JOC*Note*

Rational Combination of Two Privileged Chiral Backbones: Highly Efficient Organocatalysts for Asymmetric Direct Aldol Reactions between Aromatic Aldehydes and Acylic Ketones

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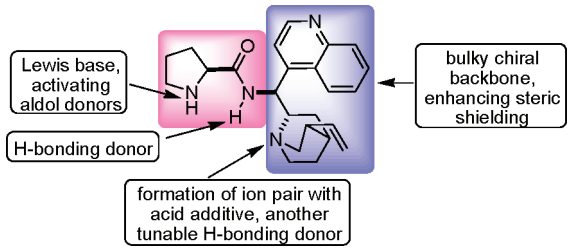

A new class of organocatalysts has been designed by rational combination of proline with cinchona alkaloids. The chiral amine **3a**, prepared from L-proline and cinchonidine, has been found to be an efficient catalyst for the direct aldol reactions of acetone or 2-butanone with a wide range of aldehydes (up to 98% ee). The cinchonidine backbone is essential to the reaction efficiency and enantioselectivity.

Since 2000, the capacity to catalyze enantioselective transformations with organic small molecules has remained a focal point for extensive research efforts in the field of asymmetric catalysis.[1] In particular, the use of chiral secondary amine as catalysts has proven to be a powerful protocol for stereoselective functionalizations of carbonyl compounds.[2–5] In this active research field, the asymmetric direct aldol reactions, which provide straightforward access to the optically active β-hydroxy carbonyl structural unit found in many natural products drugs,[6] have received remarkable attention. Since the pioneering work by Barbas,[7a] List,[7b,c] and co-workers that L-proline could act as an efficient catalyst for direct aldol reaction between acetone and aldehydes, a number of proline derivatives have been developed for this enantioselective transformation.[2c,8,9] According to the Houk−List model[10] and Gong's work[9c,d] the hydrogen bonding donor in proline and its analogues is crucial to the catalytic activity and selectivity. In our continuing efforts to develop readily tunable and highly enantioselective organocatalysts,[11] we recently designed a series of bifunctional organocatalysts based on the proline catalysis concept and double hydrogen bonding activation. For example, the catalysts **1** and **2** show superior catalytic activities for the aldol reactions

(1) (a) For general reviews on organocatalysis, see : Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis; From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (c) *Enantioselective Organocatalysis*; P. I. DalkoP. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (d) Enders, C.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (e) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. See also special issues on asymmetric organocatalysis: (f) *Acc. Chem. Res.* **2004**, *37*, issue 8. (g) *Adv. Synth. Catal.* **2004**, *346*, issue 9−10. (h) *Chem. Rev.* **2007**, *107*, issue 12.

(2) Reviews on enamine catalysis, see:(a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev* **2007**, *107*, 5407. (d) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. references cited therein.

(3) For an excellent recent review on iminium ion activation, see: Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

(4) For review on enamine-SOMO activation mode, see:(a) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7356. For pioneering examples, see: (b) Beeson, T. D.; Mastracchio, A.; Hong, J.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (c) Jang, H.; Hong, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (d) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124.

(5) Dienamine activation mode, see:(a) Hong, B.; Wu, M.; Tseng, H.; Liao, J. *Org. Lett.* **2006**, *8*, 2217. (b) Bertelsen, S.; Marigo, M.; Brandes, S.; DinIr, P.; Jørgensen; K. A, *J. Am. Chem. Soc.* **2006**, *128*, 12973, and references cited therein.

(6) For a review, see: *Modern Aldol Reactions*; Mahrwald, R, Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2.

(7) (a) Sakthievel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(8) For recent reviews on chiral secondary amine-catalyzed aldol and related reactions, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Guillena, G.; Nàjera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (d) List, B. *Chem. Commun.* **2006**, 819. (e) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2008**, *47*, 42.

(9) For representative examples of organocatalytic aldol reactions, see:(a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Northrup, A. B.; Mangion, I. K.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152. (c) Tang, Z.; Jiang, F.; Yu, L.-T.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (d) Tang, Z.; Tang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (e) Torri, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamota, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (f) Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343. (g) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247. (h) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141. (i) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (j) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (k) Gryko, D.; Lipinski, R. *Adv. Synth. Catal.* **2005**, *347*, 1948. (l) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (m) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055. (n) Krattiger, P.; Kovàsy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101. (o) Samanta, S.; Zhao, C.-G. *Tetrahedron Lett.* **2006**, *47*, 3383. (p) Gu, L.; Yu, M.; Wu, X.; Zhang, Y.; Zhao, G. *Adv. Synth. Catal.* **2006**, *348*, 2223. (q) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734. (r) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (s) Font, D.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2006**, *8*, 4653. (t) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (u) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383. (v) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. (w) Zhou, Y.; Shan, Z. *J. Org. Chem.* **2006**, *71*, 9510. (x) Cheng, C.-L.; Sun, J.; Wang, C.; Zhang, Y.; Wei, S.-Y.; Jiang, F.; Wu, Y.-D. *Chem. Commun.* **2006**, 215. (y) Wang, Y.; Wei, S.-Y.; Sun, J. *Synlett* **2006**, 3319. (z) Cheng, C.-L.; Wei, S.-Y.; Sun, J. *Synlett* **2006**, 2419. (aa) Raj, M.; Vishnumaya; Ginotra, S. K.; Singh, V. K *Org. Lett.* **2006**, *8*, 4097. (ab) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197. (ac) D'Elia, V.; Zwicknagl, H.; Reiser, O *J. Org. Chem.* **2008**, *73*, 3262. (ad) Rodriguez, B.; Rantanen, T.; Bolm, C *Angew. Chem., Int. Ed.* **2006**, *45*, 6924.

(10) (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (b) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.

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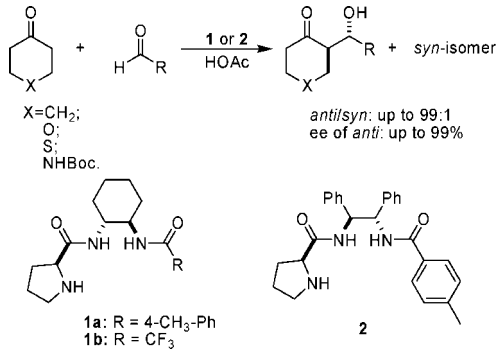
SCHEME 1. Direct Aldol Reaction of Cycloketones with Aldehydes



between a variety of cycloketones and aldehydes, and in many cases the ratio of diastereoisomers (*anti*:*syn*) is greater than 99:1 and ee is greater than 99% (Scheme 1).[11a,b] We also found that a subtle modification in the catalyst structure, which results in the change in pK_a value of the catalyst, has substantial effect on the enantioselectivity and suggest that the double hydrogen bondings play an important role in tuning the catalytic activity. However, the utilization of these catalysts in the aldol reaction of acyclic ketones with aldehydes only gave moderate results. Our objective, therefore, for the continued advancement of this field is the design of distinct catalysts that enable previously unsuccessful transformations.

Cinchona alkaloids and their derivatives have been successfully applied in a wide diversity of organocatalytic reactions,[12] acting as chiral-base,[13] phase-transfer,[14] and nucleophilic catalysts.[15] Given their extraordinary capacity revealed in various chemical transformations, we envisaged that rational incorporation of the stereocontrolling elements of proline and cinchona alkaloid in a single molecule would lead to a new class of chiral organocatalysts (Figure 1).[16] Herein, we demonstrate that these

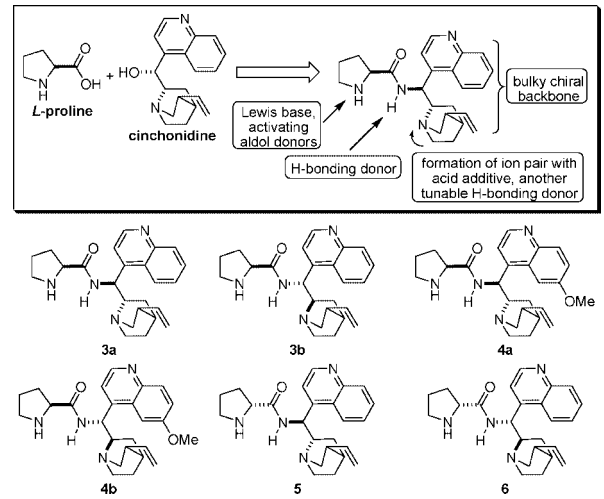
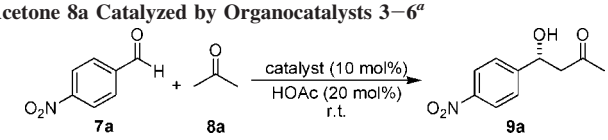


FIGURE 1. Key design elements of a new class of chiral amine catalysts.

TABLE 1. Direct Aldol Reaction of 4-Nitrobenzaldehyde 7a with Acetone 8a Catalyzed by Organocatalysts 3−6[a]



entry	catalyst	solvent	time (h)	yield (%)	ee (%)[b]
1	**3a**	acetone	0.5	89	85
2	**3b**	acetone	2	89	14
3	**4a**	acetone	2	87	66
4	**4b**	acetone	4	79	2
5	**5**	acetone	5	73	−11
6	**6**	acetone	1.5	94	−86
7	**3a**	$CHCl_3$	1.5	87	49
8	**3a**	CH_2Cl_2	1	90	64
9	**3a**	THF	1	84	58
10	**3a**	Et_2O	1.5	96	61
11	**3a**	EtOH	4	87	58
12	**3a**	MeOH	1	95	59
13	**3a**	DMF	3	84	63
14	**3a**	brine	4	71	55
15	**3a**	H_2O	3	87	53

[a] Reactions were carried out with 0.3 mmol of **7a** and 0.5 mL of acetone and 0.5 mL of solvent in the presence of 10 mol % of catalyst and 20 mol % of HOAc. [b] Determined by chiral HPLC.

organic molecules indeed show good to excellent enantioselectivities (up to 98% ee) in the direct aldol reaction of acetone and 2-butanone with aldehydes.

The organocatalysts **3**−**6** (Figure 1) were synthesized from commercially available L-proline (or D-proline) and cinchona alkaloids (see Supporting Information). Noteworthy, such type of catalyst features a big chiral backbone and one tertiary quinuclidine nitrogen, which could form an ion pair with acid additive to give another tunable hydrogen bonding donor (Figure 1). The catalytic performance of the catalyst was then evaluated in the direct asymmetric aldol reaction of 4-nitrobenzaldehyde **7a** with acetone **8a**.

As can be seen from the results summarized in Table 1, the catalysts **3**−**6** can efficiently catalyze the direct aldol reaction of aldehyde **7a** and acetone **8a** with variant ee values. It should be noted that the rational combination of the L-proline with cinchona alkaloids is critical to the stereocontrolling in the aldol reaction (Table 1, entries 1−4). The bifunctional catalysts **3a** and **4a**, derived from L-proline, cinchonidine, and quinine,

(11) (a) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543. (b) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198. (c) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J *Can. J. Chem.* **2007**, *85*, 211. (d) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847. (e) Cao, Y.-J.; Lu, H.-H.; Lai, Y.-Y.; Lu, L.-Q.; Xiao, W.-J. *Synthesis* **2006**, 3795. (f) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799. (g) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (h) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437. (i) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (j) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946.

(12) For general reviews, see:(a) Kacprzak, K.; Gawroski, J. *Synthesis* **2001**, 961. (b) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (c) Tian, S.-K.; Chen, Y.-C.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

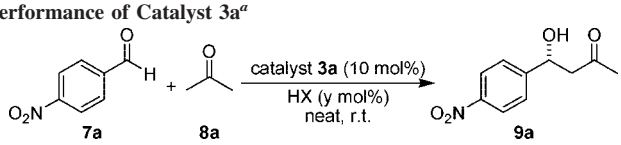
(13) For some recent examples, see: (a) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219. (b) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566. (c) Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896. (d) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614. (e) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (f) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (g) Wang, Y.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391. (h) Cantarero, J.-L.; Cid, M.-b.; Poulsen, B.-T.; Bella, M.; Ruano, J. L. G.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 7062. (i) Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 3414.

(14) (a) Ooi, T; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (e) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(15) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(16) For a comment on "privileged chiral catalysts", please see: Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

TABLE 2. Effects of the Acid Additives on the Catalytic Performance of Catalyst 3a[a]



entry	HX	*y* (mol %)	time (h)	yield (%)	ee (%)[b]
1	none		12	79	49
2	HCl	10	16	71	42
3	$NCCO_2H$	10	4.5	58	57
4	$ClCH_2CO_2H$	10	4.5	65	57
5	Cl_3CCO_2H	10	4.5	58	57
6	*p*-TsOH	10	24	20	ND
7	$3,5-2NO_2PhCO_2H$	10	4.5	53	64
8	$PhCO_2H$	10	0.5	86	67
9	TFA	10	4.5	68	64
10	CF_3SO_3H	10	4.5	85	72
11	HBr	10	4.5	70	32
12	$HClO_4$	10	4.5	84	80
13	$HClO_4$	20	24	NR	
14	$HClO_4$	30	24	NR	
15	HOAc	10	0.5	81	74
16	HOAc	20	0.5	89	85
17	HOAc	30	0.5	82	79
18	HOAc	40	0.5	73	77
19	HOAc	100	0.5	68	69
20[c]	HOAc	20	23	85	90

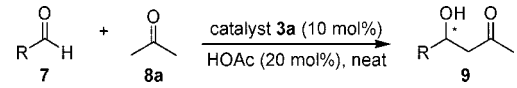
[a] Unless otherwise noted, reactions were carried out with 0.3 mmol of **7a** and 1.0 mL of acetone in the presence of 10 mol % of catalyst and *x* mol % of cocatalyst HX. ND: not determined. NR: no reaction. [b] Determined by chiral HPLC. [c] Performed at −30 °C.

showed better enantioselectivities over their pseudoenantiomers, **3b** and **4b**, respectively (Table 1, entries 1 vs 2, 3 vs 4). When the scaffold of D-proline was introduced to the catalyst backbone, the opposite enantiomer of the aldol product was obtained than with low ee values (Table 1, entry 5). As anticipated, the catalyst **6** (pseudoenantiomer of **3a**) induced higher enantioselectivity than **5**, giving the product with opposite configuration with 86% ee (Table 1, entries 6 vs 5). We then tested different solvents with **3a** as the catalyst. An enantioselectivity/solvent profile indicated that the reaction in acetone proceeded with better ee values than in other solvents (Table 1, entries 7−15).

It is well-known that the Brønsted acid additive should be involved in the intricate iminium−enamine equilibrium, and it can also play an important role in the activation of the aldol acceptor by hydrogen bonding. Therefore, a series of Brønsted acids have been examined as the cocatalyst in the direct asymmetric aldol reaction of 4-nitrobenzaldehyde (**7a**) with acetone (**8a**) (Table 2). An enantioselectivity/cocatalyst profile reveals that optimal enantiocontrol can be achieved when acetic acid or perchloric acid is employed as the cocatalyst (Table 2, entries 12 and 15). Further examinations document that the reaction efficiency as well as the enantioselectivity can be improved if the ratio of HOAc to **3a** is 2:1. Variation of this ratio proved detrimental to the reaction (Table 2, entries 15, 17−19 vs 16) and the superior level of asymmetric induction and efficiency could be reached when the reaction was performed at −30 °C with catalyst **3a** and HOAc (Table 2, entry 20, 85% yield and 90% ee).

With the optimized conditions in hand, we then examined the scope of the aldehyde substrate in the aldol reaction of acetones (Table 3). The reaction appears quite tolerant with respect to the steric contribution of the substituent in substituted benzaldehydes and the desired products could be obtained in good yields with good to excellent enantioselectivities (up to

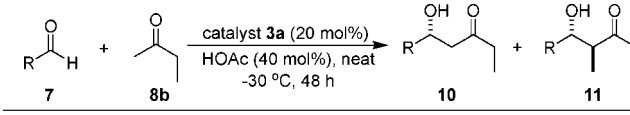
TABLE 3. Aldol Reaction between 7 and 8a Catalyzed by Catalyst 3a[a]



entry	R	9	temp (°C)	yield (%)	ee (%)[b]
1	4-NO_2-Ph (**7a**)	**9a**	−30	85	90
2	4-NO_2-Ph (**7a**)	**9a**	−40	97	92
3	3-NO_2-Ph (**7b**)	**9b**	−30	94	93
4	2-NO_2-Ph (**7c**)	**9c**	−30	80	97
5	4-NC-Ph (**7d**)	**9d**	−40	60	93
6	4-Br-Ph (**7e**)	**9e**	−30	90	89
7	4-Cl-Ph (**7f**)	**9g**	−30	95	78
8	2-Cl-Ph (**7g**)	**9h**	−30	89	87
9	2,4-Cl_2-Ph (**7h**)	**9i**	−30	84	90
10	4-CF_3-Ph (**7i**)	**9j**	−40	93	87
11	4-F-Ph (**7j**)	**9k**	−15	69	85
12	3,4-F_2-Ph (**7k**)	**9*l***	−40	87	90
13	Ph (**7*l***)	**9m**	r.t.	61	80
14	3-PhO-Ph (**7m**)	**9n**	−30	82	88
15	2-furyl (**7n**)	**9o**	−5	61	77
16	*i*-Pr (**7o**)	**9o**	r.t.	<5	
17[c]	4-NO_2-Ph (**7a**)	**9a**	−30	89	−93
18[c]	3-NO_2-Ph (**7b**)	**9b**	−30	96	−94
19[c]	2-NO_2-Ph (**7c**)	**9c**	−30	94	−97
20[c]	4-NC-Ph (**7d**)	**9d**	−30	89	−90

[a] Unless otherwise noted, the reactions were carried out with 0.3 mmol of **7** in 1.0 mL of acetone with 10 mol % of catalyst **3a** and 20 mol % of HOAc for 23−96 h. [b] Determined by chiral HPLC. [c] With **6** as the catalyst.

TABLE 4. Aldol Reaction between 7a−c and 8b Catalyzed by Catalyst 3a[a]



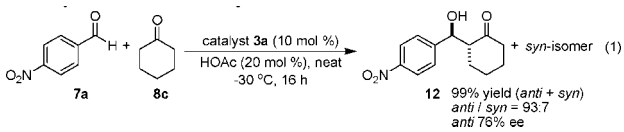
entry	R	product	yield (%)	dr[b]	ee (%)[c]
1	4-NO_2-Ph (**7a**)	**10a**	32		75
2		**11a**	53	93:7	98
3	3-NO_2-Ph (**7b**)	**10b**	26		82
4		**11b**	71	93:7	92
5	2-NO_2-Ph (**7c**)	**10c**	54		94
6		**11c**	39	96:4	92

[a] Unless otherwise noted, the reactions were carried out with 0.3 mmol of **7** in 1.0 mL of 2-butanone (**8b**) with 20 mol % of catalyst **3a** and 40 mol % of HOAc for 48 h. [b] Determined by ^1H NMR spectroscopy. *anti*/*syn*. [c] Determined by chiral HPLC for the *anti*-product.

97% ee). Heteroaromatic aldehyde, for example, 2-furaldehyde (**7n**), reacts smoothly with acetone under optimal conditions to yield the corresponding aldol product in good enantioselectivity (Table 3, entry 15). However, aliphatic aldehydes exhibited much lower reactivity in this transformation. The reaction of isobutaldehyde (**7o**) with acetone proceeds very slowly accompanied by a small amount of dehydrated product (Table 3, entry 16). Notably, the opposite enantiomeric aldol product can also be obtained with high ee values when amine **6**/HOAc is used as the catalyst under the same conditions (Table 3, entries 17−20).

The reaction of nitro-substituted benzaldehyde with 2-butanone (**8b**) was also investigated to examine the scope of the aldol donors. As shown in Table 4, in the case of 4- and 3-nitro-substituted benzaldehydes, the reaction preferentially occurred at the C-3 position to furnish the aldol adducts **11a**,**b** as the major products in remarkably high diastereoselectivities (dr 93:

7) and enantioselectivities (98% and 92% ee, respectively) (Table 4, entries 2 and 4). Interestingly, the reaction of 2-nitrobenzaldehyde and **8b** mainly took place at the C-1 position to afford the aldol product **10c** as the major product in excellent enantioselectivity (Table 4, entry 5, 94% ee). In addition, we have also preliminarily examined the feasibility of using cyclic ketones as aldol donors using **3a** as the catalyst. In the case of cyclohexanone (**8c**), excellent diastereoselectivtiy (93:7 dr) for *anti*-isomer (**12**) was obtained; however, the ee value of *anti*-isomer was somewhat low compared to that of catalysts **1** and **2** (eq 11).[11] Further extension of the reaction scope of aldehyde acceptors with 2-butanone is underway in our laboratory.



In conclusion, we have developed a new class of organocatalysts, which were prepared from commercially available and inexpensive proline and cinchona alkaloids, for the asymmetric direct aldol reactions of acetone and 2-butanone with aldehydes. High isolated yields (up to 97%) and enantioselectivities (up to 98% ee) were obtained by using these catalysts. Stereoselective formation of both enantiomers can be achieved through selection of catalysts **3a** or **6**, which are pseudoenantiomers. The present studies have demonstrated the key role of combination of privileged chiral backbone and hydrogen bonding interactions in the asymmetric aldol reaction. We hope that this strategy will give some hints in the further design of organocatalysts for other asymmetric reactions.

Experimental Section

Representative Procedure for the Direct Aldol Reaction of Aldehyde 7 with Acetone 8a. The organocatalyst **3a** (0.03 mmol) and HOAc (0.06 mmol) were stirred in 1 mL of acetone for 20 min at the indicated temperature. The corresponding aldehyde **7** (0.3 mmol) was added and the mixture was stirred for 23−96 h. The mixture was then treated with 10 mL of saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give pure aldol product **9** after flash column chromatography on silica gel (petroleum ether/ethyl acetate (3:1)).

4-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (9a). The ee was determined by HPLC (Chiralpak AS column, hexane/i-PrOH 70:30, flow rate 1 mL/min; t_R(minor) = 13.6 min; t_R(major) = 16.4 min, λ = 254 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.85−2.87 (m, 2H), 3.67 (d, J = 2.4 Hz, 1H), 5.26−5.28 (m, 1H), 7.54 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 10.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 51.4, 68.7, 123.6, 126.3, 147.1, 149.9, 208.6.

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Supporting Information Available: Experimental procedures, characterization of new compounds, ^{1}HMR and ^{13}CNMR spectra of new compounds, and HPLC spectra of aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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