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Diastereoselective Hydride Reductions of α–Hydroxy Oximino Ethers. Synthesis of *syn*-1,2-Amino Alcohols.

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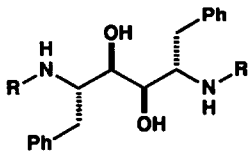
Key Words: Felkin hydride reductions; *syn*-1,2-amino alcohols.

Abstract: *Tetramethylammonium triacetoxyborohydride provides for the stereocontrolled reduction of α-hydroxy-E/Z-oximino ethers to yield* syn-*1,2-amino alcohols.*

The stereocontrolled preparation of vicinal amino alcohols has been a topic of long-standing interest in the pharmaceutical arena. Currently, the development of peptidomimetic isosteres, and in particular, the stereocontrolled synthesis of C_2-symmetric and pseudo-C_2-symmetric amino alcohols such as 1 and 2 for investigations of HIV protease inhibitors has received considerable attention.[1] Although numerous examples of nucleophilic additions to α-amino(amido) ketones and aldehydes have been recorded, little is known about the analogous chemistry of α-hydroxy(alkoxy)oximes.[2] Encouraged by our previous efforts for preparation of 1,3-amino alcohols,[3] we have examined opportunities for 1,2-asymmetric induction in hydride additions to α-hydroxy oximino ethers.



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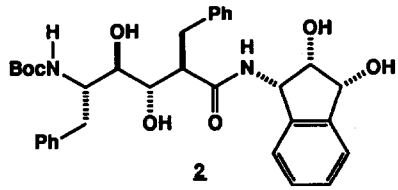
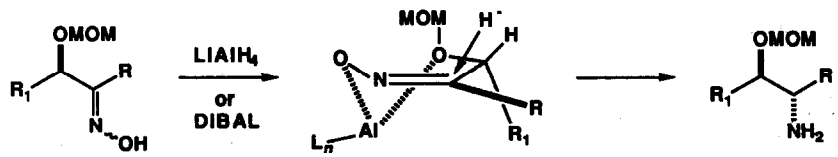


2

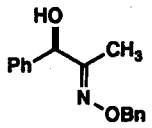
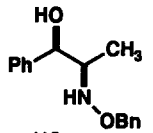
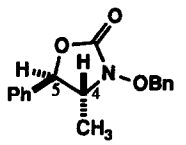
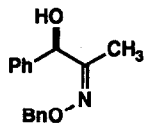
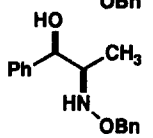
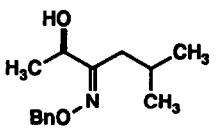
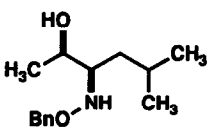
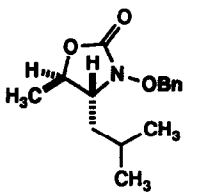
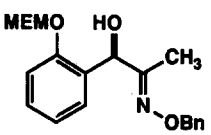
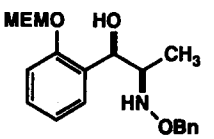
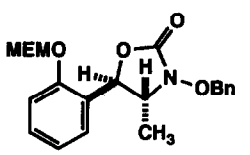
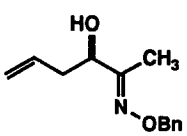
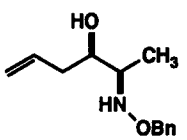
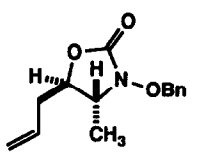
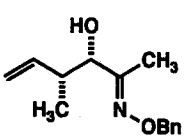
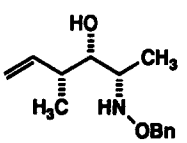
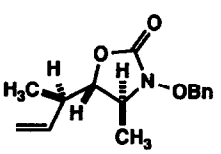
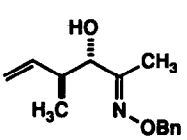
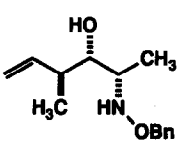
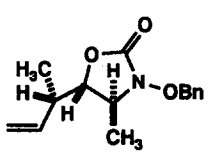
Kibayashi and co-workers have previously reported the use of aluminium hydride reagents for stereocontrolled reductions of α-alkoxy oximes 3 derived from acyclic ketones.[4] The predominant formation of *anti*-amino alcohols 4 was rationalized as the major product of an *anti*-Cram chelation model 3a. Earlier efforts by Harada and Shiono had shown that the catalytic hydrogenation of pure *E*- and *Z*-α-hydroxy ketoximes also yielded the *anti*-(erythro)-amino alcohols 4 regardless of oxime geometry.[5] Borane reduction of cyclic α-hydroxy oximino ethers has recently been described for the stereoselective formation of *cis*-1,2-amino alcohols.[6]



3 3a 4

In light of our observations of high diastereofacial selectivity in the hydride reductions of β-hydroxy oximino ethers as influenced by the configuration of the starting oxime,[3] we have undertaken a preliminary study of reductions of *E*- and *Z*-α-hydroxy oximino ethers with tetramethylammonium triacetoxyborohydride (TABH) in acetic acid-acetonitrile (1:1 by volume). Results are summarized in Table I. All reactions were

Table I

Entry	Oxime	Yield %	Product	Oxazolidinone[e]	^{1}H–NMP δ and J_{AB}
1[a]		100			H_4 = 3.60 H_5 = 4.83 $J_{4\text{-}5}$ = 9.2 Hz
2[a]		76			
3[a]		80			H_4 = 3.26 H_5 = 4.11 $J_{4\text{-}5}$ = 7.3 Hz
4[a]		77			H_4 = 3.65 H_5 = 5.22 $J_{4\text{-}5}$ = 7.9 Hz
5[b]		59[d]			H_4 = 3.39 H_5 = 3.99 $J_{4\text{-}5}$ = 8.0 Hz
6[c]		42[d]			H_4 = 3.42 H_5 = 3.76 $J_{4\text{-}5}$ = 7.2 Hz
7[c]		30[d]			H_4 = 3.48 H_5 = 3.89 $J_{4\text{-}5}$ = 8.1 Hz

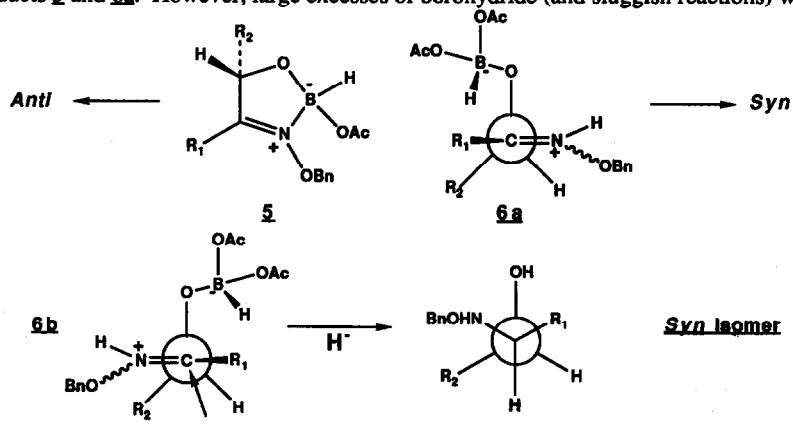
Reaction Conditions and Notes:

(a) TABH (5 eq.), CH_3COOH/CH_3CN (1:1), -35 °C for 3-5 hr, then warming to 22 °C (stirring at rt for 4 hr; entry 5). (b) TABH (15 eq.), CH_3COOH/CH_3CN (1:1), -35 °C for 4 to 16 hr, then warming to 22 °C over 2-3 hr. (c) TABH (20 eq.), CH_3CN at 22 °C, add dropwise equal volume AcOH over 15 min, then stirring for 1.5 hr. (d) Quantities of starting oxime (35-54%) were recovered unchanged in these experiments. (e) Oxazolidinones were prepared from amino alcohols with carbonyl diimidazole (1 equiv.) in benzene at reflux.

highly stereoselective affording 1,2-*syn*-amino alcohols. The mild hydride conditions do not result in reductive cleavage of the heteroatomic N-O bond. The N-benzyloxyamino alcohols were further characterized as their five-membered oxazolidinones via reaction with carbonyl diimidazole. Perhaps the most interesting feature of these reductions is the observation of high *syn*-stereoselectivity, which is opposite to previous results with aluminium hydrides or via catalytic hydrogenation. Generally, our reactions of Table I were not as facile as reductions of β-hydroxy oximino ethers. In some cases, this led to sluggish reactions and the isolation of considerable amounts of starting oxime (entries 5, 6, 7). Furthermore, these diastereofacial hydride additions were not dependent upon *E/Z*-oxime geometry as we reported for the acyclic β-hydroxy oxime derivatives.

Stereochemical Assignments: Starting alcohols were prepared via oximation of α-(dimethyl-*t*-butyl)silyloxy ketones using N-benzyloxyamine followed by fluoride-induced deprotection. The oxime geometry of purified isomers was established by ^{13}C NMR.[7] Entries 4, 6 and 7 solely provided formation of the *E*-oximino ethers. Recovery of starting oxime in entry 2 showed that some (10-20%) isomerization to the corresponding *E*-oxime had occurred under the reduction conditions. The stereochemical assignments of our vicinal amino alcohols were feasible via conversion to their *trans*-4,5-disubstituted oxazolidinones for ^1H NMR spectroscopy. The planar nature of the five-membered ring induced an eclipsing interaction for C_4-C_5 substituents. Thus, *trans*-substitution provides a shielding environment for both C_4 and C_5 methine hydrogens. The chemical shifts of H_4 and H_5 are substantially upfield compared to their *cis*-4,5-disubstituted oxazolidinones. Additionally, the coupling constants $J_{4,5}$ (Hz) for *trans*-4,5-disbustituted oxazolidinones are slightly smaller than those observed for *cis*-isomers. For entries 1 and 2, comparisons of proton NMR data were made with the corresponding cyclic carbamates of (+)-pseudoephedrine and (-)-ephedrine.[8] Alternative reductions in entries 3 and 7 ($NaCNBH_3$; MeOH; HOAc) afforded direct access to *cis*-4,5-disubstituted oxazolidinones for comparisons.[9] Finally unambiguous stereoassignments were available via an X-ray diffraction study of a derivative of the oxazolidinone of entry 7.[10]

Mechanistic Rationale: Ligand exchange of the triacetoxyborohydride may provide an equilibrating mixture of adducts 5 and 6a. However, large excesses of borohydride (and sluggish reactions) would suggest



that internal hydride delivery is not effective in these substrates. Moreover, models indicate a poor trajectory for intramolecular nucleophilic addition in 6a, and a transition state which evokes an eclipsing nonbonded interaction (R_1/R_2). We currently favor a rationale for external hydride addition to rotamer 6b with the bonded boronate,

sterically and electronically, shielding one face of the C=N unit. Thus, the Felkin model for intermolecular hydride addition to 6b may provide for formation of a *trans*-disubstituted, five-membered cyclic boronate which yields the syn-1,2-amino alcohols upon hydrolysis.

In conclusion, tetramethylammonium triacetoxyborohydride (TABH) has been shown to reduce α-hydroxy oximino ethers to afford acyclic 1,2-*syn*-N-benzyloxyamino alcohols. The high stereoselectivity is opposite to that observed for aluminium hydride reagents and catalytic hydrogenation. Results are rationalized via a Felkin addition model for external hydride delivery. Further efforts for natural product total synthesis are underway.

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References:

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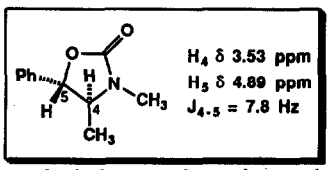
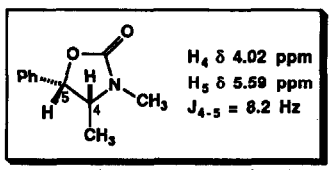
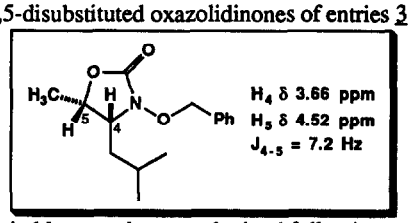
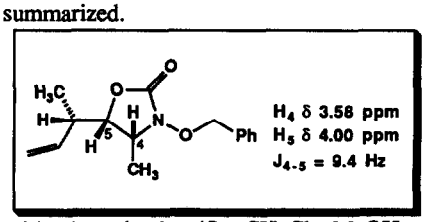
5. Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1040.
6. Ghosh, A.K.; McKee, S.P.; Sanders, W.H. *Tetrahedron Lett.* **1991**, *32*, 711.
7. The individual *anti*- and *syn*-oxime isomers were separated by silica gel flash chromatography. Determination of oxime geometry was based on ^{13}C and ^{1}H NMR data. The assignments of chemical shifts of α-carbons located *syn* to the benzyloxy substituent are observed upfield relative to the corresponding *anti* isomers due to steric compression.
8. Data for comparisons of the cyclic carbamates of (+)-pseudoephedrine 7 and (-)-ephedrine 8 are illustrated below.





9. *Trans*-amino alcohols were the major products of $NaCNBH_3$ reductions. Data for the correspondig *cis*-4,5-disubstituted oxazolidinones of entries 3 and 7 are summarized.





10. Suitable crystals were obtained following ozonolysis and *in situ* reduction (O_3; CH_2Cl_2; MeOH at -78 °C; then $NaBH_4$) with subsequent conversion of the primary alcohol to its bromide (MsCl; Et_3N; DMAP; CH_2Cl_2; then LiBr; THF at 22 °C), as white needles (mp 85-87 °C, ether). Complete X-ray crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 92305.

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