# β-Aminosulfonamide-Catalyzed Direct Asymmetric Aldol Reaction in Brine

Tsuyoshi Miura,*[a] Mariko Ina,[a] Kie Imai,[a] Kosuke Nakashima,[a] Akira Masuda,[a] Norihiro Tada,[a] Nobuyuki Imai,[b] Akichika Itoh[a]

[a] Gifu Pharmaceutical University 1-25-4, Daigaku-nishi, Gifu 501-1196, Japan
Fax +81(58)2308105; E-mail: miura@gifu-pu.ac.jp

[b] Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

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**Abstract:** Direct asymmetric aldol reactions of aldehydes with ketones in the presence of a catalytic amount of β-aminosulfonamide **2** and trifluoroacetic acid in brine results in the formation of the corresponding *anti*-aldol products in high yields with up to 96% enantiomeric excess. The *anti*-aldol products obtained by using organocatalyst **2** have the opposite absolute configuration to those obtained using the similar sulfonamide catalyst **1**, which was reported previously by us.

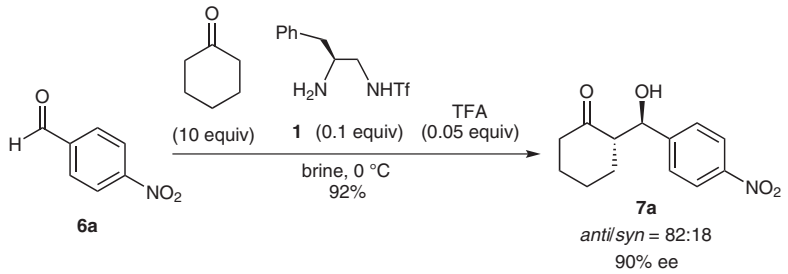
**Key words:** organocatalyst, aldol reaction, sulfonamide, brine, asymmetric

Organocatalysts play important roles in asymmetric synthesis because enantiopure molecules can be synthesized under mild, environmentally benign conditions without toxic metal catalysts.[1] Aldol reactions are one of the most important carbon–carbon bond-forming procedures available for synthetic reactions involving organocatalysts.[2] Especially, organocatalytic aldol reactions in water, as a safe and an environmentally friendly solvent, have been developed in recent years.[3] However, although one enantiomer can be selectively obtained by various reactions using an organocatalyst, it is usually difficult to synthesize the opposite enantiomer because both enantiomeric organocatalysts are rarely available. Recently, Nakayama and Maruoka[4] have reported an excellent asymmetric synthesis of both enantiomeric aldol products using two different organocatalysts, which were prepared from common chiral sources having three chiral centers. Their finding that the enantioselectivity could be switched by using separate organocatalysts derived from the same chiral source was of some interest to us.

We have recently reported on direct asymmetric aldol reactions in brine catalyzed by chiral sulfonamide **1** derived from L-phenylalanine (Scheme 1).[5] In addition, we have also developed a recyclable organocatalyst with a fluorous tag that can promote asymmetric direct aldol reactions in brine.[6] We have attempted to find further applications of β-aminosulfonamide derivatives **1** and wanted to direct asymmetric aldol reactions in water. In this letter, we describe that sulfonamide **2** catalyzes the reaction of aldehydes with ketones in brine to give the *anti*-aldol products with the opposite absolute configuration compared to those obtained by using the original organocatalyst **1** prepared from L-phenylalanine as the same chiral source.

As a novel organocatalyst, sulfonamide **2** was prepared as shown in Scheme 2. Compound **3**, as the intermediate for the synthesis of organocatalyst **1**, was prepared from L-phenylalaninol in three steps.[5,7] The Boc group of **3** was removed by treatment with hydrogen chloride in ethyl acetate, followed by treatment of **4** with tifluoromethanesulfonyl anhydride and triethylamine in dichloromethane to give sulfonamide **5**, which was converted into the desired sulfonamide organocatalyst **2** by reduction with triphenylphosphine in THF–$H_2O$.

The reaction conditions were optimized for the enantioselective direct aldol reactions as shown in Table 1. Aldol reactions were carried out with aldehyde **6a** and cyclohexanone (10 equiv) in the presence of a catalytic amount of the sulfonamide **2** and trifluoroacetic acid (TFA) in brine, based on the optimal conditions for asymmetric aldol reaction catalyzed by organocatalyst **1**.[5] When the reactions were carried out in the presence of 0.1 equivalent of **2**,




**Scheme 1** Our previous work

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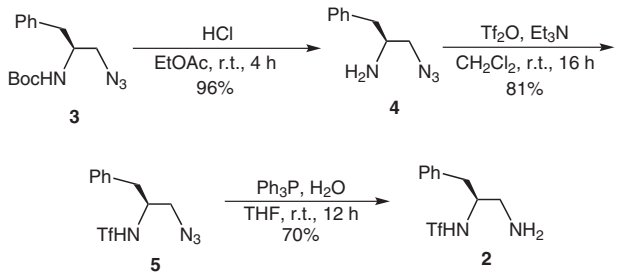
DOI: 10.1055/s-0030-1259317; Art ID: U09410ST




**Scheme 2** Preparation of the organocatalyst

high enantioselectivities with moderate yields were achieved (entries 1–4). Both high yield and enantioselectivity were obtained when using 0.2 equivalent of organocatalyst **2** (entries 5 and 6). In addition, *anti*-aldol product **8a**, obtained by using organocatalyst **2**, had the opposite absolute configuration to that of **7a** obtained by using the original catalyst **1**.[5]

Table 2 shows the scope and limitations of the direct asymmetric aldol reaction with various aldehydes **6a–i** under the optimized reaction conditions as mentioned above.[8] We chose nitro, trifluoromethyl, and halogen substituents as examples of electron-withdrawing groups (entries 1, 2, 5, 6, and 8–11), and a methoxy substituent as a representative electron-donating group (entries 3 and 7), in the benzene ring. The aldehydes substituted by an electron-withdrawing group at the *para*-position (**6a** and **6b**) were converted into the corresponding *anti*-aldol products in high yields with high enantioselectivities (entries 1 and 2). The reactions of less reactive *p*-anisaldehyde (**6c**), benzaldehyde (**6d**), and *m*-anisaldehyde (**6g**) with cyclohexanone were also carried out to afford aldol products **8c**, **8d**, and **8g** in low to moderate yields with high enantioselectivities (entries 3, 4, and 7). The aldehydes substituted by nitro groups at either the *ortho*- or *meta*-position (**6e** and **6f**) were converted into the corresponding *anti*-aldol products (**8e** and **8f**) in high yields with 93 and 96% ee, respectively (entries 5 and 6). 2,6-Dichlorobenzaldehyde (**6h**), as a sterically hindered aldehyde, also reacted with cyclohexanone to give the corresponding product **8h** in high yield with 92% ee (entry 8). The reaction of pentasubstituted aldehyde **6i** was carried out to afford the corresponding *anti*-aldol products **8i** in high yield with 84% ee and low diastereoselectivity (entry 9). We also examined reactions between other ketones and aldehyde **6a**. The aldol reaction of cyclic ketone cycloheptanone with *p*-nitrobenzaldehyde (**6a**) gave the expected aldol product **8j** in 71% yield with 89% ee (entry 10). The reaction of acyclic ketone acetone with *p*-nitirobenzaldehyde (**6a**) afforded **8k** in low yield with 70% ee (entry 11). Although the reaction of isobutyl aldehyde acting as either an aliphatic donor or acceptor was also examined with acetone and **6a**, respectively, the corresponding aldol products could not be obtained under these reaction conditions. All *anti*-aldol products **8a–k** obtained with organocatalyst **2** were determined by HPLC analysis and optical rotation measurements to be enantiomeric to the *anti*-aldol products obtained with organocatalyst **1**.[5]

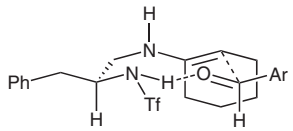
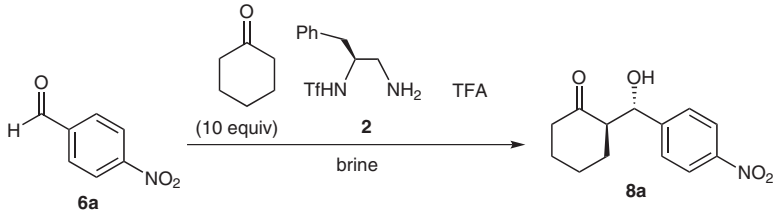



**Figure 1** Proposed transition state model of the aldol reaction

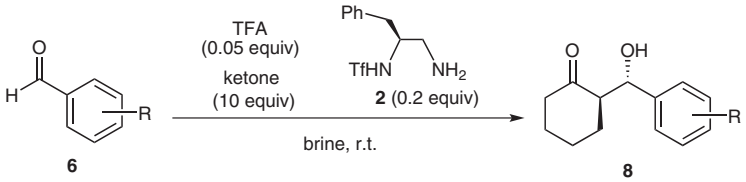
**Table 1** Optimization of Reaction Conditions




| Entry | **2** (equiv) | TFA (equiv) | Temp (°C) | Time (h) | Yield (%)[a] | *anti*/*syn*[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | 0.1 | 0.05 | 0 | 48 | 49 | 95:5 | 96 |
| 2 | 0.1 | 0.05 | r.t. | 48 | 49 | 91:9 | 94 |
| 3 | 0.1 | 0.025 | 0 | 48 | 59 | 95:5 | 96 |
| 4 | 0.1 | 0.025 | r.t. | 28 | 55 | 94:6 | 95 |
| 5 | 0.2 | 0.05 | 0 | 48 | 85 | 96:4 | 96 |
| 6 | 0.2 | 0.05 | r.t. | 36 | 81 | 92:8 | 95 |
| 7[d] | 0.2 | 0.05 | r.t. | 48 | 78 | 89:11 | 93 |

[a] $^1$H NMR yield.
[b] Determined by $^1$H NMR spectroscopic analysis.
[c] Determined by HPLC analysis using Chiralcel AS-H.
[d] The reaction was carried out with 5 equiv of cyclohexanone.

**Table 2** Direct Asymmetric Aldol Reactions Using Organocatalyst **2**



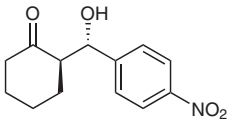
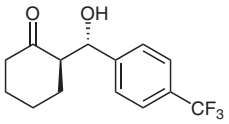
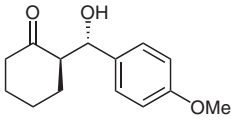
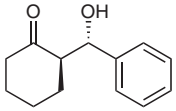
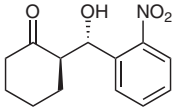
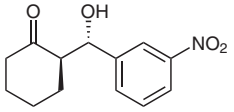
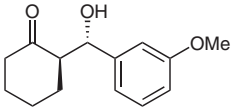
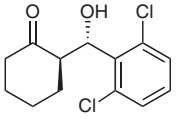
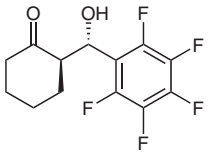
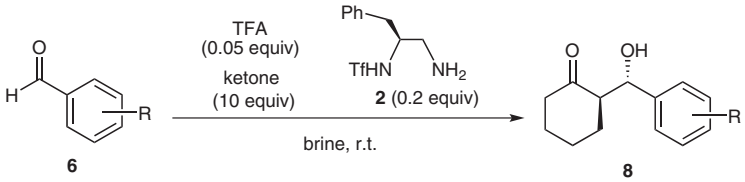
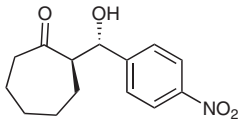
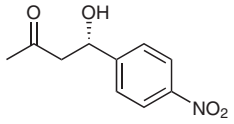

| Entry | Product | Time (h) | Yield (%)[a] | *anti*/*syn*[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 |  **8a** | 36 | 81 | 92:8 | 95 |
| 2 |  **8b** | 65 | 72 | 93:7 | 94 |
| 3 |  **8c** | 137 | 12 | 95:5 | 80 |
| 4 |  **8d** | 52 | 47 | 94:6 | 94 |
| 5[d] |  **8e** | 136 | 80 | 95:5 | 93 |
| 6 |  **8f** | 96 | 73 | 94:6 | 96 |
| 7[e] |  **8g** | 120 | 14 | 96:4 | 96 |
| 8 |  **8h** | 127 | 79 | 88:12 | 92 |
| 9 |  **8i** | 120 | 72 | 56:44 | 79 |

**Table 2** Direct Asymmetric Aldol Reactions Using Organocatalyst **2** (continued)




| Entry | Product | Time (h) | Yield (%)[a] | *anti*/*syn*[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 10 |  **8j** | 124 | 71 | 80:20 | 89 |
| 11[e,f] |  **8k** | 120 | 18 | – | 70 |

[a] $^1$H NMR yields.
[b] Determined by $^1$H NMR spectroscopic analysis.
[c] Determined by HPLC analysis.
[d] Catalyst (0.1 equiv) and TFA (0.025 equiv) were used.
[e] The reaction was carried out at 0 °C.
[f] The reaction was carried out with 30 equiv of acetone in brine.

We infer that the β-aminosulfonamide **2** catalyzed direct aldol reactions between aldehydes and ketones proceed via a transition state proposed by Córdova's group,[9] based on the stereochemistry of the aldol products **8** (Figure 1). We believe it is reasonable to assume that the sulfonamide proton of **2** coordinates to the oxygen of the aldehyde to control the direction of approach of the aldehyde to the enamine intermediate. The addition of TFA to the aldol reaction accelerates the formation of the enamine intermediate.[10]

In conclusion, the simple sulfonamide **2**, with only one chiral center, works efficiently as a catalyst in the direct aldol reaction of various aldehydes with ketones in brine[11] to give the corresponding *anti*-aldol products **8** with high enantioselectivities. The stereochemistry of *anti*-aldol products **8**, obtained by using organocatalyst **2**, had the opposite absolute configuration to those obtained by using the original catalyst **1**.[5] Thus, both enantiomeric *anti*-aldol products can be synthesized by applying organocatalysts **2** and **1**, which are easily prepared from L-phenylalanine, a commercially available, inexpensive natural amino acid. Further application to the synthesis of bioactive compounds is in progress in our laboratory.

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(8) A typical procedure for the aldol condensation using **2** and **6a** is as follows: To a colorless suspension of *p*-nitrobenzaldehyde (**6a**; 90.7 mg, 0.600 mmol) and the organocatalyst **2** (33.9 mg, 0.120 mmol) in brine (1.2 mL), were added cyclohexanone (0.62 mL, 6.00 mmol) and TFA (2.2 μL, 0.030 mmol) at r.t. The reaction mixture was stirred at r.t. for 36 h, and extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel (toluene–EtOAc, 4:1) to afford pure **8a** (121.3 mg, 81%) as a colorless solid.

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(11) We assume that the aldol reactions are accelerated by the use of brine (salting-out effect),[10] see: Maya, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117.