacetone (DHA) Promoted by Primary Amine Based Organocatalysts. In contrast to the unexplored field of direct aldol reactions of hydroxyacetone, its DHA variant has been well recognized, although only for protected donors. In particular, the successful development of a diastereo- and enantioselective organocatalytic aldol reaction with 2,2-dimethyl-1,3-dioxan-5-one as a ketone equivalent was shown to be a practical tool for the synthesis of *anti*-configured carbohydrates, mimicking tagatose and fuculose aldolases.[15] Among the screened catalysts, enantiomeric prolines proved to be superior in the construction of various carbohydrate scaffolds. The less studied *syn*-selective direct aldol reaction of silyloxy-protected DHA provided a direct route to aldol products of the type synthesized with the DHAP aldolase enzymes L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate.[18,19]

To determine the scope of the synthesis of ketohexoses from DHA by using the direct $C_3 + C_3$ protocol, we tested the same catalysts containing serine motifs (**10**, **11**; Scheme 5).[23] In our efforts, we focused mostly on the *syn*-selective reaction, as the *anti*-selective variant has been well explored by other authors. Initial tests for proline-based catalysts **8** and **9** also demonstrated their ineffectiveness, especially in terms of stereoselectivity. Having in hand efficient enantiomeric catalysts **10** and **11**, we tested reactions of the enantiomeric glyceraldehyde acetonides (*R*)-**3** and (*S*)-**12**, possibly giving short and elegant entries to D- and L-hexoses, respectively.[23] As indicated in Scheme 9, dihydroxyacetone and glyceraldehyde

Scheme 9. Stereoselective Synthesis of D- and L-Ketohexoses[a]



[a]Reactions were performed with (*R*)-**3** or (*S*)-**12** (1 mmol), DHA (2 mmol of a dimer), and catalyst (20 mol %) in a DMF/water mixture (9/1, 1 mL) at room temperature for 24 h.

were suitable substrates when the reaction was conducted in wet DMF at ambient temperature. Application of dry DMF or an increase in the amount of water in the solvent resulted in a decrease in the reaction yield and stereoselectivity.

In the case of optically pure (*R*)- and (*S*)-aldehydes, application of the appropriate D- or L-serine-based catalyst resulted in a clean and selective formation of the expected aldols as a result of formation of a matched pair. In the case of (*R*)-glyceraldehyde, application of catalyst **11** resulted in the formation of D-fructose in high yield (75%) and dr (95:5). In contrast, catalyst **10** may be used for the stereoselective formation of D-sorbose (**19**) with a good diastereoisomeric ratio (7:3). Interestingly, reactions performed in dry DMF were less efficient and delivered aldols in lower yield (ca. 20%). With (*S*)-glyceraldehyde as the starting material, protected L-fructose **20** was formed by a **10**-promoted reaction with high yield (82%) and high stereoselectivity (95:5), while efficient synthesis of L-sorbose derivative **21** was achieved via a matched chiral pair between catalyst **11** and (*S*)-glyceraldehyde substrate (70%; Scheme 9).

The plausible transition state for the elaborated *syn*-selective aldol reaction of unprotected DHA is based on the assumption that hydroxyacetone enamine attacks aldehyde enantioselectively. This mechanism was additionally confirmed via the enantioselective direct aldol reaction of DHA with 4-nitrobenzaldehyde in aqueous solvent (Scheme 10). An important feature for the *syn*-selective transition state leading to (3*R*,4*S*)-

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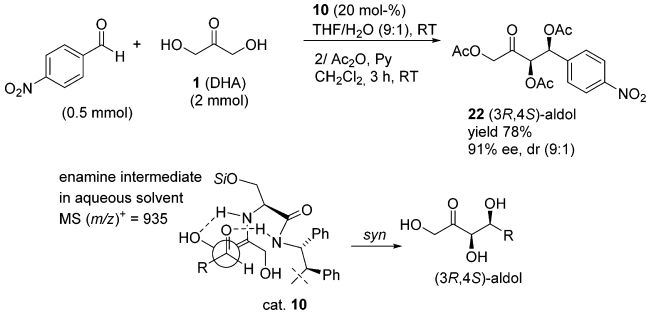
aldol is the hydrogen bond supported (*Z*)-enamine formation presented in Scheme 10.

Scheme 10. Possible Structure of Transition State in *syn*-Selective Aldol Reactions Promoted by Primary Amine Based Catalyst 10



Reaction of Dihydroxyacetone (DHA) Promoted by Tertiary Amines. Previously, we have shown that addition of hydroxy- and dihydroxyacetone to isopropylidene glyceraldehyde may result in controlled formation of aldol adducts by enamine-catalyzed aldol reactions. It was interesting, however, that reaction mixtures were contaminated by the same *syn*-aldol, in all cases. Formation of 1-deoxy-D-fructose (Scheme 6) or D-fructose (Scheme 9) was obviously an alternative reaction pathway leading to the same product, despite the catalyst used. To solve this interesting problem and to determine the reaction mechanism, we investigated the reaction of dihydroxyacetone with (*R*)-glyceraldehyde acetonide (**3**) promoted by various achiral amines (Scheme 11). All performed experiments confirmed the exclusive formation of *syn*-aldols, suggesting one common mechanism for all types of tested amines.

Scheme 11. *syn*-Selective Aldol Reaction of DHA Promoted by Tertiary Amines

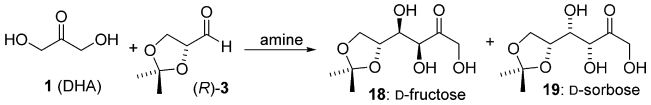


Table 2 shows that reactions promoted by representative examples of tertiary (entries 1−3), secondary (entries 4 and 5), and even primary amines (entry 6) resulted in preferential formation of D-fructose from (*R*)-glyceraldehyde. Similar stereoselectivity favoring formation of natural fructose was observed for reactions carried out in wet DMF (entry 1). Previously, in Table 1 we also showed that application of pyrrolidine instead of proline for the reaction of hydroxyacetone as the neat compounds switched the reaction selectivity to favor the formation of *syn*-aldol (Table 1, entries 7 and 8). This tendency is also visible for dihydroxyacetone donor (Table 2, entry 4).

Formation of *syn*-aldols from hydroxyketones is in full accordance with previously published results; however, it needs additional comment and should be seen as an important competitive reaction en route to enamine-controlled formation of aldols from hydroxyketones. Our predecessors also observed unexpected *syn* selectivity in the reaction of unprotected HA[8] and DHA[12] controlled by proline-based catalysts (Scheme 3). Assuming that amine catalysts can simply act as bases, formation of enol from hydroxyketone may be an important

Table 2. Direct Aldol Reaction of Dihydroxyacetone 1 with (*R*)-Glyceraldehyde 3 Promoted by Tertiary Amines

entry	catalyst[a]	solvent	yield (%)[b]	dr (**18**:**19**)[c]
1	DBU	DMF/H_2O (9/1)	46	80:20
2	DBU	$CHCl_3$	trace	
3	triethylamine	DMF/H_2O (9/1)	30	75:25
4	pyrrolidine	DMF/H_2O (9/1)	26	75:25
5	piperidine	DMF/H_2O (9/1)	16	75:25
6	benzylamine	DMF/H_2O (9/1)	55	85:15
7	quinine	DMF/H_2O (9/1)	trace	
8	quinine	$CHCl_3$	48	80:20
9	quinidine	$CHCl_3$	45	80:20
10	cinchonine	$CHCl_3$	46	75:25
11	cinchonidine	$CHCl_3$	54	75:25

[a]Reactions were performed with (*R*)-**3** (0.5 mmol), DHA **1** (2 mmol as a dimer), and catalyst (20 mol %) in $CHCl_3$ (1 mL) at room temperature for 24 h or in DMF/water (9/1, 1 mL) at room temperature for 72 h. [b]Total yield of *syn* isomers. [c]Determined by ^1H NMR and chiral HPLC analysis.

threat to the stereoselective addition of expected enamine to aldehyde. Thus, formation of protected D-fructose most likely goes through a general base mechanism instead of an enamine-controlled reaction. Especially in the case of (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine used by Barbas, formation of fructose may have resulted from competitive enol formation promoted by secondary−primary amine catalyst (Scheme 3).[12]

However, the use of tertiary amines in the reaction requires clarification. In the mid 20th century, Gutsche and co-workers demonstrated that, in addition to hydroxide ion,[26] tertiary amines are effective catalysts for the unselective addition of glyceraldehyde and dihydroxyacetone.[27] In 2007, Mahrwald showed examples of tertiary amine promoting *syn*-selective aldol reactions.[28] According to the authors, DBU-catalyzed aldol addition of DHA to **3** resulted in unselective formation of *syn*-aldols (fructose and sorbose). In contrast, the reaction promoted by cinchonine resulted in extremely high stereoselectivity of fructose formation. In our hands,[29] the reaction promoted by either DBU (Table 2, entry 1) or *Cinchona* alkaloids (Table 2, entries 7−11) resulted in the formation of fructose and sorbose with the same level of stereoselectivity (ca. 4:1), suggesting the same mechanism for both reactions.

Nevertheless, some level of enantioselectivity provided by *Cinchona* alkaloids may also be considered by using alternative reaction mechanism. Previously, we discovered that unmodified *Cinchona* alkaloids work effectively with hydroxyacetone[30] and aromatic hydroxyketones as highly *syn*-selective aldol catalysts, providing aldols from nonchiral aldehydes with good enantioselectivities up to 60−70%.[31] To investigate possible enantioselective aldol reactions between DHA and nonchiral aldehydes, we used 4-nitrobenzaldehyde as a case study (Scheme 12). Application of 20 mol % of tertiary amines in wet DMF at room temperature resulted in the preferential formation of *syn*-aldol **22** in good yields ranging from 40% for DBU to 61% for cinchonine catalysts. The reaction yield for a more reactive aromatic aldehyde was far better than that for glyceraldehyde (Table 2, entry 7). However, application of cinchonine in aqueous solvent resulted in racemic aldol **22**. Further careful optimization revealed that the reaction promoted by 20 mol % of cinchonine in $CHCl_3$ at room temperature resulted in formation of aldol **22** in good *syn* selectivity (4.4:1) and poor enantioselectivity (28% ee).

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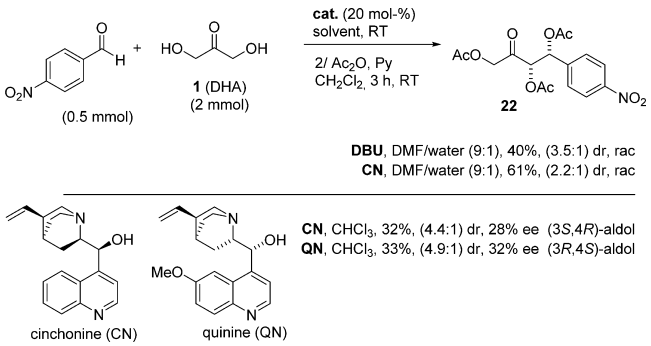
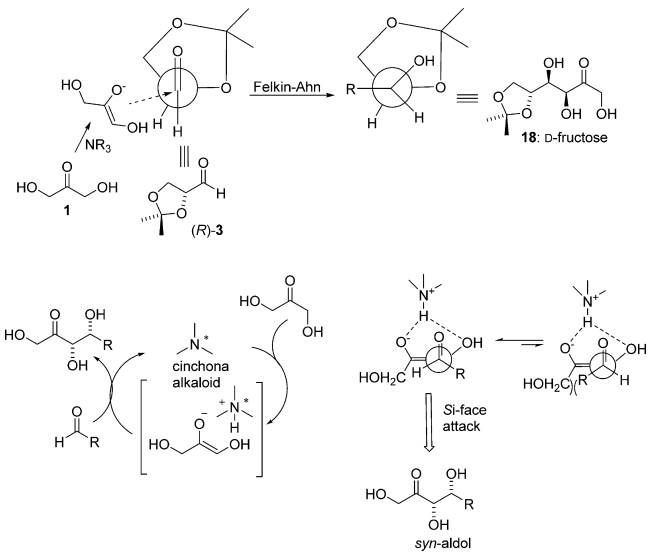
Scheme 12. *syn*-Selective Aldol Reaction of DHA with 4-Nitrobenzaldehyde Promoted by Tertiary Amines



Commenting on the correlation between structure of the catalyst and resulting aldol, we note that application of **CN** and "local pseudoenantiomeric" **QN** delivers the expected enantiomeric aldols (Scheme 12).

Taking into account all observations, we postulate that the reaction promoted by the tested tertiary amines more likely proceeds by enol formation and their subsequent stereoselective addition to optically pure aldehyde. As the Felkin–Anh transition state oxygen at C-2 of aldehyde is electronegative, it will lie perpendicular to the carbonyl group in the most reactive conformer (Scheme 13). This reaction delivers D-fructose as a result of the least hindered direction of attack of enolate on (*R*)-**3**. This explanation supports the common formation of fructose by a general base mechanism.

Scheme 13. Possible Structures of Transition States in the Reaction Promoted by Tertiary Amines (Top) and Asymmetric Aldol Reaction Promoted by *Cinchona* Alkaloids (Bottom)



While in all cases reaction of a ketone involves initial deprotonation by the amine catalyst, the high *syn* selectivity observed for *Cinchona* alkaloids in aprotic solvents could be explained by (*Z*)-enol formation from the hydroxyketone, which then attacks the *Si* face of the aldehyde. Reaction at the *Re* face of the aldehyde is more difficult due to the steric repulsion between the two larger substituents.[31]

Reactions of primary, secondary, and tertiary amines could be explained in a similar way. The reaction of glyceraldehyde with inorganic bases in aqueous solution to yield fructose and sorbose has been quite well studied,[27] although it cannot be used for the sugar synthesis described above because of at least partial racemization of optically pure glyceraldehyde.

Determination of the Structure of Sugars. Confirmation of the structures of resulting sugars was not trivial and constitutes an additional problem. Among all presented deoxyhexoses only the structures of protected 1-deoxy-D-psicose and 1-deoxy-D-tagatose have been previously described in the literature, but low-resolution NMR (80 MHz) spectra were not useful for unambiguous determination of their complex structures.[32] Determination of the structures of protected fructose also required more attention, especially in light of the difficult distinction of the two diastereoisomeric *syn*-aldols formed in the reaction.[12] Simply, deprotection and cyclization resulted in a complex mixture of anomers existing in both furanose and pyranose forms. To conclude this subject and undoubtedly confirm the absolute configuration of aldols, we decided to use CD techniques, allowing for insight into the structures of unmodified sugars.

To determine the absolute configuration (AC) of aldols (diols) **4**–**7** and **18**–**21** the so-called in situ methodology of electronic circular dichroism spectroscopy (ECD) with dimolybdenum tetraacetate acting as an auxiliary chromophore was used.[33] Recently, this methodology has gained increasingly widespread application in solving stereochemical problems of transparent molecules. This can be evidenced by its escalated use for three-dimensional structure determinations of 1,2-diols.[34] Certainly, the evidenced escalation of the in situ method is due to its simplicity, consisting of nothing less than mixing a chiral ligand with an achiral auxiliary chromophore and recording the spectra. The exchange of ligand(s) results in transferring the chirality of the ligand to the chiral complex, which is formed in solution. Application of the in situ method involves linking a positive/negative sign of the Cotton effects (CEs) occurring in the 300–400 nm spectral range in the spectra of resultant complexes with the positive/negative O–C–C–O torsion angle of the diol unit. This relationship, called the helicity rule, allows assignment of the AC of *vic*-diols with confidence through this rule.[33,35]

In the current case, however, the in situ methodology had to be modified due to carbonyl bands strongly overlapping with the bands of resultant Mo_2-complexes at around 300 nm. A workaround of the issue was carried out by subtracting from the complex spectrum of free ligand recorded under the same measurement conditions. The ECD data for diols **4**–**7** and **18**–**21** resulting after such treatment are collected in Table 3.

On the basis of the positive signs of CEs at ∼320 and ∼380 nm the 3*R*,4*R* AC was assigned to diols **4**, **19**, and **20**. Again in accordance with the helicity rule and the negative signs of CEs in the same spectral region, 3*S*,4*S* AC was assigned to diols **6**, **18**, and **21**. Sets of ECD spectra for all diols are presented in the Supporting Information.

A relatively more complex situation is observed for *erythro* diols **5** and **7**. In that case, there are two possible conformations of the diol unit after ligation to the Mo_2-core. This is because, in contrast to the *threo* diols, in *erythro* 1,2-diols two O–C–C–R groups cannot adopt an antiperiplanar conformation simultaneously. This leads to two possible arrangements of the diol unit characterized by opposite signs of decisive CEs for the same absolute configuration as shown in Figure 1B.

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Table 3. Difference ECD Data for the in Situ Formed Mo_2-Complexes of *vic*-Diols 4−7 and 18−21[a]

	ECD $\Delta\varepsilon$ (λ_{max})						
compd	band I	band II	band III	band IV	band V	A	B
4	+0.08 (280.0)	+0.96 (312.5)	−0.05 (353.5)	+0.22 (395.5)	−	+	+
5	+0.26 (276.0)	+[c]	−0.38 (344.5)	+0.19 (428.5)	−0.07 (542.5)	±	−
6	+1.06 (277.5)	−1.69 (312.0)	+[c]	−0.78 (371.0)	−	−	−
7	−0.08 (274.0)	+0.54 (312.0)	−[b]	+0.14 (378.5)	−0.06 (429.5)	±	+
18	+0.20 (277.5)	−[b]	+0.28 (315.0)	−0.82 (372.5)	+0.31 (459.0)	−	−
19	−0.46 (262.0)	+0.08 (308.0)	−[b]	+0.02 (355.5)	−0.13 (421.5)	+	+
20	−0.22 (277.0)	+[c]	−0.15 (319.0)	+0.63 (373.0)	−0.25 (453.5)	+	+
21	+0.09 (273.0)	−0.13 (307.0)	+0.19 (336.0)	−0.27 (382.0)	+0.13 (462.5)	−	−

[a]Values are given as $\Delta\varepsilon'$ (nm). A is the predicted sign of the O−C−C−O torsion angle, and B is the sign of the O−C−C−O torsion angle from ECD. Since the real complex structure and the concentration of the chiral complex formed in solution are not known, the ECD data are presented as the artificial $\Delta\varepsilon'$ values which are calculated in the usual way as $\Delta\varepsilon' = \Delta A/c \times d$, where c is the molar concentration of the chiral ligand, assuming 100% complexation. [b]Positive minimum. [c]Negative minimum.

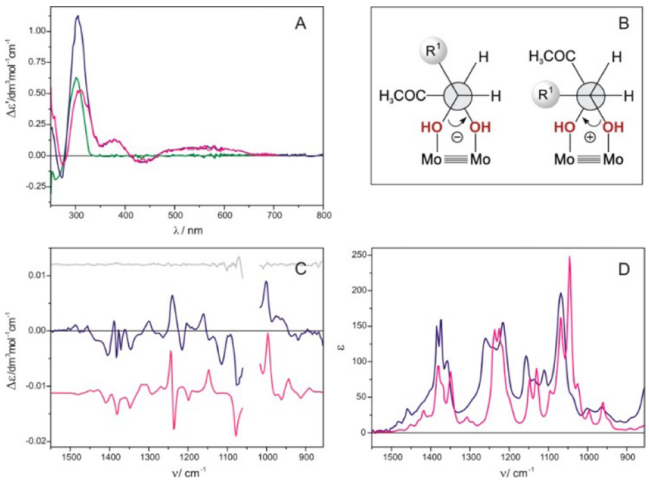

Figure 1. (A) ECD data of diol **7**: navy blue line, chiral Mo_2-complex; green line, free ligand; purple line, difference spectrum (complex spectrum minus free ligand spectrum). (B) Two possible arrangements of the *erythro* 1,2-diol unit in the chiral complex formed after complexation with the Mo_2-dimer; (C) VCD data of diol **7**: navy blue line, experimental spectrum; purple line, population weighted spectrum for 3*R*,4*S*,5*R* isomer; gray line, noise. (D) IR data of diol **7**: navy blue line, experimental spectrum; purple line, population weighted spectrum for 3*R*,4*S*,5*R* isomer.

However, on the basis of the previous statement[36] that flexible *erythro vic*-diols fall also under the helicity rule and follow signs of crucial CEs in the spectra of their Mo_2-complexes, the 3*S*,4*R* and 3*R*,4*S* ACs were assigned to the diols **5** and **7**, respectively.

In an effort to corroborate the conclusions made on the basis of the in situ dimolybdenum method, the vibrational circular dichroism (VCD) spectra were measured. This was particularly important for *erythro* diols, as the calculated Gibbs free energy difference between conformers was relatively small. Thus, ECD spectroscopy alone is not sufficient for a reliable AC determination here and independent confirmation of the results significantly increases the confidence level of the assignment.

The experimental and population weighted IR and VCD spectra for diol **7** are summarized in Figure 1C,D. As one can see, the overall agreement of the predicted and experimental spectra for this diol is excellent, and the confidence level of the 3*R*,4*S* AC assignment is equal to 100% according to the CompareVOA program.[37] The VCD results for the remaining diols collected in the Supporting Information section positively verify the absolute configuration preassignment made by means of the in situ dimolybdenum method. Thus, one can conclude that the assignment of the absolute configuration of diols under study was done in a reliable manner.

CONCLUSION

In summary, we have disclosed a short and elegant de novo synthesis of deoxyketoses and ketoses by amino acid catalyzed bond forming reactions with hydroxyacetone and dihydroxyacetone, respectively. Proline- and serine-based amides proved to be excellent catalysts in term of yield and stereoselectivity in the construction of various carbohydrates in aqueous solvents. The presented enamine-based $C_3 + C_3$ methodology provided direct entry into the synthesis of various D- and L-ketohexoses. Its synthetic potential has been demonstrated in the direct biomimetic synthesis of a series of ketohexoses and deoxyketohexoses.

In this study an (*S*)-proline-based catalyst acts as an organocatalytic mimic of tagatose aldolase, whereas its *R*-configured enantiomer can be regarded as a mimic of fuculose aldolase. Application of enantiomeric serine-based organocatalysts delivered a product with a stereoselectivity similar to that controlled by rhamnulose and fructose aldolases in nature. These enamine-based *syn*- and *anti*-aldol additions represent a very easy and elegant approach to ketohexoses with good yields and high degree of stereoselectivity. On the basis of the elaborated methodology four deoxyketohexoses, D-deoxyfructose, D-deoxysorbose, D-deoxypsicose, and D-deoxytagatose, have been obtained from hydroxyacetone and (*R*)-glyceraldehyde in an asymmetric manner. The same set of catalysts allows for the formation of L-deoxyhexoses from hydroxyacetone and (*S*)-glyceraldehyde.

Furthermore, stereoselective addition of dihydroxyacetone to optically pure glyceraldehyde has been demonstrated to operate under primary, secondary, and tertiary amine control. This reaction cannot be compared with the aldol addition catalyzed by amino acids with regard to the reaction mechanism, although it results in the stereoselective formation of *syn*-configured D-fructose as a result of the Felkin−Anh mechanism. Enantioselective version of the reaction promoted by *Cinchona* alkaloids also seems to be possible, and we believe that the procedure described above will influence the development of asymmetric synthesis and will lead to the discovery of more selective tertiary amine based organocatalysts.

Structures of all ketohexoses have been unambiguously established by using CD spectroscopy. The results of the

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combined in situ method and VCD spectra analysis of all aldols allowed assignment of the three-dimensional molecular structures of all deoxyhexoses and hexoses with great certainty. Thus, the methodology consisting of concerted ECD and VCD spectroscopy to solve structural and stereochemical problems has demonstrated its possibilities and excellent effectiveness in the case of this class of compounds, for the first time.

EXPERIMENTAL SECTION

General Information. All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents used were freshly distilled prior to use. Optical rotations were measured at room temperature with a polarimeter. High-resolution mass spectra were acquired using the electrospray ionization mode with a time-of-flight detector. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer as either a thin film on an NaCl plate (film) or as a KBr pellet (KBr). ^{1}H NMR spectra were recorded on spectrometers operating at 300, 400, 500, and 600 MHz in $CDCl_3$ or acetone-d_6. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double−doublet, m = multiplet, br = broad), coupling constants (in Hz), and assignment. ^{13}C NMR spectra were measured at 75, 100, 125, or 150 MHz with complete proton decoupling. Chemical shifts are reported in ppm from the residual solvent as an internal standard. Reactions were controlled using TLC on silica (alu-plates (0.2 mm)). Plates were visualized with UV light (254 nm) and by treatment with ethanolic *p*-anisaldehyde with sulfuric and glacial acetic acid followed by heating, aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating, or ethanolic ninhydrin solution followed by heating. All organic solutions were dried over anhydrous sodium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240−400 mesh). HPLC analysis were performed on an HPLC system equipped with chiral stationary phase columns and detection at 254 nm.

(*R*)-Glyceraldehyde acetonide ((*R*)-**3**) was prepared from D-mannitol according to the procedure found in the literature.[38] (*S*)-Glyceraldehyde acetonide ((*S*)-**12**) was prepared from L-ascorbic acid according to the procedure found in the literature.[39]

Synthesis and spectroscopic data for organocatalysts **8**−**11** were described previously.[21,23,40]

General Methods for CD Measurement and Calculations. The ECD measurements of in situ formed chiral Mo_2-complexes of diols (1.2−3 mg of ligand, ca. 0.003 M) with stock complex $[Mo_2(O_2CCH_3)_4]$ (2.8−4 mg, ca. 0.002 M) were carried out with DMSO (2.5−5 mL) so that the molar ratio of the stock complex to ligand was about 1:1.5, in general. Measurement parameters: 0.5 nm/min with an integration time of 0.25 s over the range 245−800 nm with 200 nm/min scan speed. For difference spectra the ECD measurements of diols at a concentration of ca. 0.001 M were acquired at room temperature in DMSO (for UV spectroscopy) on a spectropolarimeter and were collected with the same parameters as for chiral complexes. UV−vis spectra were measured in DMSO (for UV spectroscopy). The VCD and IR spectra of compounds **4**−**7** and **18**−**21** were measured with a VCD spectrometer at a resolution of 4 cm^{-1} using CD_3CN. The FT-VCD spectrometer was equipped with dual sources and dual-PEM technology. Solutions (0.25−0.39 M) were measured in a BaF_2 cell with a path length of 102 μm assembled in a rotating holder (14 s/cycle) at room temperature. The ZnSe photoelastic modulator of the instrument was set to 1400 cm^{-1}. To improve the *S*/*N* ratio, the spectra were measured between 6 and 24 h. Baseline correction was achieved by subtracting the spectrum of the reference CD_3CN obtained under the same conditions.

Computational Details. The conformational search was performed with ComputeVOA[41] using the MMF94 force field within 5 kcal/mol energy ranges. Further optimization was carried out at the DFT level using the meta-hybrid B3LYP functional and the aug-cc-pVDZ basis set. The polarizable continuum model (PCM) implemented in Gaussian09[42] was applied for acetonitrile. VCD and IR calculations were carried out at the same level of theory: i.e., B3LYP/aug-cc-pVDZ/PCM(CH_3CN). The final spectrum was obtained by Boltzmann averaging (T = 298 K) according to the population percentages of individual conformers based on the relative Gibbs energies calculated at the same level of theory.

Representative Procedure for Aldol Reaction of Hydroxyacetone (HA; Scheme 6). A solution of freshly distilled glyceraldehyde acetonide **3** (65 mg, 0.5 mmol) in THF/hydroxyacetone/water (1/9/1, 2 mL) and catalyst (20 mol %) was stirred at room temperature for 24 h and then directly purified through flash column chromatography on silica gel (toluene/EtOH, 20/1) to afford the pure aldols.

*5,6-O-Isopropylidene-1-deoxy-D-sorbose (**4**; Scheme 6):* 38 mg (37%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (dd, J = 12.4, 6.2 Hz, 1H), 4.11 (dd, J = 8.5, 6.5 Hz, 2H), 3.95 (d, J = 4.9 Hz, 1H), 3.88 (dd, J = 8.5, 6.2 Hz, 1H), 3.66 (d, J = 3.3 Hz, 1H), 2.54 (d, J = 6.9 Hz, 1H), 2.32 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 207.7, 110.2, 77.9, 77.4, 72.3, 66.2, 26.8, 26.0, 25.4; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0869 ([M + Na]$^+$); IR (neat) 3436, 2987, 2928, 1715, 1372, 1215, 1066, 852 cm^{-1}; $[\alpha]^{22}_D$ = −28.3 (c 0.91, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-L-sorbose (**16**; Scheme 7):* 40 mg (39%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.31 (q, J = 6.2 Hz, 1H), 4.11 (dd, J = 8.5, 6.5 Hz, 2H), 3.95 (td, J = 6.1, 2.2 Hz, 1H), 3.88 (dd, J = 8.5, 6.2 Hz, 1H), 3.67 (d, J = 4.5 Hz, 1H), 2.56 (d, J = 6.4 Hz, 1H), 2.31 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 207.7, 110.2, 77.9, 76.7, 72.3, 66.2, 26.8, 26.0, 25.4; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0881 ([M + Na]$^+$); IR (neat) 3437, 2987, 2930, 1715, 1371, 1215, 1065, 852 cm^{-1}; $[\alpha]^{22}_D$ = +27.1 (c 1.00, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-D-fructose (**6**; Scheme 6):* 48 mg (47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (d, J = 1.5 Hz, 1H), 4.16−4.12 (m, 2H), 4.07 (dd, 1H), 3.90 (dd, J = 11.1, 4.8 Hz, 1H), 3.77 (d, J = 3.5 Hz, 1H), 2.34 (s, 1H), 2.29 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 208.1, 109.6, 76.9, 75.7, 72.5, 66.9, 27.1, 25.2, 25.2; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0876 ([M + Na]$^+$); IR (neat) 3436, 2988, 2934, 1717, 1372, 1216, 1067, 846 cm^{-1}; $[\alpha]^{22}_D$ = +73.4 (c 1.10, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-L-fructose (**15**; Scheme 7):* 53 mg (52%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.41 (s, 1H), 4.18−4.10 (m, 2H), 4.09−4.04 (m, 1H), 3.91 (d, J = 6.4 Hz, 1H), 3.79 (s, 1H), 2.42 (s, 1H), 2.29 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 208.1, 109.6, 76.9, 75.7, 72.5, 66.9, 27.1, 25.3, 25.2; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0888 ([M + Na]$^+$); IR (neat) 3437, 2988, 2931, 1717, 1371, 1216, 1066, 846 cm^{-1}; $[\alpha]^{22}_D$ = −76.3 (c 1.13, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-D-psicose (**7**; Scheme 6):*[32] 56 mg (55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (t, J = 4.4 Hz, 1H), 4.17−4.08 (m, 2H), 4.03 (dd, J = 4.0, 1.4 Hz, 1H), 3.92−3.83 (m, 1H), 3.79 (d, J = 4.4 Hz, 1H), 2.57 (d, J = 7.6 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 207.0, 109.9, 78.6, 74.5, 73.4, 66.8, 26.8, 26.5, 25.1; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0885 ([M + Na]$^+$); IR (neat) 3435, 2985, 2929, 1716, 1377, 1216, 1071, 849 cm^{-1}; $[\alpha]^{22}_D$ = −36.1 (c 1.00, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-L-psicose (**13**; Scheme 7):* 56 mg (55%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.27 (d, J = 4.4 Hz, 1H), 4.13−4.11 (m, 2H), 4.04−4.02 (m, 1H), 3.88 (dd, J = 6.5, 4.7 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 207.0, 109.9, 78.6, 74.5, 73.4, 66.9, 26.7, 26.5, 25.0; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ([M + Na]$^+$), found m/z 227.0871 ([M + Na]$^+$); IR (neat) 3436, 2985, 2932, 1716, 1376, 1216, 1070, 849 cm^{-1}; $[\alpha]^{22}_D$ = +34.0 (c 1.00, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-D-tagatose (**5**; Scheme 6):*[32] 61 mg (60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (td, J = 6.6, 4.3 Hz, 1H), 4.10 (ddd, J = 8.6, 6.5, 2.9 Hz, 2H), 3.89 (dd, J = 8.6, 6.5 Hz, 1H), 3.54 (d, J = 6.3 Hz, 1H), 3.46 (ddd, J = 8.0, 6.6, 4.3 Hz, 1H), 2.75 (d, J = 6.6 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR

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(75 MHz, $CDCl_3$) δ 210.0, 109.6, 77.9, 76.2, 72.5, 66.5, 28.1, 26.5, 25.2; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ($[M + Na]^+$), found m/z 227.0890 ($[M + Na]^+$); IR (neat) 3437, 2987, 2934, 1713, 1372, 1215, 1064, 854 cm^{-1}; $[\alpha]^{22}_D$ = +58.2 (c 1.10, $CHCl_3$).

*5,6-O-Isopropylidene-1-deoxy-L-tagatose (**14**; Scheme 7):* 61 mg (60%); ^1H NMR (600 MHz, $CDCl_3$) δ 4.36 (td, J = 6.6, 4.3 Hz, 1H), 4.10 (dd, J = 8.6, 6.7 Hz, 2H), 3.89 (dd, J = 8.6, 6.5 Hz, 1H), 3.53 (d, J = 5.5 Hz, 1H), 3.48−3.43 (m, 1H), 2.74 (d, J = 6.0 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 210.0, 109.6, 77.9, 76.2, 72.5, 66.5, 28.1, 26.6, 25.2; HRMS (ESI) exact mass calcd for $C_9H_{16}O_5Na$ m/z 227.0895 ($[M + Na]^+$), found m/z 227.0892 ($[M + Na]^+$); IR (neat) 3436, 2987, 2927, 1713, 1373, 1215, 1065, 854 cm^{-1}; $[\alpha]^{22}_D$ = −55.8 (c 0.98, $CHCl_3$).

Representative Procedure for Aldol Reaction of Dihydroxyacetone (DHA; Scheme 9). To a solution of freshly distilled glyceraldehyde acetonide **3** (130 mg, 1 mmol) in DMF/H_2O (9/1, 1 mL) was added 1,3-dihydroxyacetone dimer (360 mg, 2 mmol; 4 mmol as a monomer). After the substrates were dissolved, the organocatalyst (20 mol %) was added to the flask and the reaction mixture was stirred at room temperature and monitored by TLC. After the indicated time, the reaction mixture was poured directly on a silica gel column and the column was eluted with toluene/EtOH (90/10) to yield the desired aldol.

*5,6-O-Isopropylidene-D-fructose (**18**; Scheme 9):*[12] 165 mg (75%); ^1H NMR (400 MHz, acetone-d_6) δ 4.57−4.48 (m, 2H), 4.45 (s, 1H), 4.43−4.35 (m, 1H), 4.17 (ddd, J = 8.3, 6.1, 5.1 Hz, 2H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.96 (dd, J = 8.5, 5.1 Hz, 1H), 3.94−3.83 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 213.1, 109.6, 76.5, 76.0, 73.9, 67.6, 67.5, 27.2, 25.6; HRMS (ESI) exact mass calcd for $C_9H_{16}O_6Na$ m/z 243.0845 ($[M + Na]^+$), found m/z 243.0845 ($[M + Na]^+$); IR (film, CH_2Cl_2) 3392, 2955, 2925, 2854, 1734, 1375 cm^{-1}; $[\alpha]^{22}_D$ = +14.6 (c 0.95, acetone).

*5,6-O-Isopropylidene-L-fructose (**20**; Scheme 9):* 181 mg (82%); ^1H NMR (400 MHz, acetone-d_6) δ 4.56−4.48 (m, 2H), 4.45 (s, 1H), 4.43−4.34 (m, 1H), 4.17 (ddd, J = 8.3, 6.1, 5.1 Hz, 2H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.96 (dd, J = 8.5, 5.1 Hz, 1H), 3.93−3.82 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 213.1, 109.6, 76.5, 76.0, 73.9, 67.6, 67.5, 27.2, 25.6; HRMS (ESI) exact mass calcd for $C_9H_{16}O_6Na$ m/z 243.0845 ($[M + Na]^+$), found m/z 243.0843 ($[M + Na]^+$); IR (film, CH_2Cl_2) 3391, 2986, 2925, 2854, 1727, 1373 cm^{-1}; $[\alpha]^{24}_D$ = −16.0 (c 0.83, acetone).

*5,6-O-Isopropylidene-D-sorbose (**19**; Scheme 9):* 148 mg (67%); ^1H NMR (400 MHz, acetone-d_6) δ 4.56−4.39 (m, 2H), 4.33−4.25 (m, 3H), 4.22−4.17 (m, 1H), 4.04 (dd, J = 8.2, 6.5 Hz, 1H), 3.96−3.91 (m, 1H), 3.85 (dd, J = 8.2, 7.0 Hz, 2H), 1.35 (s, 3H), 1.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 212.2, 109.8, 77.8, 77.3, 73.4, 67.5, 66.4, 26.8, 25.8; HRMS (ESI) exact mass calcd for $C_9H_{16}O_6Na$ m/z 243.0845 ($[M + Na]^+$), found m/z 243.0846 ($[M + Na]^+$); IR (film, CH_2Cl_2) 3390, 2986, 2923, 2852, 1727, 1373 cm^{-1}; $[\alpha]^{22}_D$ = −4.3 (c 0.78, acetone).

*5,6-O-Isopropylidene-L-sorbose (**21**; Scheme 9):* 154 mg (70%); ^1H NMR (400 MHz, acetone-d_6) δ 4.56−4.40 (m, 2H), 4.38−4.25 (m, 3H), 4.23−4.15 (m, 1H), 4.04 (dd, J = 8.2, 6.5 Hz, 1H), 3.98−3.91 (m, 1H), 3.85 (dd, J = 8.2, 7.0 Hz, 2H), 1.35 (s, 3H), 1.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 212.2, 109.8, 77.8, 77.3, 73.5, 67.5, 66.4, 26.8, 25.8; HRMS (ESI) exact mass calcd for $C_9H_{16}O_6Na$ m/z 243.0845 ($[M + Na]^+$), found m/z 243.0842 ($[M + Na]^+$); IR (film, CH_2Cl_2) 3392, 2986, 2925, 2854, 1727, 1373 cm^{-1}; $[\alpha]^{24}_D$ = +4.1 (c 0.80, acetone).

Enantioselective Direct Aldol Reaction of 1,3-Dihydroxyacetone and 4-Nitrobenzaldehyde (Scheme 10). In a vial containing bis(siloxyserinamide) **10** (86 mg, 0.1 mmol) in THF/H_2O (9/1, 1 mL) were placed 4-nitrobenzaldehyde (75 mg, 0.5 mmol) and 1,3-dihydroxyacetone dimer (180 mg, 1 mmol; 2 mmol as a monomer). The reaction mixture was stirred at room temperature and monitored by TLC. The reaction mixture was poured directly on silica gel. The aldol product was purified by flash column chromatography (toluene/EtOH = 90/10) and submitted for acetylation.

Acetylation was achieved by dissolving the aldol product (0.35 mmol) in DCM (2 mL) and pyridine (142 μL, 138 mg, 1.75 mmol). Acetic anhydride (165 μL, 179 mg, 1.75 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM and washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/ethyl acetate, 70/30). The racemate of the aldol product was obtained in the same manner using DMF/H_2O (9/1) as the solvent and DBU as the catalyst.

*(3R,4S)-4-(4-Nitrophenyl)-1,3,4-triacetoxybutan-2-one (**22**):*[17] 93 mg (78%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 6.33 (d, J = 3.4 Hz, 0.89H), 6.20 (d, J = 5.6 Hz, 0.11H), 5.53 (d, J = 3.4 Hz, 0.89H), 5.48 (d, J = 5.6 Hz, 0.11H), 4.98 (d, J = 17.4 Hz, 0.89H), 4.91 (d, J = 17.5 Hz, 0.11H), 4.74 (d, J = 17.5 Hz, 0.11H), 4.67 (d, J = 17.4 Hz, 0.89H), 2.17 (s, 3H), 2.17 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 197.8, 169.9, 169.4, 169.3, 148.2, 142.6, 127.7, 124.0, 77.4, 73.0, 67.0, 20.7, 20.5, 20.4; HRMS (ESI) exact mass calcd for $C_{16}H_{17}NO_9Na$ m/z 390.0801 ($[M + Na]^+$), found m/z 390.0800 ($[M + Na]^+$); IR (film, $CHCl_3$) 1752, 1524, 1374, 1349, 1211 cm^{-1}; HPLC (Chiralpak OD-H, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ 254 nm): t_R = 29.7 min (major *anti* enantiomer), t_R = 35.7 min (minor *anti* enantiomer), t_R = 47.3 min (minor *syn* enantiomer), and t_R = 58.4 min (major *syn* enantiomer).

■ ASSOCIATED CONTENT

Supporting Information

Figures and tables giving an investigation of the absolute configurations (ECD and VCD spectra) and ^1H and ^{13}C NMR spectra of all aldol products **4**−**7**, **13**−**16**, and **18**−**21**, ESI-MS spectra of ketones with catalyst **10**, and Cartesian coordinates of all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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