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A NEW CHIRAL CATALYST FOR THE ENANTIOSELECTIVE SYNTHESIS OF SECONDARY ALCOHOLS AND DEUTERATED PRIMARY ALCOHOLS BY CARBONYL REDUCTION

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Summary: An efficient synthesis of *(S)*-(-)-2-(di-β-naphthylhydroxymethyl)pyrrolidine (**1**) makes available the oxazaborolidine derivatives **2** and **3** which are excellent catalysts for borane reduction of a variety of achiral ketones to chiral secondary alcohols, e.g. acetophenone, 98% ee; α-tetralone, 95% ee; and methyl-4-oxo-4-phenyl butyrate, 96% ee. The synthesis of chiral 1-deuterio primary alcohols from achiral aldehydes with B-*n*-butyloxazaborolidine (**4**) as catalyst in the presence of ^{2}H-catecholborane as reductant has also been demonstrated, e.g. benzaldehyde, 95% ee; cyclohexanecarboxaldehyde, 92% ee; and *n*-octanal, 90% ee.

This paper reports the synthesis of the amino alcohol **1**, *(S)*-(-)-2-(di-β-naphthylhydroxymethyl) pyrrolidine, its conversion to the oxazaborolidines **2, 3** and **4**, and their use as enantioselective catalysts in the borane reduction of achiral ketones to form chiral secondary alcohols, and in the ^{2}H-catecholborane reduction of aldehydes to form chiral 1-deuterio primary alcohols. These new findings considerably extend the scope and power of the recently developed CBS method[1] of catalytic enantioselective reduction.

The synthesis of **1** was accomplished starting from *N*-benzyl-*(S)*-proline methyl ester which was added dropwise to the Grignard reagent from 2-bromonaphthalene (2.5 equiv in THF, 0°C, then 8 h at 23°C) to give after extractive isolation and passage through a short silica gel (sg) column (12 : 1 hexanes : *tert*-butylmethyl ether) the crystalline alcohol **5** (83%); mp 77-79°C, $[\alpha]^{23}_D$ +173.8° (c=1.64, $CHCl_3$). Debenzylation of **5** with 20% palladium hydroxide on carbon catalyst (0.1 mass equiv) and hydrogen (1 atm) in methanol containing acetic acid (1.1 equiv) at 23°C for 36 h, followed by filtration, concentration and extractive isolation from 1 *N* NaOH afforded amino alcohol **1** as a colorless solid (87%). This solid was further purified by precipitation of the hydrochloride salt from ether, formation of the free base by extraction from 1 *N* NaOH and crystallization from ethyl acetate - hexanes to give colorless needles of 99.4% ee (determined by HPLC analysis of the MTPA (Mosher) amide[2]); TLC R_f 0.2 (sg, ethyl acetate); mp 137-138°, $[\alpha]^{23}_D$ -130.4° (c=2.56, $CHCl_3$); IR (neat) 3600-3200, 3056, 2959, 2670, 1505, 753 cm^{-1}; 270 MHz ^{1}H NMR ($CDCl_3$) 8.10 (s, 2H), 7.9-7.4 (m, 12H), 4.53 (dd, 1H, J=6, 6 Hz), 3.05 (m, 1H), 2.97 (m, 1H), 1.76 (m, 3H), 1.62 (m, 2H); EIMS (70 ev) *m/e*: 354 (M^+).

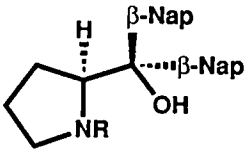
Conversion of **1** to oxazaborolidines **3** and **4** was effected by heating for 10 h at reflux with 1.2 equiv of methylboronic acid or *n*-butylboronic acid[3] respectively in toluene using a Soxhlet extractor containing 4A molecular sieves to remove water. The ^{11}B NMR spectrum of **3** in THF solution showed peaks at 31.4 ppm (monomer, broad) (downfield from BF_3•Et_2O as external standard) and 8.5 ppm (dimer); addition of 1 equiv of BH_3 in THF resulted in a BH_3 complex with ring ^{11}B-CH_3 peak at 32.5 ppm and N-BH_3 peak at -15.0 ppm.

The spectrum of **4** in toluene showed peaks at 32.0 ppm (broad) and 7.6 ppm, with the BH_3 complex having the ring ^{11}B-CH_3 peak at 33.7 ppm and the N-BH_3 peak at -15.2 ppm. These shifts are consistent with previous data on other CBS complexes.[1] Conversion of **1** to oxazaborolidine **2** was accomplished by heating at 70°C with 3 equiv BH_3•THF at 1.6 atm (maintained by a mercury U-tube seal) for 72 h.[1c] The ^{11}B NMR spectrum of **2** in THF solution showed a broadened peak at 25.8 ppm.

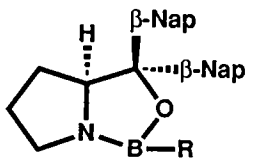
Oxazaborolidines **2** and **3** were shown to be highly effective catalysts for the borane reductions of a variety of achiral ketones to chiral secondary alcohols. Results are summarized in Table 1. Reductions were performed with either 0.05 or 0.1 equiv of catalyst by addition of ketone over 4 min to a mixture of catalyst and BH_3 (0.6 equiv) in THF at the temperature indicated; reactions were complete in less than 5 min after addition of the last reagent. The amino alcohol **1** was easily recovered as the colorless HCl salt by addition of 0.12 equiv 0.5 *N* methanolic HCl and ether followed by filtration. The resulting optically active alcohols could be isolated in >90% yield (quantitative by gas chromatographic analysis) by concentration of the filtrate followed by ether extraction, drying, and removal of ether. Absolute configuration and enantiomeric excess were determined by gas chromatographic analysis of the MTPA ester or menthyloxycarbonyl derivatives and comparison with authentic reference samples.[1]

Chiral 1-deuterio primary alcohols have proven important in studies of chemical and biochemical mechanisms.[4] Enantiospecific reduction of aldehydes is an attractive route to these compounds and a number of papers have been published utilizing this strategy. Previous methods have used stoichiometric quantities of chiral reagents[5] or enzyme catalysts.[6] The following CBS reduction process is to our knowledge the first catalytic chemical system (chemzyme) to provide chiral 1-deuterio primary alcohols in high optical purity (Table 2). This process provides alcohols of either S or R absolute stereochemistry through the use of **4** or its enantiomer and does not necessitate the synthesis of 1-deuterio aldehydes. For aldehydes, CBS conditions employing BD_3 as reductant are unsatisfactory because the achiral uncatalyzed pathway for aldehyde reduction by BD_3•THF is competitive with the chiral catalyst mediated pathway. The use of ^2H-catecholborane[7] as reductant in a non-coordinating solvent at low temperature in the presence of oxazaborolidine **4** (the B-*n*-butyl catalyst is especially suited to reactions at low temperature)[8] vastly suppresses the uncatalyzed reduction pathway. Reductions were carried out by slow addition of ^2H-catecholborane (1.5 equiv, 0.25 *M* in 1 : 1 toluene - methylcyclohexane) over 30 min with vigorous agitation to a solution of oxazaborolidine **4** (0.3 equiv) and aldehyde (1 equiv, 0.13 *M* in 2 : 2 : 1 toluene - methylcyclohexane - methylene chloride) at -126°C (methylcyclohexane / liq N_2 bath) and then stirring for 3 h. Addition of 0.7 equiv 0.5 *M* methanolic HCl to the bright yellow solution, slow warming to 23°C, recovery of the solid amino alcohol **1**-HCl salt by filtration, dilution of the filtrate with ether, washing with aqueous Na_2CO_3, concentration at 0°C, and chromatography on a short sg column (7 : 1 petroleum ether - ether), afforded pure 1-deuterio alcohols in > 90% yield. Enantiomeric excess values and the absolute configuration of the benzaldehyde reduction product *(S)*-benzyl-α-d alcohol (the S stereochemistry is consistent with the proposed mechanism for the CBS process[1] and is predicted for all entries in Table 2) were determined by 500 MHz ^1H NMR analysis of the MTPA esters.[2]

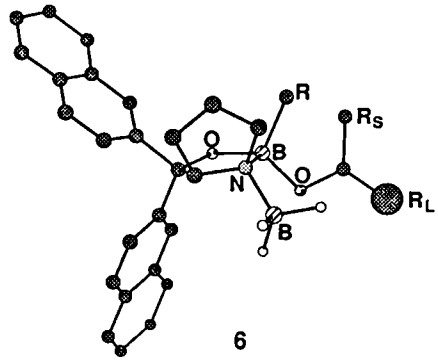
All of the examples of catalytic enantioselective reduction reported in this paper follow the stereocourse which is expected for the catalytic assembly **6**.[1] The β-naphthyl catalysts **2**-**4** are in several instances more effective than the phenyl analogs.[1] Substitution of *i*-propyl, α-naphthyl *o*–methoxyphenyl, or H for β-naphthyl or phenyl leads to catalysts which are much less effective and selective.[9]



1 R=H
5 R=CH_2Ph



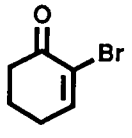
2 R=H
3 R=CH_3
4 R=*n*-butyl



6

2 or 3 + BH_3·THF 0.6 equiv → 1) R_LR_SCO 2) HCl/MeOH → R_LR_SCHOH

TABLE 1

ketone	R	equiv cat.	reaction temp °C	config of prod. ee%
$C_6H_5COCH_3$	CH_3	.1	23	R(97.8)
$C_6H_5COCH_3$	CH_3	.05	23	R(96.1)
$C_6H_5COCH_3$	H	.1	23	R(97.8)
$C_6H_5COCH_2CH_3$	CH_3	.1	0	R(97.4)
$C_6H_5CO(CH_2)_2COCH_3$	CH_3	.1	0	R(96.1)
α-tetralone	CH_3	.1	31	R(94.5)
α-tetralone	H	.1	23	R(95.3)
c-$C_6H_{11}COCH_3$	CH_3	.1	0	R(82.2)
c-$C_6H_{11}COCH_3$	H	.1	23	R(84.7)
t-$BuCOCH_3$	CH_3	.1	0	R(92.7)[a]
	CH_3	.1	36	R(90.3)[a]
	H	.1	36	R(90.7)[a]

[a] BH_3·THF added to the mixture of ketone and catalyst over 30 min.

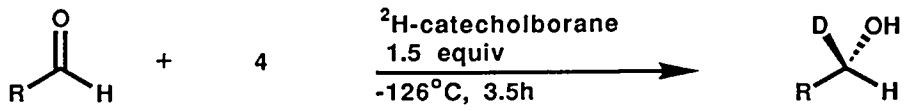


TABLE 2

aldehyde	equiv of catalyst	major diast: ^{1}H NMR, δ (J, Hz.)[a]	minor diast: ^{1}H NMR, δ (J, Hz.)[a]	ee%[a]
C_6H_5CHO	.3	5.31 s	5.36 s	95
C_6H_5CHO	.1	5.31 s	5.36 s	90
(*p*-Br)C_6H_4CHO	.3	5.26 s	5.27 s	91
(*p*-MeO)C_6H_4CHO	.3	5.23 s	5.30 s	82
n-octanal	.3	4.32 t(6.26)	4.28 t(6.67)	90
cyclohexane-carboxaldehyde	.3	4.14 d(5.69)	4.07 d(6.13)	92

[a] ^{1}H NMR data for carbinyl proton of MTPA ester derivatives (ee% determined by integration of these peaks).

References and Notes

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6. See (a) C.-H. Wong, and G. M. Whitesides, *J. Am. Chem. Soc.*, **103**, 4890 (1981); (b) E. Caspi, and C. R. Eck, *J. Org. Chem.*, **42**, 767 (1977), and references therein.

7. H. C. Brown, "Organic Synthesis via Boranes", Wiley, New York. ^{2}H-catecholborane was made from catechol and BD_3•THF which was generated from $NaBD_4$.

8. E. J. Corey, R. K. Bakshi, *Tetrahedron Letters*, in process.

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