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Direct asymmetric aldol reactions catalyzed by L-proline-2,4,6-trinitroanilide

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Abstract

Direct aldol reactions of several aromatic aldehydes with ketones using L-proline-2,4,6-trinitroanilide catalyst **2d** were conducted. Under optimized conditions, high enantioselectivity (99% ee), regioselectivity (up to 95:5), and diastereoselectivity (up to 98:2) were achieved.

Asymmetric aldol reactions are one of the most valuable fundamental C–C bond forming reactions because they give synthetically useful chiral building blocks.[1] Although first reported in the 1970s that the L-proline (**1**) catalyzed intramolecular aldol reactions,[2] L-proline remained undeveloped for the next 30 years. After List and Barbas adopted **1** for *intermolecular* aldol reactions,[3] it has been reevaluated in asymmetric aldol reactions.[4] List's work[4f,g] on the mechanism of intermolecular aldol reactions proposed that the enamine formed rigid transition states where the chirality was regulated through hydrogen-bonding with the carbonyl group of the aldehyde (Scheme 1). Recently, new additions are continuously being made to the list of organocatalysts that can yield high enantioselectivity through the transition state related to the above: L-proline aliphatic amides,[5] L-proline aromatic amides,[6] chiral pyrrolidines with tetrazole,[7] chiral pyrrolidines with sulfonamide,[8] 4-substituted L-prolines,[9] chiral diamine-protonic acids,[10] and axially chiral amino acids.[11] Gong disclosed that when L-prolineanilide analogs were used in asymmetric aldol reactions, ee of aldol adducts increased as the electron-withdrawing ability of 4-substituent of anilide increased.[5b] However, L-proline-4-nitroanilide (**2b**), which had strong electron-withdrawing group[12] on the aromatic ring, gave low enantioselectivity.[5b] In this Letter, we report asymmetric direct aldol reactions catalyzed by novel L-proline-2,4,6-trinitroanilide (**2d**), which possesses a strong acidic N–H moiety caused by three electron-withdrawing nitro groups (see Fig. 1).

Reaction of **2a**[13] with fuming nitric acid (6 equiv) and sulfuric acid in chloroform gave **2d** in high yield (Scheme 2).[14] The optical purity of **2d** was confirmed to be pure (>99% ee) in comparison with the DL-**2d** by chiral HPLC.[15]

The aldol reactions of acetone with 4-nitrobenzaldehyde (**4a**) are shown in Table 1.[16] When using catalyst **2d** and HMPA as a solvent, ee was highest (85% ee) among the solvents investigated; however, the yield of the adduct was only 20% (entry 6). This is due to the formation of

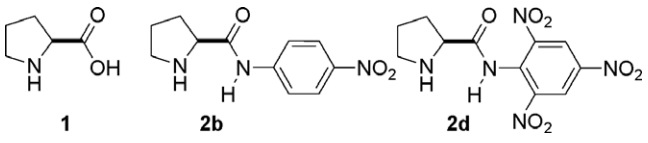

Fig. 1. L-Proline and its nitroanilide analogs.

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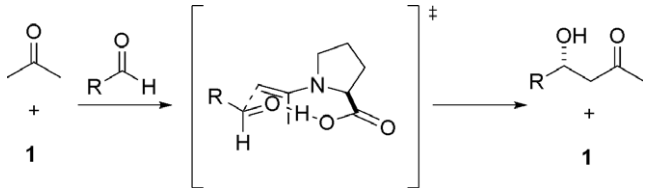


Scheme 1. Proposed mechanism for asymmetric direct aldol reaction catalyzed by L-proline (**1**).

Scheme 2. Synthesis of L-proline-2,4,6-trinitroanilide **2d**.

dehydration and double aldol reaction products. To improve catalytic turnover, water and weak acid[5o] were added (entries 7–11). The formation of byproducts was suppressed without the loss of enantioselectivity when 30 equiv of water was added (entries 8 and 9). However, the yield was not improved even in the presence of weak acids (entries 10 and 11). At best, the aldol adduct was obtained in 90% yield and 85% ee when **4a** (1 equiv) was reacted with acetone (20 equiv) in HMPA (3 mL) and water (30 equiv) for 4 d (entry 12). In the reactions using several L-proline-nitroanilide catalysts **2a**–**d**,[17] ee of aldol adducts increased as the number of nitro group of catalysts increased (entries 12–15). Similarly, ee of aldol adducts increased as the electron-withdrawing ability of 2,6-substituents of the catalysts **3a**–**e**[18] increased (entries 16–20), and the reaction using **3f**[18] gave **5a** with 88% yield and 87% ee.

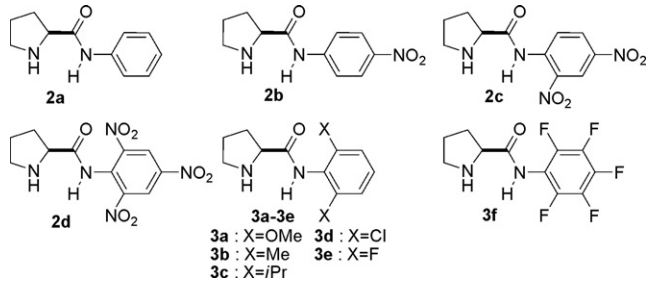
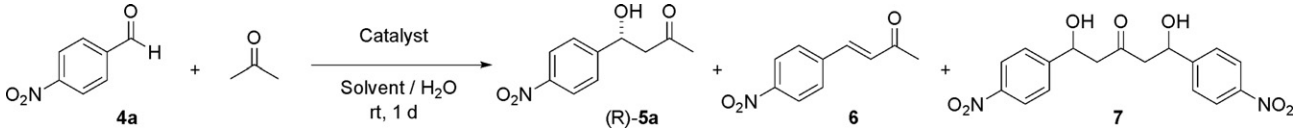


Fig. 2. Structures of L-prolineanilide analogs **2a**–**d**, **3a**–**f**.

Table 1
Direct asymmetric aldol reactions of 4-nitrobenzaldehyde **4a** with acetone



Entry[a]	Acetone	Solvent	H_2O	Weak acid	Catalyst	**5a**		**6** Yield[b] (%)	**7**[d] Yield[b] (%)	**4a** Recovery[b] (%)
						Yield[b] (%)	ee[c] (%)			
1	10 equiv	None	0 equiv	None	**2d**	79	20	Trace	Trace	18
2	10 equiv	CH_2Cl_2	0 equiv	None	**2d**	65	−17	9	Trace	11
3	10 equiv	THF	0 equiv	None	**2d**	58	20	9	7	7
4	10 equiv	DMF	0 equiv	None	**2d**	41	61	11	13	6
5	10 equiv	DMSO	0 equiv	None	**2d**	33	76	18	5	6
6	10 equiv	HMPA	0 equiv	None	**2d**	20	85	12	12	19
7	10 equiv	HMPA	5 equiv	None	**2d**	53	87	7	7	9
8	10 equiv	HMPA	30 equiv	None	**2d**	42	85	Trace	Trace	54
9	20 equiv	HMPA	30 equiv	None	**2d**	56	84	Trace	Trace	41
10	20 equiv	HMPA	30 equiv	HOAc (0.2 equiv)	**2d**	49	84	Trace	Trace	47
11	20 equiv	HMPA	30 equiv	PhCOOH (0.2 equiv)	**2d**	55	83	Trace	Trace	41
12[e]	20 equiv	HMPA	30 equiv	None	**2d**	90	85	Trace	Trace	Trace
13[e]	20 equiv	HMPA	30 equiv	None	**2a**	88	8	Trace	Trace	Trace
14[e]	20 equiv	HMPA	30 equiv	None	**2b**	80	54	Trace	18	Trace
15[e]	20 equiv	HMPA	30 equiv	None	**2c**	90	82	Trace	Trace	Trace
16[e]	20 equiv	HMPA	30 equiv	None	**3a**	18	4	Trace	Trace	70
17[e]	20 equiv	HMPA	30 equiv	None	**3b**	89	9	Trace	Trace	Trace
18[e]	20 equiv	HMPA	30 equiv	None	**3c**	80	18	Trace	7	Trace
19[e]	20 equiv	HMPA	30 equiv	None	**3d**	72	50	Trace	18	Trace
20[e]	20 equiv	HMPA	30 equiv	None	**3e**	96	63	Trace	Trace	Trace
21[e]	20 equiv	HMPA	30 equiv	None	**3f**	88	87	Trace	Trace	Trace

[a] The reaction of **4a** (0.3 mmol, 1 equiv) with acetone was conducted in the indicated solvent (3 mL) and H_2O in the presence of catalyst (0.06 mmol, 0.2 equiv) at room temperature for 1 d.

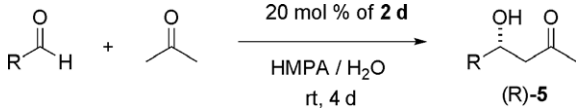
[b] Isolated yield.

[c] Optical purity was determined by chiral HPLC (CHIRALPAK AS-H). Absolute configuration of the major enantiomer was determined by comparing the measured optical rotation.[4j]

[d] Relative and absolute configuration were unclear.

[e] The reaction was conducted for 4 d.

Table 2
Direct asymmetric aldol reaction of aromatic aldehyde with acetone catalyzed by **2d**



Entry[a]	Aldehyde	R		Yield[b] (%)	ee[c] (%)
1	**4a**	4-NO_2Ph	**5a**	90	85
2	**4b**	Ph	**5b**	8	78
3	**4c**	4-OMePh	**5c**	Trace	n.d.
4[d]	**4d**	4-ClPh	**5d**	65	88
5	**4e**	2-NO_2Ph	**5e**	87	89
6	**4f**	2-Pyridyl	**5f**	48[e]	82
7	**4g**	C_6H_{11}	**5g**	Trace	n.d.

[a] The reaction of aldehyde (0.3 mmol, 1 equiv) with acetone (6.0 mmol, 20 equiv) was conducted in HMPA (3 mL) and H_2O (9.0 mmol, 30 equiv) in the presence of **2d** (0.06 mmol, 0.2 equiv) at room temperature for 4 d.
[b] Isolated yield.
[c] Optical purity was determined by chiral HPLC (CHIRALPAK AS-H). Absolute configuration of the major enantiomer was determined by comparing the measured optical rotation.[4j]
[d] The reaction was conducted for 12 d in the presence of H_2O (15 equiv).
[e] Although the reaction proceeded in good conversion, the isolation procedure was not optimized due to high hydrophilicity of **5f**.

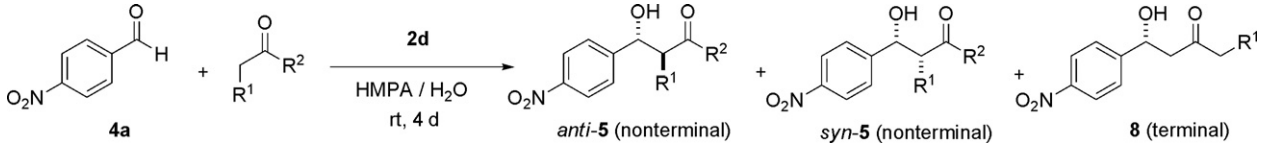
It is demonstrated that the inductive electron-withdrawing groups on the aromatic ring are also effective for high ee (see Fig. 2).

The generality of the substrates of the aldol reactions was elucidated (Table 2). In the reactions of acetone with several aldehyde catalyzed by **2d**, ee of aldol adducts was from 78% ee to 89% ee (entries 1–5). The chemical yield of the adducts increased as the strength of the electron-withdrawing property increased. Reactions of aromatic aldehyde with no electron-withdrawing group were very slow, and the reactions did not complete even after 4 days (entries 2 and 3). When **4d** was used as a substrate, the aldol adducts **5d** were obtained in 65% yield and 88% ee, but dehydrated byproducts were obtained in 30% yield (entry 4). Reaction of heteroaromatic aldehyde **4g** gave **5g** with 48% yield and 82% ee (entry 6). The reactivity of aliphatic aldehyde **4f** was very low to give trace amount of **5g** (entry 7).

Next, aldol reactions between **4a** and several ketones catalyzed by **2d** were investigated (Table 3). The reactivity of sterically hindered ketones was low (entries 4–6). Reaction of cyclopentanone with **4a** gave **5l** with high ee (96% ee), but diastereoselectivity (*anti*:*syn*) was moderate (71:29) (entry 7). Reaction of 2-butanone with 4-nitrobenzaldehyde gave *anti*-**5h** with 56% yield and 99% ee (entry 3). In this case, diastereoselectivity was very high (98:2), but regioselectivity (**5**:**8**) was low (62:38). When chloroacetone was used as a substrate, the aldol adducts **5m** were obtained in 90% yield and 98% ee (*anti*) with high diastereoselectivity (94:6) and regioselectivity (92:8) (entry 9).

In conclusion, we synthesized novel organocatalyst L-proline-2,4,6-trinitroanilide (**2d**), and applied it for direct asymmetric aldol reactions. Under optimized conditions, high enantioselectivity (up to 99% ee), regioselectivity (up to 95:5), and diastereoselectivity (up to 98:2) were achieved. Further mechanical study as well as the application of **2d** to the other reactions is currently underway.

Table 3
Direct asymmetric aldol reaction of 4-nitrobenzaldehyde **5a** with ketones catalyzed by **2d**



Entry[a]	Ketone		5			rr[c] (**5**:**8**)	8	
	R^1	R^2	Yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (%) *anti*; (*syn*)		Yield[b] (%)	ee[d] (%)
1	H	Me	90 (**5a**)	—	85	—	—	—
2	Me	Me	23 (*anti*-**5h**), Trace (*syn*-**5h**)	98:2	98; (n.d.)	63:37	13 (**8h**)	87
3[e]	Me	Me	56 (*anti*-**5h**), Trace (*syn*-**5h**)	98:2	99; (n.d.)	62:38	34 (**8h**)	93
4	Et	Me	Trace (**5i**)	n.d.	n.d.	n.d.	Trace	n.d.
5	Me	Et	None (**5j**)	—	—	—	—	—
6	H	Ph	None (**5k**)	—	—	—	—	—
7	Cyclopentanone		87 (*anti*-**5l** + *syn*-**5l**)	71:29	96; (54)		—	—
8	Cl	Me	44 (*anti*-**5m** + *syn*-**5m**)	93:7	95; (21)	95:5	Trace	n.d.
9[f]	Cl	Me	90 (*anti*-**5m** + *syn*-**5m**)	94:6	98; (21)	92:8	7 (**8m**)	80

[a] The reaction of **4a** (0.3 mmol, 1 equiv) with ketone (6.0 mmol, 20 equiv) in HMPA (3 mL) and H_2O (9.0 mmol, 30 equiv) was conducted in the presence of **2d** (0.06 mmol, 0.2 equiv) at room temperature for 4 d.
[b] Isolated yield.
[c] Diastereoisomeric and regioisomeric ratios were obtained by ^{1}H NMR of the crude mixture.
[d] Optical purity was determined by chiral HPLC (CHIRALPAK AS-H or AD-H). Absolute configuration of the major enantiomer was determined by comparing the measured optical rotation and the retention times with the reported data.[4j,5d,8b,19]
[e] The reaction was conducted for 12 d in the presence of H_2O (15 equiv).
[f] In the presence of H_2O (15 equiv) and **2d** (0.5 equiv).

Acknowledgments

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References and notes

1. (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (b) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65; (c) Guillena, G.; Najera, C.; Ramon, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249; (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
2. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496; (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
3. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
4. (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386; (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260; (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573; (d) Cordova, A.; Notz, W.; Barbas, C. F., III. *Chem. Commun.* **2002**, 3024; (e) Northrup, A. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798; (f) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16; (g) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475; (h) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839; (i) Northrup, A. B.; Mangion, I. K.; Hettche, F.; Macmillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152; (j) Zhou, Y.; Shan, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 1671.
5. (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; (c) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285; (d) 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; (e) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Cheng, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543; (f) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321; (g) He, L.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346; (h) Chimni, S. S.; Mahajan, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2108; (i) Vishnumaya, M. R.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097; (j) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198; (k) Zheng, J.-F.; Li, Y.-X.; Zhang, S.-Q.; Yang, S.-T.; Wang, X.-M.; Wang, Y.-Z.; Liu, F.-A. *Tetrahedron Lett.* **2006**, *47*, 7793; (l) Xu, X.-Y.; Wang, Y.-Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2007**, *18*, 237; (m) Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. *Tetrahedron* **2007**, *63*, 7892; (n) 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; (o) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J. *Can. J. Chem.* **2007**, *85*, 208.
6. (a) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 729; (b) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1027; (c) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 1493; (d) Guizzetti, S.; Benaglia, M.; Pignataro, L.; Puglisi, A. *Tetrahedron: Asymmetry* **2006**, *17*, 2754; (e) Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351; (f) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197; (g) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247; (h) Guillena, G.; Hita, M. C.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1272; (i) Wang, C.; Jiang, Y.; Zhang, X.-X.; Huang, Y.; Li, B.-G.; Zhang, G.-L. *Tetrahedron Lett.* **2007**, *48*, 4281; (j) Russo, A.; Botta, G.; Lattanzi, A. *Tetrahedron* **2007**, *63*, 11886; (k) Kikuchi, M.; Inagaki, T.; Nishiyama, H. *Synlett* **2007**, 1075.
7. (a) Hartikka, 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; (c) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570.
8. (a) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141; (b) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417.
9. (a) Bellis, E.; Kokotos, G. *Tetrahedron* **2005**, *61*, 8669; (b) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958; (c) Tang, X.; Liegault, B.; Renaud, J.-L.; Bruneau, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2187.
10. (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245; (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167; (c) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.
11. (a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055; (b) Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423; (c) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738.
12. Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.
13. O'Brien, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2117.
14. *Procedure for the synthesis of L-proline-2,4,6-trinitroanilide* (**2d**): To a solution of an L-prolineanilide (**2a**) (2.00 g, 10.5 mmol) in chloroform (40 mL) and sulfuric acid (8 mL), fuming nitric acid (2.6 mL, 63.5 mmol) was added at 0 °C. After being stirred at room temperature for 12 h, the reaction was quenched with saturated $NaHCO_3$ (500 mL). The resulting mixture was extracted with ethyl acetate (400 mL × 3) and the organic layers were dried over anhydrous Mg_2SO_4, and the solvent was removed in vacuo. The residue was recrystallized by acetonitrile to give **2d** as a yellow prism 2.79 g (8.6 mmol, 82%). *Analytical data for* **2d**: mp 174–178 °C. ^{1}H NMR (500 MHz, DMSO-d_6) 9.00 (1H, br), 8.66 (2H, s), 8.35 (1H, br), 4.05 (1H, dd, $J = 7.6$, 7.0 Hz), 3.23 (1H, dt, $J = 11.0$, 6.5 Hz), 3.11 (1H, dt, $J = 11.0$, 7.3 Hz), 2.16 (1H, m), 2.06 (1H, m), 1.85 (2H, m). ^{13}C NMR (125 MHz, DMSO-d_6) 170.7, 144.5, 144.4, 135.1, 122.7, 61.7, 45.7, 28.8, 23.5: $[\alpha]_D^{18.0}$ −155.2 (*c* 1.00, DMSO); IR (KBr, cm^{-1}) 3487, 3090, 2989, 2760, 2548, 1622, 1589, 1560, 1532, 1466, 1405, 1338, 1169, 1086, 1044, 975, 943, 922, 863, 779, 756, 738, 720, 617, 578, 526: Anal. Calcd for $C_{11}H_{11}N_5O_7$: C, 40.62; H, 3.41; N, 21.53. Found: C, 40.59; H, 3.36; N, 21.68.
15. Ee of **2d** was determined (>99% ee) by HPLC (SHISEIDO Chiral CD-Ph, 0.1 mol/L aq KPF_6:CH_3CN = 55:45) UV 254 nm, flow rate 0.5 mL/min, $t_{D\text{-}\mathbf{2d}} = 15.3$ min, $t_{L\text{-}\mathbf{2d}} = 16.5$ min.
16. *General procedure for the aldol reactions with* **2d**: To a solution of 4-nitrobenzaldehyde **4a** (47.75 mg, 0.3 mmol) and catalyst **2d** (19.57 mg, 0.06 mmol) in anhydrous HMPA (3 mL), water (0.162 mL, 9.0 mmol) and acetone (0.44 mL, 6.0 mmol) were added. After being stirred at room temperature for 4 d, the reaction was quenched with 1 N HCl (1 mL). The resulting mixture was extracted with ethyl acetate (50 mL) and organic layer was washed with brine (50 mL × 4). The organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by PTLC[20] (diethyl ether:*n*-hexane = 3:1) to give the aldol adducts **5a**, 56.2 mg (0.27 mmol, 90% yield).

17. Compounds **2a**[13] and **2b**[5b] are known compounds. Compound **2c** was prepared from **2a** with fuming nitric acid (2.3 equiv) and sulfuric acid in chloroform.
18. Compounds **3b**,**c** are known compounds.[6k] Compounds **3a**,**d**–**f** were prepared in the same manner as described in literature.[6k]
19. Maggiotti, V.; Wong, J.-B.; Razet, R.; Cowley, A. R.; Gouverneur, V. *Tetrahedron: Asymmetry* **2002**, *13*, 1789.
20. In the case of the aldol reactions using chloroacetone, we used ODS silica gel column chromatography (pentane:ethyl acetate = 70:1) instead of PTLC to avoid *syn*/*anti* isomerization of **5m**.