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A Highly Efficient Organocatalyst for Direct Aldol Reactions of Ketones with Aldedydes

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Abstract: L-Proline amides derived from various chiral β-amino alcohols that bear substituents with various electron natures at their stereogenic centers are prepared and evaluated for catalyzing the direct Aldol reaction of 4-nitrobenzaldehyde with acetone. Catalysts with strong electron-withdrawing groups are found to exhibit higher catalytic activity and enantioselectivity than their analogues with electron-donating groups. The presence of 2 mol % catalyst **4g** significantly catalyzes the direct Aldol reactions of a wide range of aldehydes with acetone and butanone, to give the β-hydroxy ketones with very high enantioselectivities ranging from 96% to >99% ee. High diastereoselectivity of 95/5 was observed for the anti Aldol product from the reaction of cyclohexanone, and excellent enantioselectivity of 93% ee was provided for anti Aldol product from the reaction of cyclopentanone.

Introduction

The Aldol reaction is considered one of the most important carbon−carbon bond-forming reactions in organic synthesis. Its great usefulness for building up natural products, in particular those with polyoxygenated subunits,[1] has promoted the rapid evolution of efficient chiral catalysts.[2] The direct Aldol reaction is highly atom efficient,[3] compared with well-established processes using enol or enolate derivatives as the Aldol donor.[2] Recently, the highly enantioselective direct Aldol reaction of aldehydes with ketones in the presence of a catalytic amount of bifunctional transition metal complexes has been reported.[4] Although proline-catalyzed Robinson annulation appeared in the early 1970s,[5a,b] the real breakthrough came from the pioneering work by List and Barbas and their co-wokers.[5c−e] Since then, L-proline[6] and its structural analogues[7−10] have been evaluated for use in asymmetric catalytic direct intermolecular Aldol reactions. Although impressive results were observed for α-branched aliphatic aldehydes, only fair enantioselectivities were observed for the reactions of aromatic aldehydes with acetone either by L-proline[5c,d] or its derivatives and structural analogues,[7,8] with the exception of an *N*-substituted proline amide derived from (1*S*,2*S*)-1,2-diphenylaminoethanol[9] and a proline-derived *N*-sulfonylcarboxamine,[10a] which gave high enantioselectivity for the para-substituted benzaldehydes. Thus far, the organocatalysts that have been used for the direct Aldol reaction of aldehydes with ketones are highly enantioselective for a comparably narrow range of substrates. Nonetheless, catalyst loading of as high as 20 or 30 mol % is usually required

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(1) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 229.
(2) For reviews, see: (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (c) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 29.1. (d) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (e) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. (f) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (g) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, 33, 432. (h) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.
(3) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.
(4) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (d) Trost, B. M.; Ito, H.; Siloff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (e) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.
(5) (a) Hojas, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, R.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496. (c) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (e) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.
(6) For reviews, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) List, B. *Synlett* **2001**, 1675. (c) Alcaide, B.; Almendros, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 858. (d) List, B. *Acc. Chem. Res.* 2004, 37, 548. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* 2004, 37, 580. For leading literatures, see: (f) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (g) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301. (h) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (i) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 2785. (j) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152. (l) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343.
(7) (a) Hartikaa, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983. For review, see: (c) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
(8) (a) Martin, H. J.; List, B. *Synlett*, **2003**, 1901. (b) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445.
(9) (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.
(10) (a) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141. (b) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.

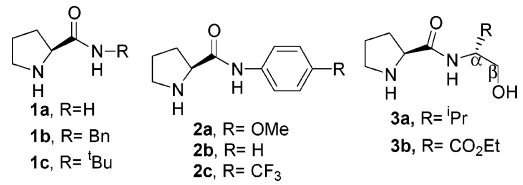
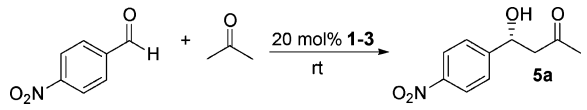


Figure 1. L-Proline amides used for direct Aldol reactions previously.[9b]

Table 1. The Direct Aldol Reaction of *p*-Nitrobenzaldehyde with Acetone Catalyzed by Organocatalysts **1**−**3**[9b]



entry	organo-catalyst	yield (%)[b]	ee (%)[c]	entry	organo-catalyst	yield (%)[b]	ee (%)[c]
1	**1a**	80	30	5	**2b**	88	37
2	**1b**	82	21	6	**2c**	88	45
3	**1c**	55	15	7	**3a**	78	33
4	**2a**	78	31	8	**3b**	63	61

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M. [b] Isolated yield based on the aldehyde. [c] The ee values were determined by HPLC, and the configuration was assigned as *R* by comparison of retention times.

to achieve a good isolated yield of the Aldol product.[5c−e,8−10] Therefore, highly efficient chiral organocatalysts, which not only show generally high enantioselectivity for a broad scope of substrates but also allow for the use of low catalyst loading (less than 5 mol %), are still limited, and further development is required.

Previously, we discovered that secondary amides with *N*-alkyl groups such as **1a**−**c** (Figure 1) show lower enantioselectivities than their analogues with *N*-aryl groups **2a**−**c** (Table 1, entries 1−6). In particular, the enantioselectivity increases as the aryl substituent of **2a**−**c** varies from an electron-donating to an electron-withdrawing group (entries 4−6). It is also interesting to compare the results obtained with catalysts **3a** and **3b**, which only differ in the electronic properties of the substituent bonding to their α-carbon on the amino alcohol moiety. **3b** containing an ester function catalyzes the reaction much more enantioselectively than **3a**, which bears an isopropyl group (entries 7 and 8).[9b]

On the basis of the above-mentioned observations, we speculated that the positive effect of the ester group on the catalytic performance of the organocatalyst might be due to the electron-withdrawing property of the ester, which makes the N−H more acidic, resulting in the formation of a stronger hydrogen bond. If this speculation is generally correct, we further hypothesize that new organocatalysts with improved catalytic performance over those reported previously[9] can be reasonably obtained by tuning the electron property of the substituent bonded to either the α- or *β*-carbon (R^1 or R^2) in organic molecules of type **4** (Figure 2). To address this hypothesis, in this study we examined the electron effect of the substituent attached to either the α- or *β*-carbon on the amino alcohol part of organocatalysts **4** (Figure 2) on catalytic performance; as a result, we discovered a new highly efficient organocatalyst for the direct Aldol reaction, which promotes the direct Aldol reactions of a broad range of aldehydes with ketones to generate *β*-hydroxy ketones with excellent enantioselectivities by using <5 mol % catalyst loading.

Results and Discussion

Preparation of New Organocatalysts. The synthetic route to approach L-proline amides **4b**−**c**, **4f**, **4i**, and **4l**, which are derived from optically pure 1,2-diphenyl-2-aminoethanols, was reported previously.[9]

The preparation of L-proline amides substituted with cyclohexyl groups (organocatalysts **4a**, **4e**, **4h**, and **4k**) started with commercially available optically pure 1,2-diphenyl-2-aminoethanols **6a**−**d**. Hydrogenation of **6a**−**d** catalyzed by Ru/Al_2O_3[11] under 100 atm of hydrogen afforded 1,2-dicyclohexyl-2-aminoethanols **7a**−**d** in 87−89% yields without loss of the enantiomeric purity, which reacted with Cbz-proline in the presence of stoichiometric amounts of ClCOOEt and triethylamine to give corresponding amides **8a**−**d**. Hydrogenolysis of the crude amides **8a**−**d** in the presence of 5% Pd−C deprotected the *N*-Cbz group to provide **4a**, **4e**, **4h**, and **4k** in high yields (77−87%, two steps from **7a**−**d**) (Scheme 1).

The synthesis of L-proline amides **4d**, **4g**, **4j** and **4m** commenced with optically pure **11a** and **11b**, respectively derived from diethyl tartrates **9a** and **9b** (Scheme 2).[12] Respective treatment of diethyl epoxysuccinates **11a** and **11b** with sodium azide in the presence of ammonium chloride in DMF provided diastereomeric mixtures of **12a,b** and **12c,d** in high yields with a diastereomeric ratio of 1:1. A crude diastereomeric mixture of either **12a** and **12b** or **12c** and **12d** was directly hydrogenated under 1 atm of hydrogen in the presence of 5% Pd−C to furnish the diastereometric mixture of diethyl 2-amino-3-hydroxysuccinates **13a** and **13b** or **13c** and **13d**. Each pure diastereomer of diethyl 2-amino-3-hydroxysuccinate was obtained by careful column chromatography. The optically pure diethyl 2-amino-3-hydroxysuccinates **13a**−**d** were respectively coupled with Cbz-proline by action of EDCI, HOBt, and NMM in dichloromethane to generate **14a**−**d**. After a hydrogenolysis of crude **14a**−**d** catalyzed by 5% Pd−C, the desired organocatalysts **4d**, **4g**, **4j**, and **4m** were obtained with 45−53% yields (two steps from **13**).

The Direct Aldol Reaction of *p*-Nitrobenzaldehyde with Acetone Catalyzed by Organocatalysts 4: Demonstration of the Electronic Effect of Side Chain on the Catalytic Performance. The L-proline amides **4a**−**g** were first screened for their ability to catalyze the model direct Aldol reaction of *p*-nitrobenzaldehyde with acetone. As shown in Table 2, the electron nature of the substituent strongly affects the enantioselectivity of the reaction. The enantioselectivity tends to increase as the substituent varies from an electron-donating group to an electron-withdrawing group. For example, the use of **4a** as a catalyst leads to the formation of Aldol product **5a** in good yield but low enantioselectivity (entry 1). Catalyst **4b**[9] with two phenyl groups, which are more electron-withdrawing than cyclohexyl groups, is more enantioselective than **4a** (entry 2). The presence of a stronger electron-withdrawing substituent such as an ester group at the α-carbon or both the α- and *β*-carbons, as seen with catalysts **4c** and **4d**, results in considerably enhanced results (entries 3 and 4). More significant cases are the reactions catalyzed by **4e**−**g**, among which **4g** shows a much higher level of stereocontrol than **4e** and **4f** [9] (entries 5

(11) (a) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309. (b) Tong, P.-E.; Li, P.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2301.
(12) Saito, S.; Komada, K.; Moriwake, T. *Organic Syntheses;* Wiley: New York, Collect. Vol. IX, p 220.

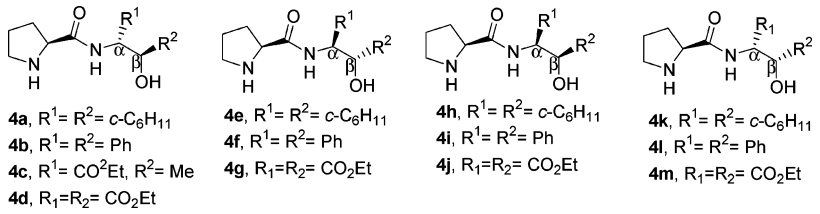
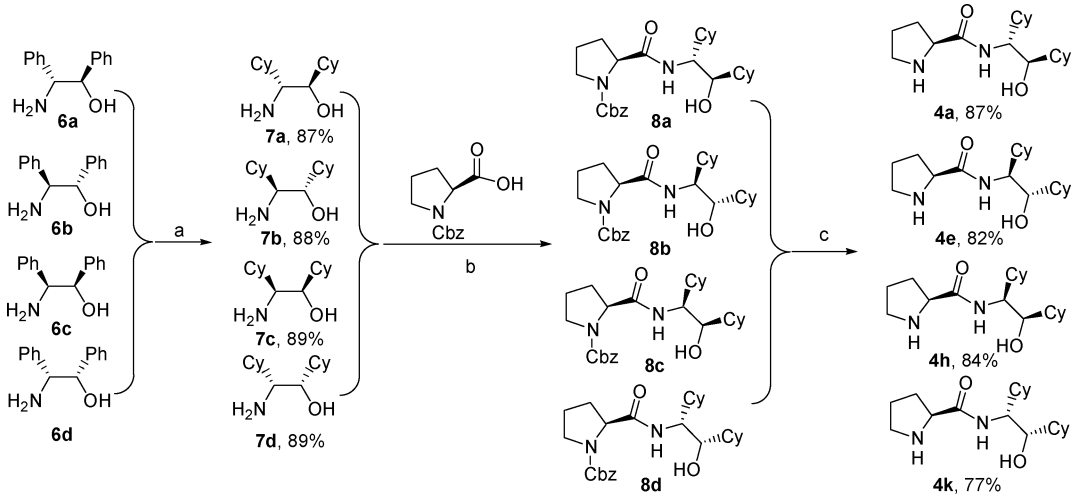


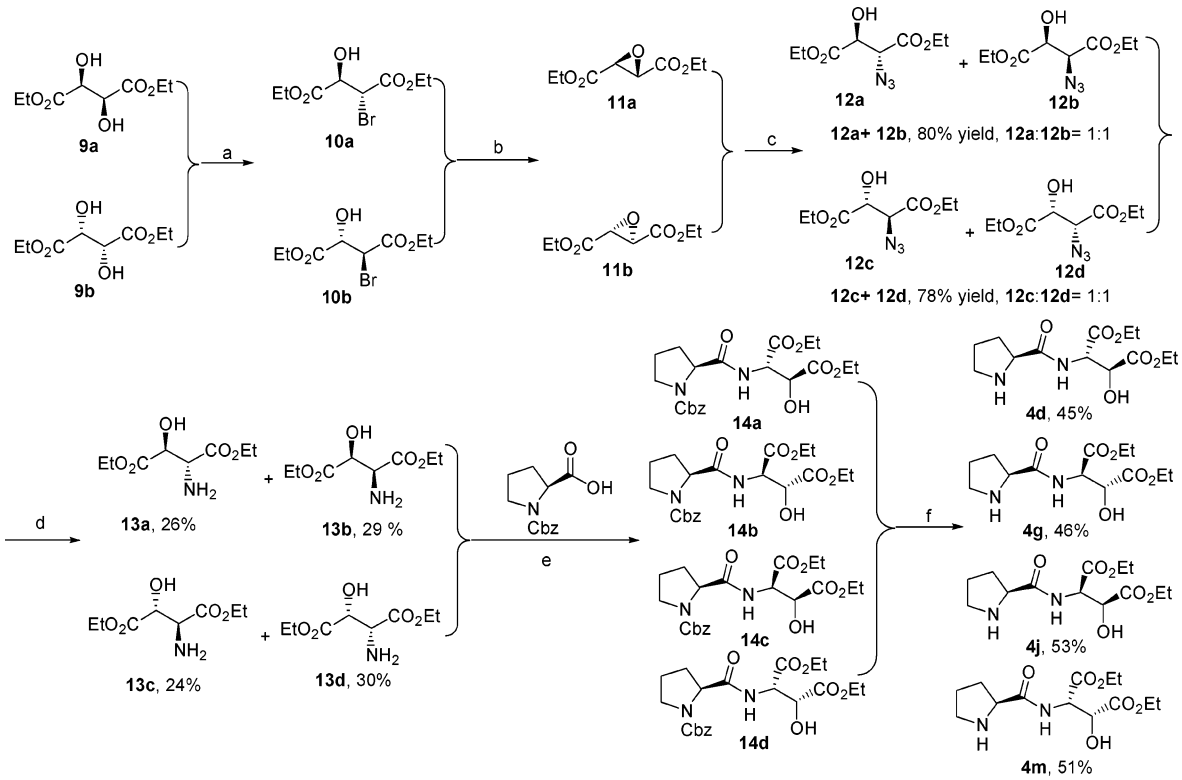
Figure 2. L-Proline amides evaluated for catalyzing direct Aldol reactions of ketones with aldehydes in this study.

Scheme 1. Preparation of L-Proline Amides Substituted with Cyclohexyl Groups[a]



[a] Reagents and conditions: (a) Ru/Al_2O_3, H_2 (100 atm), 95% EtOH, 60 °C, 12 h, 87−89%; (b) ClCOOEt/Et_3N; (c) H_2 (1 atm), Pd/C, MeOH, 77−87% (two steps).

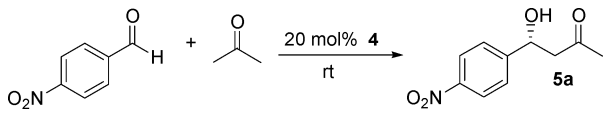
Scheme 2. Preparation of L-Proline Amides Substituted with Ester Groups[a]



[a] Reagents and conditions: (a) (1) HBr, HOAc; (2) EtOH, HCl; (b) NaOEt, EtOH; (c) NaN_3, NH_4Cl, DMF; (d) Pd/C (5%), H_2, MeOH; (e) EDCI, HOBt, NMM; (f) Pd/C (5%), H_2, MeOH, 45−53% (two steps).

and 6), to give rise to **5a** with 85% isolated yield and 87% ee (entry 7). Then, the diastereomers **4h**−**m** of organocatalysts **4a,b** and **4d**−**g** were examined for catalyzing the model reaction, once again resulting in that organocatalysts with a strongly electron-withdrawing substituent show much higher catalytic efficacy than those with electron-donating substituent (entries

Table 2. Organocatalysts **4** Catalyzed the Direct Aldol Reaction of 4-Nitrobenzaldehyde with Acetone[a]



entry	organo-catalyst	yield (%)[b]	ee (%)[c]	entry	organo-catalyst	yield (%)[b]	ee (%)[c]
1	**4a**	51	15	9	**4i**	76	64[d]
2	**4b**	77	44[d]	10	**4j**	81	75[e]
3	**4c**	76	67[d]	11	**4k**	75	17
4	**4d**	81	72[e]	12	**4l**	63	49[d]
5	**4e**	53	15	13	**4m**	80	67[e]
6	**4f**	89	69[d]	14	**4g**	60	95[e,f]
7	**4g**	85	87[e]	15	**4g**	62	99[e,g]
8	**4h**	59	12				

[a] Unless otherwise specified, the reaction was carried out in the presence of 20 mol % catalyst. [b] Isolated yield. [c] Determined by HPLC (see Supporting Information). [d] The result was reported in ref 9. [e] In the presence of 2 mol % catalyst. [f] The reaction was performed at 0 °C. [g] The reaction was performed at −25 °C.

8−13). These results confirm that the electron-nature of the substituent bonded to either the α- or *β*-carbon of organocatalysts **4** is crucial to the catalytic performance. Comparison of results observed with **4d**, **4g**, **4j**, and **4m** indicated that the (*R*)-configuration[13] of α- and *β*-carbons of catalysts with the ester group matched the L-proline to enhance the stereochemical control.

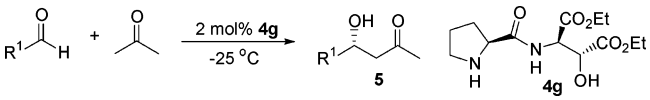
Further optimization of the reaction conditions for the best catalyst **4g** revealed that the enantioselectivity increases significantly to 99% ee with a decrease in the reaction temperature to −25 °C (entry 15). Interestingly, as little as 2 mol % of **4g** is enough to promote the reaction with high conversion and enantioselectivity (entries 14 and 15).

Scope and Limitation. The scope and limitations of the direct Aldol reaction catalyzed by **4g** were also examined. A wide range of aldehydes including both aromatic and aliphatic aldehydes react smoothly with acetone under optimal conditions, to give the Aldol adducts with excellent enantioselectivities ranging from 96% to >99% ee (Table 3). Significantly, the reactions of aromatic aldehydes bearing either an electron-withdrawing or electron-donating group with acetone lead to the formation of Aldol products **5a**−**5m** with very high enantioselectivities ranging from 96% to 99% ee (entries 1−13). However, the previously developed organocatalyst **4f** provides excellent enantioselectivity (up to 93% ee) only for special aromatic aldehydes with electron-withdrawing substituents.[9] Remarkably, the benzaldehydes substituted with an electron-donating group such as *p*-methylbenzaldehyde and *p*-*tert*-butylbenzaldehyde also react smoothly with acetone to generate Aldol adducts **5h** and **5i** with respective ee values of 97% and 96% (entries 8 and 9). Extremely high enantioselectivities ≥99% ee are also observed for α-branched aliphatic aldehydes (entries 14−16). Particularly, an improved enantioselectivity of 99% ee for cyclohexylformaldehyde (entry 16) was observed with **4g** relative to its analogue **4f**.[9]

Reactions of butanone with various para-substituted aromatic aldehydes were investigated (Table 4). The reaction preferentially occurred at the methyl group to generate Aldol adducts

(13) Actually, **4g** has the same relative configuration as **4f**. The (*R*)-configuration comes from the higher priority of the ester group based on the sequence rule of the Cahn−Ingold−Prelog convention.

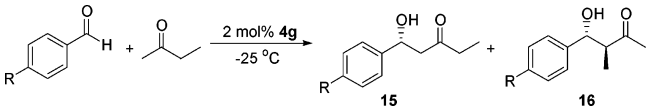
Table 3. Study on the Scope and Limitation of Aldehydes[a]



entry	product	R^1	yield (%)[b]	ee (%)[c]
1	**5a**	4-$NO_2C_6H_4$	62	99
2	**5b**	4-BrC_6H_4	41	96
3	**5c**	4-ClC_6H_4	84	99
4	**5d**	2-ClC_6H_4	99	96
5	**5e**	4-FC_6H_4	60	97
6	**5f**	Ph	68	98
7	**5g**	α-naphthyl	63	97
8	**5h**	4-MeC_6H_4	65	97[d]
9	**5i**	4-*t*-BuC_6H_4	45	96[d]
10	**5j**	2,6-$Cl_2C_6H_3$	60	96
11	**5k**	4-CNC_6H_4	56	99
12	**5l**	4-$CF_3C_6H_4$	70	98
13	**5m**	3,5-$(CF_3)_2C_6H_4$	60	98
14	**5n**	*t*-Bu	71	>99[d]
15	**5o**	*i*-Pr	75	>99[d]
16	**5p**	c-C_6H_{11}	80	99[d]

[a] The reaction was carried out in neat acetone with a concentration of 0.5 M at −25 °C for 24−48 h (see Supporting Information). [b] Isolated yields. [c] Determined by HPLC. [d] In the presence of 5 mol % **4g**.

Table 4. Direct Aldol Reactions of Aldehydes with Butanone[a]

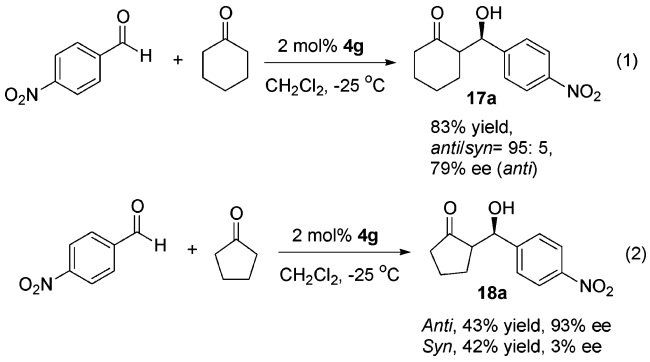


entry	R	product **15**	yield (%)[b]	ee (%)[c]	product **16**	yield (%)[b]	dr[e] anti/syn	ee[c] (%)
1	NO_2	**15a**	56	98	**16a**	42	>99:1	99
2	Cl	**15b**	43	98	**16b**	36	>99:1	98
3	CN	**15c**	62	>99	**16c**	21[d]	>99:1	99

[a] The reaction was carried out in neat butanone with a concentration of 0.5 M at −25 °C for 24−48 h. [b] Isolated yields. [c] Determined by HPLC. [d] In the presence of 5 mol % **4g**. [e] Determined by analysis of ^{1}H NMR spectra of the crude products.

15 in the majority and **16** in the minority. Although the regioselectivity is not significant (up to 3/1), remarkably high enantioselectivities of up to >99% ee are provided with **4g** for the major products **15a**−**c** generated from reactions of 4-nitrobenzaldehyde, 4-chlorobenzaldehyde, and 4-cyanobenzaldehyde with 2-butanone. It is noteworthy that the minor Aldol adducts **16a**−**c** were obtained with extremely high diastereoselectivities of over 99:1 in favor of anti-diastereomers. Enantioselectivities of 98−99% ees were observed for the anti Aldol adducts **16a**−**c**.

Cyclohexanone and cyclopentanone were finally explored as Aldol donors. Cyclohexanone reacted with *p*-nitrobenzaldehyde to generate Aldol adduct **17a** in a high yield. The diasteomeric ratio of anti/syn is 95/5 according to ^{1}H NMR analysis of the crude product, which is much higher than those observed with the organocatalysts reported previously.[5d,10b] However, lower enantioselectivity of 79% relative to L-proline was induced for the anti-product (eq 1). The reaction of cyclopentanone went smoothly to give **18a** in 85% yield. The diasteomeric ratio of anti/syn is almost 1/1. High enantioselectivity of 93% ee was observed for *anti*-**18a**, but *syn*-**18a** was produced with low enantioselectivity (eq 2).



Transition State Consideration. The organocatalyst **4f** shows much better ability at controlling the stereochemical outcome of the direct Aldol reaction than its structural analogues **4b**, **4i**, and **4l**. **4f** catalyzes the reaction via the transition state TS1 (Figure 3), which was proposed previously on the basis of the DFT calculation.[9] Catalyst **4g**, which has the same relative configuration as **4f**,[13] also provides much higher enantioselectivity than its diastereomers **4d**, **4j**, and **4m**. Therefore, we believe that the **4g** catalyzed direct Aldol reaction via the transition state TS2. The stronger double hydrogen bond in TS2 relative to that in TS1 might be formed because of the strong electron-withdrawing nature of the ester groups, which is a highly possible reason that organocatalyst **4g** shows much higher catalytic activity and enantioselectivity than **4f**.

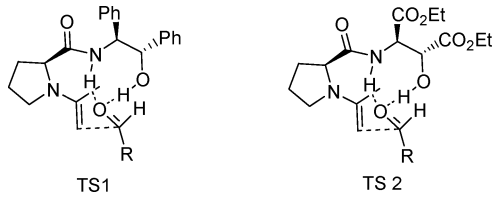


Figure 3. Proposed transition states to account for the stereochemical outcome.

Conclusion

In summary, a family of L-proline amides derived from various chiral β-amino alcohols substituted with either electron-donating or -withdrawing groups at their stereogenic centers was evaluated for their ability to catalyze the direct Aldol reaction of 4-nitrobenzaldehyde with acetone. We found that catalysts with strongly electron-withdrawing groups show much higher catalytic activity and enantioselectivity than their analogues with electron-donating groups. The presence of 2 mol % catalyst **4g** significantly catalyzes the direct Aldol reactions of a wide range of aldehydes with acetone and butanone, to give the β-hydroxy ketones with very high enantioselectivities ranging from 96% to >99% ee. The catalytic Aldol reaction of cyclohexanone led to the formation of anti Aldol product in high diastereoselectivity. Cyclopentanone reacted with 4-nitrobenzaldehyde to give excellent enantioselectivity for anti-product. In addition to these results, our finding may provide some insight for the further modification of related organocatalysts.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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