Organocatalysis

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syn-Selective and Enantioselective Direct Cross-Aldol Reactions between Aldehydes Catalyzed by an Axially Chiral Amino Sulfonamide**

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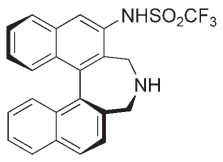
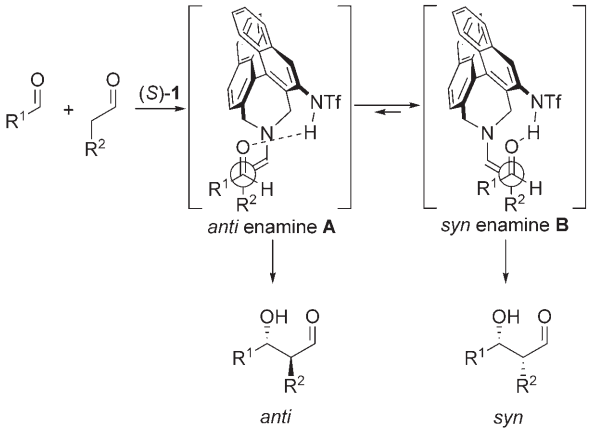
The aldol reaction has long been recognized as one of the most fundamental tools for the construction of new carbon–carbon bonds.[1] In this area, the cross-aldol reaction between two different aldehydes is known to be often problematic because of undesired side reactions, including dehydration of the product, self-aldol reaction, and multiple addition of the enolate to the aldol product. To date, however, several cross-aldol reactions using aldehyde-derived metal enolates, including silyl enol ethers as nucleophile and/or non- or slowly enolizable aldehydes as electrophile, have been reported,[2–9] and some rare examples of the catalytic asymmetric version of this reaction have recently been developed.[10–16] For example, the diastereo- and enantioselective cross-aldol reaction between aldehydes and silyl enol ethers was first accomplished by Denmark et al. with chiral Lewis base catalysts,[10] and very recently Kobayashi and co-workers demonstrated the chiral Lewis acid catalyzed diastereo- and enantioselective reaction using aldehyde-derived enecarbamates as an activated aldehyde nucleophile.[11] With these methods, both the *syn* and *anti* diastereomers, respectively, were formed in a highly enantioselective fashion. On the other hand, to the best of our knowledge, most organocatalytic direct enantioselective cross-aldol reactions of aldehydes, first reported by MacMillan and co-workers, provide predominantly *anti* aldol adducts,[12–17] albeit with only a few exceptions giving *syn* adducts.[12d] In this context, we have been interested in the possibility of developing a *syn*-selective direct cross-aldol reaction between two different aldehydes by using a chiral organocatalyst. Herein we wish to report such a *syn*-selective and enantioselective direct cross-aldol reaction catalyzed by an axially chiral amino sulfonamide of type (*S*)-**1**.



(*S*)-**1**

Our strategy is based on the recent observation that a direct asymmetric Mannich reaction is catalyzed by the axially chiral amino sulfonamide (*S*)-**1** to give the *anti* product predominantly, which is a minor diastereomer in the proline-catalyzed reaction.[18] Since it would be difficult for *anti* enamine **A**, which is generated from a donor aldehyde and (*S*)-**1**, to react with an acceptor aldehyde that is activated by the distal acidic proton of the triflamide of (*S*)-**1**, the cross-aldol reaction catalyzed by (*S*)-**1** would be expected to proceed through *syn* enamine intermediate **B**, thus giving the desired unusual *syn* product as shown in Scheme 1.



Scheme 1. Possible transition states for the enantioselective direct cross-aldol reaction catalyzed by (*S*)-**1**.

We first examined the reaction between 4-nitrobenzaldehyde and hexanal in the presence of 5 mol% (*S*)-**1** in various solvents at room temperature, and the results are summarized in Table 1. Unfortunately, the reaction in less polar solvents such as dioxane, toluene, and CH_2Cl_2 gave the cross-aldol product **2** in poor yield with low stereoselectivities (Table 1, entries 1–3). In the case of acetonitrile, only a trace amount of **2** was observed, although *syn*-**2** was slightly dominant over *anti*-**2** (Table 1, entry 4). While the use of DMSO, which is a common solvent for aldol reactions catalyzed by proline or related organocatalysts,[13a,15] led to the formation of the desired *syn*-**2** in a highly diastereo- and enantioselective manner, the yield was still low (Table 1, entry 5). When the amide solvents *N*,*N*-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP) were used, the desired *syn*-**2** was obtained in moderate yield with excellent diastereo- and enantioselectivity (Table 1, entries 6 and 7). Accordingly,

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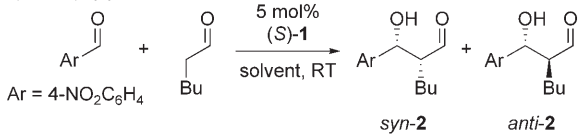
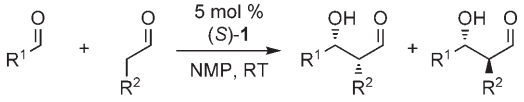
Table 1: *syn*-Selective aldol reaction of 4-nitrobenzaldehyde with hexanal catalyzed by (*S*)-**1**.[a]



Entry	Solvent	Conc [M][b]	*t* [h]	Yield [%][c]	*syn*/*anti*[d]	*ee* [%][e]
1	dioxane	0.1	36	22	1:3.4	8
2	toluene	0.1	36	26	1:1.5	6
3	CH_2Cl_2	0.1	36	31	1:1.6	25
4	CH_3CN	0.1	36	< 5	1.2:1	–
5	DMSO	0.1	36	25	13:1	96
6	DMF	0.1	36	60	17:1	98
7	NMP	0.1	36	62	> 20:1	99
8	NMP	0.1	72	74	13:1	97
9	NMP	0.25	36	73	> 20:1	99
10	NMP	1.0	36	77	> 20:1	99

[a] The reaction of 4-nitrobenzaldehyde (0.25 mmol) with hexanal (0.5 mmol) was carried out in the presence of (*S*)-**1** (0.0125 mmol) at room temperature. [b] Concentration of 4-nitrobenzaldehyde. [c] Yield of isolated product after acetalization with 2,2-dimethyl-1,3-propanediol. [d] Determined by ^{1}H NMR spectroscopy. [e] The *ee* value of *syn*-**2** was determined by HPLC by using a chiral column (Chiralpak AD-H, Daicel Chemical Industries); details are given in the Supporting Information.

Table 2: *syn*-Selective aldol reaction between various aldehydes catalyzed by (*S*)-**1**.[a]



Entry	R^1	R^2	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1		Me	36	73	12:1	98
2		*n*Bu	36	77	> 20:1	99
3		Bn	36	80	> 20:1	98
4		allyl	36	79	> 20:1	98
5		*i*Pr	40	61	> 20:1	96
6		*n*Bu	36	22	6.3:1	92
7		*n*Bu	78	73	> 20:1	99
8		*n*Bu	69	71	6.4:1	94
9[e]		*n*Bu	4.5	99[g]	2.3:1	95
10[f]		*n*Bu	20	91[g]	> 20:1	96

[a] Unless otherwise specified, the reaction of an acceptor aldehyde (0.25 mmol) with a donor aldehyde (0.5 mmol) in NMP (250 μL) was carried out in the presence of (*S*)-**1** (0.0125 mmol) at room temperature. [b] Yield of isolated product after acetalization or reduction, except in entries 9 and 10; details are given in the Supporting Information. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the *syn* product was determined by HPLC by using a chiral column (Chiralpak AS-H, AD-H, Chiralcel OD-H or OJ-H, Daicel Chemical Industries); details are given in the Supporting Information. [e] Use of 3 equiv of ethyl glyoxylate (0.75 mmol) and 1 equiv of hexanal (0.25 mmol). [f] Phenylglyoxal was used in the monohydrate form. [g] Yield of isolated product.

further optimization of the reaction conditions was investigated by using NMP as the solvent of choice. A longer reaction time resulted in a slight decrease of both diastereo- and enantioselectivity, albeit in higher yield (Table 1, entry 8). On the other hand, the reactions conducted at a higher concentration were found to give *syn*-**2** in improved yields without loss of stereoselectivities (Table 1, entries 9 and 10). The absolute configuration of *syn*-**2** in entry 10 was determined to be (2*R*,3*R*) as predicted on the basis of the transition model in Scheme 1. It should also be noted that more than 95% of (*S*)-**1** was recovered unchanged after column chromatography.

With the optimal reaction conditions, the *syn*-selective and enantioselective direct cross-aldol reaction of several other reactive acceptor aldehydes with donor aliphatic aldehydes was examined (Table 2). The reaction of 4-nitrobenzaldehyde with various aliphatic aldehydes gave the corresponding *syn* aldol adduct in moderate to good yield with excellent diastereo- and enantioselectivity (Table 2, entries 1–5). Although the reaction of a simple acceptor aldehyde such as benzaldehyde with hexanal proceeded slowly in low yield, good stereoselectivity was observed (Table 2, entry 6). On the other hand, reactive aldehydes such as fluorinated aromatic and heteroaromatic aldehydes as well as ethyl glyoxylate were found to be suitable electrophiles (Table 2, entries 7–9). The reaction catalyzed by (*S*)-**1** was also applicable to phenylglyoxal as its monohydrate (Table 2, entry 10). In all cases, the (*S*)-**1**-catalyzed method was complementary to the proline-catalyzed reactions in terms of the *syn*/*anti* selectivity. In addition, it is important to note that only trace amounts of byproducts arising from dimerization of donor aldehydes were observed.

In summary, we have developed a highly *syn*-selective and enantioselective direct cross-aldol reaction between two different aldehydes catalyzed by the axially chiral amino sulfonamide (*S*)-**1**. This organocatalytic process represents a rare example of *syn*-selective direct cross-aldol reaction via an enamine intermediate. Further investigations to expand the scope of this and related reactions are currently underway.

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