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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 organocatalyst 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.

Keywords: Direct asymmetric aldol reaction; Water; Chiral ionic liquid; Organocalatyst; Recycle

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 acids[2] and their derivatives,[3] low-molecular weight peptides[4] 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 organocatalysts bearing hydrophobic fragments, in particular long-chained hydrocarbon moieties C_nH_{2n+2} ($n \geqslant 10$),[10a] binaphthyl[10h] or trialkyl(aryl)silyl groups,[3g,10f,g] polystyrene[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.

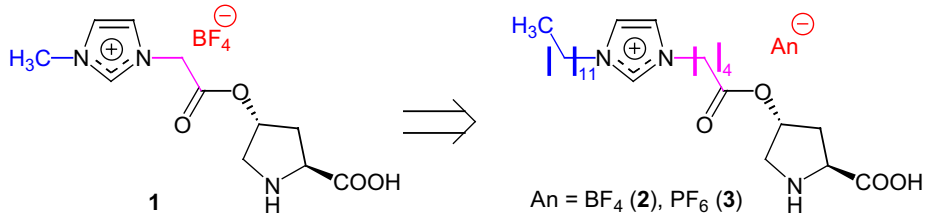
It might be expected that hydrophobic structural analogs of catalyst **1** bearing long-chain hydrocarbon groups at the imidazolium nitrogen atoms and being poorly soluble in aqueous media would possess a much higher activity in asymmetric aldol reactions in water (Scheme 1).

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-hydroxylproline 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).

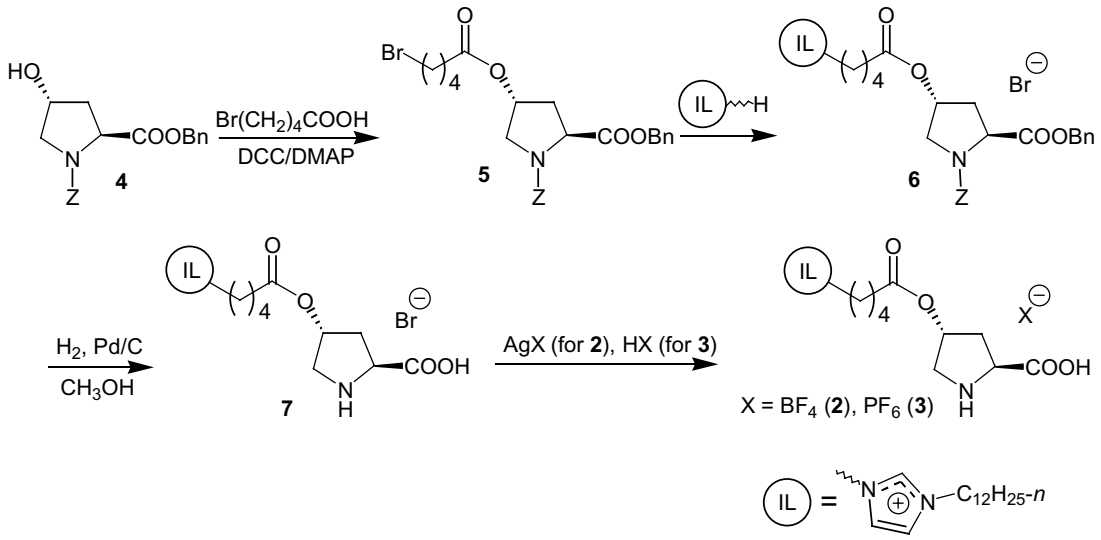
Salts **2** and **3** melt at 119 °C and 158 °C, respectively, and can be described as ionic liquids. They have quite different solubility in water. Tetrafluoroborate **2** gave a clear 5% aqueous solution at 20 °C, whereas hexafluorophosphate **3**/water mixture was a suspension under the same conditions.

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 (⩾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.

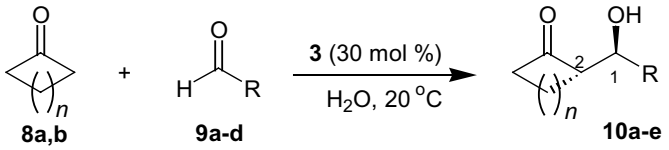


Scheme 1. Synthetic strategy.



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 (*R*)	10	Time[a] (h)	Conversion[a] (%)	dr[a] [*anti*:*syn*]	ee, *anti*-isomer[a,b] (%)
1	**a**	**a** (*p*-$NO_2C_6H_4$)	**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** (*p*-$CH_3O_2CC_6H_4$)	**b**	10	86	97:3	>99
3	**a**	**c** (C_6H_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** (*p*-$CH_3OC_6H_4$)	**d**	64 (50[25])	20 (21[25])	84:16 (5:1[25])	80 (96[25])
5	**b**	**a** (*p*-$NO_2C_6H_4$)	**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] [*anti*:*syn*]	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 ^{1}H NMR.
[b] Determined by HPLC.

According to ^{1}H NMR data ($J_{H1–H2\,anti} = 5.5–10.0$ Hz, $J_{H1–H2\,syn} < 2.4$ Hz) the *anti*/*syn* diastereomeric ratio (dr) of aldols **10b–e** was high (⩾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[9g] 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**/H_2O 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 catalyst activity and widening the reaction scope is currently underway.

[†] 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 ketone[24] or 1-(pyrrolidyl-2-methyl)-3-butylimidazolium tetrafluoroborate in water.[9g]

Acknowledgments

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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 CH_2Cl_2 (60 ml) was stirred at 5 °C for 3 h. The resulting precipitate was filtered off and washed with CH_2Cl_2 (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; $[\alpha]_D^{23}$ −30.2 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$), *δ*: 7.18–7.43 (10H, m, Ph), 5.30 (1H, s, C*H*O), 4.98–5.27 (4H, m, PhCH_2), 4.52 (1H, dt, $J = 19.5$, 7.7 Hz, C*H*COO), 3.62–3.85 (2H, m, CH_2N), 3.41 (2H, t, $J = 6.4$ Hz, BrCH_2), 2.15–2.49 (2H, m, CHCH_2CH), 2.33 (2H, t, $J = 6.4$ Hz, CH_2CH_2COO), 1.68–1.93 (4H, m, $BrCH_2CH_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$), *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 $C_{25}H_{28}BrNO_6$: 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 Et_2O (6×15 ml). The residue was dissolved in MeOH (3 ml), and Et_2O (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, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$), *δ*: 10.72 (1H, s, NC*H*N), 7.16–7.39 (12H, m, Ph, NC*H*C*H*N), 5.27 (1H, s, C*H*O), 4.98–5.23 (4H, m, CH_2Ph), 4.24–4.54 (5H, m, CH_2CH_2N, CH_2CHN), 3.61–3.82 (2H, m, CHCH_2N), 2.40 (2H, t, $J = 7.3$ Hz, CH_2CH_2COO), 2.17–2.51 (2H, m, CH_2CHN), 1.84–2.02 (4H, m, CH_2CH_2N), 1.59–2.71 (2H, m, CH_2CH_2COO), 1.21–1.38 (18H, m, $CH_3(CH_2)_9$), 0.88 (3H, t, $J = 6.8$ Hz, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$), *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 $C_{40}H_{56}BrN_3O_6$: 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 CH_3OH (35 ml) was stirred under H_2 (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 Et_2O (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, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6) *δ*: 9.26 (1H, s, NC*H*N), 7.82 (2H, s, NC*H*C*H*N), 5.18–5.23 (1H, m, C*H*O), 4.11–4.22 (4H, m, CH_2CH_2N), 3.80 (1H, t, $J = 8.9$ Hz, CH_2CHN), 3.08–3.50 (2H, m, CHCH_2N), 2.37 (2H, t, $J = 6.6$ Hz, CH_2CH_2COO), 2.04–2.23 (2H, m, CH_2CHN), 1.72–1.88 (4H, m, CH_2CH_2N), 1.43–1.55 (2H, m, CH_2CH_2COO), 1.22 (18H, s, $CH_3(CH_2)_9$), 0.85 (3H, t, $J = 6.1$ Hz, CH_3) ppm; ^{13}C 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 $C_{25}H_{44}BrN_3O_4$: 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 $AgBF_4$ (0.24 g, 1.23 mmol) in CH_3OH (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 CH_3OH (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 hydroscopic crystals, mp 117–119 °C; $[\alpha]_D^{19}$ −11.8 (*c* 1, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 9.19 (1H, s, NC*H*N), 7.79 (2H, s, NC*H*C*H*N), 5.17–5.23 (1H, m, C*H*O), 4.11–4.21 (4H, m, CH_2CH_2N), 3.81 (1H, t, $J = 8.9$ Hz, CH_2CHN), 3.08–3.50 (2H, m, CHCH_2N), 2.36 (2H, t, $J = 6.6$ Hz, CH_2CH_2COO), 2.05–2.23 (2H, m, CH_2CHN), 1.73–1.86 (4H, m, CH_2CH_2N), 1.43–1.54 (2H, m, CH_2CH_2COO), 1.23 (18H, s, $CH_3(CH_2)_9$), 0.85 (3H, t, $J = 6.1$ Hz, CH_3) ppm; ^{13}C 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; ^{11}B NMR (64.21 MHz, DMSO-d_6), *δ*: −1.08 ppm; ^{19}F NMR (188.31 MHz, DMSO-d_6), *δ*: −147.6 ppm. Anal. Calcd for $C_{25}H_{44}BF_4N_3O_4$: 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% HPF_6 (0.06 ml, 0.38 mmol) at 20 °C. The reaction mixture was then adjusted to pH ~ 8–9 with 25% NH_3. 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, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6), δ: 9.20 (1H, s, NC*H*N), 7.79 (2H, s, NC*H*C*H*N), 5.18–5.22 (1H, m, C*H*O), 4.11–4.22 (4H, m, CH_2CH_2N), 3.79 (1H, t, $J = 8.9$ Hz, CH_2CHN), 3.06–3.49 (2H, m, $CHCH_2N$), 2.37 (2H, t, $J = 6.6$ Hz, CH_2CH_2COO), 2.03–2.23 (2H, m, CH_2CHN), 1.71–1.88 (4H, m, CH_2CH_2N), 1.42–1.55 (2H, m, CH_2CH_2COO), 1.22 (18H, s, $CH_3(CH_2)_9$), 0.85 (3H, t, $J = 6.1$ Hz, CH_3) ppm; ^{13}C 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; ^{19}F NMR (188.31 MHz, DMSO-d_6), δ: −67.4, −71.1 ppm; ^{31}P NMR (81.02 MHz, DMSO-d_6), δ: −42.46 (hp, $J = 8.8$ Hz) ppm. Anal. Calcd for $C_{25}H_{44}F_6N_3O_4P$: 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 Et_2O (3 × 5 ml), the combined extracts were dried over anhydrous $NaSO_4$, 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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