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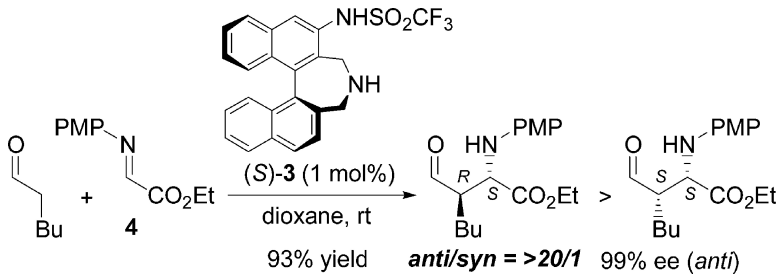

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anti-Selective Direct Asymmetric Mannich Reactions Catalyzed by Axially Chiral Amino Sulfonamide as an Organocatalyst

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Asymmetric Mannich reactions provide a powerful method for synthesizing optically active β-amino carbonyl units, which are useful chiral building blocks for a number of biologically active and pharmaceutically important compounds.[1] In particular, direct asymmetric Mannich reactions between carbonyl compounds and certain imines would be most desirable for this purpose.[2−4] Accordingly, small organic molecules, such as L-proline and its derivatives, were recently found to catalyze the reaction between aldehydes and imines to furnish *syn*- or *anti*-β-amino aldehydes as a major product, depending on the choice of catalyst.[3c,d] While a proline-catalyzed direct asymmetric Mannich reaction of imine **4** gives the *syn*-β-amino aldehyde, *syn*-**5**, preferentially with excellent enantioselectivity through the *anti*-enamine intermediate **A** (Scheme 1),[3c] a general and selective method for obtaining the opposite *anti*-β-amino aldehyde, *anti*-**5**, remains unattainable.[3d] In this context, we are interested in the possibility of obtaining *anti*-**5** via the *syn*-enamine intermediate **B** by using a certain amino acid which has a longer spatial distance between the amino and carboxyl groups than L-proline catalyst. Our recently designed axially chiral amino acid (*S*)-**1**,[5] which catalyzes the direct asymmetric aldol reaction between acetone and aldehydes, seems to be an appropriate candidate to achieve the hitherto difficult *syn*-enamine intermediate **B** resulting from a decrease of the steric repulsion between the enamine and acid moieties. In addition, the imine activated by the remote acidic proton is expected to react preferentially with the *syn*-enamine intermediate **B** to give a desired *anti*-isomer, *anti*-**5**. Our hypothesis has been verified by designing an axially chiral organocatalyst of type **3** that allows a highly *anti*-selective direct asymmetric Mannich reaction between aldehyde and imine **4** with excellent enantioselectivity.

First, we examined the direct Mannich reaction between isovaleraldehyde and α-imino ester **4** derived from *p*-anisidine and ethyl glyoxylate. Thus, in the presence of 5 mol % of (*S*)-**1**, the reaction between isovaleraldehyde (3 equiv) and α-imino ester **4** in dioxane at room temperature afforded the corresponding β-amino aldehyde **5** in 60% yield with the *anti*/*syn* ratio of 1:1.1 and enantiomeric excess of 86% for the *anti*-isomer (Table 1, entry 1). This low *anti*/*syn* selectivity prompted us to modify (*S*)-**1** and develop new axially chiral amino sulfonamides of type (*S*)-**2** and (*S*)-**3** with a more remote acidic proton from the secondary amino group than the carboxyl group in (*S*)-**1**.

The efficiency of these new catalysts (*S*)-**2** and (*S*)-**3** was evaluated under the identical conditions, except for the use of lower catalyst loadings (2 mol %). Unfortunately, attempted use of (*S*)-**2** resulted in a significant loss of reactivity and enantioselectivity, although moderate *anti*-selectivity was observed (Table 1, entry 2). In marked contrast, however, switching the catalysts from (*S*)-**2** to (*S*)-**3**, which contains a more acidic trifluoromethanesulfonamide group, dramatically enhanced both reactivity and stereoselectivities in this system (93% yield; *anti*/*syn* = >20:1; >99% ee for the major *anti*-isomer) (entry 3). We then examined the solvent effect

Scheme 1

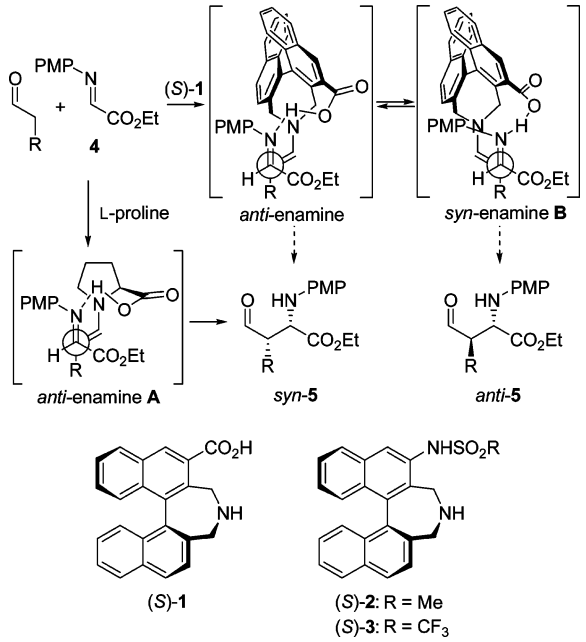
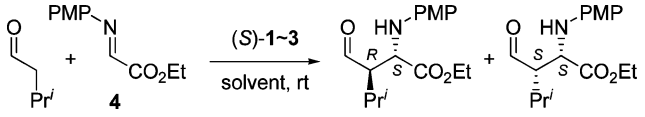


Table 1. *anti*-Selective Mannich Reactions between Isovaleraldehyde and α-Imino Ester **4** Catalyzed by (*S*)-**1**−**3**[a]



entry	catalyst	mol (%)	time (h)	solvent	% yield[b]	*anti*/*syn*[c]	% ee[d]
1	(*S*)-**1**	5	20	dioxane	60	1/1.1	86
2	(*S*)-**2**	2	24	dioxane	11	3.8/1	72
3	(*S*)-**3**	2	0.5	dioxane	93	>20/1	>99
4	(*S*)-**3**	2	6	THF	38	>20/1	99
5	(*S*)-**3**	2	6	EtOAc	72	8.3/1	90
6	(*S*)-**3**	2	6	DMSO	20	6.3/1	97
7	(*S*)-**3**	2	6	$CHCl_3$	70	9.1/1	98
8	(*S*)-**3**	2	0.5	toluene	98	9.1/1	>99

[a] The reaction of isovaleraldehyde (3 equiv) and α-imino ester **4** was carried out in a solvent in the presence of catalyst (*S*)-**1**−**3** at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the *anti*-isomer was determined by HPLC analysis using chiral column (Chiralpak AS-H, Daicel Chemical Industries, Ltd.).

by using (*S*)-**3** in the direct asymmetric Mannich reaction. Other solvents, such as THF, EtOAc, DMSO, or $CHCl_3$, were found to be less satisfactory in terms of the chemical yield and stereoselectivities (entries 4−7). Whereas the reaction in toluene solvent proceeded smoothly with excellent enantioselectivity, a slight decrease in *anti*-selectivity was observed (entry 8). Accordingly, dioxane was determined to be the solvent of choice.

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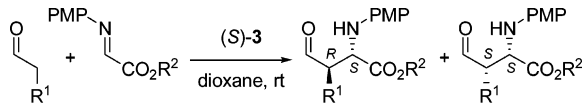
Table 2. *anti*-Selective Mannich Reactions between Various Aldehydes and α-Imino Ester **4** Catalyzed by (*S*)-**3**[a]



entry	R^1	R^2	catalyst (mol %)	time (h)	% yield[b]	*anti*/*syn*[c]	% ee[d]
1	Me	Et	1	0.5	93	13/1	>99
2	Me	Et	0.2	22	82	11/1	97
3	Bu	Et	1	4	93	>20/1	99
4	Bu	Et	0.5	8	92	>20/1	97
5	Bn	Et	1	4	92	11/1	>99
6	*i*-Pr	Et	2	0.5	93	>20/1	>99
7	*t*-Bu	Et	5	16	42	>20/1	>99
8	*i*-Pr	allyl	2	0.5	99	16/1	>99
9	*i*-Pr	*t*-Bu	2	0.5	99	16/1	>99

[a] The reaction between aldehydes (3 equiv) and α-imino esters was carried out in dioxane in the presence of (*S*)-**3** at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the *anti*-isomer was determined by HPLC analysis using chiral column. Details are given in Supporting Information.

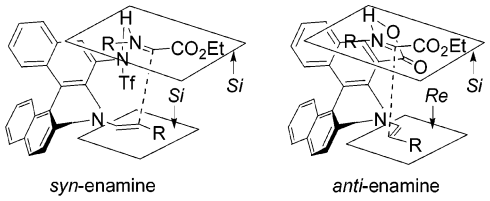


Figure 1. Possible transition states for the direct asymmetric Mannich reaction catalyzed by (*S*)-**3** (left) and (*S*)-**1** (right).

The reaction between other aldehydes and α-imino esters in the presence of a catalytic amount of (*S*)-**3** was carried out in dioxane at room temperature, and the selected data are summarized in Table 2. In the case of *primary* alkyl aldehydes, 1 mol % of (*S*)-**3** is sufficient to produce the corresponding *β*-amino aldehydes in high yields (>92%) with virtually complete enantioselectivities (99% ee) and excellent *anti*-selectivities (>11/1) (entries 1, 3, and 5). The catalyst loading can be reduced to less than 1 mol % of (*S*)-**3** with slightly decreased yield and stereoselectivities (entries 2 and 4). Although the reaction of a sterically hindered aldehyde required a higher catalyst loading and proceeded in moderate yield, optimal *anti*-selectivity and enantioselectivity were observed (entry 7). Moreover, this reaction system was also applicable to other α-imino esters (entries 8 and 9). It should be noted that self-aldol products were not detected even in the presence of excess aldehyde (3 equiv).

The observed stereochemistry in the reaction using (*S*)-**3** could be explained by a transition state in which the *Si* face of the α-imino ester approaches the *Si* face of the *syn*-enamine as directed by the rigid and distant trifluoromethanesulfonamide group (Figure 1, left). On the other hand, due to the flexibility of the carboxyl group in (*S*)-**1**, the C−C bond forming reaction catalyzed by (*S*)-**1** takes place not only on the *Si* face of the *syn*-enamine but also on the *Re* face of the *anti*-enamine in the reaction catalyzed by (*S*)-**1** (Figure 1, right). As a result, both *anti*- and *syn*-isomers are obtained.

In summary, we have developed a highly *anti*-selective direct asymmetric Mannich reaction between aldehydes and the α-imino ester catalyzed by the novel axially chiral amino sulfonamide (*S*)-**3**. The procedure converts the α-imino ester to functional *β*-amino aldehydes with significantly higher *anti*/*syn* ratio and enantioselectivity than previously possible. We are currently working to expand the scope of this methodology and to apply the novel sulfonamide catalyst for other organocatalytic asymmetric reactions.

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Supporting Information Available: Experimental details and characterization data for new compounds including the preparation of catalysts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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