Highly Enantioselective Direct Aldol Reactions Catalyzed by Proline Derivatives Based on a Calix[4]arene Scaffold in the Presence of Water

Zheng-Yi Li,[a] Jia-Wen Chen,[a] Leyong Wang,*[a] Yi Pan*[b]

[a] Key Laboratory of Mesoscopic Chemistry of Ministry of Education, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, P. R. of China
Fax +86(25)83317761; E-mail: lywang@nju.edu.cn

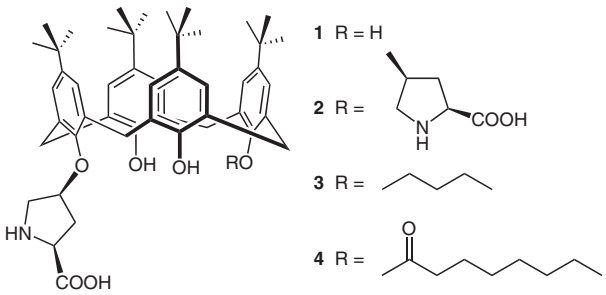
[b] State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, P. R. of China
E-mail: yipan@nju.edu.cn

Received 3 April 2009

Abstract: A series of proline-derived organocatalysts based on a calix[4]arene scaffold have been developed to catalyze direct aldol reactions in the presence of water. Under the optimal conditions, high yields (up to >99%), good enantioselectivities (up to >99% ee) and diastereoselectivities (up to 90:10) were obtained.

Key words: proline, calix[4]arene, organocatalyst, aldol reaction, water

Owing to the advantages of water over organic solvents, reactions in aqueous media have received a great deal of attention in recent years.[1] As the aldol reaction is a synthetically important carbon–carbon bond-forming reaction,[2] the development of enantioselective, aqueous aldol reactions is of considerable current interest and challenge.[3] So far, a great number of organocatalysts have been designed for the asymmetric aldol reaction in the presence of water, of which the most efficient proline-derived catalysts had been prepared by Hayashi,[4] Barbas III,[5] Armstrong,[6] Singh,[7] Gong,[8] Benaglia,[9] S. Wang,[10] W. Wang,[11] Gruttadauria,[12] Zhao,[10,13] and Fu.[14] Recently, Armstrong and co-workers developed an asymmetric catalytic system in water, mediated by sulfated β-cyclodexanone (β-CD), which can bind an organocatalyst of *tert*-butyl-phenoxyproline to catalyze stoichiometric direct aldol reactions of cyclohexanone and aryl aldehydes with excellent enantioselectivity and diastereoselectivity.[6] Calixarenes with hydrophobic cavities and hydrophilic phenolic hydroxyls such as β-CD have been used as inverse phase-transfer catalysts in many aqueous reactions.[15] Meanwhile, calix[4]arene-based organocatalysts have been developed for a direct aldol reaction under solvent-free conditions by Chen.[16] Herein, we wish to describe the design and use of novel organocatalysts possessing both an L-proline catalytic center and a calix[4]arene skeleton for the direct aqueous aldol reaction. The structures of the L-proline derivatives based on the calix[4]arene scaffold **1**–**4** are shown in Scheme 1. The hydrophobicity, reactivity, and selectivity can be appropriately tuned by ligating additional functions to the narrow (lower) rim of calix[4]arene via ether or ester linkages. Moreover, compared to **1**, catalyst **2** has two proline moieties which might act cooperatively in the catalytic process.

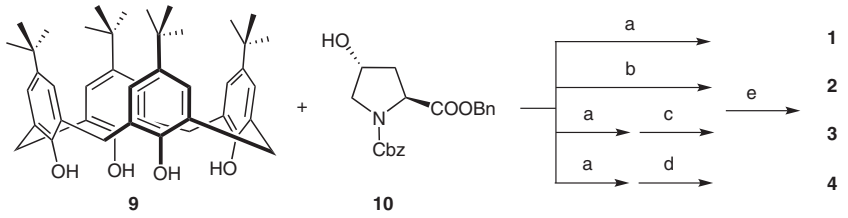


Scheme 1 Chemical structures of catalysts **1**–**4**

Catalysts **1**–**4**, with L-Proline based on calix[4]arene scaffolds, were prepared from 4-*tert*-butylcalix[4]arene **9**[17] and Cbz-L-proline derivative **10** in two or three steps (Scheme 2). First, Mitsunobu reactions of **9** and different loadings of **10** were carried out utilizing triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in toluene at 70 °C, according to a literature procedure, to smoothly give a range of proline-containing calixarene derivatives.[18] The Cbz and Bn groups were deprotected in methanol with Pd/C and H_2. For the preparation of **3** and **4**, prior to the deprotection, alkylation with 1-bromobutane in the presence of potassium carbonate in refluxing acetonitrile, or esterification with octanoyl chloride in pyridine was performed, respectively. The structures of **1**–**4**[19–22] were confirmed by ^{1}H and ^{13}C NMR spectra, ESI-MS spectrometry, and elemental analyses.

The catalytic activities of **1**–**4** for the asymmetric direct aldol reaction were evaluated by performing a model reaction between 4-nitrobenzaldehyde and cyclohexanone in the presence of water at room temperature. As a comparison, the catalytic properties of L-proline **5** and L-hydroxyproline **6** were also investigated. The results are summarized in Table 1. Catalyst **1** afforded the aldol adducts with higher diastereo- and enantioselectivities than catalysts **2**–**4** (Table 1, entries 1 *vs* 2–4), which might be attributed to their differing hydrophobicities.[1f] L-Proline **5** or L-hydroxyproline **6** without the calix[4]arene platform hardly catalyzed the aldol reaction in water at all[4e,5a,6] (Table 1, entries 5 and 6), which demonstrated the significance of the calix[4]arene skeletons in **1**–**4**. Therefore,

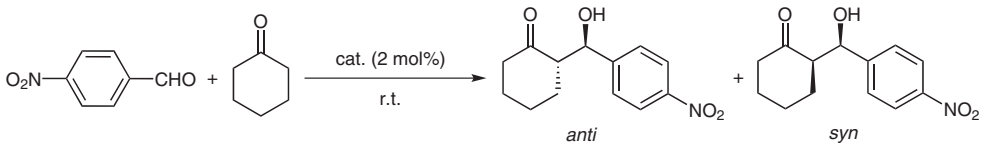
SYNLETT 2009, No. 14, pp 2356–2360
Advanced online publication: 31.07.2009
DOI: 10.1055/s-0029-1217710; Art ID: W05109ST



Scheme 2 Synthesis of catalysts **1**–**4**. *Reagents and conditions*: (a) **10** (1.1 equiv), Ph_3P, DIAD, toluene, 70 °C, 47%; (b) **10** (2.2 equiv), Ph_3P, DIAD, toluene, 70 °C, 78%; (c) 1-Bromobutane, K_2CO_3, MeCN, reflux, 96%; (d) Octanoyl chloride, pyridine, r.t., 75%; (e) Pd/C, H_2, MeOH, r.t., >99%. DIAD = diisopropyl azodicarboxylate.

catalyst **1** was chosen for further studies to determine the optimal conditions. The solvent effects on the reaction were then studied for catalyst **1**. The reactions in DMSO or under solvent-free conditions resulted in lower enantioselectivities and yields than in water (Table 1, entries 7 and 8 *vs* 1), which indicated that water was indispensable for the high enantioselectivity and yield. As depicted in Figure 1, a hydrophobic region and a hydrophilic region can be formed by the formation of hydrogen bonds between free OH groups of interfacial water molecules and OH and COOH groups of catalyst **1**, which enhances the activity of organic catalysis on water.[1f,g,12] Moreover, it is well-known that the yield, diastereo- and enantioselectivities could be significantly influenced by the loading of substrates and water.[4] Thus, different amount of 4-nitrobenzaldehyde, cyclohexanone and water were employed in order to further evaluate the catalytic efficiency of **1** (Table 1, entries 1 and 9–14). In these cases, increasing the amount of cyclohexanone could promote the yield, while the appropriate loading of water induced higher diastereo- and enantioselectivities because of solvation effect (Table 1, entries 13 *vs* 12 and 14). To our delight,

Table 1 Screening of Organocatalysts and Optimizing the Reaction Conditions for the Direct Asymmetric Aldol Reaction of Cyclohexanone with 4-Nitrobenzaldehyde[a]



Entry	Catalyst	Cyclohexanone (equiv)	Water (equiv)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%, *anti*)[c]
1	**1**	1	28	68	60:40	93
2	**2**	1	28	48	59:41	85
3	**3**	1	28	70	50:50	65
4	**4**	1	28	94	50:50	69
5	**5**	1	28	trace	–	–
6	**6**	1	28	trace	–	–
7[d]	**1**	1	–	40	60:40	56
8[e]	**1**	–	–	32	57:43	38
9	**1**	1	18	48	76:24	90
10	**1**	1	8	48	78:22	94
11	**1**	1	1	48	65:35	94
12	**1**	3	28	73	75:25	97
13	**1**	3	18	73	90:10	98
14	**1**	3	8	73	70:30	96

[a] Reagents and conditions: catalyst (2 mol%), 4-nitrobenzaldehyde (1 mmol), and cyclohexanone (1 or 3 mmol), water, r.t., 48 h.
[b] Combined yield of isolated diastereomers.
[c] Determined by HPLC analysis on a chiral phase.
[d] The reaction was performed in DMSO (0.5 mL).
[e] The reaction was performed in neat cyclohexanone (0.5 mL).

catalyst **1** could smoothly catalyze the aldol reaction in 73% yield with high diastereoselectivity (90:10, *anti*/*syn*) and enantioselectivity (98% ee) when 4-nitrobenzaldehyde (1 mmol), cyclohexanone (3 mmol), and water (18 mmol) were employed (Table 1, entries 13).

With the optimized conditions in hand, the substrate scope of the reaction was probed (Table 2 and Scheme 3). The corresponding aldol adducts were obtained in moderate to good yields (up to >99%) with up to >99% ee and up to 90:10 dr. As shown in Table 2, the electronic effects of the aromatic rings have a significant influence on the diastereo- and enantioselectivities. Aromatic aldehydes with electron-withdrawing groups afforded predominantly *anti*-products with excellent enantioselectivities (94 to >99% ee; Table 2, entries 1–4). In contrast, electron-rich 2-methoxybenzaldehyde gave more *syn*-product with 83% ee (Table 2, entry 9). In the case of neutral aromatic aldehydes, 3-chlorobenzaldehyde and benzaldehyde gave slight excesses of the *anti*-products, while good enantioselectivities (*syn*-95% ee and *anti*-81% ee) without diastereoselectivity were observed when 4-bromobenzaldehyde was employed (Table 2, entries 6–8). Moreover, moderate results were obtained when the fused-ring 2-naphthaldehyde was adopted (Table 2, entry 5). The catalytic system also worked for the challenging substrate cyclopentanone (Scheme 3). In this instance, the aldol process proceeded smoothly in high yield (>99%) with excellent enantioselectivity [99% ee *syn*- and >99% ee *anti*] and gave predominantly the *syn*-product (32:68, *anti*/*syn*). Different ketone substrates might lead to opposite diastereoselectivity in certain circumstance.[25]

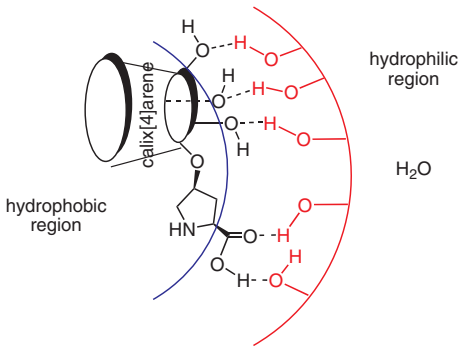
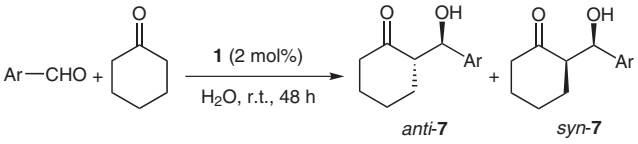


Figure 1 Proposed structure of catalyst **1** in the presence of water

Table 2 Aldol Reactions of Different Aromatic Aldehydes with Cyclohexanone Catalyzed by **1**[a]



Entry	Ar	Product	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%, *anti*)[c]	ee (%, *syn*)[c]
1	4-$O_2NC_6H_4$	**7a**	73	90:10	98	–
2	2-$O_2NC_6H_4$	**7b**	63	89:11	>99	–
3	3-$O_2NC_6H_4$	**7c**	59	66:34	94	–
4	4- $F_3CC_6H_4$	**7d**	54	67:33	96	–
5	2-naphthyl	**7e**	63	68:32	74	–
6	3-ClC_6H_4	**7f**	50	55:45	97	–
7	C_6H_5	**7g**	37	54:46	63	–
8	4-BrC_6H_4	**7h**	71	50:50	81	95
9[d]	2-$MeOC_6H_4$	**7i**	23	12:88	–	83

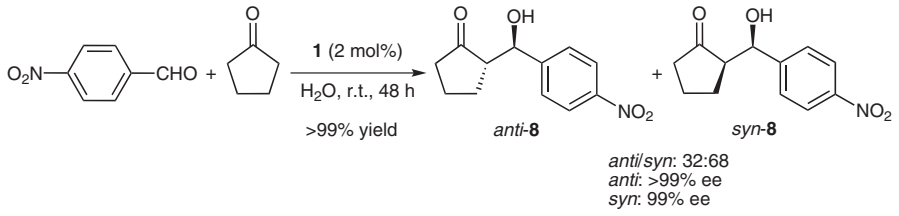
[a] Reagents and conditions: **1** (2 mol%), aromatic aldehyde (1 mmol), ketone (3 mmol), H_2O (324 μL, 18 mmol), r.t., 48 h.[23]
[b] Combined yield of isolated diastereomers.
[c] Determined by HPLC analysis on a chiral phase.[24]
[d] The reaction was carried out for 96 h.

In conclusion, a series of novel organocatalysts containing proline on calix[4]arene scaffolds have been synthesized and applied to the direct aldol reactions of aromatic aldehydes with cyclohexanone or cyclopentanone in the presence of water. Under the optimal conditions, high yields (up to >99%), enantioselectivities (up to >99% ee), and diastereoselectivities (up to 90:10) were obtained. The diastereoselectivities can be tuned by adjusting the electronic effects of the aromatic rings. Further studies on the mechanism, generality of substrates, other applications of these catalysts, and the design of more efficient catalysts for the asymmetric reactions in water are underway.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We gratefully acknowledge financial support from the Natural Science Foundation of China (No. 20602017), National Basic Research Program of China (2007CB925103), and Program for New Century Excellent Talents in University (NCET-07-0425). This work was also partially supported by research funds from the 'Qing-Lan Program' of Jiangsu Province. The referees are acknowledged for helpful comments.



Scheme 3 Direct asymmetric aldol reaction of cyclopentanone with 4-nitrobenzaldehyde catalyzed by **1** in the presence of water

References and Notes

(1) (a) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (d) Pirrung, M. C. *Chem. Eur. J.* **2006**, *12*, 1312. (e) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3798. (f) Lindström, U. M.; Andersson, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 548. (g) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492.

(2) (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim / Germany, **2005**. (b) Dean, S. M.; Greenberg, W. A.; Wong, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 1308.

(3) (a) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502. (b) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 8100.

(4) (a) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 958. (b) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5527. (c) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, 2524. (d) Hayashi, Y.; Aratake, S.; Itoh, T.; Okano, T.; Sumiya, T.; Shoji, M. *Chem. Commun.* **2007**, 957. (e) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246.

(5) (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III *J. Am. Chem. Soc.* **2006**, *128*, 734. (b) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F. III. *Org. Lett.* **2008**, *10*, 1621.

(6) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 9073.

(7) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593.

(8) (a) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1390. (b) Zhao, J.-F.; He, L.; Jiang, J.; Tang, Z.; Cun, L.-F.; Gong, L.-Z. *Tetrahedron Lett.* **2008**, *49*, 3372.

(9) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247.

(10) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417.

(11) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211.

(12) Giacalone, F.; Gruttadauria, M.; Meo, P. L.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747.

(13) Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. *Adv. Synth. Catal.* **2008**, *350*, 2690.

(14) (a) Zhang, S.-P.; Fu, X.-K.; Fu, S.-D.; Pan, J.-F. *Catal. Commun.* **2009**, *10*, 401. (b) Zhang, S.-P.; Fu, X.-K.; Fu, S.-D. *Tetrahedron Lett.* **2009**, *50*, 1173.

(15) (a) Shimizu, S.; Kito, K.; Sasaki, Y.; Hirai, C. *J. Chem. Soc., Chem. Commun.* **1997**, 1629. (b) Shimizu, S.; Suzuki, T.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Adv. Synth. Catal.* **2002**, *344*, 370. (c) Nomura, E.; Taniguchi, H.; Kawaguchi, K.; Otsuji, Y. *Chem. Lett.* **1991**, 2167. (d) Nomura, E.; Taniguchi, H.; Kawaguchi, K.; Otsuji, Y. *J. Org. Chem.* **1993**, *58*, 4709. (e) Taniguchi, H.; Nomura, E. *Chem. Lett.* **1988**, 1773. (f) Komiyama, M.; Isaka, K.; Shinkai, S. *Chem. Lett.* **1991**, 937.

(16) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *64*, 8668.

(17) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1990**, *68*, 234.

(18) Dondoni, A.; Marra, A.; Scherrmann, M.-C.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Eur. J.* **1997**, *3*, 1774.

(19) Analytical data for compound **1**: Yield: 47%. White solid, mp 233–235 °C. $[\alpha]_D^{26}$ +21.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, DMSO-d_6): δ = 1.11 [s, 9H, $C(CH_3)_3$], 1.16 [s, 18H, 2 × $C(CH_3)_3$], 1.17 [s, 9H, $C(CH_3)_3$], 3.34 (d, *J* = 8.1 Hz, 2H, CH_2), 3.40–3.47 (m, 4H, $ArCH_2Ar$), 3.34 (d, *J* = 12.3 Hz, 2H, NCH_2), 4.03–4.09 (m, 4H, $ArCH_2Ar$), 4.37–4.43 (m, 2H, NCHCO + OCH), 4.59 (s, 1H, NH), 6.98–7.22 (m, 8H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.4, 31.7, 32.6, 34.1, 34.3, 36.4, 51.0, 60.5, 84.1, 125.2, 126.1, 126.5, 128.2, 128.4, 130.2, 130.4, 133.6, 133.8, 143.0, 146.4, 148.3, 148.6, 148.9, 150.8, 171.8. IR (KBr): 3440, 2959, 2869, 1629, 1485, 1364, 1299, 1262, 1204, 1031, 909, 874, 802 cm^{-1}. Anal. Calcd for $C_{49}H_{63}NO_6$: C, 77.23; H, 8.33; N, 1.84. Found: C, 77.52; H, 8.06; N, 1.65. ESI-MS: *m/z* (%) = 762 (8) $[M + 1]^+$, 784 (100) $[M + Na]^+$.

(20) Analytical data for compound **2**: Yield: 78%. White solid, mp 261–263 °C. $[\alpha]_D^{26}$ +43.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, CD_3OD): δ = 1.07 [s, 18H, 2 × $C(CH_3)_3$], 1.24 [s, 18H, 2 × $C(CH_3)_3$], 2.72 (m, 2H, CH_2), 2.84–2.90 (m, 2H, CH_2), 3.35–3.48 (m, 4H, $ArCH_2Ar$), 3.68–3.74 (m, 2H, NCH_2), 4.17–4.38 (m, 8H, NCH_2 + $ArCH_2Ar$ + OCH), 4.65–4.69 (m, 2H, NCHCO), 5.08 (s, 2H, NH), 7.05–7.16 (m, 8H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.8, 31.5, 33.7, 51.2, 60.0, 85.1, 124.8, 124.9, 125.5, 125.9, 127.9, 128.0, 128.5, 131.0, 131.1, 131.7, 141.9, 146.5, 149.9, 173.6, 173.7. IR (KBr): 3448, 2961, 2868, 1632, 1485, 1393, 1362, 1300, 1203, 1124, 1035, 979, 873 cm^{-1}. Anal. Calcd for $C_{54}H_{70}N_2O_8$: C, 74.11; H, 8.06; N, 3.20. Found: C, 74.32; H, 7.86; N, 3.45. ESI-MS: *m/z* (%) = 898 (100) $[M + Na]^+$.

(21) Analytical data for compound **3**: Yield: 96%. White solid, mp 137–139 °C. $[\alpha]_D^{27}$ –6.7 (*c* = 8.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 [s, 9H, $C(CH_3)_3$], 0.94 [s, 9H, $C(CH_3)_3$], 1.06 (t, *J* = 7.2 Hz, 3H, CH_3), 1.25 [s, 9H, $C(CH_3)_3$], 1.31 [s, 9H, $C(CH_3)_3$], 1.58–1.72 (m, 2H, CH_2), 1.81–1.98 (m, 2H, CH_2), 2.43–2.52 (m, 1H, CH_2), 2.65–2.82 (m, 1H, CH_2), 3.21–3.34 (m, 4H, $ArCH_2Ar$), 3.58 (br s, 2H, $ArOCH_2$), 3.91–3.96 (m, 2H, NCH_2), 4.01–4.28 (m, 4H, $ArCH_2Ar$), 4.39–4.51 (m, 2H, OCH + NCHCOO), 6.53–6.81 (m, 4H, ArH), 6.98–7.06 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 19.3, 33.7, 33.8, 34.9, 59.7, 84.0, 124.8, 125.1, 125.3, 125.7, 125.8, 127.0, 127.3, 128.2, 128.4, 131.5, 132.1, 132.2, 141.4, 146.3, 146.8, 149.3, 149.4, 150.2, 173.1. IR (KBr): 3441, 2960, 2870, 1717, 1635, 1485, 1392, 1362, 1300, 1201, 1123, 1026, 872 cm^{-1}. Anal. Calcd for $C_{53}H_{71}NO_6$: C, 77.81; H, 8.75; N, 1.71. Found: C, 77.42; H, 8.96; N, 1.45. ESI-MS: *m/z* (%) = 818 (23) $[M + 1]^+$, 840 (100) $[M + Na]^+$.

(22) Analytical data for compound **4**: Yield: 75%. White solid, mp 157–159 °C. $[\alpha]_D^{27}$ –31.3 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 [s, 9H, $C(CH_3)_3$], 0.87 [s, 9H, $C(CH_3)_3$], 0.91 (t, *J* = 7.2 Hz, 3H, CH_3), 1.27 [s, 9H, $C(CH_3)_3$], 1.29–1.31 (m, 5H, CH_2), 1.32 [s, 9H, $C(CH_3)_3$], 1.46–1.51 (m, 2H, CH_2), 1.60–1.65 (m, 1H, CH_2), 1.80–1.94 (m, 2H, CH_2), 2.33 (t, *J* = 7.5 Hz, 2H, $OOCCH_2$), 2.71–2.93 (m, 2H, CH_2), 3.23–3.39 (m, 4H, $ArCH_2Ar$), 3.76 (d, *J* = 13.5 Hz, 2H, NCH_2), 3.99–4.16 (m, 4H, $ArCH_2Ar$), 4.01–4.48 (m, 2H, OCH + NCHCOO), 5.50 (s, 1H, OH), 5.63 (s, 1H, OH), 6.57–7.08 (m, 8H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.5, 24.9, 29.0, 29.1, 30.7, 30.8, 31.3, 31.4, 31.6, 33.8, 35.5, 49.0, 59.9, 84.3, 124.8, 125.0, 125.3, 126.0, 126.9, 127.3, 127.6, 127.7, 129.0, 130.7, 131.0, 131.4, 132.0, 141.8, 142.0, 142.2, 147.0, 148.0, 148.3, 149.7, 149.9, 172.0, 173.3, 178.0. IR (KBr): 3520, 2957, 2868, 1761, 1634, 1485, 1363, 1301, 1204, 1139, 1122, 1037, 873 cm^{-1}. Anal. Calcd for $C_{57}H_{77}NO_7$: C, 77.08; H, 8.74; N, 1.58. Found: C, 77.34; H, 8.46; N, 1.35. ESI-MS: *m/z* (%) = 888 (26) $[M + 1]^+$, 910 (100) $[M + Na]^+$.

(23) General procedure for asymmetric aldol reactions: Catalyst **1** (2 mol%) was added to a suspension of aldehyde (1.0 mmol) and ketone (3.0 mmol) in water (324 μL, 18 mmol) at room temperature. The mixture was allowed to stir for the

given time, then ethyl acetate (10 mL) and anhydrous $MgSO_4$ (0.6 g) were added. After filtration, the solvent was evaporated under vacuum and the crude products were purified by flash chromatography (hexane–EtOAc). The *anti*/*syn* ratio (diastereoselectivity) and enantiomeric excess (enantioselectivity) were determined by chiral HPLC analysis (see ref 24).

(24) Compound **7a**: Yield: 73%; Ratio *anti*/*syn* = 90:10. HPLC conditions: Daicel Chiralpak AD-H column; *i*-PrOH–Hexane, 5:95; flow rate 1.0 mL/min; λ = 254 nm; 20 °C. *anti*-Diastereomer: t_R(major) = 60.2 min and t_R(minor) = 43.5 min; 98% ee. For further data on **7** and HPLC spectra, see Supporting Information.

(25) (a) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Adv. Synth. Catal.* **2007**, *349*, 1041. (b) Ma, G.-N.; Zhang, Y.-P.; Shi, M. *Synthesis* **2007**, 197.