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Direct asymmetric aminoxylation reaction catalyzed by a binaphthyl-based chiral amino sulfonamide with high catalytic performance

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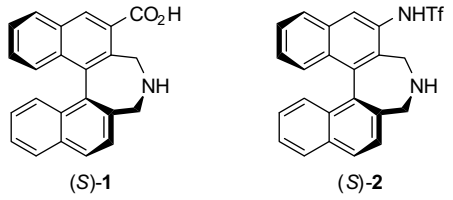
ABSTRACT

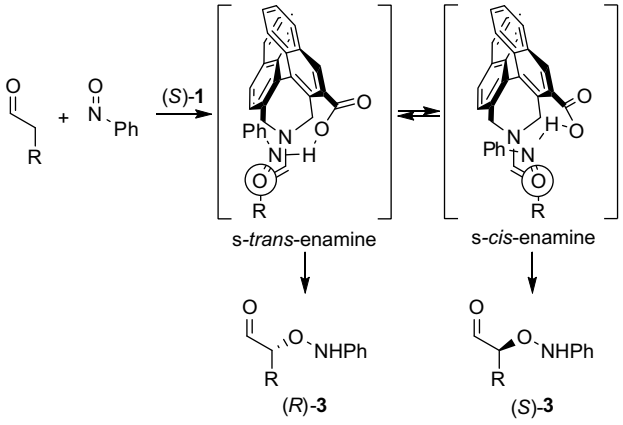
A binaphthyl-based amino sulfonamide (*S*)-2 was applied to the direct asymmetric aminoxylation of aldehydes with nitrosobenzene. The reaction catalyzed by (*S*)-2 proceeded smoothly to give the aminoxylated product in good yield with excellent enantioselectivity. This method represents a rare example of the highly enantioselective aminoxylation by a non-proline type catalyst with high catalytic performance.

Aromatic nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry,[1] and various catalytic asymmetric reactions, such as aminoxylation,[2–5] hydroxyamination,[4–7] and the nitroso Diels–Alder reaction[8] have recently been developed by exploiting their unique properties. In this area, highly enantioselective aminoxylation reactions of aldehydes and ketones using nitrosobenzene were realized by organocatalysts through the in situ generation of the reactive enamine.[3] To the best of our knowledge, however, most of the reported organocatalysts for the aminoxylation reaction are proline and its derivatives, and structurally different catalysts have not yet been studied. Very recently, we have reported a direct asymmetric aminoxylation reaction of aldehydes with nitrosobenzene by using binaphthyl-based amino acid catalysts represented by (*S*)-**1** (Fig. 1).[9] Although amino acid catalysts of type (*S*)-**1**[10] promoted the aminoxylation of aldehydes smoothly, they were found to be less effective in terms of enantioselectivity. Due to the flexibility of the carboxyl group in (*S*)-**1**, the C–O bond-forming reaction is expected to take place not only on the *Re*-face of the s-*trans*-enamine but also on the *Si*-face of the s-*cis*-enamine, thereby affording both (*R*)-**3** and (*S*)-**3** (Scheme 1). As a result, (*S*)-**1** and related catalysts would show moderate enantioselectivity. In this context, we are interested in the possibility of developing a highly enantioselective aminoxylation reaction using a binaphthyl-based amino sulfonamide (*S*)-**2**, which is known to give a single stereoisomer predominantly through the s-*cis*-enamine intermediate in the direct asymmetric Mannich reaction[11] and aldol reaction.[12] Herein, we wish to report a direct asymmetric aminoxylation reaction of aldehydes with nitrosobenzene by using the axially chiral amino sulfonamide catalyst (*S*)-**2**.



(*S*)-**1** (*S*)-**2**

Figure 1. Binaphthyl-based secondary amine catalysts.



Scheme 1. Direct asymmetric aminoxylation reaction catalyzed by (*S*)-**1**.

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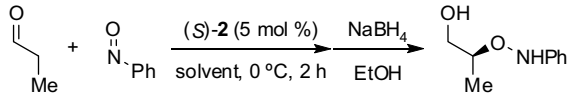
Table 1
Solvent effects in direct asymmetric aminoxylation of propanal with nitrosobenzene catalyzed by (*S*)-**2**[a]



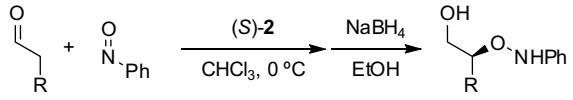
Entry	Solvent	Concn (M)	Yield[b] (%)	ee[c] (%)
1	Toluene	1.0	78	98
2	DMF	1.0	47	98
3	THF	1.0	49	98
4	CH_3CN	1.0	67	98
5	$CHCl_3$	1.0	86	98
6	$CHCl_3$	0.5	86	98
7	$CHCl_3$	2.0	85	98

[a] The reaction of propanal (0.45 mmol) with nitrosobenzene (0.15 mmol) was carried out in the solvent mentioned above in the presence of catalyst (*S*)-**2** (0.0075 mmol) at 0 °C for 2 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd).

We first attempted the direct asymmetric aminoxylation reaction catalyzed by (*S*)-**2** under the optimal conditions for the aminoxylation using (*S*)-**1**.[10] Thus, treatment of propanal with nitrosobenzene in the presence of 5 mol % of (*S*)-**2** in toluene at 0 °C and subsequent reduction with $NaBH_4$ in toluene/EtOH furnished the corresponding 2-aminoxy alcohol in good yield, and excellent enantioselectivity was observed as expected (Table 1, entry 1). We then examined the effects of solvents on the yield and enantioselectivity, and the results of the reaction using various solvents are shown in Table 1. Consequently, it was found that solvents did not affect the enantioselectivity of the present reaction (entries 1–5). In addition, the enantioselectivity was not affected by the concentration of the reaction mixture (entries 5–7). Among solvents we examined, chloroform, in which the highest yield was attained, was eventually chosen as solvent for further investigation.

The reactions using other aldehydes were then carried out under optimized conditions, and some selected examples are summarized in Table 2.[13] Similar high levels of yield and excellent enantioselectivity were obtained in most cases (entries 2–6). When a branched aldehyde 3-methylbutanal was used, the corresponding aminoxylated product was obtained in excellent yield and enantioselectivity (entry 7). The catalyst loading could be reduced without loss of enantioselectivity, and good to moderate yields of the aminoxylation product were obtained with prolonged reaction time (entries 8–10). The reaction carried out at high concentration proceeded in good yield even at low catalyst loading (0.2 mol %) (entry 11).

Table 2
Direct asymmetric aminoxylation of various aldehydes with nitrosobenzene catalyzed by (*S*)-**2**[a]



Entry	Cat (mol %)	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	5	Me	2	86	98
2	5	Et	2	90	97
3	5	Bu	2	92	98
4	5	Allyl	2	92	97
5	5	Bn	2	88	97
6	5	CH_2OBn	2	92	97
7	5	*i*-Pr	2	96	98
8	1	*i*-Pr	3	77	98
9	0.5	*i*-Pr	8	70	98
10	0.2	*i*-Pr	8	49	98
11[d]	0.2	*i*-Pr	8	76	98

[a] The reaction of an aldehyde (0.45 mmol) with nitrosobenzene (0.15 mmol) was carried out in $CHCl_3$ (150 μL) in the presence of catalyst (*S*)-**2** at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd).
[d] The reaction carried out at higher concentration (25 M).

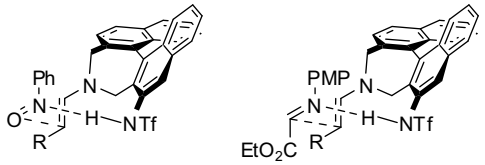
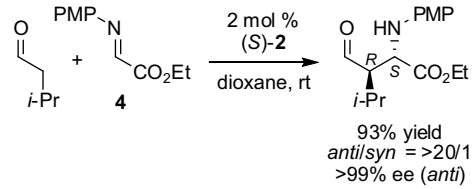


Figure 2. Transition state models for the direct asymmetric aminoxylation reaction and *anti*-selective Mannich reaction catalyzed by (*S*)-**2**.



Scheme 2. Direct asymmetric Mannich reaction catalyzed by (*S*)-**2**.

In all cases examined in this study, the absolute configuration of the aminoxylated products was determined to be *S*. Additionally, it is known that only nitrosobenzene activated by the relatively highly acidic proton such as carboxylic acid and tetrazole can react at the oxygen atom to give the aminoxylation product,[3] and the hydroxyamination product is obtained predominantly in the absence of such an acidic proton.[4,6] On the basis of the observed stereochemistry and the characteristic feature of nitrosobenzene, a plausible transition state is proposed (Fig. 2, left). The nitrosobenzene activated and directed by the distal acidic proton of triflamide group on (*S*)-**2** would approach the *Si* face of the s-*cis*-enamine. Hence, the reaction of an aldehyde with nitrosobenzene catalyzed by (*S*)-**2** provides the *S* isomer predominantly.

The results obtained in this study strongly suggest the existence of the s-*cis*-enamine intermediate, which reacts with the activated electrophile on the β-face of the enamine. This observation also supports the transition state model proposed for the *anti*-selective Mannich reaction catalyzed by (*S*)-**2**.[11] In the presence of (*S*)-**2**, the reaction between 3-methylbutanal and PMP-protected α-imino ester **4** affords the corresponding Mannich product with excellent *anti*- and enantioselectivity (Scheme 2). The observed stereochemistry is rationalized by the analogous transition state model, in which the *Si* face of the α-imino ester approaches the *Si* face of the s-*cis*-enamine as directed by triflamide group (Fig. 2, right).

In summary, we have shown that the binaphthyl-based amino sulfonamide (*S*)-**2** can be utilized as an organocatalyst in the direct asymmetric aminoxylation reaction of aldehydes. Further investigations for broadening the synthetic application of this reaction and efforts toward development of related enantioselective reactions using this catalyst are in progress in our laboratory.

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13. *Typical procedure for the direct asymmetric aminoxylation reaction with* (*S*)-**2**: To a stirred solution of chiral amino sulfonamide (*S*)-**2** (3.3 mg, 0.0075 mmol) in $CHCl_3$ (150 μL) were added propanal (32 μL, 0.45 mmol) and nitrosobenzene (16 mg, 0.15 mmol) in this order at 0 °C. After stirring for 2 h at 0 °C, EtOH (300 μL) and $NaBH_4$ (30 mg) were added at the same temperature. The mixture was allowed to warm to room temperature over 20 min, then quenched with saturated aqueous $NaHCO_3$, and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4:1) to afford the corresponding aminoxylation product (22 mg, 0.13 mmol, 86% yield, 98% ee).