# Highly Enantioselective Direct *syn*- and *anti*-Aldol Reactions of Dihydroxyacetones Catalyzed by Chiral Primary Amine Catalysts

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**ABSTRACT**
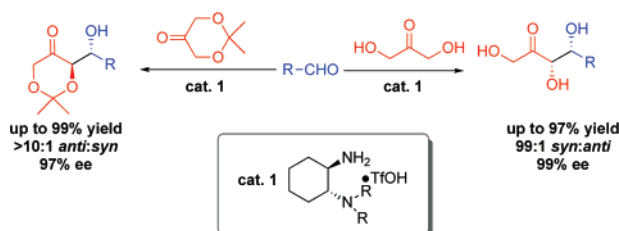


We present herein simple primary–tertiary diamine–Brønsted acid conjugates that catalyze both *syn*- and *anti*-aldol reactions of dihydroxyacetones (DHAs) with high diastereoselectivities and enantioselectivities. This type of organocatalysts functionally mimics all four DHA aldolases, namely L-fuculose-1-phosphate aldolase, D-tagatose-1,6-diphosphate aldolase, D-fructose-1,6-diphosphate aldolase, and L-rhamnulose-1-phosphate aldolase.

Dihydroxyacetone (DHA) and its derivatives are versatile $C_3$-building blocks in chemical and enzymatic synthesis of carbohydrates.[1] In nature, enzymes, e.g., DHAP-dependent aldolases, utilize dihydroxyacetone phosphate (DHAP) as a specific donor for the synthesis of carbohydrates via aldol coupling. These reactions generated two new stereocenters in the form of *syn*- or *anti*-1,2-diols. Hence, there are four types of DHAP aldolases, respectively, responsible for the formation of the four possible diastereoisomers of 1,2-diols. These DHAP-dependent processes have now been meticulously harnessed for chemo-enzymatic synthesis of a diverse range of stereochemically complex sugars.[1b,2] On the other

hand, chemists have been long pursuing simple chemical mimics for nature's aldolase enzymes. However, truly asymmetric catalysis with DHA derivatives as donors has only been achieved very recently with the emerging organocatalysts.[3] In this regard, L-proline was shown to be the sole effective organocatalyst in most of these transformations, and the reactions are largely limited to cyclic protected DHAs such as 2,2-dimethyl-1,3-dioxan-5-one (**2b**), affording mainly *anti*-aldols. Very recently, Barbas reported that primary amino acid could catalyze the *syn*-aldol reation of DHA and protected DHA.[4,5] Herein, we report the first example of small molecular catalysts that catalyzed both the *syn*- and *anti*-aldol reactions of DHAs with high yields and excellent stereoselectivity, thus providing one type of primary amines

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(1) (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304−1325. (b) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443−473.

(2) Wong, C.-H.; Machajewski, T. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1375.

catalyst that functionally imitates all the four types of DHAP-aldolases (Scheme 1).

**Scheme 1.** General Strategy for the *syn*- and *anti*-Aldol Reaction of DHAs
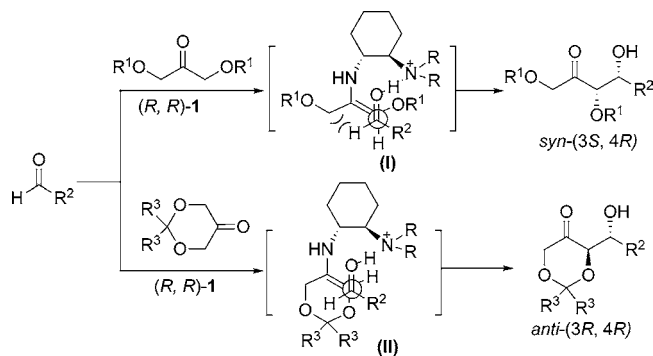


We have recently reported an organocatalytic *syn*-aldol reaction of linear aliphatic ketones catalyzed by primary−tertiary diamine−Brønsted acid catalyst.[6] This reaction occurred through a *Z*-enamine intermediate and thus led to syn stereoselectivity which is distinct from that observed with secondary amines catalysts. On the basis of the previous results, we envisioned that a significant extension of the reaction to acyclic DHA derivatives including free DHA may also induce syn selectivity via *Z*-enamine intermediates (Scheme 1, **I**). While for the reactions of cyclic DHA derivatives, which are capable of forming only *E*-enamine (Scheme 1, **II**), we expected that the same type of catalysts would lead to the formation of *anti*-aldol products.

The free DHA **2a** and protected DHA **2b** were selected to represent the acyclic and cyclic DHA donors, respectively.

(3) (a) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210−1212. (b) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383−1385. (c) Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363−3367. (d) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077−4079. (e) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079−4083. (f) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *J. Org. Chem.* **2006**, *71*, 3822−3828. (g) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383−5397. (h) Ibrahem, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 211−222. (i) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329−337. (j) Grondal, C.; Enders, D. *Adv. Catal. Synth.* **2007**, *349*, 694−702. For other organocatalytic de novo syntheses of sugars, see: (k) Chowdar, N. S.; Ramachary, D. B.; Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591−9595. (l) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752−1755. (m) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343−1345.

(4) For direct aldol reaction of free DHA with rather low stereoselectivity or racemic products, see ref 3g and: (a) Cordova, A.; Notz, W.; Barbas, C. F., III. *Chem. Commun.* **2002**, 3024−3025. (b) Market, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. *J. Am. Chem. Soc.* **2007**, *129*, 7258−7259. (c) Kofoed, J.; Darbre, T.; Reymond, J.-L. *Chem. Commun.* **2006**, 1482−1484.

(5) (a) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572−5575. (b) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III. *Org. Lett.* **2007**, *9*, 3445−3448.

(6) (a) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074−3075; For other organocatalytic *syn*-aldol reactions, see: (b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288−289. (c) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738−1740. (d) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812−816.

A series of chiral primary amine catalysts were first tested in the reactions of **2a**. It was found that the primary−tertiary diamines such as chiral *trans-N,N*-dialkylated diaminocyclohexanes **1** demonstrated activity and stereoselectivity superior to that obtained with other primary amine catalysts (see the Supporting Information for details). For example, *trans-N,N*-dimethyldiaminocyclohexane **1a** was observed to catalyze the reaction very smoothly, affording preferentially the *syn*-aldol product with 92% ee (Table 1, entry 1). Further

**Table 1.** Selected Screening Results
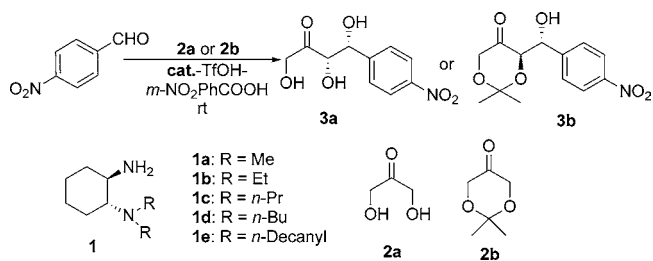


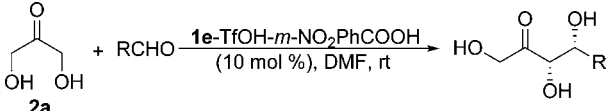| entry[a] | cat. (mol %) | time (h) | yield[b] (%) | syn/anti[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **1a** (20) | 19 | **3a**/60 | 90:10 | 92 |
| 2 | **1b** (20) | 19 | **3a**/60 | 87:13 | 94 |
| 3 | **1c** (20) | 19 | **3a**/91 | 95:5 | 98 |
| 4 | **1c** (20)[e] | 19 | **3a**/9 | 75:25 | 29 |
| 5 | **1c** (20)[f] | 19 | **3a**/85 | 95:5 | 97 |
| 6 | **1d** (20) | 19 | **3a**/68 | 93:7 | 96 |
| 7 | **1e** (20) | **19** | **3a**/99 | **97:3** | **99** |
| 8 | **1e** (10)[g] | 19 | **3a**/97 | 97:3 | 99 |
| 9 | **1a** (10) | 48 | **3b**/65 | 1:6 | 92 |
| 10 | **1b** (10) | 48 | **3b**/78 | 1:6 | 95 |
| 11 | **1c** (10) | 48 | **3b**/47 | 1:4 | 91 |
| 12 | **1e** (10) | 48 | **3b**/5 | not determined | |
| 13 | **1b** (10)[h] | **17** | **3b**/90 | **1:6** | **94** |

[a] Entries 1−7: 0.25 mmol reaction in DMSO in the presence of **cat**./TfOH/*m*-NO$_2$PhCOOH (1:1:1). Entries 9−12: 0.25 mmol reaction in CH$_2$Cl$_2$ in the presence of Cat/TfOH/*m*-NO$_2$PhCOOH (1:1:1). [b] Isolated yields. [c] Determined by $^1$H NMR or chiral HPLC. [d] ee of major isomer, determined by chiral HPLC. [e] Without TfOH and *m*-NO$_2$PhCOOH. [f] Without *m*-NO$_2$PhCOOH. [g] 10 mol % of catalyst system in DMF. [h] Under neat conditions

screening of the analogous catalysts bearing longer alkyl chains led to improved yields and stereoselectivity (Table 1, entries 2, 3, 6, and 7). The best results were obtained with the *N,N*-didecanyl derivative **1e**. Under the catalysis of **1e**, the product was isolated with a dr (syn/anti) value greater than 30:1, an ee value greater than 99%, and a quantitative yield (Table 1, entry 7). Consistent with our earlier observations, a strong Brønsted acid such as TfOH was essential for the catalysis as the reaction in the absence of TfOH was observed to give only 9% yield and poor stereoselectivity (syn/anti = 75:25, 29% ee, entry 4), suggesting a bifunctional enamine catalysis rather than a tertiary amine mediated process in our reactions.[4b] Addition of a second weak Brønsted acid could further improve the yield (Table 1, entry 3 vs 5). The reaction was further optimized to use 10 mol % of **1e** in DMF and still offered good results under these conditions (Table 1, entry 8).

Next, the direct aldol reactions of cyclic DHA **2b** were examined. The primary−tertiary diamine catalyst **1** was again found to be the optimal catalyst (for details, see the Supporting Information), affording *anti*-aldol products. The diamine catalysts (**1a**−**e**) with varied alkyl chains all gave good anti diastereoselectivity and high ee values, of which **1b** exhibited the best activity (Table 1, entry 10).

Under optimized conditions, the reaction was completed in 17 h in the presence of 10 mol % **1b**, yielding 90% of the anticipated products with 6:1 dr and 94% ee. In most cases, the current catalysis demonstrated significant improvement over previous results that required 20−30 mol % of catalyst loading and 2−3 days of reaction time.[3a−c]

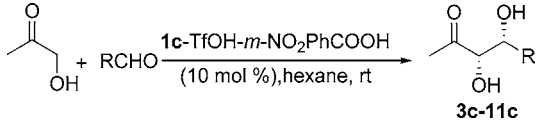**Table 2.** *syn*-Aldol Reaction of Free DHA **2a**



| entry[a] | R | time (h) | yield[b] (%) | syn/anti[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | 4-NO$_2$Ph | 19 | **3a**/97 | 97:3 | 99 |
| 2 | 2-NO$_2$Ph | 36 | **4a**/93 | 97:3 | 98 |
| 3 | 3-NO$_2$Ph | 36 | **5a**/91 | 97:3 | 98 |
| 4 | 4-CF$_3$Ph | 34 | **6a**/60 | 97:3 | 98 |
| 5 | 4-ClPh | 60 | **7a**/61 | 96:4 | 98 |
| 6[e] | 1-Napth | 60 | **8a**/40 | 98:2 | 98 |
| 7 | 4-CNPh | 40 | **9a**/74 | 97:3 | 96 |
| 8[e] | 3-BrPh | 96 | **10a**/50 | 99:1 | 84 |
| 9[e] | Ph | 84 | **11a**/43 | 92:8 | 85 |

*[a]* 0.25 mmol reaction in DMF. *[b]* Isolated yields. *[c]* Determined by chiral HPLC. *[d]* ee of syn isomer, determined by chiral HPLC. *[e]* 20 mol % of catalyst was used.

We next investigated the substrate scope of both *syn*-aldol reactions (Tables 2 and 3) and the *anti*-aldol reactions (Table

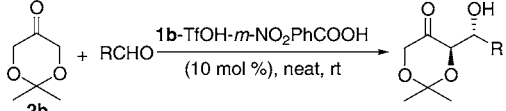**Table 3.** *syn*-Aldol Reaction of Acyclic Hydroxyacetone



| entry[a] | R | time (h) | yield[c] (%) | syn/anti[d] | ee[e] (%) |
|---|---|---|---|---|---|
| 1[b] | 4-NO$_2$Ph | 15 | **3c**/25 | 93:7 | 96 |
| 2 | 4-NO$_2$Ph | 15 | **3c**/>99 | 94:6 | 96 |
| 3 | 4-CF$_3$Ph | 18 | **4c**/99 | 88:12 | 91 |
| 4 | 4-CNPh | 18 | **5c**/88 | 91:9 | 88 |
| 5 | 2-NO$_2$Ph | 36 | **6c**/91 | 99:1 | 99 |
| 6 | 4-ClPh | 36 | **7c**/92 | 88:12 | 92 |
| 7 | 2-ClPh | 36 | **8c**/99 | 89:11 | 95 |
| 8 | 2-BrPh | 36 | **9c**/92 | 94:6 | 93 |
| 9 | Ph | 36 | **10c**/99 | 94:6 | 91 |
| 10[e] | 4-MeOPh | 36 | **11c**/50 | 94:6 | 93 |

*[a]* 0.25 mmol reaction. *[b]* Reaction in DMF. *[c]* Isolated yields. *[d]* Determined by ¹H NMR. *[e]* ee of syn isomer, determined by chiral HPLC.

4). In the catalysis of **1e**−TfOH−*m*-NO$_2$PhCOOH (10 mol %), reactions of the unprotected DHA **2a** with a variety of

**Table 4.** *anti*-Aldol Reaction of Cyclic DHA **2b**



| entry[a] | R | time (h) | yield (%)[b] | syn:anti[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | 4-NO$_2$Ph | 17 | **3b**/90 | 1:6 | 94 |
| 2 | 2-NO$_2$Ph | 24 | **4b**/99 | 1:4 | 95 |
| 3 | 3-NO$_2$Ph | 12 | **5b**/95 | 1:5 | 95 |
| 4 | 4-CF$_3$Ph | 13 | **6b**/83 | 1:4 | 94 |
| 5 | 4-CNPh | 30 | **7b**/78 | 1:4 | 97 |
| 6 | 4-PhPh | 20 | **8b**/85 | 1:5 | 85 |
| 7[e] | 4-ClPh | 60 | **9b**/40 | 1:4 | 87 |
| 8[e] | BnOCH$_2$ | 60 | **10b**/90 | <1:10 | 80 |
| 9[e] | | 72 | **11b**/83 | ---- | 65 |

*[a]* 0.25 mmol reaction. *[b]* Isolated yields. *[c]* Determined by ¹H NMR. *[d]* ee of anti isomer, determined by chiral HPLC. *[e]* 20 mol % of catalyst was used.

aldehyde acceptors produced the desired products in high yields with excellent diastereo- and enantioselectivity. Significantly, all reactions gave excellent syn diastereoselectivity (syn/anti >30:1) and high enantioselectivity (84−99% ee). The reaction of acyclic hydroxyacetone has also been examined (Table 3). Though the reaction gave a low yield in DMF, excellent syn diastereoselectivity and enantioselectivity were still achieved (Table 3, entry 1).[7]

The switch to nonpolar solvents such as hexane led to significantly improved yield (Table 3, entry 2), a result ascribale to the increased reactant concenction as both the reactants and catalysts are less soluble in hexane.[8] In this case, catalyst **1c** gave slightly better yield than that of **1e**. High syn selectivity was consistently obtained in the reactions of hydroxyacetone (Table 3, entries 2−10), validating our hypothesis (Scheme 1).

In regard to the cyclic DHA donors (Table 4), the reactions of cyclic DHA **2b** in the presence of **1b** generated *anti*-aldol products (up to >10:1 anti/syn) with excellent enantioselectivity (up to 97% ee) and high yields (up to 99%). Aliphatic aldehydes have also been tried for both the *syn*- and *anti*-aldol reactions but gave lower yields due to side reactions. The catalytic system of **1b** also catalyzed the dimerization of **2b**, giving a good yield but a moderate ee (Table 4, entry 9).

We obtained the X-ray crystal structure of product **7c** (Figure 1),[9] which proved the (3S,4R) configurations of the

(7) For examples on organocatalytic *anti*-aldol reactions of hydroxyacetone, see: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem. Eur. J.* **2007**, *13*, 689. For *syn*-aldol reaction of hydroxyacetone, see refs 5, 6, and: (d) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247−4249.

(8) The reaction under solvent-free conditions exhibited a faster rate but somehow lower enantioselectivity: 4 h, 91% yield, 89:11 syn/anti, 89% ee.
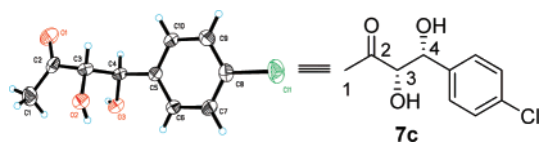
**Figure 1.** X-ray crystal structure of **7c**.

*syn* product. The configurations of other *syn*-aldol products can therefore be referred. The absolute configurations (as drawn in Scheme 1) of the *anti*-aldol products were assigned by HPLC and optical rotation comparisons with published results (see the Supporting Information for details).[3,5,10]

To conclude, we have developed here a group of highly efficient and stereoselective *syn*- and *anti*-aldol reactions of dihydroxyacetones catalyzed by the simple primary−tertiary

diamine−Brønsted acid catalysts. Since the enantiomers of catalysts **1** are easily accessible, this specific type of small molecular catalysts may thus functionally mimic all the four DHA aldolases in living systems. It is noted that the current catalysis complements the enzymatic processes by working selectively with aromatic aldehyde acceptors. This study also provides one of the most efficient de novo syntheses of sugars via organocatalysis. Further explorations along this line are currently underway.

(9) Crystal data for **7c**: $C_{10}H_{11}ClO_3$, colorless block, $M_r$ = 214.64, crystal size $0.29 \times 0.17 \times 0.08$ mm$^3$, orthorhombic, space group $P2(1)/c$, $a$ = 8.5744(17) Å, $b$ = 5.6867(11) Å, $c$ = 10.986(2) Å, $\alpha$ = 90.00°, $\beta$ = 104.5°, $\gamma$ = 90.00°, $V$ = 518.59(18) Å$^3$, $Z$ = 2, $\rho_{calcd}$ = 1.375 g cm$^{-3}$, $T$ = 296(2) K. A total of 1882 reflections and 1652 parameters were used for the full-matrix, least-squares refinement on F2. R1 = 0.0675 [$I > 2\sigma(I)$], R1 = 0.0757 (all data), wR2 = 0.1536 [$I > 2\sigma(I)$], wR2 = 0.1581 (all data).

(10) Enantiomers of catalysts **1**, e.g., (*S,S*)-**1b** and -**1e**, have also been tried in the reactions, which gave products with opposite configurations to those of the products **3**−**11**. Both enantiomers were compared with known compounds by HPLC analysis. For known compounds, see ref 3f,h and: Enders, D.; Prokopenko, O. F.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 1095.