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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5213–5217

Novel enantiocontrol system with aminoacyl derivatives of glucoside as enamine-based organocatalysts for aldol reaction in aqueous media

Ayumi Tsutsui,[a] Hiroshi Takeda,[a] Masaya Kimura,[a] Takashi Fujimoto[b] and Tomoya Machinami[a,b,*]

[a]*Department of Chemistry, College of Science and Technology, Meisei University, 2-1-1 Hodokubo, Hino, Tokyo 191-8506, Japan*
[b]*Frontier Research Center for Environmental Science, Meisei University, 2-1-1 Hodokubo, Hino, Tokyo 191-8506, Japan*

Received 19 April 2007; revised 13 May 2007; accepted 24 May 2007
Available online 26 May 2007

Abstract—Introduction of carbohydrate auxiliary into enanine-based catalyst provided a novel enantiocontrol for aqueous aldol reaction. Methyl 2-(L-prolyl)amido-2-deoxy-α-D-glucopyranosides led to the enantiocontrol as parent amino acids did in the reaction of acetone with 4-nitrobenzaldehyde, and provided *R*-aldol in an improved efficiency compared with that of L-proline in aqueous media. The enantioreversal control of that with parent amino acid was observed in the reaction with methyl 2-(L-*tert*-leucyloxy)-α-D-glucopyranoside, which provided *S*-aldol predominantly in moderate efficiency. The novel enantiocontrol system was proposed to occur as a result of the generation of the transition state through the reaction of enamine with hydroxyl group on glucoside auxiliary.

Proline and its derivatives have been reported to serve as enantioselective catalysts for aldol reaction in organic media. The proline-catalyzed asymmetric aldol reaction was proposed to proceed in the enamine mechanism, where imine functionality converts the aldol donor to enamine, whereas the carboxylic acid group provides a hydrogen bond to the acceptor.[1] The enamine attacks the carbonyl group of aldehyde to generate the transition state, whose stereochemistry is stabilized by the chiral carboxyl and leads to an enantioselectivity. In the reaction of acetone with 4-nitrobenzaldehyde in organic media, the reactions with L-proline and its derivatives typically lead to *R*-aldol, whereas the reaction with D-proline provides *S*-aldol predominantly.

Although the proposed mechanism of the proline-catalyzed aldol reaction is based on the enamine mechanism for class I aldolase, proline has not been shown to act as an asymmetric catalyst under aqueous media. Since water often alters enantioselectivities by interrupting hydrogen bonds critical for stabilizing the transition states of the asymmetric catalytic reactions,[2] water interrupts the hydrogen bonding from carboxyl group of L-proline to the transition state, and then the L-proline-catalyzed aqueous aldol reaction caused remarkable decrease in enantioselectivity. Participation of a water molecule to generate a transition state is proposed as the enamine mechanism for nornicotine-catalyzed aqueous aldol reaction.[3]

In the aldolase antibodies, the reactions are considered to occur in a hydrophobic active site,[4] although the amino functionality of lysine and the hydroxyl group of tyrosine are believed to be involved in the enamine-based catalytic cycle of class I aldolase.[5] To develop of simple and efficient chemical processes for the aldol reaction in aqueous media,[6] small organic catalysts with hydrophobic groups were designed based on the hydrophobic nature of the active site in antibodies. Although such pyrrolidine catalysts bearing hydrophobic alkyl groups proved their high efficiencies in the reaction of cyclohexanone, still moderate enantiomeric excesses were reported for the reaction of acyclic ketone with aromatic aldehyde.[6b] The high efficiency for the reaction of cyclic ketone was also reported for 4-hydroxyproline derivative bearing hydrophobic auxiliary.[6c]

* Corresponding author. Tel.: +81 42 591 5111; fax: +81 42 591 8181; e-mail: machinam@chem.meisei-u.ac.jp

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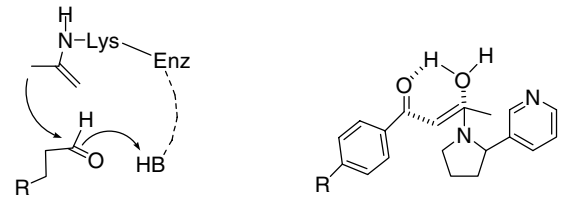
doi:10.1016/j.tetlet.2007.05.139



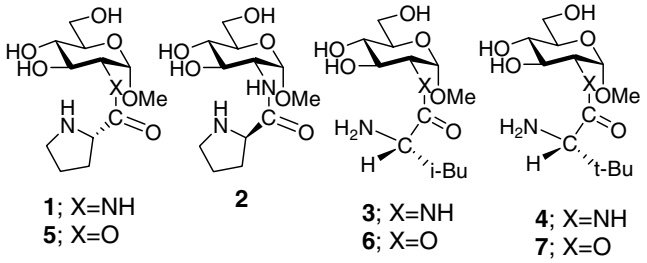
General mechanism of class I aldlase catalyzed aldol reaction[5]

Proposed mechanism of nornicotine-catayzed aqueous aldol reaction[2]

Figure 1. Transition states for aqueous aldol reaction.

As another approach to find efficient catalysts acted in aqueous media as aldolase, we designed amine catalysts bearing carbohydrate moiety as biomimetic catalysts. On the basis of the proposed mechanism for the aqueous aldol reaction[3] (Fig. 1), the hydroxyl group on the catalyst presumably competes with water molecules for its coordination to aldehyde in aqueous media. And such hydroxyl is considered to act as the hydroxyl group of tyrosine in aldolase based on the mechanism[5] (Fig. 1). In initial study for prolyl derivatives having carbohydrate auxiliary,[7] methyl 2-deoxy-2-(L-prolyl)amido-α-D-glucopyranoside proved its efficiency to lead to the *R*-enantiocontrol in the reaction of acetone with 4-nitrobenzaldehyde only under aqueous condition. Further study for the amnioacyl-glucoside catalysis showed that the novel enantiocontrol system was depended on the nature of carbohydrate auxiliary.

As amine catalysts bearing carbohydrate moiety, aminoacyl-amido-glucosides, **3** and **4**, were prepared from D-glucosamine and amino acids via carbodiimide condensation respectively.[8] Aminocyloxy-glucosides, **6** and **7**, were synthesized via regioselective acylation[9,10] of protected methyl α-D-glucopyranoside (Fig. 2). The efficiencies of the catalysts were determined in the model aldol reaction of acetone with 4-nitrobenzaldehyde



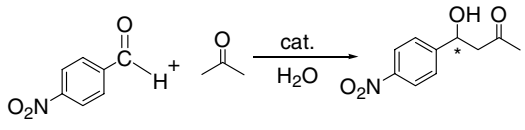
1; X=NH
5; X=O

2

3; X=NH
6; X=O

4; X=NH
7; X=O

Figure 2. Aminoacyl derivatives of methyl α-D-glucopyranoside.



Scheme 1. Asymmetric aldol reaction of 4-nitrobenzaldehyde and acetone.

(Scheme 1), wherein acetone was a component of the solvent system.

In our initial study, methyl 2-deoxy-2-(L-prolyl)amido-α-D-glucopyranoside (**1**) was found to be an efficient catalyst with respect to yield and enantioselectivity to provide *R*-aldol, (4*R*)-4-hydoxy-4-(4-nitrophenyl)-butan-2-one. The efficiency of **1** was varied on the water–acetone ratio and the quantitative aldol formation with low enantioselectivity (29%) was observed in the reaction with **1** under the condition of acetone–water (4:5) media, whereas the best result was obtained as 69% yield with 61% ee under acetone–water (20:1) media (Table 1, entries 1 and 2). Further study for pyrrolidine catalyst provided that 2-(D-prolyl)amido-glucoside **2**, isomer of **1**, revealed almost equal efficiency in opposite enantioselectivity (50% ee of *S*-aldol) with L-prolinamido isomer **1** (entry 4). These enantioselectivities showed that the aqueous aldol reactions with both of prolonamido-glucoside catalysts proceeded under the usual enantiocontrol with amino acid derivatives-catalyzed aldol reaction, in which L-amino acid derivatives lead to *R*-enantioselectivity, whereas D-amino acid derivatives provide *S*-enantiomeric excess of aldol. In the reactions with prolonamido-glucoside catalysts, **1** and **2**, the effect of water–acetone ratio on the enantiomeric excess of aldol were observed and the lower content of water in the reaction media reflected the increasing of enantioselectivities with the lower reaction rates. Since the hydroxyl group of sugar is considered to compete with water molecules for its coordination to organic molecules,[2] the effect of water–acetone ratio on the enantiomeric excess suggested that the hydroxyl groups on glucoside moiety of **1** and **2** stabilized the transition state for aldol formation. According to the proposed mechanism for nornicotine-catalyzed aqueous aldol reaction,[3] such hydroxyl groups were presumably incorporated into the generation of the transition state for C–C bond formation (Fig. 2).

To search the effect of hydroxyl group on glucoside bearing structure, primary aminoacyl-amido derivatives of methyl α-D-glucopyranoside as amine catalysts were prepared and applied to the aldol reaction in the presence of water. The reaction with L-leucylamido-glucoside **3** showed the comparative efficiency under the condition of acetone–water (4:5), but the decreased yield with the lower reaction rate under the condition of acetone–water (20:1) when compared to the reactions with L-prolinamido-glycoside **1** (entries 5, 6, 1 and 2). The bulkiness of alkyl side chain affected on the efficiency of L-*tert*-leucylamido-glucoside **4** and the seriously lowered reaction rate was observed especially in the condition of acetone–water (20:1) (entries 7 and 8). However, the effect of glucoside moiety in enantiomeric excesses of aldol formation were also observed in the model reactions with primary aminoacyl-glucosides, **3** and **4**, under the usual enantiocontrol with L-amino acid derivatives-catalyzed reaction.

In the preliminary experiments,[11] the enantioselectivities even in low enantiomeric excess (12–17% ee) were detected in the model aldol reactions under the condi-

Table 1. The effect of water in yield and ee for the (aminoacyl)amido derivatives-catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde

Entry	Catalyst[a]	Molar ratio (mol %)	Reaction (day)	H_2O[b] (vol %)	Yield[c] (%)	Enantiomeric exess[c] (% ee)
1	**1**	30	1	55	98	29 (*R*)
2	**1**	30	1	5	69	61 (*R*)
3	**2**	30	1	55	88	32 (*S*)
4	**2**	30	1	5	49	50 (*S*)
5	**3**	30	1	55	91	29 (*R*)
6	**3**	30	1	5	27	44 (*R*)
7	**4**	30	1	55	52	28 (*R*)
8	**4**	30	1	5	10	56 (*R*)

[a] *N*-Methylmorpholine was used to adjust pH for the catalysts as hydrochloride.
[b] For the reaction of acetone (0.53 mL, 90 mol equiv) with 4-nitrobenzaldehyde (10 mg), water (0.5 mL; 55%; water–acetone [4:5] or 20 μL; 5%; water–acetone [1:20]) was used to dissolve catalyst.
[c] The yields and ee were determined by chiral HPLC analysis (Shimadzu LC-10AD vp using Chiralpack AS-H from Daicel Chemical Industries, Ltd).

tion of acetone–water (4:5) with primary amino acids, L-leucine, and L-*tert*-leucine, whereas not observed in the reaction with L-proline. Although such primary amino acids showed better natures as asymmetric catalysts than that of proline alone in aqueous aldol reaction, in aminoacyl-amido-glucoside catalysts, the secondary amine catalyst **1** was more efficient than the primary amine catalysts, **3** and **4**.

On the contrary, enantiocontrols were varied on the structural features of aminoacyloxy-glucosides where L-aminoacyl residues were introduced on glucoside moiety through ester linkages (Fig. 2). Although aminoacyloxy-glucosides did not catalyze the model aldol reaction in DMSO in similar manner with aminoacyl-amido-glucosides, the different behaviors depended on the linker were observed in the aqueous acetone media. The reaction with methyl 2-(L-prolyl)oxy-α-D-glucopyranoside (**5**) under acetone–water (4:5) media resulted in quantitative racemic aldol formation and L-leucyloxy-glycoside **6** led to only retained enantiocontrol of parent L-leucine alone (Table 2, entries 1 and 2). However, the novel enantiocontrol system was appeared in the reaction with methyl 2-(L-*tert*-leucyl)oxy-α-D-glucopyranoside (**7**), in which the unexpected enantiocontrol to lead to (4*S*)-4-hydoxy-4-(4-nitrophenyl)butan-2-one was observed under in acetone–water (4:5) media (entries 3 and 4). The effect of water–acetone ratio on the enantiomeric excess of aldol was also observed in the reaction with **6** under opposite enantiocontrol, and the lower content of water in acetone–water (20:1) media reflected the increasing of enantioselectivities, up to the moderate enantiomeric excess, 42% ee of *S*-aldol (entry 5). In acetone–water (20:1) media, the observed efficiencies of parent L-*tert*-leucine,[12] L-*tert*-leucylamido-glucoside **4**, and L-*tert*-leucyloxy-glucoside **7** were evaluated to be similar with respect to yield and the ratio of enantiomeric excess, but only **7** led to opposite enantiocontrol. The results suggested that the glucoside moiety acted as the substitute of carboxyl group of L-*tert*-leucine and the stereospecific participation of glucoside moiety into the transition state was altered in analogs, **4** and **7**, due to the different linker between aminoacyl residue and glucoside moiety. Although the reaction with **7** in acetone–water (20:1) media showed that the lower content of water in the reaction media also reflected the lower reaction rates, prolonging the reaction time led to increasing in yield gradually and pushed up to the moderate efficiency (45% yield with 48% ee of *S*-aldol) after 3 days (entries 6 and 7). The efficiency shown by L-*tert*-leucyloxy-glucoside **7** catalyst was comparable to that provided by D-prolinamido-glucoside **2** (Table 2, entry 7 vs Table 1, entry 4) and the enantioreversal control providing *S*-aldol by L-amino acid derivative catalyst was accomplished unprecedentedly. The enantiocontrol led to the predominant formation of *S*-aldol was also observed in the reaction with L-phenylalanyloxy-glucoside analog having relatively bulky alkyl side chain, even in low yield with slight enantiomeric excess.[12]

Table 2. The effect of water in yield and ee for the (aminoacyl)oxy derivatives-catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde

Entry	Catalyst[a]	Molar ratio (mol %)	Reaction (days)	H_2O[b] (vol %)	Yield[c] (%)	Enantiomeric exess[c] (% ee)
1	**5**	30	1	55	98	n.d.
2	**6**	30	1	55	79	11 (*R*)
3	**7**	30	1	55	57	10 (*S*)
4	**7**	30	2	55	99	12 (*S*)
5	**7**	30	1	5	11	42 (*S*)
6	**7**	30	2	5	23	49 (*S*)
7	**7**	30	3	5	45	48 (*S*)

[a] *N*-Methylmorpholine was used to adjust pH for the catalysts as hydrochloride.
[b] For the reaction of acetone (0.53 mL, 90 mol equiv) with 4-nitrobenzaldehyde (10 mg), water (0.5 mL; 55%; water–acetone [4:5] or 20 μL; 5%; water–acetone [1:20]) was used to dissolve catalyst.
[c] The yields and ee were determined by chiral HPLC analysis (Shimadzu LC-10AD vp using Chiralpack AS-H from Daicel Chemical Industries, Ltd).

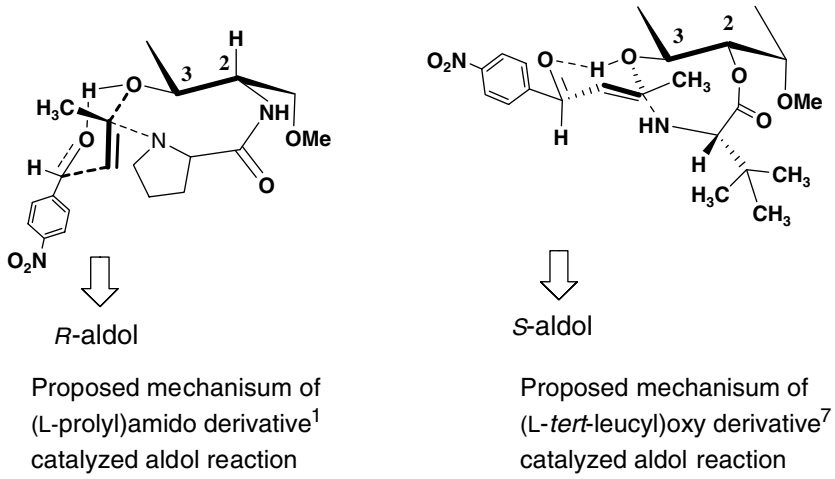


Figure 3. Proposed transition states for C–C bond formation in aqueous aldol reaction.

Such enantioreversal was proposed to occur as a result of the generation of the transition state through the reaction of enamine with hydroxyl group on glucoside moiety, which differ in their stereochemistry of the transition state for C–C bond formation, one to lead to *R*-aldol, the other to *S*-aldol predominantly.[13] On the basis of the reported proximity between lysyl ε-amino and tyrosyl hydroxyl in aldolase,[5] 3-OH on glucoside moiety in these 2-aminoacyl derivative of methyl α-D-glucopyranoside is the most provable hydroxyl group participating into the transition state for the C–C bond formation. Therefore, on the basis of the proposed mechanism for the aqueous aldol reaction,[3] the transition states for both of enantiocontrol system were currently proposed as shown in Figure 3, although the modeling study is underway.

In summary, we have shown that aminoacyl derivatives bearing glucoside moieties are efficient catalysts for the aldol reaction of acetone and 4-nitrobenzaldehyde in the presence of water. Methyl 2-(L-prolyl)amido-α-D-glucopyanoside **1** represents the catalysts led to *R*-enantioselectivity with the practical efficiency for the aldol reaction in the presence of water, whereas the enantioreversal control by L-amino acid derivative catalyst was realized by methyl 2-(L-*tert*-leucyl)oxy-α-D-glucopyranoside. The enantio-controlled reaction takes place under the novel catalytic system, in which hydroxyl group on glucoside moiety affects to provide the increased enantioselectivity and the decreased reaction rate. Therefore, the catalytic system realized here is supposed to be a good model for the class I aldolases catalysis. Although the aminoacyl-glycoside catalysts have been applied only for the reaction of acetone currently, further studies on aldol acceptor specificity and structure–catalytic ability relationships are in progress.

Aminoacyl derivatives of glucoside were used as hydrochloride with 1 equiv of *N*-methylmorpholine (NMM, which it itself did not catalyze the asymmetric reaction[14]) in the aldol reaction of acetone with 4-nitrobenzaldehyde. To aqueous solution of the catalysts was added acetone (90 mol equiv), then 4-nitrobenzaldehyde at room temperature. The reaction solution was extracted with ethyl acetate and dried over Na_2SO_4. Using aliquots of those ethyl acetate solutions (20 μl), the yields and enantiomeric excesses were determined by chiral HPLC analysis (Shimadzu LC-10AD vp using Chiralpak AS-H from Daicel Chemical Industries, Ltd, hexane/IPA = 70:30, flow rate 0.8 mL/min, $\lambda = 254$ nm), shown in Tables 1 and 2. Aminoacyl derivatives of glucoside used for the reaction were easily recovered from aqueous layer and were able to reuse.

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Compound **1**: $[\alpha]_D^{25}$ −53 (*c* 0.35, methanol); ^{1}H NMR (500 MHz, DMSO-d_6/D_2O, 80 °C) δ 1.88–1.95 (m, 3H, prolyl-H_β, prolyl-$H_\gamma \times 2$), 2.30–2.35 (m, 1H, prolyl-H_β), 3.17 (s, 3H, 1-OCH_3), 3.19–3.22 (m, 1H), 3.25–3.31 (m, 2H), 3.39 (ddd, 1H, $J_{5,6} = 5.49$ Hz, $J_{5,6'} = 2.44$ Hz, H-5), 3.51 (t, 1H, H-3), 3.53 (dd, 1H, $J_{6,6'} = 10.60$ Hz, H-6), 3.66 (dd, 1H, H-6′), 3.71 (dd, 1H, $J_{1,2} = 3.36$ Hz, H-2), 4.20–4.23 (m, 1H, prolyl-H_α), 4.60 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{12}H_{22}N_2O_6+H]^+$, 291.15561; found, 291.16116.

Compound **2**: $[\alpha]_D$ +128 (*c* 1, methanol); ^{1}H NMR (500 MHz, D_2O) δ 1.91 (m, 3H, prolyl-H_β, prolyl-$H_\gamma \times 2$), 2.30 (m, 1H, prolyl-H_β), 3.21 (s, 3H, 1-OCH_3), 3.26 (m, 2H, prolyl-$H_\delta \times 2$), 3.31 (t, 1H, $J_{3,4} = 9.46$, H-4), 3.51 (ddd, 1H, $J_{5,6} = 5.19$, $J_{5,6'} = 2.14$, H-5), 3.56 (t, 1H, $J_{2,3} = 9.68$, H-3), 3.61 (dd, 1H, $J_{6,6'} = 12.21$, H-6), 3.71 (dd, 1H, H-6′), 3.80 (dd, 1H, $J_{1,2} = 3.36$, H-2), 4.23 (t, 1H, prolyl-H_α), 4.61 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{12}H_{22}N_2O_6+H]^+$, 291.15561; found, 291.15053.

Compound **5**: $[\alpha]_D$ +50 (*c* 0.5, methanol); ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 1.83–2.07 (m, 3H, prolyl-H_β, prolyl-$H_\gamma \times 2$), 2.23–2.31 (m, 1H, prolyl-H_β), 3.11–3.29 (m, 3H), 3.23 (s, 3H, 1-OCH_3), 3.35 (dt, 1H, H-5), 3.39–3.58 (m, 2H), 3.62 (t, 1H, $J_{2,3} = 10.1$, H-3), 6.54 (t, 1H, prolyl-H_α), 4.57 (dd, 1H,$J_{1,2} = 3.66$, H-2), 4.75 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{12}H_{21}NO_7+H]^+$, 292.13963; found, 292.14152.

8. Compound **3**: $[\alpha]_D^{25}$ +74 (*c* 1, methanol), ^{1}H NMR (500 MHz, D_2O) δ 0.78, 0.79 (2 × d, 6H, $J = 6.4$ Hz, leucyl-$2 \times CH_3$), 1.47–1.62 (m, 3H, leucyl-H_γ and $2 \times H_\beta$), 3.21 (s, 3H, 1-OCH_3), 3.28 (t, 1H, $J_{3,4} = J_{4,5} = 8.9$ Hz, H-4), 3.50 (ddd, 1H, $J_{5,6} = 5.5$ Hz, $J_{5,6'} = 2.4$ Hz, H-5), 3.55 (t, 1H, $J_{2,3} = 10.7$ Hz, H-3), 3.60 (dd, 1H, $J_{6,6'} = 12.2$ Hz, H-6), 3.70 (dd, 1H, H-6′), 3.76 (dd, 1H, $J_{1,2} = 3.7$ Hz, H-2), 3.83 (t, 1H, leucyl-H_α), 4.63 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{13}H_{26}N_2O_6+H]^+$, 307.18691; found, 307.18997.

   Compound **4**: $[\alpha]_D^{25}$ +82 (*c* 1, methanol), ^{1}H NMR (500 MHz, DMSO-d_6/D_2O, 80 °C) δ 1.02 (s, 9H, *t*-butyl), 3.19 (t, 1H, $J_{4,5} = 10.0$ Hz, H-4), 3.29 (s, 3H, 1-OCH_3), 3.39 (ddd, 1H, $J_{5,6} = 5.5$ Hz, $J_{5,6'} = 2.44$ Hz, H-5), 3.51 (t, 1H, $J_{2,3} = 10.4$ Hz, H-3), 3.52 (dd, 1H, $J_{6,6'} = 11.6$ Hz, H-6), 3.63 (s, 1H, *t*-leucyl-H_α), 3.66 (dd, 1H, H-6′), 3.74 (dd, 1H, $J_{1,2} = 3.4$ Hz, H-2), 4.60 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{13}H_{26}N_2O_6+H]^+$, 307.18691; found, 307.18318.
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10. Compound **6**: mp 86–88 °C; $[\alpha]_D^{25}$ +101 (*c* 1, methanol); ^{1}H NMR (500 MHz, DMSO-d_6/D_2O, 80 °C) δ 0.91, 0.93 (d × 2, 6H, $J = 6.7$ Hz, leucyl-CH_3), 1.64–1.70, 1.73–1.80 (m × 2, 1H × 2, $J_{\alpha,\beta} = 7.0$ Hz, $J_{\beta,\gamma} = 6.7$ Hz, leucyl-$2 \times H_\beta$), 1.81–1.89 (m, 1H, leucyl-H_γ), 3.26 (t, 1H, $J_{3,4} = 8.9$ Hz, $J_{4,5} = 10.1$ Hz, H-4), 3.30 (s, 1H, 1-OCH_3), 3.42 (ddd, 1H, $J_{5,6} = 5.5$ Hz, $J_{5,6'} = 2.1$ Hz, H-5), 3.53 (dd, 1H, $J_{6,6'} = 11.9$, H-6), 3.68 (dd, 1H, H-6′), 3.71 (t, 1H, $J_{2,3} = 9.8$ Hz, H-3), 3.90 (t, 1H, leucyl-H_α), 4.55 (dd, 1H, $J_{1,2} = 3.7$ Hz, H-2), 4.77 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{13}H_{25}NO_7+H]^+$, 308.17093; found, 308.17313.
    Compound **7**: $[\alpha]_D^{25}$ +78 (*c* 0.5, methanol); ^{1}H NMR (500 MHz, DMSO-d_6/D_2O) δ 1.02 (s, 9H, *t*-butyl), 3.20 (t, 1H, $J_{3,4} = 8.9$ Hz, H-4), 3.30–3.37 (m, 1H, H-5), 3.48 (d, 1H, H-6), 3.55 (s, 3H, 1-OCH_3), 3.64 (t, 2H, $J_{2,3} = 9.8$ Hz, H-3, H-6), 4.57 (dd, 1H, $J_{1,2} = 3.7$ Hz, H-2), 4.73 (d, 1H, H-1); ESI-TOFMS *m*/*z*: calcd for $[C_{13}H_{25}NO_7+H]^+$, 308.17093; found, 308.17381.
11. In the preliminary experiments, the enantioselectivities, 17% ee (*R*) for L-leucine and 12% ee (*R*) for L-*tert*-leucine, were detected in the reaction of acetone with 4-nitrobenzaldehyde in acetone–water (4:5) using amino acid alone. In acetone–water (20:1) media, 10% yield with 44% ee (*R*) was detected for L-*tert*-leucine.
12. In the reaction of acetone with 4-nitrobenzaldehyde in acetone–water (4:5), methyl 2-(L-phenylalanyl)oxy-α-D-glucopyranoside led to 18% ee (*S*), whereas 13% ee (*R*) was detected for the reaction with L-phenylalanine alone.
13. The enantioreversal control with L-proline related catalyst only reported for Zn-proline complex, although the complex represents the model for class II aldolase. (a) Darbe, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090–1091; (b) Kofoed, J.; Darbre, T.; Reymond, J.-L. *Chem. Commun.* **2006**, 1482–1484.
14. Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445–2447, and references cited therein.