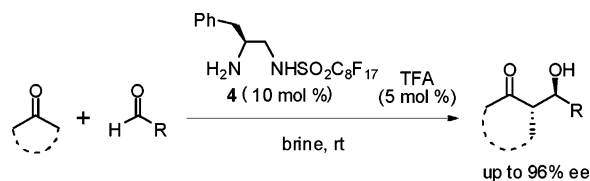


Direct Asymmetric Aldol Reaction with
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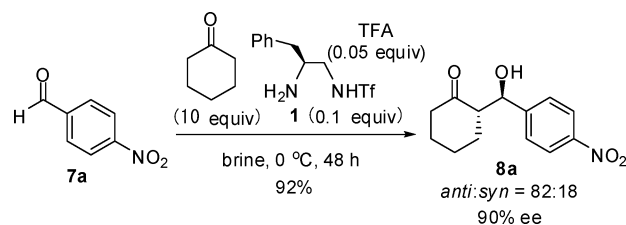
ABSTRACT



Direct asymmetric aldol reactions of aldehydes with ketones in the presence of a catalytic amount of fluorinated sulfonamide **4** and trifluoroacetic acid result in the corresponding aldol products in high yields with up to 96% ee. The fluorinated organocatalyst **4** can be readily recovered from the reaction mixture by fluorinated solid-phase extraction and could be reused without a significant loss of the catalytic activity and enantioselectivity.

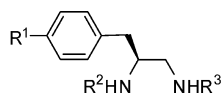
Development of an organocatalytic enantioselective aldol reaction is an attractive research theme because asymmetric aldol reactions are one of the most important carbon–carbon bond-forming procedures in organic chemistry.¹ Since List et al.² developed the first direct asymmetric aldol reaction catalyzed by proline, many effective organocatalysts have been reported.³ Especially, the direct aldol reactions with water without any organic solvent as a reaction medium have attracted a great deal of attention because water is a safe and an environmentally benign solvent from the perception of green chemistry.⁴ Although we have recently reported the direct asymmetric aldol reactions in brine catalyzed by chiral sulfonamide **1** derived from L-phenylalanine,⁵ recovery and reuse of the expensive chiral organocatalysts are usually

Scheme 1. Our Previous Work



difficult (Scheme 1). The recovery of the expensive organocatalysts from the reaction mixture after completion of reaction and its recycling are highly desirable. Curran et al.⁶ elaborated a recycling technique by the fluorinated solid-phase extraction (FSPE) methodology using fluorinated silica gel. Recently, organocatalytic reactions by FSPE concept for recovery and reuse of the expensive organocatalysts have also been reported.^{4n,7} We have also reported the enantioselective Simonth–Smith cyclopropanation using fluorinated chiral ligand **2**,⁸ which can be recyclable by the introduction of fluorinated tag into the original chiral ligand **3** (Figure 1).⁹

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- 1: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{SO}_2\text{CF}_3$
 2: $R^1 = \text{OCH}_2\text{CH}_2\text{CH}_2\text{C}_8\text{F}_{17}$, $R^2 = \text{Ms}$, $R^3 = \text{Ts}$
 3: $R^1 = \text{H}$, $R^2 = \text{Ms}$, $R^3 = \text{Ts}$
 4: $R^1 = \text{H}$, $R^2 = \text{H}$, $R^3 = \text{SO}_2\text{C}_8\text{F}_{17}$

Figure 1. Structure of organocatalysts.

To recover and reuse the valuable organocatalyst **1** for the direct asymmetric aldol reactions in water, we have attempted the development of a novel organocatalyst with a fluorous tag, and designed fluorous sulfonamide **4**. In this paper, we describe a catalytic enantioselective aldol reaction in brine using reusable fluorous sulfonamide organocatalyst **4**.

Fluorous sulfonamide **4** as a novel recyclable organocatalyst was prepared as shown in Scheme 2. **5** as the intermediate for synthesis of chiral ligands **3** was easily prepared from phenylalaninol through four steps.⁹ The treatment of **5** with perfluorooctanesulfonyl fluoride and triethylamine in dichloromethane resulted in the fluorous compound **6** with 68% yield. The Boc group of **6** was removed by treatment with hydrogen chloride in ethyl acetate to provide the desired fluorous sulfonamide **4** with 87% yield.

We optimized the reaction conditions for the enantioselective direct aldol reactions as shown in Table 1. Aldol reactions were carried out with aldehydes and cyclohexanone

(10 equiv) in the presence of a catalytic amount of the sulfonamide **4** (0.1 equiv) in brine. Although the higher enantioselectivities were observed when the reactions were carried out at 0 °C than that observed at room temperature, a long reaction time (163 h) was necessary for completion of the reaction (entries 1 and 2). The addition of trifluoroacetic acid (0.05 equiv) improved the enantioselectivity up to 93% ee (entries 3 and 4). Among our data, optimal results were obtained when 0.05 equiv of trifluoroacetic acid was used at rt (entry 3).

Table 2 shows the scope and limitation of the direct asymmetric aldol reactions with various aldehydes (**7b–l**) under the optimized reaction condition mentioned above.¹⁰ We selected nitro, trifluoromethyl, cyano, and halogen substituents as an electron-withdrawing group (entries 1–3, 5–6, and 8–11), and methoxy substituent as a representative electron-donating group (entry 7), at benzene ring. The aldehydes substituted by an electron-withdrawing group at the para-position (**7b–d**) were converted to the corresponding *anti*-aldol products in excellent yields with high enantioselectivities (entries 1–3). The reaction of less reactive benzaldehyde (**7e**) with cyclohexanone also gave **8e** in 71% yield with 87% ee (entry 4). The aldehydes substituted by a nitro group at the ortho- or meta-position (**7f** and **7g**) were also converted to the corresponding *anti*-aldol products (**8f** and **8g**) in excellent yields with 91% ee and 93% ee, respectively (entries 5 and 6). Although moderate chemical yield (66% and 41%) was obtained in the reaction of *m*-anisaldehyde (**7h**) and 2,6-dichlorobenzaldehyde (**7i**), the highest di-

Scheme 2. Preparation of Fluorous Organocatalyst

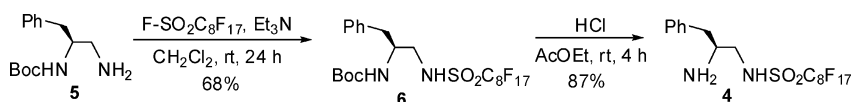
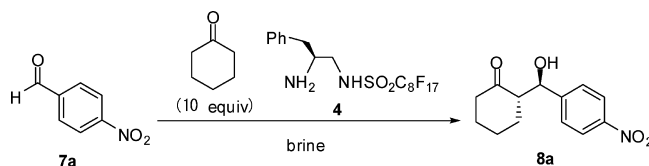


Table 1. Optimization of Reaction Conditions



entry	4 (equiv)	additive (equiv)	temp	time (h)	yield (%) ^a	<i>anti:syn</i> ^b	% ee ^c
1	0.1	non	rt	24	85	74:26	86
2	0.1	non	0 °C	163	85	81:19	91
3	0.1	TFA (0.05)	rt	6.5	87	83:17	91
4	0.1	TFA (0.05)	0 °C	53	81	89:11	93
5 ^d	0.1	TFA (0.05)	rt	6	86	80:20	85
6	0.1	TFA (0.025)	rt	47	86	84:16	89
7	0.1	TFA (0.1)	rt	6	42	80:19	90
8	0.05	TFA (0.025)	rt	6	84	83:17	88

^a Isolated yield. ^b Determined by ¹H NMR. ^c Determined by HPLC analysis with Chiralcel OD-H. ^d 5 equiv of cyclohexanone was used.

Table 2. Direct Asymmetric Aldol Reactions with Fluorous Organocatalyst

entry	product	time (h)	yields (%) ^a	anti:syn ^b	% ee ^c
1		8	100	87:13	90
2		73	93	80:20	88
3		45	81	80:20	93
4		121	71	78:22	87
5		24	94	87:13	91
6		7	93	87:13	93
7		122	66	64:36	75
8		8	41	>99:1	84
9		3	90	95:5	84
10		8	47	60:40	96
11		24	79	—	39 ^d

^a Isolated yields. ^b Determined by ¹H NMR. ^c Determined by HPLC analysis. ^d The reaction was carried out with 30 equiv of acetone in brine.

astereoselectivity (>99:1) was observed in the reaction of 2,6-dichlorobenzaldehyde (**7i**) with cyclohexanone (entries 7 and 8). The reaction of the pentasubstituted aldehyde **7j** was also carried out to afford the corresponding *anti*-aldol product **8j** in excellent yield with 84% ee (entry 9). The aldol reaction of cyclopentanone with *p*-nitrobenzaldehyde (**7a**) gave the expected aldol product **8k** in 47% yield with 96% ee (entry 10). The reaction of acetone as an acyclic ketone with *p*-nitrobenzaldehyde (**7a**) afforded **8l** in high yield and lower enantioselectivity (entry 11).

The fluororous organocatalyst **4** makes it possible to recover itself by using fluororous silica gel based on fluororous solid-phase extraction.⁶ Fluorous sulfonamide **4** was cleanly recovered (89–100%) from the reaction mixture by using fluororous solid-phase extraction and the organocatalyst **4** can be repeatedly reusable. In each reuse, the recovered **4** without further purification retains its catalytic activity and same levels of enantioselectivity for five cycles (Table 3).

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Table 3. Recycling and Reuse of the Fluorous Catalyst by FSPE

entry	time (h)	yield (%) ^a	<i>anti:syn</i> ^b	% ee ^c	cat. recovery
initial	5	89	83:17	85	100
first reuse	5	86	84:16	91	89
second reuse	6	78	85:15	90	94
third reuse	6	65	83:17	87	92
fourth reuse	9	75	85:15	90	91
fifth reuse	12	75	84:16	86	90

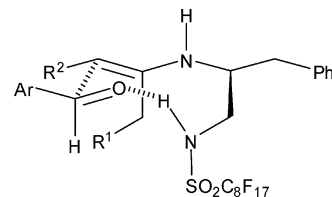
^a Isolated yield. ^b Determined by ¹H NMR. ^c Determined by HPLC analysis with Chiralcel OD-H.

We suppose that the fluorous sulfonamide **4**-catalyzed direct aldol reactions between aldehydes and ketones

(10) A typical procedure of the aldol condensation with **4** and **7a** is as follows: To a colorless suspension of **7a** (90.7 mg, 0.60 mmol) and the organocatalyst **4** (37.9 mg, 0.060 mmol) in 1.2 mL of brine were added cyclohexanone (0.620 mL, 6.00 mmol) and trifluoroacetic acid (2.2 mL, 0.030 mmol) at rt. The reaction mixture was stirred at rt for 5 h. The reaction mixture was chromatographed on fluorous silica gel with 70% methanol. Next, the fluorous silica gel was eluted with methanol, and the methanol fraction was evaporated to recover the fluorous organocatalyst **4** (37.8 mg, 100%). The 70% methanol fractions were evaporated to one-third original volume. The residue was extracted 3× with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous MgSO₄, and evaporated. The residue was purified by flash column chromatography on silica gel with a 2:1 mixture of hexane and AcOEt to afford the pure **8a** (133 mg, 89%) as a colorless crystal.

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proceed via a transition state proposed by Córdova et al.¹¹ based on the stereochemistry of aldol products **8** (Figure 2). We guess that the acidity of sulfonamide was enhanced

**Figure 2.** Proposed transition state model of the aldol reaction.

by the powerful electron-withdrawing effect of the long perfluoroalkyl chain (–C₈F₁₇) to strongly coordinate to aldehydes and stabilize the transition state.

In conclusion, fluorous sulfonamide **4**, a novel fluorous organocatalyst, efficiently works as a catalyst in the direct aldol reaction of various aldehydes with ketones in brine to give the corresponding aldol products with high enantioselectivities. Fluorous organocatalyst **4** can efficiently catalyze the aldol reactions in shorter reaction time at room temperature than the original catalyst **1**⁵ without a lowering of enantioselectivity. The organocatalyst **4** with the fluorous tag was readily recovered only by simple solid-phase extraction with fluorous silica gel after reaction, and can be reused without further purification up to five times. The catalytic activity and enantioselectivity of **4** were maintained despite repetitive use. Further application to the synthesis of bioactive compounds and novel reactions is now in progress.

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Supporting Information Available: Experimental procedures and spectral data for compounds **4** and **8a–l**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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