Asymmetric Catalysis

DOI: 10.1002/ange.200701269

Mimicking Fructose and Rhamnulose Aldolases: Organocatalytic *syn*-Aldol Reactions with Unprotected Dihydroxyacetone**

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Carbohydrates play diverse and essential roles in biology, medicine, and industry.[1] As a result of their wide range of uses, carbohydrates and carbohydrate-like molecules that contain arrays of defined stereocenters substituted with hydroxy groups have garnered significant attention from the synthetic community.[2] One might argue that the challenge of synthesizing defined arrays of stereocenters substituted with hydroxy groups in an efficient diastereo- and enantiocontrolled fashion has been best met when chemists have harnessed nature's aldolase enzymes.[3] Our own studies aimed at the creation of man-made aldolase enzymes, aldolase antibodies, led us to discover the potential of amino acids as aldolase enzyme mimics.[4] This approach has since provided organocatalytic syntheses of carbohydrates through aldol reactions catalyzed by proline and related amines.[5,6] Arguably, the $C_3 + C_n$ strategy[7] is most favored by nature for the synthesis of carbohydrates, and is facilitated by the dihydroxyacetone phosphate family of aldolases.[3] This family of four aldolases has been developed into unrivaled synthetic tools that provide efficient access to carbohydrates through the installation of 1,2-diol units in any of the four possible diastereomeric configurations (Figure 1).[3]

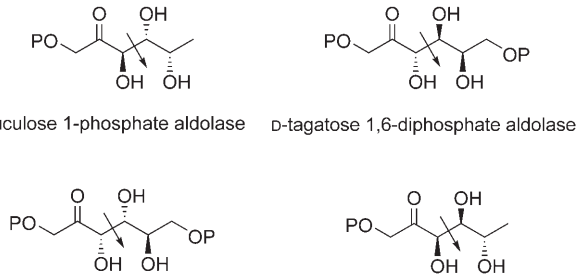

Figure 1. Substrates of the four dihydroxyacetone phosphate aldolases. Arrows indicate the bond that is formed or broken by the action of the aldolase enzyme. $P = PO_3^{2-}$.

Recently, our research group[6d,f] and the research group of Enders[6c,e,g–k] have developed efficient organocatalytic carbohydrate syntheses that emulate these particular aldolases and the $C_3 + C_n$ strategy. These studies have largely used 2,2-dimethyl-1,3-dioxan-5-one as a C_3 donor in aldol reactions catalyzed by proline or (*S*)-2-pyrrolidine tetrazole. Since these catalysts provide access to *anti* 1,2-diols, they mimic D-tagatose 1,6-diphosphate and L-fuculose 1-phosphate aldolases. Access to *syn* 1,2-diols by using organocatalysis and a C_3 dihydroxyacetone-based strategy has not been possible. Recently, we reported the first *syn*-selective organocatalytic aldol reactions that use unmodified α-hydroxyketones as donors to install a *syn* 1,2-diol functionality in the products.[8] Herein we disclose a significant elaboration of our strategy with the first successful diastereo- and enantioselective organocatalytic aldol reactions of unprotected dihydroxyacetone; these reactions functionally mimic those catalyzed by the L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate aldolases.

Based on our earlier success in the development of *syn*-aldol reactions catalyzed by amino acids that contained primary amines,[8a] we initially screened five readily available catalysts (Figure 2) in the aldol reaction of dihydroxyacetone

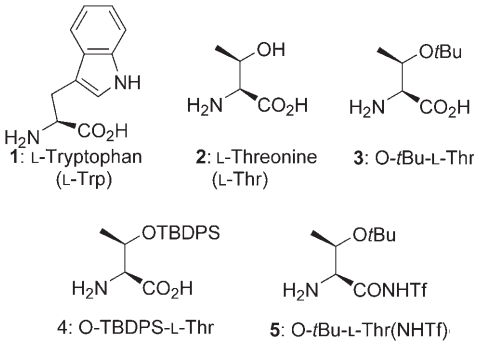

Figure 2. Structures of catalysts studied. TBDPS = *tert*-butyldiphenylsilyl, Tf = trifluoromethanesulfonyl.

with 4-nitrobenzaldehyde using *N*-methylpyrrolidone (NMP) with added water as the solvent. To facilitate determination of the stereoselectivities of these reactions, the triol product was peracetylated and analyzed by HPLC on a chiral stationary phase. All the catalysts preferentially provided the desired *syn*-aldol product (Table 1); however, considerations of stereoselectivity, reaction time, and catalyst availability led us to focus our optimization studies on the commercially available O-*t*Bu-L-Thr (**3**; Table 1, entry 3). It should be noted that earlier studies of reactions that involved unprotected

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[**] This study was supported in part by The Skaggs Institute for Chemical Biology.

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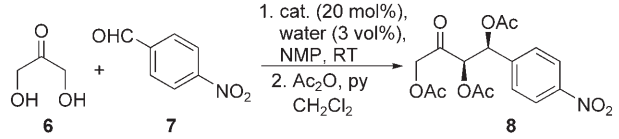
Table 1: Catalyst screening.[a]



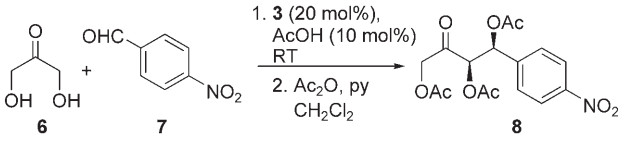
6 7 8

Entry	Cat.	*t* [days]	d.r.[b] (*syn*/*anti*)	*ee* [%][b] (*syn*/*anti*)
1	**1**	5	1.5:1	12/24
2	**2**	5	3:1	78/34
3	**3**	0.8	9:1	88/30
4	**4**	3	16:1	88/78
5	**5**	1	3:1	86/50

[a] See the Supporting Information for details. Added 3 vol% of water with respect to NMP. py = pyridine. [b] Determined by HPLC on a chiral stationary phase.

dihydroxyacetone-based aldols and secondary amine or primary amine catalysis failed to control the diastereoselectivity of this reaction.[9] In an effort to improve reaction rates and stereoselectivities, we evaluated different solvents and additives. Initially, we performed a solvent screen using O-*t*Bu-L-Thr (**3**) with acetic acid as a fixed additive at 10 mol% (Table 2). A slight enhancement was observed in reactivity

Table 2: Effect of solvents on the aldol reaction catalyzed by O-*t*Bu-L-Thr (**3**).[a]



6 7 8

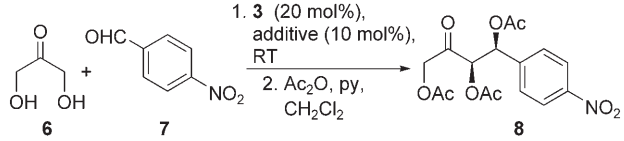
Entry	Solvent[b]	*t* [h]	d.r.[c] (*syn*/*anti*)	*ee* [%][c] (*syn*/*anti*)
1	NMP	16	6:1	92/49
2	DMF	22	8:1	94/18
3	DMSO	170	8:1	80/20
4	*i*PrOH	22	4:1	66/68
5	CH_3CN	165	4:1	90/62
6	EtOAc	170	6:1	94/28

[a] See the Supporting Information for reaction conditions. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide. [b] Reaction in methanol, trifluoroethanol, or dichloromethane was sluggish, and only a trace of product was found after 8 days of reaction. [c] Determined by HPLC on a chiral stationary phase.

and enantioselectivity with NMP as the solvent and acetic acid as the additive when compared to water. A variety of polar aprotic solvents were tolerated (Table 2). Optimal results were obtained by using NMP/acetic acid or DMF/acetic acid conditions (Table 2, entries 1 and 2). Reaction optimization then focused on the acid additive component by using either NMP or DMF as the solvent (Table 3). DMF/5-methyl-1*H*-tetrazole was identified as the optimal solvent/acid additive combination.

By using these optimized reaction conditions, we studied the enantioselective direct organocatalytic *syn*-aldol reaction of unprotected dihydroxyacetone. Reaction of unprotected dihydroxyacetone with a variety of aromatic and aliphatic

Table 3: Additive screening for the aldol reactions catalyzed by **3**.[a]



6 7 8

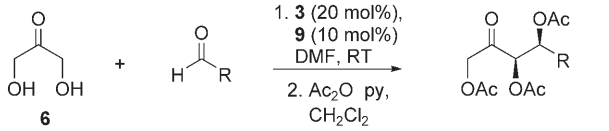
Entry	Additive	Solvent	*t* [h]	d.r.[b] (*syn*/*anti*)	*ee* [%][b] (*syn*/*anti*)
1[c]	AcOH	NMP	20	6:1	87/14
2	TFA	NMP	17	7:1	90/48
3	*p*TSA	NMP	37	9:1	85/56
4	$PhCO_2H$	NMP	30	9:1	85/46
5[c]	$PhCO_2H$	NMP	20	4:1	91/12
6	triazole	NMP	30	6:1	92/56
7[c]	triazole	NMP	20	9:1	90/20
8	triazole	DMF	48	10:1	87/2
9[c]	triazole	DMF	20	4:1	95/22
10[c]	–	NMP	20	9:1	88/30
11[c]	–	DMF	20	4:1	92/46
12[c]	**9**	NMP	20	8:1	94/44
13	**9**	NMP	20	4:1	95/50
14	**9**	DMF	16	15:1	92/20

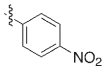
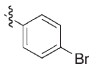
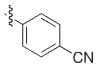
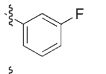
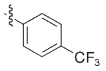
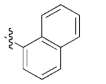
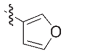
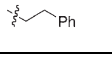
[a] See the Supporting Information for reaction conditions. TFA = trifluoroacetic acid, *p*TSA = *para*-toluenesulfonic acid, triazole = 1*H*-1,2,3-triazole, **9** = 5-methyl-1*H*-tetrazole. [b] Determined by HPLC on a chiral stationary phase. [c] Added 3 vol% of water with respect to NMP or DMF.

acceptor aldehydes provided the desired *syn*-aldol products in moderate to good yield with excellent diastereo- and enantioselectivity (Table 4). Significantly, O-*t*Bu-L-Thr catalysis provided the desired *syn*-aldol products with diastereo- and enantioselectivities (up to 15:1 d.r., *syn* favored, and > 99% *ee*, *syn* product) that typically exceeded those provided using L-proline catalysis.[6c–k] The use of protected dihydroxyacetone donor 2,2-dimethyl-1,3-dioxan-5-one and aromatic acceptor aldehydes in the *anti*-selective aldol reaction also gave excellent diastereo- and enantioselectivities (though mostly less than 6:1 d.r., *anti* favored, and up to 94% *ee*). While most of the yields of the isolated product range from modest to good, further optimization of the methods for product isolation will likely lead to significant improvements in yields given the challenges presented by these free polyol products. We assigned the absolute configuration of products by using imidazole-catalyzed epimerization of the corresponding 2,2-dimethyl-1,3-dioxan-5-one-derived products obtained through L-proline catalysis (see the Supporting Information). The 3*R*, 4*S* absolute configurations of the other products shown in Table 4 were assigned by analogy, and are in accord with our studies involving reactions of monohydroxyketones catalyzed by **3**.[8a]

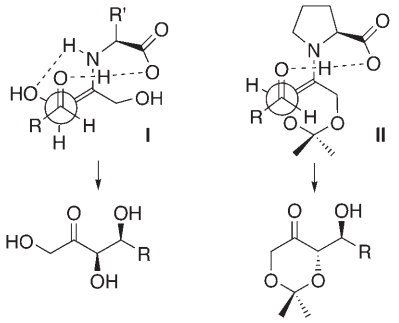
The plausible transition states for the *syn*-selective aldol reaction of unprotected hydroxyacetone **I** catalyzed by **3** is compared with the transition state of the *anti*-selective aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one **II** catalyzed by L-proline in Scheme 1. A key feature of the *syn*-selective transition state **I** is the hydrogen-bond-stabilized *Z* enamine, which is inaccessible for the reaction of the cyclic ketone 2,2-dimethyl-1,3-dioxan-5-one under proline catalysis (transition state **II**).

Table 4: *Syn*-selective dihydroxyacetone aldol reactions catalyzed by **3**.[a]



Entry	R	Prod.	*t* [days]	Yield[b] [%]	d.r.[c] (*syn*/*anti*)	*ee* [%][c] (*syn*/*anti*)
1		**8**	0.7	76	15:1	92/20
2		**10**	2.3 2.3	92 88[d]	15:1 >100:1[e]	98/24 >99[e]
3		**11**	1.9 1.9	82 91[d]	8:1 10:1	96/74 –
4		**12**	2.1	85	11:1	92/54
5		**13**	0.7	62	7:1	92/12
6		**14** **15**[f]	6 2	65 79[g]	12:1 33:1[g]	97[g]
7		**16**	3.5	72	7:1	92/62
8		**17**	3 3	21 28	5:1 9:1	99/28 >99/92[h]

[a] See the Supporting Information for detailed reaction conditions. Typical reaction conditions: a mixture of aldehyde (0.5 mmol), ketone (0.5 mmol as dimer, 1 mmol as monomer), catalyst (20 mol%), and **9** (10 mol%) in DMF (0.5 mL) was stirred at RT. [b] Yield of isolated product after purification by column chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Yield of isolated product when the reaction was performed on 15 mmol scale. [e] After a single recrystallization. [f] Excess aldehyde used. [g] Yield of unacetylated trihydroxyketone **15** after recrystallization; d.r. and *ee* values calculated after acetylation. [h] Added 3 vol% of water instead of **9**.



Scheme 1. Predicted transition states **I** and **II** for the reactions catalyzed by O-*t*Bu-L-Thr and L-proline, respectively.

In summary, we have developed highly enantioselective *syn*-aldol reactions that involve unprotected dihydroxyacetone. The unprotected dihydroxyacetone is a significantly more economical starting material than the protected variants that have been used in proline- and enzyme-catalyzed reactions.[10] The reactions catalyzed by O-*t*Bu-L-Thr and O-*t*Bu-D-Thr are organocatalytic mimics of the reactions catalyzed by L-rhamnulose 1-phosphate aldolase and D-fructose 1,6-diphosphate aldolase, respectively. Thus, the activities of each of nature's four dihyroxyacetone aldolases can now be effectively mimicked using organocatalysis. The data presented here provide further support for our original hypothesis that amino acid catalysis played a key role in prebiotic chemistry by facilitating the asymmetric synthesis of the molecules of life.[6a] Further studies concerned with the expansion of the scope of this chemistry in aldol, Mannich, and Michael-type reactions are currently underway.

Received: March 22, 2007
Published online: June 19, 2007

Keywords: aldehydes · aldol reaction · asymmetric catalysis · enamines · organocatalysis

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[10] The price per gram in US dollars is \$0.39, \$93.00, and \$4320.00 for the 1,3-dihydroxyacetone dimer, 2,2-dimethyl-1,3-dioxan-5-one, and dihydroxyacetone phosphate, respectively.

