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# Mimicking Dihydroxy Acetone Phosphate-Utilizing Aldolases through Organocatalysis: A Facile Route to Carbohydrates and Aminosugars†

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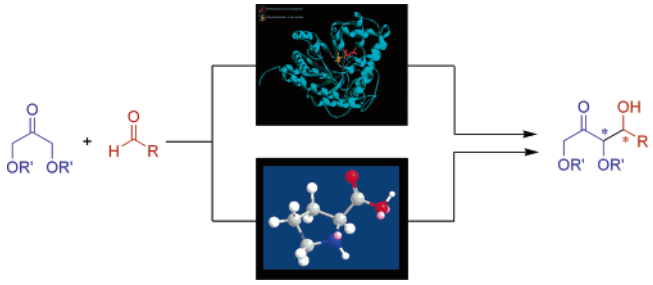
## ABSTRACT




**A practical and environmentally friendly organocatalytic strategy designed to mimic the DHAP aldolases has been developed and shown to be effective in the preparation of carbohydrates and aminosugars. (*S*)-Proline and (*S*)-2-pyrrolidine-tetrazole catalyzed the aldol reaction between dihydroxy acetone variants such as 1,3-dioxan-5-one and 2,2-dimethyl-1,3-dioxan-5-one with aldehydes to give the corresponding polyols in good yields with very high ees.**

Dihydroxy acetone phosphate-utilizing aldolases such as FDP aldolase have been developed into exceptionally powerful tools for the asymmetric synthesis of carbohydrates and their derivatives.[1] Enzymes of this family catalyze the aldol addition of dihydroxy acetone phosphate (DHAP) with a range of aldehyde acceptors to form a new C−C bond while creating two hydroxy-substituted stereogenic centers. Typically, these reactions take place with complete stereospecificity, and with the appropriate aldolase enzyme, all four stereoisomers can be generated with high levels of stereocontrol.[2] DHAP aldolases have been used to prepare a diverse range of stereochemically complex carbohydrates and azasugars,[3] molecules of great significance in medicinal chemistry and glycobiology.[4]

Although many attempts have been made to effect these same transformations using lithium- and boron-enolate chemistries,[5] highly stereoselective catalytic reactions have

† This report is cordially dedicated to Professor C.-H. Wong for his many contributions in enzymatic carbohydrate synthesis.

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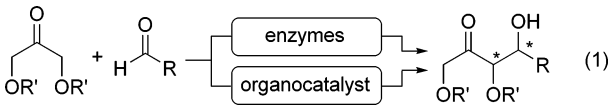
remained elusive.[6] Organocatalysis has emerged as a simple and yet powerful methodology in asymmetric enamine-based chemistries. In analogy to enzymes, organocatalysis allows for the direct coupling of aldehydes and ketones with a variety of electrophiles without the use of preformed enolates. Many reactions have been reported, and in some cases, remarkably high levels of stereoselectivity have been achieved.[7] In studies aimed at recapitulating the chemistry of aldolase enzymes with organocatalysis,[8] we report here the efficacy of this approach in aldol reactions between dihydroxy acetone derivatives and aldehyde acceptors, with the ultimate goal being to mimic the aldolase enzymes and achieve complete stereocontrol (eq 1) without the substrate restrictions endemic to natural enzymes.



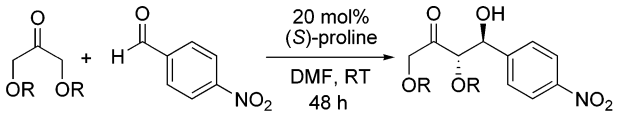
(1)

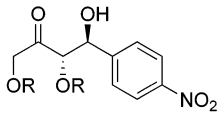
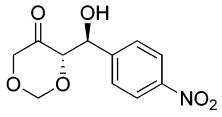
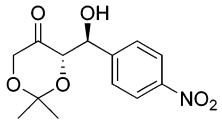
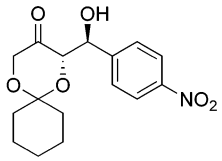
In earlier studies, we reported that under aqueous buffered conditions, (*S*)-proline can catalyze the aldol reaction between unprotected dihydroxy acetone and various aldehydes.[8b] Although moderate ees were obtained (up to 63% ee), the diastereoselectivity was low for almost all cases,[9] hampering the general utility of this reaction in asymmetric synthesis. To overcome this shortcoming we have now investigated the aldol reaction between various protected versions of dihydroxy acetone[10] and nitrobenzaldehyde in the presence of proline or (*S*)-2-pyrrolidine-tetrazole[8f] (Table 1).

In DMF at ambient temperature, the reaction with dihydroxy acetone was very sluggish, providing minimal product after 48 h (entry 1), a reaction hampered by dimerization of this ketone in organic solvent. The benzyl-protected ketone as well as the silyl-protected version (entries 2 and 3) also gave small amounts of product. However, the cyclic derivatives (entries 4−9) were found to be suitable substrates for this aldol reaction, giving polyol products in excellent yield after 48 h.[11] The degree of stereoselectivity was dependent on the protecting group. For example, 1,3-dioxan-5-one underwent aldolization, giving product with high ee and dr (entries 4 and 5, up to 94% ee and 15:1 dr), while 1,5-dioxaspiro[5.5]undecan-3-one gave the corresponding adduct with much less stereoselectivity (entries 9 and 10, up to 67% ee and 5:1 dr). At subambient temperatures, 2,2-dimethyl-1,3-dioxan-5-one gave good ees and diastereoselectivity (entries 6−8). X-ray crystallographic analysis of this adduct revealed the major product to be anti with respect to the newly formed hydroxyl group, and the absolute configuration was 3*S*,4*S* (see Supporting Information). This stereochemical outcome is in accordance with other (*S*)-proline-catalyzed aldol reactions.[7]

The scope of this reaction was then demonstrated using the commercially available 2,2-dimethyl-1,3-dioxan-5-one and various aliphatic, aromatic, and oxy- and amine-substituted acceptors (Table 2). In contrast to the aromatic substrates, greater stereoselectivity was provided with aliphatic substrates. For example, when isovaleraldehyde was

**Table 1.** Dihydroxy Acetone Derivatives in Direct Aldol Reaction




| entry | R | product | %yield[a] | *anti*:*syn*[b] | %ee[b] |
|---|---|---|---|---|---|
| 1 | H |  | trace | - | - |
| 2 | Bn | | | | |
| 3 | TIPS | | | | |
| 4 | -$CH_2$- |  | 89 | 2:1 | 92 |
| 5 | | | 91 | 15:1 | 94[c] |
| 6 | -$C(CH_3)_2$- |  | 89 | 2:1 | 60 |
| 7 | | | 90 | 6:1 | 93[c] |
| 8 | | | 86 | 16:1 | 95[c,d] |
| 9 | -$C(C_5H_{10})$- |  | 85 | 5:1 | 59 |
| 10 | | | 62 | 5:1 | 67[c] |

[a] Isolated yield after column chromatography. [b] Determined by chiral-phase HPLC analysis. [c] Performed at 4 °C. [d] Performed with 20 mol % (*S*)-2-pyrrolidine-tetrazole[8f] as a catalyst.

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(6) Excellent stereoselectivities have been obtained using chiral auxiliaries; see: (a) Enders, D.; Ince, S. J.; Bonnekessel, M.; Runsink, J.; Raabe, G. *Synlett* **2002**, 962−966. (b) Enders, D.; Ince, S. J. *Synthesis* **2002**, 619−624. (c) Enders, D.; Hundertmark, T. *Tetrahedron Lett.* **1999**, *40*, 4169−4172.

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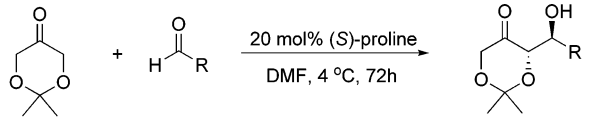
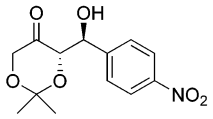
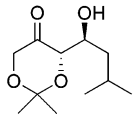
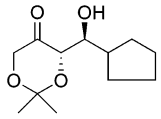
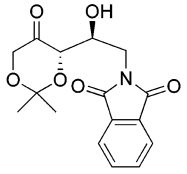
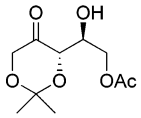
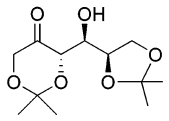
(9) Two substrates gave drs of >20:1 but without any ee.

(10) Following our initial submission, Enders et al. published an extensive review related to the use of 2,2-dimethyl 2,2-dimethyl-1,3-dioxan-5-one in synthetic chemistry and a complementary study of its use under proline catalysis. See: (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, ASAP. (b) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210−1212.

(11) Significantly, 4-thianone has been used as a masked cyclic ketone surrogate of the unreactive 3-pentanone for proline catalysis. See: (a) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347−8350. (b) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, *11*, 1891−1896.

**Table 2.** Stereoselective Direct Coupling of 2,2-Dimethyl-1,3-dioxan-5-one with Aldehyde Acceptors



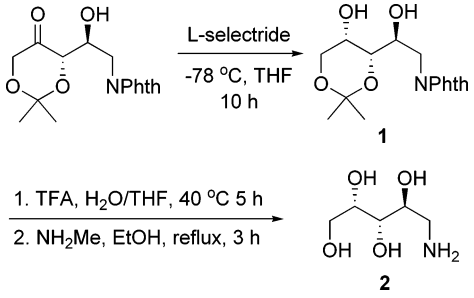

| entry | R | product | %yield[a] | *anti*:*syn*[b] | %ee[c] |
|---|---|---|---|---|---|
| 1 | *p*-$NO_2C_6H_5$ |  | 89 | 6:1 | 93[d] |
| 2 | $CH_2{}^iPr$ |  | 75 | 10:1 | 98 |
| 3 | $C_5H_9$ |  | 67 | 99:1 | 97 |
| 4 | $CH_2$Phth |  | 75 | 55:1 | 98 |
| 5 | $CH_2OAc$ |  | 60 | >15:1 | 98 |
| 6 | -CH(OCMe$_2$O)CH$_2$- |  | 40 | >15:1 | 94 |

[a] Isolated yield. [b] Determined by HPLC and NMR analysis. [c] Determined by chiral-phase HPLC analysis. [d] Reaction time = 48 h.

the donor, the corresponding adduct was obtained in 98% ee and with 10:1 dr (entry 2). The product of the reaction with cyclopentane carboxaldehyde (entry 3) was obtained in 97% ee with no other diastereomer observed. When oxy- and amino-substituted aldehydes were reacted with proline and 2,2-dimethyl-1,3-dioxan-5-one (entries 4−6), the reactions proceeded with high levels of stereocontrol (>94% ee, >15:1 dr), giving the corresponding polyols and aminols (entries 4−7). Significantly, these aldol products are protected azasugars (entry 4) and carbohydrates (L-ribulose and D-tagatose, entries 5 and 6), compounds that are otherwise most efficiently prepared via enzymatic reactions[1b] or from the chiral pool.[12] Unlike natural aldolase enzymes, we found that reactions with imines and alkenes, Mannich and Michael-type reactions, were also facile, suggesting the synthetic scope of this methodology will reach beyond that observed with enzymes with respect to electrophile range.[13]

Reactions were readily performed on a gram scale, and deprotection and further elaboration of the aldol products allowed for the rapid construction of carbohydrate architectures. For example, treatment of the aldol adducts with Dowex resin in $H_2O$/THF gave the corresponding dihydroxy products in quantitative yield (see Supporting Information). The phthalimido-protected aldol product was reduced with (L)-Selectride to give the stereochemically rich polyol **1** (Scheme 1).[14] Deprotection with TFA and methylamine-induced cleavage of the phthalimide group afforded 1-amino-1-deoxy-D-lyxitol **2**,[15] a carbohydrate construct traditionally prepared from the chiral pool of naturally occurring sugars.

**Scheme 1.** Synthesis of 1-Amino-1-deoxy-D-lyxitol




In summary, we have demonstrated the effectiveness of organocatalysis in the preparation of carbohydrates and aminosugars in a strategy designed to mimic the DHAP aldolases. This efficient strategy promises simplified routes to complex carbohydrates and their derivatives.

**Acknowledgment.** This study was supported in part by the NIH (CA27489) and the Skaggs Institute for Chemical Biology. We thank Dr. Raj K. Chadha for X-ray structural analysis and Rajeswari Thayumanavan for technical assistance.

**Supporting Information Available:** Experimental procedures, characterization data, and X-ray files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ekeberg, D.; Morgenlie, S.; Stenstrom, Y. *Carbohydr. Res.* **2002**, *337*, 779−786.
(13) Results concerning Mannich-type and Michael reactions will be reported in due course.
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(15) Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1979**, *68*, 175−187.