

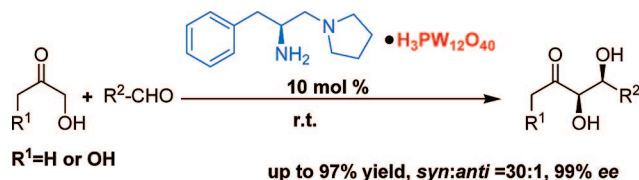
Chiral Primary–Tertiary Diamine Catalysts Derived From Natural Amino Acids for *syn*-Aldol Reactions of Hydroxy Ketones

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A series of primary-tertiary diamine catalysts were designed and synthesized from primary natural amino acids. Application of these new chiral catalysts in direct aldol reactions of α -hydroxyketones showed very good catalytic activity (up to 97% yield) and high *syn* selectivity (up to *syn/anti* = 30:1, 99% ee).

The aldol reaction has long been recognized as a useful strategy to construct various C–C bonds in organic synthesis.¹ The past decade has witnessed the extraordinary success of chiral amines, particularly chiral pyrrolidines, as efficient enamine-based asymmetric direct aldol catalysts.² In this context, the identification of chiral primary amine catalysts represents one of the recent prominent progresses. Barbas, Gong, and this group have independently reported a number of chiral primary amine catalysts that enabled *syn*-aldol reactions of ketones.³ Despite these notable achievements, development of simple and new catalysts for efficient *syn*-aldol reactions is still highly desired.^{2b}

Natural amino acids provide a versatile chiral pool for evolution of organocatalysts as evidenced by the rapid accumulation of various L-proline-based chiral pyrrolidine catalysts.⁴ However, primary amino acids (the other 20 amino acids) seem to be almost overlooked for this kind of catalysts, due partially to the initial findings of their ineffectiveness in catalyst screening processes and also to the assumed unfavorable

imine–enamine isomerization.^{2e,5} In recent years, the application of primary amino acid derivatives in organocatalysis has received rapidly growing attention because of the increasing recognition of their relationship to biogenesis,⁶ their rediscovered effectiveness in aldol catalysis,⁷ and their unprecedented *syn* stereoselectivity in some direct aldol reactions.³ In the latter cases, primary amino acids conjugated with additional chiral building blocks were proven to be promising catalysts.^{3d} Simple primary amino acid derivatives, such as chiral vicinal diamines, remain much less explored, however, though they have been applied as chiral ligands in asymmetric catalysis⁸ or used as iminium-type organocatalysts previously.⁹ In only one case was the primary–tertiary diamine–Brønsted acid conjugate examined for asymmetric catalysis of direct aldol reactions. Unfortunately, poor yield and stereoselectivity were obtained.^{10b} Here, we report a class of primary diamine catalysts derived from

(2) For reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591. (b) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. For selected examples of *anti*-aldol reactions, see: (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152. (d) Casas, J.; Engqvist, M.; Ibrahim, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343. (e) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (f) Córdova, A.; Zou, W.; Ibrahim, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (g) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (h) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210. (i) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383. (j) Ibrahim, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363. (k) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (l) 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. (m) 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. (n) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141. (o) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (p) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (q) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (r) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (s) Cheng, C.; Sun, J.; Wang, C.; Zhang, Y.; Wei, S.; Jiang, F.; Wu, Y. *Chem. Commun.* **2006**, 215–217. (t) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Chen, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543.

(3) For examples of *syn*-aldol reactions of ketones, see: (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. (b) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075. (c) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572–5575. (d) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247–4249. (e) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F., III. *Org. Lett.* **2007**, *9*, 3445–3448. (f) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F., III. *Org. Lett.* **2008**, *10*, 1621–1624. (g) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653–656. (h) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775–1778. (i) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1390–1396.

(4) For reviews, see: (a) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. For selected examples, see ref 10 and: (b) 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*, 9285–9289. (c) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093–3097. (d) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435–1439. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (f) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (g) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082–2084. (h) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.

(5) Bahmanyar, B.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283.

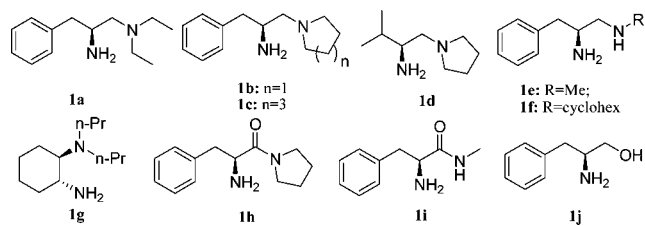
(6) Klusmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621–623. (b) Klusmann, M.; Izumi, T.; White, A. J. P.; Armstrong, A.; Klackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 7657–7660.

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[‡] Nankai University.

(1) For reviews on direct aldol reactions, see: (a) *Modern Aldol Additions*; Mahrwald, R., Eds.; Wiley-VCH: Weinheim, 2004. (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem.—Eur. J.* **2002**, *8*, 36–44. (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.

SCHEME 1. Catalysts Examined in This Study



natural amino acids to give highly efficient and enantioselective *syn*-aldol reactions of α -hydroxyketones (Scheme 1).

Chiral primary vicinal diamines were easily synthesized according to the typical procedure in the literature.^{9a,10b} After trial and error, we were delighted to find that the simple diamine–Brønsted acid conjugate could promote the direct aldol reaction of α -hydroxyketone. As is well-known, aldol reaction of hydroxyacetone is a versatile route to construct the 1,2-diol building blocks for the synthesis of various natural and biological active molecules.¹¹ In this work, we selected the aldol reaction of hydroxyacetone and *p*-nitrobenzaldehyde as a model reaction to evaluate the diamine catalysts. Interestingly, *syn* diastereoselectivity was observed in the catalysis of **1b**·TfOH,

(7) For selected primary amino acid catalyzed direct aldol reactions, see: (a) Sakathivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267. (b) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028–7032. (c) Córdova, A.; Zou, W.; Ibrahim, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586–3588. (d) Córdova, A.; Zou, W.; Ibrahim, I.; Reyes, E.; Dziedzic, P. *Chem.—Eur. J.* **2006**, *12*, 5383–5397. (e) Deng, D.-S.; Cai, J. *Helv. Chim. Acta* **2007**, *90*, 114–120. (f) Dziedzic, P.; Zou, W.; Ibrahim, I.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 6657–6661. (g) Lombardo, M.; Easwar, S.; Pasi, F.; Trombini, C.; Dhavale, D. D. *Tetrahedron* **2008**, *64*, 9203–9207. (h) Davies, S. G.; Sheppard, R. L.; Smith, A. D. *Chem. Commun.* **2005**, 3802–3804. (i) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654–5655. (j) Dziedzic, P.; Zou, W.; H'afren, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38–40. (k) Zou, W.; Ibrahim, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946–4948. (l) Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947–1951. (m) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluhackova, K.; Kocovsky, P. *Org. Lett.* **2007**, *9*, 5473–5476. (n) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812–816. (o) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801–2803. For a recent review, see: (p) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.

(8) Ito, M.; Hirakawa, M.; Murata, K.; Ikariya, T. *Organometallics* **2001**, *20*, 379–381.

(9) (a) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504–10505. (b) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893–2896. (c) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930–8931.

(10) For reviews, see: (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579. For examples, see: (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177. (c) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559. (d) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967. (e) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734–735. (f) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625. (g) Gryko, D.; Zimnicka, M.; Lipiński, R. *J. Org. Chem.* **2007**, *72*, 964–970. (h) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zheng, X.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 11307–11314. (i) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423. (j) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199–2204.

(11) For reviews, see: (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, Germany, 2003; and references cited therein. For efforts to construct 1,2-diols, see ref 3 and: (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467. (c) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178. (d) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368. (e) Shabat, D.; List, B.; Lerner, R. A.; Barbas, C. F., III. *Tetrahedron Lett.* **1999**, *40*, 1437–1440. (f) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1999**, *4*, 881–885. (g) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571. (h) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291. (i) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

TABLE 1. Screening of Catalysts in Aldol Reaction of Hydroxyacetone

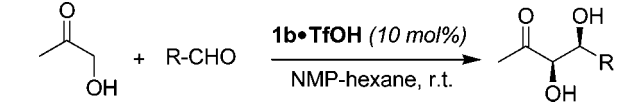
entry ^a	amine	solvent	yield ^b (%)	syn/anti ^c	ee ^d (%)
1	1b	toluene	90	9:1	83
2	1b	<i>n</i> -hexane	94	8:1	81
3	1b	DMF	34	8:1	94
4	1b	MeOH	16	10:1	94
5	1b	NMP	41	10:1	96
6	1b	neat	82	4:1	86
7	1b	NMP- <i>n</i> -hexane	81	7:1	94
8	1a	NMP- <i>n</i> -hexane	66	6:1	85
9	1c	NMP- <i>n</i> -hexane	71	6:1	89
10	1d	NMP- <i>n</i> -hexane	82	7:1	91
11	1e	NMP- <i>n</i> -hexane	48	3:1	90
12	1f	NMP- <i>n</i> -hexane	55	4:1	91
13	1g	NMP- <i>n</i> -hexane	83	12:1	93
14	1h	NMP- <i>n</i> -hexane	55	2:3	76/62 ^e
15	1i	NMP- <i>n</i> -hexane	52	1:1	46/76 ^e
16	1j	NMP- <i>n</i> -hexane	97	2:1	25

^a Unless otherwise stated, 0.25 mmol of aldehyde with 0.5 mmol of hydroxyacetone in 0.2 mL of solvent. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Determined by HPLC. ^e ee for anti product.

and the related reactions were found to be highly solvent-dependent. In nonpolar solvents such as *n*-hexane and toluene, the reactions proceeded quite smoothly, giving high product yield but moderate enantioselectivity (Table 1, entries 1 and 2). In polar solvents such as DMF, NMP, and methanol, though the reactions were much slower than those in less polar solvents, higher enantioselectivity was observed (Table 1, entries 3–5). Further examination indicated that a mixed solvent such as NMP-*n*-hexane (1:1, v/v) gave optimal results in terms of both the yield and selectivity (Table 1, entry 7). Consequently, NMP-*n*-hexane (1:1, v/v) was selected for subsequent optimization. Other acidic additives were also examined, and TfOH was found to give optimal results.

The reactions were further optimized using different chiral amines. As shown in Table 1, the primary–tertiary diamine catalysts **1a–d** (derived from either L-phenylalanine or L-valine) all worked well under the present conditions, among which **1b** gave the optimal results (Table 1, entry 7). Other primary amine catalysts such as primary–secondary diamines **1e** and **1f**, amino alcohol **1j**, and the amide-type catalysts **1h** and **1i** have also been tested in the present reaction. They generally exhibited inferior selectivity and activity (Table 1, entries 11–15). These results highlighted the importance of the primary–tertiary diamine skeleton for effective aldol catalysis. Under the optimal conditions, the reaction catalyzed by **1b**·TfOH gave 81% yield, 7:1 *syn/anti*, and 94% ee, which is comparable to those of the reaction with **1g**·TfOH (Table 1, entry 13).

The application of catalyst **1b**·TfOH in the aldol reaction of hydroxyacetone was next examined. The reaction worked well with aromatic aldehydes bearing either electron-withdrawing or electron-donating groups to give highly *syn*-selective aldol adducts and good enantioselectivity (91–97% ee) at room temperature. Slightly higher diastereoselectivity was generally observed with *ortho*-substituted aromatic aldehydes (Table 2, entries 3 and 7). Notably, aliphatic aldehydes were also applied in the present reactions offering *syn*-selective aldol adducts with high enantioselectivity. For example, the reaction of cyclohex-

TABLE 2. **1b**·TfOH-Catalyzed Aldol Reaction of Hydroxyacetone


entry ^a	R	time (h)	yield ^b (%)	syn/anti ^c	ee ^d (%)
1	4-NO ₂ Ph	24	2a /81	7:1	94
2	3-NO ₂ Ph	48	2b /94	6:1	94
3	2-NO ₂ Ph	48	2c /87	10:1	96
4	4-CF ₃ Ph	48	2d /97	8:1	93
5	4-CNPh	48	2e /92	6:1	93
6	4-ClPh	72	2f /78	8:1	91
7	2-BrPh	72	2g /82	10:1	95
8	cyclohexane	72	2h /54	7:1	93
9	2-phenylpropanal	48	2i /56	10:1 ^e	93
10	2, 2'-dimethoxyacetaldehyde	48	2j /55	3:1	80

^a Unless otherwise stated, 0.25 mmol of aldehyde with 0.5 mmol of hydroxyacetone in 0.2 mL of solvent. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Determined by HPLC. ^e For -Me, dr = 3.5:1.

anecarbaldehyde gave the desired product with 7:1 syn/anti, 93% ee, and 54% yield (Table 2, entry 9).

In light of the above results, we further examined one other important α -functionalized ketone, dihydroxyacetone (DHA). DHA and its derivatives are versatile building blocks in the chemical and enzymatic synthesis of carbohydrate.¹² Though DHA derivatives as aldol donors have been achieved via organocatalysis,¹³ direct aldol reaction of free DHA remained unsolved until Barbas's finding that primary amino acid could catalyze the *syn*-aldol reaction of DHA.^{3c,e,14} To our delight, we found that **1b**·TfOH could also catalyze the aldol reaction of DHA in NMP with high yield and selectivity (Table 3, entry 1). Other acidic additives were also examined, and the use of polyoxometalate H₃PW₁₂O₄₀, a promising solid acid support for chiral amine catalysts,¹⁵ provided the best results in terms of both the yield and selectivity (Table 3, entry 3). Significantly, the **1b**-POM hybrid catalyst can precipitate out from the reaction mixture and be easily recycled.¹⁵ The recovered catalyst could be reused up to four times while maintaining high enantioselectivity with a decrease of product yield in the third and fourth run (Table 3, entries 4–6). The reactions using other primary–tertiary diamine catalysts including diamine **1g** developed earlier from this laboratory^{3b} gave inferior results under the present conditions (Table 3, entries 7–10).

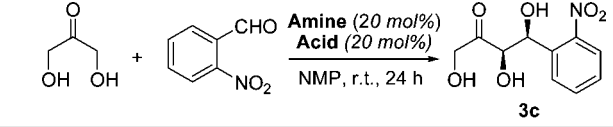
(12) For reviews, see: (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304–1325. (b) Gijzen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443–473.

(13) For selected aldol reactions of protected DHA, see: (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) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077–4079. (d) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079–4083. (e) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *J. Org. Chem.* **2006**, *71*, 3822–3828. (f) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahim, I.; Reyes, E.; Xu, Y. *Chem.–Eur. J.* **2006**, *12*, 5383–5397. (g) Ibrahim, I.; Zou, W.; Xu, Y.; Córdova, A. *Adv. Synth. Catal.* **2006**, *348*, 211–222. (h) 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.; Ibrahim, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343–1345.

(14) For early examples of direct aldol reaction of free DHA, see ref 11f and: (a) Córdova, 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.; Raymond, J.-L. *Chem. Commun.* **2006**, 1482–1484.

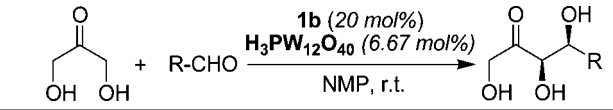
(15) (a) Luo, S.; Li, J.; Xu, H.; Zhang, L.; Cheng, J.-P. *Org. Lett.* **2007**, *9*, 3675–3678. (b) Li, J.; Hu, S.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2009**, 132–140.

TABLE 3. Screening of Catalysts in the Aldol Reaction of DHA



entry ^a	amine	acid	yield ^b (%)	syn/anti ^c	ee ^d (%)
1	1b	TfOH	94	30:1	99
2	1b	TFA	57	24:1	98
3	1b	H ₃ PW ₁₂ O ₄₀	97	30:1	99
4 ^e	1b	H ₃ PW ₁₂ O ₄₀	92	19:1	98
5 ^e	1b	H ₃ PW ₁₂ O ₄₀	82	24:1	95
6 ^e	1b	H ₃ PW ₁₂ O ₄₀	78	13:1	95
7	1a	H ₃ PW ₁₂ O ₄₀	83	19:1	96
8	1c	H ₃ PW ₁₂ O ₄₀	94	16:1	92
9	1d	H ₃ PW ₁₂ O ₄₀	87	16:1	93
10	1g	H ₃ PW ₁₂ O ₄₀	95	24:1	27

^a Unless otherwise stated, 0.25 mmol of aldehyde with 0.5 mmol of dihydroxyacetone in 0.2 mL of NMP, 6.67 mol % of H₃PW₁₂O₄₀ was used in entries 3–10. ^b Isolated yield. ^c Determined by HPLC. ^d Determined by HPLC. ^e Second, third, and fourth reuse.

TABLE 4. **1b**-POM Hybrid Catalyzed Aldol Reaction of DHA


entry ^a	R	time (h)	yield ^b (%)	syn/anti ^c	ee ^d (%)
1	4-NO ₂ Ph	24	3a /95	30:1	95
2	3-NO ₂ Ph	24	3b /90	13:1	94
3	2-NO ₂ Ph	24	3c /97	30:1	99
4	4-CF ₃ Ph	36	3d /92	24:1	96
5	4-CNPh	36	3e /86	16:1	91
6	4-ClPh	72	3f /59	8:1	91
7	3-BrPh	72	3g /86	19:1	84
8	1-Naph	72	3h /61	24:1	95

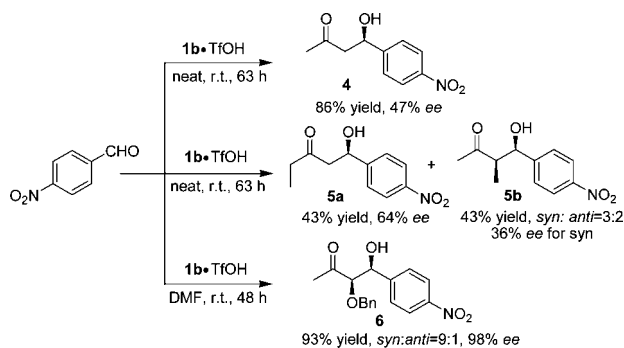
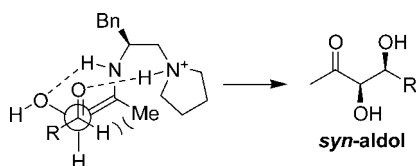
^a Unless otherwise stated, 0.25 mmol of aldehyde with 0.5 mmol of dihydroxyacetone in 0.2 mL of NMP. ^b Isolated yield. ^c Determined by HPLC. ^d Determined by HPLC.

With the identified catalyst **1b**, we next explored the scope of aldol reaction of DHA. As shown in Table 4, the reaction could be applied to a range of aromatic aldehydes to afford mainly the *syn* selective aldol adducts with high yields and excellent enantioselectivities at room temperature (Table 4). Unfortunately, the reaction with aliphatic aldehydes gave poor results due likely to the self-condensation reactions.

Other linear ketones, such as acetone, butanone, and benzyloxyacetone, were also tested with the optimal catalyst **1b**·TfOH. While both acetone and butanone provided only poor selectivity, the reaction of benzyloxyacetone exhibited high *syn* selectivity with up to 98% ee (Scheme 2).

The absolute configurations of the *syn*-aldol products were determined by comparison of the optical rotation value and HPLC traces with the known compounds.^{3g} Consistent with previous reports, the high *syn* selectivity could be explained by a *Z*-enamine transition state (Scheme 3).^{3b,4a} In this model, the N–H···O hydrogen bond was assumed to play a critical role for stabilizing the *Z*-enamine, consequently leading to high *syn* selectivity.^{3a} The observed lower selectivity with acetone and butanone, wherein the intramolecular N–H···O hydrogen bonds are absent, is clearly in line with this hypothesis.

In conclusion, we have developed a class of primary–tertiary diamine catalysts derived from natural amino acids that work effectively with α -hydroxyketones as *syn*-selective aldol cata-

SCHEME 2. 1b-Catalyzed Aldol Reaction of Linear Aliphatic Ketones

SCHEME 3. Transition State of *syn*-Aldol Reaction


lysts. Simple primary–tertiary diamine–Brønsted acids conjugates **1b**·TfOH and **1b**–POM were found to be the optimal catalysts that render *syn*-aldol reactions of hydroxyketone with up to 97% yield, 30:1 *syn*/*anti*, and 99% ee. Taking advantage of biphasic properties of POM ($\text{H}_3\text{PW}_{12}\text{O}_{40}$), the **1b**–POM hybrid catalyst can be easily recycled and reused four times.

Experimental Section

Procedure for the Aldol Reaction of Hydroxyacetone. Catalyst **1b**·TfOH (8.9 mg, 0.025 mmol), hydroxyacetone (37 mg, 0.5 mmol), and 4-nitrobenzaldehyde (0.25 mmol) were mixed together in 0.2 mL of *n*-hexane–NMP (1:1, v/v) at room temperature. The mixture was stirred for 24 h and directly purified by flash chromatography carefully to afford the aldol adducts **2a** (46 mg) as white solid. Yield: 81%. ^1H NMR (300 MHz, CDCl_3): δ 2.36 (3 H, s), 2.69 (1 H, d), 3.70 (1 H, d), 4.41 (1 H, d), 5.20 (1 H, d), 7.60–7.63 (2 H, d), 8.23–8.26 (2 H, d). ^{13}C NMR (75 MHz, CDCl_3): δ 26.0, 73.0, 80.0, 123.8, 127.2, 147.3, 157.8, 208.3. The enantiomeric excess was determined by HPLC (AD-H column, 254

nm, 2-propanol/*n*-hexane = 1:4 as eluent, 25 °C, 0.8 mL/min), t_R = 12.74 min (minor *syn* isomer), t_R = 16.72 min (major *syn* isomer), 94% ee (absolutely configuration: 3*R*,4*S*). Aldol products **2a–h**^{3a,d,g} and **4–6**^{3g,2m,t} have been reported; **2i,j** were new compounds, and their detailed characterization data are provided in the Supporting Information.

Procedure for the Aldol Reaction of Free DHA. To 0.2 mL of NMP were added **1b** (8.2 mg, 0.050 mmol) and $\text{H}_3\text{PW}_{12}\text{O}_{40}$ (48 mg, 0.0167 mmol). After the mixture was stirred for 10 min, DHA (45 mg, 0.5 mmol) and 2-nitrobenzaldehyde (0.25 mmol) were added. The homogeneous mixture was stirred for 24 h at room temperature. Ethyl ether was then added to precipitate the catalyst. The catalyst was washed three times with ethyl ether and then directly used for the next run. The combined organics were concentrated and purified by flash chromatography carefully to afford **3c** and then peracetylated with pyridine/ Ac_2O to afford 89 mg of colorless product. Yield: 97%. ^1H NMR (300 MHz, CDCl_3): δ 1.97 (3 H, s), 2.07 (3 H, s), 2.12 (3 H, s), 4.78–4.93 (2 H, m), 5.85 (1 H, d), 6.87 (1 H, d), 7.44–7.46 (1 H, m), 7.48–7.60 (2 H, m), 8.03–8.06 (1 H, d). ^{13}C NMR (75 MHz, CDCl_3): δ 20.2, 20.3, 20.6, 66.4, 69.5, 76.4, 125.2, 128.9, 129.5, 131.9, 133.5, 147.4, 169.2, 169.9, 196.8. The enantiomeric excess was determined by HPLC (AD-H column, 254 nm, 2-propanol/*n*-hexane = 1:9 as eluent, 0.8 mL/min) with free aldol adduct, t_R = 32.59 (major *anti* isomer), t_R = 36.23 (minor *anti* isomer), t_R = 38.89 (major *syn* isomer), t_R = 44.78 (minor *syn* isomer), 99% ee (absolutely configuration: 3*R*,4*S*). Free aldol adducts **3a–h** have been reported by our group,^{3g} peracetylated **3a–e,g,h** were known compounds,^{3c,i} and peracetylated **3f** was a new compound.

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Supporting Information Available: Synthesis of catalysts, general experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) In many cases, the free DHA is difficult to separate completely from the products.