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COMMUNICATION

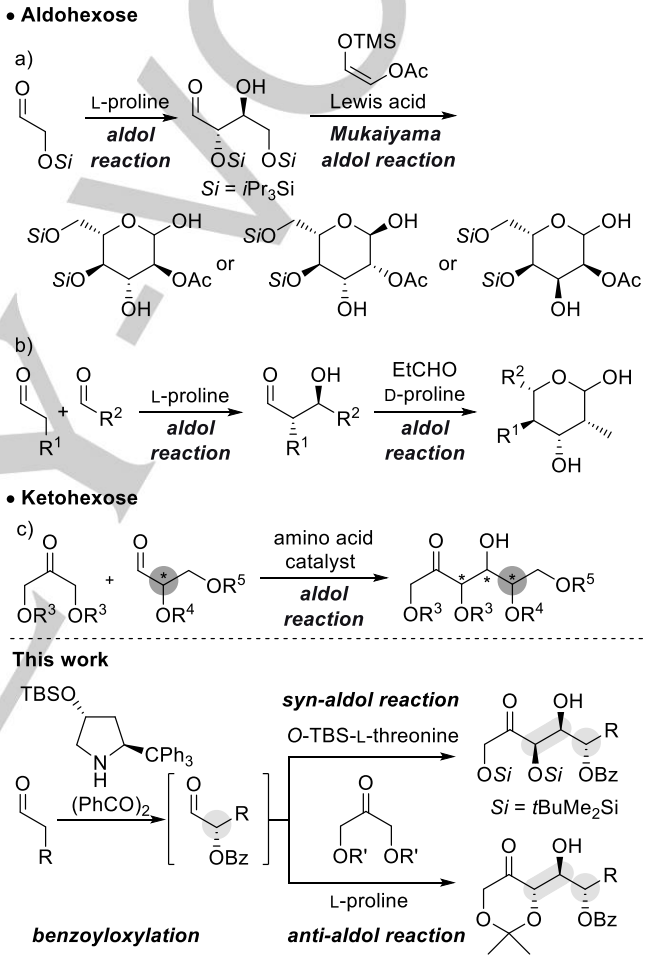
Enantioselective synthesis of monosaccharide analogues by two-step sequential enamine catalysis: benzoyloxylation and aldol reaction

Mio Shimogaki,[a] Aika Takeshima,[a] Taichi Kano*[a] and Keiji Maruoka*[a,b,c]

Abstract: An efficient route to synthesize monosaccharide analogues in an enantio- and diastereoselective manner is described. Three contiguous stereocenters can be constructed via enantioselective benzoyloxylation of aldehydes using a chiral secondary amine catalyst and a subsequent aldol reaction of the resulting α-benzoyloxyaldehydes with the protected dihydroxyacetones using chiral amino acid catalysts, and single diastereomers were obtained with excellent enantioselectivity.

Monosaccharides are widespread in nature and play important roles in an organism. Among them, hexoses, which are roughly divided into aldohexose and ketohexose, are the most widely distributed monosaccharides which also exist as glycosides, oligosaccharides and polysaccharides. They are one of the materials that living organisms use most frequently as energy sources. Aldohexoses serve as an energy source and also form a complex with polysaccharides, lipids and proteins to perform various functions in vivo. Ketohexoses also offer great potential for pharmaceutical and synthetic chemistry applications as well as nutrients of food.[1] However, they are defined as rare sugars except for D-fructose and their natural abundance is low. Therefore, the development of efficient methodologies for synthesis of ketohexoses and their analogues is highly desirable.

De novo synthesis of hexoses from simple aldehydes using amino acid catalysts has attracted much attention over the last two decades.[2–6] In 2004, MacMillan and co-workers reported the two-step synthesis of protected aldohexoses through the proline-catalyzed enantioselective aldol reaction followed by the Lewis acid-mediated diastereoselective Mukaiyama aldol reaction (Scheme 1a).[3] Córdova and co-workers described the proline-catalyzed cross-aldol reaction, in which aldohexose analogues were formed by assembling three aldehydes with excellent chemo-, diastereo-, and enantioselectivity (Scheme 1b).[4c]



Scheme 1. Enantioselective organocatalyzed synthesis of hexoses.

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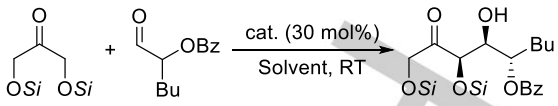
Dihydroxyacetone-based aldol reaction is a powerful tool for the construction of carbohydrates,[7,8] and this method is widely used for ketohexose synthesis. In the previous reports, the aldol reaction of dihydroxyacetone derivatives was carried out using chiral α,β-dioxyaldehydes with an α-stereogenic center (Scheme 1c).[5–7] Meanwhile, we have developed novel chiral tritylpyrrolidines, which were found to be efficient secondary amine catalysts for enantioselective benzoyloxylation of aldehydes.[9–11] We conceived that stereoselective synthesis of ketohexose analogues can be achieved through the enantioselective benzoyloxylation and the aldol reaction of the resulting α-benzoyloxyaldehydes with dihydroxyacetone

derivatives. In the amine-catalyzed aldol reaction, *Z*-enamine and *E*-enamine intermediates afford *syn*- and *anti*-adducts, respectively.[12] The stereochemistry of the enamine intermediate can be controlled by the combination of the amine catalyst and substrate. It is considered that several ketohexose analogues with controlled three stereogenic centers can be synthesized by performing the aldol reaction between each enamine intermediate and chiral α-benzoyloxyaldehydes formed by the enantioselective benzoyloxylation. Herein, we report an efficient enantioselective synthesis of ketohexose analogues by two-step sequential enamine catalysis consisting of chiral amine-catalyzed benzoyloxylation of aldehydes followed by the amino acid-catalyzed aldol reaction with dihydroxyacetones.

First, since the synthetic method for optically enriched α-benzoyloxyaldehydes has already been established, the aldol reaction between a dihydroxyacetone derivative and an α-benzoyloxyaldehyde was investigated. We chose the TBS-protected dihydroxyacetone **1** as a donor and primary amines as a catalyst to form the *Z*-enamine intermediate effectively (Table 1).[13] In the presence of L-tryptophan, the reaction of **1** with racemic α-benzoyloxyaldehyde **2a** in DMSO, DMF or *N*-methylpyrrolidone (NMP) was carried out (entries 1–3).[12d,14] Among the solvent tested, NMP showed the highest yield and was selected for further study. The reactions using other amino acid catalysts gave the products in low yield due to the low solubility of catalysts (entries 4–6). Therefore, highly soluble catalysts were then employed. Use of the TBS-protected L-threonine (*O*-TBS-L-Thr) gave the major product **3a** in 43% yield and two other diastereomers were obtained in total 29% yield (entry 7).[15] The reaction using 3,3-diphenyl-L-alanine hardly proceeded in spite of high solubility (entry 8). Reducing the amount of **1** from two equivalents to one equivalent decreased the yield (entry 9). Use of 5 equivalents of **1** increased the yield and **3a** was obtained in 49% yield with 93% ee along with a mixture of minor diastereomers in total 41% yield (entry 10). This result indicated that there is matched/mismatched relationship between α-benzoyloxyaldehydes and the catalyst. Almost all (*S*)-benzoyloxyaldehyde (ca. 46%) was preferentially consumed through the enantioselective *syn*–selective aldol reaction. Therefore, the other minor diastereomers would be formed from (*R*)-benzoyloxyaldehyde through the enantioselective *syn*- and *anti*-selective aldol reaction. Incidentlly, the reaction using *t*Bu-protected L-threonine (*O*-*t*Bu-L-Thr) gave a similar result (entry 11).[6c,12d] In terms of accessibility, *O*-TBS-L-Thr was selected for further study. The reaction with *O*-TBS-D-Thr proceeded to give the enantiomeric products in good yield with a similar diastereoselectivity (entry 12). Using the racemic catalyst *O*-TBS-DL-Thr, the ratio of the major isomer against minor isomers was improved due to increased amount of the matched pair of the catalyst and benzoyloxyaldehyde (entry 13). Based on these results, we considered that one diastereomer could be preferentially formed with high enantioselectivity by use of the optically enriched α-benzoyloxyaldehydes and the matched catalyst in the aldol reaction.

We then investigated the sequential enantioselective benzoyloxylation and aldol reaction with the TBS-protected dihydroxyacetone **1** (Table 2). The enantioselective benzoyloxylation of hexanal (**4a**) was carried out using benzoyl

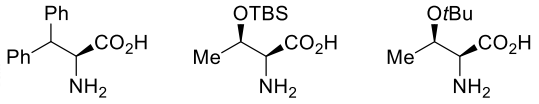
Table 1. *Syn*-selective aldol reaction of the **1** with (*rac*)–**2a**.[a]



Si = TBS

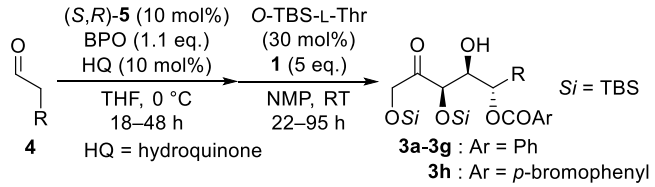
Entry	Catalyst	Solvent	*t* (h)	Yield [%][b] (dr)
1	L-tryptophan	DMSO	63	9 (9:0:0:0)
2	L-tryptophan	DMF	63	24 (14:7:3:0)
3	L-tryptophan	NMP	110	44 (24:14:6:0)
4	L-phenylalanine	NMP	42	10 (10:0:0:0)
5	L-valine	NMP	52	Trace
6	L-threonine	NMP	110	Trace
7	*O*-TBS-L-Thr	NMP	39	72 (43:20:9:0)
8	3,3-diphenyl-L-alanine	NMP	72	5 (5:0:0:0)
9[c]	*O*-TBS-L-Thr	NMP	101	62 (38:15:9:0)
10[d,e]	*O*-TBS-L-Thr	NMP	112	90 (49:27:14:0)
11[d]	*O*-*t*Bu-L-Thr	NMP	112	91 (49:26:16:0)
12[d]	*O*-TBS-D-Thr	NMP	60	76 (46:21:9:0)
13[d]	*O*-TBS-DL-Thr	NMP	41	82 (69:9:4:0)

[a] Reactions were performed on a 0.1 mmol scale in 0.1 mL of NMP. [b] ^{1}H NMR yield utilizing 1,1,2,2-tetrachloroethane as an internal standard. [c] Use of **1** (1 eq.). [d] Use of **1** (5 eq.). [e] Enantiomeric excess of major isomer was 93%.



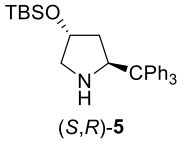
peroxide (BPO) in the presence of tritylpyrrolidine (*S*,*R*)-**5** as a catalyst in THF at 0 °C. After the reaction, NMP was added to the mixture and THF was removed under reduced pressure. Subsequently, *O*-TBS-L-Thr-catalyzed aldol reaction of **1** with the resulting (*S*)-α-benzoyloxyaldehyde gave the product **3a** as a single diastereomer in moderate yield with excellent enantioselectivity (entry 1). On the other hand, use of *O*-TBS-D-Thr in the second step led to a significant decrease in yield andenantioselectivity due to the mismatched combination of the catalyst and α-benzoyloxyaldehyde (entry 2). Since *O*-TBS-L-Thr was identified as the matched catalyst for the aldol reaction of (*S*)-α-benzoyloxyaldehyde formed by (*S*,*R*)-**5**, several other aldehydes were examined under these conditions. The reactions of 3-phenylpropanal (**4b**) and branched 3-methylbutanal (**4c**) also afforded single diastereomers in good yields with excellent enantioselectivities (entries 3 and 4). We also examined β-heteroaldehyde substrates to synthesize L-fructose analogues. The reaction using 3-benzyloxypropanal (**4d**) gave only a trace amount of the target product, because the first step reaction hardly proceeded (entry 5). Fortunately, use of β-oxyaldehyde **4e** which has a bis(4-fluorophenyl)methyl group instead of benzyl

Table 2. Sequential enantioselective benzoyloxylation of various aldehydes **4** and *syn*-selective aldol reaction with **1**.[a]



Entry	**4** (R)	Yield [%][b]	ee [%]
1	**4a** Bu	**3a** 56	99
2[c]	**4a** Bu	**3a** 5[d]	–53
3	**4b** Bn	**3b** 59	99
4	**4c** *i*Pr	**3c** 52	99
5	**4d** CH_2OBn	**3d** trace	nd
6	**4e** $CH_2OCH(4\text{-}F\text{-}C_6H_4)_2$	**3e** 40	99
7	**4f** $CH_2SiPhMe_2$	**3f** 44[e]	95
8	**4g** CH_2NHCbz	**3g** 43	99
9[f]	**4g** CH_2NHCbz	**3h** 46	99

[a] Reactions were performed on a 0.1 mmol scale. [b] Isolated yield. [c] *O*-TBS-D-Thr was used instead of *O*-TBS-L-Thr. [d] Other two diastereomers (total 14%) were obtained. [e] Another diastereomer (7%) was obtained. [f] *p*-Bromobenzoyl peroxide was used instead of BPO.



(*S*,*R*)-**5**

group increased the yield drastically,[16] giving the product **3e** in moderate yield with high ee value (entry 6). The stereoselectivity of the reaction using 3-(dimethyl(phenyl)silyl)propanal (**4f**) slightly decreased and another diastereomer was also obtained (entry 7). The reaction of the *N*-Cbz-protected β-amino aldehyde **4g** proceeded well to give **3g** in moderate yield with high enantioselectivity (entry 8). When *p*-bromobenzoyl peroxide was used instead of BPO, a similar result was obtained (entry 9). The absolute configuration of the product **3h** was determined by X-ray crystal structure analysis (Figure 1), and was consistent with the expected stereochemistry in the reaction using (*S*,*R*)-**5** and *O*-TBS-L-Thr. Those of other products were assigned by analogy of **3h**.

In order to provide other ketohexose analogues, the *anti*-selective aldol reaction through the *E*-enamine intermediate was examined. In the presence of D,L-proline catalyst, the aldol reaction of racemic α-benzoyloxyaldehyde **2a** with 2,2-dimethyl-1,3-dioxane-5-one (**6**) (dioxanone) in dimethylsulfoxide afforded two diastereomers in a ratio of approximately 1:1.[8a] This reaction did not exhibit the match/mismatch effects between the chirality of α-benzoyloxyaldehyde and that of the catalyst. The sequential enantioselective benzoyloxylation of aldehyde **4a** and the aldol reaction with the dioxanone **6** using L-proline was then carried out according to the previous method for the synthesis of **3**. However, the target product **7a** was not observed (Scheme 2a). This result can be attributed to decomposition of **6** caused by benzoic acid which is a side product of the first step reaction. To overcome this problem, the acidic substances were removed by passing through Amberlite IRA–93ZU, which is a weakly basic ion exchange resin, after benzoyloxylation (See the Supporting Information for details). Consequently, the benzoyloxylation and the subsequent aldol reaction using L-proline proceeded to give **7a** as a single diastereomer in 52% yield with 99% ee (Scheme 2b). Similarly, the reaction with D-proline at the second step afforded **7b** as a single diastereomer in 39% yield with 99% ee (Scheme 2c).

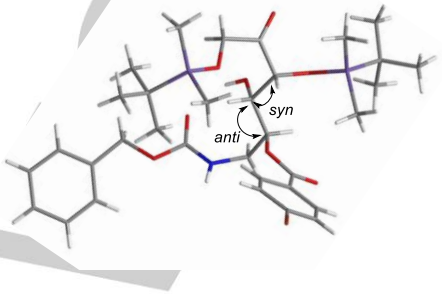
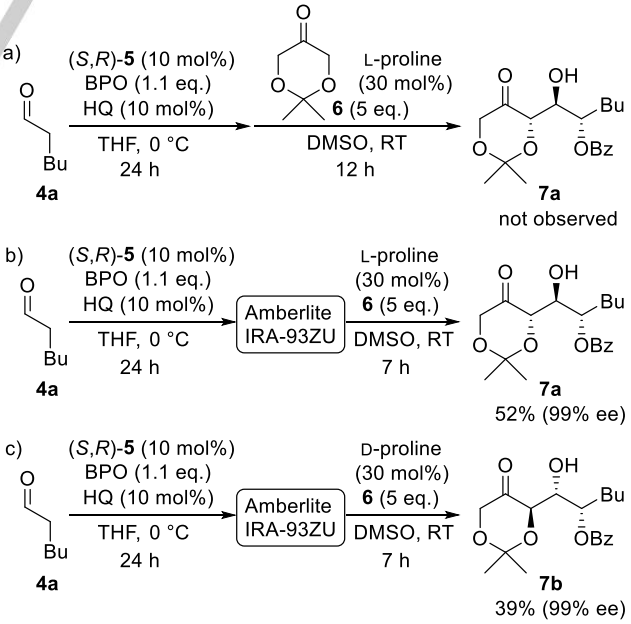


Figure 1. X–ray crystal structure of **3h**. CCDC: 1955026.

Based on the results shown in Table 2, possible transition-state models for the aldol reactions of (*S*)-α-benzoyloxyaldehydes and the TBS-protected dihydroxyacetone **1** are proposed as shown in Figure 2. In the nucleophilic addition to chiral α-oxyaldehydes, the Cornforth model, which is based on dipole minimization between the carbonyl group and the adjacent C–O bond, is supported by recent theoretical and experimental studies.[7b,17] The reaction of the mismatched pair turns out to be slow and less stereoselective compared to that of the matched pair because of the greater steric repulsion between the α-



Scheme 2. Enantioselective benzoyloxylation of aldehyde **4a** and *anti*-selective aldol reaction with the dioxanone **6**.

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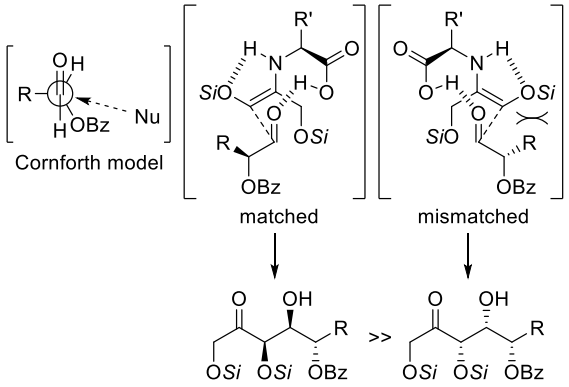

Figure 2. Proposed transition-state models for the amino acid-catalyzed aldol reaction of (*S*)-α-benzoyloxyaldehyde with **1**.

substituent of aldehydes and the silyloxy group of the enamine moiety (Table 2, entry 1 vs. 2). On the other hand, such serious steric repulsion between the α-oxyaldehyde and the enamine intermediate can be avoided in the aldol reaction via the *E*-enamine intermediate, and both diastereomers **7a** and **7b** can be formed.

In summary, we have achieved a highly enantio- and diastereoselective synthesis of ketohexose analogues through enantioselective benzoyloxylation using the secondary amine catalyst and the subsequent aldol reaction using amino acid catalysts. In the second step,the primary amine catalyst and the TBS-protected dihydroxyacetone form the *Z*-enamine intermediate, giving *syn*-aldol products as single diastereomers. In this case, the stereogenic center formed in the first step affected the reaction rate of the second step. On the other hand, the proline catalyst and the dioxanone form the *E*-enamine intermediate, giving *anti*-aldol products. The stereogenic center formed in the first step had a small effect on the reaction rate in the second step, and it was possible to provide two different diastereomers, respectively, depending on the configuration of the proline catalyst used.

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Keywords: asymmetric synthesis • aldol reaction • benzoyloxylation • carbohydrates • organocatalysis

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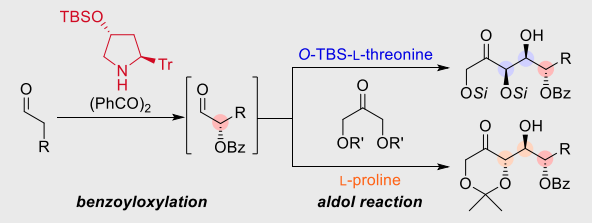

Synthesis of monosaccharide analogues in an enantio- and diastereoselective manner has been investigated. Asymmetric benzoyloxylation and subsequent aldol reaction using two amine catalysts effectively give monosaccharide analogues with controlled three stereogenic centers.

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Enantioselective synthesis of monosaccharide analogues by two-step sequential enamine catalysis: benzoyloxylation and aldol reaction