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Mimicking Aldolases through Organocatalysis: *syn*-Selective Aldol Reactions with Protected Dihydroxyacetone

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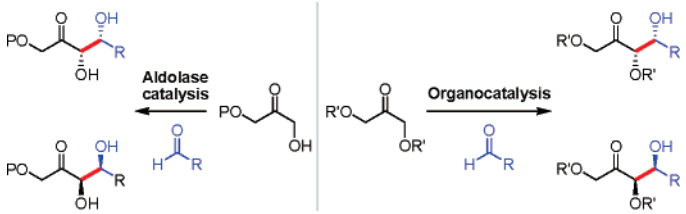
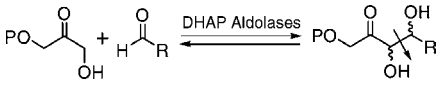
ABSTRACT



A practical organocatalytic strategy designed to mimic the L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate aldolases has been developed and shown to be effective in the preparation of carbohydrates and polyol derivatives. Threonine-based catalysts facilitated the aldol reaction of protected dihydroxyacetone or protected hydroxacetone with a variety of aldehydes to provide *syn*-aldol products with good yields and ee's up to 98%.

Among the many possible aldol reactions that might be used to synthesize carbohydrates and other medicinally significant molecules, aldol reactions that use dihydroxyacetone and its protected variants as donors stand out.[1,2] This is due, in part, to the fact that this strategy was adopted by Nature for the metabolism and catabolism of carbohydrates: aldol reactions that make and break C−C bonds at 1,2-diol junctions that link a dihydroxyacetone unit with an aldehyde (Scheme 1).

Scheme 1. Dihydroxyacetone Phosphate Aldolase Reaction



This chemistry is accomplished by a family of four enzymes that target each of the four junctional 1,2-diol stereoisomers. D-Tagatose-1,6-diphosphate and L-fuculose-1-phosphate aldolase reactions use *anti*-configured 1,2-diols as substrates, whereas the *syn*-configured 1,2-diols are the substrates or products of the L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate aldolases. By exploiting these exquisite dihydroxyacetone phosphate (DHAP) aldolase

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catalysts, chemists have developed efficient synthetic strategies of wide-ranging significance in medicinal chemistry, glycobiology, and food science.[1]

As one part of our program[3] to develop organocatalytic mimics of the aldolase enzymes that have been most widely used in synthesis, we[2a,b] and the laboratory of Enders[2c−i] have reported proline and (*S*)-2-pyrrolidine-tetrazole-catalyzed reactions that use protected dihydroxyacetone, predominantly 2,2-dimethyl-1,3-dioxan-5-one, as aldol donors in reactions that affect the synthesis of *anti*-configured 1,2-diols. These catalysts mimic the activity of D-tagatose-1,6-diphosphate and L-fuculose-1-phosphate aldolase. We then began to design catalysts to mimic L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate aldolases to provide *syn*-selective organocatalytic aldol reactions. To solve the stereochemical challenges in Mannich and aldol chemistries that are not addressed with proline and its derivatives, catalyst design has allowed us to develop efficient *anti*-Mannich,[4a,b] and more recently *syn*-aldol catalysts.[5a,b] In our *syn*-aldol studies, we demonstrated efficient and selective syntheses using unmodified α-hydroxyketones as donors in aldol reactions that install *syn*-configured 1,2-diols. Since protective groups have considerable strategic value in multistep syntheses, we were compelled to study protected forms of hydroxyketones as donors. Herein we report efficient *syn*-selective syntheses based on protected dihydroxyacetone and monohydroxyacetone donors.

Our original design for organocatalysts of the *syn*-aldol reaction was predicated on the intermediacy of a (*Z*)-enamine in the transition state.[5a,b] In accord with this design principle we studied the TBS- or Bn-protected dihydroxyacetones (**1a** and **1b**) as donors in reactions catalyzed by amino acids that contain a primary amine; acyclic dihydroxyacetone derivatives were evaluated since cyclic variants, such as 2,2-dimethyl-1,3-dioxan-5-one, can only form (*E*)-enamines. We focused on the amino acid catalysts shown in Figure 1 that had distinguished themselves in our earlier study. Catalysts were evaluated for aldol reactions of TBS- and Bn-protected dihydroxyacetones with *p*-nitrobenzaldehyde in *N*-methylpyrrolidone (NMP) with 3 vol % water (Table 1).

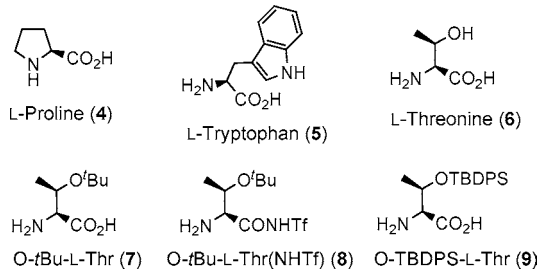
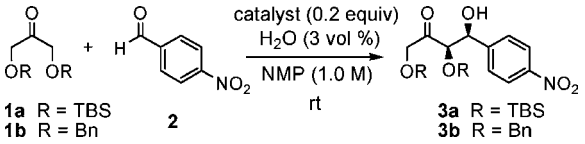


Figure 1. Catalysts screened for the *syn*-aldol reaction.

Table 1. Catalyst Screening for the Aldol Reaction of Protected Dihydroxyacetone with *p*-Nitrobenzaldehyde[a]



entry	cat.	R	time (d)	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (*syn*)[d]
1	**4**	TBS	12	<9	1:1.2	84
2	**5**	TBS	4	30	3:1	76
3	**5**	Bn	7	36	2:1	51
4	**6**	Bn	7	40	2.5:1	80
5	**7**	TBS	1	85	5:1	93
6	**7**	Bn	1	94	4:1	93
7	**8**	TBS	0.6	79	6:1	92
8	**8**	Bn	3	78	4:1	93
9	**9**	Bn	5	81	3:1	92

[a] All reactions were performed with ketone **1** (0.4 mmol, 2.0 equiv), aldehyde **2** (0.2 mmol, 1.0 equiv), catalyst (0.04 mmol, 0.2 equiv, 20 mol % to aldehyde), and H_2O (3 vol %) in NMP (0.2 mL) at room temperature. [b] Yield of isolated **3** including *syn* and *anti* mixture. [c] Determined by ^{1}H NMR spectroscopic analysis of the isolated **3**. [d] After acetylation, ee of *syn*-**3** was determined by chiral-phase HPLC.

Catalysts **5**−**9** all afforded the desired aldol product **3** with *syn*-selectivity. Proline was an extremely poor catalyst of the reaction, providing a slightly *anti*-enriched product as expected. O-*t*Bu-L-Thr (**7**) and O-*t*Bu-L-Thr(NHTf) (**8**) were the best of the catalysts screened and provided **3a** or **3b** with *syn*-favored dr's up to 6:1 and ee's up to 93%.

We chose to optimize the reaction catalyzed by O-*t*Bu-L-Thr (**7**) because the catalyst is inexpensive and commercially available. As shown in Table 2, we studied a variety of common solvents in the presence of 3 vol % water. NMP was the optimal solvent with respect to ee and dr of the product (Table 2, entry 1).

Significantly, however, when the reaction was performed neat with the addition of 5 equiv of water (Table 2, entry

(3) For select references see: (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc*. **2001**, *123*, 5260. (b) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett*. **2002**, *43*, 9591. (c) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685. (d) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541. (e) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (f) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (g) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (h) For a comprehensive review that considers the contributions of the many other laboratories that have studied the organocatalytic aldol reaction, see: Tanaka, F.; Barbas, C. F., III. In *Enantioselective Organocatalysis, Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; pp 19−55.

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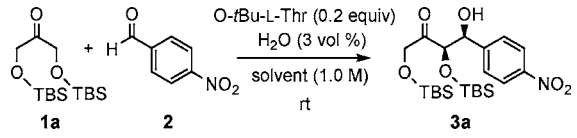
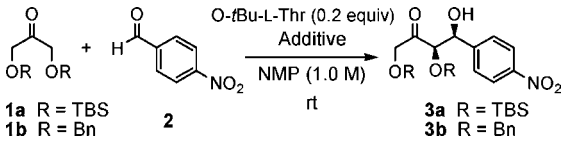
Table 2. Solvent Screening for the Aldol Reaction of Protected Dihydroxyacetone with *p*-Nitrobenzaldehyde[a]



entry	solvent	time (d)	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (*syn*)[d]
1	NMP	1	85	5:1	93
2[e]	neat	2	76	7:1	90
3[f]	neat	4	98	5:1	77
4	DMSO	3	85	3:1	90
5	DMF	2	86	3:1	94
6	dioxane	3	86	5:1	88
7	2-PrOH	2	87	6:1	89
8	CH_3CN	7	82	2:1	91
9	CH_2Cl_2	3	82	2:1	82

[a] Unless otherwise indicated, all reactions were performed with ketone **1a** (0.4 mmol, 2.0 equiv), aldehyde **2** (0.2 mmol, 1.0 equiv), O-*t*Bu-L-Thr (0.04 mmol, 0.2 equiv, 20 mol % to aldehyde), and H_2O (3 vol %) in solvent (0.2 mL) at room temperature. [b] Yield of isolated **3** including *syn* and *anti* mixture. [c] Determined by ^1H NMR spectroscopic analysis of the isolated **3**. [d] After acetylation, ee of *syn*-**3** was determined by chiral-phase HPLC. [e] H_2O 5 equiv instead of 3 vol %. [f] Without H_2O.

Table 3. Additive Screening for the Aldol Reaction of Protected Dihydroxyacetone with *p*-Nitrobenzaldehyde[a]



entry	R	additive	time (d)	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (*syn*)[d]
1	Bn	H_2O (10 vol %)	7	81	4:1	ND
2	Bn	H_2O (5 vol %)	2	80	4:1	ND
3	Bn	H_2O (3 vol %)	1	94	4:1	93
4	TBS	H_2O (3 vol %)	1	85	5:1	93
5	Bn	H_2O (1 vol %)	2	80	4:1	92
6	Bn	–	4	74	2:1	ND
7	TBS	–	2	79	3:1	87
8	TBS	5-Me-tet[e] (0.1 equiv)	4	82	3:1	87
9	Bn	AcOH (1.0 equiv)	4	56	4:1	ND
10	Bn	(−)-sparteine (0.1 equiv)	4	46	4:1	ND

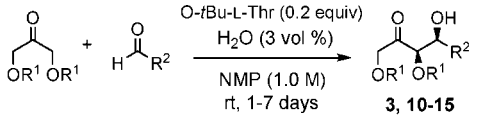
[a] All reactions were performed with ketone **1** (0.4 mmol, 2.0 equiv), aldehyde **2** (0.2 mmol, 1.0 equiv), O-*t*Bu-L-Thr (0.04 mmol, 0.2 equiv, 20 mol % to aldehyde), and additive in NMP (0.2 mL) at room temperature. [b] Yield of isolated **3** including *syn* and *anti* mixture. [c] Determined by ^1H NMR spectroscopic analysis of the isolated **3**. [d] After acetylation, ee of *syn*-**3** was determined by chiral-phase HPLC. [e] 5-Methyl-1*H*-tetrazole.

2), the product was obtained with a slightly increased dr, albiet with modestly decreased optical and chemical yield. The presence of water significantly enhanced both rate and optical yield as shown by entry 3.[6] We then sought to optimize the amount of water used in the NMP reaction and explored three other additives, 5-methyl-1*H*-tetrazole, acetic acid, and (−)-sparteine (Table 3).

Addition of water beyond 3 vol % significantly slowed the reactions (compare entries 1 and 2 with 3) as did the reduction of water to 1 vol % (entry 5). Exclusion of water significantly slowed the reaction rates and reduced the stereoselectivity of the transformation (entries 6 and 7). In contrast to our results with unprotected dihydroxyacetone, water was a better additive than 5-methyl-1*H*-tetrazole.[5b]

Using these optimal conditions, we explored the scope of the reaction with a variety of aldehydes (Table 4). Reaction of both TBS- and Bn-protected dihydroxyacetone with a variety of aromatic aldehydes (Table 4, entries 1−6) furnished the desired *syn*-aldol products in good optical and chemical yields (up to 7:1 dr, *syn*-favored, and 98% ee). Interestingly, the glyoxalic acid-based acceptors (entries 7 and 8) were poor substrates for this reaction; perhaps their enhanced electrophilicity trapped the catalyst as an imine. The methoxyacetal of glyoxal is, however, an excellent substrate affording *syn*-aldol **15** in 97% ee. Aldol **15** is related to the rabbit muscle aldolase products synthesized by Whitesides via his inversion strategy, and thus **15** is a precursor for the synthesis of L-xylose.[7] It should be noted that we and Enders have adopted Whitesides' inversion strategy using the *anti*-aldol products afforded by proline catalysis to synthesize a variety of interesting carbohydrates.[2b,g,h]

Table 4. Scope of the *syn*-Aldol Reaction with Various Aldehydes[a]



entry	R^1	R^2	product	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (*syn*)[d]
1	TBS	*p*-NO_2Ph	**3a**	85	5:1	93[e]
2	Bn	*p*-NO_2Ph	**3b**	94	4:1	93[e]
3	TBS	*p*-BrPh	**10a**	65	7:1	94[f]
4	Bn	*p*-BrPh	**10b**	80	6:1	94[e]
5	TBS	*p*-CNPh	**11**	83	6:1	93[e]
6	Bn	*o*-ClPh	**12**	86	7:1	98[f]
7	TBS	CONHPh	**13**	29	1.2:1[g]	24
8	TBS	CO_2Et	**14**	36	1:1	26[f,h]
9	TBS		**15**	71	5:1	97[f]

[a] Unless otherwise indicated, all reactions were performed with ketone **1** (0.4 mmol, 2.0 equiv), aldehyde (0.2 mmol, 1.0 equiv), O-*t*Bu-L-Thr (0.04 mmol, 0.2 equiv, 20 mol % to aldehyde) and H_2O (3 vol %) in NMP (0.2 mL) at room temperature. [b] Yield of isolated products including *syn* and *anti* mixture. [c] Determined by ^1H NMR spectroscopic analysis of the isolated products. [d] ee was determined by chiral-phase HPLC. [e] Determined after acetylation. [f] Determined after benzoylation. [g] Diastereomers were separated by silica gel column chromatography. [h] *syn*-*anti* isomers could not be assigned.

In order to establish the absolute stereochemistry of our products, we sought to synthesize D-fructose using our

(6) The addition of water to organocatalytic reactions has often been shown to increase reaction rates and/or selectivities. For some examples see: (a) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325. (c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (d) Chen, X.; Luo, S.; Tang, Z.; Cun, L.; Mi, A.; Jiang, Y.; Gong, L. *Chem. Eur. J.* **2007**, *13*, 689. (e) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957. (f) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.

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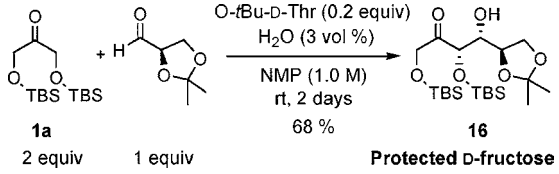
methodology. To accomplish this, we utilized O-*t*Bu-D-Thr as the catalyst for the reaction of TBS-protected dihydroxyacetone with the acetonide of D-glyceraldehyde under our standard conditions (Scheme 2). The product **16** was obtained

Scheme 2. Synthesis of Protected D-Fructose

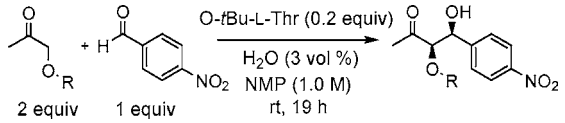


with >98:2 dr and ee of 98%. Deprotection with Dowex 50WX8-100 provided D-fructose, confirming the stereochemistry as illustrated. The remaining products are assigned analogously. The (3*R*,4*S*) configuration afforded by O-*t*Bu-L-Thr catalysis of protected dihydroxyacetone is the same configuration that is provided when unprotected dihydroxyacetone is used as a substrate.[5b]

Interestingly, as we were completing these studies, Wu et al. reported[5e] that related threonine-based catalysts afforded *syn*-aldol products with a (3*S*,4*R*) configuration when protected hydroxyacetone was used as a donor; this is in contrast to the (3*R*,4*S*) configuration we have consistently observed.[5a,b] To reconcile this apparent discrepancy, we studied the aldol reaction of three protected variants of hydroxyacetone (Table 5).

All derivatives of hydroxyacetone were good substrates under our standard conditions, and *syn*-aldol products were obtained with ee's up to 95%. Product **19**, also reported by Wu et al., was deprotected. Analytical data for the free diol of **19** matched that of the compound prepared using unprotected dihydroxyacetone as a substrate, indicating that there was no switch in the absolute stereochemistry upon protection of the hydroxy group of hydroxyacetone. Thus, reactions involving protected hydroxyacetone as a donor provide (3*R*,4*S*)-configured *syn*-aldols under our conditions.

Table 5. *syn*-Aldol Reactions of Protected Hydroxyacetones[a]



entry	R	product	yield (%)[b]	dr (*syn*/*anti*)[c]	ee (*syn*/*anti*)[d]
1	Me	**17**	79	3:1[e]	92/39
2	Bn	**18**	79	3:1	94/35
3	TBS	**19**	82	5:1	95/7

[a] All reactions were performed with ketone (0.4 mmol, 2.0 equiv), aldehyde (0.2 mmol, 1.0 equiv), O-*t*Bu-L-Thr (0.04 mmol, 0.2 equiv, 20 mol % to aldehyde) and H_2O (3 vol %) in NMP (0.2 mL) at room temperature. [b] Yield of isolated products including *syn* and *anti* mixture. [c] Determined by ^1H NMR spectroscopic analysis of the isolated products. [d] After acetylation, ee was determined by chiral-phase HPLC. [e] Diastereomers were separated by silica gel column chromatography.

In summary, we have developed an effective organocatalytic method (based on protected dihydroxyacetone and hydroxyacetone donors) for the synthesis of *syn*-aldol products. This methodology provides 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 aldolase and promises simplified and effective routes to a variety of carbohydrates and their derivatives. As such, this methodology complements proline-based strategies that have previously provided effective syntheses of the corresponding *anti*-aldol products.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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