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# Water-Compatible Organocatalysts for Direct Asymmetric *syn*-Aldol Reactions of Dihydroxyacetone and Aldehydes

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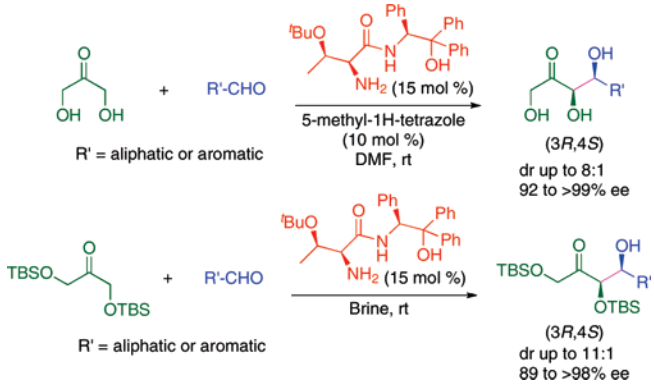
## ABSTRACT




**A novel organocatalyst was developed that effectively catalyzed the reactions of unprotected or protected dihydroxyacetone with a variety of aldehydes to provide *syn*-aldol products with good yields and ee values up to >99%. Significantly, this amide catalyst was effective with a variety of nonaromatic aldehyde acceptors that had proven difficult in the presence of other catalysts. Reactions of protected dihydroxyacetone proceeded in aqueous media without addition of organic solvents.**

Dihydroxyacetone-based aldol reactions are of considerable importance because they provide expedient access to both natural carbohydrates and unnatural molecules of significance in medicine and materials and food sciences. Prior to the emergence of organocatalysis as a broadly applicable approach to asymmetric synthesis, direct asymmetric dihydroxyacetone-based aldol reactions were the sole purview of aldolase enzymes.[1] Recently, direct enantioselective organocatalytic dihydroxyacetone aldol reactions that provide both *anti*- and *syn*-configured 1,2-diols have been developed.[2,3] The *anti*-configured 1,2-diols are directly accessible by using proline/pyrrolidine catalysis as we originally

(1) (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, UK, 1994. (b) Takayama, S.; McGarvey, G. J.; Wong, C.-H. *Chem. Soc. Rev.* **1997**, *26*, 407. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352. (d) Wymer, N.; Toone, E. J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 110. (e) Wong, C.-H.; Bryan, M. C.; Nyffeler, P. T.; Liu, H.; Chapman, E. *Pure Appl. Chem.* **2003**, *75*, 179. (f) Fessner, W. D.; Helaine, V. *Curr. Opin. Biotechnol.* **2001**, *12*, 574. For a recent study see: Sugiyama, M.; Hong, Z.; Liang, P.-H.; Dean, S. M.; Whalen, L. J.; Greenberg, W. A.; Wong, C.-H. *J. Am. Chem. Soc.* **2008**, *129*, 14811.

(2) for *anti*-dihydroxyacetone based organocatalytic aldol reactions see: (a) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383. (b) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *J. Org. Chem.* **2006**, *71*, 3822. (c) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210. (d) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079. (e) Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655. (f) Enders, D.; Vrettou, M. *Synthesis* **2006**, 2155. (g) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329. (h) Grondal, C.; Enders, D. *Adv. Synth. Catal.* **2007**, *349*, 694. (i) Enders, D.; Gasperi, T. *Chem. Commun.* **2007**, 88.

(3) for *syn*-dihydroxyacetone-based organocatalytic aldol reactions see: (a) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 5572. (b) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III *Org. Lett.* **2007**, *9*, 3445. (c) Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, *129*, 7285. (d) Markert, M.; Mahrwald, R. *Chem. Eur. J.* **2008**, *14*, 40. (e) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J. P. *Org. Lett.* **2008**, *10*, 653.

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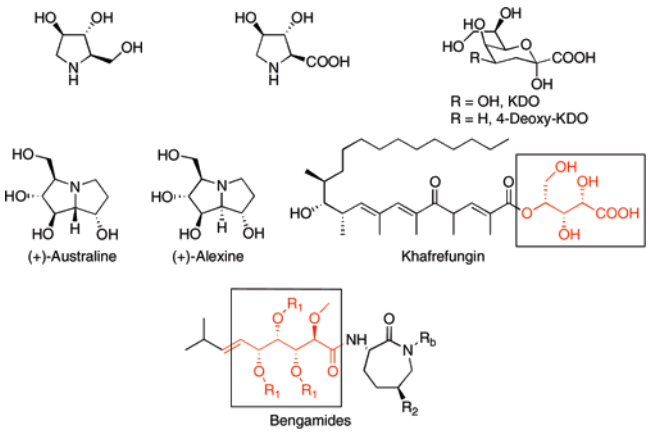
described.[4] Enantioselective approaches to the *syn*-configured products came some years later with our development of primary amino acid catalysts that provide *anti*-Mannich and *syn*-aldol products with hydroxyketone donors.[3,5] These studies indicated that O-*t*Bu-L-Thr and O-*t*Bu-L-Thr(NHTf) were promising catalysts for the direct, *syn*-selective, asymmetric dihydroxyacetone aldol reaction.[3a,b] A distinct limitation to these reactions was their relative inefficiencies with nonaromatic aldehyde acceptors, particularly with unfunctionalized aliphatic aldehydes. Additionally, these reactions were optimal in organic reaction media. Other *syn*-aldol catalysts have similar limitations: for example, a recently described diamine acid catalyst is largely restricted to aromatic acceptor aldehydes.[3e] As illustrated in Scheme 1,

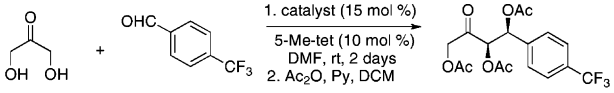
**Scheme 1.** The *syn*-1,2-Diol is a Common Structural Motif[1,6]

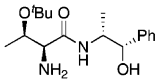
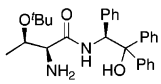
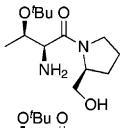
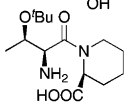
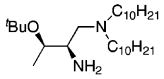



*syn*-configured 1,2-diols are structural motifs common to diverse compounds of medicinal significance and thus expansion of the scope and efficiency of this reaction is of importance.[1,6] We were also interested in developing organocatalytic approaches that use water as a reaction medium since it is an environmentally friendly, safe, and cost-effective medium.[7] In previous studies,[8] we have successfully generated catalysts for a variety of organocatalytic reactions (including aldol,[8a] Michael,[8b] Mannich,[8c] and Diels−Alder[8d]) that function efficiently in reaction media consisting largely or completely of water. Indeed, water is proving to be an effective medium for a range of organocatalytic reactions.[9]

Given the success of the amide catalyst O-*t*Bu-L-Thr-(NHTf) in our earlier dihydroxyacetone studies and advances in proline-based *anti*-aldol reactions obtained through the preparation of prolylamide derivatives pioneered by Gong and others,[10] we sought to design a family of O-*t*Bu-L-Thr-based amide catalysts for direct asymmetric aldol reactions. As shown in Table 1, we prepared three O-*t*Bu-L-Thr-based amide derivatives and studied them in the reaction of free dihydroxyacetone and *p*-trifluoromethylbenzaldehyde (Table 1, entries 1−4). This reaction was chosen for screening since it proved to be one of the lower yielding reactions in our studies of O-*t*Bu-L-Thr catalysis.[3a] Catalysts **1**−**3** were synthesized by using $\beta$-amino alcohols based on the Gong

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




| entry | catalyst | | yield[b] (%) | dr[c] (*syn/anti*) | ee[c] (*syn/anti*) |
|---|---|---|---|---|---|
| 1 |  | **1** | 46 | 2:1 | 50/56 |
| 2 |  | **2** | 75 | 3:1 | 96/50 |
| 3 |  | **3** | 6 | 1.3:1 | 95/76 |
| 4 |  | **4** | 27 | 1:1 | 91/52 |
| 5 |  | **5**[d] | 63[e] | 4.5:1 | 68/44 |
| 6 | | | 45[f] | 1.3:1 | 96/83 |

[a] See the Supporting Information for reaction conditions. [b] Isolated yield. [c] Determined by chiral phase HPLC analysis. [d] No reaction observed under aqueous conditions. [e] *p*-Nitrobenzaldehyde was used as acceptor. [f] 10 mol % trifluoroacetic acid (TFA) was used as additive. 5-Me-tet: 5-methyl-1*H*-tetrazole

(4) For select references see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 9591. (d) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2003**, *5*, 1685. (e) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 3541. (f) Mase, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (g) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (h) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734. (i) 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.; Weiley-VCH: Weinheim, Germany, 2007; pp 19−55.

(5) (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. For other *syn*-aldol studies see: (b) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738. (c) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (d) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth., Catal.* **2007**, *349*, 812. (e) Xu, Y.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247.

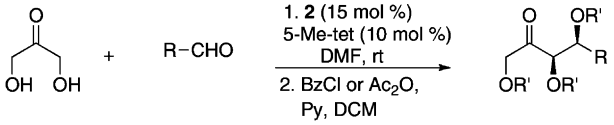
(6) (a) Auge, C.; Bouxom, B.; Cavaye, B.; Gautheron, C. *Tetrahedron Lett.* **1989**, *30*, 2217. (b) Auge, C.; Gautheron, C.; David, S.; Malleron, A.; Cavaye, B.; Bouxom, B. *Tetrahedron* **1990**, *46*, 201. (c) Australine: Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198. (d) Alexine: Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487−2490. (e) Khafrefungin: Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311* (Sphingolipid Metabolism and Cell Signalling, Part A), 335. (f) Bengamides: Madeline, A.; Emilio, Q.; Phillip, C. *J. Am. Chem. Soc.* **1989**, *111*, 647.

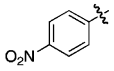
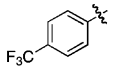
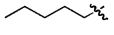
(7) For reviews on organic synthesis in water, see: (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. For a recent theoretical discussion concerning the acceleration of organic reactions on water see: (d) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

hypothesis[10] that such amides activate the electrophilic aldehyde component of the aldol reaction by forming two hydrogen bonds with its carbonyl with use of both the amide and the hydroxy functionalities. All three were found to be *syn*-selective catalysts in the presence of 5-methyl-1*H*-tetrazole as an acid additive, providing the desired aldol product with ee up to 96%. Catalyst **2** was the superior amide with respect to yield and stereochemical control. This catalyst incorporates the phenylalanine-derived $\beta$-amino alcohol component identified by Singh et al. in studies of prolylamide aldol reactions.[9i,p] Catalyst **4** was designed to incorporate a carboxylate, like that of proline, for activation of the electrophilic aldehyde. This catalyst was efficient with respect to enantioselectivity but gave a lower chemical yield than catalyst **2** and provided no diastereoselectivity. Catalyst **5** was designed based on our diamine/acid strategy[4b,f,g,8a] proven effective in pyrrolidine-based *anti*-aldol catalysts and in recent[3e,5c] *syn*-aldol catalyst designs. Catalyst **5**, together with trifluoroacetic acid or 5-methyl-1*H*-tetrazole as cocatalysts, was less optimal than catalyst **2** with DMF as a solvent and was not reactive with free dihydroxyacetone under aqueous conditions.

We then studied the scope of the free dihydroxyacetone aldol reaction using catalyst **2** in DMF with 5-methyl-1*H*-tetrazole as an additive (Table 2). The results obtained with aromatic acceptors (entries 1 and 2) were similar with respect to yield and enantioselectivity to those obtained with the parent catalyst O-*t*Bu-L-Thr; however, the diastereoselectivity was reduced.[3a] Catalyst **2** differentiated itself from O-*t*Bu-L-Thr catalysis in reactions with nonaromatic aldehydes (entries 3−6). We previously showed that O-*t*Bu-L-Thr catalysis provided the product of entry 3 with a maximum yield of 28%; here we obtained 68% yield with catalyst **2**. Yields with hexanal and cyclohexane carboxaldehyde were 70% and 74%, respectively (entries 5 and 6), with excellent ee. Product **11** is a precursor for the synthesis of L-xylose[11] previously synthesized by using organocatalysis only through the use of protected dihydroxyacetone.[3b] Earlier attempts[3a] to synthesize **11** with free dihydroxyacetone and O-*t*Bu-L-Thr catalysis failed to provide significant amounts of clean compound. Amide **2**, however, provided **11** in 62% yield and 94% ee.

**Table 2.** Scope of *syn*-Aldol Reactions of Dihydroxyacetone with Various Aldehydes[a]




| entry | R | R' | product | time (d) | yield[b] (%) | dr[c] *(syn/anti)* | ee[c] *(syn/anti)* |
|---|---|---|---|---|---|---|---|
| 1 |  | Ac | **6** | 3 | 78 | 6:1 | 92/62 |
| 2 |  | Ac[d] | **7** | 3 | 75 | 3:1 | 96/50 |
| 3 |  | Ac | **8** | 3 | 68 | 2:1 | >99/34 |
| 4 |  | Bz | **9** | 4 | 70 | 3:1 | >99/- |
| 5 |  | Bz | **10** | 3 | 74 | 8:1 | 94/40 |
| 6 |  | Bz | **11** | 3.5 | 62 | 3:1 | 94/64 |

[a] See the Supporting Information for the general procedure. [b] Isolated yield. [c] Determined by chiral-phase HPLC analysis. [d] 3 vol % water used as additive instead of 5-methyl-1*H*-tetrazole (5-Me-tet).

A goal of this study was to establish aqueous conditions for these reactions. Studies with free dihydroxyacetone in aqueous media failed to provide promising results. However, since protective groups can have considerable value in multistep syntheses, we were compelled to study TBS-protected dihydroxyacetone as a donor under aqueous conditions. Our results are shown in Table 3. Entry 1 demonstrates that our original catalyst O-*t*Bu-L-Thr is active under brine solvent conditions but suffers significantly with respect to ee as compared to our original study of this catalyst in *N*-methylpyrrolidone (NMP), which provided product **12** in 93% ee. Entries 2 and 3 compare the NMP/3 vol % water conditions[3b] originally established for O-*t*Bu-L-Thr catalysis with the use of brine as solvent with catalyst **2**. In brine, catalyst **2** provided aldol product **12** with enhanced chemical yield and diastereoselectivity maintaining essentially the same enantioselectivity compared to the original conditions. In brine, the reactions with the simple aliphatic acceptor aldehydes dihydrocinnamaldehyde and hexanal (entries 4 and 5) provided excellent results (up to 11:1 *syn*-favored dr, and 96% ee). Next we studied functionalized nonaromatic aldehydes as acceptors since their products are related to

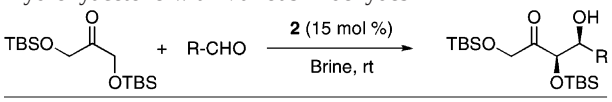
(8) (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734. (b) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (c) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanuvan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, *68*, 9624. (d) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 6743.

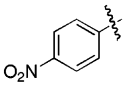
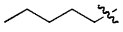
(9) For other studies concerning organocatalytic aldol reactions in aqueous media see: (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (b) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527. (c) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801. (d) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653. (e) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493. (f) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (g) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812. (h) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, 2524. (i) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (j) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.*, published online Feb.14, http://dx.doi.org/10.1021/ol800074z. For representative studies concerning the use of aqueous media in other organocatalytic reactions see: (k) Zu, L.-S.; Wang, J.; Li, H.; Yu, X-H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (l) Ramachary, B. D.; Kishor, M.; Ramakumar, K. *Tetrahedron Lett.* **2006**, *47*, 651. (m) Ramachary, D. B.; Reddy, G. B. *Org. Biomol. Chem.* **2006**, *4*, 4463. (n) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (o) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431. (p) Ramachary, D. B.; Kishor, M. *J. Org. Chem.* **2007**, *72*, 5056. (q) Singh, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117.

(10) (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (b) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755. (c) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (d) Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097.

(11) Borysenko, C. W.; Spaltenstein, A.; Straub, J. A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 9275.

**Table 3.** Scope of *syn*-Aldol Reactions of TBS-Protected Dihydroxyacetone with Various Aldehydes[a]




| entry | R | product | time (h) | yield[b] (%) | dr[c] *(syn/anti)* | ee[c] *(syn)* |
|---|---|---|---|---|---|---|
| 1 |  | **12** | 75[d] | >95 | 4:1 | 79 |
| 2 | | | 24[e] | 74 | 3:1 | 89 |
| 3 | | | 20 | 81 | 5:1 | 87 |
| 4 |  | **13** | 30[f] | 83 | 7:1 | 96 |
| 5 |  | **14** | 20[g] | 77 | 11:1 | 95 |
| 6 |  | **15** | 18 | 60 | 5:1 | 96 |
| 7 |  | **16** | 20[h] | >99 | 9:1 | 97 |
| 8 |  | **17** | 20[h] | 86 | 3:1 | 98 |
| 9 |  | **18** | 24 | 77 | 3:1 | 96[i] |
| 10 |  | **19** | 18 | 55 | 3:1 | 94 |

[a] See the Supporting Information for reaction conditions. [b] Isolated yield. [c] Determined by chiral phase HPLC analysis. [d] Reaction performed with 20 mol % *t*Bu-L-Thr as catalyst. [e] Reaction performed[3b] in NMP, water (3 vol %), rt. [f] ee determined after TBS deprotection[3b] and acetylation. [g] ee determined after TBS deprotection[3b] and benzoylation. [h] 10 mol % 5-methyl-1*H*-tetrazole was used as additive. [i] ee determined after benzoylation.

naturally occurring carbohydrates. The methoxyacetal of glyoxal was also an excellent substrate, furnishing the L-xylose precursor in quantitative yield, 9:1 *syn*-favored dr, and 97% ee (entry 7). Our earlier studies[3b] of O-*t*Bu-L-Thr catalysis of this reaction provided this product with the same ee but with a chemical yield of 71% and dr of 5:1. Reaction of the acetonide of D-glyceraldehyde was also efficient, providing the protected D-sorbose derivative **17** in 86% yield, 3:1 *syn*-favored dr, and 98% ee. This result compares favorably with our O-*t*Bu-D-Thr-catalyzed synthesis of protected D-fructose (note: D-Thr not L-Thr was used), which was prepared in 68% yield and 98% ee. No bis-aldol products were noted in our studies.

As shown in entries 7 and 8, we also explored the synthesis of glyoxalic acid derivates that had proven challenging[3b] under O-*t*Bu-L-Thr catalysis. Under O-*t*Bu-L-Thr catalysis, product **18** was provided in 36% yield and 26% ee with no diastereoselection and product **19** was provided in 29% yield and 24% ee with only a 1.2:1 dr.[3b] Amide catalyst **2**, however, provided product **18** in 77% yield, 3:1 *syn*-favored dr, and 96% ee and product **19** in 55% yield, 3:1 *syn*-favored dr, and 94% ee. Thus catalyst **2** provided dramatic improvement in both chemical and optical yields of polyol products obtained through direct asymmetric aldol reactions of protected dihydroxyacetone and nonaromatic aldehydes relative to previously employed catalysts.

In summary, amide **2** is an effective organocatalytic catalyst for the synthesis of *syn*-aldol products from free dihydroxyacetone in organic solvent and from protected dihydroxyacetone in aqueous medium. This catalyst provided substantial improvements in this important class of *syn*-aldol reactions, providing for the first time effective syntheses based on nonaromatic aldehyde acceptors, in particular simple aliphatic aldehyde acceptors that did not yield desired products or were low yielding in other catalyst systems.[3a,b,e] 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 expands the scope of simplified and effective organocatalytic routes to a variety of carbohydrates and their derivatives.

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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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