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Total Syntheses of Carbohydrates: Organocatalyzed Aldol Additions of Dihydroxyacetone

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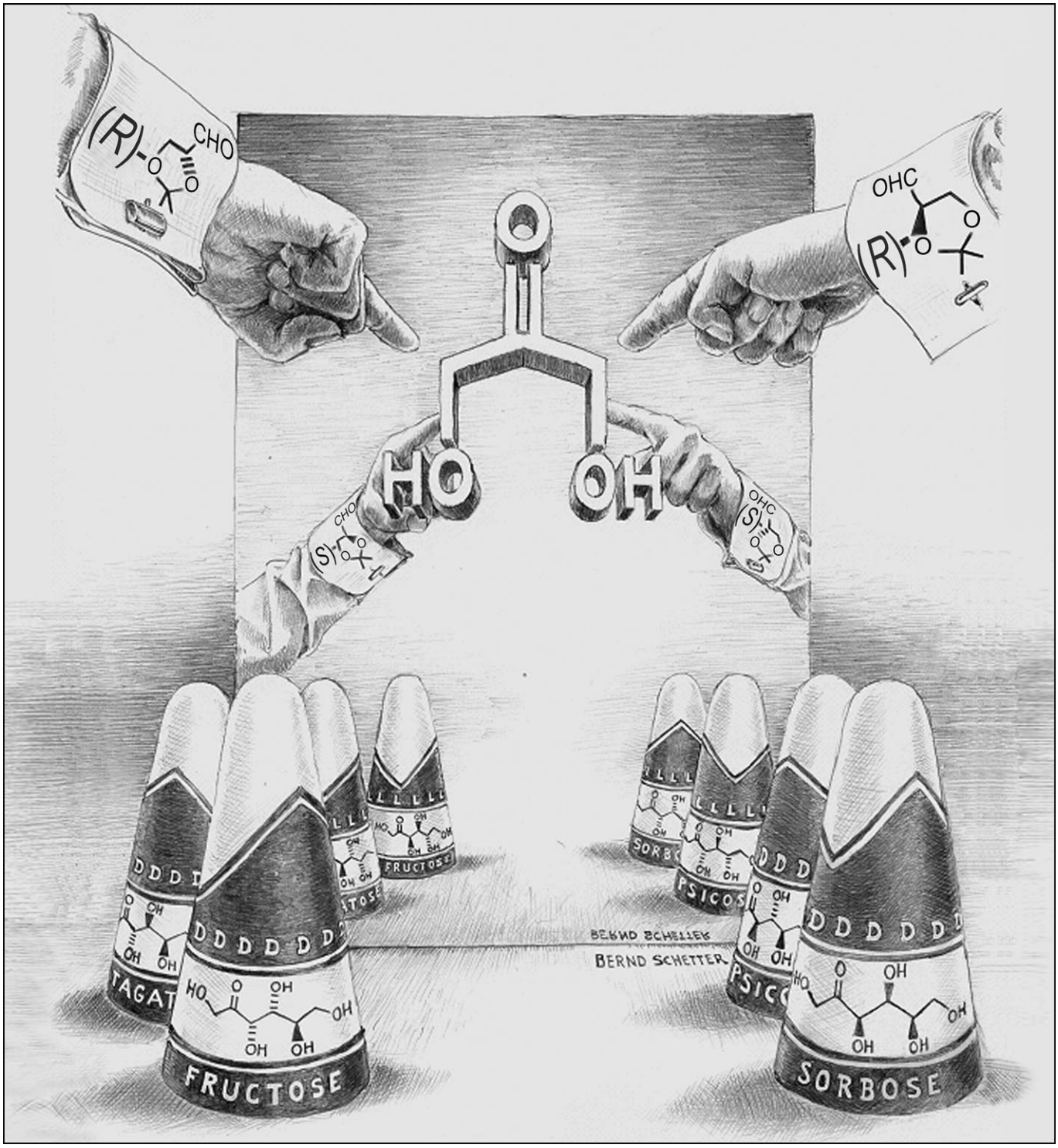

Abstract: The selective total synthesis of carbohydrates with defined configuration has been of great interest for a long time. This field has been the domain of enzymatic methods so far. But now the recent development of several organocatalyzed aldol methodologies has made a selective synthetic approach to configuratively defined carbohydrates possible. This development and different strategies will be discussed in this concept article.

Keywords: aldol reaction · aldolase · base catalysis · carbohydrates · organocatalysis

Introduction

Dihydroxyacetone (DHA) plays a key role in nature, amongst others in the anabolism of carbohydrates. The construction of the four differently configured ketohexoses by aldol additions of DHA can be realized by a set of four dihydroxyacetone phosphate dependent aldolases. The application of tagatose and fuculose aldolase in aldol additions of DHA phosphate with glyceraldehyde gives access to *anti*-configured carbohydrates. In this way psicose and tagatose can be obtained. The *syn*-configured ketohexoses sorbose and fructose are accessible by the deployment of rhamnulose and fructose aldolase in these reactions (see Frontispiece). Thus, by employing one of these four aldolases a selective and asymmetric access is given to one of the four enantiomers of the 1,2-diol junction that connect DHA with an aldehyde. The ease and the efficiency with which nature handles this extremely high stereodifferentiation during a C–C bond formation process has inspired chemists as well as biochemists for a long time. In the beginning of this development of the defined installing of configuration was the field of enzymatic methods. Very early reports described aldol additions of DHA with glyceraldehydes catalyzed by muscle extracts derived aldolases.[1]

The tremendous work and results obtained in this field of stereoselective enzymatic aldol additions are well documented in many comprehensive reviews.[2] This article reflects the current situation of constructing defined carbohydrates by means of organocatalyzed aldol additions. An early chemical approach to all eight L-aldohexoses by asymmetric epoxidation of allylic alcohols is found in the reference [3]. Later on more and more chemical methods were deployed for this stereoselective aldol addition. This development was strongly linked to the beginning deployment of selective methods of aldol additions. A very early example was published by Mukaiyama and co-workers. The authors used dibenzylated DHA in a tin(II) triflate-mediated *anti*-selective aldol addition.[4] Kim and Hong demonstrated the different stereochemical outcome in aldol additions depending on different protection groups of DHA with aldehydes. Stereoselectivities were obtained in lithium enolate aldol additions only when cyclic acetal derivates of DHA were used (Table 1).[5]

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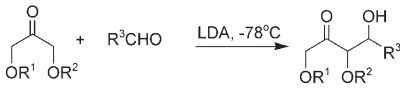
Table 1. Aldol reactions with lithium enolates of protected dihydroxyacetone.



Entry	R^1	R^2	R^3	*syn*/*anti*[a]	Yield [%][b]
1	Bn	Bn	Et	58:42	80
2	Bn	Bn	$BnOCH_2$	58:42	82
3	-$C(CH_2)_5$-		Et	0:100	73
4	-$C(CH_2)_5$-		$BnOCH_2$	0:100	80

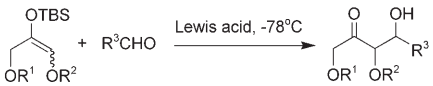
[a] Determined by HPLC using chiral OD column. [b] Isolated yield.

Moreover, the same authors investigated stereochemical Mukaiyama reactions of protected DHA. A change from *anti*- to *syn*-diastereoselectivity was observed when going from cyclohexylidene derivatives to benzyl-protected DHA using $TiCl_4$ in these transformations (compare entries 1 and 7 and 4 and 10 of Table 2).

Even enantioselective aldol additions of lithium enolates of cyclic acetals of DHA were described in a series of papers by Majewski and co-workers.[6] During these transformations the authors used chiral lithium amides for the preparation of enolates of DHA.

Later on Marco and co-workers reported aldol additions of boron enolates of acyclic protected derivatives of DHA.

Table 2. Mukaiyama aldol reactions with enol silyl ethers of dihydroxyacetone.



Entry	R^1	R^2	R^3	Lewis acid	*syn*/*anti*[a]	Yield [%][b]
1	Bn	Bn	Et	$TiCl_4$	95:5	85
2	Bn	Bn	Et	$SnCl_4$	84:16	83
3	Bn	Bn	Et	$BF_3{\cdot}Et_2O$	50:50	73
4	Bn	Bn	$BnOCH_2$	$TiCl_4$	>99.5:0.5	90
5	Bn	Bn	$BnOCH_2$	$SnCl_4$	62:38	82
6	Bn	Bn	$BnOCH_2$	$BF_3{\cdot}Et_2O$	60:40	82
7	-$C(CH_2)_5$-		Et	$TiCl_4$	0:100	73
8	-$C(CH_2)_5$-		Et	$SnCl_4$	0:100	70
9	-$C(CH_2)_5$-		Et	$BF_3{\cdot}Et_2O$	0:100	71
10	-$C(CH_2)_5$-		$BnOCH_2$	$TiCl_4$	0:100	82
11	-$C(CH_2)_5$-		$BnOCH_2$	$SnCl_4$	0:100	72
12	-$C(CH_2)_5$-		$BnOCH_2$	$BF_3{\cdot}Et_2O$	0:100	78

[a] Determined by HPLC using a chiral OD column. [b] Yield of isolated product.

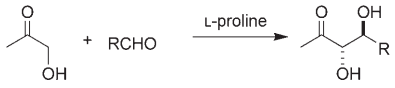
The authors also observed a strong influence of the protecting groups of DHA on the stereoselectivity of the processes.[7] When bulky silyloxy groups were employed only *syn*-configured aldol adducts were detected. Applications of boron-enolates of cyclic acetal-protected DHA in aldol additions were described by Majewski and Nowak. Aldol additions with glyceraldehyde derivatives yielded protected ketohexoses in a diastereomeric ratio of about 8:2.[6e] Application of this boron enolate methodology was reported in the total synthesis of zaragozic acid.[8]

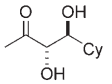
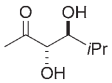
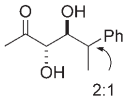
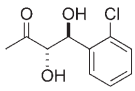
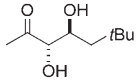
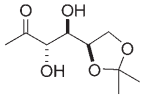
Enders and co-workers intensively studied the application of the SAMP- and RAMP-hydrazone methodology in aldol additions of suitable protected DHA derivatives.[9] In the total synthesis of (+)-(*S*)-gingerol they demonstrated the utility of this access to chiral aldol adducts.[10] Several other aldol additions of unprotected DHA with formaldehyde mediated by $Ca(OH)_2$ or NaOH in aqueous media were also reported, but the aldol adducts were obtained without any selectivities.[11] In a series of papers Morgenlie reported the base-catalyzed aldol addition of glycolaldehyde to unprotected DHA. In these investigations the author used strongly basic anion-exchange resins.[12] For direct titanium-catalyzed aldol additions of enolizable aldehydes to hydroxyacetone see also reference [13].

At that time several important reports of organocatalytic executions of aldol additions were published. This development arose from the question what were the real active species of aldolases and how small an aldolase-like organic catalyst could be doing the same job as the whole enzyme. In 2000 List and Notz described the first proline-catalyzed enantioselective aldol addition of unprotected hydroxyacetone with several enolizable aliphatic aldehydes.[14] High regioselectivities (>20:1) and extremely high enantioselectivities (>100:1) were detected. The diastereoselectivities observed depended on the aldehydes used in these reactions. Even protected glyceraldehyde was reacted with hydroxyacetone. Only moderate 1,2-asymmetric induction was observed during this transformation. Fructose and tagatose derivatives were isolated with moderate diastereoselectivities of only (2:1) (entry 6, Table 3).

This publication was the go-ahead of the lasting development of the so called organocatalysis.[15] For amine-catalyzed aldol additions as a part

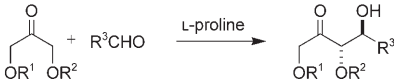
Table 3. Proline-catalyzed aldol additions of hydroxyacetone.

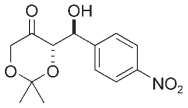
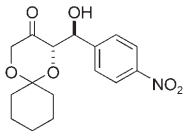
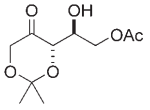
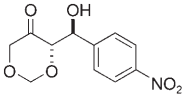
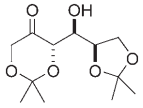


Entry	Product	Yield [%]	*anti*/*syn*[a]	*ee* [%][b]
1		60	>20:1	>99
2		62	>20:1	>99
3		51[c]	>20:1[d]	>95[d]
4		95	1.5:1[e]	67
5		38	1.7:1	>97
6		40	2:1	>97[f]

[a] The *syn*/*anti* ratio was determined by weighing the separated compounds and/or ^{1}H NMR-spectroscopy, respectively. [b] Determined by chiral-phase HPLC analysis. [c] Combined yields of separated diastereomers. [d] Identical *ee* and dr values for both 1,2-*anti* configured diastereomers. [e] Diasteromers could not be separated. [f] From optical rotation.

Table 4. Proline-catalyzed aldol additions with protected dihydroxyacetone.



Entry	R^1	R^2	R^3	Product	Yield [%][a]	*anti*/*syn*[b]	*ee* [%][c]
1	H	H	*p*-NO_2-C_6H_4	–	–	–	–
2	Bn	Bn	*p*-NO_2-C_6H_4	–	–	–	–
3	TIPS	TIPS	*p*-NO_2-C_6H_4	–	–	–	–
4	H	TMS	*p*-NO_2-C_6H_4	–	–	–	–
5	H	Bn	*p*-NO_2-C_6H	–	–	–	–
6	-$C(CH_3)_2$-		*p*-NO_2-C_6H_4		90	6:1	96
7	-$C(C_5H_{10})$-		*p*-NO_2-C_6H_4		62	5:1	67
8	-$C(CH_3)_2$-		CH_2OAc		60	>15:1	98
9	-CH_2-		*p*-NO_2-C_6H_4		91	15:1	94
10	-$C(CH_3)_2$-		glyceraldehyde		40	n.d.	n.d.

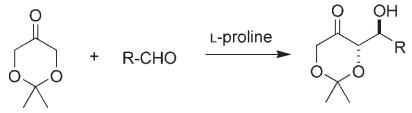
[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR and HPLC analysis. [c] Determined by chiral-phase HPLC analysis.

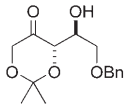
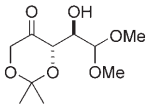
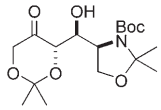
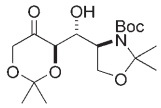
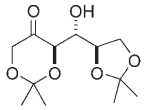
of organocatalysis see reference [16]. Short time later Barbas and co-workers reported for the first time an organocatalyzed aldol addition of unprotected DHA with acetonide protected glyceraldehyde. The reaction was catalyzed by chiral diamines derived from proline in an aqueous phosphate buffer.[17] No 1,2-asymmetric induction was observed. Protected D-fructose (one of four sugars formed in this reaction) was obtained under this reaction conditions. Recently, several groups reported organocatalyzed aldol additions of aldehydes to hydroxyacetone[18] or derivatives of dihydroxyacetone.[19] The main results of this tremendous work in the DHA series are summarized in Table 4.[19h]

The results of Table 4 clearly demonstrate that unprotected DHA is not a useful substrate for the proline-catalyzed aldol addition. Moreover, several other protecting groups are also unsuitable for this transformation. Concerning the diastereoselectivity, mainly *anti*-configured up to non-selective aldol adducts were obtained.

Table 5 summarizes further investigations reported by Enders and co-workers. These results were obtained in aldol additions with protected derivatives of glyceraldehyde as well as Garner aldehyde.[19a] When used with α-chiral aldehydes in the presence of optional use of D- or L-proline a matched-/mismatched situation becomes apparent (compare entries 3 with 4 of Table 5 and entry 5 in Table 5 with entry 10 in Table 4).

Table 5. Proline-catalyzed aldol additions of cyclic derivatives of dihydroxyacetone.

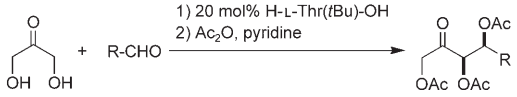


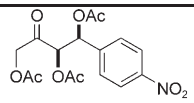
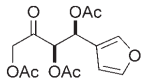
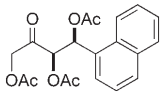
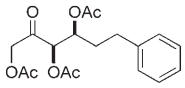
Entry	Product	Yield [%][a]	*anti*/*syn*[b]	*ee* [c]
1		40	>98:2	97
2		69	94:6	93
3		80	>98:2	≥96
4		31	>98:2	≥96[d]
5		76	>98:2	≥98[d]

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR. [c] Determined by chiral-phase HPLC analysis or based on the *ee* value of the corresponding aldehyde. [d] D-Proline was used as catalyst.

Later on, Barbas and co-workers described a second type of organocatalyzed aldol addition of aldehydes to unprotected DHA. These reactions were carried out in the presence of tryptophan or threonine derivatives in combination with methyltetrazole. By this protocol the aldol adducts of aromatic aldehydes were isolated with a high degree of *syn*-diastereoselectivity as well as enantioselectivity (Table 6).[20]

Table 6. Threonine-catalyzed aldol additions of unprotected dihydroxyacetone.



Entry	Product	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][b] (*syn*/*anti*)
1		76	15:1	92:20
2		72	7:1	92:62
3		65	12:1	97:n.d.
4		21	5:1	99:28

[a] Isolated yield after column chromatography. [b] Determined by chiral-phase HPLC analysis. DHA is commercially available as a dimer.

Also very recently, Barbas and co-workers demonstrated the utility of threonine and tryptophan derivatives in asymmetric organocatalyzed aldol additions with protected DHA.[21] Under these conditions the authors were able to isolate aldol adducts of TBS-protected DHA and protected glycolaldehyde with high degrees of enantioselectivity and with good *syn*-diastereoselectivity (entry 4 in Table 7).

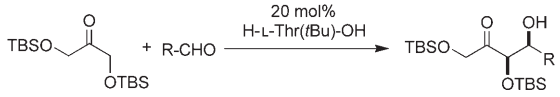
But all these transformations were discussed by the enamine mechanism of Class 1 aldolases of secondary amines (Scheme 1). For transition states explaining the *anti*-configuration by application of proline as well as the *syn*-configuration in the threonine series see Figure 1.[22]

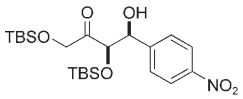
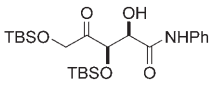
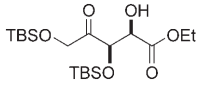
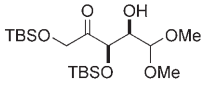
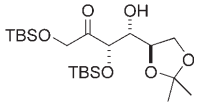
Discussion

As one part of our program to develop catalytic and stereoselective aldol processes we were able to demonstrate the utility of $LiClO_4$ in aldol transformations. We observed aldol additions as well as condensation processes in the presence of catalytic amounts of tertiary amines.[23,24] Several useful, stereoselective aldol processes were developed. Low amounts of tertiary amines were necessary for this transformations (Scheme 2).

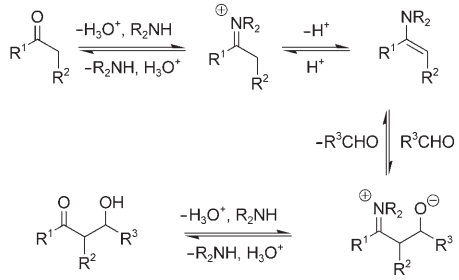
However, we were unable to react oxygen-containing ene components with aldehydes under the described reaction conditions. After optimization of these findings the follow-

Table 7. Threonine-catalyzed aldol additions of protected dihydroxyacetone.



Entry	Product	Yield [%][a]	*syn*/*anti*[b]	*ee* [%] (*syn*)[c]
1		85	5:1	93
2		29	1.2:1	24
3		36	1:1	26
4		71	5:1	97
5		68	>98:2	98[d]

[a] Isolated yield after of both diastereomers. [b] Determined by ^{1}H NMR. [c] Determined by chiral-phase HPLC analysis. [d] H-D-Thr-(*t*Bu)-OH was used as catalyst.



Scheme 1. Proposed secondary amine-catalyzed reaction mechanism of aldol additions.

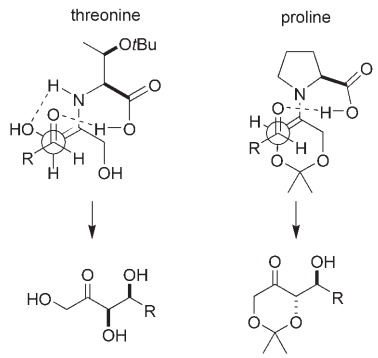
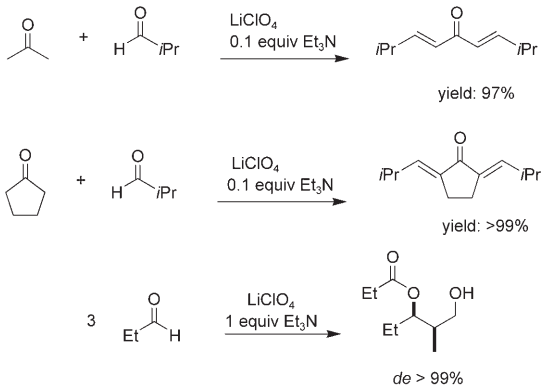


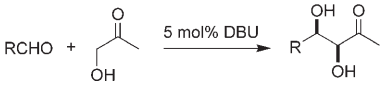
Figure 1. Proposed transitions states of proline- and threonine-catalyzed aldol additions.

ing general method was elaborated. α-Hydroxylated ketones react with aldehydes in the presence of tertiary amines without any additives.[25] The expected aldol adducts were isolated with a high degree of *syn*-diastereoselectivity. The choice of tertiary amine is crucial and depends on the substrates used. Best results so far in the hydroxyacetone series were obtained by the application of 5 mol% of DBU. Moreover, an extremely high regioselectivity was observed. The C–C bond formation process took place only at the oxygen-containing α-side of hydroxyketone (Table 8).[26]



Scheme 2. Base-catalyzed aldol processes in the presence of $LiClO_4$.

Table 8. Base-catalyzed aldol additions to hydroxyacetone.

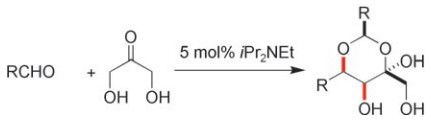


Entry	R	Yield [%][a]	*syn*/*anti*[b]
1	*i*Pr	83	91:9
2	$Ph(CH_2)_2$	87	77:23
3	Cy	92	90:10
4	Ph	89	68:32

[a] Isolated yield. [b] Determined by ^{1}H NMR.

In the dihydroxyacetone series Hünig base was the tertiary amine of choice. The *syn*-diastereoselectivity was extremely high—no *anti*-configured aldol products could be obtained (Table 9). When used with hydroxyacetone the corresponding 1,2-ketodiols were isolated, whereas in the DHA series the corresponding hemiketals of the aldol adducts were obtained.

Table 9. Base-catalyzed aldol additions to unprotected dihydroxyacetone.

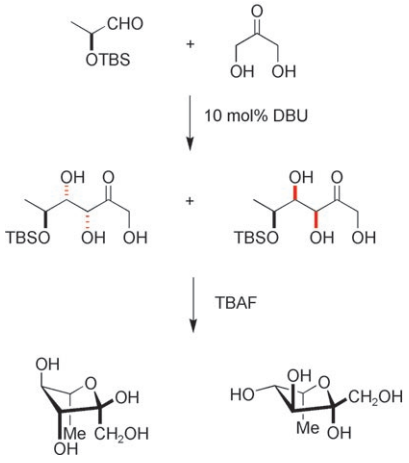


Entry	R	Yield [%][a]	*syn*/*anti*[b]
1	*i*Pr	92	>20:1
2	$Ph(CH_2)_2$	68	>20:1
3	Cy	94	>20:1
4	Ph[c]	46	>20:1

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] By the application of Ph-CHO the unprotected aldol adduct was obtained. No hemiketal could be detected. DHA is commercially available as a dimer.

Also, these results were successfully transferred to aldol additions of optically active lactaldehyde and isopropylidene-protected glyceraldehyde.

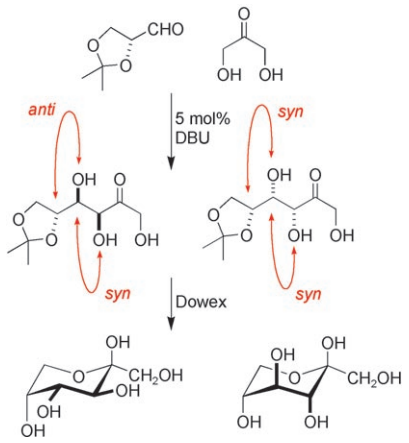
An unselective reaction was observed when we employed DBU. A diastereomeric mixture of 1:1 of the corresponding rhamnolufuranose and desoxy-sorbose was detected (Scheme 3). No 1,2-asymmetric induction of the protected lactaldehyde was observed. The extremely high *syn*-diastereoselectivity during the C–C-bond formation discussed above was observed again.



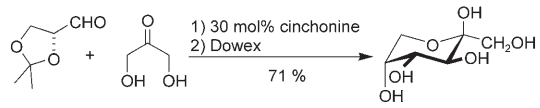
Scheme 3. Aldol additions of protected lactaldehyde to unprotected dihydroxyacetone.

The same results were also observed when protected D-glyceraldehyde was applied in this reaction. In the presence of 5 mol% of DBU fructose and sorbose were identified in a 1:1 mixture (Scheme 4). Similar ratios were obtained when we used other tertiary amines. Using cinchonine as the tertiary amine we observed extremely high diastereoselectivities. Under these conditions we were able to detect the exclusive formation of fructose (Scheme 5).

Based on these results the following actual situation in the de novo synthesis of carbohydrates is as follows. The

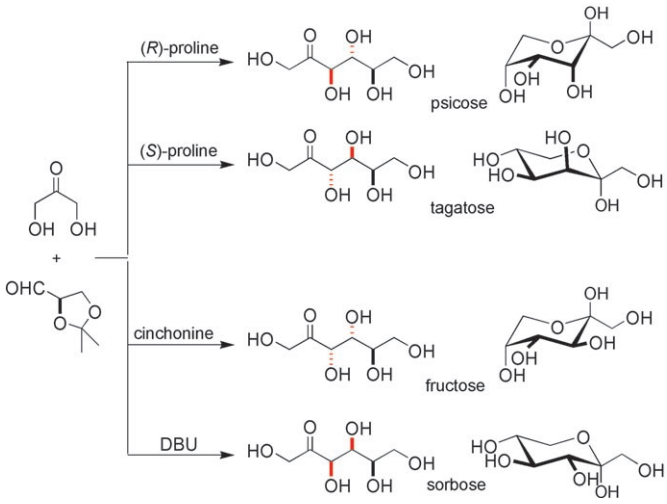


Scheme 4. Aldol additions of protected D-glyceraldehyde to unprotected dihydroxyacetone.



Scheme 5. Total synthesis of fructose.

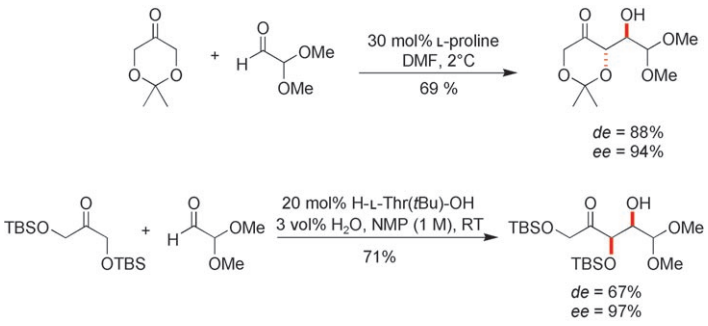
synthetic approach to the four ketohexoses appears to be solved by the methods described above. As discussed there exist several different possibilities to synthesize psicose, tagatose, fructose and sorbose. This can be easily accomplished by the $C_3 + C_3$ strategy for the de novo carbohydrate synthesis.[19a] With the help of D-glyceraldehyde and protected derivatives of DHA an approach to psicose and tagatose via proline-catalyzed aldol additions is given. This is due to the *anti*-preference of proline-catalyzed aldol additions (Figure 1). On the other hand fructose and sorbose are accessible—with the required *syn*-configuration—by the tertiary amine catalyzed aldol addition of DHA and glyceraldehyde (Scheme 6).



Scheme 6. De novo Synthesis of ketohexoses.

The $C_3 + C_2$ strategy promises a synthetic access to pentoses. Very recently Enders and Grondal described the usefulness of this concept.[19e,1,27] By reacting protected DHA as the C_3 unit with dimethoxyacetaldehyde in the presence of substoichiometric amounts of proline protected precursors of ribose and lyxose were isolated with high degrees of enantioselectivity. Again the aldol adducts were obtained with a high degree of *anti*-diastereoselectivity under these reaction conditions. An access to *syn*-configured aldol adduct of protected DHA with protected glycolaldehyde were reported very recently by Barbas and co-workers.[21] In these aldol transformations the authors used derivatives of threonine in substoichiometric amounts and isolated xylose-precursor (Scheme 7).

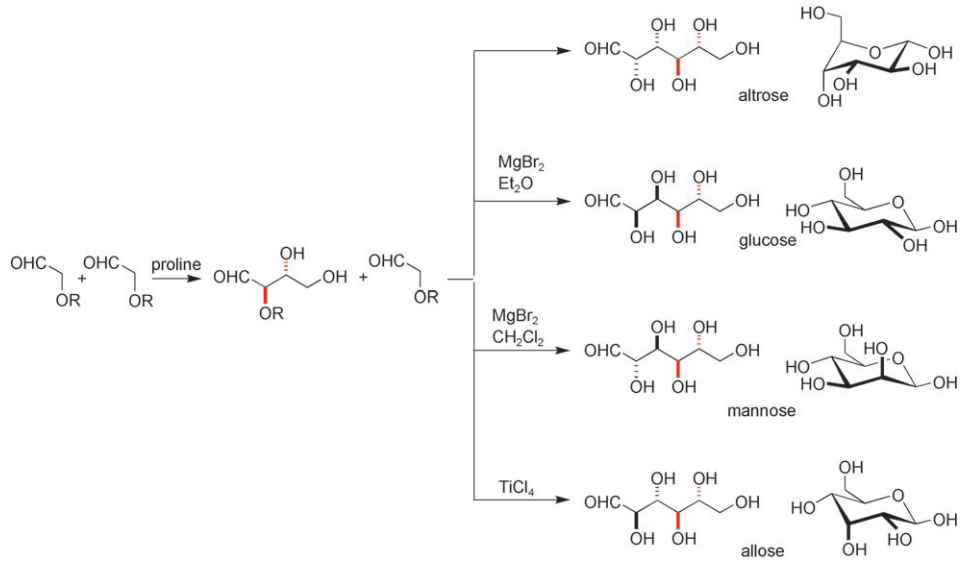
Via the $C_2 + C_2 + C_2$ strategy an synthetic access to aldohexoses is given. A necessary prerequisite for a successful



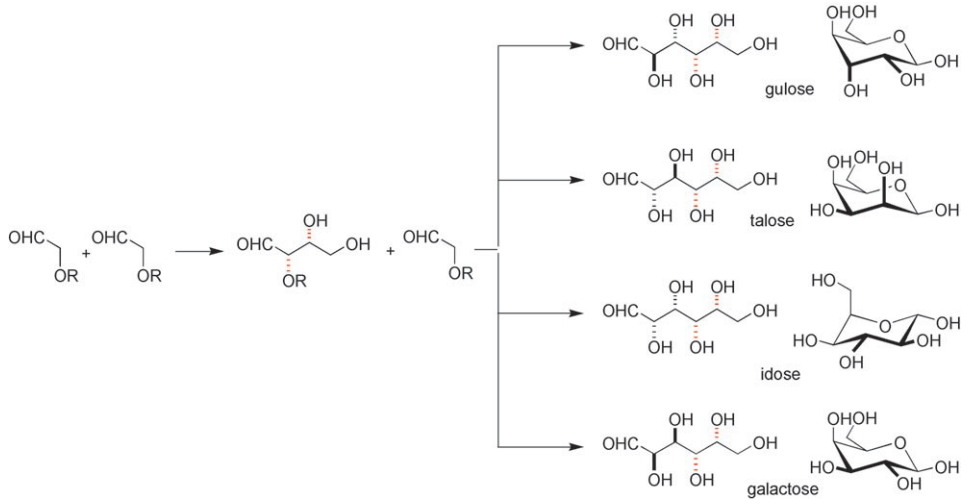
Scheme 7. $C_3 + C_2$ approach to pentoses.

execution of this strategy is the defined and stereoselective connection of three protected glycolaldehydes. This concept was realized very recently by MacMillan and co-workers.[28] The authors elaborated an organocatalyzed aldol addition/Mukaiyama aldol addition reaction sequence to reach this goal. By a proline-catalyzed aldol addition of O-protected glycol aldehydes the *anti*-configured aldol adducts (chiral C_4 unit) were isolated with a high degree of enantioselectivity. Depending on conditions of the following stereocontrolled Mukaiyama-reaction the protected glucose, mannose or allose derivatives were isolated with a high degree of stereoselectivity. (Scheme 8). For a nonselective zinc-proline catalyzed access to all eight aldohexoses using the $C_2 + C_2 + C_2$ strategy see also reference 29.

The white area in the map of synthesis of aldohexoses represents the missing selective access to *syn*-configured C_4 units. The new developed *syn*-selective methodologies described herein could provide a solution to this problem. An access to the remaining *syn*-configured aldohexoses—gulose, talose, idose and galactose—might be possible by the iterative use of protected glycolaldehydes (C_2 unit) in these new described *syn*-selective aldol methodologies (Scheme 9).



Scheme 8. Total synthesis of *anti*-configured aldohexoses.



Scheme 9. Total synthesis of *syn*-configured aldohexoses.

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