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Asymmetric reduction of ketoxime ethers to optically active O-substituted hydroxylamines with reagents prepared from borane and chiral amino alcohols

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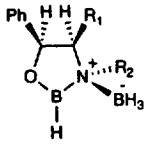
Abstract: The asymmetric reduction of ketoxime ethers to yield enantiomerically enriched chiral hydroxylamines with reagents prepared from borane and norephedrine has been investigated. Very high enantioselectivity (ca. 99% ee) was obtained in the reduction of ketoxime O-(*o*-nitrobenzyl) ether to O-(*o*-nitrobenzyl) hydroxylamine. © 1997 Elsevier Science Ltd. All rights reserved.

Although highly effective asymmetric reductions of oxime ethers to optically active amines have been reported in recent years,[1] useful enantioselective conversions of oxime ethers into O-substituted hydroxylamines have been relatively neglected and no such successful syntheses have been described.[2] In the course of our studies for the synthesis of a key intermediate of a potent and selective 5-lipoxygenase (5-LO) inhibitor we sought to discover an efficient method for the *enantioselective* preparation of chiral hydroxylamines. After surveying several chiral reducing agents for the asymmetric reduction of variously substituted 6-benzyloxy-2,3-dihydrobenzofuran-3-oxime, we found that the reagent **1a** prepared from norephedrine and borane, previously also used by Suzukamo *et al.*[2] in obtaining chiral amines, reduced the O-(*o*-nitrobenzyl) ether in moderate yield and excellent enantioselectivity to the corresponding optically active O-(*o*-nitrobenzyl) hydroxylamine. We now report our preliminary results for the reaction.



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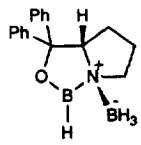

2

a. $R_1 = CH_3$, $R_2 = H$; **b.** $R_1 = CH_3$, $R_2 = CH_3$

c. $R_1 = Ph$, $R_2 = H$, **d.** $R_1 = CH_2OH$, $R_2 = H$

The reduction of ketoxime benzyl ether **3a** was initially explored with the reagents **1a**[2]**–1d** and Corey's reagent **2**.[3] The reductions were carried out under identical conditions (THF/ambient temperature, *vide infra*). Among these reagents only the norephedrine borane reagent **1a**,[2] was successful in reducing **3a** smoothly in 89.2% ee to the optically active O-benzyl hydroxylamine **4a**. The reagents **1b~d** and **2** did not reduce **3a** and starting material was recovered. These results encouraged us to investigate the asymmetric reductions of other ketoxime O-substituted ethers **3b–3k** and the results are summarized in Table 1.

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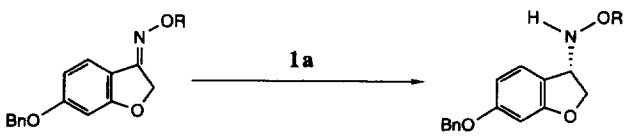
Table 1. Asymmetric reduction[a] of oxime ethers **3** with **1a**

	oxime ether 3[b] R	O-substituted hydroxyl amine product 4 ee (%)[c]	yield (%)[d]
a	CH_2Ph	89.2	63.0
b	$CH_2C_6H_4(p\text{-}OCH_3)$	64.0	54.2
c	$CH_2C_6H_4(o\text{-}NO_2)$	99.0	55.2[e]
d	CH_3	56.0	67.0
e	CH_2OCH_3	[f]	
f	$CH_2OCH_2CH_2OCH_3$	[f]	
g	$CH_2CH{=}CH_2$	[f]	
h	$C(CH_3)_3$	no reaction	
i	$C(Ph)_3$	no reaction	
j	$Si(CH_3)_2\,tBu$	no reaction	
k	$Si(CH_3)_3$	[g]	

[a] See typical experimental procedure for reaction conditions. [b] Oxime ethers were synthesized from Na salt of ketoxime and halides, and isolated as one geometrical isomer. [c] Determined by HPLC area using a CHIRALCEL-OD column eluted with 10% EtOH in hexane. [d] Isolated yield. [e] Major byproduct was over reduced amine (~15%) and product (~12%) was lost in the filtrates. [f] The reactions gave an intractable mixture. [g] Less than 5% of unprotected hydroxylamine was detected with a unidentified compound as major product.



3 **4**

The reduction of ketoxime O-(*o*-nitrobenzyl) ether **3c** with **1a**, afforded **4c** in very high optical purity (99% ee). In contrast, the asymmetric reduction of ketoxime O-(*p*-methoxybenzyl) ether **3b** and ketoxime O-methyl ether **3d** with **1a** were less effective affording **4b** and **4d** in 64 and 56% ee, respectively. The O-(t-butyldimethylsilyl) and O-(t-butyl) substituted oxime ethers were not reduced by **1a**, even when the temperature was raised to 50°C. The reduction of O-methoxymethyl, O-(2-methoxyethoxymethyl) and O-allyl substituted oxime ethers resulted in complicated reaction mixtures.

During the course of this study it was observed that the chemical yield of the desired O-substituted hydroxylamines depended critically upon the ratio of borane to norephedrine. With the reagent prepared from 1:1 molar ratio of these compounds, for example, almost no reduction occurred and the starting oxime was recovered. To find the optimum conditions, the reduction of ketoxime benzyl ether was repeated with various admixtures of norephedrine and borane. It was noted that the reagent prepared from 2 mols of borane and 1 mol of norephedrine gave the highest chemical yield of the O-substituted hydroxylamine. In contrast, larger excesses of the borane decreased the yield of O-substituted hydroxylamine and increased the yield of the amine which arises from over-reduction.

In summary, a highly efficient enantioselective reduction of benzyl protected ketoximes with a reagent prepared from norephedrine and borane to afford a substituted hydroxylamine has been described for the first time. Removal of the benzyl protection and conversion to the unprotected hydroxylamines can also be readily accomplished by standard hydrogenolytic methods. The rationale we advance at this time for the results is that the aryl residues are capable of potentiating the

reducing efficiency of the norephedrine–borane reagent by strong π-bonding interactions with both the norephedrine and boronhydride.

A typical experimental procedure is as follows: A THF solution of BH_3 (58 mL, 58 mmol) was added to a THF (32 mL) solution of 1S,2R-(+)-norephedrine (4.4 g, 29 mmol) in an ice bath under nitrogen. After the resulting mixture had been stirred in an ice bath for 5~6 h, a solution of ketoxime ether **3c** (8.5 g, 22 mmol) in THF (64 mL) was added and the stirring was continued for 17 h at room temperature. The solution was then quenched by the addition of 3N HCl (80 mL). After stirring at room temperature for 30 h, the product hydroxylamine HCl salt was isolated by filtration to give a light yellow solid, the HCl salt of **4c** (5.2 g, 55.2% yield, 99% ee). The hydroxylamine HCl salt (0.58 g) was slurried in H_2O, the solution was brought to pH 9 with NH_4OH and extracted with ethyl acetate. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to give 4c[4] as an oil (0.48 g, 90.6% yield). IR (film): 3080, 3040, 2950, 1740, 1630, 1610, 1540, 1510, 1350, 830, 740, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.22 (1 H, dd, J=3.6 and 9.7 Hz), 4.32 (1 H, dd, J=7.6 and 9.7 Hz), 4.49 (1 H, m), 4.79 (2 H, S), 4.91 (2 H, S), 6.32 (1 H, S), 6.35 (1 H, d, J=2.1 Hz), 7.06 (1 H, d, J=7.8 Hz), 7.15~7.28 (5 H, m), 7.40~7.44 (1 H, m), 7.52~7.60 (2 H, m), 7.87 (1 H, d, J=8.0 Hz). MS m/e 415 $(M+Na)^+$. Anal. Calcd. for $C_{22}H_{20}N_2O_5HCl$: C, 61.61; H, 4.94; N, 6.53; Cl, 8.27, Found: C, 61.71; H, 4.76; N, 6.69; Cl, 7.98.

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2. In their description of the asymmetric reduction of oxime ethers to amines, Suzukamo *et al.* allude to the possibility of obtaining methyl ethers of hydroxylamines, which were not characterized (Table 1 notes); Sakito, Y.; Yoneyoshi, Y.; Suzukamo, G. *Tetrahedron Letters* **1988**, 223–224.
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4. The absolute configuration of **4c** was determined as (3S) in contrast to the same compound prepared from (S)-N-(6-benzyloxy-2,3-dihydrobenzofuran-3-yl)-hydroxylamine which structure has been determined by X-ray.

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