O-(1-Phenylbutyl)benzyloxyacetaldoxime, a Versatile Reagent for the Asymmetric Synthesis of Protected 1,2-Aminoalcohols and 2-Hydroxymethyl Nitrogen Heterocycles

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Dedicated to the memory of Alex Larigo.

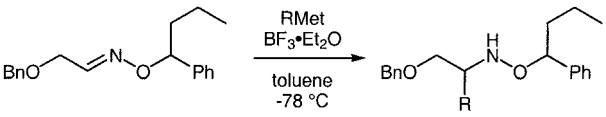
Abstract: Addition of organometallic reagents to *O*-(1-phenylbutyl)benzyloxyacetaldoxime in the presence of boron trifluoride diethyl etherate is highly diastereoselective; the resulting hydroxylamines are readily converted into protected 1,2-aminoalcohols and 2-hydroxymethyl nitrogen heterocycles, including the iminosugar 1,4-dideoxy-1,4-imino-D-ribitol, in high enantiomeric excess.

Key words: asymmetric synthesis, organometallic reagents, oximes, amino alcohols, piperidines

Compounds with a chiral centre adjacent to nitrogen occur commonly in nature and are also widely used as synthetic intermediates, ligands and chiral auxiliaries. Although many routes to this structural unit already exist,[2] new stereoselective methods remain of interest. One powerful method for the construction of such asymmetric centres is the stereoselective addition to C=N bonds of imines, hydrazones, oximes, and nitrones,[3–5] and we have described the addition reactions of *O*-(1-phenylbutyl)oxime ethers in the asymmetric synthesis of amines,[6] α-amino acids,[7] and their β-homologues.[6] We now report that *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1** is a particularly versatile intermediate for the asymmetric synthesis of a range of nitrogen-containing compounds.

The (*E*)-oxime ether **1** was prepared in either enantiomeric form by reaction of the commercially available aldehyde with either (*R*)- or (*S*)-*O*-(1-phenylbutyl)hydroxylamine,[8] followed by chromatographic separation from the corresponding *Z*-isomer.[9] Addition of organolithium or Grignard reagents in the presence of boron trifluoride diethyl etherate in toluene at low temperature proceeded smoothly and gave the corresponding hydroxylamines **2** in reasonable yield and in good diastereomeric excess (Table 1).[10] The only exception to this was the reaction involving the addition of allylmagnesium bromide which showed poor diastereoselectivity (42% de), although the major diastereomer was readily isolated. The stereochemistry at the new asymmetric centre was assigned on the basis of previous work, and on the subsequent transformations of the hydroxylamines **2**.

Table 1 Addition of Organometallic Reagents to *O*-(1-Phenylbutyl)benzyloxyacetaldoxime **1**



1 **2**

Oxime configuration	Organometallic Reagent	Hydroxylamine (configuration at new centre)	Yield/%	de[a]/%
R	MeLi	**2a** (*R*)	75	75
S	H_2C=CHLi	**2b** (*S*)	61	87
R	*n*-PrMgCl	**2c** (*R*)	82	90
R	*i*-PrMgCl	**2d** (*R*)	79	90
S	H_2C=$CHCH_2MgBr$	**2e** (*S*)	44[b]	42
R	*n*-BuLi	**2f** (*R*)	72	90
R	PhLi	**2g** (*R*)	56	>95
S	$PhCH_2MgBr$	**2h** (*S*)	83	90
S	4-$BrC_6H_4CH_2MgBr$	**2i** (*S*)	45	90
R	2-lithiothiophene	**2j** (*S*)	81	80
R	2-lithiothiazole	**2k** (*S*)	84	>95

[a] Determined from the ^{1}H NMR spectrum of **2** by integration of the C*H*NH signals.

[b] Yield of the major diastereomer after separation.

The N–O bond in the hydroxylamines **2** was readily cleaved using either zinc in acetic acid with sonication or using molybdenum hexacarbonyl. The resulting amines were not isolated but immediately protected as their *t*-butyl or benzyl carbamates. The protected 1,2-aminoalcohols **3** were formed in good yield and high enantiomeric excess as evidenced by HPLC on a chiral stationary phase (Table 2).

The *O*-benzyl-*N*-*tert*-butoxycarbonyl-1,2-aminoalcohols **3a** and **3e** were deprotected by hydrogenolysis to give the known *N*-Boc-1,2-aminoalcohols **4a** and **4b** (Scheme 1) thereby confirming the stereochemistry of the original addition to the chiral oxime ether **1**.[11–13]

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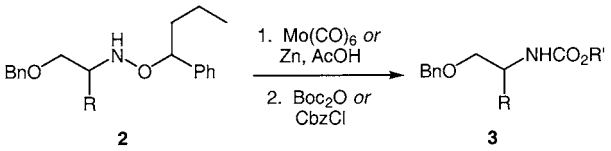
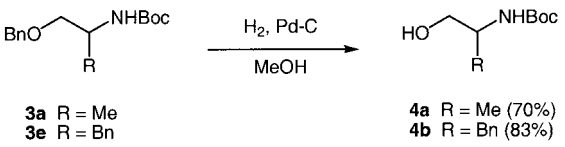
Table 2 N–O Bond Cleavage in Hydroxylamines **2** and Protection of Resulting Amines as Carbamates **3**



2 **3**

Hydroxylamine	Method[a]	R	R′	Protected 1,2-aminoalcohol **3**	configuration	Yield/%	ee[b]/%
2a	A	Me	*t*-Bu	**3a**	*R*	67	97
2b	B	H_2C=CH	Bn	**3b**	*S*	76	nd[c]
2e[d]	B	H_2C=$CHCH_2$	Bn	**3c**	*S*	70	91
2f	A	*n*-Bu	*t*-Bu	**3d**	*R*	67	93
2h	*A*	Bn	*t*-Bu	**3e**	*S*	84	83
2k	A	2-thiazolyl	*t*-Bu	**3f**	*S*	77	98

[a] Method A: $Mo(CO)_6$, aq MeCN; Method B: Zn, HOAc, ultrasound.
[b] Determined by HPLC on ChiralCel OD using hexane–*iso*propanol (85:15 to 95:5) as eluent.
[c] nd = not determined.
[d] The major diastereomer was used in this reaction.

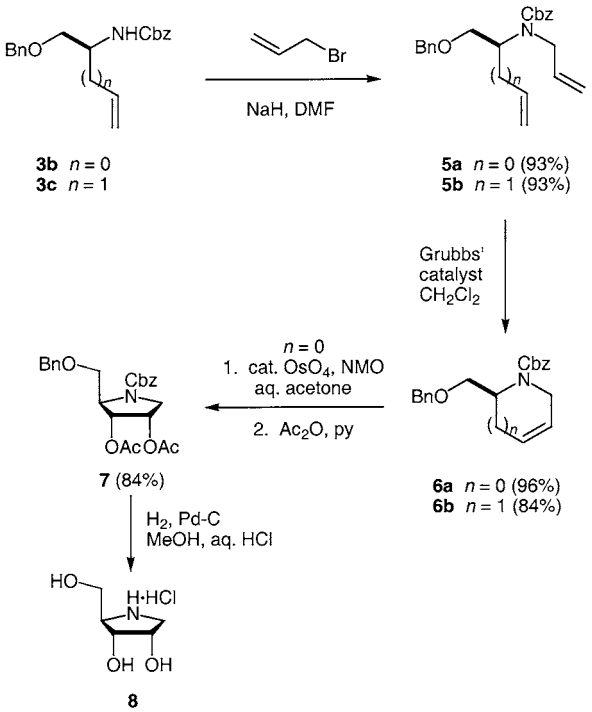


3a R = Me
3e R = Bn

4a R = Me (70%)
4b R = Bn (83%)

Scheme 1

The versatility of the 1,2-aminoalcohol derivatives obtained by stereoselective addition to *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1** was further illustrated by the synthesis of the nitrogen heterocycles **6** (Scheme 2). Thus N-allylation of the benzyl carbamates **3b** and **3c** gave the corresponding N-allyl derivatives **5** in good yield. Treatment with benzylidene bis(tricyclohexylphosphine)dichlororuthenium (Grubbs' catalyst) resulted in ring-closing metathesis (RCM) reaction to give the 2,5-dihydropyrrole **6a** (90%) and the 1,2,3,6-tetrahydropyridine **6b** (84%),[14] useful precursors to 5- and 6-membered ring iminosugars, as illustrated by the synthesis of 1,4-dideoxy-1,4-imino-D-ribitol, a naturally occurring glycosidase inhibitor isolated from the mulberry tree *Morus alba*.[15,16] Thus reaction of dihydropyrrole **6a** with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO) resulted in dihydroxylation from the least hindered face to give, after acetylation, the protected iminosugar **7** (84% over two steps). Hydrogenolysis of **7** in methanolic hydrochloric acid gave 1,4-dideoxy-1,4-imino-D-ribitol as its hydrochloride salt **8** in quantitative yield (Scheme 2).[16,17]



3b *n* = 0
3c *n* = 1

5a *n* = 0 (93%)
5b *n* = 1 (93%)

6a *n* = 0 (96%)
6b *n* = 1 (84%)

7 (84%)

8

Scheme 2

In summary, we have shown that the oxime ether **1** is a versatile reagent for the asymmetric synthesis of protected 1,2-aminoalcohols and nitrogen heterocycles.

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(9) (*E*)-(*S*)-(–)-*O*-(1-Phenylbutyl)benzyloxyacetaldoxime [(*S*)-**1**]; colourless oil; $[\alpha]_D^{24}$ –6.7 (*c* 0.90, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.54 (1 H, t, *J* = 6.8 Hz, N=CH), 7.31 (10 H, m, ArH), 5.09 (1 H, t, *J* = 7.0 Hz, OCH), 4.44 (2 H, AB, *J* = 12.5 Hz, C*H*$_2$Ph), 4.07 (2 H, m, C*H*$_2$CHN), 1.95 (1 H, m, C*H*H), 1.73 (1 H, m, CH*H*), 1.51–1.26 (2 H, m, C*H*$_2$Me), 0.95 (3 H, t, *J* = 7.3 Hz, Me); δ_C (75 MHz; $CDCl_3$) 147.5 (N=CH), 142.8 (C), 137.9 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 85.6 (OCH), 72.7 (CH_2), 67.1 (CH_2), 38.7 (CH_2), 19.3 (CH_2), 14.4 (Me).
(10) *General procedure*. The oxime ether **1** (3.9 mmol, 1 equiv) was dissolved in toluene (10 mL) under nitrogen and cooled to –78 °C or –90 °C. Boron trifluoride etherate (11.8 mmol, 3 equiv) was added and the mixture stirred for 15 min. The organometallic reagent (11.8 mmol, 3 equiv) was added dropwise over 30 min at this temperature, and the mixture stirred until all starting material was consumed. The reaction mixture was quenched at this temperature with aq sat. ammonium chloride solution (10 mL), and allowed to warm to r.t. The mixture was extracted with ether (3 × 15 mL), combined, dried (K_2CO_3), filtered and evaporated. The residue was purified by column chromatography on silica gel.
(11) (*R*)-*N*-*tert*-Butoxycarbonyl-1-hydroxy-2-propylamine (*N*-Boc-alaninol)(**4a**); mp 49–50 °C (lit.,[12] mp 52–53 °C); $[\alpha]_D^{19}$ +8.6 (*c* 0.8, $CHCl_3$) {lit.,[12] $[\alpha]_D^{26}$ +10.0 (*c* 1.0, MeOH)}; (*S*)-*N*-*tert*-butoxycarbonyl-1-hydroxy-3-phenyl-2-propylamine (*N*-Boc-phenylalaninol)(**4c**); mp 89–91 °C (lit.,[13] mp 91–92 °C); $[\alpha]_D^{17}$ –32.4 (*c* 1.0, $CHCl_3$) {lit.,[12] $[\alpha]_D^{25}$ –25.0 (*c* 1.0, MeOH)}.
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(17) 1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride salt **8**; mp 124–125 °C (lit.,[15] mp 130–132 °C); $[\alpha]_D^{25}$ +53.3 (*c* 0.75, H_2O) {lit.,[15] $[\alpha]_D^{20}$+53.9 (*c* 1.0, H_2O)}.