Tetrahedron Letters, Vol. 34, No. 5, pp. 785-788, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Enantioselective Oxazaborolidine Reduction of Ketones Containing Heteroatoms

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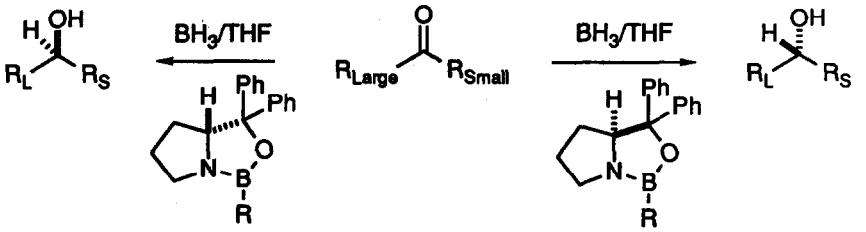
Key Words: Enantioselective reduction; Oxazaborolidine; Chiral alcohol; Catalytic reduction; Amine-borane

ABSTRACT: *Ketones which contain heteroatoms, particularly nitrogen, can be enantioselectively and catalytically reduced with chiral oxazaborolidines in the presence of excess borane.*

A practical method was required to synthesize chiral secondary alcohols for a number of heteroatom containing substrates. There are a variety of good methods for asymmetric reduction of prochiral ketones with stoichiometric reagents which provide the product alcohol in high enantiomeric excess (ee)[1]. Limitations to the use of these stoichiometric reagents for ketone reductions are their availability, cost, ease of product purification, and chiral auxilliary recovery on large scale.[2] One of the newer methods for preparation of chiral alcohols developed by Corey and coworkers, employing oxazaborolidines, appeared particularly attractive because of its catalytic nature and the high ee afforded of predictable absolute stereochemistry as depicted below.[3]

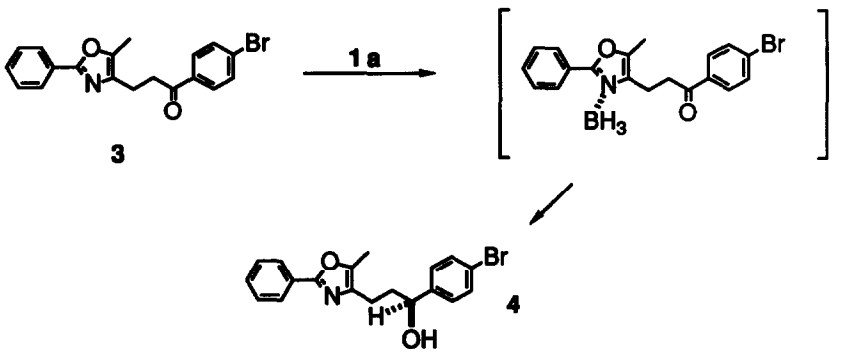


1a R=Me
1b R=Bu
1c R=Ph

2a R=Me
2b R=Bu
2c R=Ph

To date, use of this catalytic reduction has been limited to compounds which contain carbon, hydrogen, oxygen, halogen, and sulfur.[4] No published examples of high enantiomeric excess have been reported when competing nitrogen coordination sites existed in the substrate.[5] In addition, researchers at Merck found that small quantities of diphenylprolinol, methylboronic acid, triphenylboroxine, and benzophenone reduced the enantioselectivity in the ketone reduction.[6] Thus a substrate which contained borane coordinating groups was not anticipated to afford a high ee due to non-oxazaborolidine catalyzed reduction.

We have discovered that reduction of ketones which contain heteroatoms capable of coordinating borane, particularly nitrogen, can be reduced catalytically with oxazaborolidines to afford alcohols with high ee's. One of the more interesting cases was oxazole **3**. Initial attempts to reduce this oxazole **3** under the standard conditions, 0.05 equivalents (eq) of catalyst/0.7eq borane, reproducibly led to an 85:15 mixture of recovered **3** and the alcohol **4**. We hypothesized that the oxazole nitrogen was coordinating borane competitively with the catalyst and once coordinated, the amine-borane was inert under the reaction conditions. To test this tenet, a solution of oxazole **3** and the catalyst in tetrahydrofuran was titrated with borane. Complete reaction was obtained with 1.7eq of borane, and the desired (S) alcohol **4** was obtained in ≥90% ee with the methyl **1a** or phenyl **1c** catalyst at 23°C (Table 1).[7,8] Use of a more hindered borane, catecholborane as a source of hydride in conjunction with **1b**, yielded the alcohol **4** albeit in 36% ee.[9]

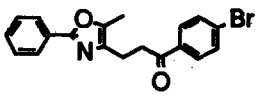
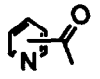
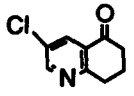
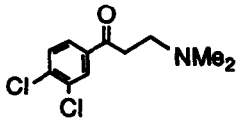
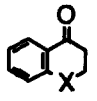
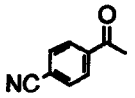
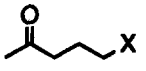


One system which has not given high ee's was the pyridine system. 2-Acetylpyridine **5** was reduced with **1a** and 1.7eq of borane to yield the alcohol in 28%ee. If an amine-borane complex was forming as with oxazole **3**, then a five membered ring transition state for the delivery of hydride could be envisioned. Thus 3-acetylpyridine **6** and 4-acetylpyridine **7** were reduced with **1a** and the ee increased to 51% and 52% respectively. The ee obtained with azatetralone **8** was comparable to 3-acetylpyridine. Using more oxazaborolidine, 0.2 and 1.0eq, increased the enantioselectivity of the acetylpyridine reduction (Table 1). The moderate ee's obtained in the catalytic reduction of the acetylpyridines may be the result of ketone activation by the pyridine-borane complex, which then allows direct borane reduction to effectively compete with the catalyzed reduction path as borane-pyridine complex itself is known to be a sluggish reducing agent.[10]

The β-aminoketone **9** was investigated to determine if an intramolecular delivery of hydride from an amine-borane precluded enantioselective ketone reduction by an oxazaborolidine. Reduction of **9** required 1.7 equivalents of borane, again suggesting formation of an amine-borane, which had the potential as 2-acetylpyridine for intramolecular delivery of hydride. In this case a 90% ee was obtained. Thus the use of oxazaborolidines provides a catalytic alternative to the low temperature reduction of Mannich bases with Chirald®.[11]

A prochiral ketone containing groups of comparable steric demands flanking the carbonyl group does not provide the secondary alcohol with high enantiomeric excess. Tetrahydrothiophen-3-one **10** gave a 23% ee of the alcohol under the standard reduction conditions. While the ee obtained with **10** was low, the

Table 1[12]

Ketone		Catalyst	ee/(Configuration)	Yield
	3	1a	94%/(S)	>95%
		1c	90%/(S)	>95%
	5 2-acetyl	1a	28%/(S)	85%
		1a*	45%/(S)	89%
	6 3-acetyl	1a	51%/(S)	94%
		1a*	63%/(S)	92%
		1a**	80%/(S)	90%
	7 4-acetyl	1a	52%/(S)	90%
		1a*	65%/(S)	93%
	8	2a	40%/(R)	85%
	9	2a	90%/(R)	92%
	10	2b	23%/(R)	76%
	11 X = O	2a	96%/(R)	92%
	12 X = S	2a	92%/(R)	94%
	13	1a	94%/(S)	90%
	14	1a	94%/(S)	91%
	15 X = CN	2a	74%/(R)	83%
	16 X = Me	2a	66%/(R)	90%

enantiomer which predominated followed the original mechanism proposed wherein the sulfur atom was the large group relative to the methylene group.[13]

The bicyclic 4-chromanone **11** and 4-thiochromanone **12** have been reduced microbially,[14] following Prelog's rule,[15] to afford the (S) alcohols in high ee. One of the advantages of the oxazaborolidine reduction is that either alcohol enantiomer is available in a predictable manner simply by choosing the appropriate chiral catalyst. To exemplify this point, reduction of 4-chromanone and 4-thiochromanone with the methyl catalyst **2a** afforded the (R) alcohols in 96% and 92%ee respectively. α-Tetralone has been reported to be reduced in 86-96%ee with **2a**,[3a,5] thus a heteroatom in the ring produces a comparable ee.

Other heteroatomic systems reduced enantioselectively were the nitrile **13** 94%ee, and thiophene **14** 94%ee. As expected, the nitriles were reduced with 0.7eq borane as these nitrogen atoms were not sufficiently basic to form discrete amine-borane complexes. Comparable enantiomeric excess were obtained with the dialkyl keto-nitrile **15** (70% ee) and the hydrocarbon analogue of **15**, namely 2-hexanone **16** (66% ee).

In summary, the enantioselective reduction of ketones catalyzed by oxazaborolidines is a powerful method to obtain chiral secondary alcohols and is often applicable to compounds which contain heteroatoms including nitrogen.

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[2]For a report on a large scale perspective in the synthesis of optically active compounds see Crosby, J. *Tetrahedron* **1991**, 4789-4846.

[3]a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. b) US patent # 4,943,635. c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Org. Chem.* **1988**, *53*, 2861-2863.

[4]Researchers at Abbott employed an acyl dithiane unit to sterically augment the enantioselectivity of the reduction. DeNinno, M. P.; Perner, R. J.; Lijewski, L *Tetrahedron Lett.* **1990**, *31*, 7415-7418.

[5]The following publication reported the reduction of substrates which contain a basic nitrogen atom, but did not detail the enantiomeric excess or stoichiometry. Labelle, M.; et. al *Bioorgan. Med. Chem. Lett.* **1992**, *2*, 1141-1146.

[6]a) Jones, T. J; et. al. *J. Org. Chem.* **1991**, *56*, 763-769. b) Mathre, D.; et. al. *J. Org. Chem.* **1991**, *56*, 751-762.

[7]At O°C a 74% ee was obtained with the **1a** catalyst.

[8]While **4** was not a conglomerate, its optical purity could be augmented from 94%ee to 98%ee and 89% yield by recrystallization of the crude alcohol. For an excellent review of conglomerates and resolutions see Jacque, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions;* Wiley-Interscience: New York. **1981**.

[9]a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275-6278. b) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611-614.

[10]Barnes, R. P.; Graham, J. H.; Taylor, M. D. *J. Org. Chem.* **1958**, *23*, 1561-62.

[11]Deeter, J.; Frazier, J.; Stanten, G.; Staszak, M; Weigel, L. *Tetrahedron Lett.* **1990**, 31, 7101-7104.

[12]All reductions were performed in tetrahydrofuran at 20-25°C with borane-dimethyl sulfide complex and 5 mole% catalyst unless noted otherwise. Catalysts were prepared by the method in reference 3c, making certain all of the prolinol and boronic acid were dissolved at 45°C prior to the addition of molecular sieves, and by using the boroxine method of reference 5b. Catalysts prepared by either method provided the same ee. Determination of ee was achieved by pmr of the corresponding Mosher's ester derivative and/or HPLC employing a chiral support. * 0.2 and ** 1.0 equivalent of oxazaborolidine were employed.

[13]Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.

[14]Holland, H. L.; Manoharan, T. S.; Schweizer, F. *Tetrahedron Asymmetry* **1991**, 2, 335-338.

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(Received in USA 6 October 1992; accepted 28 October 1992)