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Design and synthesis of a biphenyl-based chiral amino sulfonamide with high catalytic performance in Mannich reactions

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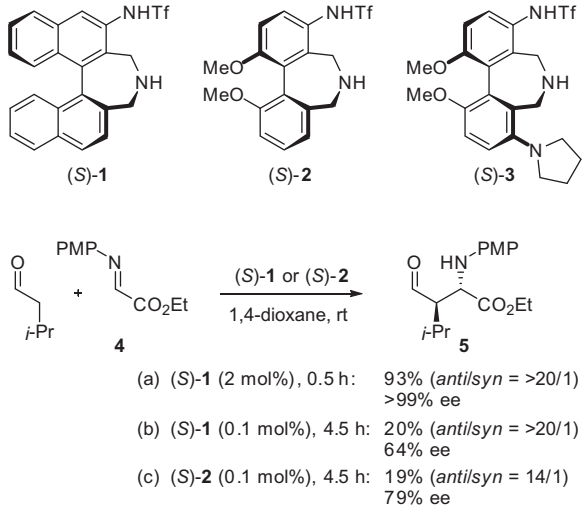
ABSTRACT

A biphenyl-based amino sulfonamide was designed to improve the intrinsic low catalytic activity of amine organocatalysts. The newly synthesized amino sulfonamide catalyst promoted the Mannich reaction in a highly enantioselective fashion and a remarkable catalyst turnover number was achieved.

Asymmetric enamine catalysis has been an active area of research for over a decade. A large number of chiral amine catalysts have been developed and used in a variety of asymmetric α-functionalizations of aldehydes and ketones.[1] In most cases, however, such transformations require relatively large amounts of amine catalyst (5∼20 mol %),[2] probably due to the catalyst consumption or deactivation by undesired reactions of amine catalysts with reactive electrophiles as well as with reaction products and side products having a carbonyl moiety.[3] Accordingly, one major challenge in this field has been the development of robust catalytic cycles that allow for efficient and rapid catalyst turnover. In this Letter, we report a synthesis of a biphenyl-based chiral amino sulfonamide with high catalytic performance and its application in the asymmetric Mannich reaction.

We have previously developed binaphthyl-based amino sulfonamide catalyst (*S*)-**1** for the asymmetric Mannich reaction,[4] aldol reaction,[5] and aminoxylation[6] of aldehydes. In the Mannich reaction with α-imino ester **4**, the catalyst (*S*)-**1** was found to show high levels of both reactivity and stereoselectivity.[2b] For instance, in the presence of 2 mol % of (*S*)-**1**, the reaction of 3-methylbutanal with **4** proceeded smoothly to give the Mannich product **5** in good yield with virtually perfect stereoselectivity (Scheme 1a). With a decreased catalyst loading (0.1 mol %), however, a significant decrease in yield and enantioselectivity was observed (Scheme 1b). This result can be rationalized through two factors: one based on the shutdown or slowing down of the highly enantioselective pathway caused by catalyst consumption or deactivation, and the other on the incorporation of **5** with low enantiomeric excess, which was formed through the less enantioselective autocatalytic process (Scheme 2).[7,8] We hypothesized that a more nucleophilic and reactive catalyst might give the desired product without significant erosion of enantioselectivity before the catalyst decomposition or deactivation. The more nucleophilic biphenyl-based amino sulfonamide (*S*)-**2**[9] was thus employed instead of (*S*)-**1**, and the Mannich product **5** was obtained in increased enantioselectivity, albeit with low yield (Scheme 1c). We then decided to



Scheme 1. Mannich reaction of 3-methylbutanal with **4**.

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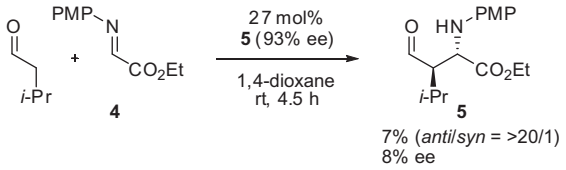


Scheme 2. Autocatalytic Mannich reaction of 3-methylbutanal with **4**.

design the more nucleophilic amino sulfonamide catalyst with the biphenyl-based amine scaffold, whose nucleophilicity can be readily tuned by introduction of electron-donating groups. It is known that the high acidity of the triflamide group is crucial to obtain high reactivity and stereoselectivity.[2b] Accordingly, both high nucleophilicity and acidity would be requirements of the catalyst design along with high performance. As shown in Figure 1, since introduction of electron-donating groups on one phenyl ring having a triflamide group would decrease the acidity of the triflamide group,[10] it seemed reasonable to introduce the electron-donating group on the other phenyl ring. Thus we designed and synthesized a novel amino sulfonamide, (*S*)-**3**, bearing a pyrrolidinyl group as an electron-donating group.

The requisite catalyst (*S*)-**3** was prepared from (*S*)-**6**, mostly according to the procedure for (*S*)-**2** as shown in Scheme 3.[9a] Introduction of a nitrogen atom was achieved by a palladium-catalyzed coupling reaction of (*S*)-**6** with benzophenone imine (1.5 equiv). The palladium-catalyzed amination of (*S*)-**7** with pyrrolidine (10 equiv) and subsequent hydrolysis gave the triamine (*S*)-**8**.[11] Treatment of (*S*)-**8** with Tf_2O afforded the triflamide (*S*)-**9**. Finally, palladium-catalyzed deallylation of (*S*)-**9** provided the biphenyl-based amino sulfonamide (*S*)-**3**.[12]

The efficiency of this new catalyst (*S*)-**3** was evaluated in the asymmetric Mannich reaction.[13] Thus, in the presence of (*S*)-**3** (0.1 mol %), the reaction of 3-methylbutanal with **4** in 1,4-dioxane at room temperature afforded the Mannich product **5** in moderate yield with high enantioselectivity (Table 1, entry 3). Although the yield was still not satisfactory, an unprecedentedly high catalytic turnover number for this type of Mannich reaction was achieved. The significant erosion of enantioselectivity could also be suppressed as expected. Both the yield and enantioselectivity were slightly improved at higher concentration (2 M) (entry 5). Only 0.4 mol % of (*S*)-**3** was sufficient to obtain the desired Mannich adduct **5** in high yield and enantioselectivity (entry 7). These results suggested that the rate of the highly enantioselective reaction catalyzed by (*S*)-**3** was much faster than that of the less enantioselective autocatalysis, and that catalyst (*S*)-**3** furnished

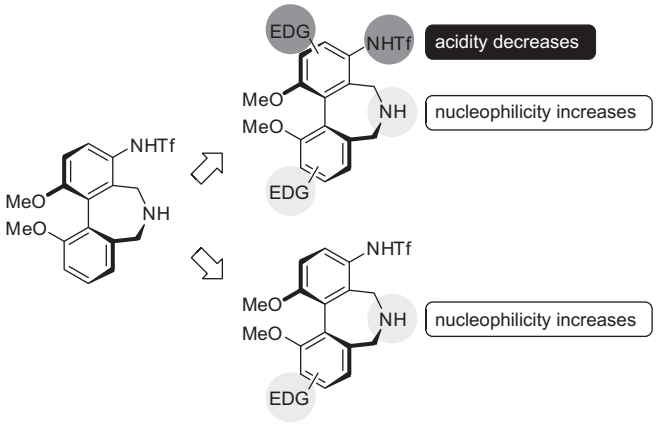
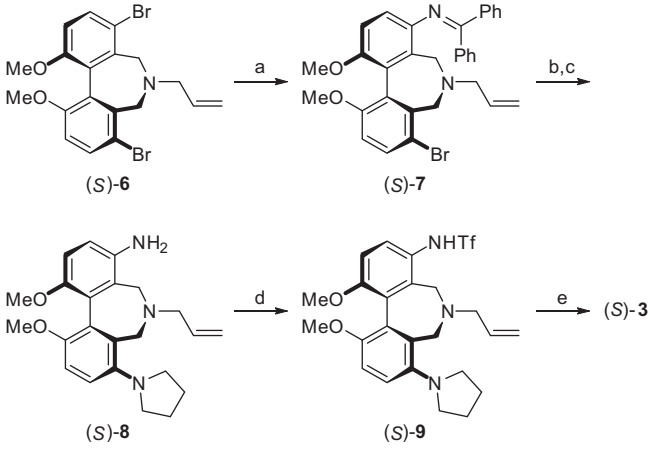
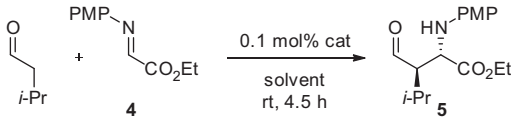


Figure 1. Design of the amino sulfonamide catalyst with increased nucleophilicity. EDG = electron-donating group.



Scheme 3. Synthesis of (*S*)-**3**. Reagents and conditions: (a) benzophenone imine, $Pd_2(dba)_3$, *rac*-BINAP, NaO*t*-Bu, toluene, 110 °C, 10 h, 68%; (b) pyrrolidine, $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, 1,4-dioxane, 100 °C, 36 h, 20%; (c) 1 M HCl, THF, 70 °C, 2 h, 89%; (d) Tf_2O, CH_2Cl_2, 0 °C to rt, 14 h, 58%; (e) NDMBA, $Pd(OAc)_2$, PPh_3, CH_2Cl_2, 30 °C, 10 h, 97%. NDMBA = 1,3-dimethylbarbituric acid.

Table 1
Mannich reaction of 3-methylbutanal with **4**[a]



Entry	Catalyst	Solvent	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	(*S*)-**1**	1,4-Dioxane (1 M)	20	>20/1	64
2	(*S*)-**2**	1,4-Dioxane (1 M)	19	14/1	79
3	(*S*)-**3**	1,4-Dioxane (1 M)	39	18/1	91
4	(*S*)-**3**	Toluene (1 M)	20	12/1	56
5	(*S*)-**3**	1,4-Dioxane (2 M)	46	12/1	93
6	(*S*)-**3**	1,4-Dioxane (4 M)	42	12/1	71
7[e]	(*S*)-**3**	1,4-Dioxane (1 M)	87	12/1	98
8[f]	(*S*)-**3**	1,4-Dioxane (1 M)	30	15/1	24

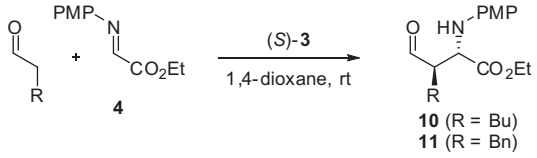
[a] Unless otherwise specified, the reaction of 3-methylbutanal (0.45 mmol) with **4** (0.15 mmol) was carried out in a solvent (150 μL) in the presence of a catalyst (0.15 μmol) at room temperature (18~22 °C) for 4.5 h.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy.
[d] Determined by HPLC analysis using a chiral column. See Ref. 14 for details.
[e] Use of 0.4 mol % of (*S*)-**3**.
[f] Reaction performed at 30 °C.

the almost optically pure adduct in a sufficient amount before the catalyst consumption or deactivation.

The reaction of hexanal (as a more reactive linear aldehyde) with **4** also proceed to completion within one hour to give the Mannich adduct **10** with high enantioselectivity in the presence of 0.3 mol % of (*S*)-**3** (Table 2, entry 1). Upon further investigation of the catalyst loading, it was found that even 0.2 mol % of (*S*)-**3** was sufficient to obtain a satisfactory yield and enantioselectivity (entry 2). While the reaction catalyzed by only 0.1 mol % of (*S*)-**3** proceeded gradually to give **10** in moderate yield with decreased enantioselectivity, an exceptionally high catalytic turnover number in the amine-catalyzed Mannich reaction was achieved (entry 3). The reaction with 3-phenylpropanal also gave the desired Mannich product **11** in high enantioselectivity (entry 4).

In summary, we have synthesized a novel biphenyl-based chiral amino sulfonamide catalyst, (*S*)-**3**, and demonstrated its effectiveness for the asymmetric Mannich reactions, in which a high catalytic turnover number for this type of reaction was achieved. We believe that the results obtained in this study are a valuable guide

Table 2
Mannich reaction of linear aldehydes with **4**[a]



Entry	R	(*S*)-**3** (mol %)	Time (h)	Yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	Bu	0.3	1	82	5.3/1	99
2	Bu	0.2	1.5	67	4.8/1	95
3	Bu	0.1	4	55	3.4/1	84
4	Bn	0.2	1.5	60	4.2/1	91

[a] Unless otherwise specified, the reaction of an aldehyde (0.45 mmol) with **4** (0.15 mmol) was carried out in 1,4-dioxane (150 μL) in the presence of (*S*)-**3** at room temperature (18∼22 °C).
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Determined by HPLC analysis using a chiral column.

in designing subsequent generations of related catalysts. Detailed mechanistic studies and further application of our catalyst in organocatalytic reactions are currently underway.

Acknowledgment

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13. *Typical procedure for the asymmetric Mannich reaction between aldehydes and ethyl (4-methoxyphenylimino)acetate (**4**):* To a stirred solution of chiral amino sulfonamide (*S*)-**3** (0.071 mg, 0.15 μmol) in 1,4-dioxane (75 μL) were added 3-phenylpropanal (48 μl, 0.45 mmol) and ethyl (4-methoxyphenylimino)acetate (**4**) (31 mg, 0.15 mmol) in this order at room temperature. After stirring at room temperature for 4.5 h, the mixture was directly purified by flash column chromatography on silica gel (hexane/EtOAc = 7/1) to afford the Mannich adduct **5** [(20 mg, 0.069 mmol, 46% yield, *anti*/*syn* = 12:1, 93% ee (*anti*)].
14. HPLC analysis of **5**: Daicel Chiralpak AS-H, hexane/isopropanol = 100:1, flow rate = 1.0 mL/min, λ = 240 nm, retention time = 30.6 min (major) and 55.9 min (minor).