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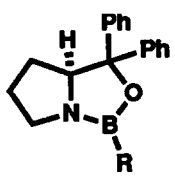
A NEW SYSTEM FOR CATALYTIC ENANTIOSELECTIVE REDUCTION OF ACHIRAL KETONES TO CHIRAL ALCOHOLS. SYNTHESIS OF CHIRAL α-HYDROXY ACIDS

E. J. Corey and Raman K. Bakshi

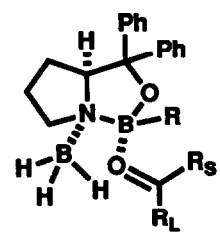
Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: The reduction of a variety of achiral ketones with catecholborane as stoichiometric reductant and 0.1 equiv of oxazaborolidine **2** as catalyst in toluene at -78°C proceeds in > 95% yield and with enantioselectivities in the range 30 : 1 to 9 : 1, depending on substrate. This reduction procedure is especially advantageous for α,β-enones, thereby providing chiral precursors for a great variety of compounds, for example, α-hydroxy acids.

The chiral oxazaborolidines **1** and **2**, readily prepared as colorless storable compounds from *(S)*-(-)-(diphenylhydroxymethyl)pyrrolidine and the corresponding alkylboronic acids, are highly effective catalysts for the enantioselective reduction of ketones to chiral secondary alcohols by borane.[1] This method (CBS reduction[1]) which involves a transition state assembly shown in **3**, is advantageous for several reasons: (1) wide scope, (2) predictable absolute stereochemistry, (3) ready availability of the chiral catalyst in either enantiomeric form, (4) easy and efficient recoverability of the chiral amino alcohol (catalyst precursor), (5) high yields and experimental simplicity, and (6) economy. Important applications of the process include highly enantioselective and efficient syntheses of such target molecules as prostanoids,[1b] *trans*-2,5-diarylfurans,[1b] oxiranes,[1c] ginkgolides A and B,[2] forskolin,[3] bilobalide,[4] fluoxetine,[5] and isoproterenol.[6] This paper reports a modification of the CBS reduction in which the B-*n*-butyl catalyst **2** and catecholborane are used in toluene solution at -78°C to effect enantioselective ketone reduction. The original CBS procedure involving **1** as catalyst and BH_3 as stoichiometric reductant is subject to interference by functionality which is sensitive to borane (e.g. olefinic or amide) and loses stereoselectivity at lower temperatures. In contrast, the catecholborane procedure functions well at low temperature which allows considerably enhanced enantioselectivity with important types of substrates (e.g. α,β-enones). The application of the CBS reduction to the enantioselective synthesis of α-hydroxy acids is also described.



1 R = CH_3
2 R = *n*-C_4H_9



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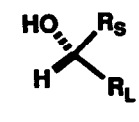
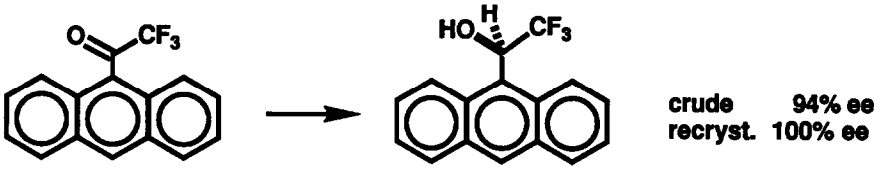
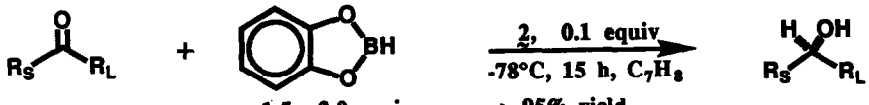


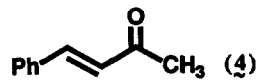
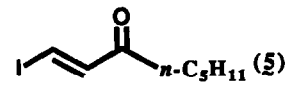
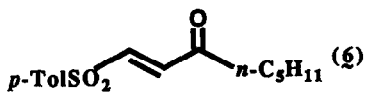
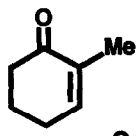
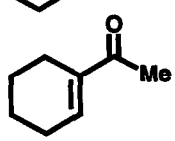
The catalytic reduction of a variety of achiral ketones to chiral secondary alcohols using catecholborane as reductant in the presence of 0.1 equiv of **2** as catalyst was found to proceed efficiently in toluene at -78°C. Consequently it was possible to develop the following standard conditions for these reductions: (1) addition of 1.5 - 2 equiv of catecholborane (1 M in toluene) over 20 min to a solution of 1 equiv of ketone and 0.1 equiv of catalyst **2** in toluene at -78°C under nitrogen; (2) stirring at -78°C until reaction was complete as determined by tlc analysis (usually 15 h); (3) quenching with water and washing with base to remove catechol, (4) extraction with acid to remove 2-(diphenylhydroxymethyl)pyrrolidine for reuse, and (5) isolation of the carbinol product. Under these conditions the various ketones were cleanly converted to chiral carbinol which could be isolated in > 95% yield. The following aromatic ketones were reduced to the corresponding chiral alcohols, of *R* configuration in each case, with the indicated enantiomeric excess (% ee) values:[7] acetophenone (94);[1] α-tetralone (93);[1] phenyl trifluoromethyl ketone (90);[8a] 9-anthryl trifluoromethyl ketone (94).[8b] In the case of *(R)*-(-)-9-anthryl trifluoromethylcarbinol, one recrystallization of the crude product from ether-hexane afforded 100% enantiomerically pure carbinol,[7,8b] mp 136°C, $[\alpha]_D^{23}$ - 30.0° (c=6, $CHCl_3$). The superior effectiveness of this enantioselective synthesis and the broad utility of chiral 9-anthryl trifluoromethyl carbinols in NMR and analytical work[8b,9] make this last result especially noteworthy. The corresponding CBS reductions of 9-anthryl trifluoromethyl ketone with **1** or **2** and borane are less enantioselective.



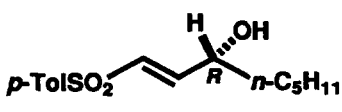
Chiral allylic alcohols are extremely useful starting points for many enantiospecific syntheses since they serve as excellent substrates for stereospecific reactions such as the Claisen rearrangement, epoxidation, cuprate S_N2' displacement, and intramolecular [2 + 1], [2 + 2] and Diels-Alder reactions. The catecholborane CBS modification is the method of choice for the synthesis of such alcohols from the corresponding enones. Presented below are data on the reduction of a sample of five enones, each of which is reduced in > 95% yield to the corresponding *R* allylic alcohol in toluene solution under standard conditions. For comparison the following yields and product ee values were observed with three of these same substrates by use of the catalyzed BH_3 reduction: for ketone **5**, 76% ee, 80% yield; for ketone **7**, 68% ee, 90% yield; for ketone **8**, 74% ee, 85% yield. Clearly, the ee values and yields obtained with catecholborane and **2** at -78°C in toluene are superior to the results using borane; lower yields in the case of borane reduction are due to the formation of more polar by-products from hydroboration.

The alcohol **9** obtained by reduction of the β-tosyl enone **6** was upgraded by a single recrystallization from hexane to > 98% enantiomeric purity[7] with 83% recovery.[10] The absolute configuration of **9** was established by correlation with *(R)*-(+)-methyl 2-acetoxyheptanoate (**10**)[11] which was obtained from **9** by the sequence: (1) acetylation of **9** using acetic anhydride, 4-*N*,*N*-dimethylaminopyridine and pyridine in CH_2Cl_2 at 23°C for 5 h to form the corresponding acetate (93%); (2) oxidation with sodium periodate in the



Ketone	Abs. Config.	% ee
 (4)	*R*	92
 (5)	*R*	86
 (6)	*R*	91
 (7)	*R*	93
 (8)	*R*	81

presence of a catalytic amount of ruthenium trichloride[12] in a mixture of CCl_4 - CH_3CN - H_2O at pH 1 and 23°C for 2 h and esterification of the resulting acid with CH_2N_2-ether to give **10** (84%), $[\alpha]_D^{23}$ + 30.3° (c=1, CH_3OH), as a colorless oil. This conversion also demonstrates a new process for the synthesis of chiral α-hydroxy acids which is at least competitive with existing methods. Mention should also be made of a second route to α-hydroxy acids which utilizes the CBS/borane enantioselective reduction. The chiral *R* benzylic alcohol **11** is available by reduction[1b] of *p*-anisyl-*n*-amyl ketone with 0.6 equiv of BH_3 and 0.1 equiv of catalyst **1** in THF at -10°C for 0.2 h (for **11**, 99% isolated yield, 96% ee,[7] $[\alpha]_D^{23}$ +20.8° (c=1.0, CH_3OH)). Sequential acetylation of **11**, ruthenium-catalyzed oxidation,[12] and esterification with CH_2N_2 in ether, as described above for **9**, afforded *(R)*-(+)-methyl 2-acetoxyheptanoate (**10**) in 80% overall yield from **11**. Thus, either the allylic alcohol **9** or the benzylic alcohol **11** can serve as a practical precursor of the chiral α-hydroxy acid derivative **10**.



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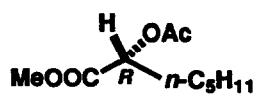

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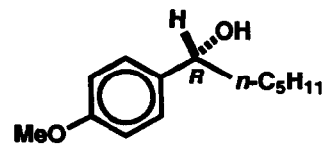

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The following procedures provide experimental detail for the synthesis of catalyst **2**.[13]

***n*-Butylboronic Acid.** To a solution of 11.53 ml (0.05 mole) of triisopropoxyborane in ether under dry N_2 at -78°C was added dropwise a solution of 35.7 ml of 1.4 M butyllithium in hexane (0.05 mole) over 30 min. After stirring the reaction mixture for 1 h at -78°C, the temperature was allowed to increase to 23°C and the reaction mixture was stirred for a further 3 h. After cooling to 0°C, 0.1 mole of a solution of dry HCl in ether was added and the precipitate of lithium chloride was removed by filtration. Water (18 ml) was added to the filtrate, the solvent was removed in vacuo and the residue was sublimed at 95 - 110°C and 0.3 Torr to afford 4.20 g (82%) of *n*-butylboronic acid as a colorless solid; ^{11}B NMR peak in D_2O solution at +32.13 ppm (downfield from $BF_3 \bullet Et_2O$ as external reference).

Oxazaborolidine 2. To a solution of 500 mg (1.98 mmoles) of *(S)*-(-)-2-(diphenylhydroxymethyl)pyrrolidine[1c] in 20 ml of toluene was added 221 mg (2.17 mmoles) of *n*-butylboronic acid and the mixture was heated at reflux under N_2 using either a Dean-Stark trap or a Soxhlet apparatus containing 4A molecular sieves in a thimble to remove water. After 4 h the reaction mixture was concentrated in vacuo and the residue of **2** was dissolved in either THF or toluene to give a 0.5 M solution which was stored under dry N_2 or Ar. The ^{11}B NMR spectrum of **2** in 0.5 M THF solution showed peaks at +33.57 ppm (monomer) and +7.68 ppm (dimer).

References and Notes

1. (a) E. J. Corey, R. K. Bakshi, and S. Shibata, *J. Am. Chem. Soc.*, **109**, 5551 (1987); (b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *ibid.*, **109**, 7925 (1987); (c) E. J. Corey, S. Shibata, and R. K. Bakshi, *J. Org. Chem.*, **53**, 2861 (1988); (d) E. J. Corey, Proceedings of the 31st National Organic Symposium, American Chemical Society, p. 1 (1989).
2. (a) E. J. Corey, *Chem. Soc. Rev.*, **17**, 111 (1988); (b) E. J. Corey and A. V. Gavai, *Tetrahedron Letters*, **29**, 3201 (1988).
3. (a) E. J. Corey, P. Da Silva Jardine, and T. Mohri, *Tetrahedron Letters*, **29**, 6409 (1988); (b) E. J. Corey and P. Da Silva Jardine, *ibid.*, in press.
4. E. J. Corey and W.-g. Su, *Tetrahedron Letters*, **29**, 3423 (1988).
5. E. J. Corey and G. A. Reichard, *Tetrahedron Letters*, **30**, 5207 (1989).
6. E. J. Corey and J. O. Link, *Tetrahedron Letters*, in press.
7. Enantiomeric purity was established by 500 MHz ^1H NMR and/or capillary gas chromatographic analysis of the MTPA (Mosher) ester; J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973). Absolute configuration was determined from measurement of the optical rotation of each isolated and purified product. Satisfactory spectroscopic data were obtained for all reaction products.
8. For optical rotations and absolute configurations of carbinol products see (a) H. M. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968); (b) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977); a reaction time of 72 h at -78°C or 8 h at -23°C was used for this ketone; (c) ref. 1.
9. (a) W. H. Pirkle and D. L. Sikkenga, *J. Org. Chem.*, **42**, 1370 (1977); (b) W. H. Pirkle and D. L. Sikkenga, *J. Chromatog.*, **123**, 400 (1976); (c) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **43**, 378 (1978).
10. Found for recrystallized **9**, $[\alpha]_D^{23}$ - 33.4° (c=1.3, CH_3OH), mp 64-66°C.
11. P. A. Grieco, T. Takigawa, and T. R. Vedananda, *J. Org. Chem.*, **50**, 3111 (1985).
12. See, (a) S. Giddings and A. Mills, *J. Org. Chem.*, **53**, 1103 (1988); (b) A. K. Chakraborti, and U. R. Ghatak, *Synthesis*, 746 (1983); (c) P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).

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