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Direct asymmetric aldol reactions in brine using novel sulfonamide catalyst

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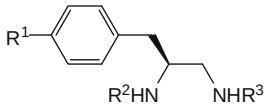
ABSTRACT

Direct asymmetric aldol reactions of aldehydes with ketones in the presence of a catalytic amount of sulfonamide **4** and trifluoroacetic acid afforded the corresponding *anti*-aldol products in moderate to excellent yields with 85–93% ee.

The aldol reaction is one of the most popular carbon–carbon bond-forming procedures and plays an important role in organic synthesis.[1] The development of organocatalyst, which promotes the direct asymmetric aldol reaction, is an attractive research field.[2] On the other hand, the exploration of the reaction using water without any organic solvent as a reaction medium has attracted a great deal of attention because water is a safe and an environmentally friendly solvent from perception of green chemistry.[3] Therefore, the development of a direct asymmetric aldol reaction using organocatalyst in water has received considerable interest, and some groups have reported organocatalytic direct asymmetric aldol reactions in water without using any organic co-solvent.[4,5] Most of the studies for organocatalytic direct asymmetric aldol reactions have been done with proline-derived chiral catalysts because proline and its derivatives with a secondary amino group were believed to be the best catalyst for direct asymmetric aldol condensation due to the ease of enamine formation.[2,4] However, chiral primary amines recently have been reported to be viable enamine organocatalysts that attain a new level of catalyst beyond secondary amino catalysts such as proline derivatives.[5,6]

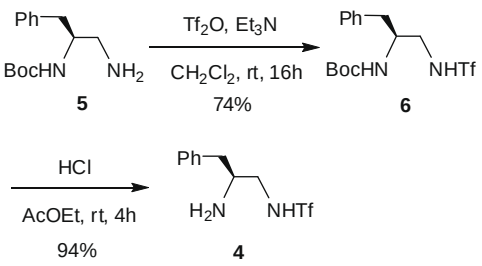
We have reported the enantioselective Simons–Smith cyclopropanation catalyzed by chiral disulfonamides (**1–3**) derived from L-phenylalanine or L-tyrosine as a primary amino acid.[7] We searched further application of disulfonamide (**1–3**) analogs to an another reaction field. In this Letter, we describe a catalytic enantioselective aldol reaction between ketones and aldehydes in brine using novel sulfonamide **4** as an analog of disulfonamide (**1–3**).

The novel organocatalyst **4** was prepared as shown in Scheme 1. The compound **5** as the intermediate for synthesis of chiral ligands **1** and **2** was easily prepared from phenylalaninol in four steps.[8] The reaction of **5** with trifluoromethanesulfonyl anhydride (Tf_2O) in dichloromethane afforded the compound **6** in 74% yield. The Boc group of **6** was removed by treatment with hydrogen chloride in ethyl acetate to afford the desired sulfonamide **4**[9] in 94% yield.



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

Aldol reactions were carried out between aldehydes and cyclohexanone (10 equiv) using the sulfonamide **4** (0.1 equiv). We optimized the reaction conditions for enantioselective aldol reaction as shown in Table 1. The various reaction solvents were examined in the presence of the organocatalyst **4** at room temperature (entries 1–8). It was found that the more suitable reaction solvent was brine (entry 8).[4g,j] The addition of trifluoroacetic acid (0.1 equiv) significantly improved the enantioselectivity up to 85% ee (entry 9).[4a,10] The more suitable reaction temperature was 0 °C as indicated in entry 10. A better result on the amount of trifluoroacetic



Scheme 1. Preparation of organocatalyst.

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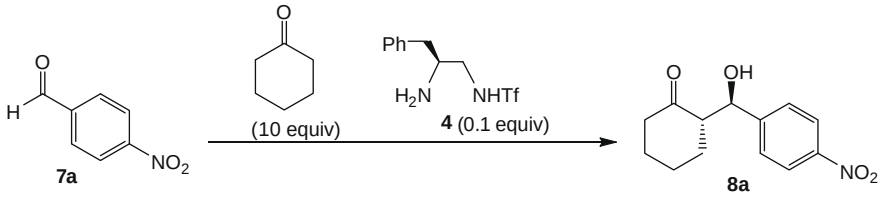
Table 1
Optimization of reaction conditions



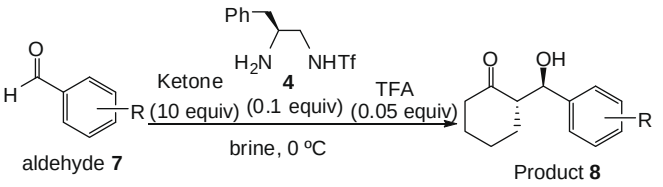
Entry	Solvent	Additive (equiv)	Temperature	Time (h)	Yield (%)[a]	*anti: syn*[b]	% ee[c]
1	MeOH	Non	rt	95	79	55:45	12
2	CH_3CN	Non	rt	94	94	53:47	23
3	NMP	Non	rt	94	83	56:44	50
4	DMSO	Non	rt	70	83	60:40	60
5	1,4-Dioxane	Non	rt	168	89	55:45	55
6	Neat[d]	Non	rt	48	85	56:44	62
7	H_2O	Non	rt	47	85	55:45	55
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 °C	120	89	77:23	87
11	Brine	CF_3CO_2H (0.2)	0 °C	120	31	78:22	81
12	Brine	CF_3CO_2H (0.05)	0 °C	48	92	82:18	90
13	Sea water	CF_3CO_2H (0.05)	0 °C	48	88	79:21	86
14	Brine[e]	CF_3CO_2H (0.05)	0 °C	48	89	79:21	88

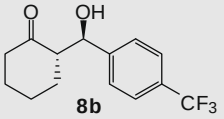
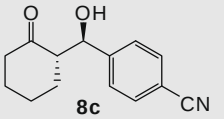
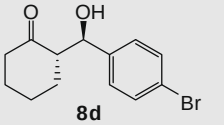
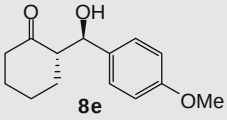
[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] Determined by HPLC analysis using Chiralcel OD-H.
[d] Solvent was not employed.
[e] Brine prepared from sea water was used.

acid (TFA) was observed in the reaction with the 0.05 equiv at 0 °C (entries 10–12). In addition, both the sea water taken directly from the Pacific Ocean and the brine prepared by addition of sodium chloride into the sea water were examined as a reaction solvent. It was observed that the yield and the enantioselectivity of the aldol reaction in the brine prepared from the sea water were nearly equal to those with the brine prepared from pure water (entries 13 and 14).

Next, the direct asymmetric aldol reactions of various aldehydes (**7b–l**) in the presence of **4** (0.1 equiv) and TFA (0.05 equiv) were examined as shown in Table 2.[11] We selected methoxy substituent as a representative electron-donating group (entries 4 and 8), nitro, trifluoromethyl, cyano, and halogen substituents as an electron-withdrawing group (entries 1–3 and 6–7) on the benzene ring. The aldehydes substituted by electron-withdrawing groups at *p*-position (**7b–d**) were converted to the corresponding *anti*-aldol products in excellent yields with high enantioselectivities (88–92% ee). Low chemical yields (12% and 23%) were obtained in the reaction of *p*-anisaldehyde (**7e**) and benzaldehyde (**7f**), respectively (entries 4 and 5). The aldehydes substituted by nitro group at *o*- and *m*-position (**7g** and **7h**) were converted to the corresponding *anti*-aldol products (**8g** and **8h**) in excellent yields with 91% ee, respectively (entries 6 and 7). The reaction of the compound **7i** substituted by methoxyl group at *m*-position afforded the highest enantioselectivity (93% ee) than those of the other aldehydes (entry 8). The highest diastereoselectivity (>99:1) was observed in the reaction of 2,6-dichlorobenzaldehyde (**7j**) with cyclohexanone (entry 9). The reactions of the penta-substituted aldehyde **7k** and the pyridine-ring containing aldehyde **7l** were also carried out to afford the corresponding *anti*-aldol products in excellent yields with 85% and 87% ee, respectively (entries 10 and 11). We examined the reactions between various ketones and aldehydes. The aldol reaction of cyclopentanone with *p*-nitrobenzaldehyde gave the expected aldol product **8m** in 71% yield with 88% ee (entry 12). The reaction of acetone as a linear ketone with *p*-nitro-

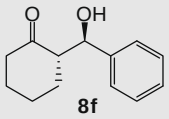
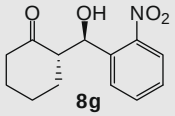
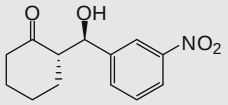
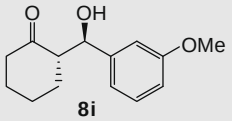
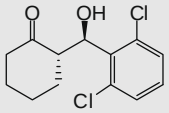
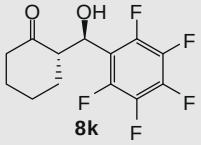
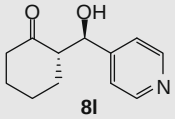
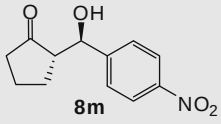
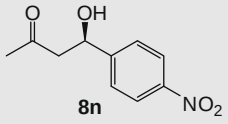
Table 2
Aldol condensation of various aldehyde in the presence of **4**



Entry	Product **8**	Time (h)	Yield[a] (%)	*anti*:*syn*[b]	% ee[c]
1	 **8b**	73	88	86:14	91
2	 **8c**	73	93	80:20	88
3[d]	 **8d**	120	87	81:19	92
4	 **8e**	119	12	87:13	92

(*continued on next page*)

Table 2 (*continued*)

Entry	Product **8**	Time (h)	Yield[a] (%)	*anti*:*syn*[b]	% ee[c]
5	 **8f**	118	23	84:16	89
6	 **8g**	120	84	88:12	91
7	 **8h**	72	92	82:18	91
8[d]	 **8i**	120	77	84:16	93
9	 **8j**	72	93	>99:1	86
10	 **8k**	72	88	93:7	85
11	 **8l**	96	81	77:23	87
12	 **8m**	72	71	71:29	88
13[e]	 **8n**	120	61	—	29

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis.
[d] The reactions were carried out with 0.2 equiv of catalyst **4**, 20 equiv of cyclohexanone, and 0.1 equiv of TFA in brine.
[e] The reaction was carried out with 30 equiv of acetone in brine.

benzaldehyde afforded a moderate yield and a low enantioselectivity (entry 13). Then, the reactions of phenylpropionaldehyde and isobutyraldehyde as an aliphatic aldehyde with cyclohexanone did not give the corresponding aldol products under the similar reaction conditions.

The stereochemistry of the aldol products **8** was determined by chiral-phase HPLC analysis and NMR spectroscopy.[4] Based on the stereochemistry of the aldol products **8**, we suppose that the sulfonamide **4**-catalyzed direct aldol reactions between ketones and aldehydes occurred via a transition state proposed by Córdova et al. (Fig. 1).[6c,12]

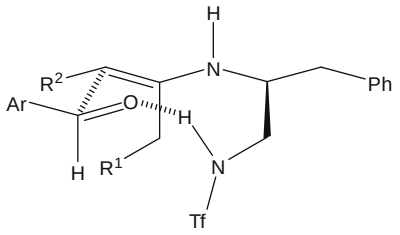


Figure 1. Proposed transition state model of aldol reaction.

In summary, the sulfonamide **4**, which is readily prepared from phenylalaninol, efficiently works as a catalyst in the direct asymmetric aldol reactions of various aldehydes with ketones in brine to give the corresponding *anti*-aldol products in moderate to excellent yields with excellent enantioselectivities. Further application to the synthesis of bioactive compounds and to novel reactions is now in progress.

Acknowledgments

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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.

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9. Organocatalyst **4**: Colorless powder; Mp = 164–166 °C; $[\alpha]_D^{25}$ +10.7 (*c* 2.01 in 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 H, 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, $^1J_{C-F}$ = 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.
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11. A typical procedure of the aldol condensation using **4** and **7a** is as follows: To a colorless suspension of **7a** (90.7 mg, 0.600 mmol) and the catalyst **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. The reaction mixture was stirred at 0 °C for 48 h. The reaction mixture 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 **8a** (137 mg, 92%).
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