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Catalytic Enantioselctive Reactions. Part 11. Asymmetric Borane Reduction of Prochiral Ketones Catalyzed by A New Chiral Oxazaborolidine Derived from D-Mannitol

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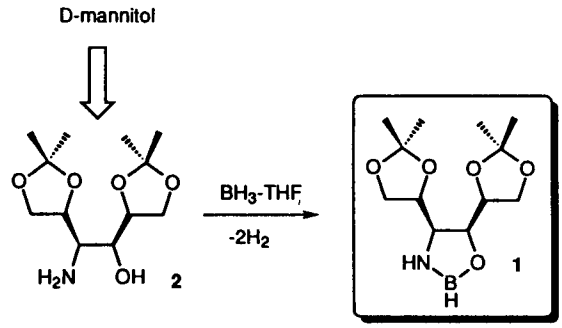
Chiral oxazaborolidine-borane adducts have been shown to be highly effective for the catalytic asymmetric reduction of prochiral ketones.[1] Although a number of chiral oxazaborolidines to provide high enantioselectivites for the reduction have been extensively developed, most of them are derived from β-amino alcohols bearing geminal diphenyl substituents obtained from natural α-amino acids.[2] Recently, it has been reported that chiral erythro β-amino alcohols which can block one face of the oxazaborolidines are also highly effective for such reduction as chiral sources, such as (1*S*,2*S*,3*R*,5*S*)-3-amino-2-hydroxy-pinane,[3a] (1*R*,2*S*)-2-amino-1-acenaphthenol,[3b] (1*R*,2*S*)-2-amino-1,2-diphenylethanol,[3c] (1*R*,2*S*)-1-amino-2-indanol,[3d,e] *endo* (or *exo*)-3-amino-2-hydroxybornanes derived from D-camphor,[3f] and (1*R*,2*S*)-ephedrine.[3g] However, to the best of our knowledge, the use of chiral oxazaborolidines derived from monosaccharides for the reduction has not been reported. In this communication, we describe the catalytic enantioselective borane reduction of ketones using a new class of chiral oxazaborolidine (**1**)[4] generated from an erythro β-amino alcohol, 3-amino-3-deoxyl-1,2;5,6-di-*O*-isopropylidene-D-altritol (**2**),[5] derived from D-mannitol (Scheme 1).

We examined asymmetric induction of the new oxazaborolidine **1** for borane reduction of acetophenone chosen as representative. The reduction was performed by dropping the ketone slowly over a period of 1 h to a solution of 0.6 equiv of borane-THF in the presence of 10 mol% of **1** in THF at room temperature (*ca.* 25 ℃). The reaction proceeded rapidly to give (R)-1-phenylethanol of 81% ee in a 98% yield within 10 min (entry 3). We then extended our investigation to several kinds of ketones under the same reaction conditions. The results are summarized in Table 1. When steric size of R in aromatic ketones, PhCOR, was varied from Me → Et → *n*-Bu → *i*-Pr, optical yields of product alcohols obtained decreased, such as 81% *ee* for acetophenone, 77% *ee* for propiophenone, 75% *ee* for butyrophenone and 12% *ee* for isobutyrophenone (entries 1, 6, 7 and 8). Absolute configurations of all the product alcohols obtained were in good agreement with the expectation based on a proposed transition models[8] to give (*R*)-enantiomers except for that of isobutyrophenone. The reason for providing opposite absolute configuration ((*S*)-isomer) in the reduction of isobutyrophenone is not fully understood. For aliphatic ketones, increase of steric size of R in MeCOR resulted in increase of enantioselectivities of product alcohols, such as 40% *ee* for 2-heptanone, 52% *ee* for cyclohexyl methyl ketone, 53% ee for 4-



Scheme 1.

Table 1. Catalytic Asymmetric Borane Reduction of Various Ketones in the Presence of 1 in THF at Room Temperature[a]

Entry	Ketones	**1** (mol%)	Product alcohols[b] % eec	Config.[d]
1	$PhCOCH_3$	2	71	*R*
2	$PhCOCH_3$	5	73	*R*
3	$PhCOCH_3$	10	81	*R*
4	$PhCOCH_3$	10	42[e]	*R*
5	$PhCOCH_3$	10	33[f]	*R*
6	$PhCOCH_2CH_3$	10	77	*R*
7	$PhCOCH_2CH_2CH_3$	10	75	*R*
8	$PhCOCH(CH_3)_2$	10	12	*S*
9	$PhCOCH_2Cl$	10	70	*S*
10	$PhCOCO_2CH_3$	10	58	*S*
11	n-$C_5H_{11}COCH_3$	10	40	*R*
12	$(CH_3)_2CHCH_2COCH_3$	10	53	*R*
13	c-$C_6H_{11}COCH_3$	10	52	*R*
14	$(CH_3)_3CCOCH_3$	10	80	*R*
15	2,2-Dimethylcyclopentanone	10	51[g]	*R*
16	$(CH_3O)_2CHCOCH_3$	10	68[g]	*S*

[a]The reactions were carried out with slow addition of ketones over a period of 1 h to mixture of 10 mol% of **1** and 0.6 eq of BH_3-THF in THF at room temperature (*ca.* 25 ℃), unless otherwise indicated. [b]The reduction proceeded rapidly to give the corresponding alcohols in >98% yields within 10 min. [c]Determined by capillary GC analyses of their (*R*)-MTPA esters,[9] unless otherwise indicated. [d]By the comparison of elution orders of (*R*)-MTPA esters of the authentic optically active alcohols. [e]% Ee of the alcohol obtained at 0 ℃. [f]% Ee of the alcohol obtained by rapid mixing of all the reagents followed by quenching and workup after 10 min. [g]Determined by capillary GC anaylses of their (−)-menthyl carbonates.[10]

methyl-2-pentanone and 80% ee for 3,3-dimethyl-2-butanone (entries 11-14). On the other hand, asymmetric reduction of functionalized ketones, such as 2-chloroacetophenone, methyl benzoylformate and 1,1-dimethoxypropanone provided the corresponding (*S*)-alcohols of 58-68% *ee* (entries 9, 10 and 16). In this case, (*S*)-configurations of product alcohols obtained is due to notations by the sequence rule.

In the asymmetric borane reduction of acetophenone using **1**, a catalytic amount less than 10 mol% of **1** gave the alcohol with lower enantiomeric excess, such as 71% ee with 2 mol% and 73% ee with 5 mol% (entries 1 and 2). When the reaction was carried out at 0 ℃, the alcohol of 42% ee was obtained (entry 4). Rapid mixing of all the reagents followed by quenching and workup after 10 min afforded the alcohol with 33% *ee* (entry 5). Decrease of enantioselectivities at low concentration of **1**, at low temperature or at high concentration of the ketone as described above is attributable to a consequence of competing uncatalyzed reductions by borane itself.

The following procedure is representative. To a mixture of **1** (0.3 M, 0.2 mmol) and BH_3-THF (0.9 M, 1.2 mmol) in THF was added acetophenone (0.5 M, 2.0 mmol) in THF over a period of 1 h *via* a syringe pump at room temperature (*ca.* 25 ℃). After 10 min, the reaction mixture was quenched by the addition of 1 N HCl and solvent was removed *in vacuo*. The residue was basified with 1 N NaOH and extracted with ether. The combined extracts were dried over anhydrous $MgSO_4$. GC analysis showed the formation of 1-phenylethanol in a 98% yield. The solvent was evaporated under reduced pressure and the product alcohol was isolated by bulb-to-bulb distillation in vacuo. Optical purity of the product alcohol was determined by capillary GC analysis of (*R*)-MTPA ester using a 50 m methyl silicon column to show 81% *ee*, *R*.

In conclusion, this is the first example for asymmetric borane reduction of ketones using a new class of chiral oxazaborolidine (**1**) obtained from D-mannitol as a catalyst. The borane asymmetric reduction of several kinds of prochiral ketones with 10 mol% of **1** provided the corresponding alcohols with moderate enantioselectivities of up to 81% *ee*.

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4. The oxazaborolidine **1** was prepared by the reaction of **2** with borane-THF and used without isolation or purification.[3]
5. The erythro β-amino alcohol **2** was prepared from D-mannitol by the known procedure.[6] **2**: mp 114-115 ℃ (lit.[6] 115-116 ℃); $[\alpha]_D^{22}$ 2.38 (*c* 1.0, $CHCl_3$) (lit.[7] $[\alpha]_D$ 2.5± 0.9 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}), 3378, 3157, 2988, 1612, 1472, 1379; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 2.84 (t, 1H, J=5.1 Hz), 3.60 (t, 1H, J=6.0 Hz), 3.85-4.20 (m, 6H), 4.32 (dt, 1H, J=5.1 and 6.6 Hz); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ 109.4, 109.2, 76.7, 76.1, 74.2, 66.9, 66.7, 54.4, 26.7, 26.5, 25.3, 25.2; Anal. Calcd for $C_{12}H_{23}NO_5$: C, 55.16; H, 8.87; N, 5.36. Found C, 55.34, H, 9.03, N, 5.25.
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Crown Ethers Bearing a Convergent Carboxylic Acid Function: Synthesis of Kemp's Triacid-Capped Crown Ethers and Their Ionophoric Properties

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There has been much recent research interest on the development of the stimuli responsive host systems.[1,2] The most common tools employed are the changes in pH, along with the thermal, light, and chemical stimuli such as redox reactions. Ionizable crown ethers are one of the most attractive ionophoric systems studied so far for the construction of a functional ionophore system by responding to the changes in pH.[3]

Kemp's triacid has been widely utilized for the developments of novel host systems by utilizing its unique and rigid U-shaped relationship between carboxylic acid functions.[4] Some of the ionophoric ligands employing Kemp's triacid structural motif were also reported and their binding properties for the recognition of various metal ions were investi-