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Direct Asymmetric Hydroxyamination Reaction Catalyzed by an Axially Chiral Secondary Amine Catalyst

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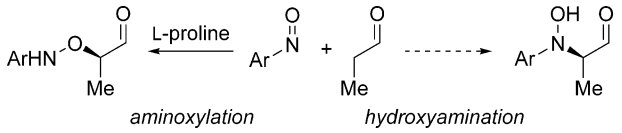
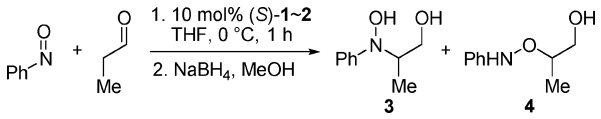
Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry,[1] and various catalytic asymmetric reactions, such as aminoxylation,[2−5] hydroxyamination,[4−6] and nitroso Diels−Alder reaction,[7] have recently been developed by exploiting their unique properties. In this area, the reactions between nitrosobenzene and activated carbonyl compounds including enolates and enamines were known to provide aminoxylation or hydroxyamination products, depending on the catalyst used, and the reaction course and enantioselectivity were successfully controlled in both metal- and organocatalytic approaches.[2,4,5] Furthermore, highly enantioselective aminoxylation reactions using simple aldehydes and ketones were also realized by proline and the related catalysts through the in situ generation of the reactive enamine (Scheme 1).[3] In marked contrast, however, the opposite chemoselectivity, i.e., the direct enantioselective hydroxyamination of aldehydes has not been realized to a synthetically useful level despite the potential application of the resulting α-amino aldehydes in organic synthesis.[6] Thus far, a highly enantioselective hydroxyamination of enamines instead of simple aldehydes has been developed by selective activation of nitroso compounds with chiral tertiary alcohols such as TADDOL.[4] In this context, we have been interested in the possibility of designing a sterically and electrically tunable organocatalyst, which may simultaneously activate both aldehydes and nitrosobenzene. Herein, we report a highly efficient organocatalytic asymmetric hydroxyamination reaction of aldehydes with nitroso compounds by using a binaphthyl-modified catalyst with dual functions.

Scheme 1



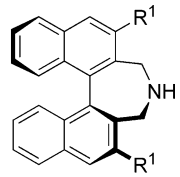
Due to the ease of modification of the binaphthyl backbone, we first attempted to use (*S*)-**1a** as a catalyst for the direct asymmetric hydroxyamination reaction. Thus, treatment of propanal with nitrosobenzene in the presence of 10 mol % of (*S*)-**1a** in THF at 0 °C and subsequent reduction with $NaBH_4$ in THF/MeOH furnished the corresponding *N*-hydroxy-*β*-amino alcohol **3** in low yield and enantioselectivity (Table 1, entry 1). We then examined the effect of an alcohol with the expectation that the hydroxyamination reaction would be facilitated by modest activation of nitrosobenzene through hydrogen bonding with alcohols. Indeed, addition of 1 equiv of either MeOH or *t*-BuOH was found to enhance the reaction rate (entries 2 and 3). These results prompted us to design new amine catalysts of type (*S*)-**1b**−**d** having hydroxyl groups at the appropriate positions to improve both reactivity and enantioselectivity. When (*S*)-**1b** having hydroxylmethyl groups at 3,3′-positions was used as a catalyst, both reactivity and enantioselectivity were significantly improved (entry 4). To our delight the reaction using (*S*)-**1c**, which has sterically congested *tert*-alcohol moieties at 3,3′-positions, proceeded smoothly under similar conditions to give the desired hydroxyamination product in good yield with excellent regio- and enantioselectivity (entry 5). Further improvement in both reactivity and enantioselectivity was achieved by using (*S*)-**1d** with hydroxydiphenylmethyl groups at 3,3′-positions (entry 6). The marked effect of hydroxyl groups in (*S*)-**1d** on the reaction rate is apparent by comparison with des-hydroxyl catalyst (*S*)-**1e**, which affords **3** in low yield with high enantioselectivity (entry 9). The catalyst loading in (*S*)-**1d** could be reduced to 5 mol % (entry 7), while the use of 1 mol % of (*S*)-**1d** resulted in a considerable decrease in both yield and enantioselectivity (entry 8). In contrast, attempted use of the proline-derived catalysts (*S*)-**2a** and (*S*)-**2b** resulted in a significant loss of reactivity and enantioselectivity, probably due to the catalyst

Table 1. Enantioselective Hydroxyamination of Propanal with Nitrosobenzene Catalyzed by (*S*)-**1**−**2**[a]

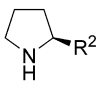


entry	catalyst	**3**/**4**	% yield[b]	% ee[c]	config[d]
1	(*S*)-**1a**	>99/1	22	29	*S*
2[e]	(*S*)-**1a**	>99/1	37	13	*S*
3[e]	(*S*)-**1a**	>99/1	36	21	*S*
4	(*S*)-**1b**	>99/1	55	77	*S*
5	(*S*)-**1c**	>99/1	78	95	*S*
6	(*S*)-**1d**	>99/1	90	99	*S*
7[f]	(*S*)-**1d**	>99/1	87	98	*S*
8[g]	(*S*)-**1d**	>99/1	36	62	*S*
9	(*S*)-**1e**	>99/1	28	83	*S*
10[h]	(*S*)-**2a**	>99/1	23	5	*R*
11[h]	(*S*)-**2b**	>99/1	9	23	*R*

[a] The reaction of propanal (3 equiv) with nitrosobenzene was carried out in THF in the presence of catalyst (*S*)-**1**−**2** at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.). [d] The absolute configuration was determined by comparison of the sign of optical rotation with reported values. See Supporting Information. [e] In the presence of 1 equiv of MeOH (entry 2) or *t*-BuOH (entry 3). [f] 5 mol % of (*S*)-**1d**. [g] 1 mol % of (*S*)-**1d**. [h] Reaction was conducted for 24 h.



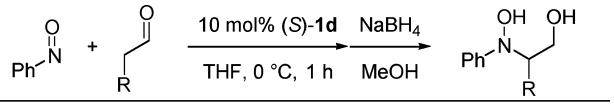
(*S*)-**1a** : R^1=H
(*S*)-**1b** : R^1=CH_2OH
(*S*)-**1c** : R^1=CMe_2OH
(*S*)-**1d** : R^1=CPh_2OH
(*S*)-**1e** : R^1=$CHPh_2$

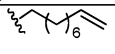
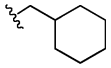
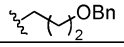


(*S*)-**2a** : R^2=CH_2OH
(*S*)-**2b** : R^2=CPh_2OH

10.1021/ja0604515 CCC: $33.50

Table 2. Enantioselective Hydroxyamination of Various Aldehydes with Nitrosobenzene and Catalyzed by (*S*)-**1d**[a]



entry	R	% yield[b,c]	% ee[d]	entry	R	% yield[b,c]	% ee[d]
1	Me	90	99 (*S*)	5		77	99
2	*i*-Pr	70	97 (*S*)	6		86	99
3	*n*-Bu	76	96				
4	Bn	80	98 (*S*)	7		86	97

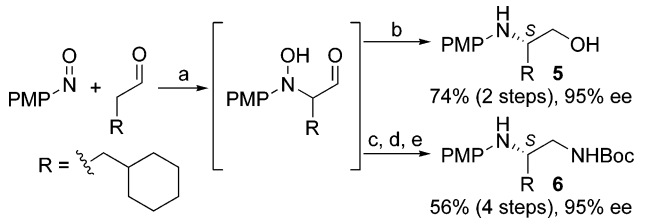
[a] The reaction of an aldehyde (3 equiv) with nitrosobenzene was carried out in THF in the presence of catalyst (*S*)-**1d** at 0 °C. [b] Isolated yield. [c] No aminoxylation product was detected. [d] Determined by HPLC analysis using chiral column. Details are given in Supporting Information.

deactivation through the undesired oxazolidine formation from catalysts and propanal (entries 10 and 11).

With the axially chiral secondary amine catalyst (*S*)-**1d** in hand, the direct asymmetric hydroxyamination reaction of several other aldehydes with nitrosobenzene was executed, and the results are shown in Table 2. In general, these direct asymmetric hydroxyamination reactions proceeded smoothly, and the subsequent reduction with $NaBH_4$ gave the corresponding *N*-hydroxy-β-amino alcohols in good isolated yields with excellent levels of enantioselectivity.

To enhance the synthetic utility of this methodology, *p*-methoxynitrosobenzene was employed instead of nitrosobenzene, and by using the resulting hydroxyamination product, one-pot procedures to prepare the β-amino alcohol or the 1,2-diamine were also developed (Scheme 2). Thus, under similar conditions, the reaction of 3-cyclohexylpropanal with *p*-methoxynitrosobenzene was carried out, and the hydroxyamination product was treated with $LiAlH_4$ in the same pot to give the (*S*)-β-amino alcohol **5** protected with a cleavable *p*-methoxyphenyl group with excellent enantioselectivity. Moreover, the hydroxyamination product could be converted to the fully protected (*S*)-1,2-diamine **6** without loss of enantiopurity by the one-pot procedure including *O*-benzyloxime formation, reduction of the N=C double bond and reductive cleavage of two N−O bonds with $LiAlH_4$, and Boc protection.

Scheme 2. One-Pot Synthesis of β-Amino Alcohol and 1,2-Diamine[a]



[a] Conditions: (a) 10 mol % (*S*)-**1d**, THF; (b) $LiAlH_4$; (c) $BnONH_2$, $MgSO_4$; (d) $LiAlH_4$; Rochelle salt, H_2O; (e) $(Boc)_2O$.

A plausible transition-state model has been proposed to account for the high selectivity of the catalyst (*S*)-**1d** (Figure 1). Each of

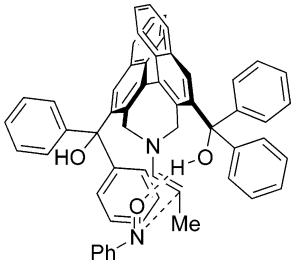


Figure 1. Possible transition state for the direct asymmetric hydroxyamination reaction catalyzed by (*S*)-**1d**.

the hydroxydiphenylmethyl groups on the catalyst (*S*)-**1d** might play a different role in the present reaction. After formation of the enamine intermediate from aldehydes and the catalyst (*S*)-**1d**, one hydroxydiphenylmethyl group shields the *re* face of the enamine effectively, and another directs and activates the nitrosobenzene by hydrogen bonding. Hence, the obtained hydroxyamination products have the *S* configuration.

In summary, we have developed a direct asymmetric hydroxyamination reaction of aldehydes with nitrosobenzene catalyzed by the novel axially chiral secondary amine catalyst (*S*)-**1d**. The resulting optically enriched hydroxyamination products are readily converted to the corresponding β-amino alcohol or 1,2-diamine in one pot. We are currently applying this and related methodologies toward the preparation of a variety of nitrogen-containing chiral building blocks.

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

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