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# *syn*-Selective asymmetric cross-aldol reactions between aldehydes and glyoxylic acid derivatives catalyzed by an axially chiral amino sulfonamide†‡

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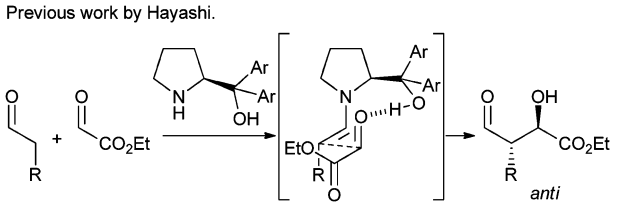
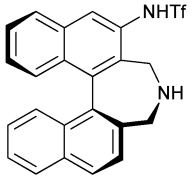
***syn*-Selective asymmetric cross-aldol reactions of aldehydes with *tert*-butyl glyoxylate and glyoxamide were realized by the use of an axially chiral amino sulfonamide (*S*)-1. The cross-aldol products obtained are densely functionalized and readily converted to synthetically useful and important chiral building blocks such as γ-lactone and γ-lactam.**

Asymmetric enamine catalysis is a powerful organocatalytic strategy for the stereoselective α-functionalization of carbonyl compounds.[1,2] In this area, the direct asymmetric aldol reactions of carbonyl compounds have been investigated by a number of research groups,[3] since the pioneering work of List, Barbas, and co-workers in 2000.[4] Among them, the cross-aldol reaction between two different aldehydes is an attractive approach toward the construction of synthetically useful building blocks. Most of such cross-aldol reactions of aldehydes proceed in a highly *anti*-selective fashion;[5] therefore, obtaining *syn*-selectivity has still been a considerable challenge.[6] Recently, Hayashi and co-workers reported the *anti*-selective asymmetric cross-aldol reaction between unmodified aldehydes and ethyl glyoxylate, which gives densely functionalized products (Scheme 1).[5p,6] In our previous report on the *syn*-selective asymmetric cross-aldol reaction catalyzed by (*S*)-**1**, ethyl glyoxylate was also examined as an acceptor aldehyde; however, exceptionally poor *syn* selectivity was observed (*syn*/*anti* = 2.3/1).[6a,b] In this context, we have been interested in developing the highly *syn*-selective asymmetric cross-aldol reaction of glyoxylic acid derivatives.




**Scheme 1** *anti*-Selective cross-aldol reaction of ethyl glyoxylate developed by Hayashi.

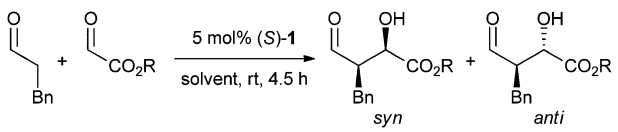
We first examined the cross-aldol reaction of 3-phenylpropanal with ethyl glyoxylate (Table 1). The reaction of 3-phenylpropanal with ethyl glyoxylate (3 equiv.) in the presence of (*S*)-**1**[7] (5 mol%) was carried out in various solvents; however, low *syn*-selectivity was observed in all solvents examined (entries 1–8).




(*S*)-**1**

To our surprise, lowering the reaction temperature decreased both *syn*-selectivity and enantioselectivity (entries 9 and 10).

**Table 1** Cross-aldol reaction of 3-phenylpropanal with alkyl glyoxylate[a]




| Entry | R | Solvent | Yield (%)[b] | *syn*/*anti*[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | Et | MeOH | 66 | 1.1/1 | 73 |
| 2 | Et | DMSO | 96 | 1.4/1 | 76 |
| 3 | Et | DMF | 99 | 1.9/1 | 92 |
| 4 | Et | EtOAc | 88 | 1.5/1 | 90 |
| 5 | Et | THF | 74 | 1.3/1 | 80 |
| 6 | Et | $CHCl_3$ | 84 | 1.3/1 | 82 |
| 7 | Et | Toluene | 90 | 1.2/1 | 79 |
| 8 | Et | $CH_3CN$ | 97 | 2.3/1 | 92 |
| 9[e] | Et | $CH_3CN$ | 99 | 1.3/1 | 84 |
| 10[f] | Et | $CH_3CN$ | 97 | 1.2/1 | 74 |
| 11 | *t*-Bu | $CH_3CN$ | 87 | 2.8/1 | 92 |
| 12[g] | *t*-Bu | $CH_3CN$ | 89 | 4.0/1 | 93 |
| 13[h] | *t*-Bu | $CH_3CN$ | 91 | 5.9/1 | 97 |

[a] Unless otherwise specified, the reaction of 3-phenylpropanal (0.25 mmol) with alkyl glyoxylate (0.75 mmol) in a solvent was carried out in the presence of (*S*)-**1** (0.0125 mmol) at room temperature for 4.5 h. [b] Isolated yield. [c] Determined by $^1$H-NMR. [d] The ee of the *syn*-isomer was determined by HPLC analysis using a chiral column. [e] Performed at 0 °C. [f] Performed at −20 °C. [g] Performed for 0.5 h. [h] Use of 3-phenylpropanal (0.75 mmol) and *t*-butyl glyoxylate (0.25 mmol).

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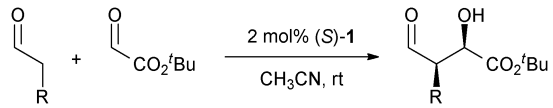
By switching the ester moiety of ethyl glyoxylate to the *tert*-butyl group, the enantioselectivity was slightly improved (entry 11). Higher *syn*-selectivity was achieved with shorter reaction time (entry 12). In this type of aldol reaction, the ratio of the major stereoisomer can be decreased by the stereoselective retro-aldol reaction.[6b,8] With expectation of suppressing such a retro-aldol reaction, we varied the substrate ratio. Interestingly, increasing the amount of 3-phenylpropanal and decreasing the amount of *tert*-butyl glyoxylate resulted in an improvement in both *syn*-selectivity and enantioselectivity (entry 13).

Under the optimized conditions, the cross aldol reactions of various donor aldehydes were examined, and the results are summarized in Table 2. All reactions examined proceeded smoothly to give the cross-aldol products in moderate *syn*-selectivity and excellent enantioselectivity.

**Table 2** Cross-aldol reaction of various aldehydes with *t*-butyl glyoxylate[a]

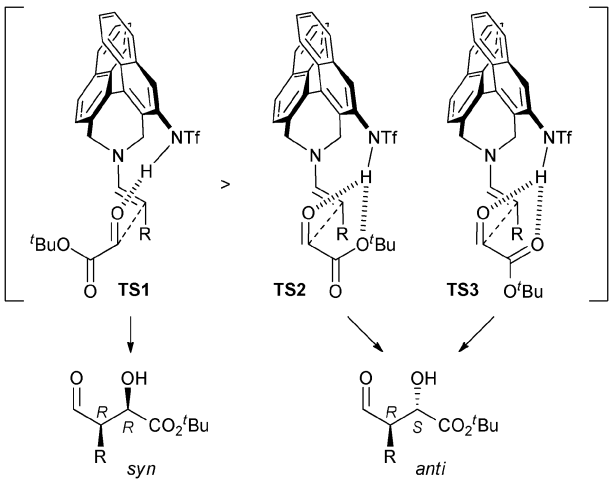



| Entry | R | Time/h | Yield (%)[b] | *syn*/*anti*[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1[e] | Me | 1 | 61 | 5.3/1 | 97 |
| 2 | Bu | 1 | 77 | 4.7/1 | 96 |
| 3 | Bn | 1 | 89 | 5.3/1 | 97 |
| 4[e] | $CH_2OBn$ | 1 | 78 | 4.5/1 | 99 |
| 5 | *i*-Pr | 4.5 | 74 | 4.9/1 | 94 |

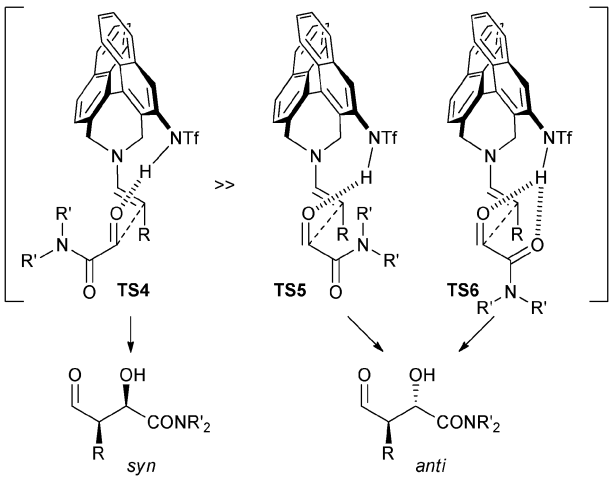
[a] The reaction of a donor aldehyde (0.75 mmol) with *t*-butyl glyoxylate (0.25 mmol) in acetonitrile was carried out in the presence of (*S*)-**1** (0.005 mmol) at room temperature. [b] Isolated yield. [c] Determined by $^1$H-NMR. [d] The ee of the *syn*-isomer was determined by HPLC analysis using a chiral column. [e] Isolated as 1,3-diol after reduction with $NaBH_4$.

Based on the absolute configuration of products, transition state models **TS1–TS3** were proposed (Scheme 2). In the reaction of 3-phenylpropanal with *tert*-butyl glyoxylate (Table 1, entry 13), a substantial amount of the *anti*-product was formed in an enantioselective fashion (69% ee). The observed stereochemistry (2*S*,3*R*) could be explained by transition states **TS2** and **TS3** in which the *Si* face of *tert*-butyl glyoxylate approaches the *Si* face of the s-*cis*-enamine as directed by the triflamide group of the catalyst. The additional interaction between the ester group of *tert*-butyl glyoxylate and the acidic proton of the catalyst might increase the reaction rate through **TS2** and/or **TS3**. Accordingly, we were interested in the development of the highly *syn*-selective cross-aldol reaction by suppression of such secondary interaction between the catalyst and an acceptor aldehyde. We hypothesized that the *syn*-selective reaction through **TS4** would be favored over **TS5** and **TS6** by switching the ester group of the acceptor aldehyde to an amide group (Scheme 3). The reaction through **TS5** would be disfavored due to the lack of the secondary interaction. In the reaction through **TS6**, the strong coordination of the amide group might decrease the acidity of the catalyst proton and the reaction rate. This hypothesis was examined by the use of glyoxamide **2**[9] instead of *tert*-butyl glyoxylate.

In the presence of (*S*)-**1**, the reaction of various donor aldehydes with glyoxamide **2** in acetonitrile was performed




**Scheme 2** Proposed transition state models **TS1–TS3**.



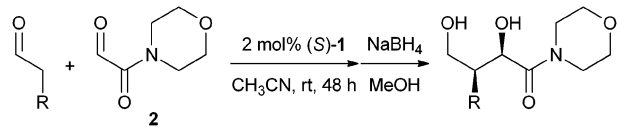

**Scheme 3** Transition state models for the reaction of a glyoxamide.

at room temperature, and the results are summarized in Table 3. While the reaction of **2** was much slower compared to that of *tert*-butyl glyoxylate and took longer to complete, the improved *syn*-selectivity was observed in all cases examined, as expected.

The obtained cross-aldol adducts were versatile intermediates in organic synthesis and readily converted to important chiral building blocks. The aldol adduct **3** (*syn*/*anti* = 4.7/1) could be converted to γ-lactam **4** (*trans*/*cis* = 4.0/1) by reductive amination and heating of the resulting amine (Scheme 4). Alternatively, γ-lactam **4** (*trans*/*cis* = 16/1) was also prepared by the aldol reaction of **2**, reductive amination and lactamization without purification of the intermediates (Scheme 5). When the aldol adduct **5** (*syn*/*anti* = 17/1) was treated with 4 N HCl under reflux, γ-lactone **6** (*trans*/*cis* = 17/1) was obtained in good yield with complete retention of stereochemistry (Scheme 6).

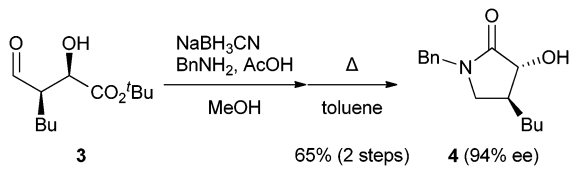
In summary, we have developed a *syn*-selective asymmetric cross-aldol reaction of aldehydes with *tert*-butyl glyoxylate and glyoxamide catalyzed by the axially chiral amino sulfonamide (*S*)-**1**. The cross-aldol products obtained are densely functionalized and versatile intermediates and could be readily

**Table 3** Cross-aldol reaction of various aldehydes with glyoxamide **2**[a]

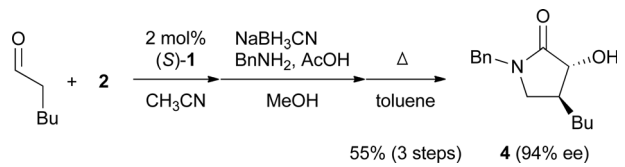



| Entry | R | Yield (%)[b] | *syn*/*anti*[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | Bu | 82 | 17/1 | 97 |
| 2 | Hex | 81 | 12/1 | 94 |
| 3 | Bn | 77 | 16/1 | 97 |
| 4[e] | $CH_2OBn$ | 64 | 6.2/1 | 97 |
| 5[e] | *i*-Pr | 43 | 13/1 | 96 |

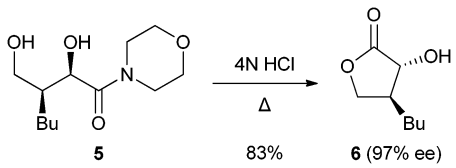
[a] The reaction of a donor aldehyde (0.75 mmol) with glyoxamide **2** (0.25 mmol) in acetonitrile was carried out in the presence of (*S*)-**1** (0.005 mmol) at room temperature. [b] Isolated yield. [c] Determined by $^1$H-NMR. [d] The ee of the *syn*-isomer was determined by HPLC analysis using a chiral column. [e] Use of (*S*)-**1** (0.0125 mmol).




**Scheme 4** Synthesis of lactam **4** from aldol adduct **3**.




**Scheme 5** Synthesis of lactam **4** from glyoxamide **2**.




**Scheme 6** Synthesis of lactone **6**.

converted to synthetically useful and important chiral building blocks such as γ-lactone and γ-lactam.

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