Tetrahedron: *Asymmetry* 22 (2011) 1028–1034

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Direct asymmetric aldol reactions in water with a β-aminosulfonamide organocatalyst

Tsuyoshi Miura [a,*], Mariko Ina [a], Kie Imai [a], Kosuke Nakashima [a], Yumi Yasaku [b], Naka Koyata [b], Yasuoki Murakami [b], Nobuyuki Imai [b], Norihiro Tada [a], Akichika Itoh [a]

[a] *Gifu Pharmaceutical University, 1-25-4, Daigaku-nishi, Gifu 501-1196, Japan*
[b] *Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan*

ARTICLE INFO

Article history:
Received 28 April 2011
Accepted 18 May 2011

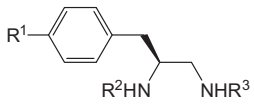
ABSTRACT

Organocatalyst **4** promoted the direct asymmetric aldol reactions of aldehydes with ketones in brine or in the presence of water to afford the corresponding *anti*-aldol products in moderate to excellent yields with up to 97% ee.

1. Introduction

The development of organocatalyzed direct aldol reactions for the stereoselective construction of carbon–carbon bonds has been intensively investigated over the past decade because of the desirable properties of many organocatalysts, such as stability, low toxicity, and convenient handling.[1] Most organocatalysts that have successfully promoted these reactions have used proline derivatives, because proline, with its cyclic secondary amino group, was expected to be suitable for aldol reaction because of the ease in enamine formation. However, type I aldolases, which are natural enzymes, employ the primary amine of a lysine residue under aqueous conditions for enamine formation and aldol reactions.[2] In this context, other chiral primary amines have recently been reported as viable enamine organocatalysts that have achieved a new level of catalytic performance beyond that of secondary amine catalysts such as proline derivatives.[3,4]Also significant from the standpoint of green chemistry, the use of water as a reaction medium in the absence of organic solvents has attracted a great deal of attention because water is inexpensive, safe, and environmentally benign.[5,6] Therefore, the development of a direct asymmetric aldol reaction using an organocatalyst in water is of considerable interest, and several groups have reported organocatalytic direct asymmetric aldol reactions under neat aqueous conditions.[3,7]

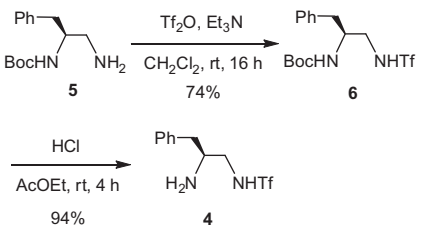
Previously, we have reported an enantioselective Simmons–Smith cyclopropanation using chiral disulfonamide ligands **1**–**3** derived from the natural amino acids L-phenylalanine or L-tyrosine.[8] Our efforts to expand the utility of disulfonamide **1**–**3** analogues to other reactions and conditions led to the application of organocatalyst **4** as a derivative of disulfonamides **1**–**3** to direct stereoselective aldol reactions in brine, and early results have been reported in a preliminary communication.[9] Herein, we would like to describe the full details of the direct aldol reactions in brine and in the presence of water using bifunctional organocatalysts **4**.



1: R^1 = H, R^2 = Ms , R^3 = $SO_2C_6H_4$-*p*-NO_2
2: R^1 = H, R^2 = Ms , R^3 = Ts
3: R^1 = $OCH_2CH_2CH_2C_8F_{17}$, R^2 = Ms , R^3 = Ts
4: R^1 = H, R^2 = H, R^3 = Tf

2. Results and discussion

β-Aminosulfonamide **4**, an organocatalyst for the direct aldol reactions, was prepared as shown in Scheme 1. Treatment of compound **5**,[10] which is an intermediate for the synthesis of chiral ligands **1** and **2**, with trifluoromethanesulfonic anhydride (Tf_2O)

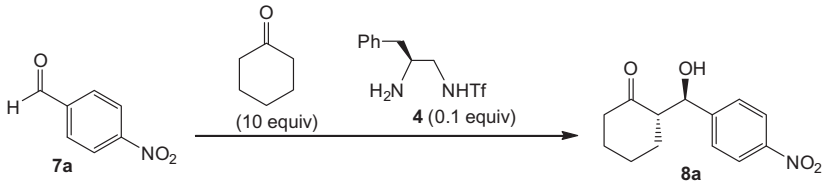


Scheme 1. Preparation of organocatalyst **4**.

* Corresponding author.
E-mail address: miura@gifu-pu.ac.jp (T. Miura).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.05.014

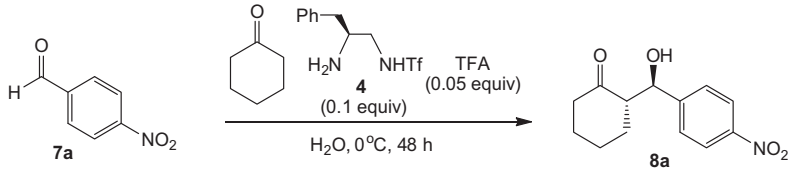
Table 1
Optimization of reaction conditions (part 1)



Entry	Solvent	Additive (equiv)	Temp (°C)	Time (h)	Yield[a] (%)	*anti*:*syn*[b]	%ee[c]
1	MeOH	Non	rt	95	79	55:45	12
2	MeCN	Non	rt	94	94	53:47	23
3	NMP	Non	rt	94	83	56:44	50
4	DMSO	Non	rt	70	83	60:40	60
5	1,4-Dioxane	Non	rt	168	89	55:45	55
6	neat[d]	Non	rt	48	85	56:44	62
7	H_20	Non	rt	47	85	55:45	55
8	Brine	Non	rt	48	92	61:39	69
9	Brine	CF_3CO_2H (0.1)	rt	48	81	76:24	85
10	Brine	CF_3CO_2H (0.1)	0	120	89	77:23	87
11	Brine	CF_3CO_2H (0.2)	0	120	31	78:22	81
12	Brine	CF_3CO_2H (0.05)	0	48	92	82:18	90
13[e]	Brine	CF_3CO_2H (0.05)	0	48	85	86:14	89
14	Brine	CH_3CO_2H (0.05)	0	48	77	85:15	90
15	Brine	$PhCO_2H$ (0.05)	0	48	89	64:36	69
16	Brine	CF_3SO_3H (0.05)	0	118	85	82:18	90
17	Sea water	CF_3CO_2H (0.05)	0	48	88	79:21	86
18	Brine[f]	CF_3CO_2H (0.05)	0	48	89	79:21	88

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] Solvent was not employed.
[e] The reaction was carried out with 5 equiv of cyclohexanone.
[f] Brine prepared from sea water was used.

Table 2
Optimization of reaction conditions (part 2)



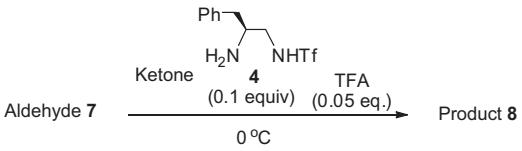
Entry	Cyclohexanone (equiv)	H_2O (equiv)	Yield[a] (%)	*anti*:*syn*[b]	%ee[c]
1	10	0	68	76:24	87
2	10	0.5	80	83:17	90
3	10	1	89	85:15	92
4	10	2	98	86:14	91
5	10	3	99	85:15	90
6	10	10	34	89:11	87
7	5	1	84	85:15	89
8	5	0.5	93	87:13	92
9	3	0.5	91	81:19	88
10	3	0.3	89	87:13	89

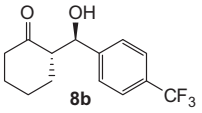
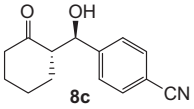
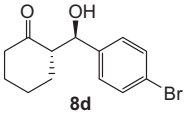
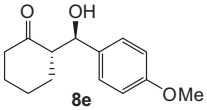
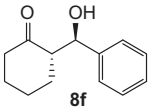
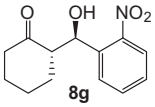
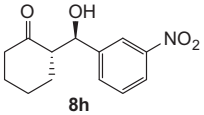
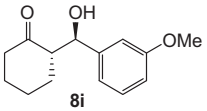
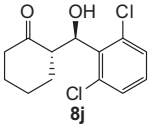
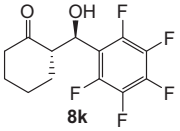
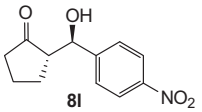
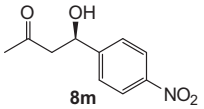
[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis using a Chiralcel OD-H column.

in the presence of triethylamine in CH_2Cl_2 afforded sulfonamide **6** in 74% yield. The Boc group of **6** was removed by treatment with HCl in ethyl acetate to afford the desired β-aminosulfonamide **4** in 94% yield.

We investigated the optimal reaction conditions for an enantioselective aldol reaction using various solvents and additives, as shown in Table 1. Aldol reactions were carried out with *p*-nitrobenzaldehyde and cyclohexanone (10 equiv) as test reactants in the presence of a catalytic amount of β-aminosulfonamide **4**. Methanol and acetonitrile are generally poor solvents for aldol reactions and provided low enantioselectivities (entries 1 and 2). Moderate enantioselectivities were observed when NMP, DMSO, and 1,4-dioxane were used as the solvent (entries 3–5). Under neat conditions, the *anti*-aldol product was obtained with 62% ee (entry 6).

Table 3
Aldol condensation of various aldehyde in the presence of **4**



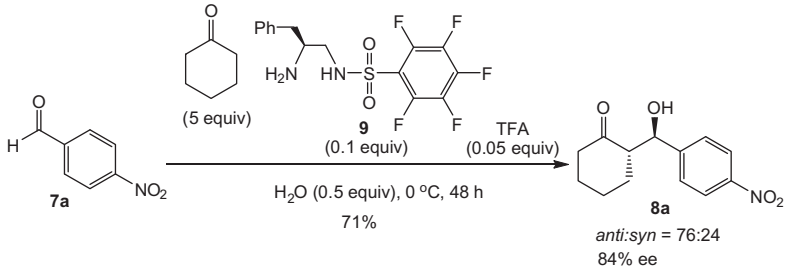
Entry	Product **8**	Method[a]	Time (h)	Yield[b] (%)	*anti*:*syn*[c]	%ee[d]
1	 **8b**	A	73	88	86:14	91
2		B	90	70	87:13	91
3	 **8c**	A	73	93	80:20	88
4		B	72	86	84:16	92
5	 **8d**	A[e]	120	87	81:19	92
6		B	120	70	84:16	93
7	 **8e**	A	119	12	87:13	92
8		B	120	10	>99:1	89
9	 **8f**	A	118	23	84:16	89
10		B	120	29	86:14	94
11	 **8g**	A	120	84	88:12	91
12		B	120	76	92:8	93
13	 **8h**	A	72	92	82:18	91
14		B	72	84	86:14	94
15	 **8i**	A[e]	120	77	84:16	93
16		B	120	60	86:14	93
17	 **8j**	A	72	93	>99:1	86
18		B	72	79	97:3	97
19	 **8k**	A	72	88	93:7	85
20		B	74	99	>99:1	85
21	 **8l**	A	72	71	71:29	88
22		B	72	61	65:35	72
23[f]	 **8m**	A	120	61	—	29
24[f]		B	120	37	—	77

[a] Method A: The reactions were carried out with 10 equiv of ketone; Method B: The reactions were carried out with 5 equiv of ketone and 0.5 equiv of H_2O.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by HPLC analysis.
[e] The reactions were carried out with 0.2 equiv of catalyst **4**, 20 equiv of cyclohexanone, and 0.1 equiv of TFA in brine.
[f] The reaction was carried out with 30 equiv of acetone in brine.

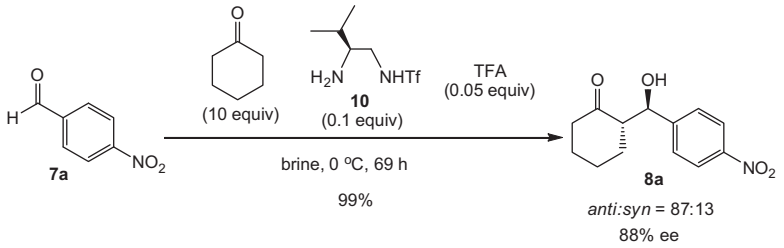
Although the aldol reaction in water, an environmentally benign solvent, occurred with 55% ee, the related conversion in brine afforded the product with 69% ee (entries 7 and 8). Therefore, brine proved to be the best medium for direct aldol reactions. Next, we examined the effects associated with the presence of an acid. Addition of trifluoroacetic acid (TFA, 0.1 equiv) to the reaction in brine significantly increased the enantioselectivity to 85% ee (entry 9). Although a longer reaction time was needed, the reaction at 0 °C under similar conditions yielded the same results (up to 87% ee, entry 10). Addition of more TFA (0.2 equiv) resulted in a reduction in both yield and stereoselectivity (entry 11). More suitable reaction conditions were obtained when 0.05 equiv of TFA was used at 0 °C (entry 12). Furthermore, we also examined other protic acids, including acetic acid, benzoic acid, and trifluoromethanesulfonic acid; however, TFA was found to be the most suitable additive (entries 14–16). In addition, both sea water taken directly from the Pacific Ocean and brine prepared by addition of sodium chloride to sea water, which is available more easily than pure water, were examined as reaction solvents. It was found that both the yield and enantioselectivity of the aldol reactions in sea water and brine prepared from sea water were nearly equal to those in brine prepared from pure water (entries 17 and 18).

We hypothesized that the amount of water from brine dissolved in cyclohexanone might play an important role in achieving enantioselectivity because the results obtained from the reactions in brine were better than those in water or run under neat conditions. Therefore, the amount of water added in comparison to the quantity of cyclohexanone was examined as shown in Table 2. The most suitable amount of water was 1 equiv when 10 equiv of cyclohexanone was used in the reaction (entries 1–6). High enantioselectivity was also achieved by the addition of 0.5 equiv of water when the level of cyclohexanone was reduced to 5 equiv (entries 7 and 8), suggesting the optimal ratio of water to cyclohexanone is 1:10 in comparison with the reactions in brine. Lowering the amount of cyclohexanone to 3 equiv resulted in slightly lower enantioselectivities (entries 9 and 10).

With the optimal conditions in hand, we next investigated substituent effects of the aromatic aldehydes on the aldol reactions in order to identify the scope and limitations of the aldehyde substrate, as shown in Table 3. The direct asymmetric aldol reactions with various aldehydes were evaluated in the presence of **4** (0.1 equiv) and TFA (0.05 equiv) using two sets of conditions. In the first set, reactions were carried out in the presence of 10 equiv of ketone in brine (method A). Alternative conditions utilized 5 equiv of ketone and 0.5 equiv of water (method B). We chose nitro, trifluoromethyl, cyano, and halogen substituents as representative electron-withdrawing groups (entries 1–6 and 11–14), and a methoxy substituent as an electron-donating group on the benzene ring (entries 7, 8, 15, and 16). The reactions of cyclohexanone with aromatic aldehydes bearing electron-withdrawing groups at the *para*-position **7b–d** proceeded smoothly to afford the corresponding *anti*-aldol products **8b–d** in excellent yields with high enantioselectivities (88–93% ee). *p*-Anisaldehyde **7e** and benzaldehyde **7f** were poor substrates for the aldol reaction giving low yields (10–29%) despite the longer reaction time; however, high enantioselectivities were observed (entries 7–10). The aldehydes substituted by a nitro group at the *ortho* or *meta* position **7g** and **7h** were converted into the corresponding *anti*-aldol products **8g** and **8h** in excellent yields with high enantioselectivities (entries 11–14). The reaction of less reactive *m*-anisaldehyde **7i** with cyclohexanone also gave **8i** in good yields with 93% ee (entries 15 and 16). The highest diastereoselectivity (>99:1) and enantioselectivity (97% ee) were observed in the reactions of 2,6-dichlorobenzaldehyde with cyclohexanone (entries 17 and 18). The reactions of the penta-substituted aldehyde **7k** were also carried out to afford the corresponding *anti*-aldol product **8k** in excellent diastereoselectivity with 85% ee (entries 19 and 20). We also examined reactions between other ketones and *p*-nitrobenzaldehyde **7a**. The aldol reaction of cyclopentanone with **7a** gave the expected aldol products **8l** in good yields and enantioselectivities (entries 21 and 22). The reaction of acetone as an acyclic ketone with **7a** in brine (method A) afforded **8m** in moderate yield and with low enantioselectivity (entriy 23), and while the aldol reaction in the presence of water (method B) resulted in low yield, the enantioselectivity improved substantially (up to 77% ee, entry 24). Aliphatic aldehydes phenylpropionaldehyde and isobutyraldehyde were also examined as reactants with cyclohexanone, but the corresponding aldol products could not be obtained under these reaction conditions. Results from these experiments have demonstrated excellent setereoselectivities for Method B, which was found to be superior



Scheme 2.



Scheme 3.

to method A in many cases. Most significantly, the reaction of **7j** with cyclohexanone using method B showed enhanced enantioselectivity (up to 97% ee) as compared to the same reaction using method A (86% ee, entries 17 and 18).

We also examined other types of organocatalysts (**9** and **10**) for the direct asymmetric aldol reactions (Schemes 2 and 3). Both organocatalysts **9** and **10** catalyzed the reaction of **7a** with cyclohexanone under similar reaction conditions to afford aldol adduct **8a** in 71% and 99% yields, respectively; however, the enantioselectivities were slightly reduced as compared to organocatalyst **4**.

The stereochemistry of all *anti*-aldol products obtained with organocatalyst **4** was determined by chiral-phase HPLC analysis and NMR spectroscopy. We infer that the β-aminosulfonamide **4**-catalyzed direct aldol reactions between aldehydes and ketones proceed via a transition state similar to that proposed by Córdova et al.,[4c,11] which is based on the stereochemistry of the aldol products **8** (Fig. 1). A plausible transition state proposed for the aldol reaction is shown in Figure 1. From this hypothesis, the primary amino group of **4** condenses with the ketone to afford an enamine intermediate. Then, it is reasonable to expect that the sulfonamide proton of **4** coordinates to the aldehyde oxygen to control the approach direction of the aldehyde to the enamine intermediate affording the corresponding *anti*-aldol products with remarkable stereo control. Moreover, the addition of TFA to the aldol reactions might accelerate the formation of the enamine intermediate,[12] as well as reinforce the rigid transition state of the aldol reaction shown in Figure 1.

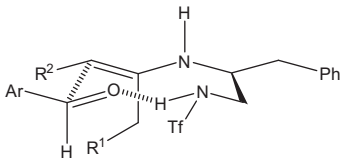


Figure 1. Proposed transition state model for the aldol reaction.

3. Conclusion

In conclusion, organocatalyst **4** can be easily prepared from L-phenylalanine, a commercially available, inexpensive natural amino acid. The simple β-aminosulfonamide **4**, with only one stereogenic center, functions efficiently as a catalyst in the direct aldol reaction of various aldehydes with ketones to give the corresponding *anti*-aldol products **8** with high enantioselectivities. Furthermore, we have demonstrated that the reaction conditions using a 1:10 ratio of water to cyclohexanone are superior to the reactions in brine. Further application of this process to the synthesis of bioactive compounds is currently in progress in our laboratory.

4. Experimental

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 ppm 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-(trifluoromethylsulfonamido) propan-2-ylcarbamate 6

To a solution of (*S*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate **5**[10] (375 mg, 1.50 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (251 μL, 1.80 mmol) at rt under an argon atmosphere. After stirring for 5 min, trifluoromethanesulfonic anhydride (277 μL, 1.65 mmol) was added to the reaction mixture at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was additionally stirred for 16 h at rt. The reaction mixture 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 4:1 mixture of hexane and AcOEt to give pure **6** (425 mg, 74%) as a colorless powder. Mp = 114–116 °C; $[\alpha]_D^{25} = -13.6$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 2.81 (m, 2H), 3.23 (m, 1H), 3.43 (d, *J* = 11.4 Hz, 1H), 3.98 (m, 1H), 4.67 (br s, 1H), 6.82 (br s, 1H), 7.16–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.2, 38.4, 49.0, 51.7, 80.9, 119.8 (q, $^1J_{C\text{-}F}$ = 321 Hz), 127.2, 128.9, 129.1, 136.2, 157.0; HRMS (ESI-TOF): calcd for $C_{15}H_{21}F_3N_2O_4SNa$ $(M+Na)^+$: 405.1066, found: 405.1045.

4.2.2. (*S*)-*N*-(2-Amino-3-phenylpropyl)-1,1,1-trifluoromethane sulfonamide 4

To a solution of **6** (404 mg, 1.06 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 3.5 h at rt, 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 pure **4** (281 mg, 94%) as a colorless powder. Mp 164–166 °C; $[\alpha]_D^{25} = +10.7$ (*c* 2.01, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 2.81 (dd, *J* = 6.9, 13.8 Hz, 1H), 2.93 (dd, *J* = 7.2, 13.8 Hz, 1H), 3.10 (dd, *J* = 7.2, 13.0 Hz, 1H), 3.23–3.35 (m, 2H), 7.24–7.35 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD): δ = 38.5, 48.7, 55.8, 123.0 (q, $^1J_{C\text{-}F}$ = 326 Hz), 128.2, 129.9, 130.4, 137.9; HRMS (ESI-TOF): calcd for $C_{10}H_{14}F_3N_2O_2S$ $(M+H)^+$: 283.0723, found: 283.0691. Anal. Calcd for $C_{10}H_{13}F_3N_2O_2S$: C, 42.55; H, 4.64; N, 9.92. Found: C, 42.47; H, 4.57; N, 9.90.

4.2.3. (*S*)-*N*-(2-Amino-3-phenylpropyl)-2,3,4,5,6-pentafluoro benzenesulfonamide 9

To a solution of (*S*)-*tert*-butyl 1-amino-3-phenylpropan-2-ylcarbamate **5** (423 mg, 1.69 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (703 μL, 5.07 mmol) at rt. After stirring for 5 min, pentafluorobenzoyl chloride (373 μL, 2.54 mmol) was added to the reaction mixture at rt. After stirring for 20 h at rt, the reaction mixture 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 4:1 mixture of hexane and AcOEt to give (*S*)-*tert*-butyl 1-(perfluorophenylsulfonamido)-3-phenylpropan-2-ylcarbamate (171 mg, 21%). Then, to a solution of (*S*)-*tert*-butyl 1-(perfluorophenylsulfonamido)-3-phenylpropan-2-ylcarbamate (161 mg, 0.335 mmol) in AcOEt (1.7 mL) was added 1.7 mL of a 4 M solution of hydrochloric acid in AcOEt at 0 °C. After stirring for 3.5 h at rt, 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 pure **9** (110 mg, 86%) as a colorless

powder. Mp = 129 °C; $[\alpha]_D^{22} = +8.7$ (*c* 1.00, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 2.62 (dd, *J* = 7.4, 13.8 Hz, 1H), 2.80 (dd, *J* = 6.3, 13.2 Hz, 1H), 2.97 (dd, *J* = 7.4, 13.2 Hz, 1H), 3.08 (dd, *J* = 4.6, 13.2 Hz, 1H), 3.12–3.17 (m, 1H), 7.19–7.23 (m, 3H), 7.27–7.30 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ = 41.1, 53.9, 127.7, 129.7, 130.3, 139.2. Anal. Calcd for $C_{15}H_{13}F_5N_2O_2S$: C, 47.37; H, 3.45; N, 7.37. Found: C, 47.11; H, 3.48; N, 7.22.

4.2.4. (*S*)-*N*-(2-Amino-3-methylbutyl)-1,1,1-trifluoromethane sulfonamide 10

To a solution of (*S*)-*tert*-butyl 1-amino-3-methylbutan-2-ylcarbamate **5**[10] (441 mg, 2.19 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (458 μL, 3.29 mmol) at rt under an argon atmosphere. After stirring for 5 min, trifluoromethanesulfonic anhydride (395 μL, 1.65 mmol) was added to the reaction mixture at 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was additionally stirred for 16 h at rt. The reaction mixture 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 4:1 mixture of hexane and AcOEt to give (*S*)-*tert*-butyl 3-methyl-1-(trifluoromethylsulfonamido)butan-2-ylcarbamate (439 mg, 61%). Then, to a solution of (*S*)-*tert*-butyl 3-methyl-1-(trifluoromethylsulfonamido)butan-2-ylcarbamate (439 mg, 1.36 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 8 h at rt, 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 pure **10** (126 mg, 39%) as a colorless powder. Mp = 146–148 °C; $[\alpha]_D^{24} = +15.1$ (*c* 0.87, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.00 (d, *J* = 7.5 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.88–1.95 (m, 1H), 2.81–2.85 (m, 1H), 3.09 (dd, *J* = 8.6, 13.2 Hz, 1H), 3.35 (dd, *J* = 3.5, 13.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ = 18.8, 19.0, 30.1, 47.2, 60.4, 123.2 (q, $^1J_{C\text{-}F}$ = 326 Hz). Anal. Calcd for $C_6H_{13}F_3N_2O_2S$: C, 30.77; H, 5.59; N, 11.96. Found: C, 30.93; H, 5.43; N, 11.83.

4.3. Typical procedure for direct aldol reactions using organocatalyst 4 (Table 3)

4.3.1. Method A

To a colorless suspension of **7a** (90.7 mg, 0.60 mmol) and organocatalyst **4** (16.9 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 0 °C. After stirring for 48 h at 0 °C, 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 2:1 mixture of hexane and AcOEt to give the pure **8a** (137 mg, 92%) as a colorless powder.

4.3.2. Method B

To a solution **7a** (90.7 mg, 0.60 mmol) and the organocatalyst **4** (16.9 mg, 0.060 mmol) in cyclohexanone (0.62 mL, 6.00 mmol) were added H_2O (5.4 μL, 0.30 mmol) and trifluoroacetic acid (2.2 μL, 0.030 mmol) at 0 °C. After stirring for 48 h at 0 °C, 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 2:1 mixture of hexane and AcOEt to give pure **8a** (139 mg, 93%) as a colorless powder.

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

4.3.3. (2*S*,1′*R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexan-1-one 8a[7b,e,13]

Enantiomeric excess was determined by HPLC with a 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.

4.3.4. (2*S*,1′*R*)-2-[(4-Trifluoromethylphenyl)hydroxymethyl] cyclohexan-1-one 8b[7e]

Enantiomeric excess was determined by HPLC with a 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.

4.3.5. 4-[Hydroxy(2-oxocyclohexyl)methyl]benzonitrile 8c[7b]

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.

4.3.6. (2*S*,1′*R*)-2-[(4-Bromophenyl)hydroxymethyl] cyclohexan-1-one 8d[7b,e]

Enantiomeric excess was determined by HPLC with a 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.

4.3.7. (2*S*,1′*R*)-2-[Hydroxy(4-methoxyphenyl)methyl] cyclohexan-1-one 8e[7b,e]

Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/2-propanol = 90:10), flow rate = 0.5 mL/min; λ = 225 nm; t_{major} = 21.0 min, t_{minor} = 29.1 min.

4.3.8. (2*S*,1′*R*)-2-(1-Hydroxy-1-phenylmethyl)cyclohexan-1-one 8f[7b,e,13]

Enantiomeric excess was determined by HPLC with a 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.

4.3.9. (2*S*,1′*R*)-2-[Hydroxy(2-nitrophenyl)methyl]cyclohexan-1-one 8g[7b,13]

Enantiomeric excess was determined by HPLC with a 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.

4.3.10. (2*S*,1′*R*)-2-[Hydroxy(3-nitrophenyl)methyl]cyclohexan-1-one 8h[7b]

Enantiomeric excess was determined by HPLC with a 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.

4.3.11. (2*S*,1′*R*)-2-[Hydroxy(3-methoxyphenyl)methyl] cyclohexan-1-one 8i[3a]

Enantiomeric excess was determined by HPLC with a 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.

4.3.12. (2*S*,1′*R*)-2-[(2,6-Dichlorophenyl)hydroxymethyl] cyclohexan-1-one 8j[13]

Enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (hexane/2-propanol = 95:5), flow rate = 1.0 mL/min; λ = 210 nm; t_{major} = 9.9 min, t_{minor} = 11.6 min.

4.3.13. (2*S*,1′*R*)-2-[(2,3,4,5,6-Pentafluorophenyl)hydroxymethyl]cyclohexan-1-one 8k[13]

Enantiomeric excess was determined by HPLC with a Chiralpak AS-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.

4.3.14. (2*S*,1′*R*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclopentan-1-one 8n[7b,13]

Enantiomeric excess was determined by HPLC with a 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.

4.3.15. (4*R*)-4-Hydroxy-*p*-nitrophenylbutan-2-one 8m[7b,e,13]

Enantiomeric excess was determined by HPLC with a 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.

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research (C) (No. 22590007) from the Japan Society for the Promotion of Science.

References

1. For selected reviews on organocatalysts, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (b) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267; (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638; (e) Lattanzi, A. *Chem. Commun.* **2009**, 1452; (f) Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 6145.
2. Heine, A.; DeSantis, G.; Luz, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A. *Science* **2001**, *294*, 369.
3. For examples of organocatalyzed aldol reactions in water using organocatalysts with primary amino group, see: (a) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801; (b) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812; (c) Zhu, M.-K.; Xu, X.-Y.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1390; (d) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas, C. F. *Org. Lett.* **2008**, *10*, 1621; (e) Tea, Y.-C.; Lee, P. P. *Synth. Commun.* **2009**, *39*, 3081; (f) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199; Ma, X.; Da, C.-S.; Yi, L.; Jia, Y.-N.; Guo, Q.-P.; Che, L.-P.; Wu, F.-C.; Wang, J.-R.; Li, W.-P. *Tetrahedron: Asymmetry* **2009**, *20*, 1419; (g) Zhou, H.; Xie, Y.; Ren, L.; Wang, K. *Adv. Synth. Catal.* **2009**, *351*, 1284; (h) Miura, T.; Imai, K.; Ina, M.; Tada, N.; Imai, N.; Itoh, A. *Org. Lett.* **2010**, *12*, 1620; (i) Li, J.; Fu, N.; Li, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2010**, *75*, 4501; (j) Ricci, A.; Bernardi, L.; Gioia, C.; Vierucci, S.; Robitzer, M.; Quignard, F. *Chem. Commun.* **2010**, 6288.
4. For examples of organocatalyzed aldol reactions in organic solvents using organocatalysts with primary amino group, see: (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (b) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, A. *Chem. Commun.* **2005**, 4946; (c) Dziedzic, P.; Zou, W.; Háfren, J.; Córdova, A. *Org. Biomol. Chem.* **2006**, *4*, 38; (d) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383; (e) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2007**, *129*, 288; (f) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074; (g) Utsumi, N.; Imai, M.; Tanaka, F.; Ramasastry, S. S. V.; Barbas, C. F. *Org. Lett.* **2007**, *9*, 3445; (h) Xu, X.-Y.; Wang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2007**, *9*, 4247; (i) Luo, S.; Xu, H.; Zhang, L.; Li, J.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 653; (j) Luo, S.; Li, J.; Zhang, L.; Xu, H.; Cheng, J.-P. *Chem. Eur. J.* **2008**, *14*, 1273; (k) Luo, S.; Xu, H.; Chen, L.; Cheng, J.-P. *Org. Lett.* **2008**, *10*, 1775; (l) Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 17666; (m) Wu, X.; Ma, Z.; Ye, Z.; Qian, S.; Zhao, G. *Adv. Synth. Catal.* **2009**, *351*, 158; (n) Li, J.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2009**, *74*, 1747; (o) Luo, S.; Zhou, P.; Li, J.; Cheng, J.-P. *Chem. Eur. J.* **2010**, *16*, 4457.
5. For reviews on organic synthesis in water, see: *(a) Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie A & P: London, 1998; (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209; (c) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (d) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.
6. For review on stereoselective organocatalytic reaction in water, see: (a) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33; (b) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288; (c) Raj, M.; Singh, K. *Chem. Commun.* **2009**, 6687; (d) Mase, N.; Barbas, C. F., III *Org. Biomol. Chem.* **2010**, *8*, 4043.
7. For examples of organocatalyzed aldol reactions in water without any organic solvent using pyrrolidine derivatives, see: (a) Chimni, S. S.; Mahajan, D.; Babu, V. V. S. *Tetrahedron Lett.* **2005**, *46*, 5617; (b) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734; (c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958; (d) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527; (e) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653; (f) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417; (g) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J. *Can. J. Chem.* **2007**, *85*, 208; (h) Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Noto, R. *Tetrahedron Lett.* **2007**, *48*, 255; (i) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, 2524; (j) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593; (k) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2007**, 4688; (l) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2008**, *10*, 337; (m) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211; (n) Lombardo, M.; Pasi, F.; Easwar, S.; Trombini, C. *Synlett* **2008**, 2471; (o) Chimni, S. S.; Singh, S.; Mahajan, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2276; (p) Chimni, S. S.; Singh, S.; Kumar, A. *Tetrahedron: Asymmetry* **2009**, *20*, 1722; (q) Zhang, S.-P.; Fu, X.-K.; Fu, S.-D. *Tetrahedron Lett.* **2009**, *50*, 1173; (r) Fu, S.-D.; Fu, X.-K.; Zhang, S.-P.; Zou, X.-C.; Wu, X.-J. *Tetrahedron: Asymmetry* **2009**, *20*, 2390; (s) Nisco, M. D.; Pedatella, S.; Ullah, H.; Zaidi, J. H.; Naviglio, D.; Ozdamar, O.; Caputo, R. *J. Org. Chem.* **2009**, *74*, 9562; (t) Vishnumaya, M. R.; Singh, V. K. *J. Org. Chem.* **2009**, *74*, 4289; (u) Mase, N.; Noshiro, N.; Mokuya, A.; Takabe, K. *Adv. Synth. Catal.* **2009**, *351*, 2791; (v) Jia, Y.-N.; Wu, F.-C.; Ma, X.; Zhu, G.-J.; Da, C.-S. *Tetrahedron Lett.* **2009**, *50*, 3059; (w) An, Y.-J.; Zhang, Y.-X.; Wu, Y.; Liu, Z.-M.; Pi, C.; Tao, J.-C. *Tetrahedron: Asymmetry* **2010**, *21*, 688; (x) Pedrosa, B.; Andrés, J. M.; Manzano, R.; Román, D.; Téllez, S. *Org. Biomol. Chem.* **2011**, *9*, 935.
8. (a) Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423; (b) Imai, N.; Nomura, T.; Yamamoto, S.; Ninomiya, Y.; Nokami, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2433; Miura, T.; Murakami, Y.; Imai, N. *Tetrahedron: Asymmetry* **2006**, *17*, 3067; (c) Miura, T.; Itoh, K.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron Lett.* **2008**, *49*, 5813; (d) Koyata, N.; Miura, T.; Akaiwa, Y.; Sasaki, H.; Sato, R.; Nagai, T.; Fujimori, H.; Noguchi, T.; Kirihara, M.; Imai, N. *Tetrahedron: Asymmetry* **2009**, *20*, 2065.
9. Miura, T.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron Lett.* **2009**, *50*, 2632.
10. Imai, N.; Nokami, J.; Nomura, T.; Ninomiya, Y.; Shinobe, A.; Matsushiro, S. *Bull. Okayama Univ. Sci.* **2002**, 47.
11. Bassan, A.; Zou, W.; Reues, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028.
12. Mase, N.; Tanaka, F.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420.
13. Tang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649.