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Catalytic asymmetric 1,4-conjugate addition of unmodified aldehyde in ionic liquid

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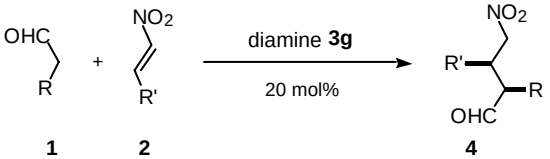
Abstract

In the presence of a catalytic amount of optically active pyrrolidine derivatives derived from L-proline, conjugate addition of an unmodified aldehyde to 3-buten-2-one in [bmim]PF_6 was achieved to afford (2*S*)-5-keto-aldehyde in up to 59% ee.

Keywords: Aldehyde; 1,4-Conjugate addition; 5-Keto-aldehyde; Ionic liquid; Organocatalyst

1. Introduction

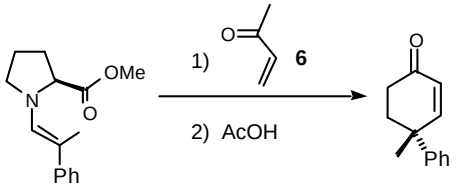
In spite of its higher versatility as an electrophile, aldehyde **1** has rarely been used intact as a nucleophile because of the difficulty incurred generating its enol or enolate quantitatively. In order to control a nucleophilic reaction of aldehyde **1**, it was transformed once into silylenol ether or enamine which reacts with an electrophile [1], though the syntheses of such aldehyde equivalents are not usually facile due to their instability to heat as well as moisture. In addition, examples of asymmetric nucleophilic reaction of an unmodified aldehyde **1** are rare. However, recent efforts in this area enabled enantioselective 1,2- and 1,4-additions of unmodified aldehydes **1** by employing organocatalysts. In the 1,2-addition reaction, successful results have been obtained in the aldol [2] or Mannich reaction [3]. In the 1,4-conjugate addition reaction, Betancort and Barbas [4] reported addition to a nitroalkene **2** employing a diamine **3g** (Fig. 1) as an organocatalyst (Eq. (1)).



1 **2** **4** (1)

An organocatalyst is an organic compound of low molecular weight that exhibits catalytic activity [5]. The catalyst does not contain heavy metal, which is an advantage from environmental as well as resource standpoint. The easy reproducibility and flexible design of the catalyst are additional advantages. The mild reactivity of an organocatalyst is suitable for transformation of fragile compounds such as an aldehyde and a highly functionalized substrate for natural product syntheses.

The pioneering work by Yamada and Otani [6] exemplified an asymmetric 1,4-conjugate addition of enamine of methyl L-prolinate **5** to 3-buten-2-one (MVK) **6**. Without isolation of the intermediary conjugate addition product, they directly transformed the product into a cyclohexenone derivative **7** in 49% optical yield (Eq. (2)). However, there has been no reported work since then on an asymmetric 1,4-conjugate addition of unmodified aldehyde to MVK **6**.



5 **7** (2)

We previously corroborated a highly efficient 1,4-conjugate addition of an unmodified aldehyde **1** to vinylketones catalyzed by a diethylaminotrimethylsilane [7], diethylamine

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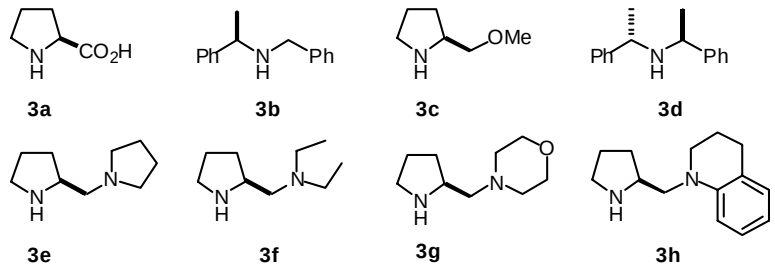
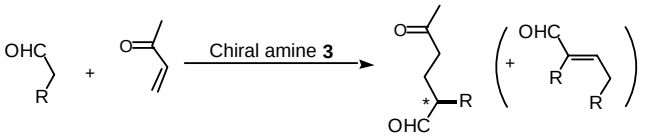


Fig. 1. Chiral amine catalysts investigated.

[8] or methylaminopropyl unit grafted on silica [9]. The reactions are environmentally friendly and the procedures are very simple. Wastes are hexamethylsiloxane, water, diethylamine or solvent, which are easy to trap. No aqueous work-up is required. By using an ionic liquid and a solid catalyst, the reaction system itself could be recycled several times [10]. These reactions were revealed to proceed via a catalytic enamine pathway [7a]. Based on these results, we delineate herein an asymmetric 1,4-conjugate addition of an unmodified aldehyde **1** to MVK **6** employing optically active pyrrolidine amines **3a**, **3c**–**h** as organocatalysts in an ionic liquid (Eq. (3), Fig. 1). The product, 5-keto-aldehyde **8**, is highly versatile as a starting material for various synthetic targets [11].



(3)

2. Experimental

2.1. General

IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer in chloroform. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J* values are in Hz. ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with a Varian Gemini 200H (50 MHz) instrument. HPLC analyses were carried out on a Hitachi L-7100 pump using Daicel chiral column with *n*-hexane–^{i}PrOH = 9:1 as an eluent at flow rate 0.5 ml/min unless otherwise indicated. HPLC peaks were monitored with a Hitachi L-7400 UV detector at 254 nm. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotation was measured with a Horiba SEPA-200 spectrophotometer for solution in chloroform.

2.2. 2-Benzyl-5-oxohexanal (*8a*)

2.2.1. Method I

A mixture of hydrocinnamaldehyde **1a** (660 μl, 5.0 mmol), MVK **6** (625 μl, 7.51 mmol), and the diamine **3g** (172 mg, 1.0 mmol) was stirred at 0 °C for 96 h under nitrogen atmosphere. After being passed through silicagel column with the aid of ethyl acetate-*n*-hexane, the solvent was evaporated to dryness and the residue was separated by MPLC (eluent: ethyl acetate–*n*-hexane = 1:2) to give keto-aldehyde **8a** [448 mg, 44%, 57% ee, $[\alpha]_D^{20}$ 3.89 (*c* 1.01, $CHCl_3$)] and self-aldol condensation product **9** (R = CH_2Ph) (98 mg, 16%) as an oil.

2.2.2. Method II

To a stirred solution of hydrocinnamaldehyde **1a** (66 μl, 0.50 mmol) in [bmim]PF_6 (1 ml) was added MVK **6** (65 μl, 0.78 mmol) and the diamine **3g** (18 mg, 0.10 mmol) under nitrogen atmosphere. After being stirred at room temperature for 48 h, the product was extracted with 5 ml of ether 10 times. The solvent was evaporated in vacuo at room temperature and the residue was passed through silicagel short column with the aid of ethyl acetate-*n*-hexane. Evaporation of the solvent followed by MPLC purification (eluent: ethyl acetate–*n*-hexane = 1:2) afforded keto-aldehyde **8a** [7a] (68 mg, 67%, 28% ee) and aldol product **9** (R = CH_2Ph) (2.5 mg, 4%) as an oil.

2.3. 2-Benzyl-5-oxohexyl benzoate (*10a*)

To a stirred solution of sodium borohydride (25 mg, 0.65 mmol) in ethanol (1.5 ml) and CH_2Cl_2 (3.5 ml) was added a solution of keto-aldehyde **8a** (33 mg, 0.16 mmol) in ethanol (0.6 ml) and CH_2Cl_2 (1.4 ml) at −78 °C. After being stirred for 1 h, the reaction was quenched by addition of acetic acid (150 μl, 2.62 mmol). The solution was diluted with CH_2Cl_2 and washed with dil. sodium hydrogencarbonate and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was used without purification.

To a stirred solution of the residue in pyridine (1.0 ml) was added benzoyl chloride (38 μl, 0.33 mmol) and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) and the resulting solution was stirred at room temperature for 18 h.

The organic layer was diluted with ethyl acetate and washed with water and brine and evaporated to dryness. The residue was purified by MPLC (eluent: ethyl acetate–*n*-hexane = 2:3) to give benzoate **10a** (44 mg, 88%); IR ν_{max} (cm^{-1}) 2942, 1713, 1603, 1495, 1453, 1277 and 1123; ^{1}H NMR (200 MHz) 1.74 (q, *J* 7.3, 2H), 2.11 (m, 1H), 2.11 (s, 3H), 2.52 (dt, *J* 14.6, 7.3, 1H), 2.54 (dt, *J* 14.6, 7.3, 1H), 2.70 (dd, *J* 13.6, 6.2, 1H), 2.78 (dd, *J* 13.6, 7.9, 1H), 4.16 (dd, *J* 11.2, 5.0, 1H), 4.23 (dd, *J* 11.2, 5.1, 1H), 7.16–7.36 (m, 5H), 7.44 (t, *J* 7.2, 2H), 7.56 (t, *J* 7.2, 1H) and 8.01 (d, *J* 7.2, 2H); ^{13}C NMR (50 MHz) 25.0 (t), 29.9 (q), 38.1 (t), 39.1 (d), 41.0 (t), 66.1 (t), 126.1 (d), 128.3 (d), 128.4 (d), 129.0 (d), 129.4 (d), 130.0 (s), 132.9 (d), 139.4 (s), 166.4 (s) and 208.2 (s); HRMS $M^+-C_6H_5COOH$ 188.1208 (calcd for $C_{13}H_{16}O$ 188.1201); HPLC condition (Daicel Chiralpak AS-H), t_R = 20.65 and 24.83 (major peak) min.

2.4. 2-(3-Oxobutyl)decanal (*8b*)

In the presence of the diamine **3g** (17 mg, 0.10 mmol), the reaction of *n*-decanal **1b** (95 μl, 0.50 mmol) and MVK **6** (65 μl, 0.78 mmol) in [bmim]PF_6 (1 ml) was carried out in the same manner as Method II to give keto-aldehyde **8b** [7a] (33 mg, 29%, 42% ee).

2.5. 2-(3-Oxobutyl)decyl p-nitrobenzoate (*10b*)

2-(3-Oxobutyl)decyl benzoate was obtained in 87% yield (37 mg) according to the same procedure as the preparation of the benzoate **10a**; ^{1}H NMR (200 MHz) 0.87 (br t, 3H), 1.15–1.56 (m, 14H), 1.64–1.90 (m, 3H), 2.15 (s, 3H), 2.53 (dd, *J* 8.0, 6.9, 2H), 4.19 (dd, *J* 11.0, 5.3, 1H), 4.27 (dd, *J* 11.0, 4.9, 1H), 7.35–7.70 (m, 3H) and 8.01 (m, 2H). Enantiomers of this benzoate could not be separated by chiral HPLC column.

A solution of the benzoate (35 mg, 0.11 mmol) and potassium carbonate (29 mg, 0.21 mmol) in methanol (1 ml) was stirred at room temperature for 2 h. The reaction was quenched by addition of aq. ammonium chloride and the organic layer was extracted with ethyl acetate twice. The combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent left a residue which was used for further reaction without purification.

A solution of the residue and *p*-nitrobenzoyl chloride (41 mg, 0.22 mmol) with a catalytic amount of DMAP in pyridine (1.2 ml) was stirred at room temperature for 16 h. The solution was diluted with ethyl acetate and the organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and subsequent MPLC purification of the residue (eluent: ethyl acetate–*n*-hexane = 2:3) afforded benzoate **10b** (40 mg, 99%); IR ν_{max} (cm^{-1}) 2930, 1721, 1609, 1532, 1469, 1350, 1279 and 1118; ^{1}H NMR (200 MHz) 0.88 (t, *J* 6.2, 3H), 1.10–1.57 (m, 14H), 1.73 (m, 2H), 1.77 (m, 1H), 2.16 (s, 3H), 2.53 (t, *J* 7.5, 2H), 4.24 (dd, *J* 11.1, 5.5, 1H), 4.31 (dd, *J* 11.1, 4.9, 1H), 8.19 (dt, *J* 9.1, 2.0, 2H) and 8.30 (dd, *J* 9.1, 2.0, 2H); ^{13}C NMR (50 MHz) 14.1 (q), 22.6 (t), 25.0 (t), 26.7 (t), 29.3 (t), 29.5 (t), 29.8 (t), 30.0 (q), 31.2 (t), 31.8 (t), 36.9 (d), 40.8 (t), 68.0 (t), 123.5 (d), 130.6 (d), 135.6 (s), 150.4 (s), 164.6 (s) and 208.3 (s); HRMS M^+-p-$NO_2C_6H_5COOH$, 210.1985 (calcd for $C_{14}H_{26}O$ 210.1984); HPLC condition (Daicel Chiralpak AS-H), t_R = 33.95 (major peak) and 36.60 min.

2.6. 2-n-Butyl-5-oxohexanal (*8c*)

Reaction of *n*-hexanal **1c** (60 μl, 0.50 mmol) and MVK **6** (65 μl, 0.78 mmol) with the diamine **3g** (18 mg, 0.10 mmol) in [bmim]PF_6 (1 ml) was carried out in the same manner according to Method II to provide keto-aldehyde **8c** [7a] (39 mg, 46%, 42% ee).

2.7. 2-n-Butyl-5-oxohexyl benzoate (*10c*)

The benzoate **10c** was obtained in 54% yield (35 mg) according to the same procedure as the preparation of the benzoate **10a** starting from keto-aldehyde **8c** (39 mg); IR ν_{max} (cm^{-1}) 2961, 1713, 1603, 1453, 1315, 1277 and 1117; ^{1}H NMR (200 MHz) 0.90 (t, *J* 5.7, 3H), 1.20–1.60 (m, 6H), 1.60–1.90 (m, 3H), 2.15 (s, 3H), 2.53 (dd, *J* 8.5, 6.7, 2H), 4.19 (dd, *J* 11.0, 5.3, 1H), 4.27 (dd, *J* 11.0, 4.9, 1H), 7.35–7.70 (m, 3H) and 8.01 (m, 2H); ^{13}C NMR (50 MHz) 14.0 (q), 22.9 (t), 25.2 (t), 28.9 (t), 30.0 (q), 31.0 (t), 37.0 (d), 40.9 (t), 67.0 (t), 128.3 (d), 129.4 (d), 130.2 (s), 132.9 (d), 166.6 (s) and 208.3 (s); HRMS $M^+-C_6H_5COOH$ 154.1358 (calcd for $C_{10}H_{18}O$ 154.1358); HPLC condition (Daicel Chiralpak AS-H), t_R = 31.61 and 33.17 (major peak) min.

2.8. 2-(3-tert-Butyldimethylsilyloxypropyl)-5-oxohexanal (*8d*)

To a stirred solution of aldehyde **1d** (108 mg, 0.50 mmol) in [bmim]PF_6 (1 ml) was added MVK **6** (65 μl, 0.78 mmol) and the diamine **3g** (17.5 mg, 0.10 mmol). After being stirred for 48 h at room temperature, the product was extracted with diethyl ether 20 times. Evaporation of the solvent of combined organic layers and subsequent MPLC purification of the residue (eluent: ethyl acetate–*n*-hexane = 1:3) afforded keto-aldhyde **8d** [7a] (25 mg, 17%, 51% ee) along with self-aldol condensation product **9** (R = C_3H_6OTBS) (29 mg, 28%).

2.9. 2-(3-Hydroxypropyl)-5-oxohexyl benzoate (*10d*)

2-(3-*tert*-Butyldimethylsilyloxypropyl)-5-oxohexyl benzoate was obtained in 70% yield (24 mg) according to the same procedure as the preparation of the benzoate **10a** starting from keto-aldehyde **8d** (25 mg); ^{1}H NMR (200 MHz) 0.04 (s, 6H), 0.88 (s, 9H), 1.35–1.68 (m, 4H), 1.68–1.90 (m, 3H), 2.15 (s, 3H), 2.54 (t like, *J* 7.4, 2H), 3.61 (t, *J* 6.0, 2H), 4.23 (dd, *J* 5.1, 1.2, 1H), 4.24 (dd, *J* 5.1, 1.2, 1H),

7.35–7.70 (m, 3H) and 8.01 (m, 2H). Enantiomers of the benzoate could not be separated by chiral HPLC column.

To a stirred solution of the keto-benzoate (23 mg, 0.06 mmol) in THF (500 μl) was added TBAF (78 μl, 1.0 M solution in THF, 0.078 mmol) and the resulting solution was stirred at room temperature for 1 h. After addition of sat. aq. NH_4Cl, the product was extracted with ethyl acetate twice and the organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate–*n*-hexane = 2:1) provided alcohol **10d** (16 mg, 100%); IR ν_{max} (cm^{-1}) 3632, 2944, 1713, 1603, 1453, 1315, 1277 and 1119; ^{1}H NMR (200 MHz) 1.30–2.00 (m, 8H), 2.16 (s, 3H), 2.55 (t, *J* 7.5, 2H), 3.67 (t, *J* 6.2, 2H), 4.26 (t, *J* 5.1, 2H), 7.44 (t, *J* 7.2, 2H), 7.58 (t, *J* 7.2, 1H) and 8.02 (d, *J* 7.2, 2H); ^{13}C NMR (50 MHz) 25.1 (t), 27.5 (t), 29.8 (t), 30.0 (q), 36.8 (d), 40.8 (t), 62.8 (t), 66.8 (t), 128.4 (d), 129.5 (d), 130.1 (s), 133.0 (d), 166.6 (s) and 208.6 (s); HRMS $M^+-C_6H_5COOH$ 156.1144 (calcd for $C_9H_{16}O_2$ 156.1150); HPLC condition (Daicel Chiralpak OB-H, flow rate 1.0 ml/min), t_R = 30.14 and 35.57 (major peak) min.

2.10. 2-(3-Acetoxypropyl)-5-oxohexanal (*8e*)

To a stirred solution of aldehyde **1e** (72 mg, 0.50 mmol) in [bmim]PF_6 (1 ml) was added MVK **6** (65 μl, 0.78 mmol) and diamine **3g** (17.5 mg, 0.10 mmol). After being stirred for 48 h at room temperature, the product was extracted with 5 ml of diethyl ether 20 times. Evaporation of the solvent of combined organic layer at room temperature and subsequent MPLC purification of the residue (eluent: ethyl acetate–*n*-hexane = 3:2) afforded keto-aldhyde **8e** [7a] (22 mg, 22%, 44% ee) along with self-aldol condensation product **9** (R = $AcOC_3H_6$) (22 mg, 33%).

2.11. 2-(3-Benzoyloxypropyl)-5-oxohexyl benzoate (*10e*)

2-(3-Acetoxypropyl)-5-oxohexylbenzoate was obtained in 79% yield (26 mg) according to the same procedure as the preparation of the benzoate **10a** starting from keto-aldehyde **8e** (22 mg); ^{1}H NMR (200 MHz) 1.30–1.55 (m, 3H), 1.60–1.95 (m, 4H), 2.03 (s, 3H), 2.16 (s, 3H), 2.54 (t like, *J* 7.4, 2H), 4.05 (d, *J* 5.1, 1H), 4.07 (t, *J* 6.5, 2H), 4.25 (d, *J* 5.1, 1H), 7.44 (tt, *J* 7.0, 1.5, 2H), 7.57 (tt, *J* 7.0, 1.5, 1H) and 8.02 (dt, *J* 7.0, 1.5, 2H). Enantiomers of this benzoate could not be separated by chiral HPLC column.

To a solution of the benzoate (25 mg, 0.079 mmol) in methanol (800 μl) was added potassium carbonate (35 mg, 0.30 mmol) under nitrogen atmosphere at room temperature. After being stirred for 4 h, the reaction was quenched by addition of sat. aq. NH_4Cl. Product was extracted with ethyl acetate twice and the combined organic layer was washed with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave residue which was used for next reaction without purification.

To a stirred solution of the residue in pyridine (1.0 ml) was added benzoyl chloride (35 μl, 0.30 mmol) and a catalytic amount of DMAP. After being stirred at room temperature for 3 h, ethyl acetate (200 ml) was added. The organic layer was washed with water and brine. Evaporation of the solvent followed by MPLC purification (eluent: ethyl acetate–*n*-hexane = 1:1) provided bis-benzoate **10e** (27 mg, 91%); IR ν_{max} (cm^{-1}) 2955, 1713, 1603, 1453, 1316, 1280 and 1115; ^{1}H NMR (200 MHz) 1.20–2.00 (m, 7H), 2.15 (s, 3H), 2.55 (t, *J* 7.6, 2H), 4.28 (t, *J* 5.1, 2H), 4.34 (t, *J* 6.4, 2H), 7.41 (tt, *J* 6.4, 1.4, 4H), 7.55 (m, 2H) and 8.03 (dt, *J* 6.6, 1.4, 4H); HRMS $M^+-C_6H_5COOH$ 260.1415 (calcd for $C_{16}H_{20}O_3$ 260.1412); HPLC condition (Daicel Chiralpak AS-H), t_R = 38.22 and 40.86 (major) min.

2.12. 2-Benzyl-5-oxohexanoic acid (*11*)

To a stirred solution of the keto-aldehyde **8a** (57% ee, 326 mg, 1.59 mmol) in acetone (5 ml) was added Jones reagent drop wise at 0 °C until yellow color remained. The reaction was quenched by addition of 2-propanol. The solution was diluted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate, Evaporation of the solvent followed by MPLC purification of the residue (eluent: ethyl acetate) provided ketocarboxylic acid **11** (344 mg, 98%); IR ν_{max} (cm^{-1}) 3520, 3042, 2957, 1713, 1605, 1497, 1455, 1372, 1285 and 1167; ^{1}H NMR (500 MHz) 1.86 (q, *J* 7.3, 2H), 2.11 (s, 3H), 2.46 (dt, *J* 17.8, 7.3, 1H), 2.54 (dt, *J* 17.8, 7.3, 1H), 2.69 (quint, *J* 7.3, 1H), 2.76 (dd, *J* 13.6, 7.3, 1H), 3.02 (dd, *J* 13.6, 7.3, 1H), 7.19 (t, *J* 7.0, 2H), 7.22 (d, *J* 7.0, 1H) and 7.28 (t, *J* 7.0, 2H); ^{13}C NMR (50 MHz) 25.2 (t), 29.9 (q), 38.1 (t), 40.9 (t), 46.2 (d), 126.4 (d), 128.4 (d), 128.8 (d), 138.4 (s), 181.0 (s) and 208.0 (s); HRMS M^+-COOH 175.1124 (calcd for $C_{12}H_{15}O$ 175.1123).

2.13. Methyl (2S)-[(2′S)-5′-oxo-2′-benzylhexanoylamino]-2-phenylacetate (S,S)-(*13*) and methyl (2S)-[(2′R)-5′-oxo-2′-benzylhexanoylamino]-2-phenylacetate (S,R)-(*13*)

PGME hydrochloric salt was prepared according to the procedure by Nagai and Kusumi [18a]. To a solution of the carboxylic acid **11** (47 mg, 0.21 mmol) and (*S*)-PGME hydrochloric salt **12** (54 mg, 0.26 mmol) in DMF (1 ml) was added PyBOP® (129 mg, 0.25 mmol), HOBT (36 mg, 0.27 mmol), *N*-methylmorpholine (85 μl, 0.77 mmol) at 0 °C under nitrogen atmosphere. After being stirred at room temperature for 3 h, benzene (20 ml) and ethyl acetate (40 ml) was added. The resulting solution was washed with 5% hydrochloric acid, sat. aq. $NaHCO_3$ and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and subsequent MPLC purification of the residue (eluent: ethyl acetate–*n*-hexane = 2:1) afforded (*S*)-PGME amide **13** (less polar diastereomer, 55 mg, 70% and more polar diastereomer, 14 mg, 18%) as solids.

The less polar diastereomer had IR ν_{max} (cm^{-1}) 3418, 1744, 1711, 1677, 1499 and 1206; ^1H NMR (500 MHz) 1.81 (m, 2H), 1.98 (s, 3H), 2.24 (dt, *J* 17.6, 7.6, 1H), 2.36 (ddd, *J* 17.6, 7.6, 5.8, 1H), 2.53 (ddt, *J* 8.5, 6.2, 5.3, 1H), 2.73 (dd, *J* 13.5, 6.2, 1H), 2.94 (dd, *J* 13.5, 8.5, 1H), 3.66 (s, 3H), 5.47 (d, *J* 7.1, 1H), 6.38 (d, *J* 7.1, 1H), 7.15–7.22 (m, 2H) and 7.25–7.35 (m, 8H); ^{13}C NMR (50 MHz) 26.3 (t), 29.8 (q), 38.9 (t), 40.6 (t), 47.8 (d), 52.7 (q), 56.1 (d), 126.3 (d), 127.0 (d), 128.4 (d), 128.8 (d), 136.6 (s), 139.0 (s), 170.7 (s), 173.6 (s) and 208.3 (s); HRMS M^+ 367.1792 (calcd for $C_{22}H_{25}NO_4$ 367.1783).

The more polar diastereomer had IR ν_{max} (cm^{-1}) 3440, 1744, 1711, 1677, 1499 and 1208; ^1H NMR (500 MHz) 1.88 (m, 2H), 2.15 (s, 3H), 2.51 (m, 1H), 2.55 (t, *J* 7.1, 2H), 2.70 (dd, *J* 13.4, 5.5, 1H), 2.88 (dd, *J* 13.4, 9.5, 1H), 3.71 (s, 3H), 5.45 (d, *J* 7.0, 1H), 6.20 (d, *J* 7.0, 1H), 7.02–7.097 (m, 4H), 7.13–7.19 (m, 3H) and 7.24–7.32 (m, 3H); ^{13}C NMR (50 MHz) 26.7 (t), 30.0 (q), 39.1 (t), 40.6 (t), 48.1 (d), 52.6 (q), 56.2 (d), 126.1 (d), 127.1 (d), 128.3 (d), 128.7 (d), 128.8 (d), 135.6 (s), 139.1 (s), 171.1 (s), 173.7 (s) and 208.8 (s).

*2.14. Methyl (2R)-[(2′S)-5′-oxo-2′-benzylhexanoylamino]-2-phenylacetate (R,S)-(**13**) and methyl (2R)-[(2′R)-5′-oxo-2′-benzylhexanoylamino]-2-phenylacetate (R,R)-(**13**)*

To a solution of keto-carboxylic acid **11** (48 mg, 0.22 mmol) and (*R*)-PGME hydrochloric salt **12** (55 mg, 0.27 mmol) in DMF (1 ml) was added at 0 °C PyBOP® (130 mg, 0.25 mmol), HOBT (35 mg, 0.26 mmol), *N*-methylmorpholine (85 μl, 0.77 mmol) under nitrogen atmosphere. After being stirred at room temperature for 3 h, benzene (20 ml) and ethyl acetate (40 ml) was added. Work-up in the same manner as above afforded (*R*)-PGME amide **13** (less polar diastereomer, 16 mg, 20%; more polar, 56 mg, 70%) as solids.

The less polar diastereomer had IR ν_{max} (cm^{-1}) 3440, 1744, 1711, 1677, 1499 and 1208; ^1H NMR (500 MHz) 1.81 (m, 2H), 1.98 (s, 3H), 2.24 (dt, *J* 17.6, 7.6, 1H), 2.36 (ddd, *J* 17.6, 7.6, 5.8, 1H), 2.53 (ddt, *J* 8.5, 6.2, 5.3, 1H), 2.73 (dd, *J* 13.5, 6.2, 1H), 2.94 (dd, *J* 13.5, 8.5, 1H), 3.66 (s, 3H), 5.47 (d, *J* 7.1, 1H), 6.38 (d, *J* 7.1, 1H), 7.15–7.22 (m, 2H) and 7.25–7.35 (m, 7H); ^{13}C NMR (50 MHz) 26.3 (t), 29.8 (q), 38.9 (t), 40.6 (t), 47.8 (d), 52.7 (q), 56.1 (d), 126.3 (d), 127.0 (d), 128.4 (d), 128.8 (d), 136.6 (s), 139.0 (s), 170.7 (s), 173.6 (s) and 208.3 (s).

The more polar diastereomer had IR ν_{max} (cm^{-1}) 3440, 1744, 1711, 1677, 1499 and 1208; ^1H NMR (500 MHz) 1.88 (m, 2H), 2.15 (s, 3H), 2.51 (m, 1H), 2.55 (t, *J* 7.1, 2H), 2.70 (dd, *J* 13.4, 5.5, 1H), 2.88 (dd, *J* 13.4, 9.5, 1H), 3.71 (s, 3H), 5.45 (d, *J* 7.0, 1H), 6.20 (d, *J* 7.0, 1H), 7.02–7.097 (m, 4H), 7.13–7.19 (m, 3H) and 7.24–7.32 (m, 3H); ^{13}C NMR (50 MHz) 26.7 (t), 30.0 (q), 39.1 (t), 40.6 (t), 48.1 (d), 52.6 (q), 56.2 (d), 126.1 (d), 127.1 (d), 128.3 (d), 128.7 (d), 128.8 (d), 135.6 (s), 139.1 (s), 171.1 (s), 173.7 (s) and 208.8 (s); HRMS M^+ 367.1782 (calcd for $C_{22}H_{25}NO_4$ 367.1783).

3. Results and discussion

3.1. Investigation on enantioselective 1,4-conjugate addition of unmodified aldehydes

One major issue involved in realizing an enantioselective 1,4-conjugate addition of an unmodified aldehyde is to find a more active amine catalyst which is effective at below room temperature, since at elevated temperature racemization of the keto-aldehyde **8** is anticipated. Another issue is to suppress competitive self-aldol condensation leading to an α,β-unsaturated aldehyde **9** [12]. Different from the reaction with nitro-olefine **2**, both substrates **1** and **6** lack points of interaction in the present reaction system, which gave rise to difficulty in designing appropriate amine catalysts. To this end, screening of chiral secondary amines (Fig. 1) was carried out initially. A reaction of hydrocinnamaldehyde **1a** with MVK **6** in an ionic liquid [bmim]PF_6 (vide infra) was employed as a probe to examine appropriate amine catalysts, and the results are listed in Table 1.

Self-aldol condensation of the aldehyde **1a** predominated to give an enal **9a** (Eq. (3)), when 10 mol% of L-proline **3a** was used (entry 1, Table 1). With an amine **3c**, considerable amount of self-aldol product **9** was accompanied (entry 3). Catalytic activity of an amine **3b** or **d** [13] derived from phenylethylamine was unsatisfactory (entry 2 or 4) even by using a stoichiometric amount of amines. Then, attention was focused on diamines **3e**–**h** [14] derived from L-proline. The catalytic activities of diamines **3e**–**h** were higher than those of previous amines. By employing 20 mol% of the diamine, self-aldol condensation [15] was suppressed and 1,4-conjugate addition product **8** was obtained in better yields (entries 5–8). Among the diamines investigated, diamine **3g** exhibited the highest 72% chemical yield with 24% ee (entry 7). Moreover, enantiomeric excess was improved to 48% ee when diamine **3h** was employed (entry 8). Considering the results from entries 5–8, increased bulkiness of the substituent of the pyrrolidine ring of the amines played a role to improve enantiomeric excess of conjugate

Table 1
Enantioselective 1,4-conjugate addition of hydrocinnamaldehyde **1a**

Entry	Amine	Reaction time (h)	Yield (%)	ee (%)
1[a]	**3a** (10 mol%)	24	8 (31)[d]	–
2[b]	**3b** (10 mol%)	24	8	–
3[c]	**3c** (10 mol%)	34	31 (29)[d]	11
4[a]	**3d** (10 mol%)	97	34	16
5[a]	**3e** (20 mol%)	48	48 (10)[d]	18
6[a]	**3f** (20 mol%)	48	67 (5)[d]	18
7[a]	**3g** (20 mol%)	48	72 (2)[d]	24
8[a]	**3h** (20 mol%)	48	44 (6)[d]	48

[a] Reaction was carried out at rt in 1 ml of [bmim]PF_6.
[b] Reaction was carried out at rt without organic solvent.
[c] Reaction was carried out at rt in 0.5 ml of CH_3CN.
[d] Yield in parentheses indicates the yield of self-aldol condensation product.

Table 2
Investigation of suitable solvent in 1,4-conjugate addition of hydrocinnamaldehyde **1a**

Entry[a]	Solvent	Yield (%)	ee (%)
1	DMI	26	43
2	CH_3CN	29	34
3	DMSO	39	34
4	[bmim]PF_6	72	24
5	[bmim]PF_6/DMI	61	29

[a] All reactions were carried out at rt for 48 h with 20 mol% of diamine **3g**.

Table 3
Effect of temperature on yield and ee in the 1,4-conjugate reaction of hydrocinnamaldehyde **1a**

Entry	Chiral amine	Condition (°C)	Yield (%)	ee (%)
1[a]	**3g** (20 mol%)	26	72	24
2[a]		10	32	48
3[b]		2	29	59
4[b,c]		0	44	57
5[b]	**3h** (20 mol%)	0	11	53

[a] Reaction was carried out in [bmim]PF6 for 48 h.
[b] Reaction was carried out without solvent.
[c] Reaction was carried out for 96 h.

addition product **8**. With appropriate amine catalyst **3g** in hand (Table 1), the effect of the solvent was investigated and the results are shown in Table 2.

Since the reaction was proposed to proceed via an enamine pathway [7a], aprotic solvents were employed. Among solvents tested, 1,3-dimethyl-2-imidazolidinone (DMI) gave the highest enantiomeric excess (entry 1, Table 2), while the ionic liquid, [bmim]PF_6 [16], provided the best chemical yield (entry 4, Table 2). Racemic product **8** was obtained in toluene, DMF or HMPA. Without solvent at room temperature, a complex mixture was obtained probably due to the higher reactivity of amine **3g**.

Lower reaction temperature recorded higher enantiomeric excess at the expense of the substrate conversion (entry 2, Table 3). At 0 °C the reactions were carried out without solvent, since mp of [bmim]PF_6 is 6 °C, which further improved enantioselectivity (entries 3–5, Table 3).

Prolonged reaction time improved chemical yields, though enantiomeric induction was reduced when the diamine **3h** was used as catalyst (Table 4). This result was understood from the results that diamine **3h** catalyzed

Table 4
Effect of time on ee in the 1,4-conjugate reaction of hydrocinnamaldehyde **1a**

Entry	Time (h)	Yield (%)	ee (%)
1	48	44	48
2	96	63	28
3	285	67	16

All reactions were carried out at rt with 20 mol% of diamine 3 h in [bmim]PF_6.

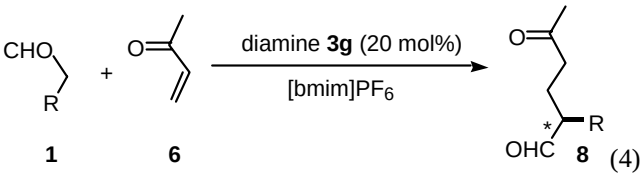
Table 5
Enantioselective 1,4-conjugate addition of various aldehyde **1** in the presence of diamine **3g** in [bmim]PF_6.

Entry[a]	Aldehyde	R	Yield (%)	ee (%)	Product
1	$PhCH_2$	**1a**	72	24	**8a**
2[b]	$PhCH_2$	**1a**	31	11	**8a**
3[c]	$PhCH_2$	**1a**	29	59	**8a**
4	C_8H_{17}	**1b**	29	42	**8b**
5	C_4H_9	**1c**	46	42	**8c**
6	$TBSOC_3H_6$	**1d**	17	51	**8d**
7	$AcOC_3H_6$	**1e**	22	44	**8e**

[a] AII reactions were carried out at rt for 48 h with 20 mol% of diamine **3g** in [bmim]PF_6.
[b] Reaction was carried out with 10 mol% of **3g** in acetonitrile.
[c] Reaction was carried out without solvent at 2 °C.

racemization of the keto-aldehyde **8a** (57% ee) at room temperature in 48 h, while the same keto-aldehyde **8a** in [bmim]PF_6 was recovered intact in the absence of diamine **3h**. Difficulty to suppress racemization arises that rigorous dehydration of the reaction system is undesirable in order to promote reaction, since a small amount of water plays an important role to drive catalytic cycle of the enamine reaction [7a].

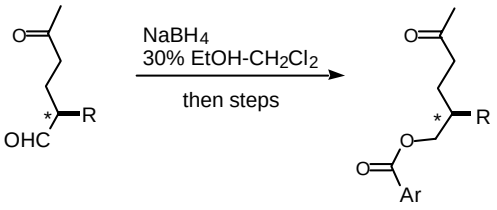
Under our optimized reaction conditions employing 20 mol% of diamine **3g** in [bmim]PF_6, conjugate addition of various unmodified aldehydes **1** was investigated and the results are listed in Table 5 (Eq. (4)). Chemical yield as well as enantiomeric excess were dependent on aldehydes **1**. In entries 2 and 3, a fairly large amount of the starting aldehydes **1** was recovered. In entries 4 and 5, self-aldol condensation products **9** were the major byproduct. Lower conversion of aldehydes **1** provided higher ee also in these reactions. Prolonged reaction time perhaps improve the conversion, but probably decreased the ee.



1 **6** **8** (4)

3.2. Determination of enantiomeric excess

The enantiomeric excess of the product **8** was determined by HPLC analysis of the corresponding benzoate **10** which was prepared as in Eq. (5), since direct HPLC analysis was unsuccessful. GLC analysis was not employed to avoid deterioration of chiral center of **8**. According to the procedure by Ward and Rhee [17], the formyl group of keto-aldehyde **8** was selectively reduced with sodium borohydride in 30% ethanol in dichloromethane at −78 °C to give an equilibrium mixture of keto-alcohol and its hemi-acetal. Without purification, treatment with benzoyl chloride afforded keto-benzoate **10**.



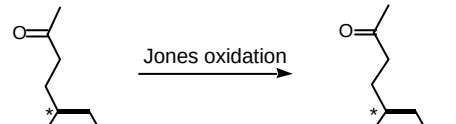
8a: R = Bn
8b: R = C_8H_{17}
8c: R = C_4H_9
8d: R = C_3H_6OTBS
8e: R = C_3H_6OAc

10a: R = Bn, Ar = Ph
10b: R = C_8H_{17}, Ar = *p*-NO_2Ph
10c: R = C_4H_9, Ar = Ph
10d: R = C_3H_6OH, Ar = Ph
10e: R = C_3H_6OCOPh, Ar = Ph (5)

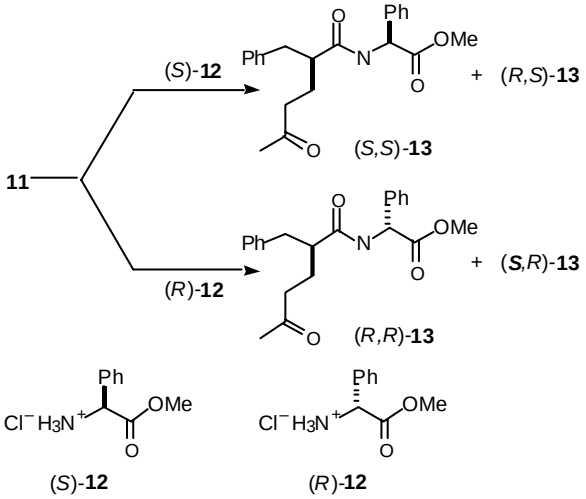
HPLC analyses of benzoates **10a** and **c** exhibited perfect base line separations (separation factor, $\alpha = 1.18$) of the two enantiomers (see Section 2). Since base line separation was not observed in the benzoate derived from **8b**, the benzoate was further transformed into *p*-nitrobenzoate **10b** which showed complete peak separation (separation factor: $\alpha = 1.08$). Enantiomeric excesses of **8d** and **e** were determined by HPLC analyses of hydroxybenzoate **10d** or bis-benzoate **10e**, respectively.

3.3. Determination of absolute stereochemistry

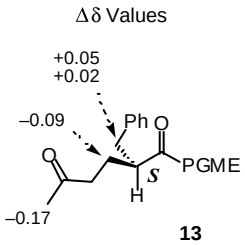
The absolute stereostructure was determined by Kusumi's PGME method [18]. Jones oxidation of keto-aldehyde **8a** (57% ee) gave acid **11** in 98% yield (Eq. (6)). Condensation with (*R*)- or (*S*)-phenylglycine methyl ester **12** provided amides **13** [19] in satisfactory yields (Eq. (7)). Both diastereomers were easily separated by MPLC. The ratio of diastereomers reflected the enantiomeric ratio of the starting keto-aldehyde **8a**, which indicates that no racemization and no kinetic resolution occurred during the synthetic operations leading to PGME ester **13**.



8a **11** (6)



(S)-**12** (R)-**12** (7)



13

Fig. 2. Determination of absolute stereochemistry.

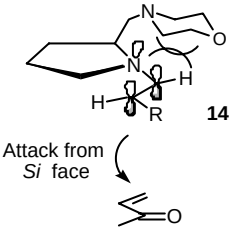


Fig. 3. Possible stereochemical course.

Differences of chemical shift data of the adjacent protons in NMR spectra of two major diastereomers of PGME esters **13** established unambiguously the absolute stereochemistry of the keto-aldehyde **8a** to be *S* as shown in Fig. 2. While recent report by Melchiorre and Jorgensen [20] assigned *S* absolute configuration on **8a** which has negative sign of optical rotation (see also our Section 2). This inconsistency is uncertain. Deducing from similar HPLC behaviors of the benzoates **10c**–**e**, the asymmetric centers of keto-aldehydes **8c**–**e** might have the *R* configurations.

Provided that the present reaction proceeds via an enamine pathway, the enantioselective 1,4-conjugate addition is initiated from the Si-face of *E*-enamine **14** to give (2*S*)-keto-aldehyde **8** (Fig. 3). Bulkiness of the substituent on the pyrrolidine ring played some role to increase enantioselectivity as shown in entries 5–8, Table 1. Melchiorre and Jorgensen [20] also attained the same conclusion using chiral diamine derived from L-proline.

In summary, we have shown that enantioselective conjugate addition of unmodified aldehydes **1** to MVK **6** in [bmim]PF_6 afforded (2*S*)-5-keto-aldehydes **8** in up to 59% ee in the presence of a catalytic amount of optically active pyrrolidine derivatives **3g** and **h** derived from L-proline. Though there are limitations to realize higher ee values, the ionic liquid played an important role to accelerate the reaction.

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