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A Designer Axially Chiral Amino Sulfonamide as an Efficient Organocatalyst for Direct Asymmetric *anti*-Selective Mannich Reactions and *syn*-Selective Cross-Aldol Reactions

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Abstract: A direct asymmetric Mannich reaction using a novel axially chiral amino sulfonamide (*S*)-**3** that is highly *anti*- and enantioselective has been developed. For instance, in the presence of a catalytic amount of (*S*)-**3**, the reactions between aldehydes and α-imino esters proceeded smoothly to give *anti* Mannich products with a significantly higher *anti*/*syn* ratio and enantioselectivity than previously possible. By utilizing *N*-Boc-protected aromatic imines instead of α-imino esters, the synthetically useful Boc protecting group and various aromatic or heteroaromatic substituents were installed into the *anti* Mannich products and consequently the substrate scope of the *anti*-selective Mannich reaction and the synthetic utility of the *anti* Mannich products have been expanded. The axially chiral amino sulfonamide (*S*)-**3** has also been successfully applied to asymmetric direct cross-aldol reaction between two different aldehydes. The catalyst (*S*)-**3** has the advantage of giving mainly *syn* products, whereas proline shows the opposite *anti* selectivity.

Keywords: aldol reaction · sulfonamides · asymmetric synthesis · Mannich reaction · organocatalysis

Introduction

In recent years, asymmetric organocatalysis has attracted great interest as a new catalytic method for the synthesis of a wide variety of chiral molecules, and various organocatalysts have been developed to date.[1] Among them, proline and its derivatives have proven to be effective organocatalysts in several powerful asymmetric transformations, such as the aldol and Mannich reactions.[2] The first example of such a proline-catalyzed asymmetric reaction, the intramolecular aldol reaction, was reported in the early 1970s,[3] and the proline-catalyzed intermolecular aldol reaction between ketones and aldehydes was realized by List and Barbas et al. nearly 30 years later.[4] Since these pioneering works in the area of enamine catalysis, a number of proline derivatives have been designed to demonstrate their efficiency in various organocatalytic reactions.[2] Most of these catalysts possess a highly nucleophilic pyrrolidine ring and a chiral center at the α carbon atom as the key structural features for obtaining high reactivity and selectivity. Indeed, 2-azetidinecarboxylic acid and pipecolic acid, which are proline analogues with a four- and six-membered ring, respectively, were found to be much less effective catalysts for the direct asymmetric aldol reaction.[4] In addition to these observations, the design of new proline-type catalysts has intrinsic limitations due to the difficulty in modifying the pyrrolidine ring. Although asymmetric enamine catalysis has been developed significantly through the derivatization of the carboxylic acid moiety of the parent proline, there is still an urgent need for structurally and electronically novel catalysts to further expand the scope of this methodology. Other amino acids and their derivatives have very recently also been utilized as organocatalysts in some asymmetric reactions, offering new possibilities for catalyst design. However, non-amino acid derived catalysts are still rare in this field.[2b,c] In this context, we were interested in the possibility of designing an amino sulfonamide catalyst with a readily derivatizable binaphthyl backbone and also of developing organocatalytic asymmetric reactions by utilizing its unique molecular geometry and electronic properties. Thus, herein we wish to report the synthesis of a novel binaphthyl-based amino sulfonamide catalyst (*S*)-**3** and its successful application in direct asymmetric Mannich[5] and aldol reactions.[6] In this study, rare examples of organocatalytic *anti*-selective

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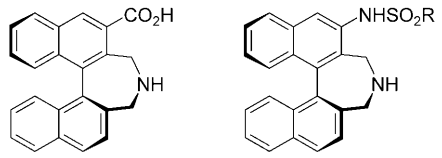
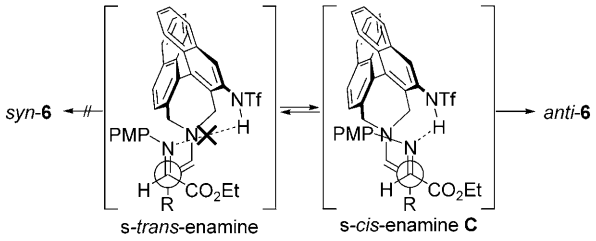
Mannich reactions and *syn*-selective cross-aldol reactions between two different aldehydes have been realized. In particular, by using our catalyst (*S*)-**3**, highly *anti*- and enantioselective Mannich reactions of *N*-Boc-protected aromatic imines have been achieved in enamine catalysis at a synthetically useful level. Aromatic imines can now be applied in hitherto difficult organocatalytic *anti*-selective Mannich reactions, thereby expanding the synthetic scope of this system.



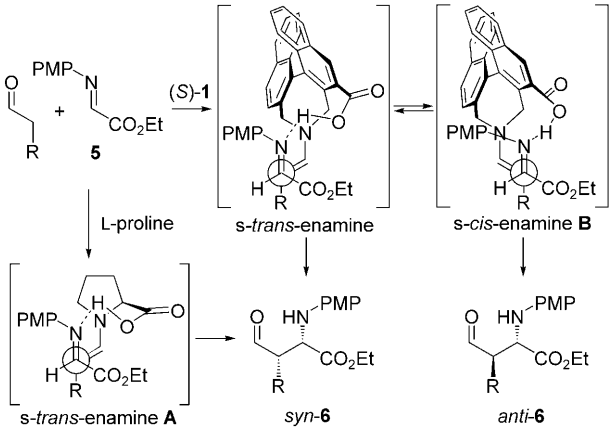
(*S*)-**1** (*S*)-**2**: R = Me; (*S*)-**3**: R = CF_3; (*S*)-**4**: R = C_6F_5

Results and Discussion

***anti*-Selective direct asymmetric Mannich reaction of *N*-PMP-protected α-imino esters**:[5a] The asymmetric Mannich reaction remains a powerful method for synthesizing optically active β-amino carbonyl units, which are useful chiral building blocks in a number of biologically active and pharmaceutically important compounds.[7] In particular, direct asymmetric Mannich reactions between unmodified carbonyl compounds and certain imines would be most desirable for this purpose.[8–12] Recently, small organic molecules such as proline and its derivatives were found to catalyze the reaction between aldehydes and imines to furnish *syn*- or *anti*-β-amino aldehydes as the major product, depending on the choice of catalyst.[10,11] For instance, a proline-catalyzed direct asymmetric Mannich reaction of α-imino ester **5** gives the *syn*-β-amino aldehyde *syn*-**6** preferentially with excellent enantioselectivity via the s-*trans*-enamine intermediate **A** (Scheme 1).[10] Some *anti*-selective direct asymmetric Mannich reactions catalyzed by carefully designed proline derivatives have also been reported.[11] In this context we were interested in the possibility of obtaining *anti*-**6** via the s-*cis*-enamine intermediate **B** by using an amino acid that has a longer spatial distance between the amino and carboxy groups than the proline catalyst. Our recently designed axially chiral amino acid (*S*)-**1**,[13] which catalyzes direct asymmetric aldol reactions between acetone and aldehydes, seemed to be an appropriate candidate for achieving the hitherto difficult s-*cis*-enamine intermediate **B** because there is no substituent at the position α to the amine nitrogen unlike proline. Thus, we first examined the direct Mannich reaction between 3-methylbutanal and α-imino ester **5** derived from *p*-anisidine and ethyl glyoxylate in the presence of 5 mol% of (*S*)-**1**. As expected, the reaction proceeded in dioxane at room temperature to afford a substantial amount of the *anti*-β-amino aldehyde *anti*-**6** (R = *i*Pr), albeit with low diastereoselectivity (Table 1, entry 1). This low *anti* selectivity prompted us to modify (*S*)-**1** and develop new axially chiral amino sulfonamides (*S*)-**2**, (*S*)-**3**, and (*S*)-**4** with an acidic proton further from the secondary amino group than the carboxy group in (*S*)-**1**. The imine activated by the remote acidic proton would be expected to react preferentially with the s-*cis*-enamine intermediate **C** to give the desired *anti* isomer, *anti*-**6** (Scheme 2).

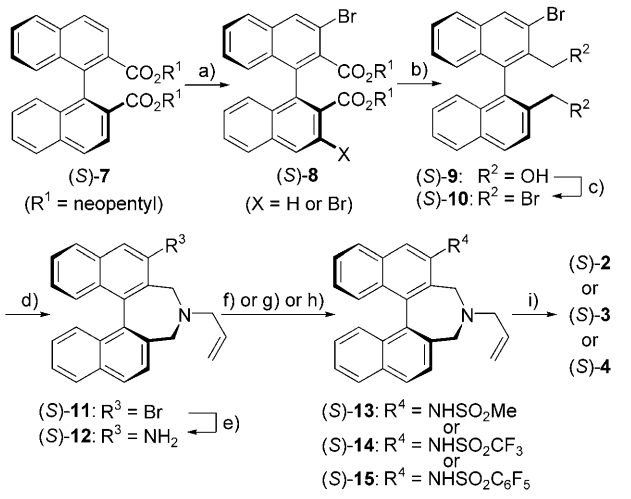


Scheme 2. Possible transition-state model for the *anti*-selective direct asymmetric Mannich reaction catalyzed by (*S*)-**3**.



Scheme 1. Proposed transition-state models for the direct asymmetric Mannich reactions catalyzed by L-proline and (*S*)-**1**.

The requisite binaphthyl-based amino sulfonamides (*S*)-**2**–**4** were prepared in a seven-step sequence from dineopentyl (*S*)-1,1′-binaphthyl-2,2′-dicarboxylate [(*S*)-**7**], as shown in Scheme 3.[13] Bromination of the neopentyl ester (*S*)-**7** was achieved by *ortho* magnesiation using magnesium bis(2,2,6,6-tetramethylpiperamide) [$Mg(tmp)_2$] followed by trapping with bromine.[14] Reduction of the resulting mixture of di- and monobrominated esters (*S*)-**8** with $LiAlH_4$ gave the corresponding diol (*S*)-**9** (42% yield over two steps) after chromatographic separation. Treatment of (*S*)-**9** with BBr_3 afforded the tribromo compound (*S*)-**10** in a yield of 86%, which was converted with allylamine into the cyclic amine (*S*)-**11** in a yield of 89%.[13] Amination of (*S*)-**11** with benzophenone imine and [$Pd_2(dba)_3$] shown in the legend to Scheme 3 gave diamine (*S*)-**12** in a yield of 93%.[15] Treatment of (*S*)-**12** with the corresponding sulfonylating agents gave methanesulfonamide (*S*)-**13**, trifluoromethanesulfonamide (*S*)-**14**, and pentafluorophenylsulfonamide (*S*)-**15**. Finally, $Pd(OAc)_2$-catalyzed deallylation of (*S*)-**13**–**15** provided



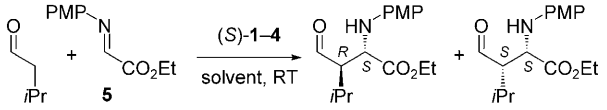
Scheme 3. Synthesis of (*S*)-**2**–(*S*)-**4**. a) $[Mg(tmp)_2]$, THF, Br_2; b) $LiAlH_4$, THF; c) BBr_3, CH_2Cl_2; d) allylamine, CH_3CN; e) $Ph_2C{=}NH$, $[Pd_2(dba)_3]$, BINAP, NaO*t*Bu, 1 N HCl, THF; f) $MeSO_2Cl$, CH_2Cl_2; g) Tf_2O, CH_2Cl_2; h) $C_6F_5SO_2Cl$, CH_2Cl_2; i) $Pd(OAc)_2$, PPh_3, *N*,*N*′-dimethylbarbituric acid, CH_2Cl_2.

the binaphthyl-based amino sulfonamides (*S*)-**2**–**4**, respectively (yields of 58% for (*S*)-**2**, 78% for (*S*)-**3** and 42% for (*S*)-**4** over two steps).

The efficiency of these new catalysts (*S*)-**2**–**4** was evaluated under identical conditions to those used in the reaction performed with (*S*)-**1**, except for the use of lower catalyst loadings (2 mol%). Unfortunately, the reaction with (*S*)-**2** resulted in a significant reduction in reactivity and enantioselectivity, although moderate *anti* selectivity was observed (Table 1, entry 2). In marked contrast, however, switching the catalyst from (*S*)-**2** to (*S*)-**3** or (*S*)-**4**, which contain a more acidic sulfonamide group, enhanced both the reactivity and stereoselectivity of the reaction (Table 1, entries 3 and 4). We then examined the effect of solvent 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 than dioxane in terms of chemical yield and stereoselectivity (Table 1, entries 5–8). In toluene, however, although the reaction proceeded smoothly and with excellent enantioselectivity, a slight decrease in *anti* selectivity was observed (Table 1, entry 9). Thus, dioxane was identified as the solvent of choice.

The reactions between other aldehydes and α-imino esters in the presence of a catalytic amount of (*S*)-**3** were carried out in dioxane at room temperature and the results are summarized in Table 2. In the case of primary alkyl aldehydes, 1 mol% of (*S*)-**3** was sufficient to produce the corresponding β-amino aldehydes in high yields (>92%) and with nearly complete enantioselectivities (99% *ee*) and excellent *anti* selectivities (>11:1) (Table 2, entries 1, 3, and 7). The catalyst loading could be reduced to less than 1 mol% of (*S*)-**3**, but gave slightly decreased yields and stereoselectivities (Table 2, entries 2 and 6). The reaction at a higher concentration (1 M) gave the same result, but with a shorter reaction time (Table 2, entry 4). The amount of aldehyde could be reduced to 1 equiv without significant loss of yield when the reaction was carried out with a higher concentration of the catalyst (Table 2, entry 5). Although the reaction of the sterically hindered 3,3-dimethylbutanal required a higher catalyst loading and proceeded in moderate yield, optimal *anti* selectivity and enantioselectivity were observed (Table 2, entry 9). When the α-imino ester was added slowly using a syringe pump, the reaction of 3,3-dimethylbutanal resulted in a somewhat improved yield (Table 2, entry 10). This reaction system could also be applied to α-imino allyl or *tert*-butyl esters (Table 2, entries 11 and 12).

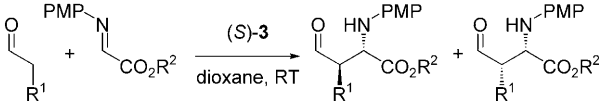
Table 1. *anti*-Selective Mannich reactions between 3-methylbutanal and α-imino ester **5** catalyzed by (*S*)-**1**–(*S*)-**4**.



Entry	Catalyst	*t* [h]	Solvent	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	(*S*)-**1**[e]	20	dioxane	60	1:1.1	86
2	(*S*)-**2**	24	dioxane	11	3.8:1	72
3	(*S*)-**3**	0.5	dioxane	93	>20:1	>99
4	(*S*)-**4**	24	dioxane	65	8.8:1	>99
5	(*S*)-**3**	6	THF	38	>20:1	99
6	(*S*)-**3**	6	EtOAc	72	8.3:1	90
7	(*S*)-**3**	6	DMSO	20	6.3:1	97
8	(*S*)-**3**	6	$CHCl_3$	70	9.1:1	98
9	(*S*)-**3**	0.5	toluene	98	9.1:1	>99

[a] The reaction of 3-methylbutanal (0.75 mmol) and α-imino ester **5** (0.25 mmol) was carried out in solvent (2.5 mL) in the presence of catalyst (*S*)-**1**–**4** (0.005 mmol) at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] The *ee* of the *anti* isomer was determined by HPLC analysis using a chiral column (Chiralpak AS-H, Daicel Chemical Industries, Ltd.). [e] With 0.0125 mmol of (*S*)-**1**.

Table 2. *anti*-Selective Mannich reactions between various aldehydes and α-imino esters catalyzed by (*S*)-**3**.



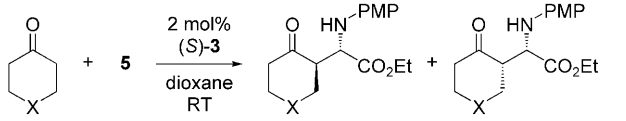
Entry	R^1	R^2	Cat. [mol%]	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Me	Et	1	0.5	93	13:1	>99
2	Me	Et	0.2	22	82	11:1	97
3	Bu	Et	1	4	93	>20:1	99
4[e]	Bu	Et	1	0.5	93	20:1	>99
5[e,f]	Bu	Et	1	0.5	86	16:1	99
6	Bu	Et	0.5	8	92	>20:1	97
7	Bn	Et	1	4	92	11:1	>99
8	*i*Pr	Et	2	0.5	93	>20:1	>99
9	*t*Bu	Et	5	16	42	>20:1	>99
10[g]	*t*Bu	Et	5	38	68	20:1	99
11	*i*Pr	allyl	2	0.5	99	16:1	>99
12	*i*Pr	*t*Bu	2	0.5	99	16:1	>99

[a] Unless otherwise specified, the reaction between the aldehyde (0.75 mmol) and the α-imino ester (0.25 mmol) was carried out in dioxane (2.5 mL) in the presence of (*S*)-**3** at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] The *ee* of the *anti* isomer was determined by HPLC analysis using a chiral column. [e] With 250 μL of dioxane. [f] With 1 equiv of hexanal (0.25 mmol). [g] α-Imino ester **5** was added slowly using a syringe pump. Details are given in the Supporting Information.

Note that self-aldol products were not detected even in the presence of excess aldehyde (3 equiv).

We next turned our attention to the *anti*-selective Mannich reactions of ketones with α-imino ester **5** (Table 3).[11] The reactions of the six-membered cyclic ketones with catalyst (*S*)-**3** proceeded smoothly to give satisfactory results in terms of both reactivity and selectivity (Table 3, entries 1–3). The observed high levels of stereoselectivity and absolute stereochemistry in the reactions of the ketones could be explained by a transition-state model similar to the one proposed for the reaction of aldehydes in Scheme 2.

Table 3. *anti*-Selective Mannich reactions between ketones and α-imino ester **5** catalyzed by (*S*)-**3**.

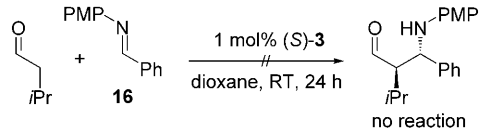


Entry	X	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	CH_2	93	10:1	98
2	O	81	7.4:1	98
3	S	86	7.8:1	99

[a] Unless otherwise specified, the reactions between the ketones (0.75 mmol) and α-imino ester **5** (0.25 mmol) were carried out in dioxane (2.5 mL) in the presence of (*S*)-**3** (0.005 mmol) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* of the *anti* isomer was determined by HPLC analysis using a chiral column.

***anti*-Selective direct asymmetric Mannich reactions of *N*-Boc-protected aromatic imines**:[5b] Proline-catalyzed direct asymmetric Mannich reactions between *N*-PMP-protected aromatic imines and aldehydes are known to give the corresponding *syn*-β-amino-β-aryl aldehydes preferentially with excellent enantioselectivity.[10d,f,g] To the best of our knowledge, however, a general and selective method for obtaining the opposite *anti*-β-amino-β-aryl aldehyde remains unattainable, although a few exceptional examples that give *anti*-Mannich adducts have been reported using an *N*-Boc-protected aromatic imine.[11m,r] Accordingly, we next turned our attention to the reaction of aromatic imines and attempted to expand the substrate scope of the present *anti*-selective Mannich reaction catalyzed by (*S*)-**3**. Unfortunately, however, the reaction between the *N*-PMP-protected aromatic imine **16** and 3-methylbutanal did not proceed under the optimized conditions used for the reaction of *N*-PMP-protected α-imino esters, probably due to the low reactivity of the aromatic imine **16** (Scheme 4). We then decided to explore the *anti*-selective Mannich reaction by using the more reactive *N*-Boc-protected aromatic imines, which were successfully utilized by List[10w] and Córdova[10x] and their co-workers in the *syn*-selective Mannich reaction catalyzed by proline.

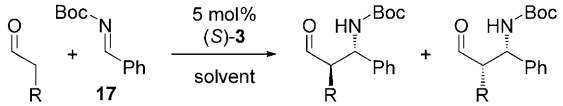
We first examined the reaction between the benzaldehyde-derived *N*-Boc-imine **17** and propanal in the presence of 5 mol% of (*S*)-**3** in various solvents at room temperature and the results are summarized in Table 4. The reaction in



Scheme 4. Reaction between 3-methylbutanal and the *N*-PMP-protected aromatic imine **16**.

dioxane gave predominantly the desired *anti* adduct in moderate yield and with excellent enantioselectivity (Table 4, entry 1). The use of DMSO resulted in a significant decrease in both the *anti* selectivity and the enantioselectivity (Table 4, entry 2). In the case of DMF, a slightly improved *anti* selectivity was observed (Table 4, entry 3). When acetonitrile and chloroform were used, the *anti* adduct was obtained in good yields and with excellent enantioselectivities (Table 4, entries 5 and 6). However, the use of 3-methylbutanal as the substrate instead of propanal lowered the yield (Table 4, entry 7). Accordingly, further optimization of the reaction conditions was investigated. The addition of water slightly increased the yield and the *anti* selectivity (Table 4, entry 8). Switching the solvent from acetonitrile to chloroform and lowering the reaction temperature did not improve the yield, although a higher *anti* selectivity was observed (Table 4, entries 9 and 10). Because a similar low yield of the *anti* adduct was obtained even with a higher catalyst loading (10 mol%) (Table 4, entry 11), we suspected that the low yield might be due to catalyst deactivation by *N*-Boc-imine **17**. Indeed, when a solution of *N*-Boc-imine **17** was slowly added to the reaction mixture using a syringe pump, the *anti* adduct was obtained in good yield with satis-

Table 4. *anti*-Selective Mannich reactions of *N*-Boc-protected imine **17** catalyzed by (*S*)-**3**.



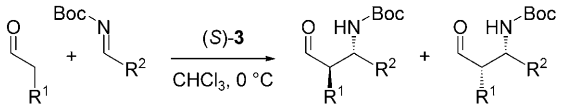
Entry	R	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Me	dioxane	RT	3.5	53	4.4:1	97
2	Me	DMSO	RT	18	98	2.3:1	53
3	Me	DMF	RT	24	70	5.5:1	95
4	Me	CH_3CN	RT	4.5	52	5.5:1	99
5	Me	CH_3CN	RT	24	78	5.1:1	99
6	Me	$CHCl_3$	RT	4	80	5.1:1	99
7	*i*Pr	CH_3CN	RT	24	30	5.0:1	99
8[e]	*i*Pr	CH_3CN	RT	24	37	6.7:1	99
9	*i*Pr	$CHCl_3$	RT	24	32	8.6:1	99
10	*i*Pr	$CHCl_3$	0	24	31	11:1	99
11[f]	*i*Pr	$CHCl_3$	0	24	30	11:1	99
12[g]	*i*Pr	$CHCl_3$	0	5	77	11:1	99

[a] Unless otherwise specified, the reactions between the aldehydes (0.75 mmol) and *N*-Boc-protected imine **17** (0.25 mmol) were carried out in solvent (250 μL) in the presence of (*S*)-**3** (5 mol%). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* of the *anti* isomer was determined by HPLC analysis using a chiral column (Chiralpak AS-H, Daicel Chemical Industries, Ltd.). [e] H_2O (5 mol%) was added. [f] With 10 mol% of (*S*)-**3**. [g] *N*-Boc-protected imine **17** was added slowly using a syringe pump. Details are given in the Supporting Information.

factory *anti* selectivity and enantioselectivity (Table 4, entry 12).

We then applied our system to various aldehydes and *N*-Boc-protected aromatic imines. As shown in Table 5, under the optimized conditions, the corresponding *anti* Mannich adducts were obtained with good *anti* selectivities and excellent enantioselectivities in all the cases examined. When a solution of *N*-Boc-imine **17** was slowly added to the reaction mixture using a syringe pump, the catalyst loading could be reduced to 1 mol% without loss of stereoselectivity (Table 5, entry 4 vs. 3). In addition, an aliphatic *N*-Boc-imine was found to be suitable for the present reaction system (entry 10).

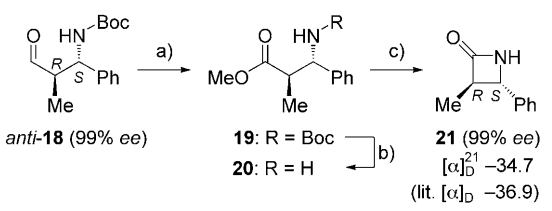
Table 5. *anti*-Selective Mannich reactions between various aldehydes and *N*-Boc-protected imines catalyzed by (*S*)-**3**.



Entry	R^1	R^2	Cat. [mol%]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	Me	Ph	5	92	7.7:1	99
2	*i*Pr	Ph	5	77	8.8:1	99
3[e]	Bu	Ph	5	93	16:1	99
4[f]	Bu	Ph	1	88	15:1	99
5	Bn	Ph	5	80	15:1	99
6	Bu	4-$MeOC_6H_4$	5	91	8.2:1	98
7	Bu	4-ClC_6H_4	5	78	11:1	99
8	Bu	2-furyl	5	88	7.5:1	99
9	Bu	3-pyridyl	5	92	16:1	99
10[e,g]	Me	cyclohexyl	10	66	>20:1	99

[a] Unless otherwise specified, the reactions between the aldehydes (0.75 mmol) and the *N*-Boc-protected imines (0.25 mmol) were carried out in $CHCl_3$ in the presence of (*S*)-**3** at 0°C. The *N*-Boc-protected imines were added by using a syringe pump over 4 h. Stirring was then continued for 1 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] The *ee* of the *anti* isomer was determined by HPLC analysis using a chiral column. Details are given in the Supporting Information. [e] Stirred for 2 h after addition of the *N*-Boc-protected imine. [f] The *N*-Boc-protected imine was added by using a syringe pump over 12 h. Stirring was then continued for 1 h. [g] With 1.25 mmol of propanal.

To assign the absolute configurations of the *anti*-β-amino aldehydes obtained and to extend the synthetic utility of this asymmetric transformation, an optically enriched *anti*-β-amino aldehyde *anti*-**18** was successfully converted into the corresponding β-lactam (Scheme 5). Thus, treatment of *anti*-**18** with $NaClO_2$ followed by the addition of $TMSCHN_2$ resulted in the clean formation of the corresponding methyl ester **19** (97% yield over two steps). Subsequent *N*-Boc deprotection and treatment of the resulting β-amino ester **20** with LDA gave β-lactam **21** without loss of enantiopurity (82% yield over two steps).[16] By comparison of the optical rotation of β-lactam **21** with the literature value,[17] the absolute configuration of *anti*-β-amino aldehyde *anti*-**18** was determined to be (1*S*,2*R*).

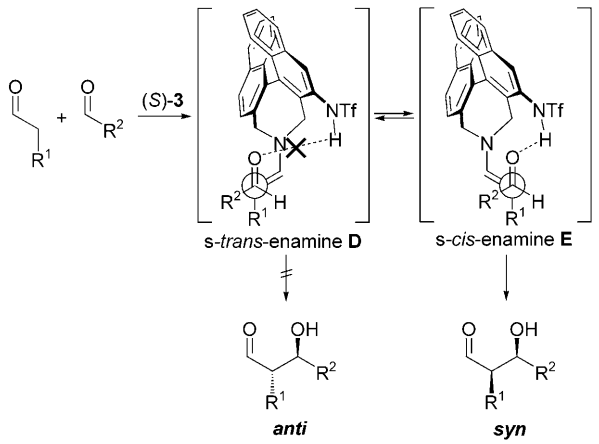


Scheme 5. Determination of the absolute configuration of *anti*-**18**. a) i) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*BuOH, H_2O; ii) $TMSCHN_2$, toluene, MeOH; b) TFA, CH_2Cl_2; c) LDA, THF.

***syn*-Selective direct asymmetric cross-aldol reaction between aldehydes**:[6] The aldol reaction is one of the most fundamental carbon–carbon bond-forming reactions.[18] However, the cross-aldol reaction between two different aldehydes is often known to be problematic because of undesired side-reactions, including dehydration of the product, self-aldol reactions, and multiple additions of the enolate to the aldol product. To date, however, several cross-aldol reactions performed with aldehyde-derived metal enolates, including silyl enol ethers as nucleophiles and/or slowly or non-enolizable aldehydes as electrophiles, have been reported.[19–26] Furthermore, some rare examples of the catalytic asymmetric version of this reaction have recently been developed.[27–37] For instance, diastereo- and enantioselective cross-aldol reactions between aldehydes and silyl enol ethers were first accomplished by Denmark and co-workers with chiral Lewis base catalysts,[27] and recently Kobayashi and co-workers demonstrated chiral Lewis acid catalyzed diastereo- and enantioselective reactions using aldehyde-derived enecarbamates as activated aldehyde nucleophiles.[28] Through these methods, both *syn* and *anti* diastereomers 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 unmodified aldehydes, first reported by MacMillan and co-workers, provide predominantly *anti*-aldol adducts,[29–36] albeit with a few exceptions giving the *syn* adducts.[29d,38] In this context, we were interested in the possibility of developing a *syn*-selective direct cross-aldol reaction between two different aldehydes using a chiral organocatalyst.

Our strategy was based on the observation that a direct asymmetric Mannich reaction can be catalyzed by the amino sulfonamide (*S*)-**3** to give predominantly the *anti* product, which is a minor diastereomer in the proline-catalyzed reaction.[5a] Because it would be difficult for s-*trans*-enamine **D**, which is generated from a donor aldehyde and (*S*)-**3**, to react with an acceptor aldehyde activated by the distal acidic proton of the triflamide of (*S*)-**3**, the cross-aldol reaction catalyzed by (*S*)-**3** would be expected to proceed through the s-*cis*-enamine intermediate **E** to give the hitherto unattainable *syn* product, as shown in Scheme 6.

We first examined the reaction between 4-nitrobenzaldehyde and hexanal in the presence of 5 mol% of (*S*)-**3** in various solvents at room temperature. In this reaction, large solvent effects were observed and the results are summarized in Table 6. The reaction in dioxane, toluene, or CH_2Cl_2 gave the cross-aldol product **22** in poor yield and with low

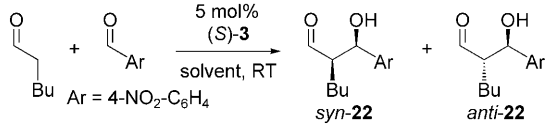


Scheme 6. Possible transition-state model for the *syn*-selective direct asymmetric aldol reaction catalyzed by (*S*)-**3**.

stereoselectivity (Table 6, entries 1–3). In the case of acetonitrile, only a trace amount of **22** was observed, although *syn*-**22** was slightly dominant over *anti*-**22** (Table 6, entry 4). The use of DMSO, which is an ordinary solvent for aldol reactions catalyzed by proline or related organocatalysts, led to the formation of the desired *syn*-**22** in a highly diastereo- and enantioselective manner in low yield (Table 6, entry 5). When the amide solvents DMF and *N*-methylpyrrolidone (NMP) were used, the desired *syn*-**22** was obtained in moderate yields with excellent diastereo- and enantioselectivities (Table 6, entries 6 and 7). A longer reaction time resulted in a slight decrease in both the diastereo- and enantioselectivity but a higher yield (Table 6, entry 8). On the other hand, the reactions conducted at higher concentrations were found to give *syn*-**22** in improved yields without loss of stereoselectivity (Table 6, entries 9 and 10). In addition, the reactions with other amide solvents, 1,3-dimethyl-2-imidazolidinone (DMI) and *N*,*N*-dimethylacetamide (DMAc), provided similar results (Table 6, entries 11 and 12). The observed large solvent effect on the selectivity of the reaction might be attributed to the change in the pK_a of the acidic proton of catalyst (*S*)-**3**, depending on the solvent used.[39] When the amino acid catalyst (*S*)-**1** was used instead of (*S*)-**3**, a low diastereoselectivity was observed, as expected from our previous studies of the Mannich reaction (Table 6, entry 13 and Table 1, entry 1).[5a]

With the optimized reaction conditions, the *syn*- and enantioselective direct cross-aldol reactions of several other reactive acceptor aldehydes with donor aliphatic aldehydes were examined (Table 7). The reactions of 4-nitrobenzaldehyde with various aliphatic aldehydes gave the corresponding *syn*-aldol adducts in moderate-to-good yields and with excellent diastereo- and enantioselectivities (Table 7, 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 7, 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 7, entries 7–9). The reaction catalyzed by (*S*)-**3** was also applicable to phenylglyoxal in its monohydrate form (Table 7, entry 10). In all cases, the reactions catalyzed by (*S*)-**3** were complementary to the proline-catalyzed reactions in terms of the *syn*/*anti* selectivity. In addition, only trace

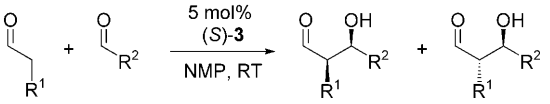
Table 6. *syn*-Selective aldol reaction of 4-nitrobenzaldehyde with hexanal catalyzed by (*S*)-**3**.



Entry	Solvent	Conc. [M]	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
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
11	DMI	0.25	36	65	>20:1	98
12	DMAc	0.25	36	77	>20:1	98
13[e]	DMF	0.1	30	50	1:1.6	85 (94)[f]

[a] The reactions of 4-nitrobenzaldehyde (0.25 mmol) with hexanal (0.5 mmol) in different solvents were carried out in the presence of (*S*)-**3** (0.0125 mmol) at room temperature. [b] Isolated yield after acetalization of the product with 2,2-dimethyl-1,3-propanediol. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* of *syn*-**22** was determined by HPLC using a chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.). [e] With catalyst (*S*)-**1**. [f] The *ee* of *anti*-**22**.

Table 7. *syn*-Selective aldol reactions between various aldehydes catalyzed by (*S*)-**3**.



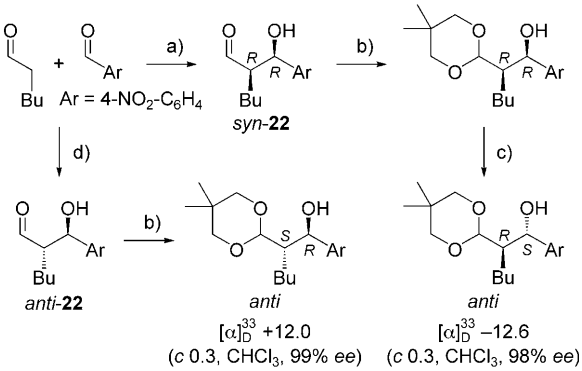
Entry	R^1	R^2	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	Me	4-NO_2-C_6H_4	36	73	12:1	98
2	Bu	4-NO_2-C_6H_4	36	77	>20:1	99
3	Bn	4-NO_2-C_6H_4	36	80	>20:1	98
4	allyl	4-NO_2-C_6H_4	36	79	>20:1	98
5	*i*Pr	4-NO_2-C_6H_4	40	61	>20:1	96
6	Bu	Ph	36	22	6.3:1	92
7	Bu	C_6F_5	78	73	>20:1	99
8	Bu	4-pyridyl	69	71	6.4:1	94
9[e]	Bu	EtO_2C	4.5	99[g]	2.3:1	95
10[f]	Bu	benzoyl	20	91[g]	>20:1	96

[a] Unless otherwise specified, the reactions of the acceptor aldehydes (0.25 mmol) with the donor aldehydes (0.5 mmol) in NMP (250 μL) were carried out in the presence of (*S*)-**3** (0.0125 mmol) at room temperature. [b] Isolated yield after acetalization or reduction of the product. Details are given in the Supporting Information. [c] Determined by ^{1}H NMR spectroscopy. [d] The *ee* of the *syn* product was determined by HPLC using a chiral column (Chiralpak AS-H, AD-H, Chiralcel OD-H or OJ-H, Daicel Chemical Industries, Ltd.). Details are given in the Supporting Information. [e] With 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] Isolated yield.

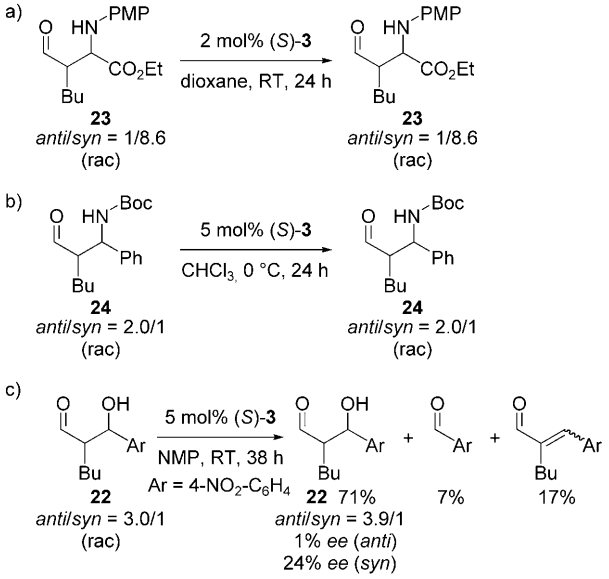
amounts of byproducts arising from dimerization of donor aldehydes were observed. Note that more than 95% of (*S*)-**3** was recovered unchanged after column chromatography.

The absolute configuration of the *anti*-aldol product *anti*-**22** obtained in the L-proline catalyzed reaction was deduced to be (2*S*,3*R*).[29a] Based on this information, the absolute configuration of the *syn*-aldol product *syn*-**22** obtained from the reaction of hexanal and 4-nitrobenzaldehyde catalyzed by (*S*)-**3** was determined to be (2*R*,3*R*) by converting it into the *anti*-aldol product using standard Mitsunobu conditions and by comparison of the signs of the optical rotation (Scheme 7). This absolute configuration of *syn*-**22** agrees with the prediction based on the transition-state model shown in Scheme 6.

Reaction mechanism: To understand the origin of the diastereoselectivity observed in the reactions catalyzed by (*S*)-**3**, diastereomixtures of Mannich adducts **23** (*anti*/*syn* = 1:8.6) and **24** (*anti*/*syn* = 2:1) were treated with (*S*)-**3** under the reaction conditions. Both diastereomixtures were recovered quantitatively with no change in the diastereomeric ratios observed in either case (Scheme 8a and b). Because the two *anti*/*syn* ratios remained below that obtained in the Mannich reactions catalyzed by (*S*)-**3**, the *anti* selectivity must originate from the C–C bond-forming step, not from isomerization between the *anti* and *syn* adducts under the reaction conditions.[11m] On the other hand, when the diastereomixture of aldol adduct **22** (*anti*/*syn* = 3.0:1) was treated with (*S*)-**3** under the reaction conditions, the retro-aldol and dehydration products were obtained and 71% of **22** was recovered (Scheme 8c).[40] Interestingly, the ratio of *syn*-**22** to *anti*-**22** in the recovered diastereomixture was found to have decreased. Moreover, the recovered *syn*-**22** was optically enriched, with (2*S*,3*S*)-*syn*-**22**, which is the minor enantiomer in the aldol reaction catalyzed by (*S*)-**3**, predominant. This result suggests that the major stereoisomer (2*R*,3*R*)-*syn*-**22** obtained in the aldol reaction might be consumed selectively through the same transition state as that which gives (2*R*,3*R*)-*syn*-**22** itself. This hypothesis is also consistent with the observation that both the *syn* selectivity and the enantioselectivity of the aldol product decreased with longer reaction times (Table 6, entry 8 vs. 7). As a consequence, the above observations indicate that the diastereoselection originates from the C–C bond-formation step in both the Mannich and the aldol reactions catalyzed by (*S*)-**3**.



Scheme 7. Determination of the absolute configuration of *syn*-**22**. a) 5 mol% (*S*)-**3**, NMP; b) 2,2-dimethylpropane-1,3-diol, $CH(OEt)_3$, PTSA, CH_2Cl_2; c) i) 4-nitrobenzoic acid, DEAD, PPh_3, THF; ii) 1 N NaOH, MeOH; d) L-proline (30 mol%), DMF.



Scheme 8. Behavior of the reaction products under the reaction conditions.

Based on the stereochemistry observed in the Mannich and aldol reactions catalyzed by (*S*)-**3**, transition-state models can be proposed, as shown in Figure 1.[11m] In each case, the *Si* face of the imines or the *Re* face of the aldehydes approaches the enamine intermediate, as directed by the distant acidic proton of the triflamide group, and consequently the C–C bond-forming reaction takes place on the *Si* face of the s-*cis*-enamine in a highly diastereo- and enantioselective fashion to give *anti*-Mannich or *syn*-aldol adducts, respectively (Figure 1a and b). Very recently we reported a direct asymmetric aminoxylation of aldehydes with nitrosobenzene catalyzed by (*S*)-**3**, which gave almost exclusively the aminoxylated product with an *S* configuration (Scheme 9).[41] The observed stereochemistry can be rationalized by an analogous transition-state model in which nitrosobenzene approaches the *Si* face of the s-*cis*-enamine, as directed by the triflamide group (Figure 1c). Because activation of nitrosobenzene by strong acids such as carboxylic acid and tetrazole is necessary to obtain the aminoxylation product,[42] only a combination of the s-*cis*-enamine and nitrosobenzene activated on the *Si* face of the enamine can provide the *S* isomer. This observation strongly suggests the existence of the s-*cis*-enamine intermediate in the Mannich and aldol reactions catalyzed by (*S*)-**3** reported herein.

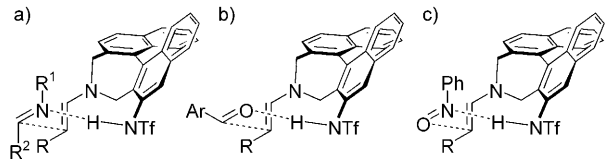
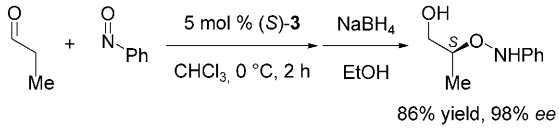


Figure 1. Transition-state models for reactions catalyzed by (*S*)-**3**.



Scheme 9. Direct asymmetric aminoxylation of propanal with nitrosobenzene catalyzed by (*S*)-**3**.

Conclusions

We have designed and synthesized a novel binaphthyl-based axially chiral amino sulfonamide, which has been utilized as a catalyst in the direct asymmetric Mannich and aldol reactions of aldehydes. The reactions reported herein are complementary to the proline-catalyzed reactions in terms of diastereoselectivity and hence represent a rare example of an *anti*-selective Mannich reaction using *N*-Boc-protected imines as well as of a highly *syn*- and enantioselective direct cross-aldol reaction with a non-proline-derived artificial organocatalyst. In particular, the synthetic utility of the *anti*-selective Mannich reaction has been significantly expanded by the use of *N*-Boc-protected aromatic imines. Thus, our axially chiral amino sulfonamide represents a new catalyst design in enamine catalysis.

Experimental Section

General procedure for the catalytic asymmetric Mannich reactions between *N*-PMP-protected iminoacetates and aldehydes: The corresponding aldehyde (0.75 mmol) and *N*-PMP-protected iminoacetate (0.25 mmol) were added in this order to a stirred solution of chiral amino sulfonamide (*S*)-**3** (1.1 mg, 0.0025 mmol) in dioxane (2.5 mL) at room temperature. After stirring at room temperature for the time indicated in Table 2, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 20:1 as eluent) to afford the corresponding Mannich adduct.

For full details of instruments used, experimental procedures, and characterization data obtained, please see the Supporting Information.

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