

A novel (*S*)-proline-modified task-specific chiral ionic liquid—an amphiphilic recoverable catalyst for direct asymmetric aldol reactions in water

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Abstract

A novel chiral (*S*)-proline-modified task-specific ionic liquid has been designed and synthesized as an efficient recoverable organo-catalyst for the direct asymmetric aldol reaction between cycloalkanones and aromatic aldehydes in the presence of water. The catalyst retains its activity and selectivity over at least five reaction cycles.

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The direct asymmetric aldol reaction between unmodified ketones and aldehydes is a convenient method for the synthesis of chiral organic compounds. In Nature this reaction is catalyzed by native aldolase ferments.¹ In the laboratory, small organic molecules, which simulate aldolase action, in particular amino acids² and their derivatives,³ low-molecular weight peptides⁴ and substituted pyrrolidines,⁵ are used as the catalysts. Aldol reactions run with an excess of the ketone,^{3a,6} in dipolar organic solvents,^{2a,b,3d,5b,6d,7} or in ionic liquids, have become popular in recent years.⁸

A few examples of asymmetric aldol reactions in the presence of water, which is the most cost-effective and environment-friendly reaction medium, have been published.^{3f,h,9,10} High conversions and selectivity were achieved in reactions catalyzed by water-insoluble organo-catalysts bearing hydrophobic fragments, in particular long-chained hydrocarbon moieties C_nH_{2n+2} ($n \geq 10$),^{10a} binaphthyl^{10h} or trialkyl(aryl)silyl groups,^{3g,10f,g} polysty-

rene^{10c,d} or dendritic fragments.^{10b} Reactions in heterogeneous aqueous systems containing hydrophobic catalysts and reagents were characterized by Sharpless as ‘reactions on water’.^{11a} Thus, organic molecules react with each other inside or on the surface of concentrated organic associates (micelles) where efficient stereo-control in the transition state is ensured by hydrogen bonds between the reagents and catalysts.^{10a,11b,12} The important role of the organic associations at the organic/water interfacial region is consistent with the moderate rate and enantioselectivity of aldol reactions catalyzed by water-soluble amino acids^{10e,f} and with the favorable influence of organic acids^{10a,e,h-j,13a} and/or surfactants^{13b,c} on heterogeneous aldol reactions ‘on water’.

In spite of the impressive results obtained during the last decade in implementing aqueous media in organic synthesis,¹⁴ the development of efficient recoverable catalysts for the asymmetric aldol reaction ‘on water’ has so far remained challenging. Indeed, the syntheses of recoverable 4-hydroxyproline and proline amide derivatives bearing polymer^{10c,d} or dendritic moieties^{10b} are rather complicated and/or require expensive starting compounds. The catalytic activity of more readily available hydroxyl amino acid

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trialkyl(aryl)silyl esters was reduced noticeably in the 2nd or 3rd runs^{10f} probably due to the gradual hydrolysis of the Si–O bond. Multi-component catalytic systems containing organic acids or surfactants could normally be used successfully only once per run.

Recoverability is a characteristic feature of amphiphilic organocatalysts containing ionic liquid fragments. Yet, the aldol reactions catalyzed by a pyrrolidine derivative modified with an imidazolium cation proceed with poor diastereo- and enantioselectivity.^{9g} In addition, we have found that (*S*)-proline-containing ionic liquid **1**, being an efficient organocatalyst of asymmetric aldol reactions in organic solution,¹⁵ is completely inactive in an aqueous environment.

It might be expected that hydrophobic structural analogs of catalyst **1** bearing long-chain hydrocarbon groups at the imidazolium nitrogen atoms and being poorly soluble in aqueous media would possess a much higher activity in asymmetric aldol reactions in water (Scheme 1).

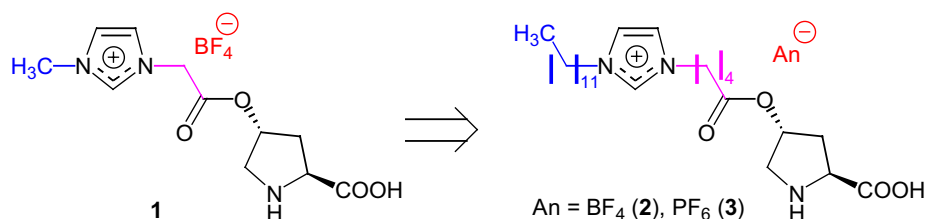
To verify this hypothesis, we synthesized new amphiphilic chiral imidazolium salts **2** and **3** bearing hydrophilic (BF_4^-) and hydrophobic (PF_6^-) anions, respectively. The synthetic scheme included esterification of (2*S*,4*S*)-*N*-Cbz-4-hydroxyproline benzyl ester (**4**)¹⁶ under the action of 5-bromovaleric acid and DCC/DMAP,¹⁷ subsequent reaction of ester **5** with *n*-dodecyl imidazole^{18,19} followed by

deprotection of the resulting salt **6**²⁰ and metathesis of the anion in the product amino acid **7**^{21,22} (Scheme 2).

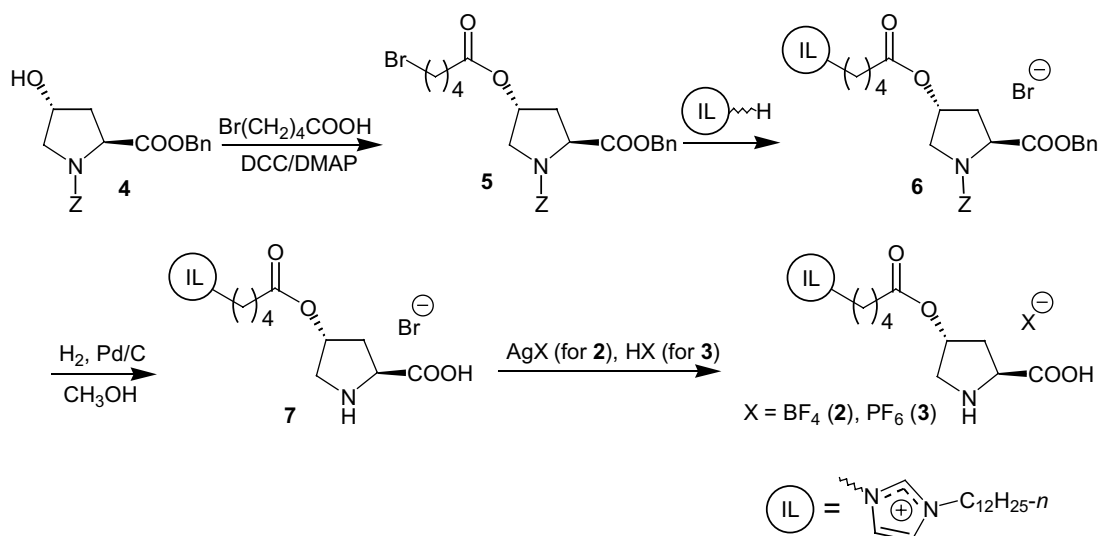
Salts **2** and **3** melt at 119 °C and 158 °C, respectively, and can be described as ionic liquids. They have quite different solubility in water. Tetrafluoroborate **2** gave a clear 5% aqueous solution at 20 °C, whereas hexafluorophosphate **3**/water mixture was a suspension under the same conditions.

We studied the catalytic activity of chiral salts **2** and **3** in the model aldol reaction between cyclohexanone **8a** (3 equiv) and *p*-nitrobenzaldehyde **9a** in the presence of water at 20 °C. The amount of organocatalyst was 30 mol % with respect to aldehyde **9a**. The reaction did not occur in the presence of the water-soluble compound **2**. However, with salt **3**/water suspension, it proceeded with high conversion to afford chiral aldol **10a** with extremely high diastereo- and enantioselectivity (Table 1, entry 1).

Next, we applied catalyst **3** in the asymmetric aldol reactions between cycloalkanones **8a,b** and aromatic aldehydes **9a–d**.²³ In all the cases, the corresponding aldols **10b–e** were obtained. High conversions ($\geq 86\%$) were achieved after 10 h in the reactions of aldehydes **9a,b** bearing electron-withdrawing groups on the aromatic ring (Table 1, entries 2 and 5). *p*-Methoxybenzaldehyde (**9d**) was found to be less active under the conditions studied: about 80% of the starting compound remained intact after 64 h.



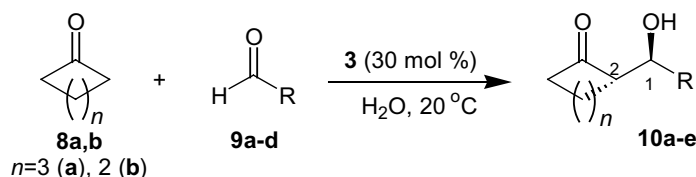
Scheme 1. Synthetic strategy.



Scheme 2. Synthesis of amphiphilic (*S*)-proline-modified chiral salts **2** and **3**.

Table 1

The catalytic asymmetric aldol reaction between compounds **8** and **9** in the presence of water catalyzed by amphiphilic organocatalyst **3**



Entry	8	9 (<i>R</i>)	10	Time ^a (h)	Conversion ^a (%)	dr ^a [<i>anti</i> : <i>syn</i>]	ee, <i>anti</i> -isomer ^{a,b} (%)
1	a	a (<i>p</i> -NO ₂ C ₆ H ₄)	a	10 (5, ²⁵ 20 ^{9g})	>95 (86, ²⁵ 93 ^{9g})	97:3 (20:1, ²⁵ 1:1 ^{9g})	>99 (>99, ²⁵ 10 ^{9g})
2	a	b (<i>p</i> -CH ₃ O ₂ CC ₆ H ₄)	b	10	86	97:3	>99
3	a	c (C ₆ H ₅)	c	36 (18, ²⁵ 80 ^{9g})	67 (78, ²⁵ 66 ^{9g})	93:7 (13:1, ²⁵ 1.3:1 ^{9g})	88 (>99, ²⁵ 9 ^{9g})
4	a	d (<i>p</i> -CH ₃ OC ₆ H ₄)	d	64 (50 ²⁵)	20 (21 ²⁵)	84:16 (5:1 ²⁵)	80 (96 ²⁵)
5	b	a (<i>p</i> -NO ₂ C ₆ H ₄)	e	10 (6 ^{9g})	>95 (87 ^{9g})	85:15 (1:2.8 ^{9g})	91 (5 ^{9g})

^a Reported data are given in brackets.

^b HPLC, chiral phase: Chiralcel OD-H, OJ-H.

Table 2

Recycling of catalyst **3** in the asymmetric aldol reaction (10 h) between compounds **8a** and **9b** 'on water'

Cycle	Conversion ^a (%)	dr of aldol 10b ^a [<i>anti</i> : <i>syn</i>]	ee of aldol 10b ^b (%)
1	86	97:3	>99
2	88	96:4	99
3	86	96:4	98
4	85	97:3	99
5	83	97:3	99

^a Determined by ¹H NMR.

^b Determined by HPLC.

According to ¹H NMR data ($J_{\text{H1-H2,anti}} = 5.5\text{--}10.0$ Hz, $J_{\text{H1-H2,syn}} < 2.4$ Hz) the *anti*/*syn* diastereomeric ratio (dr) of aldols **10b–e** was high ($\geq 84:16$) irrespective of the aldehyde structure.[†] Moreover, the ee's of the major *anti*-isomers were noticeably higher than those under the influence of the pyrrolidine-derived amphiphilic catalyst and similar to those achieved in the asymmetric aldol reactions 'on water' catalyzed by the most efficient 4-siloxy-(*S*)-proline derivatives.²⁵

The recyclability of the catalytic system **3**/H₂O was demonstrated in the asymmetric aldol reaction between compounds **8a** and **9b**. After completion of the reaction, aldol **10b** was extracted with diethyl ether and replaced with fresh starting mixtures **8a** and **9b**. Catalyst **3** retained its activity and selectivity over at least five reaction cycles (Table 2).

In conclusion, we have synthesized novel (*S*)-proline-modified task-specific chiral ionic liquid **3** and demonstrated its effectiveness as a recoverable catalyst for direct asymmetric aldol reactions in the presence of water. Ionic liquid structure optimization aimed at improving the cata-

lyst activity and widening the reaction scope is currently underway.

Acknowledgments

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[†] It is worth mentioning that the *syn*-diastereomer was the major component of aldol **10e** obtained from compounds **8b** and **9a** under the action of (*S*)-proline in an excess of ketone²⁴ or 1-(pyrrolidyl-2-methyl)-3-butyrimidazolium tetrafluoroborate in water.^{9g}

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17. *Dibenzyl 4-((5-bromopentanoyl)oxy)pyrrolidine-1,2-dicarboxylate (5)*. A mixture of compound **4**¹⁶ (4.01 g, 11.30 mmol), 5-bromovaleric acid (2.09 g, 11.55 mmol), DCC (2.38 g, 11.55 mmol), DMAP (20 mg, 0.16 mmol), and CH₂Cl₂ (60 ml) was stirred at 5 °C for 3 h. The resulting precipitate was filtered off and washed with CH₂Cl₂ (3 × 10 ml). The combined organic extracts were washed successively with 35% HCl (2 × 15 ml) and distilled water (2 × 20 ml). The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (Acros, 60–200 μm, 60 Å, eluent *n*-hexane/EtOAc 4:1) to afford compound **5** (4.73 g, 80%) as a colorless viscous oil; $[\alpha]_D^{25}$ –30.2 (*c* 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃), δ: 7.18–7.43 (10H, m, Ph), 5.30 (1H, s, CHO), 4.98–5.27 (4H, m, PhCH₂), 4.52 (1H, dt, *J* = 19.5, 7.7 Hz, CHCOO), 3.62–3.85 (2H, m, CH₂N), 3.41 (2H, t, *J* = 6.4 Hz, BrCH₂), 2.15–2.49 (2H, m, CHCH₂CH), 2.33 (2H, t, *J* = 6.4 Hz, CH₂CH₂COO), 1.68–1.93 (4H, m, BrCH₂CH₂CH₂) ppm; ¹³C NMR (75 MHz, CDCl₃), δ: 172.32, 171.78, 154.34, 136.13, 135.22, 128.58, 128.54, 128.46, 128.27, 128.00, 127.83, 72.13, 67.25, 66.96, 57.77, 52.32, 36.51, 35.47, 33.07, 31.73, 23.20 ppm. Anal. Calcd for C₂₅H₂₈BrN₃O₆: C, 57.92; H, 5.44; N, 2.70; Br, 15.41. Found: C, 58.14; H, 5.31; N, 2.74; Br, 15.27. *R*_f = 0.35 (*n*-hexane/ethyl acetate 3:1).
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19. *1-(5-((1,5-Bis((benzyloxy)carbonyl)pyrrolidin-3-yl)oxy)-5-oxopentyl)-3-dodecyl-1H-imidazol-3-ium bromide (6)*. A mixture of compound **5** (1.10 g, 2.12 mmol) and 1-(*n*-dodecyl)imidazole (0.60 g, 2.54 mmol) was heated at 90 °C for 10 min, cooled to 20 °C and washed with Et₂O (6 × 15 ml). The residue was dissolved in MeOH (3 ml), and Et₂O (15 ml) was gradually added to the stirred solution. The separated oil was dried in vacuo (0.5 Torr) for 2 h to afford compound **6** (1.13 g, 71%) as a yellow viscous oil; $[\alpha]_D^{19}$ –17.1 (*c* 1.33, CH₃OH); ¹H NMR (300 MHz, CDCl₃), δ: 10.72 (1H, s, NCHN), 7.16–7.39 (12H, m, Ph, NCHCHN), 5.27 (1H, s, CHO), 4.98–5.23 (4H, m, CH₂Ph), 4.24–4.54 (5H, m, CH₂CH₂N, CH₂CHN), 3.61–3.82 (2H, m, CHCH₂N), 2.40 (2H, t, *J* = 7.3 Hz, CH₂CH₂COO), 2.17–2.51 (2H, m, CH₂CHN), 1.84–2.02 (4H, m, CH₂CH₂N), 1.59–2.71 (2H, m, CH₂CH₂COO), 1.21–1.38 (18H, m, CH₃(CH₂)₉), 0.88 (3H, t, *J* = 6.8 Hz, CH₃) ppm; ¹³C NMR (75 MHz, CDCl₃), δ: 172.13, 171.58, 154.28, 136.61, 136.01, 135.08, 128.40, 128.31, 128.18, 127.98, 127.90, 127.63, 122.27, 121.83, 72.13, 67.14, 66.86, 57.67, 52.19, 49.93, 49.31, 35.78, 32.94, 31.68, 30.08, 29.47, 29.39, 29.31, 29.19, 29.12, 28.81, 26.07, 22.47, 21.04, 13.94 ppm. Anal. Calcd for C₄₀H₅₆BrN₃O₆: C, 63.65; H, 7.48; N, 5.57; Br, 10.59. Found: C, 63.82; H, 7.41; N, 5.69; Br, 10.48.
20. *4-((5-(3-Dodecyl-1H-imidazol-3-ium-1-yl)pentanoyl)oxy)proline bromide (7)*. A mixture of compound **6** (1.13 g, 1.50 mmol), Pd/C (5%) (0.11 mg), and dry CH₃OH (35 ml) was stirred under H₂ (760 Torr) at ambient temperature for 2 h. The resulting precipitate was filtered off, and the filtrate was evaporated in vacuo. The residue was dissolved in MeOH (2.5 ml), and Et₂O (12 ml) was gradually added to the stirred solution. The separated oil was dried in vacuo (0.5 Torr) for 2 h to afford amino acid **7** (0.70 g, 87%) as a pale yellow oil; $[\alpha]_D^{19}$ –13.2 (*c* 1.22, CH₃OH); ¹H NMR (300 MHz, DMSO-*d*₆), δ: 9.26 (1H, s, NCHN), 7.82 (2H, s, NCHCHN), 5.18–5.23 (1H, m, CHO), 4.11–4.22 (4H, m, CH₂CH₂N), 3.80 (1H, t, *J* = 8.9 Hz, CH₂CHN), 3.08–3.50 (2H, m, CHCH₂N), 2.37 (2H, t, *J* = 6.6 Hz, CH₂CH₂COO), 2.04–2.23 (2H, m, CH₂CHN), 1.72–1.88 (4H, m, CH₂CH₂N), 1.43–1.55 (2H, m, CH₂CH₂COO), 1.22 (18H, s, CH₃(CH₂)₉), 0.85 (3H, t, *J* = 6.1 Hz, CH₃) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆), δ: 172.07, 169.90, 136.04, 122.49, 122.44, 73.25, 59.37, 49.91, 48.88, 48.49, 35.06, 32.58, 31.32, 29.34, 29.04, 28.96, 28.85, 28.74, 28.68, 28.38, 25.53, 22.11, 20.72, 13.93 ppm. Anal. Calcd for C₂₅H₄₄BrN₃O₄: C, 56.60; H, 8.36; N, 7.92; Br, 15.06. Found: C, 56.79; H, 8.29; N, 8.03; Br, 14.91.
21. *4-((5-(3-Dodecyl-1H-imidazol-3-ium-1-yl)pentanoyl)oxy)proline tetrafluoroborate (2)*. A solution of AgBF₄ (0.24 g, 1.23 mmol) in CH₃OH (5 ml) was gradually added to a stirred solution of amino acid **7** (0.65 g, 1.23 mmol) in the same solvent (5 ml). The resulting precipitate was filtered off and washed with CH₃OH (5 ml). The combined organic extracts were evaporated, and the residue was dried in vacuo (0.5 Torr) for 2 h to afford tetrafluoroborate **2** (0.64 g, 98%) as colorless hygroscopic crystals, mp 117–119 °C; $[\alpha]_D^{19}$ –11.8 (*c* 1, CH₃OH); ¹H NMR (300 MHz, DMSO-*d*₆), δ: 9.19 (1H, s, NCHN), 7.79 (2H, s, NCHCHN), 5.17–5.23 (1H, m, CHO), 4.11–4.21 (4H, m, CH₂CH₂N), 3.81 (1H, t, *J* = 8.9 Hz, CH₂CHN), 3.08–3.50 (2H, m, CHCH₂N), 2.36 (2H, t, *J* = 6.6 Hz, CH₂CH₂COO), 2.05–2.23 (2H, m, CH₂CHN), 1.73–1.86 (4H, m, CH₂CH₂N), 1.43–1.54 (2H, m, CH₂CH₂COO), 1.23 (18H, s, CH₃(CH₂)₉), 0.85 (3H, t, *J* = 6.1 Hz, CH₃) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆), δ: 172.07, 169.90, 136.04, 122.49, 122.44, 73.25, 59.37, 49.91, 48.88, 48.49, 35.06, 32.58, 31.32, 29.34, 29.04, 28.96, 28.85, 28.74, 28.68, 28.38, 25.53, 22.11, 20.72, 13.93 ppm; ¹¹B NMR (64.21 MHz, DMSO-*d*₆), δ: –1.08 ppm; ¹⁹F NMR (188.31 MHz, DMSO-*d*₆), δ: –147.6 ppm. Anal. Calcd for C₂₅H₄₄BF₄N₃O₄: C, 55.87; H, 8.25; N, 7.82; F, 14.14. Found: C, 56.05; H, 8.17; N, 7.68; F, 13.99.
22. *4-((5-(3-Dodecyl-1H-imidazol-3-ium-1-yl)pentanoyl)oxy)proline hexafluorophosphate (3)*. A solution of amino acid **7** (0.10 g, 0.19 mmol) in water (5 ml) was adjusted to pH ~2–3 with 60% HPF₆ (0.06 ml, 0.38 mmol) at 20 °C. The reaction mixture was then adjusted to pH ~8–9 with 25% NH₃. The resulting precipitate was filtered off, and washed with water until the washings became neutral

and then dried in vacuo (0.5 Torr) for 2 h to afford hexafluorophosphate **3** (0.11 g, 95%) as a colorless powder, mp 156–158 °C; $[\alpha]_D^{19}$ –10.8 (*c* 1, CH₃OH); ¹H NMR (300 MHz, DMSO-*d*₆), δ : 9.20 (1H, s, NCHN), 7.79 (2H, s, NCHCHN), 5.18–5.22 (1H, m, CHO), 4.11–4.22 (4H, m, CH₂CH₂N), 3.79 (1H, t, *J* = 8.9 Hz, CH₂CHN), 3.06–3.49 (2H, m, CHCH₂N), 2.37 (2H, t, *J* = 6.6 Hz, CH₂CH₂COO), 2.03–2.23 (2H, m, CH₂CHN), 1.71–1.88 (4H, m, CH₂CH₂N), 1.42–1.55 (2H, m, CH₂CH₂COO), 1.22 (18H, s, CH₃(CH₂)₉), 0.85 (3H, t, *J* = 6.1 Hz, CH₃) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆), δ : 172.07, 169.90, 136.04, 122.49, 122.44, 73.25, 59.37, 49.91, 48.88, 48.49, 35.06, 32.58, 31.32, 29.34, 29.04, 28.96, 28.85, 28.74, 28.68, 28.38, 25.53, 22.11, 20.72, 13.93 ppm; ¹⁹F NMR (188.31 MHz, DMSO-*d*₆), δ : –67.4, –71.1 ppm; ³¹P NMR (81.02 MHz, DMSO-*d*₆), δ : –42.46 (hp, *J* = 8.8 Hz) ppm. Anal. Calcd for C₂₅H₄₄F₆N₃O₄P: C, 50.41; H, 7.45; N, 7.06; F, 19.14. Found: C, 50.59; H, 7.37; N, 6.95; F, 18.97.

23. *Typical procedure for the aldol reaction*: A mixture of organocatalyst **3** (23.2 mg, 0.039 mmol), ketone **8** (0.40 mmol), aldehyde **9** (0.13 mmol), and distilled water (0.5 ml) was stirred at 20 °C for the period given in Tables 1 and 2. Aldol **10** and the remaining starting compounds were extracted with Et₂O (3 × 5 ml), the combined extracts were dried over anhydrous NaSO₄, the solvent was evaporated in vacuo (15 Torr) and the residue was purified by column chromatography on silica gel (Acros, 40–60 μm, 60 Å, eluent *n*-hexane/EtOAc 3:1). Conversions and dr's of aldols **10** were measured by ¹H NMR of the crude reaction mixture, ee's of the *anti*-isomers of **10** were determined by HPLC, chiral phase: Chiralcel OD-H, OJ-H.
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