

# Synthesis of proline-derived dipeptides and their catalytic enantioselective direct aldol reactions: catalyst, solvent, additive and temperature effects

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**Abstract** A series of dipeptides of L-proline-L-amino acid and L-proline-D-amino acid were synthesized to evaluate the catalytic effect for asymmetric direct aldol reactions. In the direct aldol reaction, a catalyst of L-proline-L-amino acid achieves better enantioselectivity than the corresponding L-proline-D-amino acid catalyst. Solubility of the dipeptide catalysts in the solvents is a key point for achieving a better yield of the direct aldol reaction, while hydrogen bonding of solvent does not play an important role in attaining better enantioselectivity and yield. Yield and enantioselectivity of the direct aldol reaction in water were improved by NMM and SDS additives, but the results that were done in plain DMSO were even better.

**Keywords** Dipeptide · Direct aldol reaction · Enantioselective reaction

## Introduction

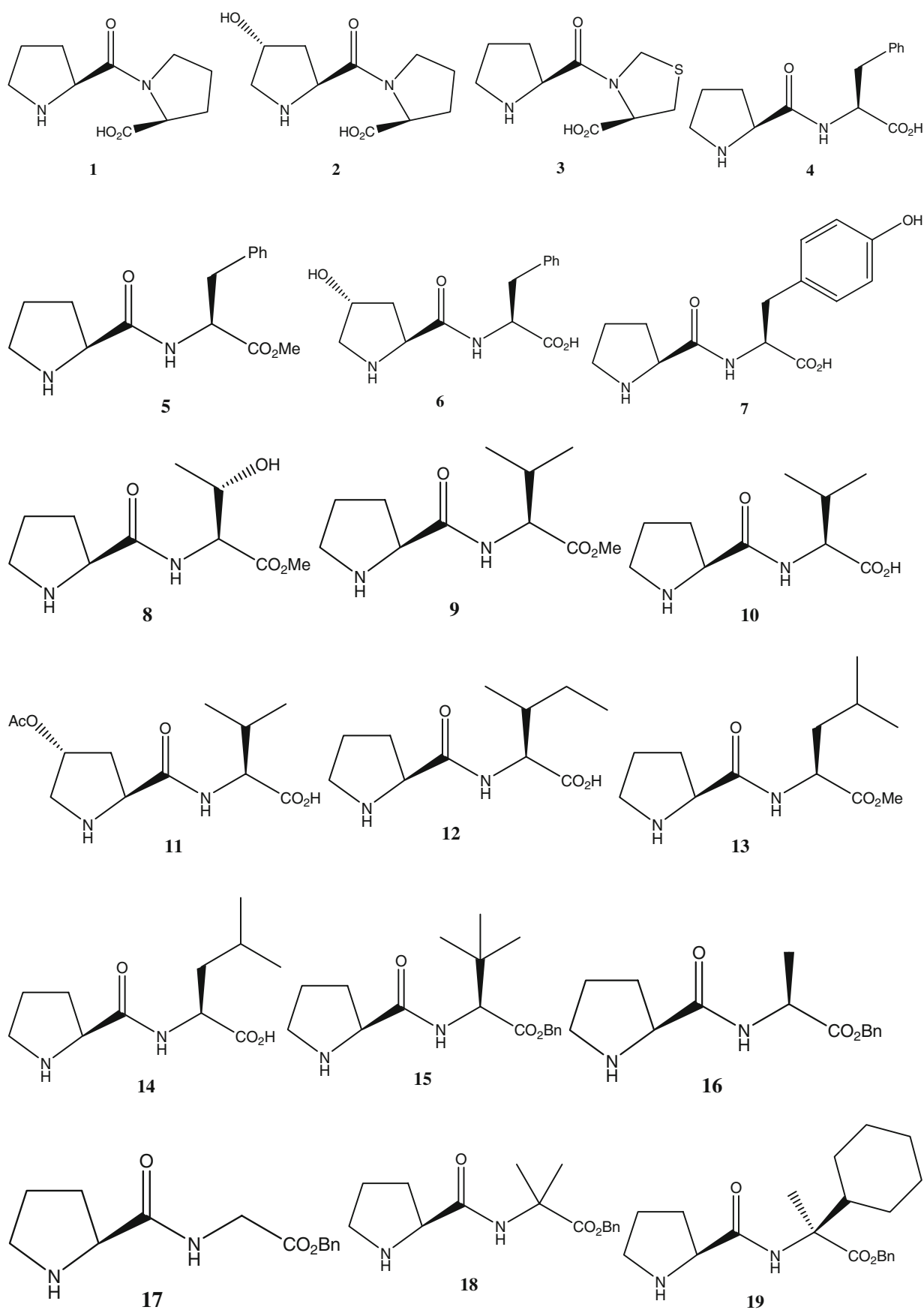
Aldolases efficiently catalyze aldol reactions of nonactivated unprotected polyfunctionalized substrates under mild ambient conditions to form a new carbon–carbon bond in a stereospecific fashion. Last decade, Barbas III, List et al. started to recreate natural aldolase enzymes with synthetic catalysts and found that L-proline and its analogs can work as chiral catalysts in direct aldol reactions (Notz et al. 2004; List 2004). Later on, the concept of small organic molecules as chiral catalysts has received great attention (Nozriere and Cordova 2008; Casas et al. 2005; Ibrahim et al. 2006; Pizzarello and Weber 2004; Northrup and MacMillan 2002;

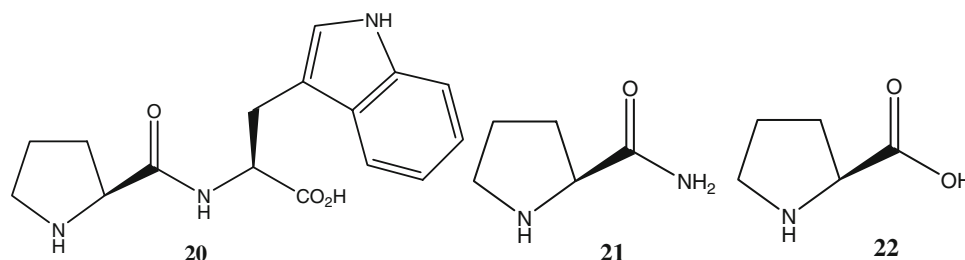
Majewski et al. 2006) because metal-free chiral organic catalysts are in high demand in the pharmaceutical industry.

Since aldolases are globular proteins, organic chemists increased the peptide length of the catalyst from a single amino acid to a dipeptide, tripeptide and oligopeptide to see if a catalyst with a longer peptide chain works better (Tang et al. 2004; Lei et al. 2007; Luppi et al. 2005; Zhao and Dodda 2007; Zheng et al. 2006; Shi et al. 2004; Tsogoeva and Jagtap 2004). Recently, some of the dipeptide catalysts have been used to carry out enantioselective direct aldol reaction. Li et al. found that dipeptide **4** catalyzed enantioselective direct aldol reaction of 4-nitrobenzaldehyde with acetone better than dipeptides **1**, **2**, **3** and **6** in DMSO with NMM base and PGME 5000 surfactant (Shi et al. 2004). Gong et al. reported that dipeptide ester **5** was better than dipeptide esters **8**, **9** and **13** for catalyzing enantioselective direct aldol reaction of 4-nitrobenzaldehyde with hydroxyacetone in THF/H<sub>2</sub>O (Tang et al. 2004). Tomasini et al. studied enantioselective direct aldol reaction of isatin with acetone catalyzed by dipeptide esters **17**, **16**, **9**, **15**, **18** or **19** at –15°C and found that **16** worked the best (Luppi et al. 2005). Fang et al. performed enantioselective direct aldol reaction of cyclohexanone with 4-pyridinecarbaldehyde in water by dipeptides **4**, **14**, **12**, **7**, or **20** with NMM base and PEG400 surfactant, and **20** worked the best (Lei et al. 2007). Zhao and Dodda found that dipeptide **11** worked best among proline **22**, prolinamide **21**, dipeptides **10** and **11**, and dipeptide ester **9** in enantioselective direct aldol reaction of ethyl glyoxylate with acetone (Zhao and Dodda 2007).

The dipeptides, which have been used for direct aldol reactions are all L-proline-L-amino acid. Thus, the question arises: will a dipeptide of L-proline-D-amino acid give a better enantioselectivity in direct aldol reactions? In this article, we will address this question.

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## Materials and methods

### Chemicals

*N*-Cbz-L-proline was prepared according to the literature (Tang et al. 2003). THF was dried with Na/benzophenone and used fresh.

### General method for preparation of **24a–e**

To a solution of **23** (498 mg, 2 mmol) in triethylamine (0.3 mL, 2 mmol) and 4 mL of dry THF, ethyl chloroformate (0.2 mL, 2 mmol) was added dropwise over a period of 3 min at 0°C, followed by stirring for 3 h. The reaction mixture was added dropwise to the solution of glycine, D-valine, L-valine, D-phenylalanine or L-phenylalanine (2 mmol) in 4 mL of NaHCO<sub>3</sub> (168 mg, 2 mmol) aqueous solution at 0°C, and then the mixture was stirred for 18 h at room temperature. The final reaction mixture was acidified with dilute HCl aqueous solution, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated by rotary evaporator to get the crude product. The crude product was purified by column chromatography with mobile phase of ethyl acetate and hexane in 1:1 ratio to get the pure product.

**24a:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.19–7.44 (m, 5H, PhH), 5.26 (d, *J* = 12.3 Hz, 1H, CH), 5.18 (d, *J* = 12.3 Hz, 1H, CH), 4.45–4.55 (m, 1H, CH), 3.97–4.12 (m, 2H, CH<sub>2</sub>), 3.58–3.67 (m, 2H, CH<sub>2</sub>), 1.96–2.26 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 172.31, 171.94, 155.93, 155.60, 135.83, 128.31, 128.00, 127.76, 67.46, 60.67, 60.20, 47.30, 46.93, 41.05, 30.88, 28.68, 24.23, 23.31; IR (CHCl<sub>3</sub>): 3,323 (OH, br), 1,682 (C=O) cm<sup>−1</sup>.

**24b:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.26–7.30 (m, 5H, PhH), 5.12 (s, 2H, CH<sub>2</sub>), 4.47–4.53 (m, 1H, CH), 4.38–4.47 (m, 1H, CH), 3.46–3.56 (m, 2H, CH<sub>2</sub>), 1.85–2.12 (m, 5H, CH and CH<sub>2</sub>CH<sub>2</sub>), 0.81–0.90 (m, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 174.01, 172.31, 155.65, 135.99, 128.29, 127.96, 127.30, 67.33, 60.78, 60.39, 56.66, 47.33, 46.91, 30.94, 30.72, 29.39, 24.08, 23.22, 18.75, 17.15; IR (CHCl<sub>3</sub>): 3,331 (OH, br), 1,681 (C=O) cm<sup>−1</sup>.

**24c:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.26–7.31 (m, 5H, PhH), 5.05–5.18 (m, 2H, CH<sub>2</sub>), 4.46–4.50 (m, 1H, CH), 4.34–4.45 (m, 1H, CH), 3.44–3.53 (m, 2H, CH<sub>2</sub>), 1.88–2.16 (m, 5H, CH and CH<sub>2</sub>CH<sub>2</sub>), 0.85–0.89 (m, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 174.33, 172.48, 172.05, 155.93, 136.02, 128.26, 127.86, 127.67, 67.32, 60.54, 60.18, 57.02, 47.21, 30.78, 28.28, 24.32, 23.33, 18.78, 17.27; IR (CHCl<sub>3</sub>): 3,321 (OH, br), 1,681 (C=O) cm<sup>−1</sup>.

**24d:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.89–7.32 (m, 10H, PhH), 4.94–5.17 (m, 2H, CH<sub>2</sub>), 4.80–4.94 (m, 1H, CH), 4.31–4.37 (m, 1H, CH), 3.4–3.64 (m, 2H, CH<sub>2</sub>), 2.95–3.2 (m, 2H, CH<sub>2</sub>), 1.79–2.06 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 173.58, 172.02, 155.51, 135.81, 129.10, 128.33, 128.26, 127.99, 127.74, 126.79, 67.36, 60.66, 60.22, 52.63, 47.02, 46.75, 37.17, 30.87, 29.40, 24.04, 23.08; IR (CHCl<sub>3</sub>): 3,315 (OH, br), 1,686 (C=O) cm<sup>−1</sup>.

**24e:** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.12–7.35 (m, 10H, PhH), 4.90–5.18 (m, 2H, CH<sub>2</sub>), 4.85 (m, 1H, CH), 4.30–4.36 (m, 1H, CH), 3.20–3.40 (m, 2H, CH<sub>2</sub>), 3.00 (m, 2H, CH<sub>2</sub>), 1.6–2.18 (m, 4H, CH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 173.64, 171.98, 171.61, 155.94, 155.31, 135.86, 135.75, 129.10, 128.32, 127.95, 127.74, 126.80, 67.37, 67.33, 60.23, 52.68, 47.13, 46.80, 37.15, 30.58, 29.46, 28.10, 24.04, 23.03; IR (CHCl<sub>3</sub>): 3,317 (OH, br), 1,682 (C=O) cm<sup>−1</sup>.

### General method for preparation of **25**, **26**, **10**, **27** or **4**

To each of the solution of **24a–e** (200 mg) in 2 mL of methanol, 10% Pd/C (20 mg) was added, followed by stirring for 3 h under a hydrogen balloon. The reaction mixture was filtered and washed with methanol, and the filtrate was concentrated by a rotary evaporator. The crude product was passed through a short column of silica with water to remove residual metal, then concentrated and dried to get the pure product.

**25:** [ $\alpha$ ]<sub>D</sub><sup>24°C</sup> = −23.8 (*c* = 0.44 g/100 mL, H<sub>2</sub>O); <sup>1</sup>H NMR (D<sub>2</sub>O, 300 MHz): δ 4.45 (t, *J* = 8.3 Hz, 1H, CH), 3.86 (q, *J* = 17.3 Hz, 2H, CH<sub>2</sub>), 3.40–3.50 (m, 2H, CH<sub>2</sub>), 2.45–2.53 (m, 1H), 2.06–2.18 (m, 4H, CH<sub>2</sub>); <sup>13</sup>C NMR (D<sub>2</sub>O, 75 MHz): δ 175.62, 169.25, 59.63, 46.16, 42.97, 29.22, 23.55.

**26:**  $[\alpha]_{\text{D}}^{24^\circ\text{C}} = -27.9$  ( $c = 0.34$  g/100 mL,  $\text{H}_2\text{O}$ );  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 300 MHz):  $\delta$  4.47 (t,  $J = 6.7$  Hz, 1H, CH), 4.17 (d,  $J = 4.3$  Hz, 1H, CH), 3.40–3.49 (m, 2H,  $\text{CH}_2$ ), 2.4–2.6 (m, 1H, CH), 2.09–2.24 (m, 4H,  $\text{CH}_2$ ), 0.94 (t,  $J = 7.3$  Hz, 6H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 75 MHz):  $\delta$  177.55, 169.21, 60.52, 59.62, 46.28, 29.96, 29.95, 23.55, 18.55, 16.76.

**10:**  $[\alpha]_{\text{D}}^{24^\circ\text{C}} = -30.9$  ( $c = 0.34$  g/100 mL,  $\text{H}_2\text{O}$ );  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 300 MHz):  $\delta$  4.44 (t,  $J = 8.4$  Hz, 1H, CH), 4.05 (d,  $J = 5.9$  Hz, 1H, CH), 3.39–3.49 (m, 2H,  $\text{CH}_2$ ), 2.4–2.6 (m, 1H, CH), 2.05–2.17 (m, 4H,  $\text{CH}_2$ ), 0.94 (t,  $J = 7.1$  Hz, 6H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 75 MHz):  $\delta$  177.88, 168.77, 61.40, 59.45, 46.24, 29.79, 29.42, 23.47, 18.51, 17.15.

**27:**  $[\alpha]_{\text{D}}^{24^\circ\text{C}} = -40$  ( $c = 0.25$  g/100 mL aq. HCl);  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 300 MHz):  $\delta$  7.29–7.41 (m, 5H, PhH), 4.63 (dd,  $J = 4.2, 10.1$  Hz, 1H, CH), 4.30 (t,  $J = 7.6$  Hz, 1H, CH), 3.28–3.38 (m, 3H, CH and  $\text{CH}_2$ ), 2.90 (t,  $J = 10$  Hz, 1H, CH), 2.18–2.25 (m, 1H, CH), 1.89–1.96 (m, 1H, CH), 1.72–1.79 (m, 1H, CH), 1.50–1.57 (m, 1H, CH);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 75 MHz):  $\delta$  177.02, 168.53, 137.34, 128.93, 128.37, 126.62, 59.44, 55.70, 46.08, 37.48, 29.64, 23.28.

**4:**  $[\alpha]_{\text{D}}^{24^\circ\text{C}} = -15.4$  ( $c = 0.13$  g/100 mL aq. HCl);  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 300 MHz):  $\delta$  7.31–7.40 (m, 10H, PhH), 4.60 (dd,  $J = 4.5, 10.3$  Hz, 1H, CH), 4.49 (dd,  $J = 5.1, 9.2$  Hz, 1H, CH), 4.25–4.34 (m, 2H, 2CH), 3.22–3.44 (m, 6H,  $\text{CH}_2$ ), 2.90–3.24 (m, 2H,  $\text{CH}_2$ ), 1.5–2.5 (m, 8H,  $\text{CH}_2$ );  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 75 MHz):  $\delta$  177.44, 177.17, 168.46, 168.33, 137.47, 128.91, 128.37, 128.34, 126.60, 126.56, 59.44, 59.39, 56.70, 56.01, 46.17, 46.07, 37.58, 37.04, 29.64, 29.24, 23.44, 23.27.

#### General method for direct aldol reactions

To the solution of catalyst **25**, **26**, **10**, **27** or **4** (0.09 mmol) in 0.8 mL of solvent and 0.2 mL of acetone or cyclohexanone, *p*-nitrobenzaldehyde (45 mg, 0.3 mmol) was added, followed by stirring at room temperature or  $0^\circ\text{C}$  for some time. Then the reaction mixture was quenched with 20 mL of ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated by a rotary evaporator to get the aldol product.

#### 4-Hydroxy-4-(4-nitrophenyl)butan-2-one

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.21 (d,  $J = 8.7$  Hz, 2H, PhH), 7.54 (d,  $J = 8.7$  Hz, 2H, PhH), 5.23–5.28 (m, 1H, CH), 3.57 (d,  $J = 3.4$  Hz, 1H, OH), 2.82–2.90 (m, 2H,  $\text{CH}_2$ ), 2.22 (s, 3H,  $\text{CH}_3$ ). The ee value was determined by HPLC analysis of the acetylated product, which was carried out by reaction with triethylamine and acetyl chloride

at room temperature. The HPLC conditions and analytic data are: chiral column, chiralcel OD-RH; mobile phase, water/acetonitrile = 7:3; flow rate, 0.4 mL/min; UV wavelength of detector, 271 nm; retention time for *R*-isomer (major) and *S*-isomer (minor), 37, 40.8 min.

#### (2*S*)-2-[(*R*)-Hydroxy(4-nitrophenyl)methyl]cyclohexanone (anti-isomer)

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.21 (d,  $J = 8.6$  Hz, 2H, PhH), 7.50 (d,  $J = 8.6$  Hz, 2H, PhH), 4.89 (dd,  $J = 3.0, 8.4$  Hz, 1H, CH), 4.06 (d,  $J = 3.0$  Hz, 1H, OH), 1.3–2.6 (m, 9H, CH &  $\text{CH}_2$ ). The ee value was determined by GC analysis of the silylated product, which was carried out by reaction with triethylamine and chlorotrimethylsilane at room temperature. The GC conditions and analytic data are: chiral column, CP-Chirasil-Dex CB; temperature,  $170^\circ\text{C}$ ; retention time for (*R,S*)-isomer (minor), (*S,R*)-isomer (major): 35.1, 36.2 min.

#### (2*R*)-2-[(*R*)-Hydroxy(4-nitrophenyl)methyl]cyclohexanone (syn-isomer)

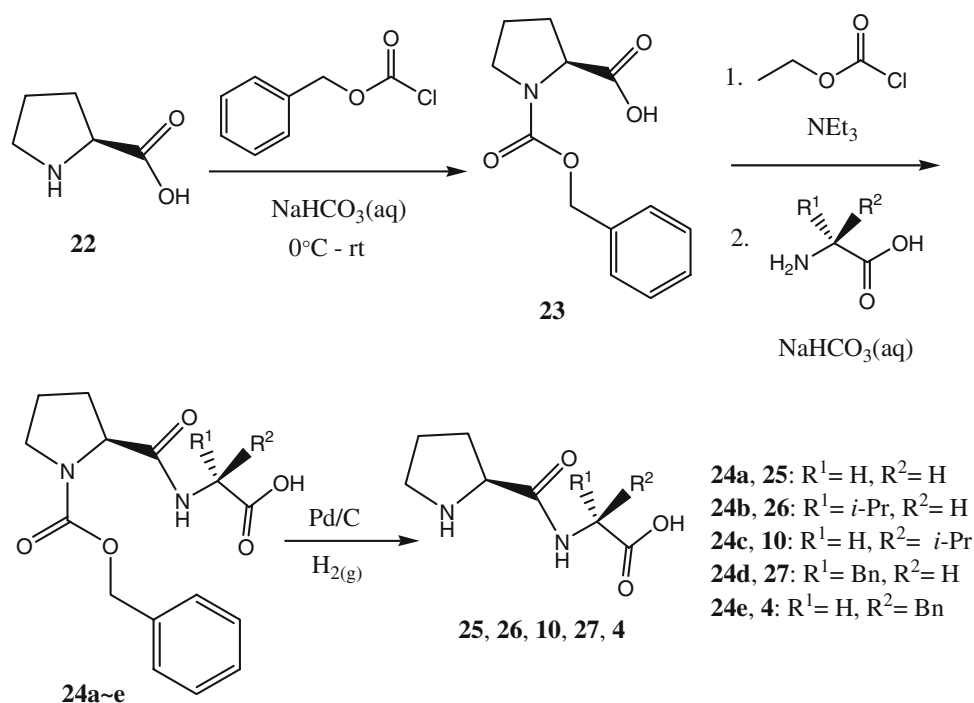
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.21 (d,  $J = 8.7$  Hz, 2H, PhH), 7.49 (d,  $J = 8.7$  Hz, 2H, PhH), 5.48 (s, 1H, CH), 3.16 (d,  $J = 3.2$  Hz, 1H, OH), 1.3–2.6 (m, 9H, CH &  $\text{CH}_2$ ). The ee value was determined by GC analysis of the silylated product, which was carried out by reaction with triethylamine and chlorotrimethylsilane at room temperature. The GC conditions and analytic data are: chiral column, CP-Chirasil-Dex CB; temperature,  $170^\circ\text{C}$ ; retention time for (*S,S*)-isomer (minor), (*R,R*)-isomer (major): 39.2, 41.4 min.

## Results and discussion

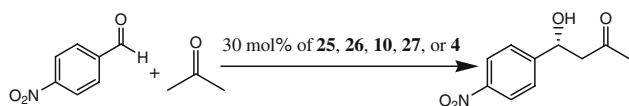
Because L-proline gives good enantioselectivity in direct aldol reactions (Notz et al. 2004; List 2004), we synthesized dipeptides from L-proline, and the second amino acids in the dipeptides were glycine, L-valine, D-valine, L-phenylalanine or D-phenylalanine, respectively. As shown in Scheme 1 for the preparation of the dipeptides, we protected the secondary amine group of L-proline (**22**) with a carbobenzyloxy (cbz) group by reaction with benzyl chloroformate in aqueous  $\text{NaHCO}_3$ . Then the carboxylic acid group of the protected L-proline was activated by reaction with ethyl chloroformate in aqueous  $\text{NaHCO}_3$ , followed by treatment with the second amino acid. Afterwards, hydrogenation of the protected dipeptides on Pd/C eliminated the cbz protecting group from the dipeptides.

Direct aldol reaction of acetone with *p*-nitrobenzaldehyde in the presence of 30 mol% L-Pro-Gly **25** in DMSO

Scheme 1



was optimized by reaction time and temperature. As shown in Table 1, a better enantioselectivity was achieved at 0°C, and a better yield was attained at a longer reaction time (19 h) and 0°C at the expense of enantioselectivity. Thus, the optimized condition of 0°C and 19 h was applied to the direct aldol reaction catalyzed by **26**, **10**, **27** or **4**. As shown in Table 2, L-Pro-L-Phe **4** accomplished the best enantioselectivity and yield in the direct aldol reaction. In addition, it was found that L-Pro-L-Phe **4** achieved better enantioselectivity than L-Pro-D-Phe **27**, and L-Pro-L-Val **10** attained better enantioselectivity than L-Pro-D-Val **26**. According to these two examples, the L-proline-L-amino acids achieve better enantioselectivity than the L-proline-D-amino acid. A strange result appears in Table 2: a poor yield of the direct aldol reaction was caused by L-Pro-L-Val **10**. A possible explanation for this repeatable result is poor solubility of **10** in DMSO.



Because L-Pro-L-Phe **4** worked the best as a catalyst in this direct aldol reaction, the direct aldol reaction catalyzed by 30 mol% of **4** at 0°C for 19 h was used for solvent optimization. Solvents with various degrees of hydrogen bonding were tested. As shown in Table 3, methanol worked the best among alcohols, and alcohols of higher hydrophobicity reduced yields of the direct aldol reaction.

**Table 1** Yields and ee values for the direct aldol reaction of acetone with *p*-nitro-benzaldehyde in the presence of 30 mol% of L-Pro-Gly **25** in DMSO

| Catalyst            | Reaction temperature (°C) | Reaction time (h) | Yield (ee value) |
|---------------------|---------------------------|-------------------|------------------|
| L-Pro-Gly <b>25</b> | 25                        | 2                 | 53% (59%)        |
| L-Pro-Gly <b>25</b> | 25                        | 5                 | 80% (65%)        |
| L-Pro-Gly <b>25</b> | 0                         | 5                 | 25% (80%)        |
| L-Pro-Gly <b>25</b> | 0                         | 19                | 88% (73%)        |

**Table 2** Yields and ee values for the direct aldol reaction of acetone with *p*-nitrobenzaldehyde in the presence of 30 mol% of dipeptide in DMSO at 0°C for 19 h

| Catalyst              | Yield (%) | ee value (%) |
|-----------------------|-----------|--------------|
| L-Pro-D-Val <b>26</b> | 89        | 60           |
| L-Pro-L-Val <b>10</b> | 32        | 71           |
| L-Pro-D-Phe <b>27</b> | 95        | 58           |
| L-Pro-L-Phe <b>4</b>  | 98        | 82           |

Highly hydrophilic water with hydrogen bonding capability, however, made both yield and enantioselectivity of the direct aldol reaction even worse, and so did water with saturated NaCl. Besides, mixed alcohols or aqueous alcohols attained intermediate yield and enantioselectivity of the direct aldol reaction. Conversely, dipolar aprotic DMSO, which is not a hydrogen bonding donor, achieved much better yield and enantioselectivity of the direct aldol reaction. According to the preceding results of solvent

**Table 3** Solvent optimization for the direct aldol reaction of acetone with *p*-nitrobenzaldehyde in the presence of 30 mol% of L-Pro-L-Phe **4** in DMSO at 0°C for 19 h

| Solvent                   | Yield (%) | ee value |
|---------------------------|-----------|----------|
| DMSO                      | 98        | 82%      |
| MeOH                      | 86        | 78%      |
| EtOH                      | 22        | 83%      |
| <i>i</i> -PrOH            | 2         | n.d.     |
| Water                     | 12        | 38%      |
| Sat. NaCl <sub>(aq)</sub> | 11        | 46%      |
| 1:1 MeOH/water            | 23        | 48%      |
| 1:1 MeOH/ <i>i</i> -PrOH  | 30        | 81%      |

**Table 4** Influence of a tertiary amine or surfactant on the direct aldol reaction of acetone with *p*-nitrobenzaldehyde in the presence of 30 mol% of L-Pro-L-Phe **4** in water at 0°C for 19 h

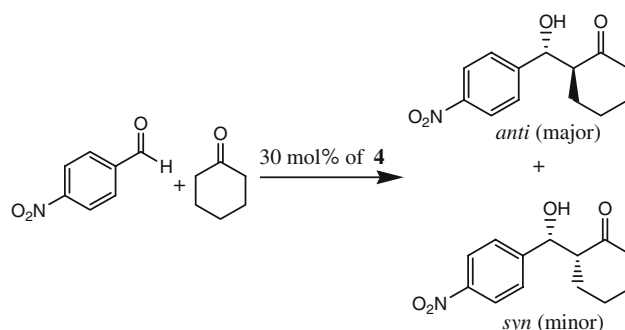
| Tertiary amine            | Surfactant     | Yield (%) | ee value |
|---------------------------|----------------|-----------|----------|
| 100 mol% NEt <sub>3</sub> | —              | 88        | 23%      |
| —                         | 28 mol% PEG400 | 0.8       | n.d.     |
| 100 mol% NEt <sub>3</sub> | 28 mol% PEG400 | 85        | 26%      |
| —                         | 30 mol% SDS    | 4.1       | n.d.     |
| 100 mol% NEt <sub>3</sub> | 30 mol% SDS    | 95        | 22%      |
| 100 mol% NEt <sub>3</sub> | 40 mol% PEG400 | 56        | 46%      |
| 35 mol% NMM               | 40 mol% PEG400 | 46        | 68%      |

optimization, hydrogen bonding does not play an important role in achieving better enantioselectivity and yield of the direct aldol reaction, but solubility of the dipeptide catalysts in the solvents is a key point of enantioselectivity and yield of the direct aldol reaction.

Because lower yield of the direct aldol reaction probably results from poor solubility of **4** in solvents, a tertiary amine or surfactant was added to the reaction system in order to improve solubility of **4**. As shown in Table 4, a surfactant of PEG400 or SDS did not improve the yield of the direct aldol reaction, but a tertiary amine

did dramatically increase the yield of the direct aldol reaction even though its enantioselectivity was limitedly improved.

As shown in Table 5, enantioselectivity dramatically increased when cyclohexanone replaced acetone in the direct aldol reaction in the presence of 30 mol% of L-Pro-L-Phe **4** in DMSO at 25°C for 19 h. Replacement of some DMSO with cyclohexanone in the direct aldol reaction resulted in a decreased yield. When this direct aldol reaction was run in water, conversion was very low. Addition of 30 mol% of NMM and SDS into the reaction system in water did increase both yield and enantioselectivity of the direct aldol reaction, but its result is still worse than that carried out in plain DMSO.



## Conclusion

The L-proline-L-amino acid achieves better enantioselectivity of the direct aldol reaction than the corresponding L-proline-D-amino acid. Hydrogen bonding of solvent does not play an important role in achieving better enantioselectivity and yield of the direct aldol reaction, while solubility of the dipeptide catalysts in the solvents is a key point in the yield of the direct aldol reaction. Yield and enantioselectivity of the direct aldol reaction are much better in plain DMSO than those in other solvents even with addition of NMM and SDS into aqueous solutions.

**Table 5** Influence of a solvent, tertiary amine or surfactant on the direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in the presence of 30 mol% of L-Pro-L-Phe **4** at 25°C for 19 h

| Solvent           | Tertiary amine | Surfactant     | Yield (anti/syn) | ee (%) for anti/syn |
|-------------------|----------------|----------------|------------------|---------------------|
| DMSO <sup>a</sup> | —              | —              | 97% (75/25)      | 89/14               |
| DMSO <sup>b</sup> | —              | —              | 96% (72/28)      | 91/13               |
| DMSO <sup>c</sup> | —              | —              | 82% (80/20)      | 89/17               |
| Water             | —              | —              | Trace            | n.d.                |
| Water             | 30 mol% NMM    | —              | 17% (92/8)       | 41/10               |
| Water             | 30 mol% NMM    | 36 mol% PEG400 | 12% (91/9)       | 40/12               |
| Water             | 30 mol% NMM    | 30 mol% SDS    | 41% (89/11)      | 72/42               |

<sup>a</sup> Cyclohexanone:DMSO = 1:4

<sup>b</sup> 4 Å molecular sieve

<sup>c</sup> Cyclohexanone:DMSO = 4:1

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