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Direct asymmetric aldol reactions in brine with recyclable fluorous β-aminosulfonamide organocatalysts

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ABSTRACT

Fluorous organocatalyst **3** promotes direct asymmetric aldol reactions of ketones with aldehydes in brine, leading to the synthesis of the corresponding *anti*-aldol products in high yields with up to 96% ee. Fluorous organocatalyst **3** is easily recovered by solid-phase extraction using fluorous silica gel and can be reused up to five times without purification.

1. Introduction

The development of an organocatalytic enantioselective aldol reaction has become a major area of research during the past decade as a result of its ability to yield stereoselective carbon–carbon bonds, generating chiral β-hydroxycarbonyl compounds as synthetic building blocks.[1] In addition, the properties of organocatalysts, such as low toxicity, high stability, and convenient handling, make them appealing candidates for synthetic chemistry. Since List et al. reported the first direct asymmetric aldol reaction catalyzed by proline in 2000,[2] many other aldol reactions using proline analogues as the main organocatalyst have been reported.[1] As an alternative approach to asymmetric aldol reactions, several groups have worked with primary amine catalysts, exchanging the cyclic secondary amine of proline derivatives.[3,4] Moreover, the use of water as a reaction medium that replaces organic solvents has attracted a great deal of attention because of its affordability, safety, and environmentally benign nature, all of which are important requirements of sustainable green chemistry.[4–6] Because type I aldolases, which are natural enzymes, employ the primary amino group of a lysine residue to catalyze aldol reactions via the enamine intermediate under aqueous conditions,[7] it was suggested that an organocatalyst with a primary amino group may be suitable for the direct asymmetric aldol reaction in water. Several excellent primary amine organocatalysts for the aldol reactions under aqueous conditions have been reported.[4] In this context, we have recently reported direct asymmetric aldol reactions in brine catalyzed by chiral β-aminosulfonamide **1** derived from L-phenylalanine (Scheme 1);[8] unfortunately the organocatalyst was discarded after the reaction because of the difficulty in recovering and reusing it. Ultimately, the ability to recover and recycle expensive organocatalysts from the reaction mixture after completion of the reaction is highly desirable. Fluorous chemistry can be used as a recycling method to overcome this problem.[9] Fluorous chemistry has been developed extensively since Horváth and Rábai first reported the concept of the fluorous biphasic system in 1994.[10] Further, Curran et al. elaborated on its use as a recycling technique by the fluorous solid-phase extraction (FSPE) methodology using fluorous silica gel.[9,11] Subsequently, fluorous recycling techniques have been applied in organocatalytic chemistry.[12] Fluorous organocatalysts were applied to asymmetric Diels–Alder reactions,[13] aldol reactions,[6n,14] Michael reactions,[15] reductions,[16] epoxidations,[17] and α-chlorinations of aldehydes[18] and could be recovered and reused by their fluorous characteristics. To recover and reuse valuable organocatalyst **1**,[8] we developed a recyclable organocatalyst **3** with a fluorous tag that promotes asymmetric direct aldol reactions in brine, as discussed in our preliminary communication.[4i] Herein, we describe in detail asymmetric direct aldol reactions in brine using fluorous organocatalysts **3** (Fig. 1).

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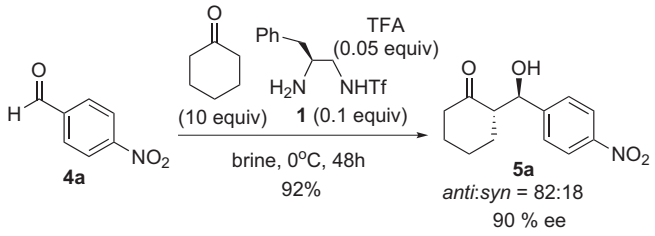


Scheme 1. Our previous work.

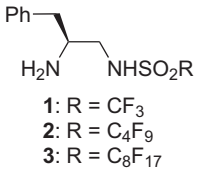
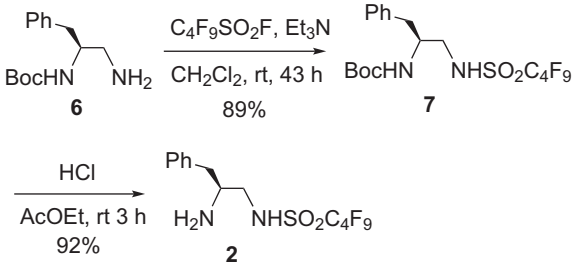


Fig. 1. Structure of organocatalysts.

2. Results and discussion

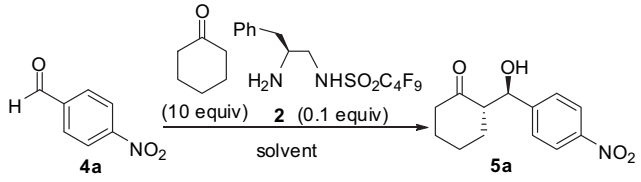
To recover and reuse valuable organocatalyst **1**, we initially attempted the preparation of fluorous organocatalyst **2**, which attached a perfluorobutyl group as a fluorous tag to **1** instead of trifluoromethyl group (Scheme 2). Treatment of compound **6**,[19] which is an intermediate in the preparation of organocatalyst **1**, with perfluorobutanesulfonyl fluoride in the presence of triethylamine in CH_2Cl_2 resulted in sulfonamide **7** with 89% yield. The Boc group of **7** was removed by treatment with HCl in ethyl acetate to afford the desired fluorous β-aminosulfonamide **2** with 92% yield.



Scheme 2. Preparation of fluorous organocatalyst **2**.

The reaction conditions were optimized for enantioselective direct aldol reactions using fluorous organocatalyst **2**, as shown in Table 1. Aldol reactions were carried out with *p*-nitrobenzaldehyde (**4a**) and cyclohexanone (10 equiv) as test reactants in the presence of a catalytic amount of **2** (0.1 equiv). Methanol, 2-propanol, and acetonitrile are poor solvents for aldol reactions and provided low enantioselectivities (entries 1–3). Moderate enantioselectivities were observed when THF, 1,4-dioxane, DMF, DMSO, and NMP were used as the other polar solvents (entries 4–8). The neat conditions without reaction solvent caused lowering of stereoselectivity to yield the *anti*-aldol product with 56% ee (entry 9). The aldol reaction in water, an environmentally benign solvent, enhances the enantioselectivity up to 85% ee. This demonstrated that water is a more suitable solvent for the aldol reactions than commonly used organic solvents (entry 10). Furthermore, although longer reaction times (120 h) were needed in water, performing the reaction at 0 °C enhanced enantioselectivity. Moreover, brine proved to be the best solvent for direct aldol reaction catalyzed by organocatalyst **2** (entry 12). Overall, organocatalyst **2** is an excellent catalyst and shows higher stereoselectivity at room temperature for shorter reaction time compared to the original organocatalyst **1** (entry 13). Unfortunately, despite our attempts to recover the catalyst by FSPE using fluorous silica gel, oraganocatalyst **2** could not be adsorbed by fluorous silica gel even at 40 wt % of fluorine content and was eluted with 70% methanol.

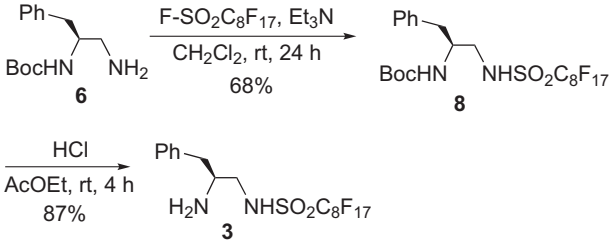
Table 1
Optimization of reaction solvents



Entry	Solvent	Temp	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	MeOH	rt	48	78	57:43	39
2	*i*-PrOH	rt	96	77	51:49	42
3	CH_3CN	rt	100	83	55:45	39
4	THF	rt	120	81	57:43	64
5	1,4-Dioxane	rt	120	79	56:44	61
6	DMF	rt	120	75	57:43	54
7	DMSO	rt	23	65	67:33	71
8	NMP	rt	45	81	73:27	75
9	Neat	rt	48	81	54:46	56
10	H_2O	rt	24	84	73:27	85
11	H_2O	0 °C	120	78	79:21	89
12	Brine	0 °C	168	81	79:21	91
13	**Brine**	**rt**	**20**	**82**	**80:20**	**92**

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

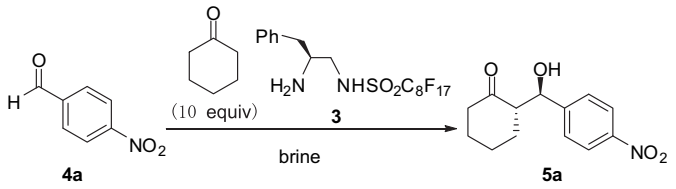
We next attempted to prepare fluorous organocatalyst **3** containing 51 wt % of fluorine, hoping to improve its recoverability with the FSPE technique (Scheme 3). Compound **6** reacts with perfluorooctanesulfonyl fluoride in the presence of triethylamine in CH_2Cl_2 to give fluorous compound **8** with 68% yield. Treatment of **8** with HCl in ethyl acetate results in the desired fluorous β-aminosulfonamide **3** with 87% yield.



Scheme 3. Preparation of fluorous organocatalyst **3**.

Based on the optimal conditions for aldol reactions using organocatalyst **2**, the reaction conditions were optimized for the enantioselective direct aldol reactions using fluorous organocatalyst **3**, as shown in Table 2. Aldol reactions were carried out with *p*-nitrobenzaldehyde (**4a**) and cyclohexanone (10 equiv) as test reactants in the presence of a catalytic amount of **3** (0.1 equiv) in brine. A lowering of stereoselectivity was observed when the aldol reaction using organocatalyst **3** was performed under the optimal conditions with **2** (Table 2, entry 1 vs Table 1, entry 13). Although the reaction at 0 °C enhanced stereoselectivity, a long reaction time (163 h) was necessary for completion of the reaction (entry 2). The addition of trifluoroacetic acid (TFA, 0.05 equiv) improved the enantioselectivity under both room temperature and 0 °C conditions (entries 3 and 4). The enantioselectivities reduced

Table 2
Optimization of reaction conditions



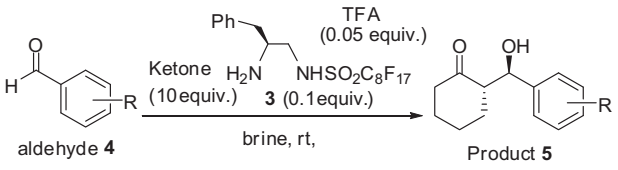
Entry	**3** (equiv)	Additive (equiv)	Temp	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	0.1	None	rt	24	85	74:26	86
2	0.1	None	0 °C	163	85	81:19	91
3	**0.1**	**TFA (0.05)**	**rt**	**6.5**	**87**	**83:17**	**91**
4	0.1	TFA (0.05)	0 °C	53	81	89:11	93
5[d]	0.1	TFA (0.05)	rt	6	86	80:20	85
6	0.1	TFA (0.025)	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 ^{1}H NMR.
[c] Determined by HPLC analysis using Chiralcel OD-H.
[d] Cyclohexanone (5 equiv) was used.

when the amount of cyclohexanone or TFA was decreased (entries 5 and 6). The reaction in the presence of 0.1 equiv amount of TFA results in a reduction of yield (entry 7). The lowering of the catalyst loading to 0.05 equiv also slightly decreased the enantioselectivity (entry 8). Ultimately, the most suitable conditions were found when the reaction was performed in the presence of TFA (0.05 equiv) and catalyst **3** (0.1 equiv) at room temperature.

To address the limitations of the reaction substrate and extend the scope of our investigation, we next examined the substitution effect of aromatic aldehydes on aldol reactions under the optimal conditions (Table 3). We selected nitro, trifluoromethyl, cyano, and halogen substituents as representative electron-withdrawing groups and methoxy substituent as an electron-donating group on the benzene ring. The reactions of cyclohexanone with aromatic aldehydes bearing electron-withdrawing groups at the *para* position (**4b**–**d**) proceeded smoothly to afford the corresponding *anti*-aldol products (**5b**–**d**) with excellent yields and high enantioselectivities (88–93% ee). *p*-Anisaldehyde (**4e**) was a poor substrate for the aldol reaction and provided a low chemical yield (34%) with poor stereoselectivity despite the longer reaction time (entry 4). Benzaldehyde (**4f**) was also less reactive, with poor efficiency, and low yield; ultimately the aldol product **5f** was obtained in only 23% yield using organocatalyst **1**.[8] Alternatively, fluorous sulfonamide **3** effectively catalyzed the aldol reaction to afford **5f** with 71% yield and 87% ee (entry 5). The aldehydes substituted with nitro groups at *ortho* and *meta* positions (**4g** and **4h**) were converted to the corresponding *anti*-aldol products (**5g** and **5h**) in excellent yields with 91% and 93% ee, respectively (entries 6 and 7). The reaction of less reactive *m*-anisaldehyde (**4i**) with cyclohexanone also gave **5i** in good yield with 75% ee (entry 8). The highest diastereoselectivity (>99:1) was observed in the reaction of 2,6-dichlorobenzaldehyde (**4j**) with cyclohexanone (entry 9). Reaction of the pentasubstituted aldehyde **4k** was also carried out, affording the corresponding *anti*-aldol product **5k** with excellent diastereoselectivity and 84% ee (entry 10). The pyridine ring containing aldehyde **4l** was also converted to the corresponding *anti*-aldol product **5l** in excellent yield with 85% ee (entry 11). We also examined the reactions between other types of ketones and *p*-nitrobenzaldehyde (**4a**). The aldol reaction of cyclopentanone with **4a** resulted in the expected aldol product **5m** in moderate yield with highest enantioselectivity (96% ee) (entry 12). Although the reaction of cycloheptanone with **4a** gave excellent product yield, low stereoselectivity was observed (entry 13). 4-Oxotetrahydropyran reacted with **4a** to afford the product **5o** with 86% yield and 77% ee (entry 14). The reaction of acetone as an acyclic ketone with **4a** afforded **5n** in good yield with low enantioselectivities (entry 15). Then, the reaction of dihydroxyacetone with **4a** did not give the corresponding aldol product **5q** under the similar reaction conditions (entry 16).

Table 3
Asymmetric aldol reactions with fluorous organocatalyst **3**



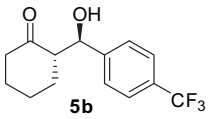
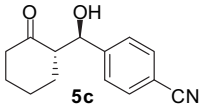
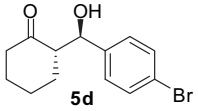
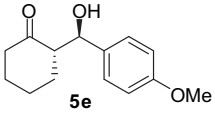
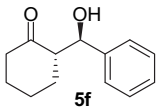
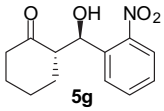
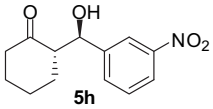
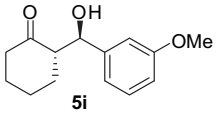
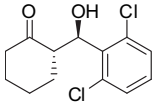
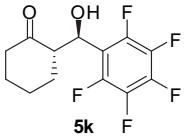
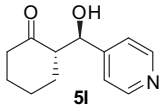
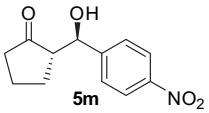
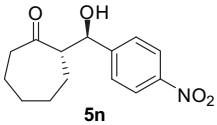
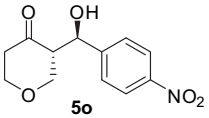
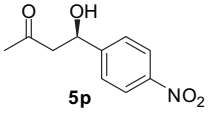
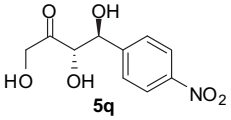
Entry	Product	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
1	 **5b**	8	100	87:13	90
2	 **5c**	73	93	80:20	88
3	 **5d**	45	81	80:20	93
4	 **5e**	120	34	52:48	30

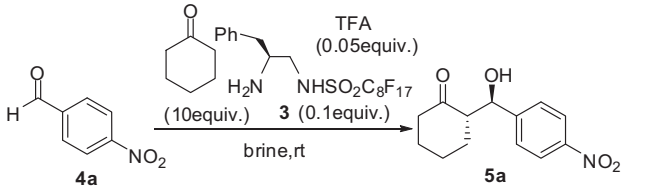
Table 3 (*continued*)

Entry	Product	Time (h)	Yield[a] (%)	*anti*/*syn*[b]	ee[c] (%)
5	 **5f**	121	71	78:22	87
6	 **5g**	24	94	87:13	91
7	 **5h**	7	93	87:13	93
8	 **5i**	122	66	64:36	75
9	 **5j**	16	91	>99:1	91
10	 **5k**	3	90	95:5	84
11	 **5l**	11	90	74:26	85
12	 **5m**	8	47	60:40	96
13	 **5n**	120	96	50:50	25
14	 **5o**	17	86	77:23	77
15	 **5p**	24	79	—	39[d]
16	 **5q**	120	0	—	—

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

The major objective of our project is to recover and reuse fluorous organocatalyst **3**. After use in the aldol reactions of aldehyde **4a** with cyclohexanone under the optimal conditions, fluorous organocatalyst **3** was readily recovered using fluorous silica gel based on FSPE.[9] Fluorous β-aminosulfonamide **3** was easily recovered in high yields (89–100%) from the reaction mixture by using FSPE. Moreover, recovered **3** can be reused for five cycles. In each reuse, recovered **3** retained its catalytic activity and enantioselectivity without further purification, although longer reaction times were necessary for the fourth and fifth reuse (Table 4).

Table 4
Recycling and reuse of the fluorous catalyst by FSPE



Entry	Time (h)	Yield[a] (%)	*anti*/*syn*[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 ^{1}H NMR.
[c] Determined by HPLC analysis using Chiralcel OD-H.

The stereochemistry of all *anti*-aldol products obtained with fluorous organocatalyst **3** was determined by chiral-phase HPLC analysis and NMR spectroscopy. We infer that the direct aldol reactions of aldehydes with ketones using fluorous organocatalyst **3** proceed via a transition state similar to that proposed by Córdova's group,[3c,20] which is based on the stereochemistry of *anti*-aldol products **5**. A plausible reaction mechanism for the aldol reaction is proposed as shown in Fig. 2. From this hypothesis, the primary amino group of **3** condenses with ketones to generate the enamine intermediates. Then, the acidic proton of sulfonamide group, which formed intramolecular coordination to nitrogen of the enamine transition state, successfully interacts with the oxygen of aldehydes to control the approach direction of aldehyde to the enamine intermediates. This ultimately affords the corresponding *anti*-aldol products with high stereoselectivity. We believe that the acidity of sulfonamide is enhanced by the powerful electron-withdrawing effect of the long perfluoroalkyl chains, such as $-C_4F_9$ and $-C_8F_{17}$ to strongly coordinate to aldehyde and stabilize the rigid transition states during aldol reactions.

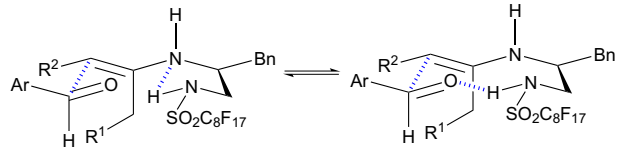


Fig. 2. Proposed transition state model of aldol reaction.

3. Conclusion

In conclusion, fluorous organocatalysts **2** and **3** can be easily prepared from L-phenylalanine, an inexpensive and commercially available amino acid. The simple β-aminosulfonamides **2** and **3**, with only one chiral center, function efficiently as a catalyst in the direct aldol reaction of various aldehydes with ketones in brine to give the corresponding *anti*-aldol products **5** with high enantioselectivity. Fluorous organocatalysts **2** and **3** can efficiently catalyze the aldol reactions in mild reaction conditions at room temperature over shorter reaction times than the original organocatalyst **1**,[8] without lowering enantioselectivity. Although recycling and reuse of organocatalyst **2** was unsuccessful, organocatalyst **3** was readily recovered by simple solid-phase extraction using fluorous silica gel and was immediately reusable up to five times without purification providing the same activity and enantioselectivity. Further application of this catalyst in the synthesis of bioactive compounds is currently in progress in our laboratory.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield™ 400 Plus spectrometer, a JEOL AL 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR), or JEOL ECA-500 spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR). The chemical shifts are expressed in parts per million downfield from tetramethylsilane (δ=0.00) as an internal standard. The high-resolution Mass spectra (HRMS) of the compounds were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}, Art 5715) were used. The products were isolated by flash column chromatography on silica gel (Kanto Chemical, silica gel 60 N, spherical, neutral, 40–50 μm).

4.2. Preparation of organocatalyst

*4.2.1. (S)-tert-Butyl 1-phenyl-3-(perfluorobutylsulfonamido) propan-2-ylcarbamate (**7**).* To a solution of (*S*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate (**6**)[19] (255 mg, 1.02 mmol) in dry CH_2Cl_2 (5 mL) was added triethylamine (0.46 mL, 3.06 mmol) at room temperature. After stirring for 5 min, perfluorobutanesulfonyl fluoride (0.58 mL, 3.06 mmol) was added to the reaction mixture at 0 °C. After stirring for 3 h at 0 °C, the reaction mixture was additionally stirred for 43 h at room temperature. The reaction mixture was added to water and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with a 4:1 mixture of hexane and AcOEt to give the pure **7** (471 mg, 87%) as a colorless powder. Mp=117–119 °C; $[\alpha]_D^{24}$ −10.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.38 (s, 9H), 2.80 (d, *J*=5.9 Hz, 2H), 3.26 (m, 1H), 3.43 (d, *J*=12.2 Hz, 1H), 3.98 (m, 1H), 4.75 (d, *J*=7.2 Hz, 1H), 7.16 (d, *J*=7.2 Hz, 2H), 7.19–7.32 (m, 3H), 7.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.2, 38.4, 49.5, 51.8, 81.0, 107.5–119.0 (complex signals of $-CF_2-$ or $-CF_3$), 127.2, 128.9, 129.0, 136.1, 157.0; HRMS (ESI-TOF): calcd for $C_{18}H_{21}F_9N_2O_4SNa$ $(M+Na)^+$: 555.0971, found: 555.0959.

*4.2.2. (S)-N-(2-Amino-3-phenylpropyl)-perfluorobutanesulfon amide (**2**).* To a solution of **7** (453 mg, 0.851 mmol) in AcOEt (5 mL) was added 5 mL of a 4 M solution of hydrochloric acid in AcOEt at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was evaporated. The residue was added to saturated aqueous $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with a 9:1:0.08 mixture of $CHCl_3$, MeOH and H_2O to give the pure **2** (339 mg, 92%) as a colorless powder. Mp=172–174 °C; $[\alpha]_D^{25}$ +10.6 (*c* 1.03, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=2.83 (dd, *J*=6.6, 13.9 Hz, 1H), 2.96 (dd, *J*=7.0, 13.9 Hz,

1H), 3.16 (dd, *J*=8.3, 14.2 Hz, 1H), 3.29–3.35 (m, 2H, overlap with solvent peaks), 7.24–7.36 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ=38.3, 56.1, 107.5–120.7 (complex signals of $-CF_2-$ or $-CF_3$), 128.2, 129.9, 130.4, 137.7; HRMS (ESI-TOF): calcd for $C_{13}H_{14}F_9N_2O_2S$ $(M+H)^+$:433.0627, found: 433.0667. Anal. Calcd for $C_{13}H_{13}F_9N_2O_2S$: C, 36.12; H, 3.03; N, 6.48. Found: C, 36.05; H, 2.99; N, 6.50.

*4.2.3. (S)-tert-Butyl 1-phenyl-3-(perfluorooctylsulfonamido) propan-2-ylcarbamate (**8**).* To a solution of (*S*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate (**6**)[19] (1.36 g, 5.43 mmol) in dry CH_2Cl_2 (25 mL) was added triethylamine (2.30 mL, 16.3 mmol) at room temperature. After stirring for 5 min, perfluorooctanesulfonyl fluoride (4.50 mL, 16.3 mmol) was added to the reaction mixture at 0 °C. After stirring for 3 h at 0 °C, the reaction mixture was additionally stirred for 48 h at room temperature. The reaction mixture was added to water and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with a 4:1 mixture of hexane and AcOEt to give the pure **8** (2.72 g, 68%) as a colorless powder. Mp 95–97 °C; $[\alpha]_D^{23}$ −8.0 (*c* 2.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.39 (s, 9H), 2.82 (d, *J*=6.4 Hz, 2H), 3.28 (m, 1H), 4.47 (br d, *J*=11.7 Hz, 1H), 3.98 (m, 1H), 4.68 (br s, 1H), 7.09 (br s, 1H), 7.16–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.2, 38.4, 49.4, 51.8, 80.9, 105.0–121.5 (complex signals of $-CF_2-$ or $-CF_3$), 127.2, 128.9, 129.1, 136.3, 157.0; HRMS (ESI-TOF): calcd for $C_{17}H_{14}F_{17}N_2O_2S$ $(M+Na)^+$: 755.0843, found: 755.0837.

*4.2.4. (S)-N-(2-Amino-3-phenylpropyl)-perfluorooctanesulfon amide (**3**).* To a solution of **8** (2.69 g, 3.67 mmol) in AcOEt (20 mL) was added 20 mL of a 4 M solution of hydrochloric acid in AcOEt at 0 °C. After stirring for 4 h at room temperature, the reaction mixture was evaporated. The residue was added to saturated aqueous $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography on silica gel with a 20:1 mixture of $CHCl_3$ and MeOH to give the pure **3** (1.67 g, 72%) as a colorless powder. Mp 185–186 °C; $[\alpha]_D^{19}$ +7.8 (*c* 0.50, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=2.83 (dd, *J*=6.6, 13.9 Hz, 1H), 2.96 (dd, *J*=7.0, 13.9 Hz, 1H), 3.16 (dd, *J*=8.3, 14.2 Hz, 1H), 3.29–3.32 (m, 2H, overlap with solvent peaks), 7.24–7.36 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ=38.3, 49.3, 56.1, 105.0–120.2 (complex signals of $-CF_2-$ or $-CF_3$), 128.3, 130.0, 130.4, 137.8; HRMS (ESI-TOF): calcd for $C_{17}H_{14}F_{17}N_2O_2S$ $(M+H)^+$:633.0499, found: 633.0531. Anal. Calcd for $C_{17}H_{13}F_{17}N_2O_2S$: C, 32.29; H, 2.07; N, 4.43. Found: C, 32.08; H, 2.23; N, 4.45.

4.3. Typical procedure for recycling and reusing fluorous organocatalyst 3 (Table 4)

A typical procedure of the aldol condensation using **3** and **5a** is as follows: to a colorless suspension of **5a** (90.7 mg, 0.60 mmol) and the organocatalyst **3** (37.9 mg, 0.060 mmol) in 1.2 mL of brine were added cyclohexanone (0.62 mL, 6.00 mmol) and trifluoroacetic acid (2.2 μL, 0.030 mmol) at room temperature. The reaction mixture was stirred at room temperature 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 **3** (37.8 mg, 100%). The 70% methanol fractions were evaporated to a one-third to original volume. The residue was extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous $MgSO_4$, 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 **6a** (133 mg, 89%) as a colorless oil.

All the aldol products in the paper are known compounds that exhibited spectroscopic data identical to those reported in the literature.

*4.3.1. (2S,1′R)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one (**5a**)[6d,e,21].* $[\alpha]_D^{25}$ +11.8 (*c* 1.00, $CHCl_3$); 92% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=80:20), flow rate=0.5 mL/min; λ=254 nm; t_{major}=17.8 min, t_{minor}=22.8 min.

*4.3.2. (2S,1′R)-2-[(4-Trifluoromethylphenyl)hydroxymethyl] cyclohexan-1-one (**5b**)[6e].* $[\alpha]_D^{25}$ −17.3 (*c* 1.00, $CHCl_3$); 90% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=80:20), flow rate=0.5 mL/min; λ=216 nm; t_{major}=10.0 min, t_{minor}=11.2 min.

*4.3.3. 4-[Hydroxy(2-oxocyclohexyl)methyl]benzonitrile (**5c**)[6b].* $[\alpha]_D^{24}$ +15.4 (*c* 1.00, $CHCl_3$); 88% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=70:30), flow rate=0.5 mL/min; λ=234 nm; t_{major}=12.9 min, t_{minor}=16.2 min.

*4.3.4. (2S,1′R)-2-[(4-Bromophenyl)hydroxymethyl] cyclohexan-1-one (**5d**)[6d,e].* $[\alpha]_D^{26}$ +18.3 (*c* 1.00, $CHCl_3$); 93% ee; enantiomeric excess was determined by HPLC with Chiralpak AS-H column (hexane/2-propanol=90:10), flow rate=0.5 mL/min; λ=217 nm; t_{major}=28.0 min, t_{minor}=29.5 min.

*4.3.5. (2S,1′R)-2-(Hydroxyphenylmethyl)cyclohexan-1-one (**5e**)[6d,e].* $[\alpha]_D^{24}$ +4.8 (*c* 1.00, $CHCl_3$); 30% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=90:10), flow rate=0.5 mL/min; λ=225 nm; t_{major}=20.2 min, t_{minor}=27.1 min.

*4.3.6. (2S,1′R)-2-(1-Hydroxy-1-phenylmethyl)cyclohexan-1-one (**5f**)[6d,e,21].* $[\alpha]_D^{25}$ +20.7 (*c* 1.00, $CHCl_3$); 87% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=95:5), flow rate=1.0 mL/min; λ=210 nm; t_{major}=11.7 min, t_{minor}=17.3 min.

*4.3.7. (2S,1′R)-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one (**5g**)[6b,21].* $[\alpha]_D^{22}$ +14.3 (*c* 1.00, $CHCl_3$); 91% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=80:20), flow rate=0.5 mL/min; λ=250 nm; t_{major}=13.4 min, t_{minor}=15.0 min.

*4.3.8. (2S,1′R)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one (**5h**)[6b].* $[\alpha]_D^{23}$ +30.1 (*c* 1.00, $CHCl_3$); 93% ee; enantiomeric excess was determined by HPLC with Chiralcel OD-H column (hexane/2-propanol=80:20), flow rate=0.5 mL/min; λ=254 nm; t_{major}=15.2 min, t_{minor}=19.2 min.

*4.3.9. (2S,1′R)-2-[Hydroxy(3-methoxyphenyl)methyl] cyclohexan-1-one (**5i**)[4a].* $[\alpha]_D^{22}$ +4.4 (*c* 1.00, $CHCl_3$); 75% ee; enantiomeric excess was determined by HPLC with Chiralpak AS column (hexane/2-propanol=90:10), flow rate=1.0 mL/min; λ=220 nm; t_{major}=13.1 min, t_{minor}=16.7 min.

*4.3.10. (2S,1′R)-2-[(2,6-Dichlorophenyl)hydroxymethyl] cyclohexan-1-one (**5j**)[21].* $[\alpha]_D^{20}$ −39.1 (*c* 1.00, $CHCl_3$); 91% ee; enantiomeric excess was determined by HPLC with Chiralcel OJ-H column (hexane/2-propanol=95:5), flow rate=1.0 mL/min; λ=210 nm; t_{major}=9.5 min, t_{minor}=11.0 min.

*4.3.11. (2S,1′R)-2-[(2,3,4,5,6-Pentafluorophenyl)hydroxy methyl]cyclohexan-1-one (**5k**)[21].* $[\alpha]_D^{23}$ −16.4 (*c* 1.00, $CHCl_3$); 84% ee; enantiomeric excess was determined by HPLC with Chiralpak AD-H

column (hexane/2-propanol=90:10), flow rate=0.5 mL/min; λ=210 nm; t_{major}=14.8 min, t_{minor}=18.8 min.

*4.3.12. (2S,1′R)-2-[Hydroxy(pyridine-4-yl)methyl] cyclohexan-1-one (**5l**)*[21]. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (hexane/2-propanol=90:10), flow rate=1.0 mL/min; λ=254 nm; t_{minor}=21.7 min, t_{major}=24.2 min.

*4.3.13. (2S,1′R)-2-[Hydroxy(4-nitrophenyl)methyl] cyclopentan-1-one (**5m**)*[6b,21]. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (hexane/2-propanol=95:5), flow rate=1.0 mL/min; λ=265 nm; t_{major}=50.7 min, t_{minor}=48.4 min.

*4.3.14. (2S,1′R)-2-[Hydroxy(4-nitrophenyl)methyl] cycloheptan-1-one (**5n**)*[6b]. $[\alpha]_D^{22}$ −4.1 (*c* 1.00, $CHCl_3$); 25% ee; enantiomeric excess was determined by HPLC with Chiralpak AD-H column (hexane/2-propanol=90:10), flow rate=1.0 mL/min; λ=254 nm; t_{major}=50.0 min, t_{minor}=20.7 min.

*4.3.15. (3S,1′R)-3-[(1′-Hydroxy-1′-(4″-nitrophenyl))methyl] tetrahydropyran-4-one (**5o**)*[21]. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (hexane/2-propanol=80:20), flow rate=1.0 mL/min; λ=254 nm; t_{minor}=20.7 min, t_{major}=23.9 min.

*4.3.16. (4R)-4-Hydroxy-p-nitrophenylbutan-2-one (**5p**)*[6d,e,21]. $[\alpha]_D^{24}$ +24.5 (*c* 1.00, $CHCl_3$); 39% ee; enantiomeric excess was determined by HPLC with Chiralcel OJ column (hexane/2-propanol=90:10), flow rate=1.0 mL/min; λ=266 nm; t_{major}=34.3 min, t_{minor}=38.8 min.

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